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Asymmetric Organocatalytic Michael Addition–Cyclization Cascade of Cyclopentane-1,2-dione with Substituted α,β-Unsaturated Aldehydes

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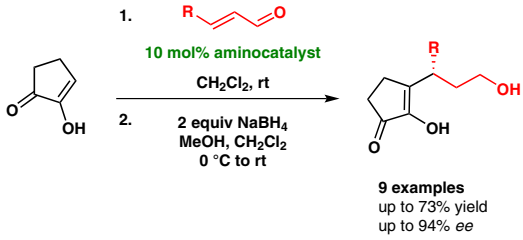

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Abstract An asymmetric organocatalytic Michael addition–cyclization cascade reaction has been developed using cyclopentane-1,2-dione as a Michael donor and α,β-unsaturated aldehydes as Michael acceptors. Bicyclic hemiacetals were obtained in excellent yields and enantioselectivities. On the basis of the results, a one-pot reaction has been developed to obtain chiral 3-substituted cyclopentane-1,2-diones and substituted dihydropyrans in good yields and excellent enantioselectivity.

Key words organocatalysis, asymmetry, diketones, dihydropyran, Michael addition

At the present time, chemical synthesis is directed at sustainability, looking for cleaner and more effective reactions to get compounds of interest. In the biomass conversion discipline, one of the conversions that has been somehow neglected is selective conversion of biomass via 5-HMF to cyclopentanone and cyclopent-2-en-1-one.[1] Both of these compounds can be easily converted into cyclopentane-1,2-diones (**1**).[2] These are compounds of many uses, including as precursors with the means to increase the heating value of conventional bio-jet fuels.[3] Also derivatives of cyclopentane-1,2-dione can be used as flavoring agents.[4] We have used these molecules as starting materials/platform molecules for making new high value-added fine chemicals, such as nucleoside analogues[5] and several bioactive natural compounds[6] and their analogues.[7] On the other hand, aminocatalysis has been an important research topic for 10 years, providing the most widely used organocatalysts in the field.[8]

We have previously shown that a Mukaiyama–Michael addition reaction of cyclopentane-1,2-dione dienol silyl ethers proceeds in an organocatalytic way with α,β-unsaturated aldehydes.[9] The preparation of the intermediate cyclopentane-1,2-dione dienol silyl ethers, however, is a laborious and complicated procedure, making the overall yield of the substituted chiral product low, although the addition reaction proceeds in excellent enantioselectivity (Scheme 1, path C).[9] We have also shown previously that α-alkylation of cyclopentane-1,2-diones in an organocatalytic manner can be carried out with β,γ-unsaturated-α-keto esters and with nitroolefins (Scheme 1, paths A and B).[10,11] Several other organocatalytic reactions of cyclic diketones with excellent stereoselectivity have also been investigated: Rueping carried out two cascade reactions with cyclohexane-1,2-dione and cyclohexane-1,3-dione, giving bicyclic product in up to excellent yields and enantioselectivity (Scheme 1, paths D and E);[12] Jørgensen's group has also shown that cyclopentane-1,3-diones undergo a cascade reaction with α,β-unsaturated aldehydes, giving bicyclic product in excellent yields and stereoselectivity (Scheme 1, path F).[13] Here we present the results of using α,β-unsaturated aldehydes as electrophiles in a direct reaction with cyclopentane-1,2-dione.

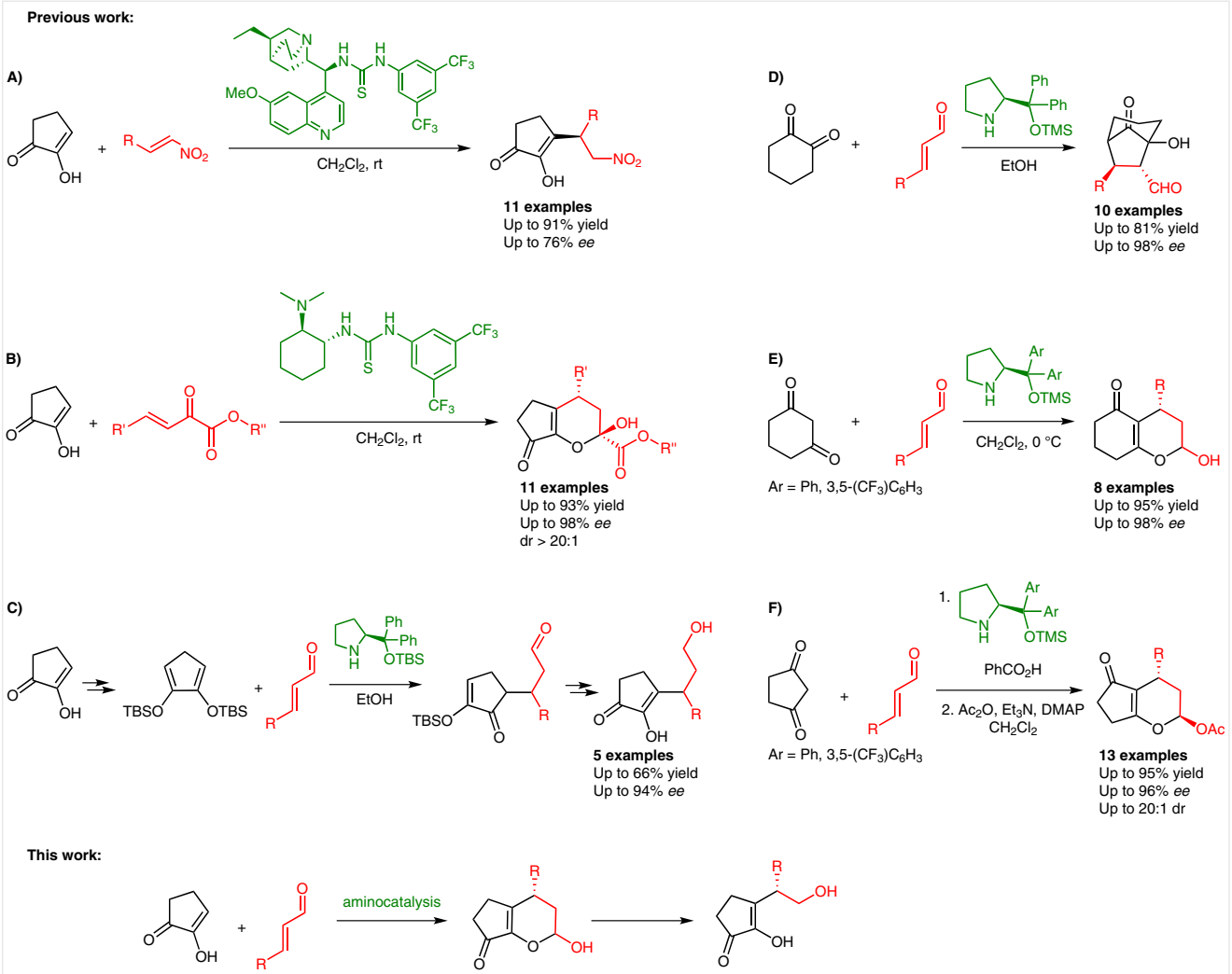
We started with cyclopentane-1,2-dione (**1**) and *trans*-cinnamaldehyde (**2a**) with L-proline (**4a**) as the aminocatalyst in ethanol and obtained hemiacetal **3a** in very low yield (6.5%) and with low enantioselectivity (16%; Table 1, entry 1). By using bulkier aminocatalysts, better yields and enantioselectivities were obtained (Table 1, entries 2–5). The best result was achieved with the bulkiest catalyst, **4e**, giving 83% yield and 85% ee (Table 1, entry 5). The opposite enantiomer was also obtained with a catalyst derived from D-proline (Table 1, entry 4).

In a search for an optimal solvent for the reaction, different polar and non-polar solvents were screened. The results are presented in Table 2. We found that the halogen-containing solvents gave the best stereoselectivity. In chloroform, the reaction was complete in 2 hours, giving a good yield (76%) and with excellent enantioselectivity (98% ee; Table 2, entry 5). In 1,2-dichloroethane, similar results were obtained after 6 hours of reaction (72% yield and 96% ee; Table 2, entry 6). The best result was obtained with dichloromethane, affording an excellent yield (93%) and enantioselectivity (95% ee; Table 2, entry 7) in a fast reaction (after 2 h).

Using these optimal conditions the scope of the reaction with different aldehydes was investigated. As seen in Scheme 2, the reaction tolerates different α,β-unsaturated aldehydes with various electronic densities. Electron-donating and -withdrawing groups at the aromatic ring both gave good to excellent yields and enantioselectivities (**3b** and **3e**). Also, a heteroaromatic ring was tolerated, giving product **3g** in 68% yield and 81% ee. Furthermore, an alkyl α,β-unsaturated aldehyde can also be used in the reaction, affording **3h** with good enantioselectivity (86% ee), although with low yield (33% only). Finally, hexa-2,4-dienal (**2i**) resulted in a 1,4-addition reaction only, giving **3i** in an average yield 65% and enantioselectivity 51% ee. As the used starting material **2i** was a 1:7 mixture of *cis*- and *trans*-isomers, the product obtained was also a 1:7 mixture of *cis*/*trans* isomers.

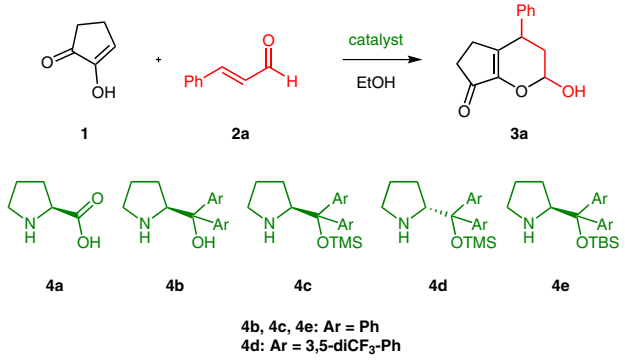
The absolute configuration of compound **3c** was determined by a single-crystal X-ray diffraction to be (2*S*,4*S*) (Figure 1) and the absolute configurations of compounds **3** were assigned by analogy.

As excellent yields were obtained only in some cases with *trans*-cinnamaldehydes, additional screening of possible basic additives, with the usual co-catalyst enhancing



Scheme 1 Previous and proposed work on cyclic diketones

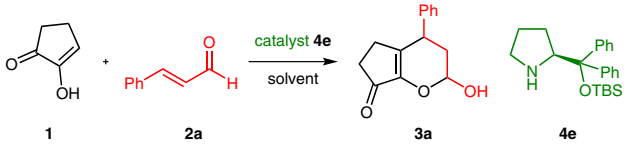
Table 1 Screening of Organocatalysts[a]



Entry	Catalyst (10 mol%)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**4a**	18	6.5	16
2	**4b**	24	61	21
3	**4c**	1.5	59	79
4	**4d**	24	20	70[d]
5	**4e**	18	83	85

[a] Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), catalyst **4** (0.02 mmol), EtOH (0.7 mL), r.t.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC.
[d] Opposite enantiomer formed.

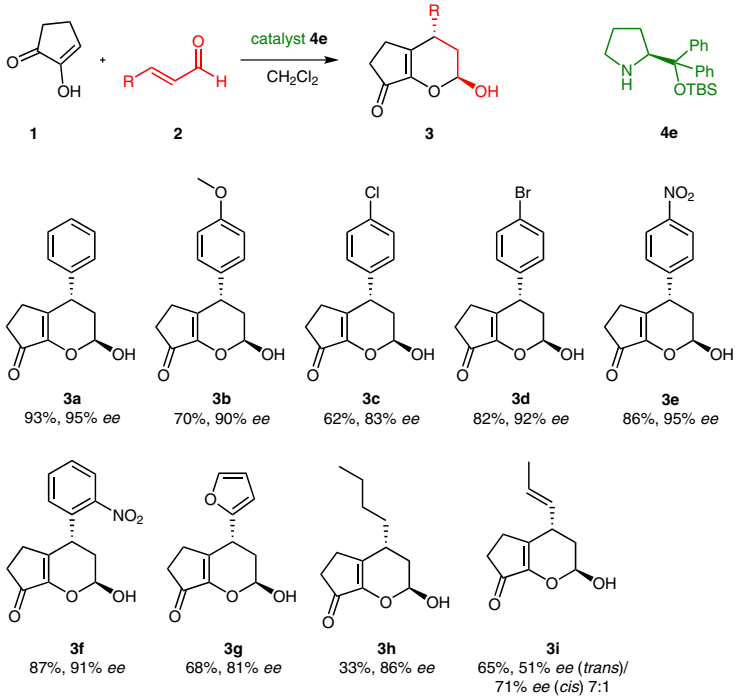
Table 2 Screening of Solvents[a]



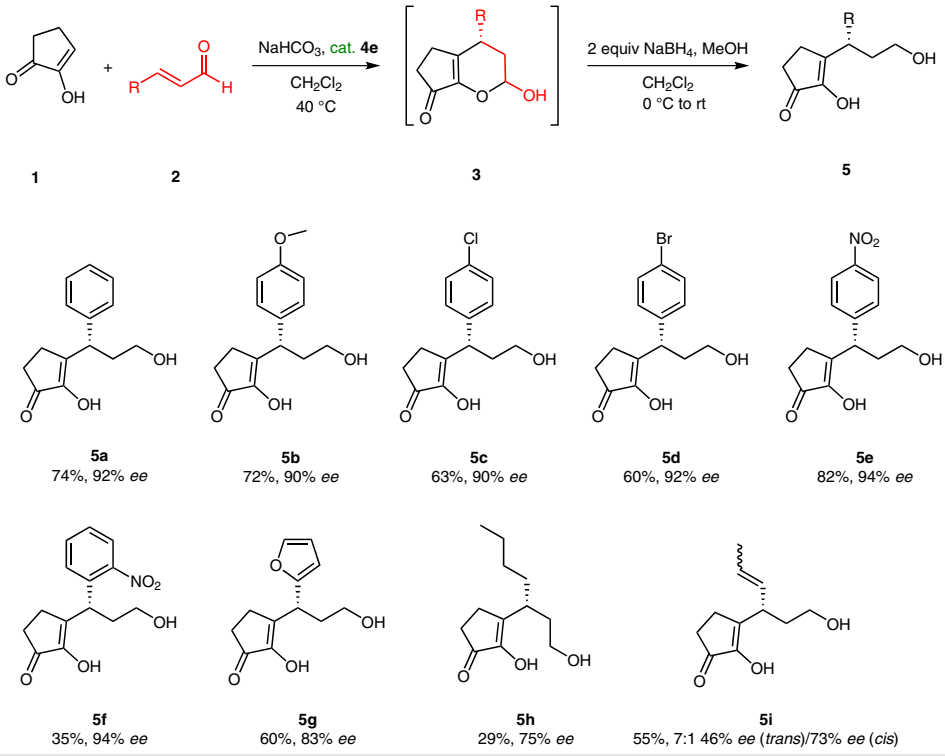
Entry	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	EtOH	18	83	85
2	MeOH	24	74	88
3	THF	24	72	96
4	toluene	5	83	97
5	$CHCl_3$	2	76	98
6	$C_2H_4Cl_2$	6	72	96
7	CH_2Cl_2	2	93	95

[a] Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), catalyst **4e** (0.02 mmol), solvent (0.7 mL), r.t.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC.

the condensation of aminocatalyst to aldehyde, was performed. It was found (see Table 3) that the best additive was $NaHCO_3$, leading to perfect yield (98%) and outstanding enantioselectivity (>99% ee) of the reaction (Table 3, entry 6).



Scheme 2 Scope of the reaction. *Reagents and conditions*: **1** (0.24 mmol), **2** (0.2 mmol), catalyst **4e** (0.02 mmol), CH_2Cl_2 (0.7 mL), r.t.; isolated yields after column chromatography, the major diastereomer is presented; ee determined by chiral HPLC.



Scheme 3 One-pot reaction in the synthesis of chiral 3-substituted cyclopentane-1,2-diones **5**. *Reagents and conditions*: **1** (0.24 mmol); **2** (0.2 mmol), $NaHCO_3$ (0.02 mmol), catalyst **4e** (0.02 mmol), CH_2Cl_2 (0.7 mL), r.t.; isolated yields after column chromatography, ee determined by chiral HPLC.

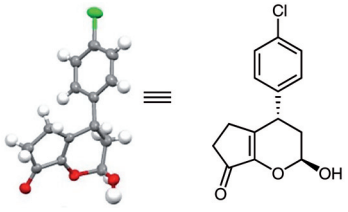
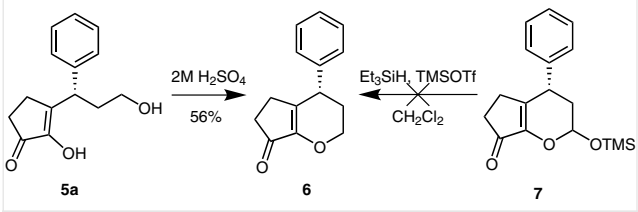


Figure 1 X-ray crystal structure (see Supporting Information for details) and the absolute configuration of **3c**



Scheme 4 Transformation to dihydropyran

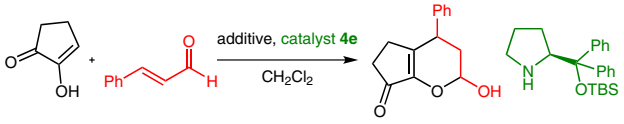
With these optimum conditions (solvent CH_2Cl_2, catalyst **4e**, and additive $NaHCO_3$), we developed a one-pot procedure for the reaction sequence: Michael addition, cyclization reaction and reduction of the formed aldehyde with $NaBH_4$. This cascade of reactions resulted in a single product **5** (Scheme 3).

All of the used substrates gave excellent enantioselectivities, with good to satisfactory overall yields. We made an attempt to reduce acetal **7** directly to the dihydropyran according to Oshima et al.[14] but without success. Instead, the cyclization of enol **5** proceeded easily in the presence of a strong acid, yielding dihydropyran **6** in 56% yield (not optimized) (Scheme 4).

In conclusion, a novel efficient method of making bicyclic hemiacetals **3a–i** and 3-substituted cyclopentane-1,2-diones **5a–i** has been developed, giving good yields and excellent enantioselectivities. The method may be used for the synthesis of a wide variety of substituted dihydropyrans **6**.

Full assignment of ^1H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz instrument. Residual solvent peaks ($CHCl_3/CDCl_3$, δ = 7.26/77.2) or TMS (δ = 0.00) were used as chemical shift references. Chiral HPLC was performed using Phenomenex Lux® 3µm amylose-2, Chiralcel OD-H, and Chiralpak AS-H and OJ-H columns. Mass spectra were recorded by using Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS

Table 3 Screening of Additives[a]



1 2a 3a 4e

Entry	Additive (10 mol%)	Time (h)	Yield (%)[b]	ee (%)[c]
1	–	2	93	95
2	NaOAc	1.5	93	94
3	pyridine	3	95	94
4	DMAP	1	93	94
5	K_2CO_3	4	84	94
6	$NaHCO_3$	3.5	98	>99
7	Na_2CO_3	2.5	98	95
8	Et_3N	2.5	94	94
9	DIPEA	1.5	93	94
10	DABCO	2	99	95
11	DBU	2.5	82	95
12	imidazole	1	99	93

[a] Reaction conditions: **1** (0.24 mmol), **2a** (0.2 mmol), additive (0.02 mmol), catalyst **4e** (0.02 mmol), CH_2Cl_2 (0.7 mL), r.t.
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC.

spectrometer by using AJ-ESI ionization. Optical rotations were obtained using an Anton Paar GWB Polarimeter MCP 500. IR spectra were recorded on a Bruker Tensor 27 Fourier transform infrared spectrophotometer. Absolute structure of the single crystal with Bruker-Nonius Kappa CCD diffractometer. TLC: Merck precoated silica gel 60 F_{254} plates; column chromatography: Merck 60 (0.040–0.063 mm) mesh silica gel. Commercial reagents and solvents were generally used as received. Racemic samples of all compounds were prepared following the general procedure using pyrrolidine as catalyst.

Cyclopentane-1,2-dione (**1**) was prepared according to a literature procedure[2a] from commercially available cyclopentanone. Aldehydes **2a–i** and catalysts **4a–e** are commercially available and were used without further purification.

4-Substituted 2-Hydroxy-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one 3a–i; General Procedure A

2-Hydroxycyclopent-2-en-1-one (**1**, 23.5 mg, 0.24 mmol), aldehyde **2** (25.2 µL, 0.2 mmol), and aminocatalyst **4e** (7.3 mg, 0.02 mmol) were dissolved in CH_2Cl_2 (0.7 mL). The mixture was stirred at r.t. until completion of the reaction (TLC monitoring). The mixture was purified by column chromatography (CH_2Cl_2/EtOAc 25:1) to yield the product.

(2*S*,4*S*)-2-Hydroxy-4-phenyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3a)

Following GPA gave **3a** after purification as a white solid; yield: 43 mg (93%); mp 149 °C; 95% ee [HPLC (Chiralcel OD-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 8.2 (major), 6.8 min (minor)]; $[\alpha]_D^{25}$ +186.8 (*c* 0.04, $CHCl_3$).

IR (KBr): 3377, 2929, 1701, 1645, 1494, 1454, 1408, 1394, 1283, 1121, 1090, 910, 733, 705 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 2 H), 7.32–7.27 (m, 1 H), 7.24–7.19 (m, 2 H), 5.82 (d, *J* = 2.8 Hz, 1 H), 5.09 (s, 1 H), 4.00 (dd, *J* = 11.5, 6.1 Hz, 1 H), 2.40–2.31 (m, 3 H), 2.28–2.24 (m, 2 H), 1.99 (dd, *J* = 13.5, 11.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.8, 148.6, 148.5, 140.7, 129.1 (2 C), 128.3 (2 C), 127.4, 92.9, 37.6, 35.7, 32.7, 23.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}O_3$: 231.1016; found: 231.1016.

(2*S*,4*S*)-2-Hydroxy-4-(4-methoxyphenyl)-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3b)

Following GPA gave **3b** after purification as a yellow oil; yield: 36 mg (70%); 90% ee [HPLC (Chiralpak AS-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 18.6 (major), 29.5 min (minor)]; $[\alpha]_D^{25}$ +133.9 (*c* 0.05, $CHCl_3$).

IR (KBr): 3379, 2932, 1703, 1644, 1611, 1583, 1513, 1442, 1394, 1347, 1250, 1087, 1034, 794 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.09 (m, 2 H), 6.93–6.86 (m, 2 H), 5.77 (br s, 1 H), 4.53 (br s, 1 H), 3.93 (dd, *J* = 11.4, 6.1 Hz, 1 H), 3.82 (s, 3 H), 2.40–2.36 (m, 2 H), 2.31 (ddd, *J* = 13.8, 6.2, 2.5 Hz, 1 H), 2.27–2.23 (m, 2 H), 2.01–1.91 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.3, 158.9, 148.7, 148.4, 132.5, 129.3 (2 C), 114.5 (2 C), 92.9, 55.5, 36.7, 35.7, 32.8, 23.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}O_4$: 261.1121; found: 261.1103.

(2*S*,4*S*)-4-(4-Chlorophenyl)-2-hydroxy-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3c)

Following GPA gave **3c** after purification as a white solid; yield: 33 mg (62%); mp 168 °C; 83% ee [HPLC (Chiralpak AS-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 13.9 (major), 18.8 min (minor)]; $[\alpha]_D^{25}$ +233.2 (*c* 0.04, $CHCl_3$).

IR (KBr) 3356, 2947, 1699, 1649, 1492, 1435, 1230, 1088, 844 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.3 Hz, 2 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 5.79 (s, 1 H), 4.68 (s, 1 H), 3.97 (dd, *J* = 11.3, 6.0 Hz, 1 H), 2.41–2.36 (m, 2 H), 2.36–2.29 (m, 1 H), 2.27–2.20 (m, 2 H), 1.94 (t, *J* = 12.6 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.4, 148.7, 147.4, 139.1, 133.3, 129.7 (2 C), 129.3 (2 C), 92.8, 37.0, 35.6, 32.7, 23.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_3Cl$: 265.0626; found: 265.0626.

(2*S*,4*S*)-4-(4-Bromophenyl)-2-hydroxy-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3d)

Following GPA gave **3d** after purification as a white solid; yield: 50 mg (82%); mp 173 °C; 92% ee [HPLC (Chiralpak AS-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 16.0 (major), 27.7 min (minor)]; $[\alpha]_D^{25}$ +190.1 (*c* 0.04, $CHCl_3$).

IR (KBr): 3354, 2947, 1699, 1649, 1489, 1127, 870, 843, 531 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.3 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 5.80 (d, *J* = 1.9 Hz, 1 H), 5.11 (s, 1 H), 3.97 (dd, *J* = 11.3, 5.9 Hz, 1 H), 2.41–2.36 (m, 2 H), 2.36–2.28 (m, 1 H), 2.28–2.21 (m, 2 H), 1.94 (t, *J* = 12.7 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.3, 148.7, 147.2, 139.6, 132.3 (2 C), 130.1 (2 C), 121.3, 92.7, 37.1, 35.5, 32.7, 23.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_3Br$: 309.0121; found: 309.0130.

(2*S*,4*S*)-2-Hydroxy-4-(4-nitrophenyl)-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3e)

Following GPA gave **3e** after purification as a white solid; yield: 47 mg (86%); mp 160 °C; 95% ee [HPLC (Chiralpak AS-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 27.8 (major), 41.5 min (minor)]; $[\alpha]_D^{25}$ +184.7 (*c* 0.03, $CHCl_3$).

IR (KBr): 3305, 2931, 1693, 1646, 1607, 1516, 1345, 862, 754, 715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.6 Hz, 2 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 5.85 (d, *J* = 2.0 Hz, 1 H), 5.27 (s, 1 H), 4.16 (dd, *J* = 12.4, 6.5 Hz, 1 H), 2.45–2.40 (m, 2 H), 2.40–2.34 (m, 1 H), 2.33–2.21 (m, 2 H), 1.98 (t, *J* = 12.7 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.5, 149.0, 148.3, 147.4, 145.9, 129.3 (2 C), 124.4 (2 C), 92.5, 37.5, 35.5, 32.7, 23.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_5N$: 276.0866; found: 276.0875.

(2*S*,4*R*)-2-Hydroxy-4-(2-nitrophenyl)-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3f)

Following GPA gave **3f** after purification as a white solid; yield: 48 mg (87%); mp 160 °C; 91% ee [HPLC (Chiralpak AS-H, hexane/*i*-PrOH 8:2, 1 mL/min, 254 nm): t_R = 28.5 (major), 43.9 min (minor)]; $[\alpha]_D^{25}$ +234.3 (*c* 0.05, $CHCl_3$).

IR (KBr): 3356, 2925, 1700, 1648, 1607, 1524, 1351, 789, 750, 719 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.62 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.49–7.43 (m, 1 H), 7.30 (dd, *J* = 7.8, 1.0 Hz, 1 H), 5.80 (d, *J* = 1.8 Hz, 1 H), 4.71 (br s, 1 H), 4.57 (dd, *J* = 10.7, 6.2 Hz, 1 H), 2.56 (ddd, *J* = 13.6, 6.1, 2.5 Hz, 1 H), 2.45–2.39 (m, 2 H), 2.35–2.28 (m, 1 H), 2.27–2.18 (m, 1 H), 1.99 (t, *J* = 11.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.4, 150.4, 149.5, 146.2, 135.2, 133.3, 130.4, 128.3, 124.9, 92.7, 35.4, 33.2, 32.7, 23.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_5N$: 276.0866; found: 276.0872.

(2*S*,4*R*)-4-(Furan-2-yl)-2-hydroxy-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3g)

Following GPA gave **3g** after purification as a white solid; yield: 30 mg (68%); mp 160 °C; 81% ee [HPLC (Chiralcel OD-H, hexane/*i*-PrOH 95:5, 1 mL/min, 254 nm): t_R = 19.6 (major), 15.8 min (minor)]; $[\alpha]_D^{25}$ +162.1 (*c* 0.04, $CHCl_3$).

IR (KBr): 3375, 2926, 1702, 1647, 1505, 1120, 1088, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 1.8, 0.7 Hz, 1 H), 6.35 (dd, *J* = 3.1, 1.9 Hz, 1 H), 6.19 (d, *J* = 3.1 Hz, 1 H), 5.80 (d, *J* = 2.7 Hz, 1 H), 5.05 (s, 1 H), 4.13 (dd, *J* = 11.1, 5.9 Hz, 1 H), 2.44–2.36 (m, 3 H), 2.33–2.21 (m, 2 H), 2.15 (t, *J* = 12.4 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.6, 153.3, 148.1, 146.4, 142.3, 110.4, 106.9, 92.7, 32.8, 31.8, 31.1, 23.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}O_4$: 221.0808; found: 221.0815.

(2*S*,4*R*)-4-Butyl-2-hydroxy-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3h)

Following GPA gave **3h** after purification as a yellow oil; yield: 14 mg (33%); 86% ee [HPLC (Chiralcel OJ-H, hexane/*i*-PrOH 9:1, 1 mL/min, 254 nm): t_R = 10.7 (major), 8.6 min (minor)]; $[\alpha]_D^{25}$ +36.7 (*c* 0.04, $CHCl_3$).

IR (KBr): 3316, 2926, 1691, 1634, 1461, 1395, 1098, 948, 846, 715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (s, 1 H), 4.79 (s, 1 H), 2.81–2.70 (m, 1 H), 2.61–2.52 (m, 1 H), 2.49–2.36 (m, 3 H), 2.18–2.09 (m, 1 H), 1.81–1.70 (m, 1 H), 1.58–1.47 (m, 1 H), 1.42–1.28 (m, 5 H), 0.97–0.88 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.4, 150.6, 147.8, 92.9, 32.8, 32.3, 31.5, 30.1, 29.0, 23.5, 22.9, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{18}O_3Na$: 233.1148; found: 233.1151.

(2*S*,4*S*)-2-Hydroxy-4-[(*E*)-prop-1-en-1-yl]-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (3i)

Following GPA from **2i** (*trans*/*cis* 7:1) gave **3i** after purification as an orange oil; yield: 25 mg (65%); ratio *trans*/*cis* 7:1; *cis*-isomer 71% ee [HPLC (Chiralcel OJ-H, hexane/*i*-PrOH 9:1, 1 mL/min, 254 nm): t_R = 16.9 (major), 13.8 min (minor)]; *trans*-isomer 51% ee [HPLC (Chiralcel OJ-H, hexane/*i*-PrOH 9:1, 1 mL/min, 254 nm): t_R = 24.4 (major), 11.3 min (minor)]; $[\alpha]_D^{25}$ +99.7 (*c* 0.05, $CHCl_3$).

IR (KBr): 3382, 2925, 1698, 1643, 1440, 1395, 1102, 914, 733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75–5.59 (m, 2 H), 5.38–5.29 (m, 1 H), 4.82 (br s, 1 H), 3.36 (dd, *J* = 15.5, 8.6 Hz, 1 H), 2.57–2.33 (m, 4 H), 2.14–2.05 (m, 1 H), 1.77–1.67 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.4, 149.2, 147.6, 129.5, 128.7, 92.7, 34.6, 33.3, 32.8, 23.9, 18.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}O_3Na$: 217.0835; found: 217.0837.

2-Hydroxy-3-(1-substituted 3-hydroxypropyl)cyclopent-2-en-1-ones 5a–i; General Procedure B

2-Hydroxycyclopent-2-en-1-one (**1**, 23.5 mg, 0.24 mmol), aldehyde **2** (25.2 µL, 0.2 mmol), aminocatalyst **4e** (7.3 mg, 0.02 mmol), and $NaHCO_3$ (0.02 mmol) were dissolved in CH_2Cl_2 (0.7 mL). The mixture was stirred at 40 °C until completion of the reaction (TLC and NMR monitoring). The mixture was cooled to 0 °C and dry MeOH (0.5 mL) and $NaBH_4$ (12.6 mg, 0.33 mmol) were added. The mixture was stirred at 0 °C for 30 min and was warmed to r.t. When the reaction was completed CH_2Cl_2 (0.5 mL) and sat. aq NH_4Cl solution (0.5 mL) were added to the mixture. The mixture was extracted with CH_2Cl_2 (3 × 1 mL) and organic phase was dried with phase separator and concentrated. Mixture was purified by column chromatography (CH_2Cl_2/MeOH, 50:1) to yield the product.

(*S*)-2-Hydroxy-3-(3-hydroxy-1-phenylpropyl)cyclopent-2-en-1-one (5a)

Following GPB gave **5a** after purification as a white solid; yield: 28 mg (74%); mp 117 °C; 92% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 9.1 (major), 13.8 min (minor)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 5 H), 6.52 (br s, 1 H), 4.20 (t, *J* = 7.9 Hz, 1 H), 3.71–3.61 (m, 2 H), 2.45–2.17 (m, 6 H), 2.09 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.6, 148.5, 148.3, 141.3, 128.8 (2 C), 128.0 (2 C), 127.0, 60.8, 41.4, 34.5, 31.8, 23.0.

The spectral properties of the compound coincided with literature data.[9]

(*S*)-2-Hydroxy-3-(3-hydroxy-1-(4-methoxyphenyl)propyl)cyclopent-2-en-1-one (5b)

Following GPB gave **5b** after purification as a white solid; yield: 32 mg (72%); mp 106 °C; 90% ee [HPLC (Chiralpak AS-H, hexane/EtOH 9:1, 1 mL/min, 254 nm): t_R = 29.6 (major), 26.4 min (minor)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 6.10 (s, 1 H), 4.13 (t, *J* = 8.0 Hz, 1 H), 3.79 (s, 3 H), 3.71–3.60 (m, 2 H), 2.44–2.18 (m, 6 H), 1.86 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.3, 158.6, 148.3, 148.1, 133.3, 128.9 (2 C), 114.1 (2 C), 60.8, 55.3, 40.6, 34.9, 31.7, 23.0.

The spectral properties of the compound coincided with literature data.[9]

(*S*)-3-[1-(4-Chlorophenyl)-3-hydroxypropyl]-2-hydroxycyclopent-2-en-1-one (5c)

Following GPB gave **5c** after purification as a white amorphous solid; yield: 28 mg (63%); 90% ee [HPLC (Chiralpak AS-H, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 8.9 (major), 11.2 min (minor)]; $[\alpha]_D^{25}$ –55.1 (*c* 0.11, $CHCl_3$).

IR (KBr): 3317, 2919, 1691, 1646, 1490, 1031, 822 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 2 H), 7.26–7.21 (m, 2 H), 6.24 (s, 1 H), 4.21–4.13 (m, 1 H), 3.71–3.60 (m, 2 H), 2.43–2.15 (m, 6 H), 1.92 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.3, 148.5, 147.1, 139.8, 132.8, 129.3 (2 C), 128.9 (2 C), 60.6, 40.8, 34.7, 31.7, 23.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}ClO_3$: 267.0782; found: 267.0785.

(*S*)-3-[1-(4-Bromophenyl)-3-hydroxypropyl]-2-hydroxycyclopent-2-en-1-one (5d)

Following GPB gave **5d** after purification as a white solid; yield: 31 mg (60%); mp 105 °C; 92% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 8.9 (major), 10.6 min (minor)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.4 Hz, 2 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 6.16 (s, 1 H), 4.18–4.12 (m, 1 H), 3.69–3.61 (m, 2 H), 2.44–2.15 (m, 6 H), 1.71 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.2, 148.4, 146.9, 140.3, 131.8 (2 C), 129.7 (2 C), 120.9, 60.5, 40.9, 34.6, 31.7, 23.1.

The spectral properties of the compound coincided with literature data.[9]

(*S*)-2-Hydroxy-3-[3-hydroxy-1-(4-nitrophenyl)propyl]cyclopent-2-en-1-one (5e)

Following GPB gave **5e** after purification as a white solid; yield: 49 mg (82%); mp 109 °C; 94% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 16.8 (major), 19.5 min (minor)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 9.0, 1.2 Hz, 2 H), 7.49 (d, *J* = 8.7 Hz, 2 H), 6.09 (s, 1 H), 4.34–4.27 (m, 1 H), 3.68 (t, *J* = 6.1 Hz, 2 H), 2.46–2.21 (m, 6 H), 1.77 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.9, 149.0, 148.9, 147.0, 145.0, 128.8 (2 C), 124.0 (2 C), 60.3, 41.4, 34.5, 31.7, 23.3.

The spectral properties of the compound coincided with literature data.[9]

(*S*)-2-Hydroxy-3-[3-hydroxy-1-(2-nitrophenyl)propyl]cyclopent-2-en-1-one (5f)

Following GPB gave **5f** after purification as a yellow oil; yield: 16 mg (35%); 94% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 20.6 (major), 36.4 min (minor)]; $[\alpha]_D^{25}$ +100.3 (*c* 0.11, $CHCl_3$).

IR (KBr): 3332, 2922, 1697, 1653, 1526, 1355, 1108, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.60 (dtd, *J* = 9.1, 8.0, 1.4 Hz, 2 H), 7.40 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1 H), 6.42 (s, 1 H), 4.56 (t, *J* = 7.7 Hz, 1 H), 3.71–3.61 (m, 2 H), 2.52–2.22 (m, 6 H), 2.16 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.0, 149.7, 148.6, 144.6, 135.3, 132.3, 129.3, 127.3, 123.7, 59.9, 36.4, 35.0, 31.2, 24.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}NO_5$: 278.1023; found: 278.1027.

(*R*)-3-[1-(Furan-2-yl)-3-hydroxypropyl]-2-hydroxycyclopent-2-en-1-one (5g)

Following GPB gave **5g** after purification as a white solid; yield: 22 mg (60%); mp 120 °C (dec.); 83% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 9.9 (major), 14.4 min (minor)]; $[\alpha]_D^{25}$ –86.0 (*c* 0.11, $CHCl_3$).

IR (KBr): 3427, 3124, 2939, 1697, 1651, 1506, 1447, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 1.8, 0.7 Hz, 1 H), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1 H), 6.17 (d, *J* = 3.2 Hz, 1 H), 5.73 (s, 1 H), 4.39 (dd, *J* = 8.8, 7.0 Hz, 1 H), 3.74–3.59 (m, 2 H), 2.49–2.38 (m, 3 H), 2.33–2.21 (m, 2 H), 2.09 (m, 1 H), 1.79 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.7, 154.2, 148.6, 144.9, 141.9, 110.2, 106.3, 60.3, 34.4, 33.5, 31.7, 22.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}O_4$: 223.0965; found: 223.0967.

(*R*)-2-Hydroxy-3-(1-hydroxyheptan-3-yl)cyclopent-2-en-1-one (5h)

Following GPB gave **5h** after purification as a white solid; yield: 11 mg (29%); mp 97 °C; 75% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 6.7 (major), 21.0 min (minor)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (s, 1 H), 3.63 (ddd, *J* = 11.0, 6.2, 4.7 Hz, 1 H), 3.52 (ddd, *J* = 11.1, 8.9, 5.4 Hz, 1 H), 3.05–2.94 (m, 1 H), 2.46–2.35 (m, 4 H), 1.95–1.81 (m, 1 H), 1.70–1.60 (m, 1 H), 1.58–1.50 (m, 2 H), 1.39–1.15 (m, 4 H), 0.88 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.2, 150.4, 149.6, 60.8, 35.9, 34.6, 32.8, 31.9, 29.9, 22.7, 21.7, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{21}O_3$: 213.1485; found: 213.1487.

The spectral properties of the compound coincided with literature data.[9]

(*S*,*E*)-2-Hydroxy-3-(1-hydroxyhex-4-en-3-yl)cyclopent-2-en-1-one (5i)

Following GPB from **2i** (*trans*/*cis* 7:1) gave **5i** after purification as a white amorphous solid; yield: 18 mg (55%); ratio *trans*/*cis* 7:1; *trans*-isomer 46% ee; *cis*-isomer 73% ee [HPLC (Phenomenex Lux® 3µm amylose-2, hexane/EtOH 8:2, 1 mL/min, 254 nm): t_R = 7.8 (major *trans*), 20.0 (minor *trans*), 7.3 (major *cis*), 10.8 min (minor *cis*)]; $[\alpha]_D^{25}$ –14.2 (*c* 0.09, $CHCl_3$).

IR (KBr): 3340, 2920, 1697, 1650, 1102 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.19 (s, 1 H), 5.66–5.64 (m, 1 H), 5.54–5.44 (m, 1 H), 3.70–3.59 (m, 2 H), 3.55 (dd, *J* = 15.0, 7.2 Hz, 1 H), 2.47–2.37 (m, 4 H), 2.06 (br s, 1 H), 1.95–1.78 (m, 2 H), 1.69 (dd, *J* = 7.9, 2.7 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.2, 148.7, 148.1, 130.0, 127.3, 60.7, 38.9, 35.3, 31.8, 22.7, 17.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{17}O_3$: 197.1172; found: 197.1173.

4-Phenyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (6)

Compound **6** was synthesized using the following modified procedure of Rueping et al.[12b] Precursor **5a** (27 mg, 0.1 mmol) was dissolved in 2 M H_2SO_4 solution (0.6 mL). The mixture was stirred at r.t. for 1 h. The solution was quenched with aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 1 mL). The combined organic phases were dried and the residue was purified by column chromatography (CH_2Cl_2/EtOAc 5:1) to give a colorless oil; yield: 14 mg (56%).

IR (KBr): 3491, 2916, 1701, 1650, 1408, 1234, 1126, 1015, 773, 707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5 H), 4.2 (dd, *J* = 8.6, 7.3 Hz, 1 H), 3.72–3.60 (m, 2 H), 2.46–2.16 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.5, 148.4, 148.2, 141.3, 128.7 (2 C), 128.0 (2 C), 127.0, 60.8, 41.4, 34.7, 31.8, 23.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}O_2$: 215.1067; found: 215.1076.

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