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Catalytic Enantioselective Vinylogous Mukaiyama-Michael Addition of 2-Silyloxyfurans to Cyclic Unsaturated Oxo Esters

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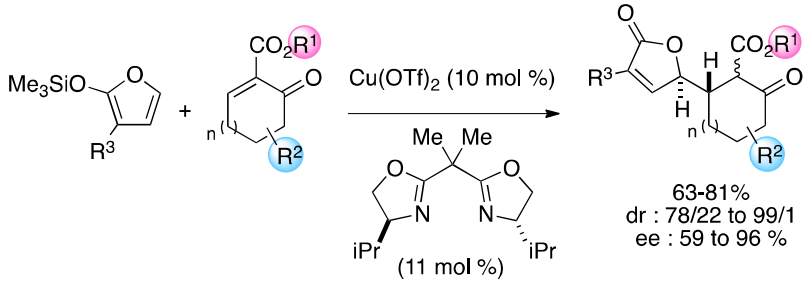
ABSTRACT.



The copper-catalyzed asymmetric addition of 2-silyloxyfurans to cyclic unsaturated oxo esters is reported. The reaction proceeds with excellent diastereocontrol (usually dr : 99/1) and modest to high

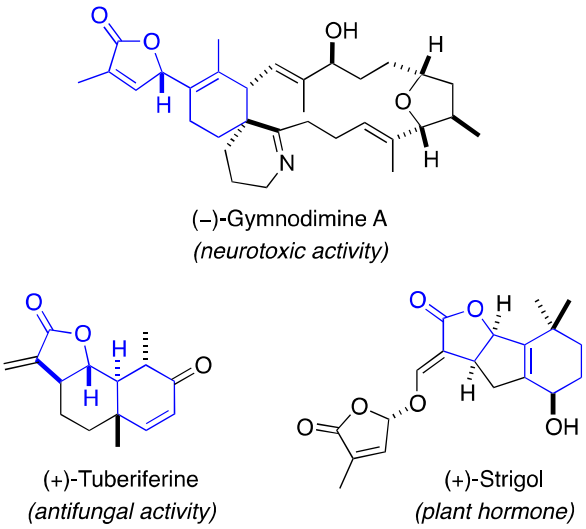
enantioselectivity, depending on the nature of the ester group and the subtitution of the cyclic oxo ester. We shown that these substrates can be transformed into a variety of building blocks bearing a γ-butenolide or γ-lactone connected to a cycloalkane or cycoalkene moiety.

KEYWORDS. asymmetric synthesis · butenolide · copper · homogeneous catalysis · Michael reaction.

INTRODUCTION

γ-Butenolides and γ-lactones represent a subunit of numerous natural products which display a wide range of biological activities including antitumor, antibiotic, antifungal, neurotoxic properties or are found in some plant hormones (Figure 1).[1] Thus, access to optically active γ-butenolides is of great interest.

Figure 1. Some examples of natural products containing γ-butenolide/γ-lactone connected to a cyclic framework



The catalytic asymmetric addition of 2-silyloxyfurans to carbonyl compounds[2] and acyclic Michael acceptors[3] is a powerful method to synthesize γ-butenolides in a diastereo- and enantioselective manner. Numerous efforts in the development of Lewis acid- and organo-catalyzed asymmetric reactions of 2-silyloxyfurans with α,β-unsaturated imides,[3a-3f] aldehydes,[3g-3i] and ketones,[3j-3n] have been reported. To the best of our knowledge only one study of asymmetric reaction of silyloxyfurans with cyclic Michael

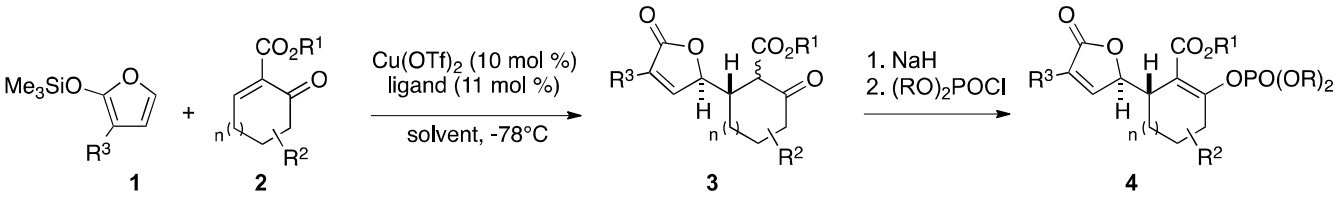
acceptor (benzoquinone) has been reported with low enantioselectivity (33% ee) and using a stoichiometric amount of copper-(II)-PyBox complex.[4]

We recently reported a copper-catalyzed diastereoselective addition of 2-silyloxyfurans to cyclic unsaturated oxo esters.[5] Herein, we describe a catalytic asymmetric conjugate addition of 2-silyloxyfurans to cyclic unsaturated oxo esters that proceeds with high diastereocontrol (usually dr : 99/1) and enantioselectivity up to 96% ee. This approach provides a straightforward access to chiral butenolides connected to a cycloalkane moiety.

RESULTS AND DISCUSSION

The copper-catalyzed addition of silyloxyfurans **1** to cyclic Michael acceptors **2** affords β-ketoesters **3** with three contiguous stereogenic centers (Scheme 1). We previously observed that the β-ketoesters products exist as a mixture of ketone and enol forms in solution, leading to complex ^{1}H NMR spectra. As expected, this equilibrium prevented the direct determination of the diastereo- and enantioselectivies of butenolides **3** by chiral HPLC. Thus, all β-ketoesters **3** were transformed into the corresponding phosphate **4** prior to HPLC analysis. It is worth mentioning that no epimerization of the allylic hydrogen atom of the butenolide was observed during the derivatization.

Scheme 1. Copper-catalyzed asymmetric addition of silyloxyfurans to cyclic unsaturated oxo esters

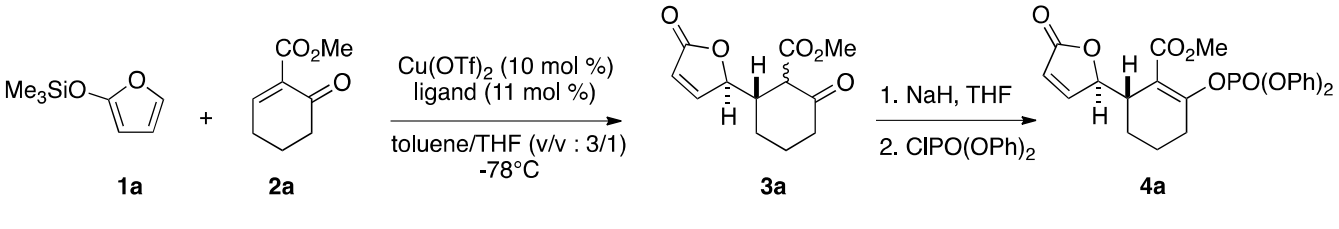


Reaction solvents and ligand survey.

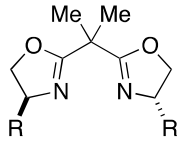
We began our study by using the conditions we previously reported for the diastereoselective addition of 2-silyloxyfuran **1a** to methyl oxo ester **2a**.[5] In the presence of $Cu(OTf)_2$ (10 mol %), *iso*-propyl-bis(oxazoline) ligand **L1** in CH_2Cl_2 at -78°C, we obtained butenolide **3a** in poor yield (38%) and enantiomeric excess (ee = 10%, dr : 95/5). We then undertook a screening of solvents which revealed that the best results were obtained in a mixture of toluene/THF (v/v = 3/1) at -78°C.[6] Under these

conditions, the Michael adduct **3a** was isolated in 73% yield as one diastereomer (dr >99/1) with 69 % enantiomeric excess (table 1, entry 1). A variety of commercially available bis(oxazoline) (**L1-L4**) and Py-box ligands (**L5-L6**) were screened to identify a more effective catalytic system (Table 1). We first observed that all chiral ligands produced butenolide **3a** with high diastereocontrol (dr >98/2). However, the enantiomeric excess was more dependent on the nature of the chiral ligand. When the reaction was carried out with bis(oxazoline) ligand **L2** (R = *i*Pr, entry 2) the ee was slightly improved to 71% though the isolated yield dropped to 33%. With ligand **L4** (R = Bn, entry 4) butenolide **3a** was obtained with 77% ee and good yield (68%). The chiral ligand **L3** bearing a bulkier R group (R = *t*Bu) dramatically diminished the enantioselectivity (entry 3, ee = -3%). The same trend was observed with tridentate Py-box ligands **L5-L6**, resulting in a complete loss of enantioselectivity (ee = 0%) (entries 5-6).

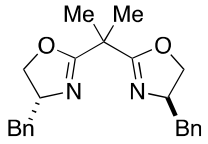
Table 1. Ligand screening for the enantioselective conjugate addition of 2-silyloxyfuran **1a** to methyl oxo ester **2a**



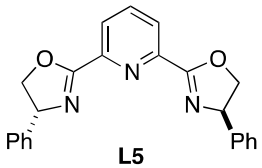
1a **2a** **3a** **4a**



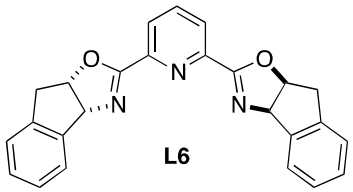
L1-L3



L4



L5



L6

Entry	ligand	R	Yield **3a** (%)[a]	dr (ee%)[b]
1	**L1**	Ph	73	>99/1 (69)
2	**L2**	*i*Pr	33	>99/1 (71)
3	**L3**	*t*Bu	52	>98/2 (-3)

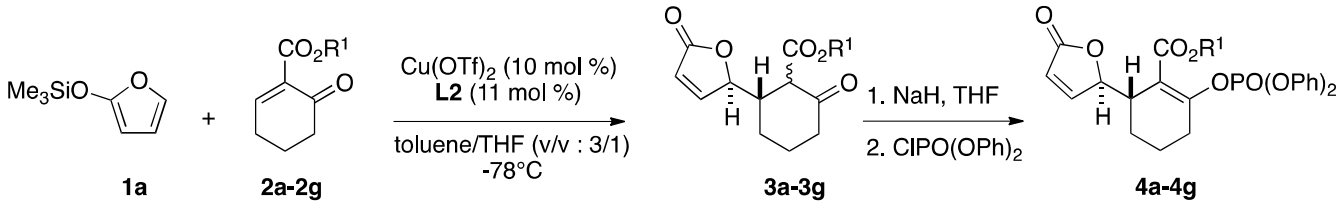
4	**L4**	-	68	98/2 (-77)
5	**L5**	-	52	99/1 (0)
6	**L6**	-	44	99/1 (0)

[a] Isolated yield. [b] Determined by chiral HPLC on the corresponding enol phosphate, see supporting information.

Effect of the ester group on the stereoselectivity

The effect of the ester group of the Michael acceptor on the enantioselection was then evaluated. Both ligands **L2** (R = *i*Pr, ee = 71%) and **L4** (R = Bn, ee = -77%) were tested on substrates **2b-g** having esters of varying steric hindrance. Although ligand **L4** (R = Bn, table 1, entry 4) proved to be more efficient with the methyl ester **2a**, we found that bis(oxazoline) **L2** (R = *i*Pr) generally gave better enantiomeric excess with the other oxo esters (see supporting information). A summary of the results with ligand **L2** is shown in table 2.

Table 2. Influence of the ester group size on the enantioselectivity with ligand **L2**



1a **2a-2g** **3a-3g** **4a-4g**

Entry	Oxo ester	R^1	Product Yield (%)[a]	dr (ee%)[b]
1	**2a**	Me	**3a** (33)	>99/1 (71)
2	**2b**	Et	**3b** (75)	99/1 (88)
3	**2c**	*i*Bu	**3c** (73)	>99/1 (74)
4	**2d**	*i*Pr	**3d** (74)	99/1 (85)
5	**2e**	*t*Bu	**3e** (36)	95/5 (26)
6	**2f**	Ph	**3f** (76)	96/4 (73)
7	**2g**	Bn	**3g** (57)	99/1 (95)
8	**2g**	Bn	**ent-3g** (57)	99/1 (-91)[c]

[a] Isolated yield. [b] Determined by chiral HPLC on the corresponding enol phosphate, see supporting information. [c] Ligand **L4** was used.

As shown in entry 2 of table 2, ethyl ester **2b** delivered butenolide **3b** with improved yield (75%) and enantioselectivity (ee = 88%) compared to the methyl ester **2a** (entry 1).[7] Increasing the steric hindrance using the *iso*-butyl ester (*ie* **2c**, entry 3) led to lower enantioselectivity, but the *iso*-propyl group (*ie* **2d**, entry 4) gave similar results to those obtained with the ethyl ester **2b** (entry 2). The more sterically demanding *tert*-butyl ester **2e** was less reactive and provided butenolide **3e** with low selectivity (entry 5). The use of phenyl ester **2f** did not improve the stereoselectivity (entry 6), however the benzyl ester **2g** furnished butenolide **3g** in good yield and with excellent enantioselectivity (95% ee) (entry 7).[8] Interestingly, the other enantiomer ent-**3g** could be obtained in good enantiomeric excess using the commercial ligand **L4** (R = Bn) (entry 8).

All these results showed the significant role of the ester moiety on the enantioselectivity, a point that has never been addressed in the copper-catalyzed asymmetric Michael addition on cyclic oxo esters.[9,10]

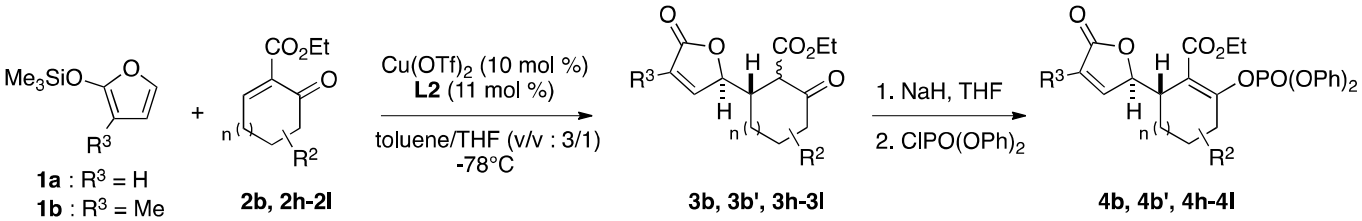
Scope of the reaction.

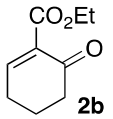
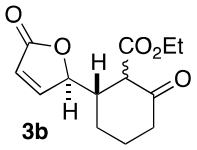
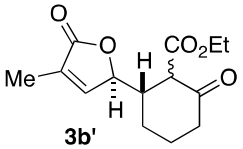
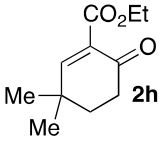
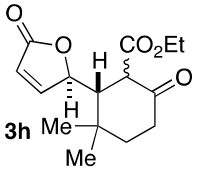
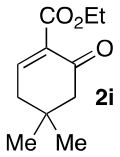
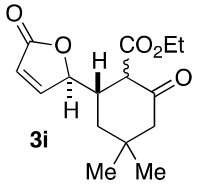
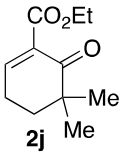
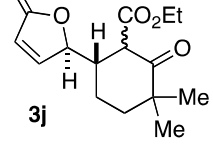
The scope of the reaction was explored with a variety of ethyl oxo esters **2b**, **2h**-**2l**, that proved to be more stable than the corresponding benzyl oxo esters (table 3). All substrates reacted effectively to give butenolides as one diastereomer, except for the five-membered ring (entry 6). We found that further improvement of the enantioselectivity could be achieved on substrate **2b** by carrying out the reaction at -95°C instead of -78°C, giving **3b** with 91% ee (table 3, entry 1). The high reactivity of ketoester **2b** even at low temperature allowed us to conduct the reaction with lower catalyst loading ($Cu(OTf)_2$, 5 mol %, **L2**, 6 mol %) to afford **3b** in 60% yield and 92% ee.

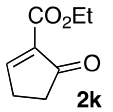
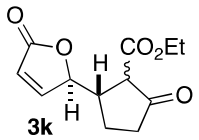
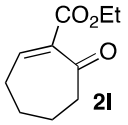
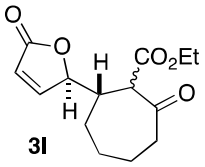
The 4-methylsilyloxyfuran **1b** could also be used but a significant decrease in enantioselectivity was observed (entry 2).[11] A *gem*-dimethyl substituent at the 4- or 5-position of the oxo ester ring was tolerated and provided an excellent 96% ee and 90% ee respectively (entries 3-4). For substrate **2j** having the sterically hindered *gem*-dimethyl group in α-position of the ketone function, the reaction still proceeded with high diastereoselectivity and low enantiocontrol was observed (entry 5). The five- and

seven-membered rings **2k** and **2l** also reacted in good yields with silyloxyfuran **1a** even at -95°C. As shown in entry 6, the five-membered ring **2k** led to a 78/22 ratio of diastereomers, formed with 84% ee and 88% ee respectively. The use of the seven-membered ring **2l** allowed the isolation of one diastereomer with moderate enantioselectivity (entry 7).[12]

Table 3. Copper-catalyzed enantioselective conjugate addition of 2-silyloxyfurans to oxo esters



Entry	R^3	Oxo ester	Product	Product Yield (%)[a]	dr (ee%)[b]
1	H	 **2b**	 **3b**	81	>99/1 (91)[c]
2	Me	**2b**	 **3b'**	69	99/1 (59)
3	H	 **2h**	 **3h**	74	>99/1 (96)
4	H	 **2i**	 **3i**	79	>99/1 (90)
5	H	 **2j**	 **3j**	82	99/1 (60)[d]

6	H	 **2k**	 **3k**	63	78/22 (84/88) [c,e]
7	H	 **2l**	 **3l**	72	>99/1[c] (79)

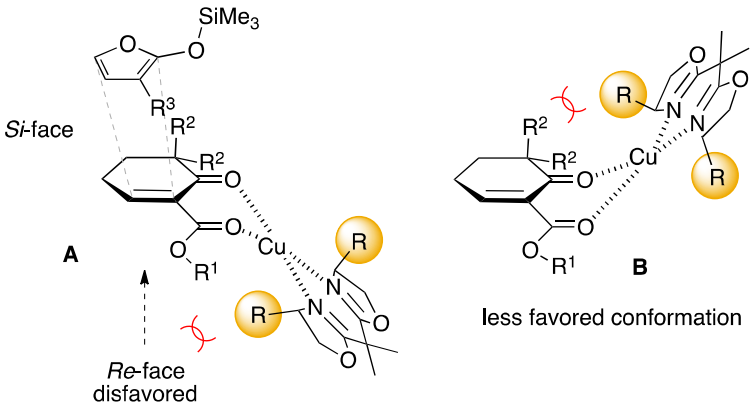
[a]Isolated yield. [b]Determined by chiral HPLC on the corresponding enol phosphate, see supporting information.[c]reaction carried out at -95°C. [d]Determined by chiral HPLC on the *p*-nitrobenzoyl derivative, see supporting information. [e]The ee of the major and minor diastereomers, respectively.

Stereochemical model.

The relative and absolute configuration was determined by single crystal X-ray analysis of the enol form of **3b** and **3h**.[13-14] The sense of asymmetric induction is consistent with an attack of the silyloxyfuran from the *Si*-face of the coordinated oxo ester.

Evans and coworkers have shown by X-ray cristallography that the metal atom in the alkylidene malonate/copper-(II) complex is in a distorted square-planar geometry, and the six-membered ring formed by the dicarbonyl, alkene carbon, and copper atom adopts a boat conformation.[10] On the basis of these observations, two complexes **A** and **B** can be depicted (Figure 2). Complex **B** might be higher in energy than complex **A** because of non-bonding interactions between the ligand and the R^2 substituents (R^2 = H or Me). In the complex **A**, the bottom *Re*-face is shielded by the box ligand, preventing the approach of the nucleophile. Thus, the attack of the silyloxyfuran occurs on the *Si*-face of complex **A** through an *exo* Diels-Alder type transition state (relative to the ketone) that may explain respectively, the sense of the enantioselectivity and the high level of diastereoselectivity observed in most cases.

Figure 2. Oxo ester/copper-(II) complex geometry and proposed stereochemical model



In this model, it is also expected that both faces will be hindered if R^2 is a methyl group, resulting in a poor enantiotopic face differentiation and low e.e. (table 3, entry 5).

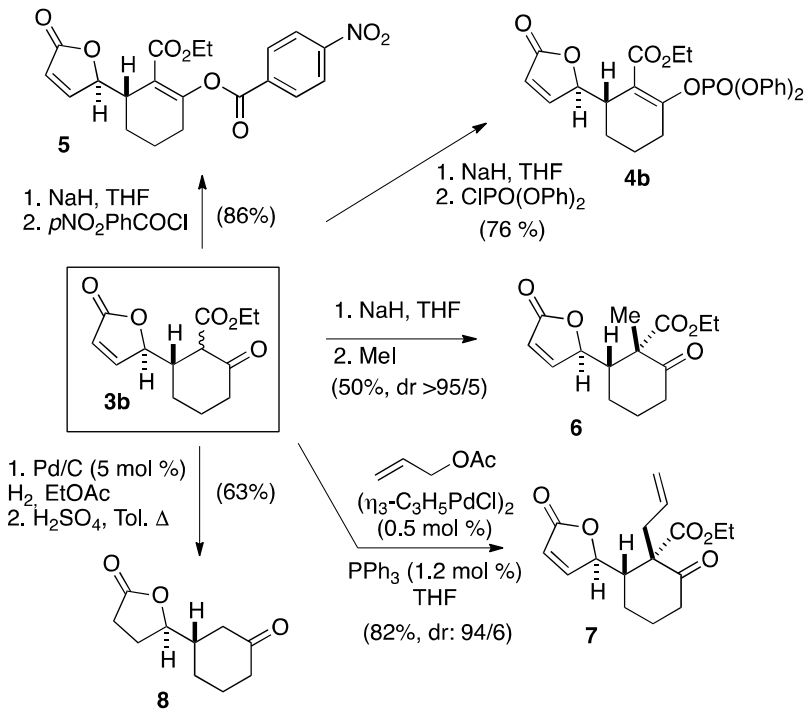
As shown in table 2 the ester substituent R^1 has an influence on the enantioselectivity. Although its exact role is not clear, it might be possible that the box ligand directs the R^1 group towards the opposite *Si*-face. Thus, for the bulky *tert*-butyl ester **2e**, both faces will be hindered, resulting in low ee (table 2, entry 5). Unfavorable interactions between the R^1 group (and/or the carbonyl of the ester) with the R^3 substituent (R^3 = Me) might also explain the breakdown in enantioselectivity observed with silyloxyfuran **1b**. However, for these last two examples, an antiperiplanar open-TS cannot be ruled out.[5a]

Substrate functionalization.

Scheme 2 illustrates some possible functionalizations of the optically active butenolide **3b**. For instance, butenolide **3b** was easily *O*-acylated by treatment with sodium hydride then *p*-nitrobenzoylchloride to give compound **5**. Alternatively, butenolide **3b** reacted with chlorophosphate to give enol phosphate **4b**.[15] Upon treatment with sodium hydride and methyl iodide, *C*-alkylation occurred diastereoselectively (dr > 95/5) to form **6** bearing a quaternary carbon atom. Interestingly, further functionnality could be introduced by mean of allylation reaction under Tsuji-Trost conditions to give product **7** in 82% (dr : 94/6).

Hydrogenation of butenolide **3b** afforded a γ-lactone which under acidic conditions gave the decarboxylated γ-lactone **8**. Interestingly, this decarboxylation product is equivalent to a vinylogous Mukaiyama-Michael addition of silyloxyfuran to cyclohex-2-en-1-one followed by hydrogenation.[5a]

Scheme 2. Functionalization of butenolide **3b**



CONCLUSION.

In conclusion, we have developed the first copper-catalyzed asymmetric addition of silyloxyfuran to cyclic oxo esters. The C_2-symmetric *iso*-propyl-box (**L2**) copper (II) complex has been found to be an excellent catalyst for this transformation, providing functionalized butenolide derivatives with high diastereo- and enantioselectivities. During the course of the optimisation, we examined the role of the ester group on the reactivity and the enantioselectivity. This point, unexplored in the copper-catalyzed Michael addition on cyclic oxo esters until now revealed a significant contribution of the ester group size on the enantioselectivity. Taking advantage of the different functionalities of the Michael adducts, we have shown that the enantioenriched butenolides can be transformed into a variety of building blocks

bearing a γ-butenolide or γ-lactone connected to a cycloalkane or cycoalkene moiety. Current efforts are now directed toward the extension of this reaction to different Michael acceptors and nucleophiles.

EXPERIMENTAL SECTION.

General method. All reactions were carried out under argon with dry solvents unless otherwise noted. Reactions were monitored by thin-layer chromatography on silica gel plates ($60F_{254}$) with a fluorescent indicator. Yields refer to chromatographically or crystalline pure compounds. All commercially available reagents were used without further purification. CH_2Cl_2 and THF were dried by activated alumina. Et_2O extra dry 99.5% was purchased. $CHCl_3$ and 1,2-dichloroethane were distilled over $CaCl_2$. Anhydrous toluene, 99.8%, Active dry, was purchased. All separations were carried out under flash chromatographic conditions on silica gel prepacked column (230-400 mesh) at medium pressure (20psi). All new compounds gave satisfactory spectroscopic analyses (IR, ^{1}H NMR, ^{13}C NMR, HRMS). NMR spectra were determined on 300 MHz or 500 MHz spectrometers. ^{1}H NMR spectra are reported in parts per million (δ) relative to residual solvent peak. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, sxt = sextet, sept = septuplet, dd = double-doublet, td = triple-doublet, dt = double-triplet, ddd = double double doublet, m = multiplet), coupling constant in Hz, and integration. ^{13}C NMR spectra were obtained on 75.5 MHz spectrometer and are reported in parts per million (δ) relative to the residual solvent peak. HRMS spectra were obtained on an E.S.I. TOF spectrometer. Infrared (IR) (υ, cm^{-1}) spectra were recorded on a Fourier Spectrum FT-IR. Melting points were measured in capillary tubes and are uncorrected.

Representative procedures.

General procedure A : Copper-catalyzed asymmetric conjugate addition of silyloxyfuran to cyclic oxo esters. To a cooled solution (-78°C) of copper-(II) triflate (0.1 eq) and ligand (0.11 eq) in the appropriate solvent (38 mL/mmol) under argon was added a solution of β-ketoester **2** in the appropriate

solvent (0.8 mL/mmol). The reaction mixture was stirred for 30 min, then the silyloxyfurane was added (1.2 eq). The reaction was monitored by TLC until completion. The reaction was quenched with aqueous saturated ammonium chloride, at -78°C, then allowed to warm up to 25°C and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting oil was treated with THF/aqueous hydrochloric acid 1N (v/v: 1/1, 10mL/mmol) at 25°C for 30 min. The reaction mixture was then diluted with water and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography (Heptane/EtOAc) to afford the title compound. Racemic mixtures were prepared by the same method, without the use of the chiral ligand.

General procedure B : Derivatization of substrates to enol phosphate for NMR and HPLC analysis. To a cooled suspension (0°C) of sodium hydride (1.2 eq) (Caution : hydrogen gas evolution) in THF (4.5 mL/mmol) under argon was added a solution of butenolide **3** (1.0 eq) in THF (4.5 mL/mmol). After stirring for 30 min, diphenyl phosphoryl chloride (0.95 eq) was added and the reaction mixture allowed to warm up slowly to 25°C. The reaction was monitored by TLC. The reaction was quenched with aqueous saturated ammonium chloride and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (heptane/EtOAc) to afford the phosphate **4**.

General Procedure C: Synthesis of β-ketoesters.

To a solution of *tert*-butyl 6-(1,3-dioxolan-2-yl)-3-oxohexanoate[16] (1.0 eq) in xylene/cyclohexane (v/v: 1/1; 1.0-3.0 mL/mmol) was added the corresponding alcohol (1.05 to 6.0 eq) and the mixture was heated at 135°C until completion was reached. All volatiles were removed by distillation (azeotrope *t*-BuOH/cyclohexane) then xylene in vacuo. The resulting oil was purified by flash chromatography (heptane/EtOAc) to afford the corresponding ester.

A solution of the ester in 50% aqueous acetic acid at 25°C was stirred until the completion was reached. The mixture was then diluted with water and saturated with NaCl, and extracted with ethyl

acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The traces of acetic acid were azeotroped with toluene. The resulting oil was purified by flash chromatography or distilled under reduce pressure to afford the title compound.

***Iso*-butyl 6-oxocyclohex-1-enecarboxylate (2c).**

Prepared according to general procedure C form *tert*-butyl 6-(1,3-dioxolan-2-yl)-3-oxohexanoate (1.43 g, 5.54 mmol, 1.0 eq), 2-methylpropan-1-ol (1.54 mL, 16.61 mmol, 3.0 eq), in xylene/cyclohexane (v/v: 1/1; 20.0 mL) and refluxed for 15 hrs. The crude mixture was purified by flash chromatography (heptane/EtOAc 80/20) to afford the *iso*-butyl ester **C1** as a colorless oil (1.13 g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) (keto/enol 90/10) δ (ppm): 4.81 (t, *J* = 4.3 Hz, 1H), 3.98-3.76 (m, 4H), 3.88 (d, *J* = 6.7 Hz, 2H), 3.40 (s, 2H), 2.58 (t, *J* =7.0 Hz, 2H), 1.98-1.83 (m, *J* = 6.7 Hz, 1H), 1.78-1.58 (m, 4H), 0.89 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 202.5 (Cq), 167.4 (Cq), 104.3 (CH), 71.6 (CH_2), 65.0 (2xCH_2), 49.4 (CH_2), 42.8 (CH_2), 33.1 (CH_2), 27.8 (CH), 19.2 (2xCH_3), 18.0 (CH_2). I.R υ (neat): 2961, 2878, 1739, 1714, 1233, 1137 cm^{-1}. M.S. (ESI, m/z) 257.1 $[M-H]^-$, 281.1 $[M+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{13}H_{22}O_5Na$: 281.1365, found: 281.1360.

Iso-butyl 6-(1,3-dioxolan-2-yl)-3-oxohexanoate **C1** (1.13 g, 4.375 mmol, 1.0 eq), in 50% aqueous acetic acid (57.0 mL) was stirred for 30 hrs. The crude mixture was purified by flash chromatography (heptane/AcOEt 80/20) to afford compound **2c** as a colorless oil (207 mg, 24%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/enol 82/18 δ (ppm): 7.64 (t, *J* = 4.3 Hz, 1H), 3.97 (d, *J* = 6.7 Hz, 2H), 2.55-2.46 (m, 4H), 2.10-1.91 (m, 3H), 0.95 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 194.5 (Cq), 164.8 (Cq), 155.7 (CH), 133.4 (Cq), 71.2 (CH_2), 38.7 (CH_2), 27.7 (CH), 26.1 (CH_2), 22.2 (CH_2), 19.1 (2xCH_3). I.R υ (neat): 2961, 1736, 1712, 1647, 1265, 1220 cm^{-1}. M.S. (ESI, m/z) 195.1 $[M-H]^-$, 197.1 $[M+H]^+$, 219.1 $[M+Na]^+$, 260.1 $[M+CH_3CN+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{11}H_{16}O_3Na$: 219.0997, found: 219.0998.

***Iso*-propyl 6-oxocyclohex-1-enecarboxylate (2d).**

Prepared according to general procedure C from *tert*-butyl 6-(1,3-dioxolan-2-yl)-3-oxohexanoate (100 mg, 0.387 mmol, 1.0 eq), propan-2-ol (70 mg, 1.161 mmol, 3.0 eq), in xylene/cyclohexane (v/v: 1/1; 2.0 mL) and refluxed for 3 days. The crude mixture was purified by flash chromatography (heptane/EtOAc 70/30) to afford the *iso*-propyl ester **C2** as a colorless oil (54 mg, 57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.03 (sept, J = 6.3 Hz, 1H), 4.82 (t, J = 4.3 Hz, 1H), 3.98-3.76 (m, 4H), 3.37 (s, 2H), 2.58 (t, J = 7.0 Hz, 2H), 1.78-1.60 (m, 4H), 1.23 (d, J = 6.3 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 202.5 (Cq), 166.8 (Cq), 104.2 (CH), 69.0 (CH), 64.9 (2xCH_2), 49.7 (CH_2), 42.5 (CH_2), 32.8 (CH_2), 21.7 (2xCH_3), 17.8 (CH_2). I.R υ (neat): 2989, 2882, 1736, 1713, 1141, 1103 cm^{-1}. M.S. (ESI, m/z) 245.1 $[M+H]^+$, 262.2 $[M+NH_4]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{12}H_{21}O_5$: 245.1389, found: 245.1393.

Iso-propyl 6-(1,3-dioxolan-2-yl)-3-oxohexanoate **C2** (1.3 g, 5.322 mmol, 1.0 eq), in 50% aqueous acetic acid (70.0 mL) was stirred for 24 hrs. The crude mixture was purified by flash chromatography (heptane/MTBE 50/50) to afford compound **2d** as a colorless oil (420 mg, 43%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/enol 82/18 δ (ppm): 7.57 (t, J = 4.2 Hz, 1H), 5.14 (sept, J = 6.3 Hz, 1H), 2.52-2.44 (m, 4H), 2.09-1.97 (m, 2H), 1.27 (d, J = 6.3 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 194.4 (Cq), 164.2 (Cq), 154.9 (CH), 133.7 (Cq), 68.6 (CH), 38.7 (CH_2), 26.1 (CH_2), 22.2 (CH_2), 21.7 (2xCH_3). I.R. υ (neat): 2981, 1732, 1709, 1710, 1682, 1373, 1268 cm^{-1}. M.S. (ESI, m/z) 183.1 $[M+H]^+$, 205.1 $[M+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{10}H_{15}O_3$: 183.1021, found: 183.1016.

Phenyl 6-oxocyclohex-1-enecarboxylate (2f).

Prepared according to general procedure C from *tert*-butyl 6-(1,3-dioxolan-2-yl)-3-oxohexanoate 2.0 g, 7.743 mmol, 1.0 eq), phenol (3.64 g, 38.72 mmol, 5.0 eq), in xylene/cyclohexane (v/v: 1/1; 40.0 mL) and refluxed for 3.5 days. The crude mixture was purified by flash chromatography (heptane/EtOAc 70/30) to afford the phenyl ester **C3** as a colorless oil (1.11 g, 52%). ^{1}H NMR ($CDCl_3$, 300 MHz) (keto/enol 90/10) δ (ppm): 7.41 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 2H), 4.88 (t, J = 4.6 Hz, 1H), 4.03-3.83 (m, 4H), 3.70 (s, 2H), 2.73 (t, J =7.1 Hz, 2H), 1.87-1.66 (m, 4H). ^{13}C

NMR ($CDCl_3$, 75 MHz) δ (ppm): 201.9 (Cq), 165.9 (Cq), 150.5 (Cq), 129.5 (2xCH), 126.2 (CH), 121.5 (2xCH), 104.2 (CH), 64.9 (2xCH_2), 49.2 (CH_2), 42.7 (CH_2), 32.7 (CH_2), 17.8 (CH_2). I.R υ (neat): 2953, 2885, 1741, 1714, 1139 cm^{-1}. M.S. (ESI, m/z) 279.1 $[M+H]^+$, 296.2 $[M+NH_4]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{15}H_{19}O_5$: 279.1232, found: 279.1241.

Phenyl 6-(1,3-dioxolan-2-yl)-3-oxohexanoate **C3** (1.11 g, 3.990 mmol, 1.0 eq), in 50% aqueous acetic acid (50.0 mL) was stirred for 24 hrs. The crude mixture was purified by recrystallization in MTBE to afford the title compound **2f** as white solid (725 mg, 84%). ^1H NMR ($CDCl_3$, 300 MHz) keto/enol 82/18 δ (ppm): 7.88 (t, *J* = 4.1 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 2.65-2.52 (m, 4H), 2.16-2.04 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 194.0 (Cq), 163.0 (Cq), 157.4 (CH), 150.6 (Cq), 132.7 (Cq), 129.4 (2xCH), 126.0 (CH), 121.6 (2xCH), 38.7 (CH_2), 26.4 (CH_2), 22.1 (CH_2). I.R υ (neat): 1737, 1677, 1262, 1181 cm^{-1}. M.S. (ESI, m/z) 217.1 $[M+H]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{13}H_{13}O_3$: 217.0865, found: 217.0870. mp : 70-72°C.

Benzyl 6-oxocyclohex-1-enecarboxylate (2g).

Prepared according to general procedure C from *tert*-butyl 6-(1,3-dioxolan-2-yl)-3-oxohexanoate (2.0 g, 7.743 mmol, 1.0 eq), benzyl alcohol (4.8 mL, 46.46 mmol, 6.0 eq), in xylene/cyclohexane (v/v: 1/1; 40.0 mL) and refluxed for 3.5 days. The crude mixture was purified by flash chromatography (heptane/EtOAc 70/30) to afford the benzyl ester **C4** as a colorless oil (2.07 g, 92%). ^1H NMR ($CDCl_3$, 300 MHz) (keto/enol 90/10) δ (ppm): 7.36-7.31 (m, 5H), 5.15 (s, 2H), 4.81 (t, *J* = 4.4 Hz, 1H), 3.98-3.75 (m, 4H), 3.46 (s, 2H), 2.57 (t, *J* =7.1 Hz, 2H), 1.77-1.58 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 202.1 (Cq), 167.1 (Cq), 135.3 (Cq), 128.6 (2xCH), 128.5 (CH), 128.4 (2xCH), 104.2 (CH), 67.1 (CH_2), 64.9 (2xCH_2), 49.3 (CH_2), 42.6 (CH_2), 32.7 (CH_2), 17.8 (CH_2). I.R υ (neat): 2953, 2885, 1741, 1714, 1139 cm^{-1}. M.S. (ESI, m/z) 293.1 $[M+H]^+$, 310.2 $[M+NH_4]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{16}H_{21}O_5$: 293.1389, found: 293.1381.

Benzyl 6-(1,3-dioxolan-2-yl)-3-oxohexanoate **C4** (1.57 g, 5.371 mmol, 1.0 eq), in 50% aqueous acetic acid (70.0 mL) was stirred for 24 hrs. The crude mixture was purified by distillation under reduce pressure (P = 0.54 mbar, bp = 150-165°C) to afford **2g** as a yellow oil (850 mg, 69%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/enol 88/12 δ (ppm): 7.74 (t, *J* = 4.2 Hz, 1H), 7.48-7.34 (m, 5H), 5.29 (s, 2H), 2.59-2.50 (m, 4H), 2.15-2.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 194.3 (Cq), 164.4 (Cq), 156.4 (CH), 135.7 (Cq), 133.0 (Cq), 128.6 (2xCH), 128.3 (CH), 128.2 (2xCH), 66.8 (CH_2), 38.8 (CH_2), 26.2 (CH_2), 22.1 (CH_2). I.R υ (neat): 2949, 1734, 1645, 1253, 1215 cm^{-1}. M.S. (ESI, m/z) 231.1 $[M+H]^+$, 253.1 $[M+Na]^+$, 294.1 $[M+CH_3CN+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{14}H_{14}O_3Na$: 253.0841, found: 253.0833.

(6*S*)-methyl 2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (3a). Prepared according to general procedure A from methyl 6-oxocyclohex-1-enecarboxylate **2a** (30.0 mg, 0.195 mmol, 1.0 eq), copper-(II) triflate (7.2 mg, 0.020 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (5.7 mg, 0.022 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (40 µL, 0.234 mmol, 1.2 eq), in toluene/THF (v/v: 3/1) and stirred for 3 days at -78°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3a** as a colorless oil (15.3 mg, 33%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/enol 44/56 δ (ppm): 12.66 (s, 1H, OH enol), 7.48 (dd, *J* = 5.7 1.6 Hz, 1H, enol), 7.40 (dd, *J* = 5.8, 1.7 Hz, 1H, keto), 6.11 (m, 2H, enol+keto), 5.37 (td, *J* = 4.7, 1.9 Hz, 1H, enol), 5.10 (td, *J* = 3.4, 1.7 Hz, 1H, keto), 3.83 (s, 3H, enol), 3.73 (s, 3H, keto), 3.33 (m, 1H, enol), 3.29 (d, *J* = 11.4 Hz, 1H, keto), 2.87 (m, 1H, keto), 2.55 (m, 1H, keto), 2.44-2.28 (m, 3H, keto+enol), 2.24-1.52 (m, 8H, keto+enol). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 204.3 (Cq), 178.7 (Cq), 176.3 (Cq), 173.1 (Cq), 170.1 (Cq), 155.4 (CH), 154.3 (CH), 121.6 (CH), 121.5 (CH), 95.6 (Cq), 85.2 (CH), 84.7 (CH), 56.7 (CH), 52.3 (CH_3), 51.7 (CH_3), 42.9 (CH), 40.8 (CH_2), 34.6 (CH), 28.7 (CH_2), 27.3 (CH_2), 24.1 (CH_2), 22.3 (CH_2), 18.9 (CH_2). IR υ (neat): 2950, 1743, 1711 cm^{-1}. M.S. (ESI, m/z) 261 $[M+Na]^+$. HRMS (ESI, m/z) calcd. for $C_{12}H_{14}NaO_5$: 261.0739 ; found: 261.0742.

(*S*)-methyl 2-((diphenoxyphosphoryl)oxy)-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-enecarboxylate (4a). Prepared according to general procedure B from methyl 2-oxo-6-(5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3a** (24 mg, 0.101 mmol, 1.0 eq), sodium hydride (60%, 4.9 mg, 0.121 mmol, 1.2 eq), diphenylphosphoryl chloride (20 μL, 0.096 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **4a** as a colorless oil (34.4 mg, 76%). (Rf = 0.2 heptane/EtOAc 50/50). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.36 (dd, *J* = 5.7, 1.2 Hz, 1H), 7.31-7.25 (m, 4H), 7.20-7.11 (m, 6H), 5.98 (dd, *J* = 5.7, 1.8 Hz, 1H), 5.09 (m, 1H), 3.47 (s, 3H), 3.30 (brs, 1H), 2.36 (m, 2H), 1.73-1.52 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.7 (Cq), 166.6 (Cq), 154.9 (CH), 154.8 (d, J_{P-C} = 8.2 Hz, Cq), 150.5 (d, J_{P-C} = 7.7 Hz, 2xCq), 130.1 (4xCH), 125.8 (2xCH), 122.1 (CH), 120.2 (d, J_{P-C} = 1.1 Hz, 2xCH), 120.0 (d, J_{P-C} = 1.1 Hz, 2xCH), 115.4 (d, J_{P-C} = 8.2 Hz, Cq), 84.9 (d, J_{P-C} = 2.2 Hz, CH), 52.1 (CH_3), 38.1 (CH), 28.7 (d, J_{P-C} = 1.1 Hz, CH_2), 23.0 (CH_2), 19.7 (CH_2). I.R υ (neat): 2944, 1754, 1717, 1589, 1487, 1434, 1364, 1295, 1184, 1159, 1129, 940. M.S. (ESI, m/z) 471.1 $[M+H]^+$. H.R.M.S. (ESI, m/z) Calculated for $C_{24}H_{23}O_8PNa$: 493.1028 ; found: 493.1035. $[\alpha]_D^{25}$ +32.6 (c = 0.973, $CHCl_3$, 71% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 80/20).

(6*S*)-ethyl 2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (3b). Prepared according to general procedure A from ethyl 6-oxocyclohex-1-enecarboxylate **2b** (35.0 mg, 0.208 mmol, 1.0 eq), copper-(II) triflate (7.6 mg, 0.021 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (6.2 mg, 0.023 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (42 μL, 0.250 mmol, 1.2 eq), in toluene/THF (v/v: 3/1) and stirred for 2.5 hrs at -78°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3b** as a colorless oil (39.4 mg, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz) keto/enol 56/44 δ (ppm): 12.70 (s, 1H, OH enol), 7.44 (dd, *J* = 5.7 1.5 Hz, 1H, enol), 7.36 (dd, *J* = 5.8, 1.6 Hz, 1H, keto), 6.07 (dd, *J* = 5.8, 2.2 Hz, 1H, enol), 6.03 (dd, *J* = 5.8, 2.2 Hz, 1H, keto), 5.33 (ddd, *J* = 4.8, 2.1, 1.6 Hz, 1H, enol), 5.05 (ddd, *J* = 3.2, 2.0, 1.6 Hz, 1H, keto), 4.35-4.03 (m, 4H, keto+enol), 3.28 (m, 1H, enol), 3.21 (d, *J* = 11.5 Hz, 1H, keto), 2.82 (m, 1H, keto), 2.48 (m, 1H,

keto), 2.39-2.22 (m, 3H, keto+enol), 2.18-1.47 (m, 8H, keto+enol), 1.30 (t, J = 7.1 Hz, 3H, enol), 1.24 (t, J = 7.1 Hz, 3H, keto). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 204.4 (Cq), 176.2 (Cq), 173.1 (Cq), 172.2 (Cq), 171.9 (Cq), 169.6 (Cq), 155.4 (CH), 154.4 (CH), 121.7 (CH), 121.5 (CH), 95.2 (Cq), 85.2 (CH), 84.8 (CH), 61.4 (CH_2), 60.8 (CH_2), 56.9 (CH), 42.8 (CH), 40.8 (CH_2), 34.5 (CH), 28.7 (CH_2), 27.2 (CH_2), 24.1 (CH_2), 22.4 (CH_2), 18.9 (CH_2), 14.2 (CH_3), 14.0 (CH_3). IR υ (neat): 2940, 1745, 1711, 1641, 1613, 1220, 818 cm^{-1}. M.S. (ESI, m/z) 275 $[M+Na]^+$. HRMS (ESI, m/z) calcd. for $C_{13}H_{16}NaO_5$ 275.0895; found 275.0899.

(*S*)-ethyl-2-((diphenoxyphosphoryl)oxy)-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-enecarboxylate (4b). Prepared according to general procedure B from ethyl 2-oxo-6-(5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3b** (39.4 mg, 0.156 mmol, 1.0 eq), sodium hydride (60%, 6.3 mg, 0.187 mmol, 1.2 eq), diphenylphosphoryl chloride (31 μL, 0.148 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **4b** as a colorless oil (57.4 mg, 76%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.45 (dd, J = 5.7, 1.6 Hz, 1H), 7.39-7.30 (m, 4H), 7.26-7.16 (m, 6H), 6.07 (dd, J = 5.7, 2.4 Hz, 1H), 5.17 (m, 1H), 4.19 (m, 2H), 3.39 (m, 1H), 2.46 (m, 2H), 1.87-1.53 (m, 4H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.5 (Cq), 165.9 (d, J_{P-C} = 1.7 Hz, Cq), 154.7 (CH), 154.0 (d, J_{P-C} = 8.0 Hz, Cq), 150.3 (d, J_{P-C} = 7.6 Hz, 2xCq), 129.8 (CH, 4xCH), 125.6 (CH, 2xCH), 122.0 (CH), 120.0 (d, J_{P-C} = 2.0 Hz, 2xCH), 119.9 (d, J_{P-C} = 2.0 Hz, 2xCH), 115.6 (d, J_{P-C} = 7.6 Hz, Cq), 84.7 (d, J_{P-C} = 1.7 Hz, CH), 61.2 (CH_2), 37.9 (CH), 28.4 (CH_2), 22.7 (CH_2), 19.5 (CH_2), 13.9 (CH_3). I.R υ (neat): 2942, 1753, 1713, 1487, 1434, 1296, 948. M.S. (ESI, m/z) 507.1 $[M+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{25}H_{25}O_8PNa$: 507.1185, found: 507.1200. $[\alpha]_D^{25}$ +47.2 (c = 0.992, $CHCl_3$, 88% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 80/20).

(6*S*)-*iso*-butyl 2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (3c). Prepared according to general procedure A from *iso*-butyl 6-oxocyclohex-1-enecarboxylate **2c** (35.0 mg, 0.178

mmol, 1.0 eq), copper-(II) triflate (6.5 mg, 0.018 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (5.3 mg, 0.020 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (36 µL, 0.214 mmol, 1.2 eq), in toluene/THF (v/v : 3/1) and stirred for 24 hrs at -78°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3c** as a colorless oil (36.3 mg, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/enol 40/60 δ (ppm): 12.65 (s, 1H, OH enol), 7.41 (dd, *J* = 5.7, 1.6 Hz, 1H, enol), 7.31 (dd, *J* = 5.8, 1.6 Hz, 1H, keto), 6.01 (dd, *J* = 5.7, 2.0 Hz, 1H, enol), 5.98 (dd, *J* = 5.7, 2.2 Hz, 1H, keto), 5.32 (td, *J* = 4.7, 1.6 Hz, 1H, enol), 5.01 (td, *J* = 3.3, 1.9 Hz, 1H, keto), 3.86 (m, 4H, keto+enol), 3.26 (m, 1H, enol), 3.19 (d, *J* = 11.5 Hz, 1H keto), 2.78 (m, 1H, keto), 2.50-1.40 (m, 14H, keto+enol), 0.90 (dd, *J* = 6.7, 0.6 Hz, 6H, enol), 0.85 (d, *J* = 6.7 Hz, 6H, keto). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 204.4 (Cq), 176.7 (Cq), 173.1 (Cq), 172.2 (Cq), 172.0 (Cq), 169.7 (Cq), 155.3 (CH), 154.4 (CH), 121.6 (CH), 95.3 (Cq), 85.1 (CH), 84.8 (CH), 71.6 (CH_2), 70.9 (CH_2), 56.8 (CH), 42.3 (CH), 40.8 (CH_2), 34.6 (CH), 28.7 (CH_2), 27.7 (CH), 27.5 (CH), 27.3 (CH_2), 24.1 (CH_2), 21.8 (CH_2), 19.23 (CH_3), 19.21 (CH_3), 19.1 (CH_3), 19.01 (CH_3), 18.99 (CH_2). IR υ (neat): 2960, 1750, 1713, 1644, 1610, 1222, 1157 cm^{-1}. M.S. (ESI, m/z) 344.1 $[M+NH_4]^+$. HRMS (ESI, m/z) calcd. for $C_{15}H_{24}NO_5$: 298.1654 ; found: 298.1662.

(6*S*)-*iso*-butyl-2-((diphenoxyphosphoryl)oxy)-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-enecarboxylate (4c). Prepared according to general procedure B from *iso*-butyl 2-oxo-6-(5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3c** (36.3 mg, 0.129 mmol, 1.0 eq), sodium hydride (60%, 6.2 mg, 0.155 mmol, 1.2 eq), diphenylphosphoryl chloride (25 µL, 0.123 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/AcOEt 40/60) to afford compound **4c** as a colorless oil (45.0 mg, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.49 (dd, *J* = 5.8, 1.6 Hz, 1H), 7.43-7.32 (m, 4H), 7.31-7.19 (m, 6H), 6.12 (dd, *J* = 5.7, 2.1 Hz, 1H), 5.20 (m, 1H), 3.85 (m, 2H), 3.44 (brs, 1H), 2.51 (m, 2H), 1,91 (m, 1H), 1.86-1.57 (m, 4H), 0.92 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.6 (Cq), 166.1 (Cq), 154.7 (CH), 154.0 (d, J_{P-C} = 7.7 Hz, Cq), 150.4 (d, J_{P-C} = 7.1 Hz, 2xCq), 129.9 (4xCH), 125.6 (2xCH), 122.1 (CH), 120.09 (d, J_{P-C} = 4.9 Hz, 2xCH), 120.04 (d, J_{P-C} =

4.9 Hz, 2xCH), 115.6 (d, J_{P-C} = 8.2 Hz, Cq), 84.8 (d, J_{P-C} = 2.0 Hz, CH), 71.5 (CH_2), 37.9 (CH), 28.5 (CH_2), 27.5 (CH), 22.7 (CH_2), 19.6 (CH_2), 19.20 (CH_3), 19.19 (CH_3). I.R υ (neat): 2964, 1778, 1757, 1714, 1487, 1304, 1140, 953 cm^{-1}. M.S. (ESI, m/z) 511.1 $[M-H]^-$, 547.1 $[M+Cl]^-$, 530.2 $[M+NH_4]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{27}H_{29}O_8PNa$: 535.1498, found: 535.1490. $[\alpha]_D^{25}$ +30.9 (c = 1.607, $CHCl_3$, 74% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 80/20).

(6*S*)-*iso*-propyl 2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (3d). Prepared according to general procedure A from *iso*-propyl 6-oxocyclohex-1-enecarboxylate **2d** (35.0 mg, 0.192 mmol, 1.0 eq), copper-(II) triflate (7.4 mg, 0.019 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (5.6 mg, 0.021 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (39 µL, 0.230 mmol, 1.2 eq), in toluene/THF (v/v: 3/1) and stirred for 3 hrs at -78°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3d** as a colorless oil (37.6 mg, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/enol 50/50 δ (ppm): 12.74 (s, 1H, OH enol), 7.40 (dd, *J* = 5.8 1.6 Hz, 1H, enol), 7.32 (dd, *J* = 5.8, 1.6 Hz, 1H, keto), 6.02 (dd, *J* = 5.7, 2.2 Hz, 1H, enol), 5.98 (dd, *J* = 5.8, 2.2 Hz, 1H, keto), 5.27 (ddd, *J* = 4.7, 2.2, 1.6 Hz, 1H, enol), 5.12-4.91 (m, 3H, keto+enol), 3.23 (m, 1H, enol), 3.12 (d, *J* = 11.5 Hz, 1H, keto), 2.78 (m, 1H, keto), 2.43 (m, 1H, keto), 2.30-2.19 (m, 2H, keto+enol), 2.07 (m, 1H, keto), 1.97 (m, 1H, keto), 1.80 (m, 1H, keto), 1.46-1.73 (m, 5H, keto+enol), 1.29-1.12 (m, 12H, keto). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 204.5 (Cq), 176.1 (Cq), 173.1 (Cq), 172.2 (Cq), 171.5 (Cq), 169.2 (Cq), 155.5 (CH), 154.5 (CH), 121.8 (CH), 121.5 (CH), 95.4 (Cq), 85.3 (CH), 84.8 (CH), 69.2 (CH), 68.6 (CH), 56.9 (CH), 42.7 (CH), 40.9 (CH_2), 34.5 (CH), 29.7 (CH), 28.7 (CH), 27.2 (CH), 24.1 (CH_2), 22.3 (CH_2), 22.0 (CH_3), 21.8 (CH_3), 21.7 (CH_3), 21.8 (CH_3), 18.9 (CH_2). IR υ (neat): 2938, 1754, 1713, 1638, 1226, 1106 cm^{-1}. M.S. (ESI, m/z) 284.1 $[M+NH_4]^+$. HRMS (ESI, m/z) calcd. for $C_{14}H_{22}NO_5$: 284.1498 ; found: 284.1491.

(*S*)-*iso*-propyl-2-((diphenoxyphosphoryl)oxy)-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-enecarboxylate (4d). Prepared according to general procedure B from *iso*-propyl 2-oxo-6-(5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3d** (37.6 mg, 0.141 mmol, 1.0 eq), sodium hydride (60%, 6.8

mg, 0.169 mmol, 1.2 eq), diphenylphosphoryl chloride (28 µL, 0.134 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **4d** as a white solid (49.7 mg, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.39 (dd, *J* = 5.7, 1.6 Hz, 1H), 7.32-7.22 (m, 4H), 7.19-7.09 (m, 6H), 6.02 (dd, *J* = 5.8, 2.2 Hz, 1H), 5.10 (m, 1H), 4.97 (sept, 1H), 3.33 (brs, 1H), 2.41 (m, 2H), 1.78-1.43 (m, 4H), 1.16 (d, *J* = 5.1 Hz, 3H), 1.14 (d, *J* = 5.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.6 (Cq), 165.6 (Cq), 154.7 (CH), 153.6 (d, J_{P-C} = 7.7 Hz, Cq), 150.3 (d, J_{P-C} = 7.1 Hz, 2xCq), 129.9 (d, J_{P-C} = 1.7 Hz, 4xCH), 125.6 (2xCH), 122.2 (CH), 120.1 (d, J_{P-C} = 5.1 Hz, 2xCH), 120.0 (d, J_{P-C} = 5.1 Hz, 2xCH), 116.1 (d, J_{P-C} = 8.7 Hz, Cq), 84.7 (d, J_{P-C} = 1.7 Hz, CH), 69.2 (CH), 38.0 (CH), 28.4 (CH_2), 22.7 (CH_2), 21.7 (CH_3), 21.6 (CH_3), 19.6 (CH_2). I.R υ (neat): 2980, 1757, 1708, 1486, 1301, 953 cm^{-1}. M.S. (ESI, m/z) 497.1 $[M-H]^-$, 533.1 $[M+Cl]^-$, 516.2 $[M+NH_4]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{26}H_{27}O_8PNa$: 521.1341, found: 521.1343. mp : 136-138°C. $[\alpha]_D^{25}$ +47.6 (c = 1.40, $CHCl_3$, 85% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 80/20).

(6*S*)-*tert*-butyl 2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (3e). Prepared according to general procedure A from *tert*-butyl 6-oxocyclohex-1-enecarboxylate **2e** (35.0 mg, 0.178 mmol, 1.0 eq), copper-(II) triflate (6.5 mg, 0.018 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (5.9 mg, 0.020 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (36 µL, 0.214 mmol, 1.2 eq), in toluene/THF (v/v: 3/1) and stirred for 2 days at -78°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3e** as a colorless oil (18.2 mg, 36%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/enol 50/50 δ (ppm): 12.80 (s, 1H, OH enol), 7.42 (dd, *J* = 5.7, 1.6 Hz, 1H, enol), 7.35 (dd, *J* = 5.7, 1.6 Hz, 1H, keto), 6.03 (dd, *J* = 5.6, 2.1 Hz, 1H, enol), 6.00 (dd, *J* = 5.6, 2.1 Hz, 1H, keto), 5.25 (m, 1H, enol), 5.01 (m, 3H, keto), 3.15 (m, 1H, enol), 3.01 (d, *J* = 11.4 Hz, 1H, keto), 2.74 (m, 1H, keto), 2.40 (m, 1H, keto), 2.29-2.18 (m, 2H, keto+enol), 2.05 (m, 1H, keto), 1.96 (m, 1H, keto), 1.79 (m, 1H, keto), 1.72-1.42 (m, 5H, keto+enol), 1.46 (s, 9H, keto), 1.39 (s, 9H, keto). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 205.0 (Cq), 175.4 (Cq), 173.2 (Cq), 172.3 (Cq), 171.7 (Cq), 168.8 (Cq), 155.5 (CH), 154.7 (CH), 121.7 (CH), 121.5 (CH), 96.4 (Cq), 85.4 (CH), 84.9 (CH), 57.4 (CH),

42.7 (CH), 41.0 (CH_2), 34.9 (CH), 28.7 (CH_2), 28.3 (CH_3), 28.0 (CH_3), 27.1 (CH_2), 24.1 (CH_2), 22.4 (CH_2), 18.9 (CH_2). IR υ (neat): 2938, 1753, 1711, 1638, 1228, 1143 cm^{-1}. M.S. (ESI, m/z) 298.2 $[M+NH_4]^+$. HRMS (ESI, m/z) calcd. for $C_{15}H_{24}NO_5$: 298.1654 ; found: 298.1663.

(6*S*)-*tert*-butyl-2-((diphenoxyphosphoryl)oxy)-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-enecarboxylate (4e). Prepared according to general procedure B from *tert*-butyl 2-oxo-6-(5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3e** (33.2 mg, 0.118 mmol, 1.0 eq), sodium hydride (60%, 5.7 mg, 0.142 mmol, 1.2 eq), diphenylphosphoryl chloride (23.0 µL, 0.112 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **4e** as a colorless oil (42.4 mg, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.52 (dd, J = 5.7, 1.6 Hz, 1H), 7.32-7.22 (m, 4H), 7.19-7.09 (m, 6H), 6.14 (dd, J = 5.7, 2.1 Hz, 1H), 5.21 (m, 1H), 3.40 (brs, 1H), 2.51-2.46 (m, 2H), 1.88-1.52 (m, 4H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.6 (Cq), 165.2 (d, J_{P-C} = 1.7 Hz, Cq), 154.8 (CH), 152.6 (d, J_{P-C} = 7.7 Hz, Cq), 150.8 (d, J_{P-C} = 7.1 Hz, 2xCq), 129.7 (4xCH), 125.6 (2xCH), 122.2 (CH), 120.1 (2xCH), 120.0 (2xCH), 117.1 (d, J_{P-C} = 9.1 Hz, Cq), 84.7 (d, J_{P-C} = 2.0 Hz, CH), 82.4 (Cq), 38.0 (CH), 28.2 (CH_2), 28.0 ($3xCH_3$), 22.5 (CH_2), 19.7 (CH_2). I.R υ (neat): 2978, 1755, 1703, 1488, 1298, 1184, 1154, 1129, 950 cm^{-1}. M.S. (ESI, m/z) 530.2 $[M+NH_4]^+$, 547.1 $[M+Cl]^-$. H.R.M.S. (ESI, m/z) Calcd for $C_{27}H_{29}O_8PNa$: 535.1498, found: 535.1494. $[\alpha]_D^{25}$ +14.4 (c = 0.927, $CHCl_3$, 26% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 80/20).

(6*S*)-phenyl 2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (3f). Prepared according to general procedure A from phenyl 6-oxocyclohex-1-enecarboxylate **2f** (40.0 mg, 0.185 mmol, 1.0 eq), copper-(II) triflate (7.0 mg, 0.019 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (5.4 mg, 0.020 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (37 µL, 0.232 mmol, 1.2 eq), in toluene/THF (v/v : 3/1) and stirred for 2 hrs at -78°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3f** as a colorless oil (42.3 mg, 76%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/enol 63/37 δ (ppm): 12.35 (s, 1H, OH enol), 7.49 (dd, J = 5.7, 1.7 Hz,

1H, enol), 7.38-7.28 (m, 5H, keto+enol), 7.23-7.11 (m, 2H, keto+enol), 7.09-7.00 (m, 4H, keto+enol), 6.09-6.05 (m, 2H, keto+enol), 5.32 (m, 1H, enol), 5.06 (m, 1H, keto), 3.43 (d, J = 11.7 Hz, 1H, keto), 3.39 (m, 1H, enol), 2.83 (m, 1H, keto), 2.51 (m, 1H, keto), 2.40-2.29 (m, 3H, keto+enol), 2.12 (m, 1H, keto), 2.03 (m, 1H, keto), 1.90 (m, 1H, keto), 1.78-1.56 (m, 5H, keto+enol). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 204.1 (Cq), 178.3 (Cq), 173.0 (Cq), 172.1 (Cq), 170.7 (Cq), 168.6 (Cq), 155.5 (CH), 154.8 (CH), 150.4 (Cq), 149.9 (Cq), 129.6 (CH), 129.5 (CH), 126.3 (CH), 126.2 (CH), 121.8 (CH), 121.6 (CH), 121.4 (CH), 94.8 (Cq), 85.7 (CH), 84.9 (CH), 56.9 (CH), 43.0 (CH), 41.0 (CH_2), 34.8 (CH), 28.8 (CH_2), 27.5 (CH_2), 24.2 (CH_2), 23.6 (CH_2), 18.5 (CH_2). IR υ (neat): 2949, 1751, 1713, 1593, 1185, 1160, 733 cm^{-1}. M.S. (ESI, m/z) 318.1 $[M+NH_4]^+$. HRMS (ESI, m/z) calcd. for $C_{17}H_{20}NO_5$: 318.1341 ; found: 318.1326.

(6*S*)-phenyl 2-((diphenoxyphosphoryl)oxy)-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-enecarboxylate (4f). Prepared according to general procedure B from phenyl 2-oxo-6-(5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3f** (44.5 mg, 0.148 mmol, 1.0 eq), sodium hydride (60%, 7.1 mg, 0.178 mmol, 1.2 eq), diphenylphosphoryl chloride (29 μL, 0.141 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **4f** as a white solid (60.0 mg, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.54 (dd, J = 5.7, 1.6 Hz, 1H), 7.39-7.05 (m, 15H), 6.17 (dd, J = 5.8, 2.2 Hz, 1H), 5.26 (m, 1H), 3.49 (brs, 1H), 2.62 (m, 2H), 2.04-1.75 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.4 (Cq), 164.7 (d, J_{P-C} = 1.9 Hz, Cq), 155.7 (d, J_{P-C} = 7.7 Hz, Cq), 154.8 (CH), 150.4 (Cq), 150.2 (d, J_{P-C} = 7.2 Hz, 2xCq), 129.89 (2xCH), 129.85 (2xCH), 129.4 (2xCH), 125.9 (CH), 125.7 (2xCH), 122.1 (CH), 121.6 (2xCH), 120.1 (d, J_{P-C} = 5.0 Hz, 4xCH), 115.0 (d, J_{P-C} = 8.5 Hz, Cq), 85.2 (d, J_{P-C} = 2.0 Hz, CH), 38.3 (CH), 28.7 (CH_2), 23.6 (CH_2), 19.6 (CH_2). I.R υ (neat): 2949, 1752, 1487, 1297, 1184, 1159, 948.cm^{-1}. M.S. (ESI, m/z) 531.1 $[M-H]^-$, 567.1 $[M+Cl]^-$, 550.2 $[M+NH_4]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{29}H_{25}O_8PNa$: 555.1185, found: 555.1176. mp : 145-147 °C. $[\alpha]_D^{25}$ +3.2 (c = 0.700, $CHCl_3$, 95% *ee*). HPLC analysis: chiralcel IC, hexane/EtOH (v/v: 85/15).

(6*S*)-benzyl 2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (3g). Prepared according to general procedure A from benzyl 6-oxocyclohex-1-enecarboxylate **2g** (40.0 mg, 0.174 mmol, 1.0 eq), copper-(II) triflate (6.2 mg, 0.017 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (5.1 mg, 0.019 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (35 µL, 0.209 mmol, 1.2 eq), in toluene/THF (v/v: 3/1) and stirred for 2.5 hrs at -78°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3g** as a colorless oil (31.2 mg, 57%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/eno 37/63 δ (ppm): 12.57 (s, 1H, OH enol), 7.36-7.23 (m, 11H, keto+enol), 7.13 (dd, *J* = 5.6, 1.7 Hz, 1H, keto), 5.90 (dd, *J* = 5.7, 2.1 Hz, 1H, enol), 5.57 (dd, *J* = 5.7, 2.1 Hz, 1H, keto), 5.22 (m, 1H, enol), 5.16 (s, 2H, enol), 5.12 (d, *J* = 12.2 Hz, 1H, keto), 5.03 (d, *J* = 12.2 Hz, 1H, keto), 4.94 (m, 1H, keto), 3.25 (m, 1H, enol), 3.19 (d, *J* = 11.4 Hz, 1H, keto), 2.77 (m, 1H, keto), 2.44 (m, 1H, keto), 2.32-2.32 (m, 3H, keto+enol), 2.06 (m, 1H, keto), 1.95 (m, 1H, keto), 1.90-1.43 (m, 6H, keto+enol). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 204.3 (Cq), 176.8 (Cq), 173.1 (Cq), 172.1 (Cq), 171.6 (Cq), 169.5 (Cq), 155.5 (CH), 154.3 (CH), 135.2 (Cq), 135.1 (Cq), 128.9 (CH), 128.8 (CH), 128.61 (CH), 128.59 (CH), 128.5 (CH), 128.4 (CH), 121.6 (CH), 121.3 (CH), 121.4 (CH), 94.89 (Cq), 85.3 (CH), 84.7 (CH), 67.2 (CH_2), 66.5 (CH_2), 56.8 (CH), 43.0 (CH), 40.9 (CH_2), 34.5 (CH), 28.7 (CH_2), 27.4 (CH_2), 24.1 (CH_2), 22.8 (CH_2), 18.8 (CH_2). IR υ (neat): 2948, 1748, 1713, 1643, 1602, 1267, 1219, 1158, 818 cm^{-1}. M.S. (ESI, m/z) 332.1 $[M+NH_4]^+$. HRMS (ESI, m/z) calcd. for $C_{18}H_{22}NO_5$: 332.1498 ; found: 332.1497.

(*S*)-benzyl 2-((diphenoxyphosphoryl)oxy)-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-enecarboxylate (4g). Prepared according to general procedure B from benzyl 2-oxo-6-(5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3g** (27.4 mg, 0.087 mmol, 1.0 eq), sodium hydride (60%, 4.2 mg, 0.104 mmol, 1.2 eq), diphenylphosphoryl chloride (18 µL, 0.083 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **4g** as a colorless oil (23.0 mg, 51%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.36-7.11 (m, 16H), 5.80 (dd, *J* = 5.7, 2.1 Hz, 1H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.06 (dt, *J* = 4.6, 1.8 Hz, 1H), 4.88 (d, *J* = 12.0 Hz, 1H),

3.33 (brs, 1H), 2.49-2.40 (m, 2H), 1.89-1.53 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.6 (Cq), 165.8 (Cq), 154.7 (d, J_{P-C} = 5.0 Hz, Cq), 154.6 (CH), 150.3 (d, J_{P-C} = 4.4 Hz, 2xCq), 135.3 (Cq), 129.9 (2xCH), 129.8 (2xCH), 128.8 (2xCH), 128.5 (2xCH), 128.4 (CH), 125.7 (2xCH), 121.9 (CH), 120.1 (d, J_{P-C} = 2.0 Hz, 2xCH), 120.0 (d, J_{P-C} = 2.0 Hz, 2xCH), 115.1 (d, J_{P-C} = 5.0 Hz, Cq), 84.8 (d, J_{P-C} = 2.0 Hz, CH), 67.0 (CH_2), 38.0 (CH), 28.5 (CH_2), 23.1 (CH_2), 19.5 (CH_2). I.R υ (neat): 2953, 1755, 1720, 1488, 1297, 1185, 1160, 1131, 952 cm^{-1}. M.S. (ESI, m/z) 545.1 $[M-H]^-$, 581.1 $[M+Cl]^-$, 564.2 $[M+NH_4]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{30}H_{27}O_8PNa$: 569.1341, found: 569.1334. $[\alpha]_D^{25}$ +36.9 (c = 1.540, $CHCl_3$, 95% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 60/40).

(2*S*)-ethyl 2-((*S*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)-6-oxocyclohexanecarboxylate (3b'). Prepared according to general procedure A from ethyl 6-oxocyclohex-1-enecarboxylate **2b** (35.0 mg, 0.208 mmol, 1.0 eq), copper-(II) triflate (7.6 mg, 0.021 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (6.2 mg, 0.023 mmol, 0.11 eq), 2 trimethyl((3-methylfuran-2-yl)oxy)silane (43 mg, 0.250 mmol, 1.2 eq), in toluene/THF (v/v: 3/1) and stirred for 2 hrs at -78°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3b'** as a colorless oil (38.2 mg, 69%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto (d.r. 60/40)/enol 65/35 δ (ppm): 12.72 (s, 1H, OH enol), 7.04 (t, J = 1.0 Hz, 1H, enol), 6.97 (t, J = 0.9 Hz, 1H, keto dia.1), 6.95 (t, J = 1.2 Hz, 1H, keto dia.2), 5.44 (m, 1H, keto dia.1), 5.22 (m, 1H, enol), 4.95 (m, 1H, keto dia.2), 4.37-4.04 (m, 6H, keto dia.1+ keto dia.2+enol), 3.66 (d, J = 2.7 Hz, 1H, keto dia.1), 3.26 (m, 1H, enol), 3.19 (d, J = 11.4 Hz, 1H, keto dia.2), 3.08 (m, 1H, enol), 2.86-2.46 (m, 5H, keto dia.1+ keto dia.2+enol), 2.38-2.27 (m, 3H, keto dia.1+keto dia.2), 2.23-1.52 (m, 20H, keto dia.1+ keto dia.2+enol), 1.40-1.22 (m, 9H, keto dia.1+ keto dia.2+enol). ^{13}C NMR ($CDCl_3$, 75 MHz) keto A/keto B/enol δ (ppm): 208.1 (Cq), 204.7 (Cq), 175.9 (Cq), 175.0 (Cq), 172.0 (Cq), 169.8 (Cq), 147.8 (CH), 146.7 (CH), 146.6 (CH), 130.5 (Cq), 129.8 (Cq), 95.5 (Cq), 83.0 (CH), 82.8 (CH), 82.5 (CH), 61.4 (CH_2), 60.8 (CH_2), 60.7 (CH_2), 56.7 (CH) 48.9 (CH), 42.9 (CH), 40.9 (CH_2), 36.7 (CH_2), 34.5 (CH), 28.7 (CH_2), 27.2 (CH_2), 26.8 (CH_2), 24.1 (CH_2), 22.8 (CH_2), 22.3 (CH_2), 18.9 (CH_2), 14.4 (CH_3), 14.3 (CH_3), 14.1 (CH_3), 10.7 (CH_3), 10.6 (CH_3), 10.5 (CH_3).

IR υ (neat): 2930, 1755, 1715, 1646, 1616, 1248, 1225, 1060, 734 cm^{-1}. M.S. (ESI, m/z) 284.1 $[M+NH_4]^+$. HRMS (ESI, m/z) calcd. for $C_{14}H_{22}NO_5$: 284.1498 ; found: 284.1487.

(*S*)-ethyl 2-((diphenoxyphosphoryl)oxy)-6-((*R*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-enecarboxylate (4b'). Prepared according to general procedure B from ethyl 2-oxo-6-(4-methyl-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3b'** (35.0 mg, 0.131 mmol, 1.0 eq), sodium hydride (60%, 6.3 mg, 0.157 mmol, 1.2 eq), diphenylphosphoryl chloride (26 µL, 0.124 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **4b'** as a colorless oil (15.0 mg, 24%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.43-7.34 (m, 4H), 7.31-7.19 (m, 6H), 7.04 (m, 1H), 5.07-5.01 (m, 1H), 4.22-4.01 (m, 2H), 3.33 (brs, 1H), 2.54-2.45 (m, 2H), 1,92 (t, *J = 1.9 Hz*, 3H), 1.90-1.68 (m, 4H), 1.23 (t, *J = 7.1 Hz*, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 173.7 (Cq), 166.2 (Cq), 153.7 (d, J_{P-C} = 7.9 Hz, Cq), 150.4 (d, J_{P-C} = 7.3 Hz, 2xCq), 147.0 (CH), 130.6 (Cq), 129.9 (2xCH), 129.8 (2xCH), 125.6 (d, J_{P-C} = 2.8 Hz, 2xCH), 120.1 (d, J_{P-C} *= 2.7 Hz*, 2xCH), 120.0 (d, J_{P-C} = 2.7 Hz, 2xCH), 115.9 (d, J_{P-C} = 8.2 Hz, Cq), 82.6 (d, J_{P-C} = 2.0 Hz, CH), 61.3 (CH_2), 38.1 (CH), 28.4 (CH_2), 23.0 (CH_2), 19.6 (CH_2), 14.0 (CH_3), 10.7 (CH_3). I.R υ (neat): 2928, 1756, 1714, 1488, 1297, 1185, 952 cm^{-1}. M.S. (ESI, m/z) 499.2 $[M+H]^+$, 516.2 $[M+NH_4]^+$, 521.1 $[M+Na]^+$, 497.1 $[M-H]^-$, 533.1 $[M+Cl]^-$. H.R.M.S. (ESI, m/z) Calcd for $C_{26}H_{28}O_8P$: 499.1522, found: 499.1507. $[\alpha]_D^{25}$ +15.5 (c = 0.917, $CHCl_3$, 59% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 80/20).

(2*R*)-ethyl 3,3-dimethyl-6-oxo-2-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (3h). Prepared according to general procedure A from ethyl 3,3-dimethyl-6-oxocyclohex-1-enecarboxylate **2h** (40.0 mg, 0.204 mmol, 1.0 eq), copper-(II) triflate (7.2 mg, 0.020 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (5.9 mg, 0.022 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (42 µL, 0.245 mmol, 1.2 eq), in toluene/THF (v/v: 3/1) and stirred for 2 hrs at -78°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3h** as a solid (42.0 mg, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/enol 10/90 δ (ppm): 12.46 (s, 1H, OH enol), 7.37 (dd, *J* = 5.7, 1.7 Hz, 1H,

enol), 7.25 (dd, *J* = 5.7, 1.7 Hz, 1H, keto), 5.90-5.85 (m, 2H, keto+enol), 5.28-5.24 (m, 2H, keto+enol), 4.22-4.00 (m, 4H, keto+enol), 3.33 (d, *J* = 11.5 Hz, 1H, keto), 2.66 (t, *J* = 2.1 Hz, 1H enol), 2.55-2.00 (m, 6H, keto+enol), 1.33-1.15 (m, 8H, keto+enol), 1.13 (s, 6H, keto+enol), 0.93 (s, 6H, keto+enol).^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 205.1 (Cq), 176.3 (Cq), 173.2 (Cq), 171.8 (Cq), 157.1 (CH), 157.0 (CH), 120.3 (CH), 120.1 (CH), 92.7 (Cq), 82.8 (CH), 81.2 (CH), 61.3 (CH_2), 60.4 (CH_2), 53.2 (CH), 50.1 (CH), 45.4 (CH), 39.2 (CH), 37.2 (CH), 32.6 (Cq), 30.7 (CH_2), 29.6 (CH_3), 28.4 (CH_3), 27.7 (CH_3), 26.2 (CH_2), 22.1 (CH_3), 14.2 (CH_3), 13.9 (CH_3). IR υ (neat): 2965, 1752, 1714, 1636, 1604, 1284, 1218, 812 cm^{-1}. M.S. (ESI, m/z) 298.2 $[M+NH_4]^+$. HRMS (ESI, m/z) calcd. for $C_{15}H_{24}NO_5$: 298.1654 ; found: 298.1645. mp = 109-112 °C.

(*S*)-ethyl 2-((diphenoxyphosphoryl)oxy)-5,5-dimethyl-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-enecarboxylate (4h). Prepared according to general procedure B from ethyl 3,3-dimethyl-6-oxo-2-(5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3h** (20.0 mg, 0.071 mmol, 1.0 eq), sodium hydride (60%, 3.4 mg, 0.086 mmol, 1.2 eq), diphenylphosphoryl chloride (14 μL, 0.068 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **4h** as a colorless oil (15.0 mg, 44%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.38-7.26 (m, 5H), 7.22-7.12 (m, 6H), 5.92 (dd, *J* = 5.7, 2.2 Hz, 1H), 5.31 (m, 1H), 4.12-3.83 (m, 2H), 3.00 (brs, 1H), 2.54-2.43 (m, 2H), 2.16 (m, 1H), 1.34 (m, 1H), 1.19 (s, 3H), 1.12 (t, *J* = 7.2, Hz, 3H), 1.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.6 (Cq), 166.1 (d, J_{P-C} = 1.7 Hz, Cq), 156.3 (CH), 155.6 (d, J_{P-C} = 8.8 Hz, Cq), 150.4 (d, J_{P-C} = 7.1 Hz, Cq), 150.3 (*d*, J_{P-C} = 7.1 Hz, Cq), 129.9 (2xCH), 129.8 (2xCH), 125.6 (d, J_{P-C} = 1.1 Hz, CH), 125.5 (d, J_{P-C} = 1.1 Hz, CH), 121.0 (CH), 120.1 (d, J_{P-C} = 5.2 Hz, 2xCH), 120.0 (d, J_{P-C} = 5.2 Hz, 2xCH), 112.6 (d, J_{P-C} = 8.2 Hz, Cq), 82.2 (d, J_{P-C} = 2.2 Hz, CH), 61.2 (CH_2), 48.3 (CH), 32.0 (Cq), 31.4 (CH_2), 27.8 (CH_3), 27.2 (CH_3), 26.7 (CH_2), 14.0 (CH_3). I.R υ (neat): 2962, 1756, 1703, 1488, 1296, 1186, 946 cm^{-1}. M.S. (ESI, m/z) 511.1 $[M-H]^-$, 513.2 $[M+H]^+$, 530.2 $[M+NH_4]^+$, 535.1 $[M+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{27}H_{29}O_8PNa$: 535.1498, found:

535.1475. $[\alpha]_D^{25}$ +42.0 (c = 0.808, $CHCl_3$, 96% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 90/10).

(6S)-ethyl 4,4-dimethyl-2-oxo-6-((R)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (3i). Prepared according to general procedure A from ethyl 4,4-dimethyl-6-oxocyclohex-1-enecarboxylate **2i** (40.0 mg, 0.204 mmol, 1.0 eq), copper-(II) triflate (7.2 mg, 0.020 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (5.9 mg, 0.022 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (42 µL, 0.245 mmol, 1.2 eq), in toluene/THF (v/v: 3/1) and stirred for 2 hrs at -78°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3i** as a colorless oil (45.0 mg, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/enol 90/10 δ (ppm): 12.57 (s, 1H, OH enol), 7.34 (m, 1H, enol), 7.31 (dd, *J* = 5.8, 1.7 Hz, 1H, enol), 6.11 (m, 1H, enol), 5.98 (dd, *J* = 5.8, 2.1 Hz, 1H, keto), 5.02 (m, 1H, enol), 4.98 (m, 1H, keto), 4.30-3.98 (m, 4H, keto+enol), 3.30 (m, 1H, enol), 3.05 (d, *J* = 11.8 Hz, 1H, keto), 2.91 (m, 1H, keto), 2.24-2.08 (m, 2H, keto+enol), 1.85 (t, *J* = 13.2 Hz, 1H, keto), 1.66 (s, 1H, keto), 1.55-1.14 (m, 7H, enol), 1.19 (t, *J* = 7.2 Hz, 3H, keto), 1.05 (s, 3H, keto), 0.99 (s, 3H, enol), 0.91 (s, 3H, enol), 0.88 (s, 3H, keto). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 204.6 (Cq), 172.2 (Cq), 169.9 (Cq), 154.6 (CH), 121.6 (CH), 84.8 (CH), 61.4 (CH_2), 55.6 (CH), 53.7 (CH_2), 40.6 (CH_2), 39.3 (CH), 34.4 (Cq), 31.6 (CH_3), 25.0 (CH_3), 14.0 (CH_3). IR υ (neat): 2964, 1752, 1713, 1636, 1604, 1284, 1218, 812 cm^{-1}. M.S. (ESI, m/z) 298.2 $[M+NH_4]^+$. HRMS (ESI, m/z) calcd. for $C_{15}H_{24}NO_5$: 298.1654 ; found: 298.1653.

(*S*)-ethyl 2-((diphenoxyphosphoryl)oxy)-4,4-dimethyl-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-enecarboxylate (4i). Prepared according to general procedure B from ethyl 4,4-dimethyl-2-oxo-6-(5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3i** (45.0 mg, 0.161 mmol, 1.0 eq), sodium hydride (60%, 7.7 mg, 0.193 mmol, 1.2 eq), diphenylphosphoryl chloride (32 µL, 0.153 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **4i** as a colorless oil (62.5 mg, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.35-7.25 (m, 5H), 7.20-7.09 (m, 6H), 6.05 (dd, *J* = 5.8, 2.2 Hz, 1H), 5.20 (dt, *J* = 5.2, 1.9 Hz, 1H), 4.14-3.94 (m, 2H),

3.28 (m, 1H), 2.26-2.02 (m, 2H), 1.43 (ddd, J = 13.5, 5.8, 2.3 Hz, 1H), 1.13 (t, J = 7.1 Hz, 3H), 0.98-0.89 (m, 1H), 0.91 (s, 3H), 0.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.5 (Cq), 166.0 (d, J_{P-C} = 1.6 Hz, Cq), 154.3 (CH), 151.1 (d, J_{P-C} = 7.7 Hz, Cq), 150.4 (d, J_{P-C} = 5.2 Hz, Cq), 150.3 (d, J_{P-C} = 5.2 Hz, Cq), 129.9 (4xCH), 125.7 (2xCH), 122.8 (CH), 120.1 (2xCH), 120.0 (2xCH), 115.8 (d, J_{P-C} = 8.9 Hz, Cq), 83.8 (d, J_{P-C} = 1.7 Hz, CH), 61.4 (CH_2), 41.8 (CH_2), 37.0 (CH), 34.6 (CH_2), 30.8 (CH_3), 30.4 (Cq), 24.6 (CH_3), 14.0 (CH_3). I.R υ (neat): 2960, 1756, 1722, 1590, 1488, 1297, 1186, 950 cm^{-1}. M.S. (ESI, m/z) 511.1 $[M-H]^-$, 547.1 $[M+Cl]^-$, 530.2 $[M+NH_4]^+$, 535.1 $[M+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{27}H_{30}O_8P$: 513.1678, found: 513.1665. $[\alpha]_D^{25}$ +80.7 (c = 1.225, $CHCl_3$, 90% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 90/10).

(6*S*)-ethyl 3,3-dimethyl-2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (3j). Prepared according to general procedure A from ethyl 3,3-dimethyl-6-oxocyclohex-1-enecarboxylate **2j** (30.0 mg, 0.153 mmol, 1.0 eq), copper-(II) triflate (5.5 mg, 0.015 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (4.5 mg, 0.017 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (31 µL, 0.183 mmol, 1.2 eq), in toluene/THF (v/v: 3/1) and stirred for 2 hrs at -78°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3j** as a colorless oil (35.0 mg, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz) keto/enol 50/50 δ (ppm): 12.95 (s, 1H, OH enol), 7.38 (dd, J = 5.7, 1.5 Hz, 1H, enol), 7.30 (dd, J = 5.8, 1.8 Hz, 1H, keto), 6.03 (dd, J = 5.7, 2.1 Hz, 1H, enol), 5.97 (dd, J = 5.8, 2.1 Hz, 1H, keto), 5.27 (ddd, J = 1.8, 2.1, 4.8 Hz, 1H, enol), 5.00 (m, 1H, keto), 4.24-3.98 (m, 4H, keto+enol), 3.38 (d, J = 12.2 Hz, 1H, keto), 3.23 (m, 1H, enol), 2.76 (m, 1H, enol), 2.00 (m, 1H, keto), 1.84-1.30 (m, 7H, keto+enol), 1.26 (t, J = 7.1, 3H, enol), 1.20 (t, J = 7.1, 3H, keto), 1.14 (s, 3H, keto), 1.12 (s, 3H, enol), 1.11 (s, 3H, enol), 1.01 (s, 3H, keto). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 209.1 (Cq), 182.2 (Cq), 173.1 (Cq), 172.5 (Cq), 172.3 (Cq), 170.3 (Cq), 155.4 (CH), 154.5 (CH), 121.5 (CH), 121.4 (CH), 93.6 (Cq), 85.0 (CH), 84.9 (CH), 61.4 (CH_2), 60.9 (CH_2), 53.0 (CH), 44.7 (Cq), 43.1 (CH_2), 38.0 (CH), 35.8 (Cq), 35.3 (CH_2), 35.0 (Cq), 27.1 (CH_2), 26.9 (CH_3), 24.9 (CH_2), 24.4 (CH_3), 23.5 (CH_3), 18.9 (CH_3), 14.2 (CH_3), 14.1 (CH_3). IR υ (neat): 2977, 1751, 1707, 1642, 1601, 1259, 1080,

1032, 734 cm^{-1}. M.S. (ESI, m/z) 298.2 $[M+NH_4]^+$. HRMS (ESI, m/z) calcd. for $C_{15}H_{24}NO_5$: 298.1654 ; found: 298.1659.

(*S*)-2-(ethoxycarbonyl)-6,6-dimethyl-3-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-en-1-yl 4-nitrobenzoate (4j). Prepared according to general procedure B (replacing diphenylphosphoryl chloride by 4-nitrobenzoyl chloride) from ethyl 3,3-dimethyl-2-oxo-6-(5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3j** (33.0 mg, 0.118 mmol, 1.0 eq), sodium hydride (60%, 5.6 mg, 0.193 mmol, 1.2 eq), 4-nitrobenzoyl chloride (26 mg, 0.141 mmol, 2.0 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford compound **4j** yellow oil (45.0 mg, 89%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.36. (d, *J* = 8.7 Hz, 2H), 8.29. (d, *J* = 8.7 Hz, 2H), 7.60. (dd, *J* = 5.7, 1.5 Hz, 1H), 6.15. (dd, *J* = 5.7, 2.0 Hz, 1H), 5.33 (ddd, *J* = 1.6, 2.0, 4.9 Hz, 1H), 4.06-3.94 (m, 2H), 3.54 (m, 1H), 1.92-1.46 (m, 4H), 1.15 (s, 6H), 1.01 (t, *J* = 7.2 Hz, 3H).^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.8 (Cq), 165.0 (Cq), 162.6 (Cq), 162.5 (Cq), 155.1 (CH), 150.9 (Cq), 134.8 (Cq), 131.2 (2xCH), 123.8 (2xCH), 122.0 (CH), 115.9 (Cq), 84.6 (CH), 61.2 (CH_2), 38.1 (CH_2), 36.7 (Cq), 35.2 (CH_2), 26.7 (CH_3), 26.3 (CH_3), 19.5 (CH_2), 13.9 (CH_3). I.R υ (neat): 2933, 1754, 1737, 1714, 1528, 1347, 1263, 1100 cm^{-1}. M.S. (ESI, m/z) 279.1 $[M+Cl]^-$, 447.2 $[M+NH_4]^-$, 452.1 $[M+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{22}H_{23}NO_8Na$: 452.1321, found: 452.1331. $[\alpha]_D^{25}$ +59.9 (c = 1.067, $CHCl_3$, 60% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 80/20).

(5*S*)-ethyl 2-oxo-5-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclopentanecarboxylate (3k). Prepared according to general procedure A from ethyl 3 ethyl 5-oxocyclopent-1-enecarboxylate **2k** (40.0 mg, 0.259 mmol, 1.0 eq), copper-(II) triflate (9.4 mg, 0.026 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (7.6 mg, 0.029 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (53 µL, 0.311 mmol, 1.2 eq), in toluene/THF (v/v: 3/1) and stirred for 2 hrs at -95°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford **3k** as a colorless oil (39.0 mg, 63%). ^{1}H NMR (CDCl3, 300 MHz) keto/enol 75/25 (d.r. 75/25) δ (ppm): 7.37 (dd, *J* = 5.7, 1.7 Hz, 1H), 6.05 (dd, *J* = 5.8, 2.1 Hz, 1H), 5.13 (td, *J* = 3.8, 1.8 Hz, 1H), 4.26-4.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ

(ppm): 208.5 (Cq), 172.1 (Cq), 168.4 (Cq), 154.6 (CH), 122.1 (CH), 83.0 (CH), 61.9 (CH_2), 54.8 (CH), 42.9 (CH), 37.8 (CH_2), 23.5 (CH_2), 14.1 (CH_3). IR υ (neat): 2983, 1751, 1721, 1658, 1268, 1160, 1101, 1025, 733 cm^{-1}. M.S. (ESI, m/z) 256.1 $[M+NH_4]^+$. HRMS (ESI, m/z) calcd. for $C_{12}H_{18}NO_5$: 256.1185 ; found: 256.1190.

(*S*)-ethyl2-((diphenoxyphosphoryl)oxy)-5-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclopent-1-enecarboxylate (4k). Prepared according to general procedure B from ethyl 2-oxo-5-(5-oxo-2,5-dihydrofuran-2-yl)cyclopentanecarboxylate **3k** (39.0 mg, 0.164 mmol, 1.0 eq), sodium hydride (60%, 7.8 mg, 0.196 mmol, 1.2 eq), diphenylphosphoryl chloride (32 µL, 0.155 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **4k** as a colorless oil (major diastereomer, 33.0 mg, 45%) and **4k'** as a colorless oil (minor diastereomer, 10.0 mg, 14%). Major diastereomer **4k:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.45-7.35 (m, 5H), 7.34-7.22 (m, 6H), 6.16 (dd, *J* = 5.9, 1.9 Hz, 1H), 5.53 (dt, *J* = 4.4, 1.9, 1.9 Hz, 1H), 4.25-4.12 (m, 2H), 3.65 (m, 1H), 2.75-2.64 (m, 2H), 2.10 (m, 1H), 1.64 (m, 1H), 1.24 (t, *J* = 7.1, Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.8 (Cq), 162.9 (d, J_{P-C} = 1.6 Hz, Cq), 159.9 (d, J_{P-C} = 6.5 Hz, Cq), 154.0 (CH), 150.2 (d, J_{P-C} = 3.8 Hz, Cq), 150.1 (d, J_{P-C} = 3.8 Hz, Cq), 130.0 (2xCH), 129.9 (2xCH), 125.9 (2xCH), 122.9 (CH), 120.1 (d, J_{P-C} = 3.3 Hz, 2xCH), 120.0 (d, J_{P-C} = 3.3 Hz, 2xCH), 113.7 (d, J_{P-C} = 8.3 Hz, Cq), 84.2 (d, J_{P-C} = 1.7 Hz, CH), 60.7 (CH_2), 43.9 (CH), 32.6 (d, J_{P-C} = 1.1 Hz, CH_2), 20.5 (CH_2), 14.2 (CH_3). I.R υ (neat): 2979, 1754, 1698, 1652, 1589, 1487, 1301, 1182, 1159, 944 cm^{-1}. M.S. (ESI, m/z) 469.1 $[M-H]^-$, 505.1 $[M+Cl]^-$, 488.1 $[M+NH_4]^+$, 493.1 $[M+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{24}H_{24}O_8P$: 471.1209, found: 471.1205. $[\alpha]_D^{25}$ +52.7 (c = 1.50, $CHCl_3$, 84% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 80/20).

(7*S*)-ethyl 2-oxo-7-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cycloheptanecarboxylate (3l). Prepared according to general procedure A from ethyl 3 ethyl 5-oxocyclopent-1-enecarboxylate **2l** (40.0 mg, 0.220 mmol, 1.0 eq), copper-(II) triflate (8.0 mg, 0.022 mmol, 0.1 eq), 2,2-Bis((4*S*)-(–)-4-isopropyloxazoline)propane (6.5 mg, 0.024 mmol, 0.11 eq), 2-(trimethylsiloxy)furan (44 µL, 0.263

mmol, 1.2 eq), in toluene/THF (v/v: 3/1) and stirred for 2 hrs at -95°C. The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford **3l** as a colorless oil (42.2 mg, 72%).^{1}H NMR ($CDCl_3$, 300 MHz) keto (d.r. 50/50)/enol 80 /20 δ (ppm): 13.34 (s, 1H, OH enol), 7.58 (dd, *J* = 5.8, 1.6 Hz, 1H, keto dia. 1), 7.36 (dd, *J* = 5.8, 1.6 Hz, 2H, keto dia. 2+enol), 6.12-6.06 (m, 2H, keto dia. 1+ keto dia. 2), 6.00 (m, *J* = 5.7, 1.9 Hz, 1H, enol), 5.20 (td, *J* = 1.8, 8.4 Hz, 1H, keto dia. 1), 5.15 (td, *J* = 1.8, 5.1 Hz, 1H, enol), 5.02 (td, J = 1.8, 4.6 Hz, 1H, keto dia . 2), 4.29-4.00 (m, 6H, keto dia. 1+keto dia.2+enol), 3.86 (dd, J = 1.2, 3.6 Hz, 1H, keto dia.1), 3.37 (m, 1H, enol), 3.27 (d, J = 9.8 Hz, 1H, keto dia.2), 2.92-1.10 (m, 35H, ketodia.1+keto dia. 2+enol). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 206.6 (Cq), 205.6 (Cq), 181.0 (Cq), 172.2 (Cq), 172.0 (Cq), 169.1 (Cq), 168.9 (Cq), 155.2 (CH), 154.8 (CH), 153.7 (CH), 123.0 (CH), 122.4 (CH), 121.5 (CH), 86.3 (CH), 85.1 (CH), 84.4 (CH), 62.0 (CH_2), 61.4 (CH_2), 60.8 (CH_2), 60.4 (CH) 59.5 (CH), 42.7 (CH_2), 42.6 (CH), 41.4 (CH_2), 40.0 (CH), 38.0 (CH), 34.3 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 28.1 (CH_2), 28.0 (CH_2), 27.4 (CH_2), 25.9 (CH_2), 24.3 (CH_2), 24.0 (CH_2), 23.6 (CH_2), 14.3 (CH_3), 14.1 (CH_3), 14.0 (CH_3). IR υ (neat): 2936, 1753, 1703, 1629, 1601, 1159, 1025, 817, 734 cm^{-1}. M.S. (ESI, m/z) 284.1 $[M+NH_4]^+$. HRMS (ESI, m/z) calcd. for $C_{14}H_{22}NO_5$: 284.1498 ; found: 284.1484.

(*S*)-ethyl-2-((diphenoxyphosphoryl)oxy)-7-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohept-1-enecarboxylate (4l). Prepared according to general procedure B from ethyl 2-oxo-7-(5-oxo-2,5-dihydrofuran-2-yl)cycloheptanecarboxylate **3l** (38.0 mg, 0.142 mmol, 1.0 eq), sodium hydride (60%, 6.8 mg, 0.171 mmol, 1.2 eq), diphenylphosphoryl chloride (28 μL, 0.135 mmol, 0.95 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **4l** as a colorless oil (35.0 mg, 52%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.51 (dd, *J* = 5.7, 1.9 Hz, 1H), 7.43-7.32 (m, 4H), 7.29-7.18 (m, 6H), 6.13 (dd, *J* = 5.7, 1.9 Hz, 1H), 5.27 (td, *J* = 5.7, 1.9, 1.9 Hz, 1H), 4.20-4.01 (m, 2H), 3.30 (m, 1H), 2.99 (m, 1H), 2.58 (m, 1H), 2.00-1.68 (m, 6H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.4 (Cq), 167.4 (d, J_{P-C} = 2.2 Hz, Cq), 155.9 (CH), 155.8 (Cq), 154.7 (2xCq), 150.4 (d, J_{P-C} = 8.7 Hz, Cq), 129.9 (4xCH), 125.6 (2xCH), 122.2 (CH), 120.1 (d, J_{P-C} =

2.2 Hz, 2xCH), 120.0 (d, J_{P-C} = 2.2 Hz, 2xCH), 85.0 (d, J_{P-C} = 2.2 Hz, CH), 61.4 (CH_2), 41.6 (CH), 32.3 (CH_2), 27.9 (CH_2), 24.8 (CH_2), 23.6 (CH_2), 14.0 (CH_3). I.R υ (neat): 2933, 1754, 1706, 1589, 1488, 1294, 1185, 1024, 944 cm^{-1}. M.S. (ESI, m/z) 497.1 $[M-H]^-$, 533.1 $[M+Cl]^-$, 516.2 $[M+NH_4]^+$, 521.1 $[M+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{26}H_{28}O_8P$: 499.1522, found: 499.1529. $[\alpha]_D^{25}$ +23.0 (c = 1.42, $CHCl_3$, 79% *ee*). HPLC analysis: chiralcel OJ-H, hexane/EtOH (v/v: 80/20)

(*S*)-2-(ethoxycarbonyl)-3-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohex-1-en-1-yl 4-nitrobenzoate (5). Prepared according to general procedure B (replacing diphenylphosphoryl chloride by 4-nitrobenzoyl chloride) from ethyl 2-oxo-6-(5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3b** (30.0 mg, 0.119 mmol, 1.0 eq), sodium hydride (60%, 5.7 mg, 0.143 mmol, 1.2 eq), 4-nitrobenzoyl chloride (27 mg, 0.143 mmol, 1.2 eq). The crude mixture was purified by flash chromatography (heptane/EtOAc 50/50) to afford compound **5** as a colorless oil (41.0 mg, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.36. (d, *J* = 8.9 Hz, 2H), 8.29. (d, *J* = 8.9 Hz, 2H), 7.59. (dd, *J* = 5.8, 1.6 Hz, 1H), 6.16. (dd, *J* = 5.8, 2.1 Hz, 1H), 5.32 (ddd, *J* = 4.8, 2.1, 1.6 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.58 (brs, 1H), 2.54-2.31 (m, 2H), 2.01-1.72 (m, 4H), 1.05 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.7 (Cq), 164.9 (Cq), 162.3 (Cq), 158.1 (Cq), 155.0 (CH), 150.9 (Cq), 134.6 (Cq,), 131.2 (2xCH), 123.7 (2xCH), 122.0 (CH), 117.0 (Cq), 84.78 (CH), 61.2 (CH_2), 37.3 (CH), 28.7 (CH_2), 22.6 (CH_2), 19.3 (CH_2), 14.0 (CH_3). I.R υ (neat): 2933, 1754, 1706, 1589, 1488, 1294, 1185, 1024, 944 cm^{-1}. M.S. (ESI, m/z) 400.1 $[M-H]^-$, 436.1 $[M+Cl]^-$, 419.1 $[M+NH_4]^+$, 424.1 $[M+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{20}H_{19}NO_8Na$: 424.1008, found: 424.0998. $[\alpha]_D^{25}$ +68.6 (c = 1.48, $CHCl_3$, 88% *ee*).

(1*S*,6*S*)-ethyl 1-methyl-2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (6). To a cooled (0°C) solution of sodium hydride (60%, 5.8 mg, 0.143 mmol, 1.2 eq) in THF (1.0 mL) was added a solution of (6*S*)-ethyl 2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3b** (30 mg, 0.119 mmol, 1.0 eq) in THF (1.0 mL). The mixture was stirred at 0°C for 15 minutes then iodomethane (150 µL, 2.38 mmol, 20.0 eq) was added and the misture was allowed to slowly warm up

to 25°C and stirred for 15h. The reaction was quenched with aqueous saturated ammonium chloride then extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **6** as a colorless oil (16 mg, 50 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.83 (dd, *J* = 5.8, 1.6 Hz, 1H), 6.13. (dd, *J* = 5.8, 2.2 Hz, 1H), 5.47. (ddd, *J* = 3.4, 2.2, 1.6 Hz, 1H), 4.24-4.12. (m, 2H), 2.54-2.44 (m, 2H), 2.08-1.95 (m, 2H), 1.79-1.47 (m, 3H), 1.52 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 204.8 (Cq), 172.6 (Cq), 171.8 (Cq), 156.2 (CH), 122.2 (CH), 83.6 (CH), 61.8 (CH_2), 59.7 (Cq), 51.0 (CH_2), 39.9 (CH), 25.0 (CH_2), 24.2 (CH_2), 19.3 (CH_3), 14.0 (CH_3). I.R υ (neat): 2943, 1756, 1712, 1449, 1089 cm^{-1}. M.S. (ESI, m/z) 265.1 $[M-H]^-$, 267.1 $[M+H]^+$, 284.1 $[M+NH_4]^+$, 289.1 $[M+Na]^+$, 330.1 $[M+Na+CH_3CN]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{14}H_{18}O_5Na$: 289.1052, found: 289.1038. $[\alpha]_D^{25}$ +80.8 (c = 1.00, $CHCl_3$).

(1*S*,6*S*)-ethyl 1-allyl-2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate (7). To a solution of allylpalladium(II) chloride dimer (1 mg, $1.98x10^{-3}$ mmol, 0.5%) and triphenylphosphine (1.3 mg, $4.75x10^{-3}$ mmol, 1.2%) in THF (1.5 mL) was added allylacetate (64 μL, 0.594 mmol, 1.5 eq), and the mixture was cooled to 0°C. A cooled solution (0°C) of sodium (6*S*)-ethyl 2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate in THF (3 mL) (made from (6*S*)-ethyl 2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3b** (100 mg, 0.396 mmol, 1.0 eq), and sodium hydride (17 mg, 0.436 mmol, 1.1 eq) at 0°C), was added dropwise. The solution was slowly warmed up to 25°C over a period of 15h. The mixture was then quenched with 1M HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed under vacuo. The crude mixture was purified by flash chromatography (heptane/EtOAc 65/35) to afford **7** as a colourless oil (95 mg, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.71 (dd, *J* = 5.8, 1.6 Hz, 1H), 6.09 (dd, *J* = 5.8, 2.1 Hz, 1H), 5.65 (m, *J* = 5.7, 2.1 Hz, 1H), 5.42 (m, 1H), 5.18-5.05 (m, 2H), 4.22-4.07 (m, 2H), 3.00 (dd, *J* = 14.1, 5.9 Hz, 1H), 2.59 (dd, *J* = 14.1, 5.8 Hz, 1H), 2.52-2.39 (m, 2H), 2.30 (m, 1H), 1.96 (m, 1H), 1.60-1.39 (m, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm):

204.3 (Cq), 172.5 (Cq), 170.9 (Cq), 132.7 (CH), 122.2 (CH), 120.0 (CH_2), 121.3 (CH), 83.1 (CH), 62.9 (Cq), 61.9 (CH_2), 46.0 (CH), 40.3 (CH_2), 36.3 (CH_2), 24.1 (CH_2), 23.6 (CH_2), 14.0 (CH_3). I.R. υ (neat): 2939 1757, 1712, 1448, 1233, 1206, 1088, 820 cm^{-1}. M.S. (ESI, m/z) 293.1 (100) $[M+H]^+$, 315.1 $[M+Na]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{16}H_{21}O_5$: 293.1389, found: 293.1385. $[\alpha]_D^{25}$ -138.7 (c = 0.87, $CHCl_3$).

(*R*)-5-((S)-3-oxocyclohexyl)dihydrofuran-2(3H)-one (8). To a solution of (6*S*)-ethyl 2-oxo-6-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)cyclohexanecarboxylate **3b** (100 mg, 0.396 mmol, 1.0 eq) in ethyl acetate (4 mL) was added supported palladium on charcoal (10%, 15 mg), and the mixture was stirred under an atmosphere of hydrogen (P_{atm}) for 15h. The mixture was filtered on a pad of celite®, and the filtrate was concentrated in vacuo. The resulting oil was engaged into the next step without further purification. A solution of (6*S*)-ethyl 2-oxo-6-((*R*)-5-oxotetrahydrofuran-2-yl)cyclohexanecarboxylate in toluene (1.5 mL) and sulfuric acid (2N, 1.5mL) was refluxed for 2h. The reaction mixture was then diluted with water and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography (heptane/EtOAc 40/60) to afford compound **7** as a colorless oil (45.0 mg, 63% over 2 steps). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.31 (td, *J* = 8.6, 6.4 Hz, 1H), 2.60-2.46 (m, 3H), 2.43-1.79 (m, 8H), 1.76-1.42. (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 209.7 (Cq), 176.5 (Cq), 83.2 (CH), 43.3 (CH), 43.0 (CH_2), 41.2 (CH_2), 28.7 (CH_2), 26.9 (CH_2), 25.5 (CH_2), 24.7 (CH_2). I.R υ (neat): 2935, 1772, 1710, 1181 cm^{-1}. M.S. (ESI, m/z) 181.1 $[M-H]^-$, 205.1 $[M+Na]^+$, 246.1 $[M+Na+CH_3CN]^+$. H.R.M.S. (ESI, m/z) Calcd for $C_{10}H_{15}O_3$: 183.1021, found: 183.1013. $[\alpha]_D^{25}$ -30.4 (c = 0.50, $CHCl_3$).

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SUPPORTING INFORMATION. Tables of solvent and ligand **L2** and **L4** screening, copies of ^{1}H, ^{13}C NMR spectra, HPLC chromatograms, CIF files and crystallographic details (CCDC 865835- CCDC 865836- CCDC 865837-CCDC 914992). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The lower yield is likely due to the relative instability of the starting material **2e** which was purified by distillation under reduced pressure to prevent decomposition.

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(12) See the supporting information for additionnal experiments with the seven- and five-membered rings.

(13) See Supporting information. Analysis of the absolute structure using likelihood methods was performed using PLATON. The results confirmed the value of the Flack absolute structure parameter 0.0 (2) as well as the Hooft parameter y 0.00(18) indicating that the absolute configuration had probably been correctly assigned. CCDC 914992 and CCDC 865837 contain the supplementary crystallographic data of compounds **3b** and **3h**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. (a) Hooft, R. W. W.; Straver, L. H.; Spek, A. L. *J. Appl. Cryst.* **2008**, *41*, 96. (b) Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876. (c) Speck, A. L. *Acta Cryst.* **2009**, *D65*, 148.

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