Supporting Information for

**Asymmetric Synthesis of (*S*)-Dihydrokavain from L-Malic acid**

Mustafa Eskicia, Abdullah Karanfilb, M. Sabih Özera, Yalçın Kabaka, İnci Durucasua

*1Department of Chemistry, Faculty of Arts and Science, Ordu University, 52200, Ordu, Turkey*

*2Department of Chemistry, Faculty of Arts and Science, Manisa Celal Bayar University, 45140, Manisa, Turkey*

*Fax: +90 236 2013040; Tel: +90 236 2013163; E-mail: mustafa.eskici@cbu.edu.tr*

**General Experimental Parameters**

1H and 13C NMR spectra were recorded in CDCl3 on a Varian AS 400 MHz NMR spectrometer with TMS as an internal. Chemical shifts are expressed in δ (parts per million) units downfield from TMS. IR spectra were recorded on a Perkin Elmer Spectrum BX spectrometer as thin films on NaCl plates. Elemental analysis and Mass Spectra were taken from TUBITAK Marmara Research Centre (MAM), Gebze, Istanbul. Optical rotations were measured with Rudolph Research Analytical Autopol I Automatic Polarimeter. THF and ether were freshly distilled from LiAlH4 before use. TLC was performed using aluminium plates coated with silica gel (254 nm) and use of the basic permanganate dying system. Flash column chromatography was performed using silica gel (0.063–0.2 mm). Removal of solvents in vacuo was achieved using an IKA rotary evaporator at room temperature unless otherwise stated. Yields refer to isolated material, homogeneous by TLC and NMR spectroscopy, unless otherwise stated. L–Malic acid and D-Malic acid were purchased from Merck, Germany.

**(*S*)-4-Phenylbutane-1,2-diol 15a**

To a solution of **14a** (4.25 g, 23.59 mmol) in anhyrous ethanol 125 mL was added concentrated H2SO4 (1,5 mL). The reaction mixture was stirred under reflux for 4 hours and evaporated under reduced pressure to remove excees ethanol. The residue was partitioned between water (50 mL) and ethylacetate (200 mL). The organic layer was washed with saturated NaHCO3 solution, brine, dried over anhyrous Na2SO4, filtered and evaporated in *vacuo* to give the crude ester product as a light yellow oil. The crude product was directly subjected to the reduction reaction without characterization.

To a stirred suspension of LiAlH4 (4 g, 110 mmol) in dry THF (150 mL) cooled in an ice-bath was added dropwise a solution of the crude ester in dry THF (20 mL). The resulting mixture was then stirred for 1 h over the ice-bath. Excess LiAlH4 was quenched with sequential addition

of water (10 mL) and 10% NaOH solution (10 mL). The reaction mixture was stirred at room temperature for 2 h for hydrolysis and the aluminum residues were removed by filtration. Aluminum residues were washed with Et2O. Combined organics were dried over Na2SO4 and concentrated *in vacuo* to give the diol product **15a** as light yellow viscous oil,3.3 g in 84% yield over two steps. Small amount of diol **15a** was purified by flash column chromatography for structural characterization, [α]D31 = −31.0 (*c*=1.28, EtOH); (Lit[1],[α]D20= −34 (*c*=1.33, EtOH); R*f*: 0,31[(EtOAc:hexane) 1:1], IR (film) υmax/cm-1 : 3361 (OH); 1H NMR δH (400 MHz, CDCl3) (ppm) 1.65-1.79 (2H, m), 2.62-2.69 (1H, m), 2.75-2.82 (1H, m), 3.41 (1H, dd, *J*= 8 and 11.6), 3.59 (1H, dd, *J*= 2.4 and 11.6), 3.63-3.70 (1H, m), 3.86 (2H, s, br), 7.14-7.18 (3H, m, ArH), 7.23-7.26 (2H, m, ArH);13C NMR δC (100 MHz, CDCl3) (ppm) 32.05, 34.88, 66.88, 71.73, 126.11, 128.58, 128.60, 141.88. ESI-Tof (m/z): [M+Na]+ found 189.0847, C10H14NaO2 requires 189.0891.

**(*S*)-4-Phenethyl-1,3,2-dioxathiolane-2,2-dioxide 9a**

To a solution of diol **15a** (8.5 g, 51 mmol) and NEt3 (17 mL, 121 mmol) in DCM (120 mL) cooled in an ice-bath was added dropwise SOCl2 (4,5 mL, 62 mmol). The resulting solution was stirred for 30 minutes over the ice bath. The reaction mixture was diluted with water (150 mL) and organic layers were separated. Aqueous layer was further extracted with DCM (2x100 mL). Combined organics were sequentially washed with 1N HCl (50 mL), saturated NaHCO3 (50 mL), brine (50 mL), dried over Na2SO4 and concentrated *in vacuo* to give the crude intermediate sulfite (11.9 g). Colored impurities were removed by passing through a small pad of silicagel. The intermediate sulfite was used directly in the oxidation step without characterization.

To a stirred cooled (0 °C) solution of the sulfite in CHCl3 (50 mL) and MeCN (50 mL) was added RuCl3 (30 mg), followed by NaIO4 (19 g, 88 mmol) and then water (75 mL). The resulting solution was stirred for one hour over the bath. The reaction mixture was diluted with ether (250 mL) and phases were separated. The aqueous phase was extracted with ether (2x250 mL). Combined organics were washed with NaHCO3 solution (100 mL), brine (100 mL), dried over MgSO4 and concentrated *in vacuo* to give the crude sulfate **9a**. Colored ruthenium impurities were removed by passing through a small pad of silica gel. Solid sulfate was further purified by recrystallization from Et2O/hexane to give 10.2 g colorless crystals in 88% yield. m.p.:49-49,5 °C (ether-hexane), Lit.[2], 48 °C (petroleum ether-ether); [α]D31= −50 (*c*=1.0, CHCl3), Lit.[2], [α]D25= −51 (*c*=1.0, CHCl3); TLC, R*f*: 0,32 [(EtOAc:Hexane) 1:3], IR (nujol) υmax/cm-1 :1376, 1200 (SO2); 1H NMR δH (400 MHz, CDCl3) (ppm) 1.99-2.07 (1H, m), 2.25-2.34 (1H, m), 2.70-2.78 (1H, m), 2.84-2.94 (1H, m), 4.29 (1H, t, *J*=8), 4.60 (1H, ddd, *J*=0.4, 6 and 8.8), 4.89-4.95 (1H, m), 7.12-7.37 (5H, m, ArH); 13C NMR δC (100 MHz, CDCl3) (ppm) 31.05, 34.11, 72.91, 82.17, 127.01, 128.55, 129.08, 139.34; Elemental analysis calcd (%) for C10H12O4S: C 52.62, H 5.30; found: C 52.84, H 5.16.

**(*S*)-Ethyl-5-hydroxy-7-phenylhept-2-ynoate 11a**

To a stirred solution of triethylorthopropiolate (1.5 g, 8.72 mmol) in freshly distilled THF (20 mL) cooled to -10 °C (salt-ice bath) under argon atmosphere was added *n*-butyllithium (5.45 mL, 8.69 mmol, 15% solution in hexane), and the solution was stirred at this temperature for 1 h. A solution of the sulfate **9a** (1.1 g, 4.82 mmol) in dry THF (5 mL) was then added dropwise to the acetylide solution via a syringe. After stirring at -10 °C for 2 h, the reaction mixture was then treated with 15 drops concentrated H2SO4 and 15 drops water to hydrolyze the ring-opened intermediate for 2 h before neutralization with saturated NaHCO3 solution. Extraction with ether (2x50 mL) and drying over anhydrous Na2SO4 followed by evaporation of volatiles *in vacuo* gave the crude hydroxy ester product **11a**. Purification by flash column chromatography eluting with the ((EtOAc/hexane) 1:8 to 1:3 gradient) solvent system afforded analytical pure (*S*)-ethyl-5-hydroxy-7-phenylhept-2-ynoate **11a** as light yellow viscous oil 1.17 g in 92% yield. [α]D31= −8.7 (*c*=1.42, CHCl3); TLC, R*f*: 0,46 [(EtOAc:hexane) 1:3], IR (nujol) υmax/cm-1 :3412 (OH), 2237 (C≡C), 1712 (C=O ester); 1H NMR δH (400 MHz, CDCl3) (ppm) 1.30 (3H, t, *J*=7.2), 1.85-1.91 (2H, m), 2.27 (1H, s, br), 2.49 (1H, dd, *J*=6.4 and 17.2), 2.56 (1H, dd, *J*=5.2 and 17.2), 2.66-2.74 (1H, m), 2.77-2.85 (1H, m), 3.85 (1H, quintet, *J*=6.4), 4.22 (2H, q, *J*=7.2), 7.17-7.21 (3H, m, ArH), 7.25-7.30 (2H, m, ArH); 13C NMR δC (100 MHz, CDCl3) (ppm) 14.22, 27.99, 31.99, 38.15, 62.19,68.95, 85.83, 126.24, 128.63, 128.70, 141.54, 153.83; ESI-Tof (m/z): [M+Na]+ found 269.1165, C15H18NaO3 requires 269.1154.

**(*S*)-(+)-Dihydrokavain 1a**

To a solution of hydroxy ester **11a** (560 mg, 2.27 mmol) in MeOH (3 mL) was added a solution of LiOH.H2O (110 mg, 2.57 mmol) in water (2 mL). The resulting solution was stirred at room temperature for 1 hour. Methanol was removed under reduced pressure and the residue was partitioned between water (50 mL) and ether (50 mL). Organic layer was separated. Aqueous layer was acidified with concentrated H2SO4 (pH=1-2) in order to convert the corresponding carboxylate salt into free acid and exracted with ether three times (3x50 mL). Combined organics were dried over anhyrous Na2SO4 and concentrated *in vacuo* to give the crude free acid **16a**. The product was directly subjected to the lactonization step without characterization.

A solution of the crude acid (500 mg), conc. H2SO4 (60 mg, 0.61 mmol) and (65 mg, 0.30 mmol) HgO in MeOH (6 mL) was stirred at room temperature for 24 hours. Methanol was removed carefully under reduced pressure and the residue was partitioned between water (50 mL) and ether (50 mL). Organic layer was separated and sequentially washed with saturated NaHCO3 solution, brine, dried over anhyrous MgSO4 and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography eluting with the ((EtOAc/hexane) 1:4 gradient) afforded (*S*)-(+)-Dihydrokavain **1a** 396 mg in 75% yield over two steps. Recrystallization from ether-hexane produced analytical pure (*S*)-(+)-dihydrokavain **1** as colorless crystals. m.p.:55-57 °C (ether-hexane), Lit.[3], 56-58 °C (ether-hexane); [α]D31= +30.1 (*c*=1.08, EtOH), Lit.[1], [α]D20= +29 (*c*=1.21, EtOH); TLC, R*f*: 0,25[(EtOAc:hexane) 1:4], IR (nujol) υmax/cm-1 :1700 (C=O), 1622 (C=C); 1H NMR δH (400 MHz, CDCl3) (ppm) 1.88-1.97 (1H, m), 2.08-2.18 (1H, m), 2.30 (1H, dd, *J*=4 and 17.2), 2.50 (1H, ddd, J=1.2,11.6 and 16.8), 2.74-2.81 (1H, m), 2.84-2.91 (1H, m), 3.72 (3H, s), 4.32-4.39 (1H, m), 5.13 (1H,d, *J*=1.2), 7.17-7.21 (3H, m, ArH), 7.26-7.30 (2H, m, ArH); 13C NMR δC (100 MHz, CDCl3) (ppm) 31.20, 33.25, 36.54, 56.20, 75.01, 90.58, 126.35, 128.68, 128.74, 141.05, 167.43, 172.91.

**(*R*)-4-Phenylbutane-1,2-diol 15b**

Using similar sets of reaction conditions as **15a** (*R*)-4-phenylbutane-1,2-diol **15b** was obtained from D-malic acid **7**. [α]D31= +30 (c=0.84, EtOH), (Lit.[1], [α]D20= +33 (c=1.88, EtOH)).

**(*R*)-4-Phenethyl-1,3,2-dioxathiolane 2,2-dioxide 9b**

Using similar sets of reaction conditions as **9a** (*R*)-4-phenethyl-1,3,2-dioxathiolane 2,2-dioxide **9b** was synthesized from **15b**. [α]D31=+48 (c=1.0, CHCl3)

**(*R*)-Ethyl 5-hydroxy-7-phenylhept-2-ynoate 11b**

Using similar sets of reaction conditions **11a** (*R*)-ethyl 5-hydroxy-7-phenylhept-2-ynoate **11b** was synthesized from **9b**. [α]D31=+8.2 (c=1.58, CHCl3)

**(*R*)-(+)-Dihydrokavain (1b)**

Using similar sets of reaction conditions **1a** (*R*)-(+)-Dihydrokavain **1b** was prepared from **11b**.[α]D31=−29 (c=1,34, EtOH), (Lit.[1], [α]D20= −28 (c=1,92, EtOH).

**(*S*)-ethyl-7-phenyl-5-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hept-2-ynoate 17a**[4]

To a solution of (*R*)-(+)-MTPA (80 mg, 0.34 mmol) and DMF (25 mg, 0.34 mmol) in hexane (10 mL) was added oxalyl chloride (0.15 mL, 205 mg, 1.61 mmol) at room temperature. A white precipitate was formed immediately. After 1 hour the reaction mixture was filtered and concentrated. A solution of (*S*)-ethyl 5-hydroxy-7-phenylhept-2-ynoate **11a** (49 mg, 0.20 mol) and NEt3 (0.05 mL) and DMAP (several crystals) in DCM (5 mL) was added to the residue. After stirring for 1h, TLC showed complete consumption of the alcohol **11a**. The reaction mixture was diluted with DCM (10 mL) and sequentially washed with water (10 mL), saturated NaHCO3 solution (10 mL), brine (10 mL), dried over anhyrous Na2SO4 and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography eluting with the ((EtOAc/hexane) 1:4) afforded the corresponding Mosher ester derivative 17**a** 84 mg 91% yield. 1H NMR δH (400 MHz, CDCl3) (ppm) 1.28 (3H, t, *J*=7.2), 2.01-2.20 (2H, m), 2.59-2.75 (4H, m), 3.56 (3H, s), 4.19 (2H, q, *J*=7.2), 5.18-5.24 (1H, m), 7.13-7.31 (5H, m, ArH), 7.40-7.43 (3H, m, ArH), 7.56-7.58 (2H, m, ArH); 13C NMR δC (100 MHz, CDCl3) (ppm) 14.18, 24.04, 31.46, 35.01, 55.70, 62.13, 73.40, 75.60, 83.00, 122.05, 126.58, 127.73, 128.49, 128.72, 128.85, 129.91, 132.07, 140.50, 153.36, 166.32.

(***R*)-ethyl-7-phenyl-5-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hept-2-ynoate 17b**[4]

Using similar sets of reaction conditions as **17a** Mosher ester derivative **17b** was prepared from **16b**. 1H NMR δH (400 MHz, CDCl3) (ppm) 1.29 (3H, t, *J*=7.2), 1.92-2.14 (2H, m), 2.44-2.58 (2H, m), 2.68 (1H, dd, *J*=6 and 17.6) 2.81 (1H, dd, *J*=5.6 and 17.2), 3.63 (3H, s), 4.21 (2H, q, *J*=6.8), 5.15-5.21 (1H, m), 7.04-7.27 (5H, m, ArH), 7.40-7.44 (3H, m, ArH), 7.59-7.62 (2H, m, ArH); 13C NMR δC (100 MHz, CDCl3) (ppm) 14.19, 24.23, 31.14, 35.01, 55.96, 62.20, 73.34, 75.79, 83.25, 126.49, 127.49, 128.47, 128.71, 128.78, 129.92, 132.36, 140.50, 153.37, 166.37.

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**Supporting Information**

1H and 13C NMR spectra for the compounds included in the manuscript is given. This material can be found via the “Supplementary Content” section of this article’s webpage.

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