Total Synthesis of (+)-Lithospermic Acid by Asymmetric Intramolecular Alkylation via Catalytic C-H Bond Activation

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Supporting Information

Experimental:

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. THF was distilled under N₂ from sodium benzophenone ketyl, pyridine from calcium hydride, and methanol from magnesium methoxide immediately prior to use. Degassed toluene was purified by passage through an activated alumina column. Methyl chloroformate was purchased from Acros, quinoline was purchased from Aldrich, and (*R*)-(-)-aminoindane was purchased from Lancaster, and all were distilled prior to use. All organic reactions were performed under an atmosphere of N₂ in flame-dried or oven-dried glassware unless otherwise stated. All C-H activation experiments were prepared in a N₂-filled Vac inert atmosphere box. The following compounds were prepared according to referenced literature procedures: [RhCl(coe)₂]₂¹ and FcPCy₂.² Thin-layer chromatography was performed on Merck 60 F₂₅₄ 250-μm silica gel plates. Visualization of the developed chromatogram was performed by fluorescence quenching, KMnO₄ stain, or *para*-anisaldehyde stain. Flash chromatography was carried out according to the general procedure of Still³ using Merck 60 230-240 mesh silica gel or activity I basic Al₂O₃ as noted. Organic extracts were dried over MgSO₄ or Na₂SO₄ and were concentrated using

(1) Van der Ent, A.; Onderdelinden, A.L. *Inorg. Synth.* **1973**, *14*, 92-93.

(2) Guillaneaux, D.; Kagan, H. *J. Am. Chem. Soc.* **1995**, *60*, 2502.

(3) Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

a Buchi rotary evaporator under high vacuum pressure. Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory, and only partial data are listed. Unless otherwise noted, ^1H and ^{13}C NMR spectra were obtained in CDCl_3 . NMR chemical shifts are reported in ppm and referenced to residual protonated solvent. Mass spectra were performed by the University of California, Berkeley Micro-Mass Facility. Chiral HPLC analyses were performed on an Agilent 1100 system with a Chiral PAK AS column (250 mm $\times$ 4.6 mm) with a flow rate of 1 mL/min and with *i*-PrOH/hexanes as the mobile phase. Reverse phase preparative HPLC purifications were performed on an Agilent 1100 system using a MicrosorbTM C_{18} (250 $\times$ 21.4 mm) column with a flow rate of 20 mL/min and with acetonitrile/water 0.1% TFA as the mobile phase. A Perkin-Elmer 241 polarimeter with a sodium lamp was used to determine specific rotations and concentrations are reported in g/dL. The sense of induction in the asymmetric alkylation by C-H bond activation reaction was ascertained through derivatization to a crystalline hydrazone derivative.

4-(2,2-Dibromo-vinyl)-1,2-dimethoxy-benzene. Carbon tetrabromide (34.67 g, 104.5 mmol, 1.0 equiv) and CH₂Cl₂ (175 mL) were added to a 500 mL round bottom flask equipped with a magnetic stir bar and septum. The reaction flask was cooled to 0 °C with an ice bath for 10 min. Triphenylphosphine (54.84 g, 209.1 mmol, 2.0 equiv) was added in portions over 5 min, and the dark red solution was stirred at 0 °C for 30 min. 3,4-Dimethoxybenzaldehyde (17.37g, 104.5 mmol, 1.0 equiv) was added and the mixture was stirred at 0 °C for 1 h. A 1:1 mixture of H₂O:brine was added and the layers were separated. The aqueous layer was extracted with a 1:1 mixture of hexanes:CH₂Cl₂, and the combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude material was chromatographed on SiO₂ (0-15% EtOAc/hexanes as eluent) to afford 29.37 g (88%) of the dibromide as a yellow oil. IR (ZnSe): 2994, 2955, 2928, 2897, 2831, 1592, 1507, 1456, 1433, 1417, 1254, 1223, 1146, 1017 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.41 (s, 1H, **HC=CHBr₂**), 7.19 (s, 1H, **ArH**), 7.10 (d, 1H, *J* = 7.9 Hz, **ArH**), 6.86 (d, 1H, *J* = 8.4 Hz, **ArH**), 3.90 (s, 3H, **OCH₃**), 3.89 (s, 3H, **OCH₃**). ¹³C NMR (100 MHz, CDCl₃): δ 148.9, 148.1, 136.0, 127.4, 121.6, 110.7, 110.4, 86.8, 55.5, 55.4. EI(+)-HRMS Calcd. for C₁₀H₁₀O₂Br⁸¹Br [M]⁺: 321.9027. Found: 321.9024.

(3,4-Dimethoxy-phenyl)-propynoic acid methyl ester (8). Dibromide (4.41 g, 13.79 mmol, 1.0 equiv) and THF (45 mL) were added to a 250 mL round bottom flask equipped with a magnetic stir bar and septum, and the reaction flask was cooled to -78°C . $n\text{-BuLi}$ (11.6 mL, 2.5 M in hexanes, 2.1 equiv) was added slowly via syringe and the reaction solution was stirred at -78°C for 45 min and then at 0°C for 45 min. The flask was recooled to -78°C , and freshly distilled methyl chloroformate (1.1 mL, 1.3 mmol, 1.0 equiv) was added slowly via syringe. The mixture was stirred at -78°C for 10 min, then 0°C for 1 h. Saturated aqueous NH_4Cl solution was added, and the layers were separated. The aqueous layer was extracted with Et_2O , and the combined organic layers were dried, filtered and concentrated under reduced pressure. The residue was chromatographed on SiO_2 (2-20% EtOAc /hexanes as eluent) to afford 2.83 g (93%) of ester **8** as a white solid. Melting point: $76\text{--}77^\circ\text{C}$. IR (ZnSe): 3002, 2967, 2936, 2893, 2835, 2202, 1693, 1592, 1503, 1437, 1247, 1223, 1134, 1010 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.23 (d, 1H, $J = 8.3\text{ Hz}$, ArH), 7.07(s, 1H, ArH), 6.85 (d, 1H, $J = 8.3\text{ Hz}$, ArH), 3.91 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, CDCl_3): δ 154.3, 151.3, 148.5, 127.0, 114.9, 111.0, 110.8, 87.1, 79.3, 55.7, 55.7, 52.4. EI(+)-HRMS Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_4$ $[\text{M}]^+$: 220.0736. Found 220.0736.

3-(3,4-Dimethoxy-phenyl)-3-(5-formyl-2-methoxy-phenoxy)-acrylic acid methyl ester (9). To a sealed tube equipped with a magnetic stir bar was added MeOH (55 mL) followed by Na metal (2.10 g, 91.5 mmol, 1.6 equiv, cut into small pieces). Once all the Na had dissolved, isovanillin (64.1 g, 421 mmol, 7.4 equiv) was added and the reaction mixture became a thick, yellow slurry. After stirring at room temperature for 5 min, pyridine (55 mL) was added, followed by **8** (12.6 g, 57.2 mmol, 1.0 equiv), and the reaction mixture was stirred at 120 °C for 1 h 45 min. The mixture was cooled to room temperature, diluted with EtOAc, and saturated aqueous NH₄Cl solution was added. The layers were separated and the organic layer was washed several times with saturated aqueous K₂CO₃ solution to remove excess isovanillin. The combined organic layers were dried, filtered and concentrated under reduced pressure. The crude material was chromatographed on basic alumina (0-20 % EtOAc/CH₂Cl₂ as eluent) to afford a mixture of *E* and *Z* **9**, which was crystallized using CH₂Cl₂/pentane mixtures to afford 4.99 g (23%) of *Z* **9**. Purification of the mother liquor on SiO₂ (5-75% EtOAc/hexanes as eluent) and subsequent crystallization with CH₂Cl₂/pentane mixtures (repeated twice) afforded 6.94 g (33%) and 0.67 g (3%), respectively, of *Z* **9** (12.6 g total, 59% overall yield of pure *Z* **9**). Melting point: 144-145 °C. IR (ZnSe): 3060, 3007, 2950, 2840, 1716, 1683, 1601, 1513, 1448, 1434, 1344, 1272, 1257, 1222, 1190, 1162, 1127, 1123, 1018, 915, 878, 809 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 9.72 (s, 1H, CHO), 7.50 (dd, 1H, *J* = 1.8, 8.3 Hz, ArH), 7.27 (d, 1H, *J* = 1.8 Hz, ArH), 7.21 (dd, 1H, *J* = 2.0, 8.5 Hz, ArH), 7.10 (d, 1H, *J*

= 2.0 Hz, ArH), 7.04 (d, 1H, J = 8.3 Hz, ArH), 6.79 (d, 1H, J = 8.5 Hz, ArH), 6.08 (s, 1H, CHCO₂Me), 4.04 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.66 (s, 3H, CO₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 190.2, 164.4, 162.2, 154.3, 151.2, 148.8, 146.6, 129.7, 127.5, 125.5, 120.5, 115.0, 111.4, 110.8, 109.1, 104.2, 56.1, 55.7, 55.6, 51.1. FAB(+)-HRMS Calcd. for C₂₀H₂₀O₇ [M]⁺: 372.1209. Found: 372.1213.

3-(3,4-Dimethoxy-phenyl)-3-[5-(inan-1-yliminomethyl)-2-methoxy-phenoxy]-acrylic

acid methyl ester (6). To a 50 mL round bottom flask equipped with a magnetic stir bar and septum was added **9** (1.02 g, 2.75 mmol, 1.0 equiv), benzene (14 mL), 4 Å molecular sieves (8.0 g), and (*R*)-(-)-aminoindane (0.385 g, 2.89 mmol, 1.05 equiv). The reaction flask was then equipped with a reflux condenser and the mixture was heated to reflux for 14 h. The reaction mixture was cooled to room temperature, diluted with benzene, dried over Na₂SO₄, filtered through Celite[®] and concentrated. The residue was dissolved in minimal CH₂Cl₂ and precipitated with pentane to afford 1.33 g (99%) of **6** as a white foam. IR (ZnSe): 2946, 2361, 1719, 1636, 1601, 1579, 1510, 1457, 1431, 1347, 1264, 1218, 1127, 1064, 1020, 913, 807, 762, 728 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.18 (s, 1H, CH=NCH), 7.38 (d, 1H, *J* = 8.4 Hz, ArH), 7.31-7.11 (m, 6H, ArH x 6), 7.00 (d, 1H, *J* = 7.3 Hz, ArH), 6.90 (d, 1H, *J* = 8.4 Hz, ArH), 6.73 (d, 1H, *J* = 8.5 Hz, ArH), 5.97 (s, 1H, CHCO₂CH₃), 4.78 (t, 1H, *J* = 7.2 Hz, CH₂CHN=CH), 3.93 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.76 (s, 3H, OCH₃), 3.64 (s, 3H, CO₂CH₃), 3.07-3.01 (m, 1H, one of ArCH₂CH₂), 2.92-2.84 (m, 1H, one of ArCH₂CH₂), 2.39-2.35 (m, 1H, one of ArCH₂CH₂), 2.19-2.09 (m, 1H, one of ArCH₂CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 164.6, 162.6, 159.0, 151.3, 150.8, 148.6, 146.0, 144.1, 143.4, 129.2, 128.0, 127.2, 126.0, 124.4, 124.0, 124.0, 120.5, 116.1, 111.6, 110.6, 109.5, 103.6, 74.5, 55.8, 55.5, 55.4, 50.9,

33.9, 30.7. $[\alpha]_D$ (*c* 1.12, CH₂Cl₂) +7.7°. FAB(+)-HRMS Calcd. for C₂₉H₃₀NO₆ [M+H]⁺:
488.2073. Found: 488.2079.

2-(3,4-Dimethoxy-phenyl)-4-formyl-7-methoxy-2,3-dihydro-benzofuran-3-carboxylic acid methyl ester (5). In a dry box, a solution of $[\text{RhCl}(\text{coe})_2]_2$ (0.463 g, 0.644 mmol, 0.1 equiv) and FcPCy_2 (0.739 mg, 1.93 mmol, 0.3 equiv) in toluene (20 mL) was added to a sealed tube equipped with a magnetic stir bar. A solution of imine **6** (3.14 g, 6.44 mmol, 1.0 equiv) in toluene (45 mL) was then added and the reaction vessel was sealed and the solution was stirred at 75 °C for 20 h. The reaction solution was cooled to room temperature, transferred to a round bottom flask with EtOAc rinses and concentrated under reduced pressure. The residue was washed with 1 N HCl (aq) and stirred for 20 min. The mixture was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried, filtered and concentrated under reduced pressure. The crude material was chromatographed on SiO_2 (2-20 % EtOAc/hexanes as eluent) to afford 2.1 g (88%) of **5**, which was recrystallized three times from benzene/pentane mixtures to afford 1.34 g (56%) of enantiopure **5** (determined by HPLC analysis) as a white solid. Melting point: 119-120 °C. IR (ZnSe): 3085, 2983, 2938, 2893, 2827, 1728, 1683, 1614, 1581, 1512, 1434, 1283, 1238, 1140, 1091, 1025, 943, 862, 805 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 9.82 (s, 1H, CHO), 7.39 (d, 1H, $J = 8.3$ Hz, ArH), 6.98 (d, 1H, $J = 8.3$ Hz, ArH), 6.96-6.62 (m, 2H, ArH x 2), 6.82 (d, 1H, $J = 8.2$, ArH), 6.00 (d, 1H, $J = 10.2$ Hz, ArOCHAr), 4.89 (d, 1H, $J = 10.2$ Hz, ArCHCO₂CH₃), 3.97 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 3.23 (s,

3H, CO₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 190.6, 169.7, 149.9, 149.5, 149.0, 148.5, 128.7, 128.2, 126.4, 125.3, 119.4, 111.5, 110.3, 109.4, 87.7, 56.0, 55.8, 55.7, 54.1, 51.7. [α]_D (c 0.95, CH₂Cl₂) -112.9°. FAB(+)-HRMS Calcd. for C₂₀H₂₀O₇ [M]⁺: 372.1209. Found: 372.1213. HPLC analysis (AS column, 70% hexanes: 30% *i*-PrOH, 20 min wait time): peak 1 = 17.5 min (minor enantiomer) and peak 2 = 37.0 min (major enantiomer).

4-(2-Carboxy-vinyl)-2-(3,4-dimethoxy-phenyl)-7-methoxy-2,3-dihydro-benzofuran-

3-carboxylic acid methyl ester (3). To a round bottom flask equipped with a magnetic stir bar and septum was added **5** (0.259 g, 0.696 mmol, 1.0 equiv), malonic acid (0.217 g, 2.09 mmol, 3.0 equiv), pyridine (23 mL) and piperidine (0.7 mL). The reaction mixture was heated to 100 °C for 5 h, then cooled to room temperature, diluted with EtOAc and washed with 1 N HCl (aq). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried, filtered and concentrated under reduced pressure. The crude material was chromatographed on SiO₂ (3-15% Et₂O/CH₂Cl₂ doped with 1% MeOH as eluent) to afford 0.245 g (85%) of acid **3** as a white foam. IR (ZnSe): 3318, 2954, 2840, 1736, 1679, 1605, 1507, 1438, 1262, 1156, 1140, 1082, 1021 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.81 (d, 1H, *J* = 15.9 Hz, CH=CHCO₂H), 7.23 (d, 1H, *J* = 8.6 Hz, ArH), 6.96-6.81 (m, 4H, ArH x 4), 6.27 (d, 1H, *J* = 15.9 Hz, CH=CHCO₂H), 6.04 (d, 1H, *J* = 5.7 Hz, ArOCHAr), 4.49 (d, 1H, *J* = 5.7 Hz, ArCHCO₂CH₃), 3.93 (s, 3H, OCH₃), 3.85 (s, 6H, OCH₃ x 2), 3.79 (s, 3H, CO₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 172.3, 171.7, 149.2, 149.2, 148.4, 146.5, 143.2, 132.2, 125.2, 124.0, 120.8, 118.0, 116.6, 112.9, 111.1, 108.7, 87.4, 56.1, 55.9, 55.9, 55.9, 52.8. [α]_D (c 0.50, CH₂Cl₂) +168.4°. FAB(+)-HRMS Calcd. for C₂₂H₂₂O₈ [M]⁺: 414.1315. Found: 414.1312.

3-(3,4-Dimethoxy-phenyl)-2-hydroxy-propionic acid methyl ester (4). To a 1 L round bottom flask equipped with a magnetic stir bar and reflux condenser was added rosmarinic acid (3.08 g, 8.55 mmol, 1.0 equiv), acetone (400 mL), dimethyl sulfate (10.78 g, 85.48 mmol, 10.0 equiv) and potassium carbonate (11.81 g, 85.48 mmol, 10.0 equiv). The reaction mixture was heated at reflux for 14 h, cooled to room temperature, and diluted with Et_2O and saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The crude material was chromatographed on SiO_2 (10-40% Et_2O /benzene as eluent) to afford pentamethyl rosmarinic acid as a light yellow foam. IR (ZnSe): 3003, 2950, 2934, 2835, 1753, 1708, 1630, 1593, 1503, 1462, 1422, 1258, 1230, 1131, 1029, 976, 805 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.58 (d, 1H, $J = 15.9$ Hz, $\text{CH}=\text{CHCO}_2\text{CH}_3$), 7.00 (d, 1H, $J = 8.3$ Hz, ArH), 6.96 (s, 1H, ArH), 6.77 (d, 1H, $J = 8.3$ Hz, ArH), 6.73-6.72 (3H, m, ArH x 3), 6.27 (d, 1H, $J = 15.9$ Hz, $\text{CH}=\text{CHCO}_2\text{CH}_3$), 5.29 (dd, 1H, $J = 5.0, 7.9$ Hz, CHCO_2CH_3), 3.81 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.66 (s, 3H, CO_2CH_3), 3.14-3.04 (m, 2H, $\text{ArCH}_2\text{CHCO}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3): δ 170.0, 165.9, 151.0, 148.9, 148.4, 147.7, 145.7, 128.1, 126.7, 122.6, 121.1, 114.2, 112.2, 110.9, 110.7, 109.3, 72.7, 55.6, 55.5, 55.5, 55.5, 52.0, 36.8. $[\alpha]_D^{25}$ (c 1.60, CH_2Cl_2) +40.7°. FAB(+)-HRMS Calcd. for $\text{C}_{23}\text{H}_{26}\text{O}_8$ $[\text{M}]^+$: 430.1628. Found:

430.1628. Pentamethyl rosmarinic acid was dissolved in MeOH (40 mL) and NaOMe (0.462 g, 8.55 mmol, 1.0 equiv) was added. The reaction mixture was stirred at room temperature for 2 h. Saturated aqueous NH₄Cl solution was added and the mixture was diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried, filtered and concentrated under reduced pressure. The crude material was chromatographed on SiO₂ (1-10% Et₂O/CH₂Cl₂ as eluent) to afford 1.79 g (87% for two steps) of alcohol **4**. IR (ZnSe): 3387, 3007, 2987, 2942, 2905, 2831, 1720, 1593, 1516, 1417, 1262, 1205, 1156, 1140, 1095, 1025, 964, 858, 784 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 6.69 (m, 3H, ArH), 4.35-4.27 (m, 1H, CHOH), 3.73 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.63 (s, 3H, CO₂CH₃), 3.18-3.11 (m, 1H, OH), 2.94 (dd, 1H, *J* = 4.4, 14.0 Hz, one of ArCH₂CH(OH)CO₂CH₃), 2.79 (dd, 1H, *J* = 6.9, 14.0 Hz, one of ArCH₂CH(OH)CO₂CH₃). ¹³C NMR (75 MHz, CDCl₃): δ 174.1, 148.3, 147.5, 128.6, 121.1, 112.3, 110.7, 71.1, 55.3, 55.3, 51.8, 39.6. [α]_D (*c* 0.67, CH₂Cl₂) +10.6°. FAB(+)-HRMS Calcd. for C₁₂H₁₆O₅ [M]⁺: 240.0998. Found: 240.0998. Melting point: 53-54 °C.

2-(3,4-Dimethoxy-phenyl)-4-{2-[2-(3,4-dimethoxy-phenyl)-1-methoxycarbonyl-ethoxycarbonyl]-vinyl}-7-methoxy-2,3-dihydro-benzofuran-3-carboxylic acid methyl ester (2). To a 50 mL round bottom flask equipped with a magnetic stir bar and septum was added *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC) (2.54 g, 13.3 mmol, 5.4 equiv), 4-dimethylaminopyridine (DMAP) (1.62 g, 13.3 mmol, 5.4 equiv), acid **3** (1.02 g, 2.46 mmol, 1.0 equiv), alcohol **4** (0.96 g, 3.98 mmol, 1.6 equiv) and CHCl_3 (15 mL), and the reaction mixture was stirred at room temperature for 2.5 d. Acetic acid (0.5 mL) was added and the reaction mixture was stirred for 10 min to convert excess alcohol **4** to a more easily separable acetate. The mixture was washed with saturated aqueous NH_4Cl solution, diluted with Et_2O , and the layers were separated. The aqueous layer was extracted with Et_2O , and the combined organic layers were dried, filtered and concentrated under reduced pressure. The crude material was chromatographed on SiO_2 (10-90% EtOAc /hexanes as eluent) to afford 1.25 g (80%) of ester **2** as a white foam. IR (ZnSe): 3003, 2958, 2933, 2831, 1732, 1712, 1610, 1511, 1434, 1258, 1234, 1152, 1140, 1078, 1021, 800, 760 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.71 (d, 1H, $J = 15.9$ Hz, $\text{CH}=\text{CHCO}_2\text{CH}$), 7.17 (d, 1H, $J = 8.5$ Hz, ArH), 6.89-6.85 (m, 3H, ArH x 3), 6.81 (d, 1H, $J = 8.2$ Hz, ArH), 6.77-6.74 (m, 3H, ArH x 3), 6.29 (d, 1H, $J = 15.9$ Hz, $\text{CH}=\text{CHCO}_2\text{CH}$), 6.01 (d, 1H, $J = 5.6$ Hz, ArOCHAr), 5.31 (dd, 1H, $J = 4.8$, 8.2 Hz, $\text{ArCH}_2\text{CHCO}_2\text{CH}_3$), 4.45 (d, 1H, $J = 5.6$ Hz, $\text{ArCHCO}_2\text{CH}_3$), 3.91 (s, 3H, OCH_3),

3.84 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 3.71 (s, 6H, CO₂CH₃ x 2), 3.16 (dd, 1H, *J* = 4.7, 14.3 Hz, one of ArCH₂CHCO₂CH₃), 3.09 (dd, 1H, *J* = 8.2, 14.3 Hz, one of ArCH₂CHCO₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 171.4, 170.0, 165.8, 149.0, 149.0, 148.5, 148.2, 147.8, 146.1, 142.2, 132.1, 128.8, 128.1, 124.7, 124.1, 121.2, 120.6, 117.7, 116.2, 112.7, 112.2, 110.9, 110.9, 108.5, 87.2, 72.8, 55.9, 55.6, 55.6, 55.6, 55.5, 52.5, 52.0, 36.8. [α]_D (*c* 0.49, CH₂Cl₂) +134.5°. FAB(+)-HRMS Calcd. for C₃₄H₃₆O₁₂ [M]⁺: 636.2207. Found: 636.2216.

4-{2-[1-Carboxy-2-(3,4-dimethoxy-phenyl)-ethoxycarbonyl]-vinyl}-2-(3,4-dimethoxy-phenyl)-7-methoxy-2,3-dihydro-benzofuran-3-carboxylic acid (21). To a 100 mL round bottom flask equipped with a magnetic stir bar and septum was added heptamethyl lithospermic acid **2** (0.643 g, 1.01 mmol, 1.0 equiv), Me₃SnOH (0.913 g, 5.05 mmol, 5.0 equiv) and 1,2-dichloroethane (50 mL). The reaction mixture was stirred at 80 °C for 21 h. The flask was then cooled to room temperature, and the mixture was diluted with 1 N HCl (aq) and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried, filtered and concentrated under reduced pressure. The crude material was chromatographed on SiO₂ (5-50% acetone/CH₂Cl₂ doped with 0.5% AcOH as eluent) to afford 0.573 g (93%) of diacid **18** as a white foam. IR (ZnSe): 3514, 3240, 3007, 2933, 2835, 1708, 1601, 1511, 1434, 1266, 1234, 1156, 1140, 1082, 1025, 805, 764 cm⁻¹. ¹H NMR (400 MHz, CD₃COCD₃): δ 7.86 (d, 1H, *J* = 16.0 Hz, CH=CHCO₂CH), 7.37 (d, 1H, *J* = 8.6 Hz, ArH), 7.08 (s, 1H, ArH), 7.02 (d, 1H, *J* = 8.6 Hz, ArH), 6.98-6.82 (m, 5H, ArH x 5), 6.44 (d, 1H, *J* = 15.9 Hz, CH=CHCO₂CH), 6.08 (d, 1H, *J* = 5.1 Hz, ArOCHAr), 5.27 (dd, 1H, *J* = 4.1, 8.3 Hz, ArCH₂CHCO₂H), 4.61 (d, 1H, *J* = 5.1 Hz, ArCHCO₂H), 3.91 (s, 3H, OCH₃), 3.78 (s, 6H, OCH₃ x 2), 3.77 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.20 (dd, 1H, *J* = 4.0, 14.3 Hz, one of ArCH₂CHCO₂H), 3.11 (dd, 1H, *J* = 8.4, 14.2 Hz, one of ArCH₂CHCO₂H). ¹³C NMR (100 MHz, CD₃COCD₃): δ 173.2, 171.4, 166.6, 150.5,

150.1, 149.5, 149.3, 147.4, 143.1, 133.9, 130.0, 129.2, 127.0, 125.3, 122.6, 121.5, 118.9,
117.3, 114.3, 114.2, 112.7, 112.6, 110.6, 88.3, 73.9, 56.5, 56.5, 56.1, 56.1, 56.0, 55.0,
37.7. $[\alpha]_D$ (*c* 0.56, CH₂Cl₂) +173.8°. ES(-)-LRMS (negative ionization) Calcd. for
C₃₂H₃₁O₁₂ [M-H]⁻: 607.2 Found: 607.1.

1-Trimethylsilylquinolinium iodide (TMSI-quinoline). Prepared according to a modified procedure of Brossi and Minamikawa.⁴ In a dry box, a solution of iodotrimethylsilane (5.0 mL, 36.7 mmol, 1.0 equiv) in hexanes (20 mL) was slowly added to a solution of freshly distilled quinoline (8.7 mL, 73.5 mmol, 2.0 equiv) in hexanes (50 mL) with vigorous stirring, and a yellow precipitate formed immediately. The mixture was filtered, and the solid was transferred to a sublimator and sublimed at 100 °C to afford 12 g (99%) of 1-trimethylsilylquinolinium iodide as a yellow solid which was stored in a dry box. Melting point: 225-230 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.93 (d, 1H, *J* = 4.0 Hz, ArH), 8.20 (d, 1H, *J* = 8.3 Hz, ArH), 8.15 (d, 1H, *J* = 8.5 Hz, ArH), 7.83 (d, 1H, *J* = 8.2 Hz, ArH), 7.74 (t, 1H, *J* = 7.6 Hz, ArH), 7.56 (t, 1H, *J* = 7.5 Hz, ArH), 7.43 (dd, 1H, *J* = 4.3, 8.3 Hz, ArH), 0.79 (s, 9H, Si(CH₃)₃). ¹³C NMR (100 MHz, CDCl₃): δ 149.9, 147.6, 136.7, 129.8, 128.9, 128.3, 127.8, 126.8, 121.1, 5.5.

⁴ Minamikawa, J.; Brossi, A. *Tetrahedron Lett.* **1978**, 34, 3085-3086.

Lithospermic acid (1). In a dry box, diacid **18** (0.185 g, 0.304 mmol, 1.0 equiv) and 1-trimethylsilylquinolinium iodide (4.01 g, 12.2 mmol, 40.0 equiv) were added to a 20 mL sealed tube equipped with a magnetic stir bar. The reaction vessel was sealed and heated to 104 °C for 5 h. The reaction mixture was then cooled to room temperature, vented and 1 N HCl (aq) was slowly added. The reaction mixture was diluted with EtOAc, shaken vigorously, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried, filtered and concentrated under reduced pressure. The crude material was chromatographed on SiO₂ (5-40% MeOH/CH₂Cl₂ doped with 1% AcOH as eluent) to afford a dark residue. This residue was further purified by preparative HPLC (C₁₈ column, 5-65% MeCN/H₂O with 0.1% TFA over 90 min, 20 mL/min, monitoring 220 nm, injecting with a minimal amount of MeOH, collecting fractions eluted from 31.5 min through 33.0 min). The collected fractions were extracted with EtOAc, dried, filtered and concentrated under reduced pressure to afford 57 mg (35%) of lithospermic acid as a dark solid. Lyophilizing a solution of lithospermic acid from H₂O/MeCN mixtures liberates the product as a pale yellow powder. Melting point: 183-188 °C. IR (ZnSe): 3334, 2954, 2921, 2856, 1691, 1605, 1507, 1446, 1364, 1283, 1266, 1180, 1111, 1070, 976, 813 cm⁻¹. ¹H NMR (400 MHz, CD₃COCD₃): δ 7.85 (d, 1H, *J* = 16.0 Hz, CH=CHCO₂CH), 7.30 (d, 1H, *J* = 8.5 Hz, ArH), 6.90 (d, 1H, *J* = 8.3 Hz, ArH), 6.89 (m, 1H, ArH), 6.86 (d, 1H, *J* = 2.0 Hz, ArH), 6.82 (d, 1H, *J* = 8.1 Hz,

ArH), 6.81 (dd, 1H, $J = 1.8, 8.1$ Hz, ArH), 6.73 (d, 1H, $J = 8.0$ Hz, ArH), 6.67 (dd, 1H, $J = 2.0, 8.1$ Hz, ArH), 6.37 (d, 1H, $J = 15.9$ Hz, CH=CHCO₂H), 5.98 (d, 1H, $J = 4.6$ Hz, ArOCHAr), 5.18 (dd, 1H, $J = 4.1, 8.5$ Hz, ArCH₂CHCO₂H), 4.53 (d, 1H, $J = 4.7$ Hz, ArCHCO₂H), 3.10 (dd, 1H, $J = 4.1, 14.3$ Hz, one of ArCH₂CHCO₂H), 3.01 (dd, 1H, $J = 8.6, 14.3$, one of ArCH₂CHCO₂H). ¹³C NMR (125 MHz, CD₃OD, ¹H coupled): δ 175.1 (s), 173.5 (s), 168.2 (s), 148.8 (s), 146.7 (s), 146.6 (s), 146.0 (s), 145.3 (s), 145.2 (s), 144.2 (d), 133.8 (s), 129.3 (s), 127.6 (s), 124.6 (s), 122.1 (d), 121.8 (d), 118.6 (d), 118.3 (d), 117.4 (d), 116.4 (d), 116.4 (d), 116.4 (d), 113.4 (d), 88.8 (d), 74.8 (d), 57.5 (d), 37.9 (t). $[\alpha]_D$ (*c* 0.69, MeOH) +136.9° (lit. +78°).⁵ ES(-)-LRMS (negative ionization) Calcd. for C₂₇H₂₁O₁₂ [M-H]⁻: 537.1 Found: 537.0.

⁵ Lin, Y.L.; Wang, C.N.; Shiao, Y.J.; Liu, T.Y.; Wang, W.Y. *J. Chin. Chem. Soc.* **2003**, *50*, 1079-1083.

Lithospermic acid comparison table

¹H NMR data (acetone-d₆)⁶

	Natural (220 MHz) δ (m, <i>J</i> in Hz)	Synthetic (400 MHz) δ (m, <i>J</i> in Hz)
H-7	7.80 (d, 16)	7.85 (d, 16.0)
H-6	7.21 (d, 8)	7.30 (d, 8.5)
H-5	6.83 (d, 8)	6.90 (d, 8.3)
H-13	6.82 (d, 2)	6.89 (s)
H-23	6.81 (d, 2)	6.86 (d, 2.0)
H-26	6.77 (d, 8)	6.82 (d, 8.1)
H-27	6.72 (dd, 2, 8)	6.81 (dd, 1.8, 8.1)
H-16	6.69 (d, 8)	6.73 (d, 8.0)
H-17	6.61 (dd, 2, 8)	6.67 (dd, 2.0, 8.1)
H-8	6.32 (d, 16)	6.37 (d, 15.9)
H-21	5.94 (d, 4.8)	5.98 (d, 4.6)
H-10	5.15 (dd, 5, 8)	5.18 (dd, 4.1, 8.5)
H-20	4.47 (d, 4.8)	4.53 (d, 4.7)
H-11	3.03 (q, 5, 14)	3.10 (dd, 4.1, 14.3)
H-11	3.03 (q, 8, 14)	3.01 (dd, 8.6, 14.3)

¹³C NMR data (CD₃OD, ¹H coupled)⁷

	Natural (125 MHz) δ (m)	Synthetic (125 MHz) δ (m)
C-28	175.0 (s)	175.1 (s)
C-29	173.4 (s)	173.5 (s)
C-9	168.1 (s)	168.2 (s)
C-3	148.6 (s)	148.8 (s)
C-25	146.4 (s)	146.7 (s)
C-24	146.3 (s)	146.6 (s)
C-15	145.8 (s)	146.0 (s)
C-14	144.9 (s)	145.3 (s)
C-4	144.9 (s)	145.2 (s)
C-7	143.0 (d)	144.2 (d)
C-22	133.5 (s)	133.8 (s)
C-12	129.1 (s)	129.3 (s)
C-2	127.3 (s)	127.6 (s)
C-1	124.4 (s)	124.6 (s)
C-27	121.9 (d)	122.1 (d)
C-6	120.9 (d)	121.8 (d)
C-17	118.3 (d)	118.6 (d)
C-5	118.2 (d)	118.3 (d)
C-23	117.4 (d)	117.4 (d)
C-8	116.4 (d)	116.4 (d)
C-26	116.3 (d)	116.4 (d)
C-16	116.2 (d)	116.4 (d)
C-13	113.3 (d)	113.4 (d)
C-20	88.6 (d)	88.8 (d)
C-10	74.7 (d)	74.8 (d)
C-21	57.2 (d)	57.5 (d)
C-11	37.6 (t)	37.9 (t)

⁶ Natural ¹H-NMR data have been reproduced from the reported isolation, see: Kelley, C.J.; Mahajan, J.R.; Brooks, L.C.; Neubert, L.A.; Breneman, W.R.; Carmack, M. *J. Org. Chem.* **1975**, *40*, 1804-1815.

⁷ Natural ¹³C-NMR data have been reproduced from the reported isolation, see: Lin, Y.L.; Wang, C.N.; Shiao, Y.J.; Liu, T.Y.; Wang, W.Y. *J. Chin. Chem. Soc.* **2003**, *50*, 1079-1083.

2-(2-Bromo-4,5-dimethoxy-phenyl)-4-formyl-7-methoxy-2,3-dihydro-benzofuran-3-

carboxylic acid methyl ester. To a 25 mL round bottom flask equipped with a magnetic

stir bar and septum was added aldehyde **5** (0.259 g, 0.696 mmol, 1.0 equiv) and CHCl₃ (7

mL). The flask was cooled to 0 °C in an ice water bath and Br₂ (0.036 mL, 0.696 mmol,

1.0 equiv) was added. The mixture was stirred for 20 min followed by diluting with

saturated aqueous sodium thiosulfate solution and CH₂Cl₂. The layers were separated

and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were

dried, filtered and concentrated under reduced pressure. The crude material was

chromatographed on SiO₂ (1-10% Et₂O/CH₂Cl₂ as eluent) to afford 0.246 g (79%) of the

mono-brominated compound as a white foam. IR (ZnSe): 3007, 2970, 2946, 2835, 1712,

1740, 1614, 1581, 1507, 1438, 1385, 1283, 1262, 1201, 1164, 1176, 1091, 1025, 800, 768

cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 9.85 (s, 1H, CHO), 7.43 (d, 1H, *J* = 8.4 Hz, ArH),

7.07-7.00 (m, 3H, ArH x 3), 6.27 (d, 1H, *J* = 9.6 Hz, ArOCHAr), 5.03 (d, 1H, *J* = 9.9 Hz,

ArCHCO₂CH₃), 4.00 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.22 (s,

3H, CO₂CH₃). ¹³C NMR (75 MHz, CDCl₃): δ 190.4, 169.5, 149.6, 149.5, 149.2, 148.0,

128.7, 128.1, 127.2, 126.3, 125.2, 114.6, 112.3, 111.5, 110.4, 86.8, 56.0, 56.0, 52.0, 51.6.

[α]_D (c 1.43, CH₂Cl₂) -174.9°. FAB(+)-HRMS Calcd. for C₂₀H₁₉BrO₇Li [M+Li]⁺: 457.0477.

Found: 457.0481.

2-(2-Bromo-4,5-dimethoxy-phenyl)-4-[(2,4-dinitrophenyl)-hydrazonomethyl]-7-methoxy-2,3-dihydro-benzofuran-3-carboxylic acid methyl ester. 2,4-

dinitrophenylhydrazine (1.0 g, 5.0 mmol) was dissolved in concentrated sulfuric acid (5 mL) and added to a flask containing EtOH (25 mL) and H₂O (7 mL). A 2 mL portion of this solution was then added to a solution of bromide (0.098 g, 0.217 mmol) in EtOH (2 mL). A red precipitate formed immediately, which was filtered through filter paper and crystallized from CH₂Cl₂/pentane by vapor diffusion to afford 0.081 g (59%) of the 2,4-dinitrophenylhydrazone derivative as red needles. Melting point: 242-244 °C. IR

(ZnSe): 3277, 3117, 3003, 2950, 2840, 1736, 1610, 1585, 1499, 1438, 1332, 1283, 1262, 1201, 1136, 1082, 1025, 739. ¹H NMR (300 MHz, CDCl₃): δ 11.24 (s, 1H, NH), 9.08 (d, 1H, *J* = 2.2 Hz, ArH), 8.31 (dd, 1H, *J* = 2.6, 9.6 Hz, ArH), 8.08 (s, 1H, CH=N), 7.97 (d, 1H, *J* = 9.6 Hz, ArH), 7.12-7.08 (m, 3H, ArH x 3), 6.96 (d, 1H, *J* = 8.4 Hz, ArH), 6.28 (d, 1H, *J* = 9.4 Hz, ArOCHAr), 5.07 (d, 1H, *J* = 9.4 Hz, ArCHCO₂CH₃), 3.99 (s, 3H, OCH₃), 3.90 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 3.18 (s, 3H, CO₂CH₃). ¹³C NMR (75 MHz, CDCl₃): δ 169.5, 153.7, 149.8, 149.4, 148.3, 148.0, 147.2, 144.3, 138.0, 129.9, 129.1, 127.3, 125.8, 123.3, 122.6, 116.6, 114.8, 112.5, 112.2, 110.4, 86.7, 56.2, 56.1, 56.0, 53.4, 51.7. [α]_D (c 1.17, CH₂Cl₂) -43.8°. FAB(+)-HRMS Calcd. for C₂₆H₂₃BrN₄O₁₀ [M]⁺: 630.0597. Found: 630.0595.

**Total Synthesis of (+)-Lithospermic Acid by Asymmetric Intramolecular Alkylation
via Catalytic C-H Bond Activation**

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Supporting Information (Spectral data)

NOESY spectrum of (Z)-olefin

10
9
8
7
6
5
4
3
2
1
0 ppm

1.00

1.08

7.06

1.09

1.07

1.03

1.01

1.00

3.16

3.06

3.03

3.03

1.05

1.08

1.05

1.08

8.184
7.387
7.366
7.313
7.262
7.237
7.218
7.189
7.170
7.152
7.137
7.118
7.106
7.009
6.991
6.915
6.894
6.744
6.722
5.974
5.197
4.798
4.780
4.762
3.928
3.883
3.871
3.852
3.787
3.764
3.645
3.530
3.066
3.035
3.027
3.013
2.917
2.897
2.877
2.857
2.837
2.387
2.377
2.367
2.356
2.347
2.188
2.166
2.147
2.135
2.116
2.094
1.802
1.316
1.300
1.282
1.265

(±)

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
17.508	MM	1.4655	1839.18848	20.91621	49.4512
37.010	MM	3.1124	1880.01306	10.06739	50.5488

73% ee

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
17.086	PB	0.9753	322.14838	3.94263	13.6041
36.301	BB	2.0803	2045.87610	11.50673	86.3959

>99% ee

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
18.925	MM	0.8719	22.54470	4.30954e-1	0.4301
33.650	BB	1.8085	5219.41797	33.89576	99.5699

9.855
8.025
7.825
7.786
7.607
7.339
7.260
7.238
7.216
6.958
6.909
6.899
6.889
6.873
6.827
6.807
6.708
6.468
6.293
6.253
6.049
6.035
4.625
4.498
4.484
4.107
4.026
3.970
3.928
3.848
3.789
3.762
3.665
3.602
3.484
3.466
3.436
3.277
2.157
2.094
1.214
1.196
1.179
-0.014

AVQ-400 som-II-198b (in acetone-d₆, just more scans)

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

- 168.22
- 148.85
- 146.64
- 146.04
- 145.23
- 144.78
- 124.61
- 122.39
- 118.97
- 117.70
- 117.04
- 115.84
- 49.67
- 49.50
- 49.33
- 49.16
- 48.99
- 48.82
- 48.65

2D gCOSY (128 exp., 1 scan each)
5 min 20 sec total time

gHMBC

8.935
8.926
8.208
8.188
8.163
8.142
7.844
7.824
7.755
7.737
7.716
7.582
7.563
7.544
7.445
7.435
7.425
7.414
7.260

0.936
0.785
0.631

0.184
0.056
-0.011

0.13

0.97

0.14

1.01

0.36

3.03

0.08

1.00

0.97

0.49

3.04

0.47

3.59

2.94

0.59

0.34

2.93

0.26

0.35

0.54

10.540

10.190

10.174

9.845

7.952

7.924

7.439

7.411

7.251

7.118

7.074

7.047

7.018

6.994

6.964

6.826

6.771

6.282

6.250

6.164

6.138

5.279

5.050

5.017

4.590

4.449

4.439

4.427

4.417

4.402

4.244

4.220

4.198

4.117

4.108

4.084

4.061

4.004

3.977

3.928

3.877

3.870

3.815

3.798

3.770

3.763

3.626

3.572

3.465

3.222

2.974

2.151

2.139

2.115

2.025

1.926

1.863

1.841

1.765

1.742

1.235

1.093

10
9
8
7
6
5
4
3
2
1
0 ppm