Dynamic Kinetic Resolution of Azlactones Catalyzed by Chiral Brønsted Acids

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SUPPORTING INFORMATION: Experimental procedures (11 pages), ^1H NMR and ^{13}C NMR spectra (52 pages).

1. General. All reagents were obtained commercially and used as received unless otherwise specified. The BINOL phosphoric acid catalysts **3a-g** were prepared according to a combination of published procedures.¹ Synthesis and characterization of the previously unreported phosphoric acid **3h** is described below. Azlactone substrates were prepared by dehydration of the corresponding ($\pm$)-N-aroyl- α -amino acids with N,N'-dicyclohexylcarbodiimide² and were recrystallized prior to the reaction. Commercial samples of 1-naphthylmethanol were typically contaminated with up to 5% of the 2-naphthyl isomer, which was removed by recrystallization from hexanes.

Solvents used for chromatography were ACS or HPLC grade, as appropriate. Reactions were monitored by thin layer chromatography (TLC) and by ^1H NMR. EM Science 60F silica gel plates were used for TLC analyses. Flash column chromatography was performed over ICN Ecochrom silica gel (32-63 mm). HPLC analyses were performed on a Shimadzu LC system using Chiralcel OD-H, Chiralpak AD and Chiralpak AD-H analytical chiral stationary phase columns (4.6x250 mm, Chiral Technologies, Inc.). ^1H NMR and ^{13}C NMR spectra were recorded on a Mercury 300 MHz Varian spectrometer. The chemical shifts are reported as δ values (ppm) relative to TMS using residual CHCl_3 peak (7.26 ppm) as the reference. High Resolution mass spectral analyses were performed at Washington University MS Center on a Kratos MS-50TA spectrometer using Electro Spray Ionization (ESI) method. Melting points were measured on a Mel-Temp II capillary melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer Spectrum Bx FTIR spectrophotometer using potassium bromide plates.

2. Synthesis of catalyst **3h**

2a. (*R*)-3,3'-bis-(9-phenylanthracen-10-yl)-2,2'-dihydroxy-1,1'-binaphthyl.

To a mixture of (*R*)-3,3'-diiodo-2,2'-dimethoxy-1,1'-binaphthyl^[1a] (297 mg, 0.53 mmol), 9-phenylanthracen-10-ylboronic acid^[3] (650 mg, 2.18 mmol), $\text{Pd}(\text{PPh}_3)_4$ (66 mg, 0.053 mmol) and Cs_2CO_3 (1.04 g, 3.18 mmol) was added 32 mL of degassed aqueous 1,2-dimethoxyethane

(DME/H₂O=3/1) under argon. Then the mixture was stirred under reflux for 24 h, cooled to room temperature, extracted with CH₂Cl₂, filtered through Celite, washed with saturated aqueous NH₄Cl solution, water, and brine, dried with Na₂SO₄ and concentrated on a rotary evaporator. The resulting crude intermediate was dissolved in 20 mL of CH₂Cl₂ and treated at 0 °C with BBr₃ (0.35 mL, 3.71 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. It was then quenched with water, washed with saturated aqueous NaHCO₃, water, and brine, dried by Na₂SO₄, and rotary evaporated. Column chromatography (Hexane/EtOAc = 20:1) gave 0.35 g of beige powder (83% yield). **¹H NMR** (300 MHz, CDCl₃): δ 8.10 (s, 2H), 7.98-7.92 (m, 4H), 7.78-7.71 (m, 6H), 7.65-7.37 (m, 20H), 7.34-7.23 (m, 4H); **¹³C NMR** (75 MHz, CDCl₃): δ 151.34, 139.07, 138.59, 134.21, 133.47, 131.48, 131.06, 130.77, 130.72, 130.36, 130.31, 129.62, 128.76, 128.67, 127.82, 127.72, 127.68, 127.63, 127.52, 126.50, 126.43, 126.12, 125.49, 125.19, 124.56, 113.77; **IR** (KBr, cm⁻¹) 3529, 3059, 1497, 1438, 1379, 1259, 1208, 1091, 1025, 912, 770, 747, 702, 611. **MS**: HR-ESI calculated for C₆₀H₃₈O₂ [M+Na]: 813.2764, found: 813.2763. **[α]_D** = +69.7° (c 0.4, CH₂Cl₂)

2b. (R)-3,3'-bis-(9-phenylanthracen-10-yl)-1,1'-binaphthyl-2,2'-diyl-phosphoric acid.

To a solution of the BINOL derivative prepared above (100 mg, 0.126 mmol) in 15 mL of CH₂Cl₂ stirring at 0 °C was added Et₃N (88 μl, 0.630 mmol), followed by POCl₃ (18 μl, 0.190 mmol), and the mixture was allowed to warm to room temperature and stirred overnight, whereupon the reaction was complete by TLC. The mixture was treated with 2 mL of Et₃N and 10 mL of H₂O stirred for one more day and acidified with 6N HCl to adjust the pH to 2. After stirring for 2h, the mixture was washed with H₂O and brine, dried by Na₂SO₄, and rotary evaporated. Column chromatography (CH₂Cl₂/MeOH=100:1 to 100:2) yielded 85 mg of the product as pale orange powder (79% yield). **¹H NMR** (300 MHz, CDCl₃): δ 7.97 (s, 2H), 7.90 (d, *J*=7.8 Hz, 2H), 7.82 (d, *J*=8.4 Hz, 2H), 7.71 (d, *J*=8.1 Hz, 2H), 7.56-7.18 (m, 20H), 7.07-7.05 (m, 4H), 6.75-6.70 (m, 2H), 6.47-6.44 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃): δ 148.19, 138.98, 137.60, 133.51, 133.24, 132.83, 131.56, 131.40, 130.53, 130.23, 129.68, 129.61, 128.75, 128.58, 127.80, 127.43, 127.17, 127.06, 126.51, 126.24, 126.14, 125.90, 125.30, 125.05, 124.60, 123.27; **IR** (KBr, cm⁻¹) 3629, 3300, 3061, 2360, 1599, 1496, 1441, 1381, 1254, 1110, 1097, 911, 771, 744, 703. **MS**: HR-ESI calculated for C₆₀H₃₇O₄P [M+Na]: 875.2322, found: 875.2322. **[α]_D** = +119.1° (c 0.96, CH₂Cl₂)

3. Optimization of the DKR procedure (Tables 1-3).

To a mixture of a freshly prepared azlactone substrate (0.10 mmol), an alcohol indicated (0.10 mmol) and *ca.* 50 mg of anhydrous sodium sulfate, was added a solution of a catalyst (0.005 mmol) in 1 mL of a solvent. The reaction mixture was stirred at room temperature for 2 days, while the reaction progress was monitored by ^1H NMR and/or TLC. After the reaction was complete, the mixture was applied directly to a silica gel column and eluted with hexane/ CH_2Cl_2 /EtOAc (50:15:15). Enantiomeric excess was determined by direct HPLC analysis of the ester product (for conditions, see Section 7.)

4. Comparison of untreated and activated forms of catalyst **3c**.

Table 1S.

Time (h)	Untreated catalyst, 5 mol%	Catalyst washed w/HCl, 5 mol%	Catalyst washed w/HCl, 2 mol%	Catalyst washed w/HCl, 1 mol%
0.5	4	52	25	16
1	8	57	39	24
2	14	75	53	33
3	22	81	59	39
4	26	87	66	47
5	35	90	69	50
6	37	92	75	57
12	66	100	86	73
24	82	-	100	87
36	92	-	-	-
48	100	-	-	100
%ee	90.3	89.0	88.6	88.0

Untreated catalyst. Catalyst **3c** was purified by chromatography (CH_2Cl_2 /MeOH = 100:2). Solvent removal left yellow, compact residue, which was taken up in CH_2Cl_2 , diluted with hexanes and evaporated again to dryness to produce flocculent, off-white powder.

Acid-washed catalyst. A solution of the purified catalyst **3c** in CH_2Cl_2 (see above) was shaken in a separatory funnel with 4M aqueous HCl, separated from the aqueous layer, dried over Na_2SO_4 , diluted with hexane and evaporated to dryness.

Catalytic activity measurements. Stock solutions of both forms of catalyst **3c** in CDCl₃ (0.005 M) were prepared. These were added separately to identically prepared mixtures of azlactone **1a** (0.10 mmol), 1-naphthylmethanol (0.10 mmol), and Na₂SO₄. The solutions were transferred into NMR tubes and checked by ¹H NMR at time intervals indicated below, monitoring peaks at δ 5.5 ppm (singlet, starting material) and δ 5.8 ppm (doublet, product). The test was conducted analogously with lower catalyst loadings of acid-washed catalyst **3c** (using 0.002 M and 0.001 M stock solutions, respectively). In each case, enantiomeric purity of the product was determined. The data shown in on the graph in Figure 2 are listed in Table 1S.

5. Optimized DKR procedure (Table 4).

To a mixture of a freshly prepared azlactone substrate (0.10 mmol), 1-naphthylmethanol (0.11 mmol), and *ca.* 50 mg of Na₂SO₄, was added a solution of catalyst **3c** (0.005 mmol, *washed w/HCl*) in 1 mL of CHCl₃. After 12-24 h, the mixture was applied directly to a silica gel column and eluted with hexane/CH₂Cl₂/EtOAc (10:3:3). Enantiomeric excess of the ester products was determined either directly by HPLC analysis or (for R¹ = *i*-Pr) after LAH reduction to the alcohol.

6. Absolute configuration of the products.

Absolute configuration of the major enantiomer was determined in the case of esters with R¹ = Ph, Me and *i*-Pr by HPLC comparison with authentic samples derived from commercially available amino acids. In the case of other e with R¹ = Aryl, the absolute configuration was assigned by analogy with R¹ = Ph.

7. Characterization data and HPLC properties

¹H NMR (300 MHz, CDCl₃): δ 7.74-7.71 (m, 2H), 7.44-7.10 (m, 13H), 5.75 (d, *J*=7.2 Hz, 1H), 5.13 (A of AB, *J*_{AB}=12.6 Hz, 1H), 5.09 (B of AB, *J*_{AB}=12.6 Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ 171.13, 166.79, 136.75, 135.34, 133.88, 132.10, 129.23, 128.84, 128.77, 128.61, 128.18, 127.62, 127.41, 67.77, 57.17; **IR** (thin film): 3319, 3062, 1742, 1644, 1520, 1485, 1327, 1171, 696; **MS**:

HR-ESI calculated for C₂₂H₁₉NO₃H (M+H⁺) *m/z*: 346.1445, found: *m/z*: 346.1438. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (R)-enantiomer: 27.1 min; (S)-enantiomer: 33.8 min.

¹H NMR (300 MHz, CDCl₃): δ 7.77-7.74 (m, 2H), 7.42-7.28 (m, 9H), 7.23-7.19 (m, 2H), 7.13 (d, *J* = 6.6 Hz, 1H), 5.80 (d, *J* = 6.9 Hz, 1H), 5.23 (A of AB, *J*_{AB}=12.6 Hz, 1H), 5.18 (B of AB, *J*_{AB}=12.6 Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃): δ 171.02, 165.71, 138.40, 136.53, 135.23, 132.23, 129.26, 129.11, 128.90, 128.82, 128.77, 128.64, 128.17, 127.58, 100.08, 67.85, 67.20; **IR** (KBr, cm⁻¹) 3323, 3033, 2922, 1739,

1639, 1525, 1484, 1172, 696; **MS**: HR-ESI calculated for $C_{22}H_{18}ClNO_3H$ ($M+H^+$) m/z : 380.1048, found m/z : 380.1035. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (R)-enantiomer: 8.8 min; (S)-enantiomer: 19.8 min.

1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 8.7 Hz, 2H), 7.43-7.29 (m, 8H), 7.22-7.19 (m, 2H), 7.23-7.19 (m, 2H), 6.92 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 6.6 Hz, 1H), 5.82 (d, J = 6.9 Hz, 1H), 5.22 (A of AB, J_{AB} =12.6 Hz, 1H), 5.17 (B of AB, J_{AB} =12.6 Hz, 1H), 3.84 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.25, 166.29, 162.72, 136.90, 135.36, 129.24,

129.18, 128.74, 128.57, 128.14, 127.59, 126.14, 114.02, 67.71, 57.11, 55.64; **IR** (KBr, cm^{-1}) 3317, 2922, 1741, 1641, 1606, 1496, 1254, 1175, 697. **MS**: HR-ESI calculated for $C_{23}H_{21}NO_4H$ ($M+H^+$) m/z : 376.1543, found m/z : 376.1536. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (R)-enantiomer: 11.9 min; (S)-enantiomer: 24.6 min.

1H NMR (300 MHz, $CDCl_3$): δ 7.43-7.26 (m, 8H), 7.23-7.16 (m, 2H), 6.94-6.93 (m, 2H), 6.59-6.57 (m, 1H), 5.80 (d, J = 6.9 Hz, 1H), 5.22 (A of AB, J_{AB} =12.6 Hz, 1H), 5.17 (B of AB, J_{AB} =12.6 Hz, 1H), 3.80 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.99, 166.65, 161.13, 136.63, 136.05, 135.32, 129.21, 128.82, 128.76, 128.59, 128.16, 127.61, 105.32, 104.23, 67.75, 57.24, 55.81. **IR** (KBr, cm^{-1})

1) 3315, 2923, 1743, 1648, 1594, 1521, 1205, 1157, 697; **MS**: HR-ESI calculated for $C_{24}H_{23}NO_5H$ ($M+H^+$) m/z : 406.1649, found m/z : 406.1643. **HPLC** (CHIRALCEL OD-H, IPA/hexane= 3/10, 1.0 mL/min): (S)-enantiomer: 18.9 min; (R)-enantiomer: 28.0 min.

1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.34 (m, 5H), 7.12 (d, J = 6.6 Hz, 1H), 6.94-6.93 (m, 2H), 6.59-6.57 (m, 1H), 5.74 (d, J = 6.9 Hz, 1H), 3.81 (s, 6H), 3.76 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.82, 166.82, 161.33, 136.90, 136.22, 129.46, 129.06, 127.76, 105.52, 104.37, 57.31, 56.02, 53.33; **IR** (KBr, cm^{-1}) 3315, 2923, 1743, 1648, 1594, 1521, 1205, 1157, 697; **MS**: HR-ESI calculated for $C_{18}H_{19}NO_5H$ ($M+H^+$) m/z : 330.1336, found m/z : 330.1327. **HPLC** (CHIRALCEL OD-H,

IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 15.6 min; (R)-enantiomer: 18.1 min.

1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.25 (m, 5H), 7.14 (d, J = 6.9 Hz, 1H), 6.94-6.93 (m, 2H), 6.59-6.57 (m, 1H), 5.69 (d, J = 6.6 Hz, 1H), 5.12-5.04 (m, 1H), 3.81 (s, 6H), 1.29 (d, J = 6.3 Hz, 3H), 1.12 (d, J = 6.0 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.63, 166.55, 161.12, 137.03, 136.21, 129.11, 128.63, 127.43, 105.29, 104.15, 70.09, 57.20, 55.82, 21.94, 21.57; **IR** (KBr, cm^{-1}) 3319, 2922, 1737, 1651, 1594, 1520, 1456, 1354, 1206, 1157,

1105, 1064, 698; **MS**: HR-ESI calculated for $C_{20}H_{23}NO_5H$ ($M+H^+$) m/z : 358.1649, found m/z : 358.1636. **HPLC** (CHIRALCEL AS-H, IPA/hexane=2/10, 1.0 mL/min): (S)-enantiomer: 11.3 min; (R)-enantiomer: 14.2 min.

¹H NMR (300 MHz, CDCl₃): δ 7.45-7.42 (m, 2H), 7.39-7.29 (m, 3H), 7.19 (d, *J* = 6.6 Hz, 1H), 6.95-6.94 (m, 2H), 6.59-6.57 (m, 1H), 5.74 (d, *J* = 6.9 Hz, 1H), 3.96-3.93 (m, 2H), 3.81 (s, 6H), 1.98-1.80 (m, 1H), 0.82 (m, 6H); **¹³C NMR** (75 MHz, CDCl₃): δ 171.20, 166.59, 161.13, 137.01, 136.13, 129.14, 128.72, 127.47, 105.30, 104.18, 72.12, 57.20, 55.80, 27.88, 19.04; **IR** (KBr, cm⁻¹) 3316, 2961, 1741, 1651, 1595, 1522, 1456, 1353, 1206, 1157, 1065, 699; **MS**: HR-ESI calculated for C₂₁H₂₅NO₅H (M+H⁺) *m/z*: 372.1805, found *m/z*: 372.1808. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 21.3 min; (R)-enantiomer: 34.6 min.

¹H NMR (300 MHz, CDCl₃): δ 7.46-7.43 (m, 2H), 7.39-7.31 (m, 3H), 7.21 (d, *J* = 6.9 Hz, 1H), 6.96-6.95 (m, 2H), 6.59-6.58 (m, 1H), 5.75 (d, *J* = 6.9 Hz, 1H), 3.91 (A of AB *J*_{AB}=10.5 Hz, 1H), 3.80 (B of AB *J*_{AB}=10.5 Hz, 1H), -3.81 (s, 6H), 0.82 (s, 6H); **¹³C NMR** (75 MHz, CDCl₃): δ 171.20, 166.58, 161.14, 137.09, 136.15, 129.12, 128.71, 127.43, 105.30, 104.18, 75.27, 57.25, 55.82, 31.72, 26.41; **IR** (KBr, cm⁻¹) 3318, 2958, 1741, 1648, 1594, 1522, 1205, 1157, 698; **MS**: HR-ESI calculated for C₂₂H₂₇NO₅H (M+H⁺) *m/z*: 386.1962, found *m/z*: 386.1968; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 15.6 min; (R)-enantiomer: 39.9 min.

¹H NMR (300 MHz, CDCl₃): δ 7.46-7.31 (m, 5H), 7.13 (d, *J* = 6.9 Hz, 1H), 6.94-6.93 (m, 2H), 6.59-6.57 (m, 1H), 5.91-5.79 (m, 1H), 5.76 (d, *J* = 6.9 Hz, 1H), 5.24-5.20 (m, 1H), 5.18-5.17 (m, 1H), 4.68-4.64 (m, 2H), 3.81 (s, 6H); **¹³C NMR** (75 MHz, CDCl₃): δ 170.83, 166.62, 161.13, 136.69, 136.05, 131.47, 129.24, 128.85, 118.94, 105.31, 104.19, 66.54, 57.19, 55.81; **IR** (KBr, cm⁻¹) 3313, 2921, 1742, 1646, 1594, 1521, 1455, 1352, 1205, 1157, 1054, 699; **MS**: HR-ESI calculated for C₂₀H₂₁NO₅H (M+H⁺) *m/z*: 356.1492, found *m/z*: 356.1483; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (R)-enantiomer: 31.8 min; (S)-enantiomer: 58.8 min.

¹H NMR (300 MHz, CDCl₃): δ 7.43-7.33 (m, 7H), 7.11-7.04 (m, 3H), 6.93-6.92 (m, 2H), 6.59-6.58 (m, 1H), 5.76 (d, *J* = 6.9 Hz, 1H), 5.13 (apparent s, 2H), 3.80 (s, 6H); **¹³C NMR** (75 MHz, CDCl₃): δ 170.88, 166.70, 161.14, 136.40, 135.94, 134.36, 131.91, 129.76, 129.29, 128.96, 127.61, 122.64, 105.32, 104.20, 66.86, 57.27, 55.82; **IR** (KBr, cm⁻¹) 3315, 2922, 1744, 1652, 1594, 1519, 1455, 1352, 1205, 1157, 1069, 698; **MS**:

HR-ESI calculated for $C_{24}H_{22}BrNO_5H$ ($M+H^+$) m/z : 484.0754, found m/z : 484.0735; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 24.4 min; (R)-enantiomer: 41.7 min.

1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.32 (m, 4H), 7.19-7.12 (m, 3H), 6.85-6.82 (m, 2H), 6.59-6.57 (m, 1H), 5.17 (A of AB, J_{AB} =12.0 Hz, 1H), 5.10 (B of AB, J_{AB} =12.0 Hz, 1H), 3.81 (s, 6H), 3.79 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.23, 166.59, 161.13, 159.97, 136.71, 136.09, 130.13, 129.17, 128.76, 127.56, 114.14, 105.30, 104.20, 67.71, 57.19, 55.80, 55.48. **IR** (KBr, cm^{-1}) 3316, 2918, 2849, 1739, 1653,

1593, 1514, 1456, 1352, 1248, 1205, 1157, 1064, 1032, 822, 699; **MS**: HR-ESI calculated for $C_{25}H_{25}NO_6H$ ($M+H^+$) m/z : 436.1755, found m/z : 436.1769. **HPLC** (CHIRALCEL OD-H, IPA/hexane=2/10, 1.0 mL/min): (S)-enantiomer: 27.4 min; (R)-enantiomer: 36.4 min.

1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.33 (m, 5H), 6.97 (d, J = 6.6 Hz, 1H), 6.92-6.91 (m, 2H), 6.59-6.58 (m, 1H), 5.73 (d, J = 6.9 Hz, 1H), 5.28 (apparent s, 2H), 3.81 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.50, 166.75, 161.15, 135.84, 135.80, 129.29, 129.08, 127.48, 105.31, 104.22, 57.16, 55.81, 54.72. **IR** (KBr, cm^{-1})

3316, 2921, 1751, 1657, 1594, 1523, 1508, 1456, 1353, 1206, 1157, 1061, 941, 698; **MS**: HR-ESI calculated for $C_{24}H_{18}F_5NO_5H$ ($M+H^+$) m/z : 496.1178, found m/z : 496.1172. **HPLC** (CHIRALCEL AD-H, IPA/hexan=2/10, 1.0 mL/min): (S)-enantiomer: 15.3 min; (R)-enantiomer: 31.3 min.

1H NMR (300 MHz, $CDCl_3$): δ 7.87-7.82 (m, 2H), 7.77-7.74 (m, 1H), 7.51-7.37 (m, 6H), 7.32-7.28 (m, 3H), 7.2 (d, J = 6.9 Hz, 1H), 6.95-6.93 (m, 2H), 6.59-6.58 (m, 1H), 5.79 (d, J = 6.9 Hz, 1H), 5.64 (s, 2H), 3.78 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.04, 166.68, 161.13, 136.52, 136.05, 133.88, 131.67, 130.72, 129.76, 129.18, 128.85, 128.80, 127.68, 127.58, 126.82, 126.19, 125.36, 123.63, 105.33, 104.24, 66.46, 57.34, 55.82; **IR**

(KBr, cm^{-1}) 3327, 2920, 1740, 1651, 1594, 1512, 1456, 1353, 1263, 1205, 1156, 1063, 1049, 792, 776; **MS**: HR-ESI calculated for $C_{28}H_{25}NO_5H$ ($M+H^+$) m/z : 456.1805, found m/z : 456.1814. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 24.8 min; (R)-enantiomer: 46.1 min.

1H NMR (300 MHz, $CDCl_3$): δ 7.83-7.72 (m, 3H), 7.62 (s, 1H), 7.51-7.42 (m, 4H), 7.36-7.34 (m, 3H), 7.31-7.28 (m, 1H), 7.15 (d, J = 6.6 Hz, 1H), 6.95-6.94 (m, 2H), 6.59-6.58 (m, 1H), 5.83 (d, J = 6.9 Hz, 1H), 5.34 (m, 2H), 3.80 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.00, 166.66, 161.14, 136.65, 136.05,

133.33, 133.30, 132.77, 129.26, 128.88, 128.59, 128.21, 127.90, 127.64, 127.16, 126.54, 125.54, 105.30, 104.23, 67.80, 57.30, 55.82; **IR** (KBr, cm^{-1}) 3318, 2920, 1741, 1652, 1594, 1510, 1455, 1353, 1205, 1156, 1064, 698; **MS**: HR-ESI calculated for $\text{C}_{28}\text{H}_{25}\text{NO}_5\text{H}$ ($\text{M}+\text{H}^+$) m/z : 456.1805, found m/z : 456.1816. **HPLC** (CHIRALCEL OD-H, IPA/hexane=4/10, 1.0 mL/min): (S)-enantiomer: 30.1 min; (R)-enantiomer: 42.3 min.

^1H NMR (300 MHz, CDCl_3): δ 8.21-8.19 (m, 2H), 8.11-8.00 (m, 6H), 7.93 (d, $J = 7.8$ Hz, 1H), 7.39-7.36 (m, 3H), 7.26-7.24 (m, 2H), 7.13 (d, $J = 6.9$ Hz, 1H), 6.92-6.91 (m, 2H), 6.57-6.55 (m, 1H), 5.89 (s, 2H), 5.81 (d, $J = 6.9$ Hz, 1H), 3.76 (s, 6H); **^{13}C NMR** (75 MHz, CDCl_3): δ 171.06, 166.66, 161.10, 136.49, 136.04, 132.11, 131.38, 130.86, 129.73, 129.17, 128.78, 128.45, 128.17, 128.02, 127.84, 127.54, 126.32, 125.77, 125.74, 125.02, 125.76, 124.70, 122.90, 195.29, 104.20, 66.68, 57.39,

55.79; **IR** (KBr, cm^{-1}) 3329, 2922, 1734, 1639, 1593, 1520, 1455, 1352, 1260, 1205, 1156, 1064, 844, 750. **MS**: HR-ESI calculated for $\text{C}_{34}\text{H}_{27}\text{NO}_5\text{Na}$ ($\text{M}+\text{Na}^+$) m/z : 552.1781, found m/z : 552.1805. **HPLC** (CHIRALCEL OD-H, IPA/hexane=4/10, 1.0 mL/min): (S)-enantiomer: 22.8 min; (R)-enantiomer: 40.7 min.

^1H NMR (300 MHz, CDCl_3): δ 7.87-7.83 (m, 2H), 7.69 (d, $J = 8.1$ Hz, 1H), 7.52-7.47 (m, 4H), 7.43-7.37 (m, 5H), 7.28-7.18 (m, 5H), 6.91 (d, $J = 2.4$ Hz, 2H), 6.59-6.57 (m, 1H), 5.72 (d, $J = 6.6$ Hz, 1H), 5.65 (d, $J = 12.3$ Hz, 1H), 5.60 (d, $J = 12.3$ Hz, 1H), 3.79 (s, 6H); **^{13}C NMR** (75 MHz, CDCl_3): δ 170.64, 166.56, 161.16, 135.80, 135.17, 134.67, 133.89, 131.63, 130.43, 129.95, 129.24, 128.89, 128.82, 127.99, 126.85, 126.26, 125.30, 123.49, 105.29, 104.29, 66.77, 56.67, 55.81; **IR** (KBr, cm^{-1}) 3299, 2923,

1740, 1644, 1594, 1513, 1492, 1352, 1205, 1157, 1091, 1064, 794, 775; **MS**: HR-ESI calculated for $\text{C}_{28}\text{H}_{24}\text{ClNO}_5\text{H}$ ($\text{M}+\text{H}^+$) m/z : 490.1416, found m/z : 490.1410. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 35.6 min; (R)-enantiomer: 47.9 min.

^1H NMR (300 MHz, CDCl_3): δ 7.86-7.82 (m, 2H), 7.77-7.74 (m, 1H), 7.51-7.38 (m, 4H), 7.30-7.26 (m, 2H), 7.07 (d, $J = 6.6$ Hz, 1H), 6.91 (d, $J = 2.1$ Hz, 2H), 6.82-6.77 (m, 2H), 6.57 (t, $J = 2.1$ Hz, 1H), 5.70 (d, $J = 6.9$ Hz, 1H), 5.63 (s, 2H), 3.79 (s, 6H), 3.77 (s, 3H); **^{13}C NMR** (75 MHz, CDCl_3): δ 192.25, 171.22, 166.62, 161.11, 159.97, 136.11, 133.87, 131.68, 130.77, 129.73, 128.79, 128.59, 127.71, 126.77, 126.15, 125.35, 123.68, 114.54, 105.28, 104.20, 66.38, 56.77, 55.51; **IR** (KBr, cm^{-1}) 3316, 2924, 1741,

1653, 1594, 1512, 1458, 1353, 1249, 1205, 1177, 1157, 1063, 797; **MS**: HR-ESI calculated for $\text{C}_{29}\text{H}_{27}\text{NO}_6\text{H}$ ($\text{M}+\text{H}^+$) m/z : 486.1911, found m/z : 486.1934. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 35.0 min; (R)-enantiomer: 49.9 min.

¹H NMR (300 MHz, CDCl₃): δ 7.87-7.82 (m, 2H), 7.77-7.75 (m, 1H), 7.51-7.38 (m, 4H), 7.26-7.18 (m, 1H), 7.11 (d, *J* = 6.6 Hz, 1H), 6.97-6.81 (m, 5H), 6.59-6.58 (m, 1H), 5.75 (d, *J* = 7.2 Hz, 1H), 5.64 (s, 2H), 3.80 (s, 6H), 3.66 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃): δ 170.90, 166.66, 161.13, 160.17, 137.88, 136.04, 133.88, 131.68, 130.72, 130.20, 129.78, 128.83, 127.78, 126.84, 126.19, 125.35, 123.64, 119.69, 114.63, 112.96, 105.31, 104.24, 66.49, 57.26, 55.40; **IR** (KBr, cm⁻¹) 3313, 2923, 1741, 1651, 1595, 1513, 1456, 1353, 1263, 1205, 1156, 1063, 1049, 792, 776; **MS**: HR-ESI calculated for C₂₉H₂₇NO₆H (M+H⁺) *m/z*: 486.1911, found *m/z*: 486.1910. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 26.5 min; (R)-enantiomer: 47.0 min.

¹H NMR (300 MHz, CDCl₃): δ 7.85-7.76 (m, 3H), 7.49-7.36 (m, 5H), 7.32-7.13 (m, 4H), 6.92-6.91 (m, 2H), 6.58-6.56 (m, 1H), 6.11 (d, *J* = 7.2 Hz, 1H), 5.66 (s, 2H), 3.78 (s, 6H); **¹³C NMR** (75 MHz, CDCl₃): δ 170.33, 166.59, 161.11, 135.94, 134.83, 133.83, 133.78, 131.63, 130.70, 130.67, 130.36, 129.92, 129.69, 128.80, 127.63, 127.44, 126.72, 126.11, 125.30, 123.57, 105.32, 104.27, 66.64, 57.79, 55.67; **IR** (KBr, cm⁻¹) 3315, 2924, 1743, 1651, 1594, 1512, 1456, 1352, 1205, 1157, 1063, 797, 754, 735; **MS**: HR-ESI calculated for C₂₈H₂₄ClNO₅H (M+H⁺) *m/z*: 490.1416, found *m/z*: 490.1410; **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 32.6 min; (R)-enantiomer: 79.1 min.

¹H NMR (300 MHz, CDCl₃): δ 7.82 (t, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.49-7.32 (m, 5H), 7.27-7.20 (m, 2H), 6.95-6.88 (m, 3H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.56-6.55 (m, 1H), 5.96 (d, *J* = 8.1 Hz, 1H), 5.66 (A of AB, *J*_{AB}=12.3 Hz, 1H), 5.57 (B of AB, *J*_{AB}=12.3 Hz, 1H), 3.78 (s, 6H), 3.30 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃): δ 171.04, 166.73, 161.03, 157.10, 136.61, 133.84, 131.76, 131.34, 131.12, 129.96, 129.40, 128.68, 127.72, 126.66, 126.03, 125.50, 125.36, 123.81, 121.18, 111.03, 105.34, 103.94, 66.04, 55.76, 55.13, 54.49; **IR** (KBr, cm⁻¹) 3353, 2922, 1743, 1659, 1594, 1512, 1495, 1461, 1351, 1252, 1205, 1147, 1063, 755; **MS**: HR-ESI calculated for C₂₉H₂₇NO₆H (M+H⁺) *m/z*: 486.1911, found *m/z*: 486.1895. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 26.9 min; (R)-enantiomer: 38.8 min.

¹H NMR (300 MHz, CDCl₃): δ 8.16-8.13 (m, 1H), 7.86-7.78 (m, 3H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.49-7.24 (m, 8H), 7.05 (d, *J* = 7.5 Hz, 2H), 6.90-6.89 (m, 2H), 6.56-6.52 (m, 2H), 5.66 (s, 2H), 3.76 (s, 6H); **¹³C NMR** (75 MHz, CDCl₃): δ 171.53, 166.92, 161.09, 135.96, 134.31, 133.79, 132.41, 131.60, 131.30, 130.72, 129.71, 129.65, 129.10, 128.72, 127.75, 127.25, 126.67, 126.35, 126.07, 125.37,

125.27, 123.58, 123.44, 105.33, 104.27, 66.41, 55.80, 54.50; **IR** (KBr, cm^{-1}) 3312, 2922, 1740, 1653, 1594, 1511, 1457, 1349, 1205, 1194, 1156, 1063, 792, 776; **MS**: HR-ESI calculated for $\text{C}_{32}\text{H}_{27}\text{NO}_5\text{H}$ ($\text{M}+\text{H}^+$) m/z : 506.1962, found m/z : 506.1941. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 22.9 min; (R)-enantiomer: 66.6 min.

^1H NMR (300 MHz, CDCl_3): δ 7.82-7.74 (m, 5H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.51-7.34 (m, 6H), 7.27-6.95 (m, 2H), 6.95-6.94 (m, 1H), 6.59-6.58 (m, 1H), 5.96 (d, $J = 6.6$ Hz, 1H), 5.64 (s, 2H), 3.79 (s, 6H); **^{13}C NMR** (75 MHz, CDCl_3): δ 170.05, 166.70, 161.14, 136.04, 133.88, 133.84, 133.47, 133.44, 131.65, 130.64, 129.81, 129.10, 128.77, 128.33, 127.87, 126.93, 126.73, 126.68, 126.63, 126.14, 125.30, 124.98, 123.55, 105.33, 104.29, 66.61, 57.43, 55.80; **IR** (KBr, cm^{-1}) 3313, 2923, 1741, 1654, 1595, 1511, 1458, 1351, 1205, 1157, 1064, 793, 776. **MS**: HR-ESI calculated

for $\text{C}_{32}\text{H}_{27}\text{NO}_5\text{H}$ ($\text{M}+\text{H}^+$) m/z : 506.1962, found m/z : 506.1939. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 27.1 min; (R)-enantiomer: 50.7 min.

^1H NMR (300 MHz, CDCl_3): δ 8.01-7.98 (m, 1H), 7.91-7.86 (m, 2H), 7.57-7.43 (m, 4H), 6.90 (d, $J = 2.4$ Hz, 2H), 6.73 (d, $J = 6.9$ Hz, 1H), 6.58-6.57 (m, 1H), 5.70 (A of AB, $J_{AB}=12.6$ Hz, 1H), 5.63 (B of AB, $J_{AB}=12.6$ Hz, 1H), 4.87-4.77 (m, 1H), 3.80 (s, 6H), 1.48 (d, $J = 7.2$ Hz, 3H); **^{13}C NMR** (75 MHz, CDCl_3): δ 173.20, 166.92, 161.11, 136.36, 133.98, 131.79, 130.98, 129.84, 129.00, 127.91, 126.97, 126.28, 125.45, 123.62, 105.16, 104.17, 66.00, 55.79,

48.99, 18.76; **IR** (KBr, cm^{-1}) 3319, 2925, 1741, 1645, 1594, 1532, 1456, 1354, 1205, 1156, 1063, 776; **MS**: HR-ESI calculated for $\text{C}_{23}\text{H}_{37}\text{NO}_5\text{H}$ ($\text{M}+\text{H}^+$) m/z : 394.1649, found m/z : 394.1640. **HPLC** (CHIRALCEL OD-H, IPA/hexane=3/10, 1.0 mL/min): (S)-enantiomer: 33.4 min; (R)-enantiomer: 38.6 min.

^1H NMR (300 MHz, CDCl_3): δ 8.03-7.99 (m, 1H), 7.91-7.86 (m, 2H), 7.58-7.43 (m, 4H), 6.90 (d, $J = 2.1$ Hz, 2H), 6.60-6.58 (m, 2H), 5.70 (A of AB, $J_{AB}=12.0$ Hz, 1H), 5.62 (B of AB, $J_{AB}=12.0$ Hz, 1H), 4.82 (dd, $J_1 = 8.7$ Hz, $J_2 = 4.5$ Hz, 1H), 3.80 (s, 6H), 2.32-2.17 (m, 1H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 6.9$ Hz, 3H); **^{13}C NMR** (75 MHz, CDCl_3): δ 172.18, 167.40, 161.13, 136.64, 133.95, 131.80, 130.99, 129.84, 128.99, 128.11, 126.94, 126.27,

125.45, 123.65, 105.23, 103.96, 65.73, 57.76, 55.79, 31.84, 19.27, 17.91; **IR** (KBr, cm^{-1}) 3328, 2961, 2924, 1736, 1654, 1594, 1525, 1458, 1355, 1205, 1156, 1064, 794, 777. **MS**: HR-ESI calculated for $\text{C}_{25}\text{H}_{27}\text{NO}_5\text{H}$ ($\text{M}+\text{H}^+$) m/z : 422.1962, found m/z : 422.1960. **HPLC** (for alcohol obtained by LAH reduction) (CHIRALCEL AS-H, IPA/hexane=1/10, 1.0 mL/min): (S)-enantiomer: 13.2 min; (R)-enantiomer: 26.7 min.

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Precursor to 3h

Precursor to 3h

3h

Table 2, entry 1

Table 2, entry 1

Table 2, entry 2

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Table 2, entry 3

Table 2, entry 3

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Table 4, entry 10

Table 4, entry 11

Table 4, entry 11

Table 4, entry 14

Table 4, entry 14