One-pot Sequential Organocatalytic Michael-Tishchenko-Lactonization Reactions. Synthesis of Enantioenriched 4,5,6-Trisubstituted δ-Lactones.

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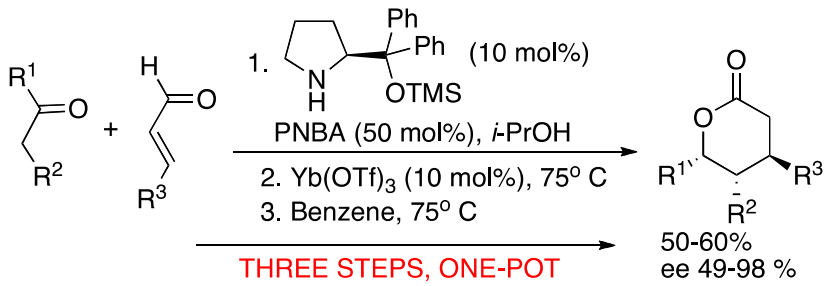


Abstract. Enantioenriched trisubstituted lactones were obtained in good yields and moderate to very good enantioselectivities in one-pot process, which implies a sequential organocatalyzed Michael addition of ketones to enals, followed by catalytic intramolecular diastereoselective Tishchenko reaction and lactonization. The final lactones were obtained as single diastereoisomers, demonstrating that the mixture of the anti and syn diastereomers epimerized to the syn hydroxy ester during the oxido-reduction step.

INTRODUCTION

The synthesis of polysubstituted chiral δ-lactones has received much attention because they are present in a large number of biologically important compounds.[1] Some synthetic approaches to these compounds or their analogs have been developed, including the use of chiral templates,[2] asymmetric epoxidation,[3] asymmetric

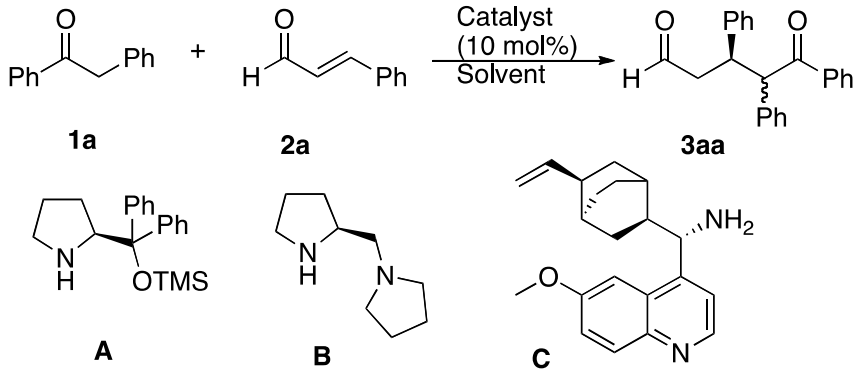
dihydroxylation,[4] metal-catalyzed transformations,[5] enzymatic resolutions,[6] or the chiral pool approach.[7]

Enantioenriched α-methylene-δ-lactones have been also prepared by sequential organocatalyzed Michael addition,[8] of aldehydes to α-phosphorylacrylates, followed by lactonization, and Horner-Wadsworth-Emmons protocol.[9] In a different approach, unsaturated carboxylic acids cyclize to substituted δ-lactones by stereoselective halolactonization promoted by chiral dual organocatalysts.[10]

Recently, a number of one-pot processes initiated by organocatalyzed stereoselective Michael addition, followed by different transformations of the adducts, have been reported in the synthesis of more complex molecules.[11] The success of this methodology requires that not only the initial Michael addition, but all the additional transformations were highly stereoselective. It has been previously demonstrated that both inter- and intramolecular Lewis acid promoted Tishchenko reactions are diastereoselective,[12] and we report here our results on the one-pot synthesis of enantioenriched trisubstituted δ-lactones by sequential organocatalyzed Michael addition followed by catalytic intramolecular oxido-reduction Tishchenko reaction.

RESULTS AND DISCUSSION

The best reaction conditions for the initial Michael addition was studied by reacting benzyl phenyl ketone **1a**, just in the upper border of pKa to participate in this reaction,[13] and cinnamaldehyde **2a**, in the presence of prolinol derivative **A**,[14] diamine **B**,[15] and quinidine derivative **C**[16] as organocatalysts (Scheme 1 and Table 1).



Scheme 1. Organocatalyzed Michael addition of benzyl-phenyl ketone to cinnamaldehyde.

Table 1. Effects of the solvent, temperature and catalysts in the Michael addition of **1a** to **2a**.

Entry	Catalyst	Solvent	T (^{o} C)	Time (h)	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	**A**	DCM	20	45	50	1:2	80
2	**B**	DCM	20	16	70	1:7	40
3	**B**	DCM	- 18	45	70	1:7	60
4	**C**	DCM	20	100	---	---	---
5	**A**	DCM	- 18	105	50	1:3	88
6	**A**	Et_2O	20	50	80	1:2	40
7	**A**	Et_2O	- 18	100	80	1:3	60
8	**A**	Toluene	- 18	90	93	1:7	71
9	**A**	EtOH	20	38	98	1:2	50
10	**A**	EtOH	- 18	70	98	1:2	56
11	**A**	MeOH	20	38	92	1:3	40
12	**A**	MeOH	- 18	70	92	1:3	44
13	**A**[d]	DCM	20	45	75	1:2	88
14	**A**[d]	MeOH	20	38	92	1:3	80
15	**A**[d]	MeOH	0	45	92	1:3	83
16	**A**[d]	MeOH	- 18	70	92	1:3	83
17	**A**[d]	*i*-PrOH	20	45	95	1:3	74
18	**A**[d]	*i*-PrOH	0	60	95	1:3	83

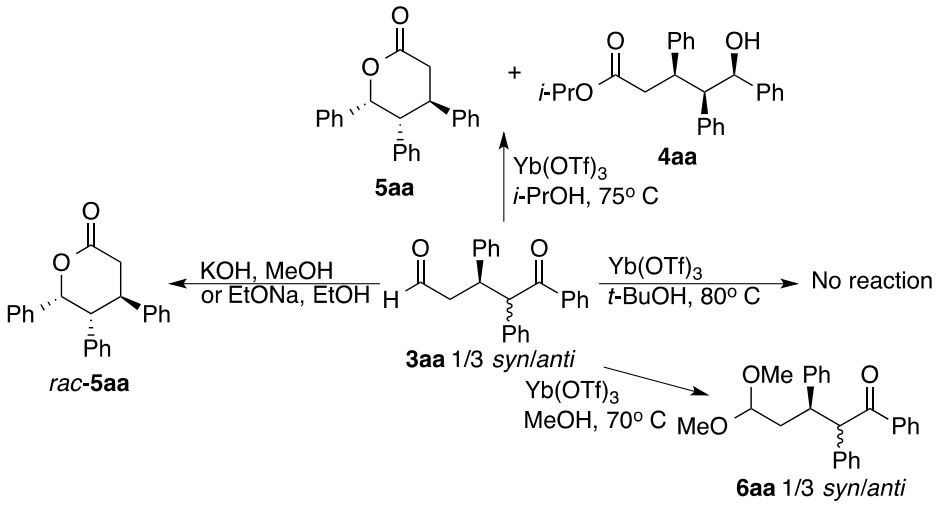
[a] Yields refer to isolated compounds. [b] Determined by ^{1}HNMR of the reaction mixtures, the ratio 1:x refers to *syn/anti* diastereoisomers. [c] Determined by chiral HPLC, and refer to the major diastereoisomer. [d] PNBA was used as co-catalyst.

As a general trend, an inseparable mixture of Michael adducts, epimers at C-4, was obtained in all assayed conditions, but prolinol derivative **A** has showed to be better catalyst than **B** in terms of enantioselectivity (entries 1-3, in table 1), whereas quinidine derivative **C** was unable to catalyze the reaction (entry 4). The enantioselection was low when the reactions were carried out in diethyl ether, toluene, ethanol or methanol as

solvents (entries 6-12), although it increased when the temperature was lowered to – 18° C (compare entries 6 and 7, 9 and10, or 11 *versus* 12).

Much better results were obtained in the reactions catalyzed by 10 mol% **A** and 50 mol% of *p*-nitrobenzoic acid (PNBA) as co-catalyst (entries 13-18). In all cases the presence of the acidic co-catalyst increased both the reactivity and enantioselectivity, maintaining the diastereoselectivity, and the best results were obtained when the reaction was carried out in 2-propanol, at 0° C, by using 10 mol% of catalyst **A** and 50 mol% of PNB acid as co-catalyst as summarized in entry 18 in Table 1.

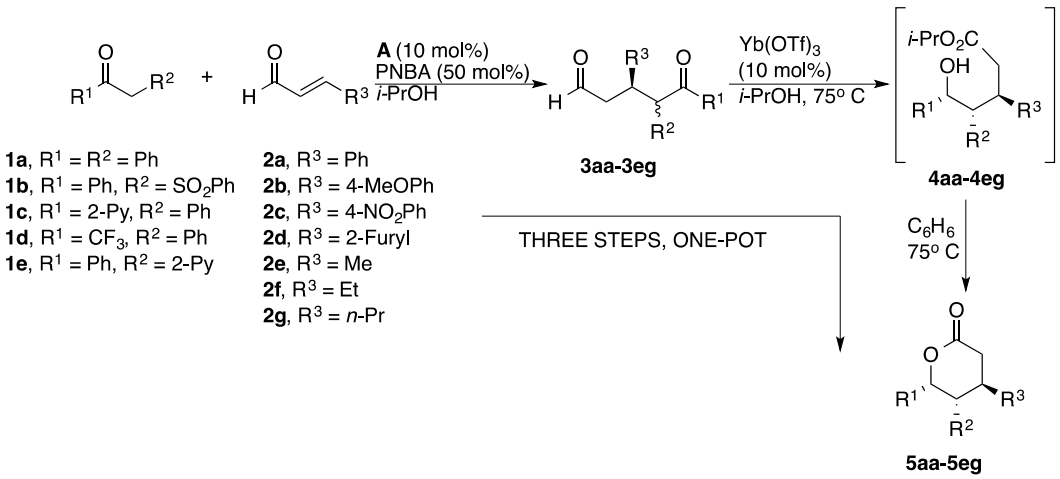
The transformation of the mixture of the Michael adduct **3aa** into δ-lactones was studied in different conditions (Scheme 2). The treatment of the ketoaldehyde **3aa** with a solution of potassium hydroxide in methanol or sodium ethoxide in ethanol,[17] for 15 min. at room temperature, led to a single diastereoisomer of lactone **5aa** in 70% yield but as a racemic mixture. The reaction failed when **3aa** was heated under MW irradiation in the presence of neutral alumina,[18] and only decomposition products were observed by treatment with 1,1,3,3,-tetramethyl guanidine in water or THF/water mixtures.[19] Successful results were obtained by Tishchenko reaction promoted by catalytic ytterbium triflate,[12f] although the choice of the alcohol used as solvent is crucial to get the oxido-reduction reaction. The heating of a solution of **3aa** in methanol and 10 mol% of $Yb(OTf)_3$ for 20 h leaded to 1,1-dimethyl acetal **6aa** as a 3/1 mixture of epimers at C-4, but **3aa** was recovered unchanged after heating at 80° C, for 200 h, in tert-butanol. Fortunately, the heating of a solution of **3aa** in 2-propanol and 10 mol% of $Yb(OTf)_3$ at 75° C gave an equimolar mixture of the *syn-syn*-hydroxy ester **4aa** and lactone **5aa** in 65% yield as single diastereoisomers, indicating that the Tishchenko reaction proceed completely, but only partial lactonization had occurred. This problem was easily solved by changing 2-propanol to benzene as solvent in the lactonization step, and additional heating. It is interesting to note that lactone **5aa** and hydroxy ester **4aa** were formed with the same ee.



Scheme 2. Attempts of intramolecular oxido-reduction of **3aa**.

Next, we studied the possibility to do the direct transformation of ketone **1a** and cinnamaldehyde **2a** into trisubstituted δ-lactone **5aa** in one-pot because this protocol saves purification steps, the generation of waste chemicals, and minimizes the time increasing the yield of the process.[20] To this end, a solution of **1a** (1.2 equiv), **2a** (1 equiv), prolinol derivative **A** (0.1 equiv) as catalyst, and PNBA (0.5 equiv) as co-catalyst in 2-propanol was stirred at 0º C until the reaction was completed (45 h). Then, 0.1 equiv of $Yb(OTf)_3$ was added and the mixture heated until disappearance of **3aa** (TLC, ca. 100h). The 2-propanol was removed under vacuun and the residue was redissolved in benzene and heated until **4aa** was not detected by TLC (ca. 23 h). The solvent was evaporated and the residue subjected to flash chromatography to yield 56 % of lactone **5aa** as a single diastereoisomer in 83 % ee (Scheme 3 and entry 1 in Table 2).

Once established the conditions for the three-steps one-sequence reaction, the methodology was extended to different enals **2a-g** and ketones **1a-g** with a single enolizable methylene group to prevent undesired transformations (Scheme 3 and Table 2).



Scheme 3. Three-steps one-pot synthesis of trisubstituted lactones.

Table 2. One-pot synthesis of lactones by sequential Michael-Tishchenko-lactonization process.

Entry	Reagents	T (º C)[a]	Time (h)[b]	Product	Yield (%)[c]	Ee (%)[d]
1	**1a/2a**	0	168	**5aa**	55	83
2	**1a/2b**	0	170	**5ab**	58	80
3	**1a/2c**	0	135	**5ac**	60	98
4	**1a/2d**	0	145	**5ad**	59	89
5	**1a/2e**	0	190	**5ae**	50	84[e]
6	**1b/2a**	- 18	130	**5ba**	48	71
7	**1b/2b**	-18	135	**5bb**	50	48
8	**1b/2c**	- 18	120	**5bc**	52	71
9	**1b/2d**	- 18	115	**5bd**	57	54
10	**1b/2e**	- 18	100	**4be**	62	82[f]
11	**1b/2f**	- 18	98	**5bf**	59	84
12	**1b/2g**	- 18	99	**5bg**	57	88
13	**1c/2a**	- 18	80	**5ca**	56	67
14	**1c/2g**	- 18	85	**5cg**	57	49
15	**1d/2a**	- 18	86	**4da**	43	20[f]

[a] Temperature refers to the Michael reaction. [b] Time refers to the total Michael-Tishchenko-lactonization processes. [c] Numbers refer to the total yields for the three

steps process, and was calculated after purification of lactones by flash chromatography. [d] Determined by chiral HPLC. [e] Ee refers to the hydroxy ester **4ae**. [f] Ee refers to the hydroxy esters.

Benzyl phenyl ketone **1a** reacted with aryl-substituted α,β-unsaturated aldehydes **2a-d** leading to lactones **5aa-5ad** in good overall yields and very good enantioselectivities (entries 1-4 in Table 2). The best result was obtained for the reaction *p*-nitrophenyl-substituted aldehyde **2c**, which yielded the lactone **5ac** as a nearly single enantiomer. Both the yield and stereoselectivity was almost identical for an alkyl-substituted aldehyde such as crotonaldehyde **2e** (entry 5 in Table 2). When the phenyl group attached to the carbonyl was changed to a 2-pyridyl substituent in ketone **1c** the Michael reaction was accelerated, but the enantioselection dropped to 67% ee in the reaction with **2a**, or to 49% ee for the reaction with alkyl-substituted enal **2g** (entries 13, 14 in Table 2).

Benzyl trifluoromethyl ketone (**1d**) also reacted with cinnamaldehyde (**2a**), but the hydroxy ester **4da**, which was unable to cyclize to the lactone, was isolated as a single diastereoisomer in very low ee (entry 15 in Table 2), whereas methyl-(2-pyridinyl) phenyl ketone (**1e**) easily reacted with crotonaldehyde leading to the Michael adduct **3ee** but as an equimolar mixture of racemic diastereoisomers. This reaction also worked in the absence of catalyst.

The interest of the sulfonyl derivatives in organocatalyzed reactions[21] led us to consider phenylsulfonylacetophenone **1b** as a nucleophile towards β-aryl- and β-alkyl-substituted enals. It was found that the more acidic ketosulfone reacted in milder conditions than **1a** (- 18^{o} C for the initial Michael reaction) with alkyl-substituted aldehydes **2f-g**, leading to lactones **5bf** and **5bg** as single diastereomers in good overall yield and very good enantioselectivities (entries 11, 12 in Table 2). On the contrary, **1b** reacted with crotonaldehyde (**2e**) yielding, with high ee, a single diastereoisomer of the hydroxy ester **4be**, which did not lactonize in the described conditions (entry 10 in Table 2). Additionally, and contrary to previously reported, **1b** also reacted with aryl-substituted enals **2a-d** affording lactones **5ba-5bd** although with moderate or poor enantioselection (entries 6-9 in Table 2).

Because we were unable to obtain any crystal for XR-diffraction analysis, the absolute stereochemistry at C-3 of the adducts **3aa-3eg** (C-4 in the lactone ring) was assigned on the basis of the well known stereoselection of the Michael addition of ketosulfones to unsaturated carbonyls promoted by (*S*)-**1**.[11j, 22] The relative stereochemistry was established for compound **5bg** on the basis of ^{1}H NMR experiments as indicated in figure 1, and extended to all the lactones.[23] The NOESY contact of H-5 with the methylene of the substituent at C-4 points to a diaxial *cis* relationship between this hydrogen and the propyl group, and consequently a *trans* disposition between the substituents at C-4 and C-6 in the lactone ring. Additionally, the *cis* relationship between the Ph and SO_2Ph substituents at C-6 and C-5 respectively was deduced from the coupling constant of H-5 and H-4 (J = 3.2 Hz), which is consistent with a *cis* axial-equatorial arrangement of these protons.

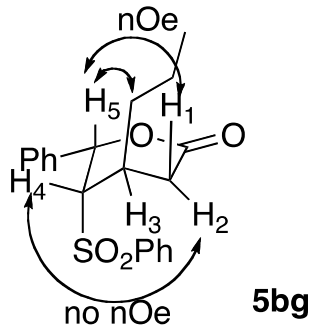
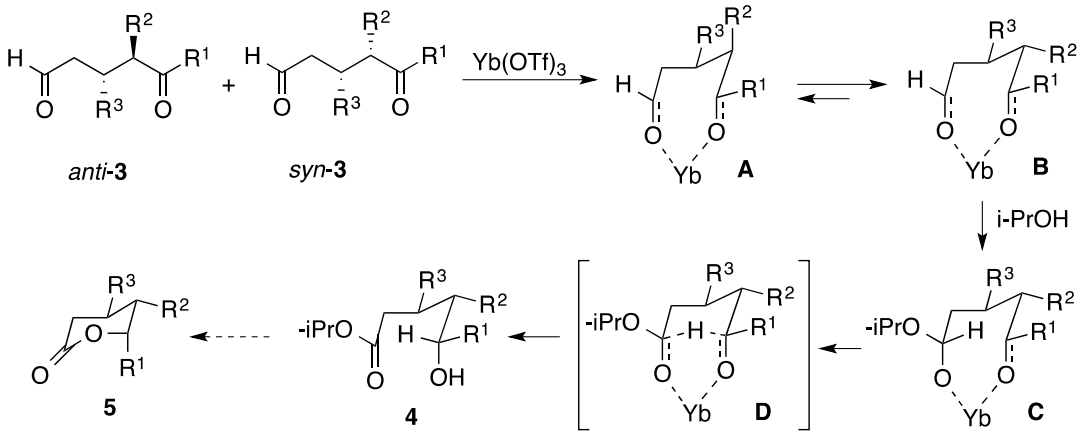


Figure 1. Some ^{1}H NOESY contacts for compound **5bg**.

Two different stereoselective transformations occur during the sequential process described. The first one is a diastereo- and enantioselective Michael addition promoted by (*S*)-**1**, and the second one consists on a catalytic diastereoselective intramolecular Tishchenko reaction transforming ketoaldehydes **3** into hydroxy esters **4**, which cyclized to the final lactones **5**. We will center our discussion on the last one because the catalytic cycle and the stereochemical outcome of the conjugated addition are well known and accepted.

It is noteworthy that, although a mixture of diastereomeric adducts were formed in the first Michael reaction, only a single lactone was isolated as final products. This fact, previously observed in related transformations, has been explained by accepting that the epimerization occurs after the cyclization process leading to the most stable isomer.[24] In our case, the epimerization take place prior or during the oxido-reduction process

because not only lactones but also hydroxy esters **4be** and **4da** were isolated as single diastereoisomers (see entries 10 and 15 in Table 2). Epimerization by retro-Michael/ re-addition process promoted by $Yb(OTf)_3$ can be discarded because, in that case, a racemic mixture of **4aa** and **5aa** must be obtained in the experiment described in Scheme 2. Additionally, the Tishchenko reaction is stereospecific[12d,25] because a single diastereoisomer at the carbon bearing the hydroxyl group was formed in the process.



Scheme 4. Proposed pathway for the transformation of adducts **3** into hydroxy esters **4**.

The stereochemical outcome of the Tishchenko reaction could be explained as summarized in Scheme 4. The coordination of the metal to both carbonyl groups leads to a mixture of activated diastereomeric complexes **A** and **B**, which quickly isomerizes to the most stable complex **B** because all the substituents occupy equatorial positions. The addition of *i*-PrOH to the 5-oxopentanal derived complex **B** occurs to the external less hindered *Re*-face of the formyl group leading to a chelated hemiacetal complex **C**. The intramolecular hydride transfer throughout a 6-membered concerted transition state **D** dictates the stereochemistry at C-5 in the hydroxy ester **4**, which was obtained as a single diastereoisomer. The change of the solvent and subsequent cyclization of **4** gives the final lactones **5**.

CONCLUSIONS

In summary, we have developed a sequential stereoselective organocatalyzed Michael addition, followed by catalyzed diastereoselective Tishchenko reaction and

lactonization leading to enantioenriched trisubstituted lactones in good yields and moderate to good enantioselectivity. The process works well for benzyl ketones and ketosulfones as nucleophiles, and for both β-substituted alkyl- and aryl-enals as electrophiles. The results indicate that epimerization of the *anti* to the *syn* diastereoisomers obtained in the first Michael addition occurs during the oxido-reduction step, because lactones are obtained as a single diastereoisomer. The total process has been carried out in one-pot conditions saving wastes, time and purification steps.

EXPERIMENTAL SECTION

General information

^{1}H–NMR (400 MHz or 500 MHz) and ^{13}C–NMR (100 MHz) spectra were recorded in $CDCl_3$ or acetone-d_6. Chemical shifts for protons are reported in ppm from tetramethylsilane as internal reference. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Specific rotations were measured using a 5-mL cell with a 1-dm path length, and concentration is given in g per 100 mL. TLC analysis was performed on glass-backed plates coated with silica gel 60 and an F_{254} indicator, and visualized by either UV irradiation or by staining with phosphomolybdic acid solution. Flash chromatography was carried out using silica gel (230-240 mesh). Chiral HPLC analysis was performed using different chiral columns. IR spectra were recorded on a FT-IR instrument. High resolution mass spectra were performed by positive electro spray ionization using quadrupole-time of flight detector (ESI+-Q-TOF) instrument. All compounds were purchased from commercial sources and used as received.

General procedure for the one-pot transformation:

A mixture of **1a** (0.48mmol), **2a** (0.40 mmol), p-nitrobenzoic acid (0.2 mmol) and catalyst **A** (0.04 mmol) in i-PrOH (5 mL) was stirred at 0 ^{o}C until the aldehyde was consumed (TLC, *ca.* 45 h). After this time, ytterbium triflate (0.04mmol) was added and the temperature was rised to 75 °C. The mixture was stirred until the Michael adduct **3aa** was completely consumed (TLC, *ca.* 100h). The solvent was then removed under reduced pressure and the residue was dissolved in benzene (4mL) and heated at 75 °C for 20 hrs to complete the lactonization. After evaporation of the solvent under vacuum,

the crude product was subjected to FC on silica gel (CH_2Cl_2/Hexane 4:1) to yield the desired lactone **5aa**.

(4R,5R,6R)-4,5,6-Triphenyltetrahydro-2H-pyran-2-one (5aa). White solid (69 mg, 55% yield); mp 138-140 ^{0}C (Hexane) (lit.[26] 141-142 ^{o}C). $[\alpha]_D^{20}$ = - 63.4, (c = 1, $CHCl_3$, 83% ee) ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.21 – 2.94 (m, 2H), 3.82 – 3.47 (m, 2H), 5.85 (d, 1H, *J* = 4.4 Hz), 7.02 – 6.77 (m, 4H), 7.40 – 7.03 (m, 11H); ^{13}C-NMR ($CDCl_3$, 126 MHz,) δ 29.8, 37.2, 42.3, 52.7, 82.2, 126.4, 127.0 (2C), 127.1, 127.3 (2C), 127.8, 127.9, 128.3 (2C), 129.1 (2C), 129.4 (2C), 136.3, 138.5, 142.6, 171.9; IR 3029, 2925, 1742, 1498, 1244, 1036 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=90:10) 1.0 mLmin^{-1} λ = 220 nm) t_R=17.45 (major); t_R=26.81 (minor); HRMS Calcd for $C_{23}H_{21}O_2$ (M+H) 329.1536 , found:329.1537.

(4R,5R,6R)-4-(4-Methoxyphenyl)-5,6-diphenyltetrahydro-2H-pyran-2-one (5ab). White solid (83 mg, 58% yield); mp 103-106 ^{0}C (Hexane). $[\alpha]_D^{20}$= - 76.5, (c = 1, $CHCl_3$, 80% ee); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.05 (dd, 2H, *J* = 8.4, 6.9 Hz), 3.59 (ddd, 2H, *J* = 17.1, 9.0, 5.7 Hz), 3.76 (s, 3H), 5.83 (d, 1H, *J* = 4.6 Hz), 7.16 – 6.82 (m, 14H); ^{13}C-NMR ($CDCl_3$, 126 MHz,) δ 37.4, 41.4, 52.8, 55.4, 82.2, 114.5 (2C), 126.4 (2C), 127.1, 127.8, 127.9 (2C), 128.0 (2C), 128.2 (2C), 129.4, 134.6, 136.4, 138.5, 158.7, 172.0; IR 2920, 2853, 1726, 1514, 1244, 1026 cm^{-1}; HPLC (Chiralpack AD-H (hexane/iPrOH=90:10) 1.0 mLmin^{-1} λ =220 nm) t_R=26.54 (major); t_R=36.61 (minor); HRMS Calcd for $C_{24}H_{23}O_3$ (M+H) 359.1642, found: 359.1635.

(4R,5R,6R)-4-(4-Nitrophenyl)-5,6-diphenyltetrahydro-2H-pyran-2-one (5ac). White solid (90 mg, 60% yield); mp 69-72 ^{0}C (Hexane). $[\alpha]_D^{20}$= -39.2, (c = 1, $CHCl_3$, 98% ee); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.10 (m, 2H), 3.72 (dt, 2H, *J* = 13.6, 7.3 Hz), 5.85 (d, 1H, *J* = 4.6 Hz), 7.51 – 6.63 (m, 12H), 8.13 (d, 2H, *J* = 8.8 Hz); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 37.3, 41.0, 51.7, 82.7, 124.3 (2C), 126.5 (2C), 126.9, 127.5, 127.9, 127.9, 128.0, 128.1, 128.4, 128.5, 128.7, 128.9, 129.2, 135.4, 136.9, 149.3, 170.3; IR. 2925, 2853, 1732, 1514, 1342, 1021 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=80:20) 1.0 mLmin^{-1} λ = 254nm) t_R=24.0 (major); t_R=28.5 (minor); HRMS Calcd for $C_{23}H_{18}NO_4$ (M-H) 372.1241, found: 372.1238.

(4R,5R,6R)-4-(Furan-2-yl)-5,6-diphenyltetrahydro-2H-pyran-2-one (5ad). White solid (75 mg, 59% yield); mp 78-81 ^{0}C (Hexane). $[\alpha]_D^{20}$= - 14.9, (c = 1, $CHCl_3$, 89%

ee); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.26 – 2.99 (m, 2H), 3.70 (t, 2H, *J* = 6.2 Hz), 5.78 (d, 1H, *J* = 3.5 Hz), 6.09 (d, 1H, *J* = 3.2 Hz), 6.30 (dd, 1H, *J* = 3.2, 1.9 Hz), 7.24 – 6.81 (m, 10H), 7.38 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 33.7, 36.7, 49.6, 81.2, 106.2 (2C), 110.3 (2C), 126.1 (2C), 127.1, 127.7, 127.9 (2C), 128.2 (2C), 129.0 (2C), 136.2, 142.2, 171.2; IR. 3024, 2936, 1737, 1446, 1249, 1041 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=90:10) 1.0 $mLmin^{-1}$ λ = 220 nm) t_R=14.5.0 (major); t_R=18.69 (minor); HRMS Calcd for $C_{21}H_{19}O_3$ (M+H) 319.1329, found: 319.1331.

(4R,5R,6R)-4-Methyl-5,6-diphenyltetrahydro-2H-pyran-2-one (5ae). White solid (53 mg, 50% yield); mp 105-108 ^{0}C (Hexane). $[\alpha]_D^{20}$= - 22.5, (c = 1, $CHCl_3$, 84% ee); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.10 (d, 3H, *J* = 6.3 Hz), 2.64 – 2.34 (m, 2H), 2.95 (d, 1H, *J* = 11.0 Hz), 3.08 (dd, 1H, *J* = 7.4, 4.8 Hz), 5.64 (d, 1H, *J* = 4.8 Hz), 6.82 (ddd, 4H, *J* = 19.4, 5.6, 4.1 Hz), 7.14 (td, 6H, *J* = 5.6, 1.8 Hz); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 21.1, 30.1, 38.1, 53.1, 82.5, 126.7 (2C), 127.2, 127.8, 127.8 (2C), 128.2 (2C), 129.4 (2C), 136.4, 138.4, 172.2; IR. 2967, 2925, 1737, 1456.9, 1249, 1031 cm^{-1}; HRMS Calcd for $C_{18}H_{19}O_2$ (M+H) 267.1380, found: 267.1383. It was not possible to found the conditions to separate the enantiomers of **5ae**, but we were successful in the separation of the hydroxy ester **4ae**: HPLC (Chiralpak AD-H (hexane/iPrOH=90:10) 1.0 $mLmin^{-1}$ λ = 220 nm) t_R=12.9 (minor); t_R=17.1 (major) .

(4S,5S,6S)-4,6-Diphenyl-5-(phenylsulfonyl)tetrahydro-2H-pyran-2-one (5ba). White solid (75 mg, 48% yield), mp 207-210 ^{0}C (Hexane). $[\alpha]_D^{20}$= - 6.9, (c = 0.9, acetone, 71% ee); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.98 (dd, 1H, *J* = 17.6, 6.4 Hz), 3.26 (dd, 1H, *J* = 17.6, 7.3 Hz), 3.90 (t, 1H, *J* = 3.7 Hz), 4.28 (dd, 1H, *J* = 6.8, 4.0 Hz), 5.73 (d, 1H, *J* = 3.3 Hz), 7.20 (m, 15H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 33.6, 36.3, 68.7, 75.7, 126.0 (2C), 126.9 (2C), 127.8 (2C), 128.1 (2C), 128.2, 128.3 (2C), 128.8 (2C), 129.5 (2C), 133.1, 133.9, 140.7, 169.0; IR. 3065, 2925, 1752, 1306, 1238, 1145 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=70:30) 1.0 $mLmin^{-1}$ λ = 220 nm) t_R=6.6 (minor); t_R=30.0 (major); HRMS Calcd for $C_{23}H_{21}O_4S$ (M+H) 393.1155, found: 393.1150.

(4S,5S,6S)-4-(4-Methoxyphenyl)-6-phenyl-5-(phenylsulfonyl)tetrahydro-2H-pyran-2-one (5bb). White solid (84 mg, 50% yield); mp 171-173 ^{0}C (Hexane). $[\alpha]_D^{20}$= - 22 (c = 0.8, acetone, 48% ee); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.01 (dd, 1H, *J* = 17.5, 6.2 Hz), 3.32 (dd, 1H, *J* = 17.6, 7.3 Hz), 3.81 (s, 3H), 3.91 (s, 1H), 4.31 (d, 1H, *J* = 4.9 Hz), 5.79

(s, 1H), 7.58 – 6.69 (m, 14H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 33.9, 35.7, 55.5, 69.0, 75.8, 115.0 (2C), 126.2 (2C), 127.9 (2C), 128.3 (2C), 128.4 (2C), 129.0 (2C), 132.6, 133.2 (2C), 134.2, 139.8, 159.4, 169.3; IR. 2962, 2925, 1747, 1514, 1306, 1249 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=50:50) 1.0 $mLmin^{-1}$ λ = 220 nm) t_R=18.5 (minor); t_R=47.2 (major); HRMS Calcd for $C_{24}H_{23}O_5S$ (M+H) 423.1261, found: 423.1252.

(4S,5S,6S)-4-(2-Nitrophenyl)-6-phenyl-5-(phenylsulfonyl)tetrahydro-2H-pyran-2-one (5bc). White solid (90 mg, 52% yield); mp 166-169 ^{0}C (Hexane). $[\alpha]_D^{20}$= + 79.8, (c = 0.5, acetone, 71% ee); ^{1}H-NMR (acetone, 500 MHz) δ 3.17 (dd, 1H, *J* = 16.3, 5.9 Hz), 3.34 (dd, 1H, *J* = 16.3, 10.6 Hz), 4.82 – 4.69 (m, 1H), 4.83 (dd, 1H, *J* = 6.0, 4.3 Hz), 6.36 (d, 1H, *J* = 4.3 Hz), 7.98. – 7.15 (m, 14H); ^{13}C-NMR (126 MHz, acetone) δ 33.7, 36.4, 68.5, 77.3, 110.9, 124.4, 125.8, 127.6 (2C), 128.2 (2C), 128.7 (2C), 129.0 (2C), 129.7 (2C), 129.7, 130.6, 131.7, 133.8, 134.8, 135.3, 137.2, 169.5; IR. 3065, 2925, 2853, 1747, 1700, 1524, 1311 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=50:50) 1.0 $mLmin^{-1}$ λ = 220nm) t_R=16.5 (minor); t_R=27.2 (major); HRMS Calcd for $C_{23}H_{20}NO_6S$ (M+H) 438.1006, found: 438.1006.

(4S,5S,6S)-4-(Furan-2-yl)-6-phenyl-5-(phenylsulfonyl)tetrahydro-2H-pyran-2-one (5bd). Colorless oil (87 mg, 57% yield); $[\alpha]_D^{20}$= - 19.9, (c = 1, CH_2Cl_2, 54% ee); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.07 (dd, 1H, *J* = 17.7, 5.0 Hz), 3.38 (dd, 1H, *J* = 17.7, 7.4 Hz), 4.15 (t, 1H, *J* = 3.3 Hz), 4.54 – 4.39 (m, 1H), 5.68 (d, 1H, *J* = 3.3 Hz), 6.28 (d, 1H, *J* = 3.3 Hz), 6.37 (dd, 1H, *J* = 3.3, 1.9 Hz), 7.40 – 7.10 (m, 11H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 31.2, 31.6, 65.3, 75.9, 108.1, 111.0, 125.9 (2C), 127.9 (2C), 128.2 (2C), 128.3, 128.9 (2C), 133.2, 134.2, 139.5, 143.1, 152.4, 168.3; IR. 2960, 1755, 1447, 1304, 1145, 1086 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=70:30) 1.0 $mLmin^{-1}$ λ = 220 nm) t_R=23.4 (major); t_R=41.5 (minor); HRMS Calcd for $C_{21}H_{19}O_5S$ (M+H) 383.0948, found: 383.0945.

(4R,5S,6S)-4-Ethyl-6-phenyl-5-(phenylsulfonyl)tetrahydro-2H-pyran-2-one (5bf). White solid (81 mg, 59% yield); mp 214-218 ^{0}C (Hexane); $[\alpha]_D^{20}$=-36.8, (c = 0.5, acetone, 84% ee); ^{1}H-NMR(acetone, 400 MHz) δ = 0.98 (t, 3H, *J* = 7.4 Hz), 1.87 – 1.58 (m, 2H), 2.93 – 2.59 (m, 3H), 4.09 (t, 1H, *J* = 3.3 Hz), 5.95 (d, 1H, *J* = 3.3 Hz), 7.51 – 7.13 (m, 10H); ^{13}C-NMR (101 MHz, acetone) δ 11.3, 33.7, 34.3, 67.7, 76.2, 124.4, 126.9 (2C), 128.4, 128.7 (2C), 129.0 (2C), 129.7 (2C), 131.7, 133.9, 136.1, 170.6; IR.

2962, 2925, 1737, 1446, 1306, 1254, 1062 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=70:30) 1.0 $mLmin^{-1}$ λ = 220 nm) t_R=13.5 (minor); t_R=24.5 (major); HRMS Calcd for $C_{19}H_{21}O_4S$ (M+H) 345.1155, found: 345.1157.

(4R,5S,6S)-6-Phenyl-5-(phenylsulfonyl)-4-propyltetrahydro-2H-pyran-2-one (5bg). White solid (82 mg, 57% yield); mp 190-193 ^{0}C (Hexane); $[\alpha]_D^{20}$= - 28.85, (c = 0.7, acetone, 88% ee); ^{1}H-NMR (acetone, 400 MHz) δ 0.89 (t, 3H, *J* = 7.3 Hz), 1.41 (m, 2H, *J* = 12.2, 7.3, 4.1 Hz), 1.76 – 1.59 (m, 2H), 2.75 – 2.62 (m, 1H), 2.84 (m, 2H, *J* = 17.4, 7.1 Hz), 4.08 (t, 1H, *J* = 3.2 Hz), 5.96 (d, 1H, *J* = 3.3 Hz), 7.53 – 7.12 (m, 10H); ^{13}C-NMR (101 MHz, acetone) δ 14.1, 20.2, 31.9, 34.5, 39.0, 68.0, 76.2, 124.4, 126.9, 128.4, 128.7, 129.0, 129.5, 129.7, 130.0, 131.7, 133.9, 136.1, 141.0, 170.6; IR 2956, 2930, 1732, 1306, 1140, 740 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=80:20) 1.0 $mLmin^{-1}$ λ = 220nm) t_R=19.9 (minor); t_R=42.3 (major); HRMS Calcd for $C_{20}H_{23}O_4S$ (M+H) 359.1312, found: 359.1312.

(4R,5R,6R)-4,5-Diphenyl-6-(pyridin-2-yl)tetrahydro-2H-pyran-2-one (5ca). Colorless oil (74 mg, 56% yield); $[\alpha]_D^{20}$= - 29.5, (c = 1, $CHCl_3$, 67% ee); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.02 (ddd, 2H, *J* = 28.1, 16.5, 8.7 Hz), 3.68 (dd, 1H, *J* = 5.8, 3.4 Hz), 3.86 (dd, 1H, *J* = 8.0, 4.8 Hz), 5.82 (d, 1H, *J* = 4.7 Hz), 7.45 – 6.55 (m, 12H), 8.35 (dd, 2H, *J* = 13.9, 11.5 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 37.9, 42.0, 51.1, 82.4, 122.4, 122.9, 123.6, 127.1 (2C), 127.2 (2C), 127.3 (2C), 128.3, 129.0, 129.0, 131.2, 136.4, 138.5, 142.5, 148.4, 155.9, 171.9; IR 3060, 3029, 2925, 1732, 1524, 1244 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=70:30) 1.0 $mLmin^{-1}$ λ = 220 nm) t_R=9.8 (major); t_R=15.8 (minor); HRMS Calcd for $C_{22}H_{20}NO_2$ (M+H) 330.1489, found: 330.1493.

(4R,5R,6R)-5-Phenyl-4-propyl-6-(pyridin-2-yl)tetrahydro-2H-pyran-2-one (5cg). Colorless oil (67 mg, 57% yield); $[\alpha]_D^{20}$= - 14.86, (c = 0.4, acetone, 49% ee); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.83 (t, 3H, *J* = 7.3 Hz), 1.38 – 1.21 (m, 2H), 1.50 – 1.41 (m, 1H), 1.59 (ddd, 1H, *J* = 12.5, 9.8, 6.6 Hz), 2.52 – 2.36 (m, 1H), 2.64 – 2.47 (m, 1H), 2.96 (dd, 1H, *J* = 15.5, 5.6 Hz), 3.48 – 3.24 (m, 1H), 5.68 (d, 1H, *J* = 4.4 Hz), 7.15 – 6.57 (m, 6H), 7.39 (td, 1H, *J* = 7.8, 1.7 Hz), 8.47 (ddd, 2H, *J* = 10.8, 5.8, 3.6 Hz); ^{13}C- NMR (126 MHz, $CDCl_3$) δ 14.1, 19.8, 36.2, 36.6, 38.5, 50.7, 81.7, 122.1, 122.7, 123.7, 127.0, 128.3, 129.0, 131.2, 136.4, 139.7, 148.4, 156.3, 173.0; IR. 3060, 2962, 1742, 1244, 1057 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=90:10) 1.0 $mLmin^{-1}$ λ = 220 nm)

t_R=16.4 (major); t_R=17.97 (minor); HRMS Calcd for $C_{19}H_{22}NO_2$ (M+H) 296.1645, found: 296.1653.

(3R,4S,5S)-Isopropyl 5-hydroxy-3-methyl-5-phenyl-4-(phenylsulfonyl)pentanoate (4be). White solid (101 mg, 65% yield); mp 97-100 ^{0}C (Hexane); $[\alpha]_D^{20}$= - 32.9, (c = 0.8, acetone, 82% ee); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.10 (d, 3H, *J* = 6.8 Hz), 1.16 (dd, 6H, *J* = 13.0, 6.3 Hz), 2.54 – 2.15 (m, 2H), 3.01 (dd, 1H, *J* = 18.4, 9.7 Hz), 3.48 (s, 1H), 3.89 (dd, 1H, *J* = 8.0, 2.1 Hz), 4.91 (dt, 1H, *J* = 12.5, 6.3 Hz), 5.25 (d, 1H, *J* = 7.8 Hz), 7.26 (td, 5H, *J* = 4.6, 2.0 Hz), 7.67 – 7.33 (m, 3H), 7.82 (dd, 2H, *J* = 8.4, 1.2 Hz); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 17.1, 21.9, 22.0, 30.8, 38.9, 68.0, 72.7, 73.4, 126.0, 127.0, 128.0, 128.2, 128.4, 128.6, 128.8, 129.0, 129.0, 133.3, 140.4, 142.4, 172.1; IR. 3501, 2975, 1718, 1283, 1134, 1108 cm^{-1}; HPLC (Chiralpak AD-H column (hexane/iPrOH=70:30) 1.0 mLmin^{-1} λ = 220nm) t_R=5.8 (minor); t_R=6.5 (major); HRMS Calcd for $C_{21}H_{27}O_5S$ (M+H) 391.1574, found: 391.1575.

(3R,4R,5R)-Isopropyl 6,6,6-trifluoro-5-hydroxy-3,4-diphenylhexanoate (4da). Colorless oil (65 mg, 43% yield); $[\alpha]_D^{20}$= - 13, (c = 0.5, $CHCl_3$, 20% ee); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.11 (dd, 6H, *J* = 34.1, 6.3 Hz), 2.75 (dd, 1H, *J* = 15.7, 7.1 Hz), 2.90 (dd, 1H, *J* = 15.7, 6.8 Hz), 3.14 (d, 1H, *J* = 7.3 Hz), 3.27 (dd, 1H, *J* = 10.1, 3.2 Hz), 3.83 – 3.64 (m, 1H), 4.55 – 4.28 (m, 1H), 4.93 (dt, 1H, *J* = 12.5, 6.3 Hz), 7.18 – 6.79 (m, 10H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 21.7 (2C), 40.2, 43.4, 51.0, 68.7, 70.5 (q), 123.9 (q), 126.1, 126.7, 127.2, 128.0 (2C), 128.2 (2C), 128.5, 128.7, 130.1, 136.4, 141.5, 172.6; IR. 3429, 3034, 2936, 1700, 1259, 1104, 699 cm^{-1}; HPLC (Chiralpak AD-H (hexane/iPrOH=90:10) 1.0 mLmin^{-1} λ = 220 nm) t_R=7.0 (major); t_R=11.8 (minor); HRMS Calcd for $C_{21}H_{24}F_3O_3$ (M+H) 381.1672, found: 381.1680.

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Supporting Information Available: Copies of ^{1}H-NMR and ^{13}C-NMR spectra for all new compounds, COSY and NOESY experiments for **5bg**, and copies of the HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org

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