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A Catalytic Asymmetric Electrocyclization-Protonation Reaction

Magnus Rueping[a,*] and Winai Ieawsuwan[a]

[a] Degussa Endowed Professorship, Institute of Organic Chemistry and Chemical Biology, Goethe University Frankfurt am Main, Max-von-Laue Strasse 7, 60438 Frankfurt, Germany
Fax: (+49)-69-798-29248; e-mail: M.Rueping@chemie.uni-frankfurt.de

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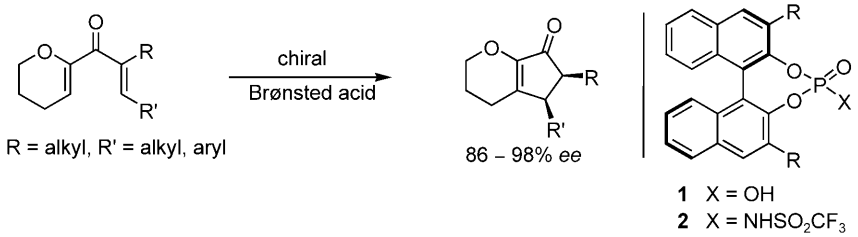
Abstract: The first enantioselective Brønsted acid-catalyzed electrocyclization-protonation reaction has been developed which provides a number of different cyclopentenones in good yields and with high enantioselectivities. The stereodetermining step of this asymmetric Nazarov cyclization reaction is an asymmetric Brønsted acid-catalyzed kinetic protonation.

Keywords: Brønsted acids; cascade reaction; cyclopentenone; domino reaction; Nazarov reaction; organic catalysis

The Nazarov reaction[1] is an electrocyclic reaction and is one of the most versatile methods in organic synthesis to rapidly access cyclopentenones which are the key structural element of numerous natural products.[2] In general, the Nazarov reaction involves the transformation of a divinyl ketone to a cyclopentenone by activation of Brønsted or Lewis acids. However, to date only a few asymmetric variants have been described of which most require the use of chiral metal complexes.[3,4] Within this context and based on our previous work in the field of asymmetric Brønsted acid catalysis, we recently developed the first metal-free highly enantioselective Nazarov cyclization. Applying this newly developed organocatalytic electrocyclization reaction we were, for instance, able to prepare valuable alkyl- and aryl-substituted cyclopentenones in good yields and with excellent enantioselectivities (Scheme 1).[5]

In this first organocatalytic electrocyclization reaction the activation of the divinyl ketone **A** is achieved by a catalytic protonation through a chiral phosphoric acid diester **1**[6,7] or chiral *N*-triflylphosphoramide catalyst **2**[8,9] resulting in the formation of adduct **B**. Subsequent conrotatory 4π electrocyclization leads to the oxyallyl cation **C** which upon elimination of a proton forms the enolate **D**. Protonation of this enolate results in the formation of the desired cyclopentenone **E** and the regenerated Brønsted acid catalyst (Figure 1).

The mechanistic considerations of the asymmetric Brønsted acid-catalyzed Nazarov reaction of 2,3-disubstituted divinyl ketone derivatives **3** illustrate that the key step in these reactions consists of an enantioselective electrocyclization reaction. The subsequent diastereoselective kinetic protonation of intermediate **D** results in the *cis*-cyclopentenones **4** as the major products (Scheme 2a). The *cis*-cyclopentenones can readily be transformed into the corresponding *trans*-products without loss of enantiomeric purity. However, in the case of 2-substituted derivatives **5** the stereodetermining step of the asymmetric Nazarov cyclization is different. In this case the key step of the overall transformation to 2-substituted cyclopent-



Scheme 1. Enantioselective Brønsted acid-catalyzed Nazarov cyclization.

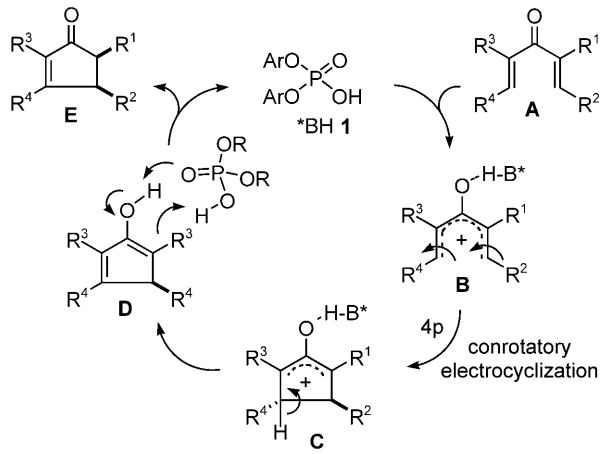


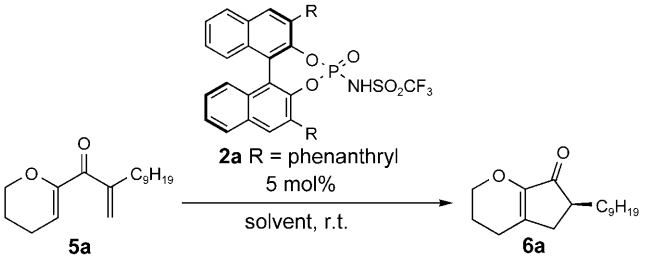
Figure 1. Catalytic cycle of the Brønsted acid-catalyzed Nazarov reaction.

enones **6** is a Brønsted acid-catalyzed enantioselective protonation of intermediate **D** (Scheme 2b).[4,10–12]

Given the importance of cyclopentenones in organic synthesis together with our recently developed enantioselective organocatalytic Nazarov reaction[5] and carbonyl activations,[8] we decided to examine a Brønsted acid-catalyzed enantioselective cyclization-protonation reaction. This would not only be the first organocatalytic enantioselective protonation within the Nazarov reaction but, more importantly, would provide direct and fast access to optically active 2-substituted cyclopentenones (Scheme 2b).

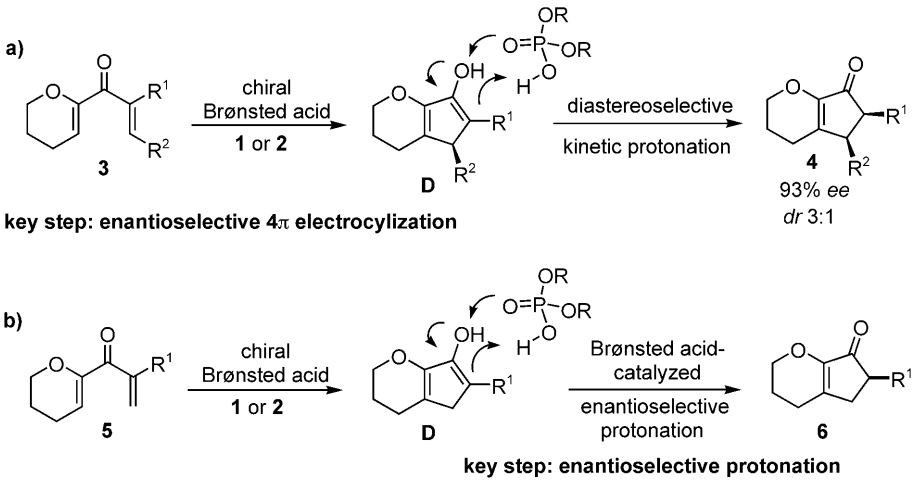
Hence, our initial investigation of the enantioselective protonation concentrated on the evaluation of various solvents in the *N*-triflylphosphoramide (**2a**)-catalyzed transformation of divinyl ketone **5a** to the corresponding cyclopentenone **6a** (Table 1). These experiments showed that the reactivities and selectivities are strongly dependent on the solvent. While reactions in polar solvents gave almost no selectivities (Table 1, entries 8–11), both better reactivities and selectivities were observed if aromatic and halogenated solvents were employed (entries 1–7). This tendency

Table 1. Influence of solvent on the enantioselectivity of Brønsted acid-catalyzed protonation.



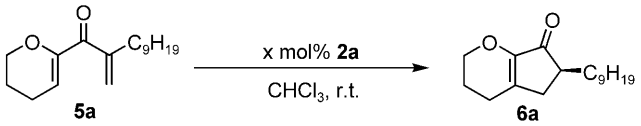
Entry[a]	Solvent	Time	Yield [%][b]	*ee* [%][c]
1	Toluene	1 h	85	47
2	CF_3Ph	1 h	96	26
3	Benzene	1 h	87	44
4	$CHCl_3$	30 min	89	53
5	CH_2Cl_2	30 min	93	43
6	CCl_4	1 h	92	42
7	$ClCH_2CH_2Cl$	15 min	96	34
8	CH_3CN	1 h	88	5
9	*n*-Bu_2O	2 h	30	12
10	EtOAc	2 h	60	12
11	MeOH	5 h	28	4

[a] *Reaction conditions:* **5a** (0.113 mmol), 5 mol% **2a** in solvent at room temperature.
[b] Isolated yield after chromatography.
[c] Determined by HPLC analysis using a chiral stationary column.



Scheme 2. Origin of enantioselectivity in the Brønsted acid-catalyzed asymmetric synthesis of cyclopentenones: **a)** for 2,3-disubstituted divinyl ketones enantioselection is induced by an asymmetric electrocyclization followed by a diastereoselective kinetic protonation and **b)** in the case of 2-substituted divinyl ketones through the new Brønsted acid-catalyzed enantioselective protonation.

Table 2. Assessment of catalyst loading and solvent concentration.



Entry[a]	x [mol%]	M [mol/L]	Time	Yield [%][b]	*ee* [%][c]
1	5	0.057	1.5 h	92	53
2	5	0.227	30 min	96	51
3	2	0.113	2 h	92	53
4	1	0.113	4 h	85	52
5	5	0.113	30 min	96	53
6[d]	5	0.113	3 h	70	64

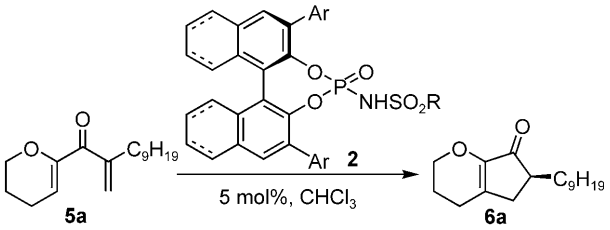
[a] *Reaction conditions:* **5a** (0.113 mmol), x mol% **2a** in $CHCl_3$ at room temperature.
[b] Isolated yield after chromatography.
[c] Determined by HPLC analysis using a chiral stationary column.
[d] At 0 °C.

is in agreement with our earlier observations on Brønsted acid-catalyzed reactions where halogenated and aromatic solvents typically gave superior results.[5,7,8] Thus chloroform was identified as the solvent of choice for the organocatalytic Nazarov cyclization-enantioselective protonation sequence.

Further examination of the enantioselective cyclization-protonation reaction focused on the catalyst loading and solvent concentration (Table 2). While a decrease in catalyst loading and concentration resulted in longer reaction times no significant changes with regard to enantioselection were observed. However, decreasing the temperature had a considerable impact on the enantioselectivity (Table 2, entry 6).

In further experiments aiming to improve the enantioselectivities we decided to apply different chiral *N*-triflylphosphoramide catalysts **2a–l** in this asymmetric Brønsted acid-catalyzed protonation reaction. While the reaction could be catalyzed by all Brønsted acids employed, the *N*-triflylphosphoramides with sterically more demanding residues in the 3,3-position of the BINOL skeleton provided better enantioselectivities (Table 3, entries 1 and 2). Therefore, we decided to vary the sulfonamide residue of the phenanthryl-substituted catalyst **2a** (Table 3, entries 9–11). Interestingly, catalyst **2i** ($R = p\text{-}CF_3\text{-}C_6H_4$) showed better selectivities but considerably lower reactivities. Introduction of longer fluorinated alkyl chains (catalysts **2j** and **k**) did not result in improved selectivities. Recently we found that, for certain Brønsted acid-catalyzed transformations, the octahydro-BINOL-phosphoric acid diesters gave superior results. Hence, we

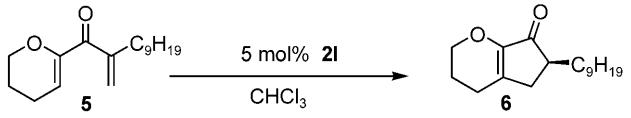
Table 3. Chiral *N*-triflylphosphoramides in the catalytic enantioselective protonation.



Entry[a]	Ar	R	Time [h]	Yield [%][b]	*ee* [%][c]
1[e]	9-phenanthryl (**2a**)	CF_3	3	70	64
2	anthracenyl (**2b**)	CF_3	5	69	53
3	2-naphthyl (**2c**)	CF_3	5	68	42
4	1-naphthyl (**2d**)	CF_3	5	60	54
5	4-NO_2-C_6H_4 (**2e**)	CF_3	2	75	28
6	3,5-$(CF_3)_2$-C_6H_3 (**2f**)	CF_3	5	66	35
7	4-Ph-C_6H_4 (**2g**)	CF_3	4	38	40
8	phenyl (**2h**)	CF_3	5	31	40
9[d]	9-phenanthryl (**2i**)	4-CF_3-C_6H_4	72	10	86
10[d]	9-phenanthryl (**2j**)	C_8F_{17}	72	61	63
11[d]	9-phenanthryl (**2k**)	C_4F_9	72	47	60
12[e]	[H_8]-9-phenanthryl (**2l**)	CF_3	20	96	75

[a] *Reaction conditions:* **5a** (0.113 mmol), 5 mol% **2** in $CHCl_3$ at 5 °C.
[b] Isolated yield after chromatography.
[c] Determined by HPLC analysis using a chiral stationary column.
[d] Room temperature.
[e] At 0 °C.

Table 4. Evaluation of the reaction temperature.



Entry[a]	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	0	20	96	75
2	−10	20	83	78
3	−20	18	40	80
4	−30	18	24	81

[a] *Reaction condition:* **5a** (0.113 mmol), 5 mol% **2l** in $CHCl_3$.
[b] Isolated yield after chromatography.
[c] Determined by HPLC analysis using a chiral stationary column.

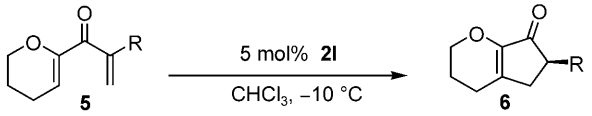
prepared the corresponding *N*-triflylphosphoramide **2l** and applied it in the catalytic enantioselective protonation. Pleasingly, we obtained the cyclopentenone **6a** in good yields and with an enantiomeric excess of 75% *ee* (Table 3, entry 12).

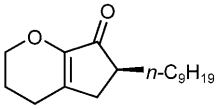
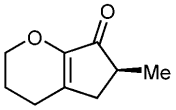
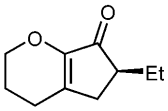
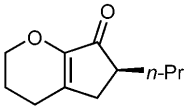
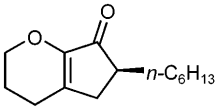
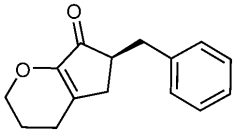
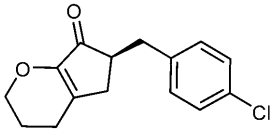
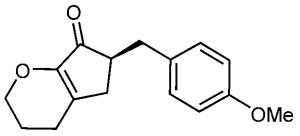
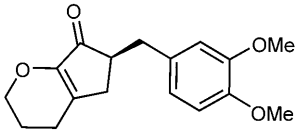
Our earlier studies showed that Brønsted acid-catalyzed carbonyl activations are strongly dependent on reaction temperature. Hence, we decided to evaluate the reaction temperature employing catalyst **2l**. These experiments demonstrated that higher enantioselectivities could be obtained at lower temperature (81% *ee* at −30 °C), however, the cyclopentenone was isolated in only 24% yield (Table 4, entry 4). The best temperature for the Brønsted acid-catalyzed enantioselective electrocyclization-protonation reaction was found to be −10 °C, and the product **6a** was obtained in 83% yield and with 78% enantiomeric excess.

With the optimized conditions in hand we explored the scope of the Brønsted acid-catalyzed asymmetric Nazarov cyclization *via* enantioselective protonation of various dienones **5** (Table 5). In general, it was possible to successfully transform differently substituted dienones **5a–i** into the corresponding products, whereby alkyl- and benzyl-substituted cyclopentenones **6a–i** were obtained in good isolated yields and with high enantioselectivities (67–78% *ee*).[13]

In summary, we have developed the first enantioselective Brønsted acid-catalyzed electrocyclization-protonation reaction which provides a number of different cyclopentenones in good yield and with high enantioselectivities (67–78% *ee*). Special features of our newly developed organocatalytic Brønsted acid-catalyzed protonation are the low catalyst loadings as well as the mild reaction conditions. Further studies to improve the scope and selectivities and the application in the synthesis of biologically active compounds and natural products are currently under investigation.

Table 5. Scope of the Brønsted acid-catalyzed enantioselective protonation.



Entry[a]	Product		Yield [%][b]	*ee* [%][c]
1		**6a**	83	78
2		**6b**	44	70
3		**6c**	72	70
4		**6d**	71	76
5		**6e**	79	78
6		**6f**	81	71
7		**6g**	93	67
8		**6h**	87	71
9		**6i**	49	67

[a] *Reaction conditions:* substrate **5a–i**, 5 mol% **2l** in $CHCl_3$ (0.1 M).
[b] Isolated yield after chromatography.
[c] Determined by HPLC analysis using a chiral stationary column.

Experimental Section

General Remarks

Unless otherwise stated, all commercially available compounds were used as provided without further purification. Solvents for chromatography were technical grade and distilled prior to use. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminum plates with F-254 indicator, visualized by irradiation with UV light. Column chromatography was carried out using silica gel Merck 60 (particle size 0.063–0.200 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 250 or AV 300 spectrometer in $CDCl_3$. Chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. Mass spectra (MS-EI, 70 eV) were conducted on a GC-MS Shimadzu QP2010 (column: Equity®-5, length × I.D. 30 m × 0.25 mm, d_f 0.25 μm, lot # 28089-U, Supelco). IR spectra were recorded on a Jasco FT/IR-420 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Elemental analysis (C, H, N) were recorded on a Perkin–Elmer Elemental Analyzer 2400 CHN. Substrates **5a–i** were prepared according to the reported procedure.[4]

General Pocedure for Nazarov Cclization

The substrate **5** was suspended in chloroform (0.1 M) in a screw-capped test-tube and allowed to stir at −10 °C for 10 min. The catalyst **2l** (5 mol%) was added to the solution and the reaction mixture was stirred at −10 °C for 20–96 h. The reaction mixture was purified by column chromatography on silica gel (ethyl acetate/hexane as eluent) to afford the cyclopentenone **6**.

(*S*)-6-Nonyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (6a): colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.07–4.00 (m, 2H), 2.54 (tdd, *J* = 1.6, 6.2, 17.4 Hz, 1H), 2.32–2.20 (m, 3H), 2.05 (ddd, *J* = 1.6, 1.6, 17.4 Hz, 1H), 1.95–1.83 (m, 2H), 1.82–1.67 (m, 1H), 1.37–1.07 (m, 15H), 0.81 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 203.07, 150.68, 144.06, 66.81, 43.63, 32.89, 31.93, 31.55, 29.65, 29.60, 29.54, 29.34, 27.14, 24.13, 22.72, 21.71, 14.16; IR (KBr): $\tilde{\nu}$ = 2956, 2918, 2851, 1698, 1649, 1463, 1399, 1289, 1169, 1112, 1068, 949, 722 cm^{-1}; EI-MS: *m/z* (relative intensity) = 264 (19) $[M]^{+\bullet}$, 193 (4), 179 (14), 165 (85), 152 (100), 138 (14), 123 (11), 111 (30), 95 (13), 81 (12), 69 (14), 67 (14); anal. calcd. for $C_{17}H_{28}O_2$: C 77.22, H 10.67; found: C 76.96, H 10.57; $[\alpha]_D^{r.t.}$: +31.8 (*c* 1.0, $CHCl_3$, 78% *ee*); HPLC (conditions OD-H column, *n*-hexane/2-propanol = 95/5, flow rate = 1 mL min^{-1}): major enantiomer: t_R = 12.90 min; minor enantiomer: t_R = 10.53 min.

(*S*)-6-Methyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (6b): colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.07–4.00 (m, 2H), 2.63 (tdd, *J* = 1.7, 6.2, 17.4 Hz, 1H), 2.39–2.28 (m, 1H), 2.27 (t, *J* = 6.2 Hz, 2H), 1.97 (ddd, *J* = 1.8, 1.8, 17.4 Hz, 1H), 1.92–1.83 (m, 2H), 1.13 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 203.52, 150.23, 143.83, 66.79, 38.04, 34.91, 24.08, 21.67, 16.55; IR (neat): $\tilde{\nu}$ = 2937, 2875, 1758, 1631, 1453, 1282, 1180, 1069, 1002, 936 cm^{-1}; EI-MS: *m/z* (relative intensity) = 152 (100) $[M]^{+\bullet}$, 137 (39), 124 (30), 109 (23), 96 (35), 95 (34), 81 (29), 68 (47), 67 (54), 53 (32); $[\alpha]_D^{r.t.}$: +12.7 (*c* 1.0, $CHCl_3$, 70% *ee*); HPLC (conditions OD-H column, *n*-hexane/2-propanol = 98/2, flow rate = 1 mL min^{-1}): major enantiomer: t_R = 31.29 min; minor enantiomer: t_R = 27.83 min.

(*S*)-6-Ethyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (6c): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08–4.00 (m, 2H), 2.55 (tdd, *J* = 1.7, 6.3, 17.4 Hz, 1H), 2.28 (t, *J* = 6.3 Hz, 2H), 2.25–2.17 (m, 1H), 2.06 (ddd, *J* = 1.8, 1.8, 17.4 Hz, 1H), 1.95–1.84 (m, 2H), 1.84–1.70 (m, 1H), 1.44–1.26 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.86, 150.66, 144.36, 66.76, 44.75, 32.22, 24.39, 24.06, 21.63, 11.15; IR (neat): $\tilde{\nu}$ = 2960, 2929, 2875, 1704, 1648, 1461, 1402, 1292, 1168, 1116, 1076, 1051, 952 cm^{-1}; EI-MS: *m/z* (relative intensity) = 166 (24) $[M]^{+\bullet}$, 151 (5), 138 (100), 132 (7), 120 (8), 110 (28), 95 (23), 81 (14), 79 (15), 67 (33); $[\alpha]_D^{r.t.}$: +40.0 (*c* 1.0, $CHCl_3$, 70% *ee*); HPLC (conditions AD-H column, *n*-hexane/2-propanol = 95/5, flow rate = 0.6 mL min^{-1}): major enantiomer: t_R = 21.28 min; minor enantiomer: t_R = 19.88 min.

(*S*)-6-Propyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (6d): colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.07–4.00 (m, 2H), 2.55 (tdd, *J* = 1.6, 6.2, 17.4 Hz, 1H), 2.32–2.22 (m, 1H), 2.27 (t, *J* = 6.2 Hz, 2H), 2.05 (ddd, *J* = 1.7, 1.7, 17.4 Hz, 1H), 1.96–1.82 (m, 2H), 1.81–1.65 (m, 1H), 1.45–1.14 (m, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 203.06, 150.62, 144.08, 66.79, 43.37, 33.66, 32.86, 24.09, 21.68, 20.34, 14.05; IR (neat): $\tilde{\nu}$ = 2956, 2934, 2874, 1758, 1451, 1382, 1183, 1144, 1065, 1033, 958, 938 cm^{-1}; EI-MS: *m/z* (relative intensity) = 180 (6) $[M]^{+\bullet}$, 151 (5), 138 (100), 120 (5), 110 (24), 95 (12), 91 (7), 82 (8), 81 (8), 79 (8), 67 (15), 55 (13); $[\alpha]_D^{r.t.}$: +40.4 (*c* 1.0, $CHCl_3$, 76% *ee*); HPLC (conditions AD-H column, *n*-hexane/2-propanol = 99/1, flow rate = 1 mL min^{-1}): major enantiomer: t_R = 32.58 min; minor enantiomer: t_R = 35.13 min.

(*S*)-6-Hexyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (6e): colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.07–4.00 (m, 2H), 2.55 (tdd, *J* = 1.6, 6.2, 17.4 Hz, 1H), 2.32–2.19 (m, 1H), 2.27 (t, *J* = 6.2 Hz, 2H), 2.05 (ddd, *J* = 1.8, 1.8, 17.4 Hz, 1H), 1.94–1.83 (m, 2H), 1.83–1.67 (m, 1H), 1.38–1.08 (m, 9H), 0.81 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 203.06, 150.64, 144.07, 66.78, 43.59, 32.86, 31.70, 31.51, 29.27, 27.05, 24.10, 22.61, 21.68, 14.07; IR (neat): $\tilde{\nu}$ = 2929, 2857, 1758, 1454, 1376, 1174, 1068 cm^{-1}; EI-MS: *m/z* (relative intensity) = 222 (6) $[M]^{+\bullet}$, 151 (21), 138 (100), 123 (4), 110 (16), 95 (8), 82 (5), 81 (5), 79 (6), 67 (3), 55 (11); anal. calcd. for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found: C 75.78, H 10.07; $[\alpha]_D^{r.t.}$: +33.9 (*c* 1.0, $CHCl_3$, 78% *ee*); HPLC (conditions: OD-H column, *n*-hexane/2-propanol = 95/5, flow rate = 1 mL min^{-1}): major enantiomer: t_R = 13.87 min; minor enantiomer: t_R = 11.74 min.

(*S*)-6-Benzyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (6f): colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.25–7.17 (m, 2H), 7.17–7.08 (m, 3H), 4.10–3.94 (m, 2H), 3.20 (dd, *J* = 3.6, 13.4 Hz, 1H), 2.66–2.54 (m, 1H), 2.46 (dd, *J* = 10.6, 13.4 Hz, 1H), 2.39 (tdd, *J* = 1.6, 6.0, 17.4 Hz, 1H), 2.21 (t, *J* = 6.3 Hz, 2H), 2.10 (ddd, *J* = 1.8, 1.8, 17.4 Hz, 1H), 1.91–1.79 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 201.91, 150.61, 144.70, 139.40, 128.91, 128.48, 126.36, 66.86, 44.91, 37.16, 32.09, 24.10, 21.63; IR (neat): $\tilde{\nu}$ = 3025, 2923, 1707, 1648, 1495, 1454, 1402, 1291, 1167, 1113, 1071, 955, 752, 701 cm^{-1}; EI-MS: *m/z* (relative intensity) = 228 (100) $[M]^{+\bullet}$, 211 (8), 199 (4), 184 (6), 172 (4), 156 (8), 151 (12), 137 (31), 128 (10), 115 (10), 109 (17), 91 (50), 77 (8), 65 (13); anal. calcd. for $C_{15}H_{16}O_2$: C 78.92, H 7.06; found: C 78.78, H 6.97;

$[\alpha]_D^{r.t.}$: +68.4 (*c* 1.0 in $CHCl_3$, 71% *ee*); HPLC (conditions OD-H column, *n*-hexane/2-propanol = 95/5, flow rate = 1 mL min^{-1}): major enantiomer: t_R = 29.76 min; minor enantiomer: t_R = 26.62 min.

(*S*)-6-(4-Chlorobenzyl)-3,4,5,6-tetrahydrocyclopenta[*b*]-pyran-7(2*H*)-one (6g): pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.13 (m, 2H), 7.08–7.02 (m, 2H), 4.08–3.94 (m, 2H), 3.11 (dd, *J* = 2.8, 12.6 Hz, 1H), 2.61–2.53 (m, 1H), 2.50 (dd, *J* = 10.0, 12.6 Hz, 1H), 2.40 (tdd, *J* = 1.7, 6.0, 17.5 Hz, 1H), 2.21 (t, *J* = 6.2 Hz, 2H), 2.05 (ddd, *J* = 1.8, 1.8, 17.5 Hz, 1H), 1.90–1.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.41, 149.66, 143.57, 136.73, 131.17, 129.27, 127.56, 65.84, 43.61, 35.32, 30.88, 23.06, 20.59; IR (KBr): $\tilde{\nu}$ = 2926, 1704, 1645, 1491, 1406, 1291, 1166, 1091, 1069, 1013, 952, 805 cm^{-1}; EI-MS: *m/z* (relative intensity) = 264 (33) $[M]^{+\bullet}$ ($C_{15}H_{15}{}^{37}ClO_2$), 262 (100) $[M]^{+\bullet}$ ($C_{15}H_{15}{}^{35}ClO_2$), 245 (9), 233 (4), 218 (6), 199 (4), 190 (7), 181 (5), 165 (5), 151 (17), 137 (48), 125 (52), 115 (18), 109 (30), 91 (13), 89 (17), 79 (13), 77 (12); anal. calcd. for $C_{15}H_{15}ClO_2$: C 68.57, H 5.75; found: C 68.69, H 5.96; $[\alpha]_D^{r.t.}$: +51.2 (*c* 1.0, $CHCl_3$, 67% *ee*); HPLC (conditions OD-H column, *n*-hexane/2-propanol = 90/10, flow rate = 1 mL min^{-1}): major enantiomer: t_R = 21.88 min; minor enantiomer: t_R = 18.29 min.

(*S*)-6-(4-Methoxybenzyl)-3,4,5,6-tetrahydrocyclopenta[*b*]-pyran-7(2*H*)-one (6h): colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.10–3.93 (m, 2H), 3.71 (s, 3H), 3.11 (dd, *J* = 3.5, 13.4 Hz, 1H), 2.62–2.51 (m, 1H), 2.44 (dd, *J* = 10.2, 13.4 Hz, 1H), 2.38 (dd, *J* = 6.1, 17.5 Hz, 1H), 2.21 (t, *J* = 6.2 Hz, 2H), 2.09 (dd, *J* = 1.7, 17.5 Hz, 1H), 1.91–1.79 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 202.03, 158.14, 150.61, 144.69, 131.29, 129.85, 113.84, 66.82, 55.27, 45.06, 36.20, 31.96, 24.07, 21.61; IR (KBr): $\tilde{\nu}$ = 2992, 2963, 2931, 2873, 2834, 1698, 1644, 1612, 1512, 1440, 1401, 1289, 1246, 1166, 1113, 1057, 1030, 948, 816 cm^{-1}; EI-MS: *m/z* (relative intensity) = 258 (46) $[M]^{+\bullet}$, 207 (11), 150 (4), 121 (100), 115 (4), 108 (7), 91 (10), 77 (11); anal. calcd. for $C_{16}H_{18}O_3$: C 74.39, H 7.02; found: C 74.14, H 6.99; $[\alpha]_D^{r.t.}$: +61.5 (*c* 1.0, $CHCl_3$, 71% *ee*); HPLC (condition: OD-H column, *n*-hexane/2-propanol = 90/10, flow rate = 0.6 mL min^{-1}): major enantiomer: t_R = 38.22 min; minor enantiomer: t_R = 34.48 min.

(*S*)-6-(3,4-Dimethoxybenzyl)-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (6i): white solid (mp. 106–109 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.74–6.61 (m, 3H), 4.10–3.94 (m, 2H), 3.79 (s, 6H), 3.10 (dd, *J* = 3.2, 13.0 Hz, 1H), 2.64–2.54 (m, 1H), 2.48 (dd, *J* = 9.8, 13.0 Hz, 1H), 2.40 (dd, *J* = 6.0, 17.5 Hz, 1H), 2.21 (t, *J* = 6.0 Hz, 2H), 2.10 (dd, *J* = 1.7, 17.5 Hz, 1H), 1.92–1.80 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 202.05, 150.65, 148.85, 147.56, 144.78, 131.81, 120.87, 112.10, 111.10, 66.82, 55.91, 55.88, 45.05, 36.70, 31.97, 24.08, 21.60; IR (neat): $\tilde{\nu}$ = 2917, 2838, 1697, 1643, 1517, 1455, 1417, 1261, 1158, 1141, 1113, 1070, 1025, 948, 883, 802, 734 cm^{-1}; EI-MS: *m/z* (relative intensity) = 288 (37) $[M]^{+\bullet}$, 151 (100), 138 (5), 107 (8), 91 (6), 77 (5); anal. calcd. for $C_{17}H_{20}O_4$: C 70.81, H 6.99; found: C 70.69, H 7.26; $[\alpha]_D^{r.t.}$: +46.3 (*c* 1.0, $CHCl_3$, 67% *ee*); HPLC (conditions AS-H column, *n*-hexane/2-propanol = 80/20, flow rate = 0.6 mL min^{-1}): major enantiomer: t_R = 51.54 min; minor enantiomer: t_R = 58.33 min.

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