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Asymmetric Michael/hemiketalization of 5-hydroxy-2-methyl-4*H*-pyran-4-one to β,γ-unsaturated α-ketoesters catalyzed by a bifunctional rosin-indane amine thiourea catalyst

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Abstract: A highly efficient asymmetric cascade reaction namely Michael-hemiketalization of 5-hydroxy-2-methyl-4*H*-pyran-4one to β,γ-unsaturated α-ketoesters has been developed using a chiral bifunctional rosin-indane amine thiourea catalyst. The products are obtained in excellent yields with high degree of enantiomeric excess (up to 99% ee), in a short reaction time with low catalyst loading of 2.5 mol%.

Introduction

Kojic acid (a fungal metabolite) is used as an additive in cosmetics to lighten the skin color and is known to inhibit the copper containing enzyme tyrosinase that causes melanization in humans (Figure 1).[1] It is also found to exhibit a wide range of biological activities such as antifungal [2], anti-neoplastic [3], anti-proliferative[4], anti-HIV[5], anti-convulsant [6], anti-inflammatory [7], antioxidative[8], anti-bacterial[9] and tyrosinase inhibitory activity.[10]

In this context, 5-hydroxy-2-methyl-4*H*-pyran-4one **1** (allomaltol) is used for the treatment of pigmentation disorders, sunburn prevention and also useful as an antioxidant for oils and fats[11]. In view of the significance of kojic acid and its derivatives in the field of medicinal chemistry (Figure 1), the development of efficient approaches to generate pharmaceutical relevant scaffolds are still a challenging task for the synthetic chemists. Recently, organocatalytic Michael reaction has been recognized as one of the most elegant approaches for carbon–carbon bond forming reactions.[12] In this prospect, a bifunctional thiourea-amine catalyzed conjugate addition has extensively been investigated over the past decade due to their extensive H-bonding ability to induce the chirality.[13] In particular, β,γ-unsaturated α-ketoesters act as effective Michael acceptors in asymmetric conjugate addition reactions.[14] However, a few methods are reported on Michael addition/heketalization of β,γ-unsaturated α-ketoesters with different nucleophiles[15-20] including cyclic 1,3-dicarbonyls and 2-hydroxy-1,4-naphtha-quinones using chiral metal complexes or organocatalysts such as thioureas or squaramides. Nevertheless, there are still some drawbacks in these procedures, such as high catalyst loading, low temperature and long reaction time for high enantioselectivity.

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#Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectrum of products. see DOI: 10.1039/b000000x/

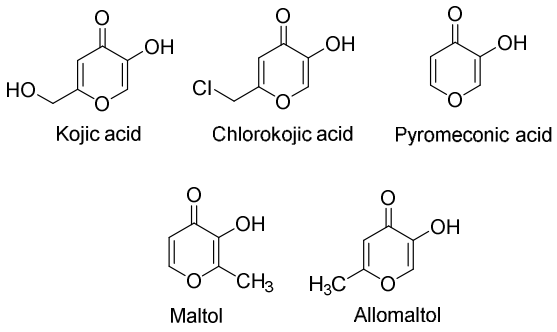


Figure 1. Kojic acid and its derivatives

Therefore, still there is a demand for efficient catalytic systems in exploring β,γ-unsaturated α-ketoesters as Michael acceptors. Recently, we have successfully demonstrated a novel bifunctional rosin-indane amine thiourea catalyzed asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone and 1,3-dicarbonyl compounds to *β*-nitroalkenes to produce the chiral molecules in good yields with excellent enantioselectivity.[21] Inspired by the unique catalytic performance of rosin-indane amine thiourea organocatalysis[22] for synthesizing chiral molecules, we attempted a novel asymmetric cascade reaction of allomaltol with β,γ-unsaturated α-ketoesters to produce the chiral tetrahydro pyrano[3,2-*b*]pyran scaffolds.

To evaluate the efficacy of thiourea catalysts, we performed the conjugate addition of 5-hydroxy-2-methyl-4*H*-pyran-4-one to (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate using a series of bifunctional thiourea and squaramide catalysts bearing different chiral diamines I–IX (Figure 2). Allomaltol was prepared from

the commercially available kojic acid in two-steps according to the procedure reported in literature.[23] In a model reaction, 5-hydroxy-2-methyl-4*H*-pyran-4-one was treated with (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate in the presence of 10 mol% of catalyst in DCM at 25 ºC (Table 1).

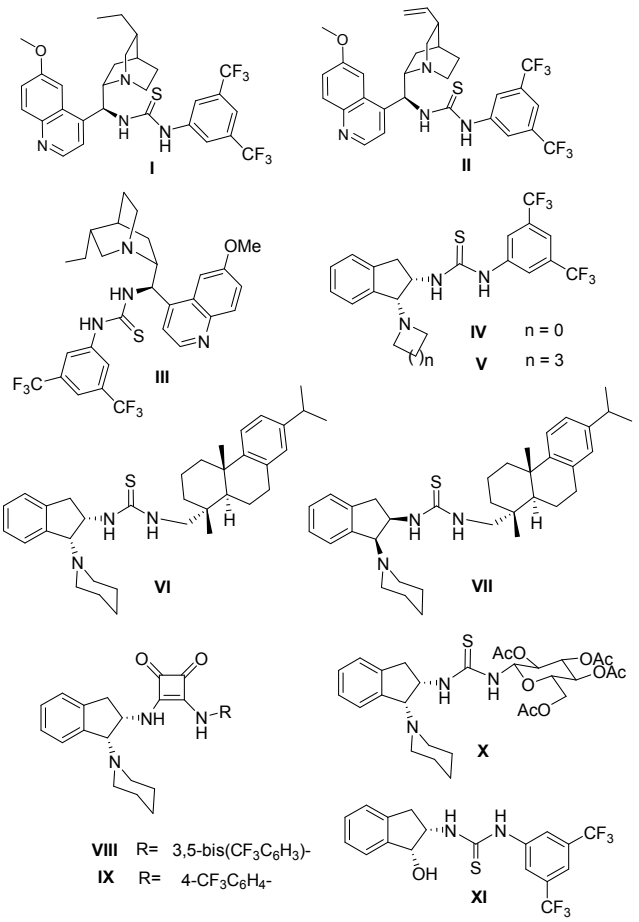
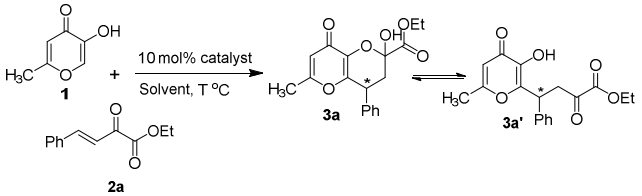


Figure 2. Bifunctional thiourea catalysts

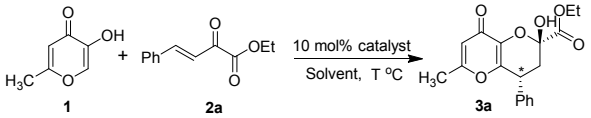
The corresponding Michael adduct was found to exist in a rapid equilibrium between the cyclic hemiketal **3a** and acyclic Michael adduct **3a'** in a ratio of 1.5:1 as shown in scheme 1 revealed by ^{1}H and ^{13}C NMR spectra.[24]



Scheme 1. Equilibrium of the product **3a** and **3a'**

As shown in Table **1,** the 9-*epi*-dihydroquinine-derived thiourea catalyst **I** afforded the desired Michael adduct reasonably in good yield and enantioselectivity (87% ee, Table 1, entry a). Using quinine-derived catalyst **II,** there was a drop in enantioselectivity (82% ee, Table 1, entry b) compared to catalyst **I**. Moreover, a slight decrease in enantioselectivity with an opposite sense of asymmetric induction was observed using psuedodiastereomeric dihdroquininidine-derived thiourea **III** catalyst (-80% ee, Table 1, entry c). By using indane-thiourea catalysts **IV** and **V**[25], the desired product was obtained with 78% and 88% ee respectively (Table 1, entries d and e). Gratifyingly, the rosin-indane amine thiourea catalyst **VI** shows a remarkable catalytic effect in this reaction affording the desired Michael adduct in 95% yield with 90% ee (Table 1, entry f). However, a significant decrease in enantioselectivity was observed with catalyst **X** derived from (1*R*,2*R*)-amino-1,2-indanol bearing a sugar moiety (81% ee, Table 1, entry j). Similarly, indane-derived squaramides **VII** and **IX** bearing mono- or *bis*-trifluoromethyl groups also showed a detrimental effect in terms of enantioselectivity (77% ee and 71% ee, Table 1, entries h and i). Furthermore, a poor enantioselectivity was observed even with aminoindanol based thiourea catalyst **XI** (36% ee, Table 1, entry k).

Table 1. Screening of catalysts in the formation of **3a**[a]



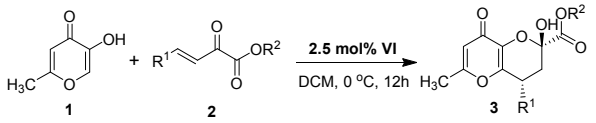
Entry	Catalyst	Solvent	T °C	Time (h)	Yield (%)[b]	ee (%)[c]
a	I	CH_2Cl_2	25	4	96	87
b	II	CH_2Cl_2	25	6	93	82
c	III	CH_2Cl_2	25	8	96	-80
d	IV	CH_2Cl_2	25	5	95	78
e	V	CH_2Cl_2	25	5	94	88
f	VI	CH_2Cl_2	25	6	95	90
g	VII	CH_2Cl_2	25	6	94	-83
h	VIII	CH_2Cl_2	25	12	93	77
i	IX	CH_2Cl_2	25	12	96	71
j	X	CH_2Cl_2	25	6	92	81
k	XI	CH_2Cl_2	25	15	68	36
l	VI	CH_2Cl_2	0	12	96	97
m	**VI**	**CH_2Cl_2**	**0**	**12**	**96**	**97[d]**
n	V	CH_2Cl_2	0	12	97	92[d]
o	VI	CH_2Cl_2	-20	24	90	75
p	VI	$PhCH_3$	25	7	92	73
q	VI	DCE	25	7	91	76
r	VI	*o*-xylene	25	7	88	45
s	VI	CH_3CN	25	7	84	64
t	VI	*i*-PrOH	25	7	76	37

[a]Unless noted the reaction was carried out with 1 (0.2 mmol), 2a (0.22 mmol) in the presence of 10 mol% organocatalyst.
[b]Isolated yields after column chromatography.
[c] Determined by chiral HPLC.
[d]2.5 mol% catalyst used.

After several experiments, the catalyst **VI** was found to be optimal for this reaction in terms of enantioselectivity. With the best catalyst in hand, we next focused our attention towards the screening of different solvents, catalyst loading and effect of temperature. Among various solvents tested, high conversions and good enantioselectivity were achieved in dichloromethane (Table 1, entry f), whereas moderate enantioselectivity was observed in non-polar solvents like toluene and *o*-xylene (Table 1, entries p and r). Polar solvents like acetonitrile and *i*PrOH gave poor enantioslectivity due to their interference in H-bonding

catalysis (64% and 34% ee, Table 1, entries s and t). Furthermore, the reaction temperature was found to have a significant influence on the enantioselectivity of this reaction. By lowering the temperature to, the enantio selectivity was remarkedly increased to 97% ee (Table 1, entry l) while a slight deterioration and longer time were observed when the reaction was carried out at -20 °C (87% ee, Table 1, entry o). Furthermore, retention of the enantioselectivity was observed with similar yield when the catalyst loading was decreased to 2.5 mol% at 0 °C (97% ee, Table 1, entry m). The superiorty of catalyst **VI** over **V** was further confirmed by performing the model reaction using 2.5 mol% of **V** at 0 °C. However, the desired Michael adduct was obtained with 92% ee with catalyst **V**, which is lower compared to 97% ee that was obtained from catalyst **VI** (Table 1, entries m and n). These results clearly indicate that **VI** is the better catalyst in term of enantioselectivity than catalyst **V** (entries m and n, Table 1). Thus, the best optimal reaction conditions for this Michael addition were determined to be 0.2 mmol of 5-hydroxy-2-methyl-4*H*-pyran-4-one (**1**), 0.22 mmol of (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate (**2a**) with 2.5 mol% of catalyst **VI** in 2 mL DCM at 0 °C for 12 h.

Table 2. Asymmetric Michael/hemiketalization reaction using thiourea catalyst VI[a]

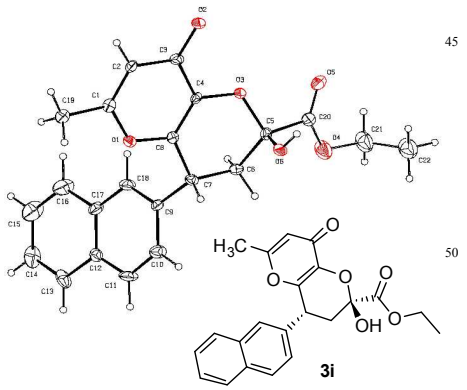


1 2 3

Entry	R^1	R^2	Product	Yield (%)[b]	ee (%)[c]	Config.
a	C_6H_5	Et	**3a**	93	97	*R*
b	4-BrC_6H_4	Et	**3b**	95	96	*R*
c	4-ClC_6H_4	Et	**3c**	94	95	*R*
d	4-FC_6H_4	Et	**3d**	95	94	*R*
e	4-MeC_6H_4	Et	**3e**	95	95	*R*
f	3-ClC_6H_4	Et	**3f**	93	86	*R*
g	3-FC_6H_4	Et	**3g**	91	96	*R*
h	2,4-$Cl_2C_6H_3$	Et	**3h**	92	95	*R*
i	2-Napthyl	Et	**3i**	94	>99	*R*
j	2-Thienyl	Et	**3j**	96	93	*R*
k	4-MeOC_6H_4	Me	**3k**	90	90	*R*
l	2-Furyl	Me	**3l**	90	>99	*R*
m	C_6H_5	Me	**3m**	95	99	*R*
n	C_6H_5	*i*Pr	**3n**	91	88	*R*
o	C_6H_5	*t*Bu	**3o**	88	90	*R*

[a]Reaction was carried out with 1 (0.2 mmol), 2a (0.22 mmol) in 2 mL of DCM.
[b]Isolated yields after column chromatography.[c] Determined by chiral HPLC.

With a set of optimized reaction conditions in hand, we then investigated the scope of this asymmetric Michael reaction with a range of β,γ-unsaturated α-ketoesters. The results are summarized in Table 2. In general, the substituents present on aromatic ring of the β,γ-unsaturated α-ketoesters are well tolerated under the reaction conditions (Table 2, entries a-o). As shown in Table 2, the desired (4*R*)-ethyl 4-(phenyl)-2-hydroxy-6-methyl-8-oxo-2,3,4,8-tetrahydropyrano[3,2-*b*]pyran-2-carboxylate derivatives (**3a-o)** were obtained in 88-95% yields with 86 to > 99% ee (Table 2, entries a-o). However, the electronic properties and position of the substituent on aromatic ring of the β,γ-unsaturated α-ketoesters didnot show significant influence on the outcome of the reaction. Notably, disubstituted aromatic substrates, naphthalen-2-yl and heteroaromatic alkenes also participated well to give the corresponding products in excellent yields and enantioselectivity (95% ee, >99% ee and 93% ee, Table 2, entries h, i, j and l). The crystal structures of **3i** and **5c** were elucidated by single crystal X-ray diffraction (Figs. 2). The absolute configuration of the **5c** was confirmed by unambiguous refinement of the absolute structure parameter[26].



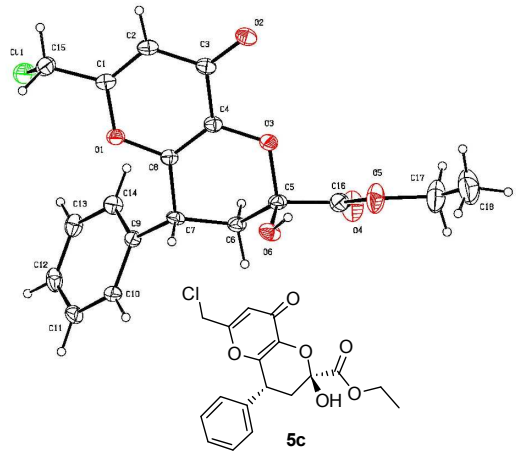
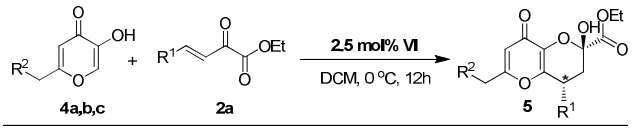


Figure 2. A view of **3i** and **5c,** showing the atom-labelling scheme

In figure 2, displacement ellipsoids are drawn at the 30% probability level and H atoms are represented by circles of arbitrary radii. Minor disordered components (O4'/O5'/C21'/C22') of **3i** have been omitted for clarity.

Encouraged by the above results, we extended this process to different kojic acid derivatives. In general, the reaction proceeded smoothly with TBS protected kojic acid **(4a)**, chloro-kojic acid **(4b)** and thio-kojic acid **(4c)** to afford the Michael adducts **(5a-5d)** in good yields (93−95%) and excellent enantioselectivity (92-95%) (entries 1 and 2, Table 3).

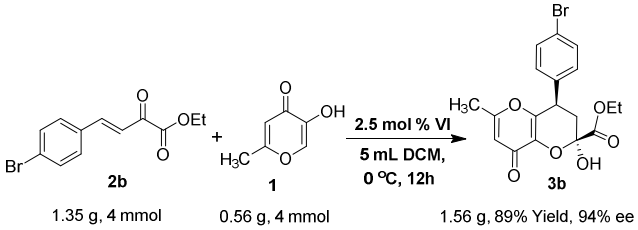
Table 3. Asymmetric Michae/hemiketalizationl addtion of kojic acid derivatives (**4a**,**b,c**)[a]



Entry	R^1	R^2	Product	Yield (%)(b)	ee (%)(c)
a	C_6H_5	OTBS	**5a**	93	92(*R*)
b	4-BrC_6H_4	OTBS	**5b**	95	94(*R*)
c	C_6H_5	Cl	**5c**	94	95(*R*)
d	C_6H_5	4-ClC_6H_4S	**5d**	95	95(*R*)

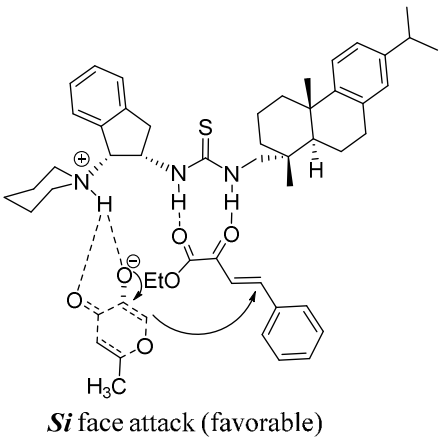
[a]Reaction was carried out with 4 (0.2 mmol), 2a (0.22 mmol) in the presence of 2.5 mol% organocatalyst.
[b]Isolated yields.
[c]Determined by chiral HPLC.

In order to show its practicality, the reaction was performed in gram quantities (Scheme 2). The desired Michael adduct **3b** was still obtained in excellent yield and enantioselectivity (1.67 g, 89% yield, 94% ee) using 2.5 mol% of the organocatalyst VI (Scheme 2)



Scheme 2. Asymmertic Michael/hemiketalization reaction in gram scale

On the basis of previous mechanistic aspects, we imagined that a ternary complex of thiourea catalyst **VI**, 5-hydroxy-2-methyl-4*H*-pyran-4one and (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate is invoved in the transition state. In the plausible transition state, as shown in Figure 3, the thiourea moiety of the catalyst IV activates the (*E*)-ethyl-2-oxo-4-phenylbut-3-enoate (**2a**) through hydrogen bonding, while tertiary amine activates the 5-hydroxy-2-methyl-4*H*-pyran-4one **(1)**. With these synergistic interactions, the nucleophile attacks from the *Si* face leading to the formation (*R*)-enantiomer as a major stereoisomer.



Si face attack (favorable)

Figure 3. A ternary complex

Conclusion

In conclusion, we have successfully demonstrated a rosin-indane amine thiourea catalyzed first asymmetric Michael addition of 5-hydroxy-2-methyl-4*H*-pyran-4one to β,γ-unsaturated α-keto esters. This asymmetric cascade reaction provides the Michael adducts in high yields (upto 98%) and excellent enantiomeric excess (upto >99% ee) under mild conditions with lower catalyst loading (2.5 mol%). Further investigation of the application of this organocatalyst is in progress in our group.

Experimental

General Remarks. All the solvents were purchased from commercial source and dried prior to use. All the enantioselective Michael reactions were performed in an oven-dried Schlenk flask under an inert atmosphere of argon. All products were purified by column chromatography on silica gel 60-120 mesh using a mixture of ethyl acetate-hexane as eluents. Progress of the reaction was monitored by Thin Layer Chromatography. ^{1}H NMR spectra were recorded in $CDCl_3$ using 300 MHz or 500 MHz spectrometers. ^{13}C NMR spectra were recorded in $CDCl_3$ using 75 MHz and 125 MHz NMR spectrometers. The chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. The coupling constants (J) are quoted in Hertz (Hz). Mass spectra were recorded on mass spectrometer by Electrospray ionization (ESI) technique. HPLC analysis was carried out in a Shimadzu LC-20 using chiral columns. A mixture of hexane-isopropyl alcohol was used as eluent. Optical rotations of the products were recorded on Digipol-781 M6U Polarimeter.

Catalyst **I** was directly used from Sigma Aldrich. Catalysts **II** and **III** were prepared according to the procedures reported in literature.[27] Catalysts **IV**, **V** and **XI** were prepared according to the procedures reported in literature.[25]

General procedure for preparing thiourea catalysts VI and VII.

To a stirred solution of chiral aminoindane (2 mmol) in dichloromethane (8 mL) was added a solution of dehydroabiethyl isothiocyanate (2.4 mmol) in dichloromethane (12 mL) dropwise under nitrogen atmosphere. After completion, the resulting mixture was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel (Hexane/EtOAc = 1:1) to give the thiourea catalyst as a white solid.

Spectral data for ligand VI 1-(((1*R*,4a*S*,10a*R*)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)-3-(1-(piperidin-1-yl)-2,3-dihydro-1*H*-inden-2-yl)thiourea: White solid, yield 85%, m.p. = 132-134 ^{0}C, $[\alpha]_D^{28}$ = -86.9 (*c* = 0.5, in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 3H), 1.15-1.27 (m, 9H), 1.29-1.50 (m, 4H), 1.53-1.89 (m, 9H), 2.33 (d, *J* = 13.0 Hz, 1H) 2.45-2.61 (m, 4H), 2.77-3.01 (m, 4H), 3.01- 3.21 (m, 1H), 3.50 (brs, 1H, NH), 6..33 (brs, 1H, NH), 6.92 (s, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 7.16-7.30 (m, 5H), 7.38 (d, *J* = 6.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 18.4, 19.3, 23.9, 24.0, 25.2, 30.0, 33.4, 37.4, 38.2, 38.4, 50.7, 73.2, 123.7, 124.3, 125.0, 126.8, 127.4, 129.1, 134.8, 145.6, 147.1, 182.9. IR (KBr): υ 3273, 2928, 2857, 1545, 1453, 1376, 1269, 1114, 886, 752 cm^{-1}; MS (ESI) *m/z* 544 $[M+H]^+$; HRMS (ESI): Exact mass calcd for $C_{35}H_{50}N_3S$ 544.37200. Found: 544.37236

Spectral data for ligand VII Off White solid, yield 78%, m.p = 128-130 ^{0}C, $[\alpha]_D^{28}$ = +84.04 (*c* = 0.5, in $CHCl_3$). MS (ESI) *m/z* 544 $[M+H]^+$; HRMS (ESI): Exact mass calcd for $C_{35}H_{50}N_3S$ 544.37200. Found: 544.37232.

General procedure for the preparation of thiourea catalyst X.

To a stirred solution of chiral aminoindane (4 mmol) in dichloromethane (10 mL) was added a solution of glycosyl isothiocyanate (4.4 mmol) in dichloromethane (15 mL) dropwise manner under nitrogen atmosphere. The resulting mixture was stirred at room temperature until total consumption of the isothiocyanate (monitored by TLC). After removal of the solvent, the residue was purified through column chromatography on silica gel (EtOAc/MeOH = 85/15) to give the thiourea catalyst as a off-white solid.

Spectral data for ligand X Off White solid, yield 86%, m.p. = 101-103 ^{0}C, $[\alpha]_D^{28}$ = -40.8 (*c* = 0.25, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53-1.90 (m, 6H), 2.01-2.11 (m, 12H), 2.56-2.75 (s, 4H), 2.93 (dd, *J* = 8.9, 15.9 Hz, 1H), 3.20 (dd, *J* = 7.9, 15.9 Hz, 1H), 3.52 (q, *J* = 7.9, 15.9 Hz, 1H) 3.93 (d, *J* = 8.9 Hz, 1H), 4.14 (d, *J* = 10.9 Hz, 1H), 4.37 (dd, *J* = 3.9, 11.9 Hz, 1H), 5.00 (t, *J* = 4.9 Hz, 1H), 5.07-5.17 (m, 2H), 5.37-5.44 (m, 1H), 6.10 (t, *J* = 8.9 Hz, 1H), 6.53 (d, *J* = 4.9 Hz, 1H), 7.20-7.34 (m, 4H), 10.48 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.6, 20.7, 24.2, 25.8, 26.3, 50.6, 61.7, 62.4, 68.2, 71.7, 72.9, 73.9, 74.6, 84.8, 123.7, 125.4, 127.5, 129.1, 138.0, 141.0, 169.6, 169.8, 170.5. IR (KBr): υ 3354, 2937, 1752, 1541, 1373, 1373, 1225, 1038, 909, 752 cm^{-1}; MS (ESI) *m/z* 606 $[M+H]^+$; HRMS (ESI): Exact mass calcd for $C_{29}H_{40}O_9N_3S$ 606.24798. Found: 606.24919.

General procedure for the preparation of squaramide catalysts VIII and IX.

To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (2.0 g, 14.1 mmol) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline (15.5 mmol, 1.1 equiv) or 4-trifluoromethylaniline (15.0 mmol) at 25 ˚C. The mixture was stirred at 25 ˚C for 3 days. The reaction mixture was filtered and washed with MeOH. The resulting yellow solids were dried in vacuo to give the mono-aminoaryl squaramide in good yields. A solution of (1*S*,2*S*)- aminoindane (2.0 mmol) in 10 mL CH_2Cl_2 was added to the mono-aminoaryl squaramide (2.0 mmol). The resulting mixture was stirred at room temperature until total consumption of precursors (monitored by TLC). The crude products **VII** or **IX** were obtained as white solids after filtration. Removal of the solvent followed by purification through column chromatography on silica gel (EtOAc/MeOH = 85/15) gave the thiourea catalysts **VII** or **IX** as off-white solids.

Spectral data for ligand VIII White solid, yield 74%, m.p. = 290-292 ^{0}C, $[\alpha]_D^{28}$ = -73.5 (*c* = 0.5, in $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-D_6): δ 1.40-1.76 (m, 6H), 2.56-2.80 (m, 4H), 3.43-3.28 (m, 3H), 5.83 (brs, 1H), 7.37-7.08 (m, 4H), 7.41 (s, 1H), 8. 16-7.84 (m, 2H), 8.04 (m, 3H), 9.86 (brs, NH, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.2, 24.9, 30.3, 50.4, 59.2, 74.1, 113.7, 116.8, 122.9, 123.9, 125.0, 125.9, 127.4, 130.9, 131.3, 138.8, 139.8, 140.1, 161.7, 168.4, 179.4, 183.2; IR (KBr): υ 3257, 2939, 1793, 1686, 1606, 1560, 1442, 1379, 1279, 1177, 1133, 883, 745 cm^{-1}; MS (ESI) *m/z* 524 $[M+H]^+$; HRMS (ESI): Exact mass calcd for $C_{26}H_{24}F_6N_3O_2$ 524.17672. Found: 524.17600.

Spectral data for ligand IX White solid, yield 71%, m.p. = 270-272 ^{0}C, $[\alpha]_D^{28}$ = -71.2 (*c* = 0.5, in $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-D_6): δ 1.37-1.77 (m, 6H), 2.48-2.77 (m, 4H), 2.91-2.38 (m, 3H), 5.75-5.91 (m, 1H), 7.14-7.38 (m, 3H), 7.49-7.74 (m, 5H), 7.92 (d, *J* = 8.3 Hz, 1H), 9.51 (brs, NH, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.9, 24.6, 30.0, 50.0, 58.8, 73.8, 116.5, 122.7, 123.6, 125.0, 125.6, 127.0, 138.5, 139.7, 141.1, 161.9, 167.9, 178.9, 182.9; IR (KBr): υ 3167, 2933, 1795, 1682, 1613 1554, 1446, 1323, 1118, 1015, 840, 748, 671 cm^{-1}; MS (ESI) *m/z* 456 $[M+H]^+$; HRMS (ESI): Exact mass calcd for $C_{25}H_{25}F_3N_3O_2$ 456.18934. Found: 456.18833.

General procedure for the enantioselective Michael /hemeketalization addition reaction

A mixture of organocatalyst IV(2.5 mol %) and (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate (2a) (0.22 mmol) in dry DCM (1 mL) was stirred for 10 min at room temperature. The reaction mixture was cooled to 0 ^{o}C and then 5-hydroxy-2-methyl-4*H*-pyran-4-one 1 (0.2 mmol) was added. The resulting mixture was stirred for 12 h at the same temperature. After completion of the reaction, the mixture was concentrated in vacuo and the resulting residue was purified by column chromatography on silica gel (hexane/acetone) to afford the corresponding optically active Michael adduct.

(4*R*)-Ethyl 2-hydroxy-6-methyl-8-oxo-4-phenyl-2,3,4,8-tetrahydro pyrano[3,2-*b*]pyran-2-carboxylate (3a). Brown solid; m.p. 156-158 °C; $[\alpha]_D^{27}$ = -85.4 (c = 0.5, $CHCl_3$); Yield: 93%. The product was found to exist in rapid equilibrium with its acyclic form and hemiketal **3a** form in solution. The equilibrium is very rapid and therefore one pair of enantiomers are observed during HPLC analysis. The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 0.80 mL/min, 254 nm; t_{minor} = 31.1 min, t_{major} = 38.2 min (97% **ee**); **^{1}H-**NMR (300 MHz, $CDCl_3$): δ 7.41-7.30 (m, 4.2H), 7.27-7.20 (m,1.7H), 6.19 (d, *J* = 8.2 Hz, 1H), 5.18 (brs, 0.5H) 4.78 (dd, *J* = 6.4, 8.9 Hz, 0.5H), 4.36-4.25 (m, 2.3H), 3.82 (dd, *J* = 8.9, 18.6 Hz, 0.5H), 3.53 (dd, *J* = 6.4,18.8 Hz, 0.5H), 2.49 (t, *J* = 13.6 Hz, 0.7H), 2.40 (dd, *J* = 6.7, 13.6 Hz, 0.9H), 2.33-2.28 (m, 2.5H), 1.37-1.30(m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 191.3, 173.9, 173.2, 168.2, 165.4, 164.2, 160.4, 150.5, 149.1, 140.7, 139.3, 139.1, 138.5, 128.8, 128.0, 128.1, 127.6, 127.4, 113.4, 110.4, 94.0, 62.9, 62.6, 41.7, 39.6, 37.9, 37.4, 19.9, 19.4, 13.8; IR (KBr): 3070, 2932, 2851, 1751, 1652, 1607, 1447, 1384, 1227, 1151, 1021, 949, 982, 701 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}O_6$: 331.11761, found: 331.11722.

(4*R*)-Ethyl 4-(4-Bromophenyl)-2-hydroxy-6-methyl-8-oxo-2,3,4,8-tetrahydropyrano[3,2-*b*]pyran-2-carboxylate (3b): Brown solid; m.p. 146-148 °C; Yield: 95%; $[\alpha]_D^{27}$ = -83.2 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 21.2 min, t_{major}= 27.3 min (96% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.9 Hz, 1.2H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1.4H), 6.18 (d, *J* = 9.0 Hz, 1H) , 4.99 (brs, 0.4H), 4.74 (t, *J* = 7.2 Hz, 0.5H), 4.37-4.25 (m, 3H), 3.77 (dd, *J* = 8.6, 18.8 Hz, 0.5H), 3.52 (dd, *J* = 6.4, 18.8 Hz, 0.5H), 2.45 (t, *J* = 13.2 Hz, 0.6H), 2.37 (dd, *J* = 6.8, 13.9 Hz, 0.7H), 2.28 (s, 1.4H), 2.10 (s, 2.5H), 1.39-1.28 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): 191.1, 173.2, 168.1, 164.3, 160.4, 149.3, 148.8, 139.4, 138.1, 137.7, 137.6, 131.9, 129.8, 121.4, 113.5, 110.5, 94.0, 63.0, 41.9, 39.0, 37.5, 37.2, 19.5, 13.8; IR (KBr): 3072, 2982, 2929, 1652, 1608, 1451, 1347, 1226, 1152, 1019, 981, 821, 738 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}O_6BrNa$: 431.01007, found: 431.00930.

(4*R*)-Ethyl 4-(4-chlorophenyl)-2-hydroxy-6-methyl-8-oxo-2,3, 4,8-tetrahydro pyrano[3,2-*b*]pyran-2-carboxylate (3c). Off-white solid; m.p. 120-122 °C; Yield: 94%; $[\alpha]_D^{27}$ = -79.1 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 20.1 min, t_{major} = 26.1 min (95% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.39-7.27 (m, 0.6H), 7.24-7.18 (m, 1.1H), 7.11-6.97 (m, 2H), 6.18 (s, 1H), 5.10 (brs, 0.19H), 4.77 (t, *J* = 7.2 Hz, 0.3H), 4.39-4.22 (m, 2.7H), 3.77 (dd, *J* = 8.2, 16.9 Hz, 0.27H), 3.52 (dd, *J* = 6.4, 18.5 Hz, 0.39H), 2.46 (t, *J* = 13.3 Hz, 0.3H), 2.38 (dd, *J* = 6.6, 13.6 Hz, 0.27H), 2.28 (s, 1.3H), 2.09 (s, 3H), 1.38-1.29 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): 190.9, 173.9, 173.2,

168.1, 165.5, 164.4, 160.3, 149.3, 148.4, 140.5, 139.4, 137.8, 134.6, 130.1, 128., 127.8, 126.4, 126.0, 113.5, 110.5, 94.0, 63.0, 62.7, 41.5, 39.2, 37.7, 37.2, 29.6, 19.5, 13.8; IR (KBr): 3418, 3075, 1750, 1651, 1608, 1452, 1426, 1347, 1226, 1153, 1110, 1025, 981, 690 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{18}O_6Cl$: 365.07864, found: 365.07884.

(4*R*)-Ethyl 4-(4-fluorophenyl)-2-hydroxy-6-methyl-8-oxo-2,3,4,8-tetra hydropyrano[3,2-*b*]pyran-2-carboxylate (3d). Brown solid; m.p. 116-118 °C; Yield: 95%; $[\alpha]_D^{27}$ = -75.6(c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 18.6 min, t_{major} = 24.1 min (94% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.57-7.39 (m, 2H), 7.33-7.18 (m, 1H), 7.12 (d, *J* = 7.3 Hz, 1H), 6.27-6.14 (m, 1H), 5.29 (brs, 0.3H), 4.75 (t, *J* = 7.2 Hz, 0.3H), 4.41-4.18 (m, 2.4H), 3.78 (dd, *J* = 9.1, 18.7 Hz, 0.3H), 3.53 (dd, *J* = 9.1, 18.7 Hz, 0.3H), 2.51-2.34 (m, 0.6H), 2.28 (s, 1.3H), 2.10 (s, 2.5H), 1.40-1.19 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): 191.0, 173.2, 168.1, 165.4, 160.3, 149.3, 148.7, 139.3, 138.1, 137.5, 132.0, 129.8, 121.1, 113.5, 110.5, 94.0, 63.0, 62.8, 41.5, 39.1, 37.5, 37.2, 20.0, 19.5, 13.8; IR (KBr): 3517, 3278, 2991, 2848, 2585, 1743, 1650, 1619, 1511, 1451, 1294, 1213, 1165, 1026, 853, 699 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{18}O_6F$: 349.10819, found: 349.10782.

(4*R*)-Ethyl 2-hydroxy-6-methyl-8-oxo-4-(p-tolyl)-2,3,4,8-tetrahydro pyrano[3,2-*b*]pyran-2-carboxylate (3e). Off-white solid; m.p. 152-154 °C; Yield: 95%; $[\alpha]_D^{27}$ = -75.4 (c = 0.75, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 15.8 min, t_{major} = 20.2 min (95% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J* = 7.5 Hz, 0.7H) , 7.18 (d, *J* = 7.5 Hz, 1.3H), 7.16-7.10 (m, 2.4H), 6.17 (s, 1.3H), 4.98 (brs, 0.4H), 4.74 (t, *J* = 7.0 Hz, 0.4H), 4.37-4.23 (m, 3.2H), 3,79 (dd, *J* = 9.0, 18.6 Hz, 1.3H), 3.50 (dd, *J* = 6.4,18.6 Hz, 0.4H), 2.47 (t, *J* =13.5 Hz, 0.7H), 2.40-2.22 (m, 7.3H), 1.37-1.29 (m, 3.3H); ^{13}C-NMR (75 MHz, $CDCl_3$): 191.3, 173.9, 173.2, 168.2, 165.3, 164.1, 160.4, 150.2, 149.4, 140.6, 139.2, 137.1, 136.0, 135.4, 129.4, 127.5, 113.3, 110.4, 94.1, 62.8, 62.5, 41.7, 39.1, 37.5, 20.9, 19.9, 19.4, 13.8; IR (KBr): 3251, 2929, 2855, 1652, 1630, 1589, 1553, 1455, 1378, 1253, 1215, 1081, 843, 782 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}O_6$: 345.13326, found: 345.13298.

(4*R*)-Ethyl 4-(3-chlorophenyl)-2-hydroxy-6-methyl-8-oxo-2,3,4,8-tetra hydropyrano[3,2-*b*]pyran-2-carboxylate (3f). White solid; m.p. 118-120 °C; Yield: 93%; $[\alpha]_D^{27}$ = -80.9 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 15.8 min, t_{major} = 20.7 min (86% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38-7.19 (m, 3H),7.12 (s,1H), 6.18 (s, 1H), 5.47 (brs, 0.3H), 4.75 (t, *J* = 7.4 Hz, 0.3H), 4.40-4.21 (m, 3H), 3.80 (dd, *J* = 8.7, 18.3 Hz, 0.3H), 3.52 (dd, *J* = 6.5, 18.3 Hz, 0.3H), 2.48-2.38 (m, 1H), 2.32-2.24 (m, 1.3H), 2.17(s, 3H), 1.39-1.28 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$+ DMSO-d_6): 191.0, 173.9, 173.2, 168.1, 165.5, 164.9, 149.3, 148.4, 140.5, 139.4, 134.6, 130.1, 128.3, 127.8, 126.4, 126.0, 113.5, 110.5, 94.0, 63.0, 62.7, 41.4, 39.2, 37.7, 37.2, 29.6, 20.0, 19.5, 13.8; IR(KBr): 3424, 3077, 1755, 1654, 1609, 1453, 1426, 1347, 1225, 1153, 1111, 1020, 981, 690 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{18}O_6Cl$: 365.07864, found: 365.07879.

(4*R*)-Ethyl 4-(3-fluorophenyl)-2-hydroxy-6-methyl-8-oxo-2,3,4,8-tetra hydropyrano[3,2-*b*]pyran-2-carboxylate(3g): Brown solid; m.p. 116-118 °C; Yield: 91%; $[\alpha]_D^{27}$ = -82.1 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 14.3 min, t_{major} = 18.3 min (96% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.39-7.27 (m, 0.5H), 7.14 (d, *J* = 7.5 Hz 1H), 7.09-7.00 (m, 2H), 7.00-6.92 (m, 1.3H), 6.24-6.16 (m, 1.4H), 5.12 (brs, 0.3 H), 4.78 (t, *J* = 7.5 Hz, 0.5H), 4.38-4.23 (m, 2.6H), 3.79 (dd, *J* = 8.5, 18.6 Hz, 0.5H), 3.53 (dd, *J* = 6.4, 18.6 Hz, 0.6H), 2.47 (t, *J* = 13.6 Hz, 0.5H), 2.40 (dd, *J* = 6.6, 13.6 Hz, 0.6H), 2.29 (s, 1.5H), 2.10 (s, 2.8H), 1.38-1.28 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): 191.0, 173.9, 173.2, 168.0, 165.5, 164.3, 163.9, 161.9, 149.3, 148.5, 141.0, 139.4, 130.5, 123.9, 123.5, 115.2, 115.0, 114.7, 114.5, 113.5, 110.5, 94.0, 63.1, 62.7, 41.5, 39.2, 37.8, 37.1, 20.0, 19.5, 13.8; IR (KBr): 3256, 2955, 2932, 2858, 1653, 1630, 1590, 1552, 1451, 1378, 1251, 1085, 841, 781, 704 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{18}O_6F$: 349.10819 found: 349.10826.

(4*R*)-Ethyl 4-(2,4-dichlorophenyl)-2-hydroxy-6-methyl-8-oxo-2, 3,4,8-tetrahydropyrano[3,2-*b*]pyran-2-carboxylate (3h): Brown solid; m.p. 128-130 °C; Yield: 92%; $[\alpha]_D^{27}$ = -58.6 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a DaicelChiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 13.8 min, t_{major} = 28.1 min (95% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.41-7.18 (m, 3.7H),7.14 (s,0.5H), 6.18 (s, 1H), 5.19 (brs, 0.5H), 4.74 (t, *J* = 7.4 Hz, 0.4H), 4.40-4.17 (m, 2.8H), 3.81 (dd, *J* = 8.5, 18.7 Hz, 0.4H), 3.52 (dd, *J* = 5.6, 18.3 Hz, 0.3H), 2.54-2.33 (m, 0.9H), 2.11(s, 3H), 1.34 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): 190.9, 173.9, 173.2, 168.1, 165.5, 164.4, 160.3, 149.3, 148.4, 140.5, 139.4, 137.8, 134.6, 130.1, 128.3, 127.8, 126.4, 126.0, 113.5, 110.5, 94.0, 63.0, 62.7, 41.5, 39.2, 37.7, 37.2, 29.6, 19.5, 13.8;)IR (KBr): 3071, 2980, 2929, 1651, 1608, 1449, 1345, 1226, 1152, 1019, 980, 821, 735 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{17}O_6Cl_2$: 399.03967, found: 399.03959.

(4*R*)-Ethyl 2-hydroxy-6-methyl-4-(naphthalen-2-yl)-8-oxo-2,3,4,8-tetrahydropyrano[3,2-*b*]pyran-2-carboxylate (3i). Brown solid; m.p. 122-124 °C; Yield: 94%; $[\alpha]_D^{27}$ = -86.2 (c = 0.6, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 18.0 min, t_{major} = 25.7 min (>99% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.90-7.78 (m, 3H), 7.75 (s, 1H), 7.58-7.44 (m, 3H), 7.30 (dd, *J* = 1.3, 8.5 Hz, 1H), 6.20 (s, 1H), 5.13 (brs, 0.3H), 4.95 (t, *J* = 7.9 Hz, 0.4H), 4.50 (dd, *J* = 6.6, 12.5 Hz, 1H), 4.38-4.24 (m, 2H), 3.92 (dd, *J* = 8.9, 18.7 Hz, 0.5H), 3.64 (dd, *J* = 6.4, 18.7 Hz, 0.4H), 2.60 (t, *J* = 13.4Hz, 0.8H), 2.45 (dd, *J* = 6.2, 13.9 Hz, 0.7H), 2.28 (s, 3H), 1.38-1.28 (m, 3.4H); ^{13}C-NMR (125 MHz, $CDCl_3$): 191.3, 173.9, 173.3, 168.3, 165.5, 164.3, 160.5, 150.1, 149.0, 140.4, 139.4, 136.5, 135.9, 133.4, 132.7, 128.7, 127.7, 127.6, 127.5, 126.4, 126.3, 126.1, 125.6, 125.5, 110.4, 94.1, 63.1, 62.7, 41.7, 39.9, 38.2, 37.3, 29.6, 20.0, 19.5, 13.9; IR(KBr): 3077, 1757, 1653, 1608, 1508, 1452, 1341, 1225, 1201, 1144, 1022, 984, 820, 744, 616 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{21}O_6$: 381.13326, found: 381.13318.

(4*R*)-Ethyl 2-hydroxy-6-methyl-8-oxo-4-(thiophen-2-yl)-2,3,4,8-tetra hydropyrano[3,2-*b*]pyran-2-carboxylate (3j). Brown solid; m.p. 128-130 °C; Yield: 96%; $[\alpha]_D^{27}$ = -78.1 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-

hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 17.6 min, t_{major} = 21.0 min (93% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.33-7.25 (m, 1.3H), 7.21(d, *J* = 7.6 Hz, 0.4H), 7.09-6.99 (m, 2H), 6.95 (d, *J* = 3.8 Hz, 0.3H), 6.18 (d, *J* = 6.8 Hz, 1.3H), 5.12 (t, *J* = 7.6 Hz, 0.5H), 4.92 (brs, 0.5H),4.66 (dd, *J* = 6.0, 12.1 Hz, 0.6H), 4.33 (q, *J* = 7.6 Hz, 2H), 3.77 (dd, *J* = 8.3, 18.9 Hz, 0.5H), 3.62 (dd, *J* = 6.8,18.9 Hz, 0.5H), 2.63 (t, *J* = 13.6 Hz, 0.5H), 2.49 (dd, *J* = 6.8, 13.6 Hz, 0.6H), 2.32 (s,1.5H), 2.16 (s, 3H),1.35 (t, *J* = 6.8 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): 190.7, 174.0, 173.2, 168.0, 165.5, 164.2, 160.3, 148.8, 148.0, 141.1, 140.4, 140.0, 138.5, 126.8, 126.4, 125.6, 124.9, 124.8, 113.5, 94.0, 63.1, 62.7, 42.8, 37.0, 34.7, 33.0, 20.0, 19.5, 13.9; IR (KBr): 3072, 2850, 1750, 1650, 1606, 1450, 1384, 1273, 1207, 1023, 981, 700, 617 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{17}O_6S$: 337.07404, found: 337.07374.

(4*R*)-Methyl 2-hydroxy-4-(4-methoxyphenyl)-6-methyl-8-oxo-2, 3,4,8-tetrahydropyrano[3,2-*b*]pyran-2-carboxylate (3k): Brown solid; m.p. 128-130 °C; Yield: 90%; $[\alpha]_D^{27}$ = -78.3 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 70:30, flow rate 1.00 mL/min, 254 nm; t_{minor} = 12.3 min, t_{major} = 16.1 min (90% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28 (d, *J* =8.3 Hz, 1.4H), 7.15 (d, *J* = 8.3 Hz, 1.3H), 6.94-6.82 (m, 2.4H), 6.18(s, 1.3H), 5.04 (brs, 0.2H), 4.73 (dd, *J* = 6.8, 8.3 Hz, 0.4H), 4.27 (dd, *J* = 6.8, 12.1 Hz, 0.5H), 3.92-3.76 (m, 6H), 3.51 (dd, *J* = 6.6, 18.5 Hz, 0.3H), 2.54-2.32 (m, 1H), 2.28 (s, 1.3H), 2.09 (s, 2.5H); ^{13}C-NMR (75 MHz, $CDCl_3$): 171.4, 167.6, 162.7, 157.5, 148.9, 137.8, 129.2, 127.9, 127.4, 113.0, 112.0, 93.3, 53.9, 51.5, 36.9, 35.8, 18.2; IR (KBr): 3070, 3001, 2932, 2838, 1752, 1651, 1607, 1512, 1456, 1350, 1258, 1170, 1111, 1029, 980, 829 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}O_4NNa$: 347.11280, found: 347.11126.

(4*R*)-Methyl 4-(furan-2-yl)-2-hydroxy-6-methyl-8-oxo-2,3,4,8-tetra hydropyrano[3,2-*b*]pyran-2-carboxylate (3l):Brown solid; m.p. 130-132 °C; Yield: 90%; $[\alpha]_D^{27}$ = -90.2 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{major} = 29.4 min (>99% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.45-7.30 (m, 1.2H), 6.34-6.27 (m, 2H), 6.25-6.11 (m, 1.4H), 5.22 (brs, 0.4H), 4.92 (t, *J* = 6.6 Hz, 0.4H), 4.51(dd, *J* = 6.1, 12.5 Hz, 0.5H), 3.92-3.84 (m, 4H), 3.66 (t, *J* = 6.5 Hz, 0.8H), 2.70 (t, *J* = 13.1 Hz, 0.7H), 2.39 (dd, *J* = 5.6, 13.3 Hz, 0.6H), 2.31-2.14 (m, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$+DMSO-d_6): 190.3, 172.9, 173.7, 172.9,168.4, 165.1, 163.8, 160.4, 150.0, 147.7, 136.7, 142.2, 141.8, 138.4, 128.6, 127.9, 113.2, 110.2, 110.1, 108.0, 94.2, 52.9, 33.4, 31.7, 19.7, 19.3; IR (KBr): 3075, 2951, 2927, 2842, 1752, 1653, 1606, 1452, 1345, 1279, 1207, 1159, 1027, 904, 879, 738 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{15}O_7$: 307.08123, found: 307.07984.

(4*R*)-Methyl 2-hydroxy-6-methyl-8-oxo-4-phenyl-2,3,4,8-tetra hydro pyrano[3,2-*b*]pyran-2-carboxylate (3m). Yellow solid; m.p. 150-152 °C; Yield: 95%; $[\alpha]_D^{27}$ = -57.4 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 21.9 min, t_{major} = 27.2 min (99% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.40-7.29 (m, 3H), 7.22(d, *J* = 7.1 Hz, 2H), 6.22 (s, 0.5H), 6.19 (s, 0.8H), 5.85 (brs, 0.5H), 4.79(dd, *J* = 6.6, 8.7 Hz, 0.4H), 4.34 (dd, *J* = 7.2, 11.7 Hz, 1H), 3.88-3.79 (m, 4H), 3,54 (dd, *J* = 6.4, 18.8 Hz, 0.4H), 2.51-2.38 (m, 2H), 2.29 (s, 1.3H), 2.17 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$): 171.4, 167.6, 162.7, 157.8, 148.9, 137.8, 129.2, 127.9, 127.4, 112.9, 112.0, 93.3, 53.9, 51.5, 36.9, 35.8, 18.2; IR (KBr): 3074, 2948, 2930, 2852, 1754, 1727, 1653, 1606, 1534, 1426, 1203, 1169, 1209, 1025, 948, 878, 701 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{17}O_6$: 317.10196, found: 317.10158.

(4*R*)-Isopropyl 2-hydroxy-6-methyl-8-oxo-4-phenyl-2,3,4,8-tetrahydr-opyrano[3,2-*b*]pyran-2-carboxylate (3n). Off-white solid; m.p. 136-138 °C; Yield: 81%; $[\alpha]_D^{27}$ = -78.2 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 11.7 min, t_{major} = 16.6 min (88% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.41-7.30 (m, 4.5H), 7.29-7.21(m, 2.4H), 6.18 (d, *J* = 9.6 Hz, 1.4H), 5.16-5.07 (m, 1H), 5.03 (brs, 0.1H), 4.78 (t, *J* = 7.3 Hz, 0.5H), 4.31(dd, *J* = 6.6, 12.4 Hz, 0.6H), 3.80 (dd, *J* = 9.0, 18.5 Hz, 0.6H), 3.51(dd, *J* = 6.3, 18.5Hz, 0.5H), 2.47 (t, *J* = 1.7 Hz, 0.7H), 2.36 (d, *J* = 6.6, 13.7 Hz, 0.6H), 2.33-2.24 (m, 2.7H), 1.36-1.26 (m, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$ + DMSO-d_6): 191.3, 172.6, 167.4, 164.3, 163.5, 159.5, 149.6, 140.5, 138.9, 138.4, 128.3, 128.2, 127.6 127.5, 127.2, 126.9, 112.9, 111.2, 110.3, 93.9, 70.4, 69.8, 41.2, 38.7, 37.6, 37.4, 21.0, 19.0; IR (KBr): 3083, 2984, 2935, 1745, 1654, 1615, 1448, 1351, 1289, 1235, 1205, 1163, 1099, 1026, 986, 851, 619 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}O_6$: 345.13326, found: 345.13293.

(4*R*)-*tert*-Butyl 2-hydroxy-6-methyl-8-oxo-4-phenyl-2,3,4,8-tetrahydro pyrano[3,2-*b*]pyran-2-carboxylate (3o): Brown solid; m.p. 108-110 °C; Yield: 88%; $[\alpha]_D^{27}$ = -56.2 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 9.3 min, t_{major} = 10.0 min (90% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42-7.18(m, 5H), 6.30 (s, 0.6H), 6.18 (d, *J* = 9.0 Hz, 1H),5.41 (brs, 0.5H), 4.79 (t, *J* = 6.6 Hz, 0.5H), 4.30 (dd, *J* = 7.4, 11.1 Hz, 0.9H), 3.75 (dd, *J* = 8.7, 18.3 Hz, 0.5H), 3.48 (dd, *J* = 6.4, 18.5 Hz, 0.4H), 2.47-2.34 (m, 1.6H), 2.29 (s, 3H), 1.50 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): 192.3, 174.3, 173.9, 173.3, 167.2, 166.4, 165.2, 164.0, 159.8, 150.0, 149.4, 145.2, 140.8, 139.5, 139.2, 138.8, 137.3, 128.8, 128.1, 127.6, 127.4, 111.3, 110.5, 94.1, 84.2, 41.5, 39.5, 38.1, 37.5, 29.5, 27.6, 19.9, 19.4; IR (KBr): 3081, 2923, 2852, 1756, 1652, 1609, 1493, 1447, 1363, 1252, 1205, 1149, 1111, 984, 840, 700 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{23}O_6$: 359.14891, found: 359.14756.

(4*R*)-Ethyl 6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-hydroxy -8-oxo-4-phenyl-2,3,4,8-tetrahydropyrano[3,2-*b*]pyran-2-carboxylate (5a). Brown solid; m.p. 140-142°C; Yield: 93%; $[\alpha]_D^{27}$ = -80.1 (c = 0.6, $CHCl_3$) .The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 0.08 mL/min, 254 nm; t_{minor} = 5.4 min, t_{major} = 6.8 min (92% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42-7.30 (m, 3.9H), 7.28 (d, *J* = 8.8 Hz, 0.3 H), 7.25 (dd, *J* = 6.6 Hz, 1.3H), 6.51-6.45 (m, 1H), 5.38 (brs, 0.4H), 4.82 (t, *J* = 6.6 Hz, 0.4H), 4.49 (s, 1H), 4.39-4.29 (m, 5H), 3.82 (dd, *J* = 8.8, 18.8 Hz, 0.4H), 3.55 (dd, *J* = 5.5, 17.7 Hz, 0.5H), 3.24 (t, *J* = 13.3 Hz, 0.5H), 2.43 (dd, *J* = 6.6, 13.3 Hz, 0.6H), 1.39-1.32 (m, 3H), 0.91 (m, 9H), 0.08 (m, 6.6H); ^{13}C-NMR (125 MHz, $CDCl_3$): 191.2, 174.0, 173.2, 168.1, 167.0, 165.9, 160.4, 149.7, 149.0, 141.2, 139.7, 139.7, 139.0, 138.4, 128.8, 128.1, 127.6, 127.5, 111.2, 108.2, 94.1, 62.8, 62.5, 61.3, 61.0, 41.7, 39.6, 38.0, 37.5, 25.5, 18.0, 13.8, -5.6, -5.8; IR (KBr): 3177, 2930, 2887, 2857, 1741, 1657, 1630, 1595, 1449, 1366, 1252, 1205, 1164, 1104, 1008, 838, 775,

701 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{33}O_7Si$: 461.19901, found: 461.19782.

(4*R*)-Ethyl4-(4-bromophenyl)-6-(((tert-butyldimethylsilyl)oxy)methyl)-2-hydroxy-8-oxo-2,3,4,8-tetrahydropyrano[3,2-*b*]pyran-2-carboxylate (5b). White solid; m.p. 148-150°C; Yield: 95%; $[\alpha]_D^{27}$ = -96.4 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 0.8 mL/min, 254 nm; t_{minor} = 9.3 min, t_{major} = 12.1 min (94% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42-7.27 (m, 3.9H), 7.13 (d, *J* = 7.6 Hz, 0.7 H), 7.01(d, *J* = 8.3, Hz, 2H), 6.35 (s, 1.1H), 5.21 (brs, 0.3H), 4.35 (s, 0.8H), 4.27-4.08 (m, 4.6H), 3.67 (dd, *J* = 8.3, 18.6 Hz, 0.6H), 3.42 (dd, *J* = 6.8, 18.9 Hz, 0.3H), 2.41-2.19 (m, 1.6H), 1.28-1.16 (m, 3H), 0.78 (m, 9H), 0.05 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): 191.1, 173.9, 173.2, 168.1, 166.0, 154.1, 148.9, 139.8, 137.4, 132.2, 132.0, 129.9, 129.4, 121.6, 111.4, 108.2, 93.9, 63.8, 62.7, 61.4, 61.1, 41.5, 39.2, 37.6, 37.2, 25.6, 18.1, 13.9, -5.5,-5.6; IR (KBr): 3177, 2930, 2887, 2857, 1741, 1657, 1630, 1595, 1449, 1366, 1252, 1205, 1164, 1104, 1008, 838, 775, 701 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{32}O_6BrSi$: 434.1993, found: 434.2000.

(4*R*)-Ethyl 6-(chloromethyl)-2-hydroxy-8-oxo-4-phenyl-2,3, 4, 8-tetrahydropyrano[3,2-*b*]pyran-2-carboxylate (5c): Brown solid; m.p. 102-104°C; Yield: 94%; $[\alpha]_D^{27}$ = -86.3 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 80:20, flow rate 0.8 mL/min, 254 nm; t_{minorr} = 16.2 min, t_{major} = 28.3 min (95% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42-7.31 (m, 3.7H), 7.29-7.22 (m, 1.8H), 6.46 (s, IH), 5.03 (brs, 0.5H), 4.83 (dd, *J* = 6.3, 9.2 Hz, 0.4H), 4.39-4.27 (m, 4H), 4.20-4.06 (m, 1.7H), 3.85 (dd, *J* = 9.2, 18.8 Hz, 0.5H), 3.54 (dd, *J* = 6.3, 18.9 Hz, 0.4H), 2.51 (t, *J* = 13.4Hz, 0.7H), 2.42 (dd, *J* = 6.6, 13.7 Hz, 0.7H), 1.37-1.30 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$+ DMSO-d_6): 172.0, 167.6, 160.0, 150.0, 139.4, 137.7, 128.2, 127.5, 126.9, 113.5, 94.1, 61.6, 40.2, 37.4, 37.3, 13.3 IR (KBr): 3250, 2958, 2931, 2855, 1652, 1630, 1590, 1554, 1458, 1375, 1254, 1220, 1083, 1011, 842, 782, 734, 682 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{18}O_6Cl$: 365.07864, found: 365.07837.

(4*R*)-Ethyl 6-(((4-chlorophenyl)thio)methyl)-2-hydroxy-8-oxo-4-phenyl-2,3,4,8-tetrahydropyrano[3,2-*b*]pyran-2-carboxylate (5d): Brown solid; m.p. 92-94°C; Yield: 95%; $[\alpha]_D^{27}$ = -76.7 (c = 0.5, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 254 nm; t_{minor} = 18.9 min, t_{major} = 23.7 min (95% ee); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.41-7.25 (m, 4H), 7.24-7.14 (m, 4h), 7.11 (d, *J* = 8.4 Hz, 1H), 6.21 (s, 0.6H), 6.13 (s, 0.4H), 4.75 (dd, *J* = 6.1, 9.3 Hz, 0.4H), 4.35-4.22 (m, 2.5H), 3.83-3.75 (m, 1.5H), 3.70-3.58 (m, 1H), 3.47 (dd, *J* = 6.1, 18.8 Hz, 0.4H), 2.47 (t, *J* = 13.4 Hz, 0.5H), 2.39 (dd, *J* = 6.7, 13.7 Hz, 0.5H), 1.37-1.27 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) 173.0, 163.1, 150.2, 140.3, 138.4, 132.4, 132.0, 129.2, 128.8, 127.8, 127.9, 127.5, 113.0, 62.7, 38.7, 36.7, 13.8; IR(KBr): 3412, 2985, 1746, 1647, 1475, 1446, 1293, 1227, 1199, 1096, 1008, 755 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}O_6ClS$: 473.08201, found: 473.08087**.**

X-ray Crystallography

Crystal data for 3i: $C_{22}H_{20}O_6$, *M* = 380.38, colorless block, 0.18 × 0.15 × 0.06 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 6.2121(16), *b* = 9.387(3), *c* = 32.186(9) Å, *V* = 1876.9(9) $Å^3$, *Z* = 4, D_c = 1.346 g/cm^3, F_{000} = 800, CCD Area Detector, MoKα radiation, λ = 0.71073 Å, *T* = 294(2)K, $2\theta_{max}$ = 50.0º, 17714 reflections collected, 1956 unique (R_{int} = 0.0705). Final *GooF* = 1.339, *R1* = 0.0955, *wR2* = 0.2149, *R* indices based on 1843 reflections with I>2σ(I) (refinement on F^2), 295 parameters, 94 restraints, μ = 0.098 mm^{-1}. CCDC 979348 contains supplementary Crystallographic data for the structure.

Crystal data for 5c: $C_{18}H_{17}ClO_6$, *M* = 364.77, colorless block, 0.16 × 0.15 × 0.06 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 7.9426(11), *b* = 8.8414(12), *c* = 24.229(3) Å, *V* = 1701.4(4) $Å^3$, *Z* = 4, D_c = 1.424 g/cm^3, F_{000} = 760, Bruker SMART APEX CCD area-detector, MoKα radiation, λ = 0.71073 Å, *T* = 294(2)K, $2\theta_{max}$ = 50.0º, 16379 reflections collected, 2999 unique (R_{int} = 0.0503). Final *GooF* = 1.102, *R1* = 0.0508, *wR2* = 0.1232, *R* indices based on 2573 reflections with I>2σ(I) (refinement on F^2), 231 parameters, 0 restraints, μ = 0.256 mm^{-1}. Absolute structure parameter = -0.07(10) (Flack & Bernardinelli, 2000). CCDC 1017996 contains supplementary Crystallographic data for the structure. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

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Supporting Information Available: (see footnote on the first page of this article): Additional characterization data and copies of the NMR spectra of the Michael adducts

Notes and references

1. (a) S. Briganti, E. Camera, M. Picardo, *Pigment Cell Res.* 2003, **16**, 101; (b) T. S. Chang, *Int. J. Mol. Sci.* 2009, **10**, 2440; (c) S. Parvez, M. Kang, H. S. Chung, H. Bae, *Phytother. Res.* 2007, **21**, 805; (d) M. T. H. Khan, *Pure Appl. Chem.* 2007, **29**, 2277.

2. (a) S. Balaz, M. Uher, J. Brtko, M. Veverka, J. Bransova, J. Dobias, M. Podova, J. Buchvald, *Folia Microbiol*. 1993, **38**, 387; (b) M. Uher, J. Cizmarik, *Farm. Obz*. 2001, **70**, 46.

3. (a) L. Novotny, P. Rauko, M. Abdel-Hamid, A. Vachalkova, *Neoplasma* 1999, **46**, 89; (b) J. Alverson, *J. Invertebr Pathol*. 2003, **83**, 60.

4. M. Fickova, E. Pravdova, L. Rondhal, M. Uher, J. Brtko, *J. Appl. Toxicol*. 2008, **28**, 554.

5. R. Tanaka, H. Tsujii, T. Yamada, T. Kajimoto, F. Amano, J. Hasegawa, Y. Hamashima, M. Node, K. Katoh, Y. Takebe, *Bioorg. Med. Chem*. 2009, **17**, 5238.

6. M. D. Aytemir, E. Septioglu, U. Calis, *Arzneim. Forsch*, 2010, **60**, 22.

7. H. S. Rho, S. M. Ahn, D. S. Yoo, M. K. Kim, D. H. Cho, J. Y. Cho, *Bioorg. Med. Chem. Lett.* 2010, **20**, 6569.

8. Y. Abe, Y. Takahashi, *Yukagaku* 1970, **19**, 23.

9. (a) J. Brtko, L. Rondahl, M. Ficková, D. Hudecová, V. Eybl, M. Uher, *Cent Eur J Publ Health* 2004, **12**, 8-12; (b) M. D.

Aytemir, D. D. Erol, R. C. Hider, M. Özalp, *Turk J Chem*. 2003, **27**, 757; (c) M. D. Aytemir, R. C. Hider, D. D. Erol, M. Özalp, M. Ekizoglu, *Turk J. Chem*. 2003, **27**, 445-452; d) A. Fassihi, D. Abedi, L. Saghaie, R. Sabet, H. Fazeli, G. Bostaki, *Eur J. Med. Chem*. 2009, **44**, 2145-2157.

10. J. Kim, S. Lim, *Yakhak Hoechi*, 1999, **43**, 28-33.

11. M. Wempe, M. Fitzpatrick, 2009 Patent WO 2009/ 108271 A1.

12. For review, see: Perlmutter, P. Conjugate addition reactions in organic synthesis; Pergamon: Oxford, UK, 1992. For selected reviews of asymmetric Michael additions see: (a) B. L. Li, Y. F. Wang, S. P. Luo, A. G. Zhong, Z. B. Li, X. H. Du, D. Q. Xu, *Eur. J. Org. Chem*. 2010, 656; (b) J. R. Chen, Y. J. Cao, Y. Q. Zhou, F. Tan, L. Fu, X. Y. Zhu, W. J. Xiao, *Org. Biomol. Chem*. 2010, **8**, 1275; (c) X. Y. Cao, J. C. Zheng, Y. X. Li, Z. C. Shu, X. L. Sun, B. Q. Wang, Y. Tang, *Tetrahedron* 2010, **66**, 9703; (d) C. Yu, Y. Zhang, A. Song, Y. Ji, W. Wang, *Chem. Eur. J.* 2011, **17**, 770; (e) Y. Zhang, W. Wang, *Catal. Sci. Technol.* 2012, **2**, 42.

13. For selected reviews on hydrogen-bonding organocatalysis, see: (a) Y. Zhang, W. Wang, *Catal. Sci. Technol*. 2012, **2**, 42; (b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev*. 2007, **107**, 5713; (c) X. Yu, W. Wang, *Chem. Asian J*. 2008, **3**, 516; (d) T. Akiyama, Chem. Rev. 2007, **107**, 5744; (e) S. J. Connon, *Chem. Eur. J*. 2006, **12**, 5418; (f) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed*. 2006, **45**, 1520; (g) J. Seayad, B. List, *Org. Biomol. Chem*. 2005, **3**, 719; (h) P. R. Schreiner, *Chem. Soc. Rev.* 2003, **32**, 289.

14. For selected examples of asymmetric conjugate addition reactions of β,γ-unsaturated α-ketoesters, see: (a) R. P. Herrera, D. Monge, E. Martin-Zamora, R. Fernandez, J. M. Lassaletta, *Org. Lett.* 2007, **9**, 3303; (b) S. L. Zhao, C. W. Zheng, G. Zhao, *Tetrahedron: Asym*. 2009, **20**, 1046; (c) H. F. Wang, C. W. Zheng, Y. Q. Yang, Z. Chai, G. Zhao, *Tetrahedron: Asym*. 2008, **19**, 2608; (d) X. S. Wang, C. W. Zheng, S. L. Zhao, Z. Chai, G. Zhao, G. S. Yang, *Tetrahedron: Asym*. 2008, **19**, 2699; (e) L. Zhou, L. L. Lin, W. T. Wang, J. Ji, X. H. Liu, X. M. Feng, *Chem. Commun.* 2010, **46**, 3601.

15. N. Halland, T. Velgaard, K. A. Jorgensen, *J. Org. Chem*. 2003, **68**, 5067.

16. (a) Z. Dong, J. Feng, W. Cao, X. Liu, L. Lin, X. Feng, *Tetrahedron Lett*. 2011, **52**, 3433; (b) Z. Dong, J. Feng, X. Fu, X. Liu, L. Lin, X. Feng, *Chem. Eur. J.* 2011, **17**, 1118.

17. M. A. Calter , J. l. Wang, *Org. Lett.* 2009, **11**, 2205.

18. X. -K. Chen, C. -W. Zheng, S. -Li Zhao, Z. Chai, Y.-Q. Yang, G. Zhao, W.-G. Cao, *Adv. Synth. Catal.* 2010, **352**, 1648.

19. (a) Q. Xu, Y. F. Wang, W. Zhang, S. P. Luo, A. G. Zhong, A. B. Xia, Z. Y. Xu, *Chem. Eur. J*. 2010, **16**, 4177; (b) J. Seayad, B. List, *Org. Biomol. Chem*. 2011, **10**, 3691.

20. J. H. Lee, D. Y. Kim, *Bull. Korean Chem. Soc*. 2013, **6**, 1619.

21. B. V. S. Reddy, M. Swain, S. M. Reddy, J. S. Yadav, *RSC Adv*. 2013, **3**, 8756.

22. (a) B. V. S. Reddy, S. M. Reddy, M. Swain, *RSC Adv*. **2013**, **3**, 930; (b) B. V. S. Reddy, S. M. Reddy, M. Swain, S. Dudem, S. V. Kalivendi, C. S. Reddy, *RSC Adv*. 2014, **4**, 9107.

23. (a) M. D. Aytemir, Ü. Çalış, M. Özalp, *Arch. Pharm. Med. Chem.* 2004, **337**, 281; (b) M. D. Aytemir, E. Septioğlu, Ü. Çalış, *Arzneim. Forsch. Drug Res.* 2010, **60**, 22.

24. The product **3a** was found in a rapid equilibrium between the cyclic hemiketal **3a** and the Michael-type product **3a'**. The equilibrium is very rapid in that only one pair of enantiomers is detected by HPLC and the equilibrium is slow enough that they show up as separate compounds by ^{1}H and ^{13}C NMR spectroscopy analysis, see: S. L. Zhao, C. W. Zheng, H. F. Wang, G. Zhao, *Adv. Synth. Catal*. 2009, **351**, 2811. For studies on similar equilibriums of related compounds, see: (a) W. R. Porter, W. F. Trager, *J. Heterocycl. Chem*. 1982, **19**, 475; (b) L. D. Heimark, W. F. Trager, *J. Med. Chem*. 1984, **27**, 1092; (c) N. Halland, T. Velgaard, K. A. Jørgensen, *J. Org. Chem*. 2003, **68**, 5067.

25. Q. Ren, Y. Gao, J. Wang, *Chem. Eur. J*. 2010, **16**, 13594.

26. Flack, H. D. & Bernardinelli, G. (2000). J. Appl. Cryst. 33, 1143–1148.

27. (a) B. Vakulya, S. Varga, A. Csampai, T. Soos, *Org. Lett*., 2005, **7**, 1967; (b) S. H. McCooey, S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367.