Supporting Materials For

Regiospecific Hydration of γ -Hydroxy- α,β -Acetylenic Esters: A Novel Asymmetric Synthesis of Tetronic Acids

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General Data. All reactions were carried out under nitrogen. All reagents were purchased from Aldrich Chemical Co and used directly unless indicated otherwise. Diethylzinc (95%) was purchased from Strem. Toluene was distilled over sodium under nitrogen. Methylene chloride, diethyl ether and tetrahydrofuran were dried by passing through activated alumina columns under nitrogen. NMR spectra were obtained using the Varian-300 MHz spectrometer. Mass spectra were recorded on a LCQ Finnigan mass spectrometer by using APCI (Atmospheric Pressure Chemical Ionization). HPLC analyses were carried out on the Waters 600 instrument by using the Diacel Chiralcel OD of otherwise mentioned column and eluting with 10% *i*-PrOH in hexane at 1.0 mL/min and were detected or otherwise mentioned at 254 nm by the Waters 486. GC analyses were carried out with HP 6890 series GC by using Supelco Beta-Dex 120 Fused silica capillary Column (30 m Length $\times$ 0.25 mm ID $\times$ 0.25 μ m film thickness). The optical rotations were measured on the JASCO DIP-1000 Polarimeter.

General Procedure for the Asymmetric Addition. To a stirred solution of (*S*)-BINOL (0.343 g, 1.2 mmol, 40 mol %), HMPA (1.04 mL, 6.0 mmol) and methyl propiolate (1.06 mL, 12.0 mmol) in methylene chloride (36 mL) under N₂ is slowly added Et₂Zn (1.255 mL, 12.0 mmol). After the solution has been stirred at room temperature for 16 h, Ti(O^{*i*}Pr)₄ (0.855 mL, 3.0 mmol) is added and stirring continued for another hour. Then, the aldehyde (3.0 mmol, neat) is added in one portion and the reaction is allowed to proceed at room temperature for 4 h. Ammonium chloride (saturated aq.) is added to quench the reaction, and the mixture is extracted with methylene chloride and dried with sodium sulfate. After column chromatography on silica gel eluted with 2-10% ethyl acetate in hexanes, the optically active γ -hydroxy- α,β -acetylenic ester product is isolated. The enantiomeric purity of the product is determined by analyzing the ¹H NMR spectrum of the mandelate acetate derivative or by using HPLC-Chiralcel OD column.

Preparation of the O-Ac mandalate derivative: To a stirred solution of a γ -hydroxy- α,β -acetylenic ester (10 mg, 1 equiv) in dry methylene chloride, DCC (1.1 equiv) is added followed by (*R*)-O-Acetyl mandalic acid. The reaction is monitored by TLC (add more reagent if necessary to assure the complete conversion of the starting material). After 2-3 h, the reaction is completed. The crude mixture is concentrated and purified by column chromatography on silica gel eluted with ethyl acetate/5-8% hexane. The ee was determined based the chiral proton $\delta \sim 5.9$ ppm in the ^1H NMR spectrum.

General Procedure for Hydration of Propargylic Alcohol. A solution of propargylic alcohol (0.1 mmol) and Zeise's dimer (2 mol %) in methanol (3 mL) and water (1 mL) is heated under N_2 at reflux with stirring for 16-18 h. After the reaction is completed, the solvent is evaporated and the product is extracted with methylene chloride. The organic solution is dried with sodium sulfate. Then the solvent is removed by roto-evaporation, and the pure product **2** was obtained by recrystallised in hexane or ethyl acetate/ hexane.

The racemic tetronic acid is prepared in a similar way by using the racemic propargylic alcohol.

The acetates of the tetronic acids are prepared as described below: To a stirred solution of a purified tetronic acid (20 mg) in dichloromethane, pyridine (80 μL) and acetic anhydride (25 μL) are added. The resulting mixture is heated at reflux for 2 h (except for the cyclohexyl derivative which is kept at 0 $^\circ\text{C}$ for 2 h). The crude product is purified by passing through a short silica gel column eluted with methylene chloride. The yield is nearly quantitative.

Methyl 4-hydroxy-undec-2-ynoate. 72 % isolated yield. 81 % *ee* determined by analyzing the ^1H NMR spectrum of its (*R*)-mandalate ester. $[\alpha]_{\text{D}} = -0.46$ ($c = 1.01$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 4.48 (t, 1H, $J = 6.6$ Hz), 3.78 (s, 3H), 1.86 (bs, 1H), 1.80 – 1.72 (m, 2H), 1.48 – 1.45 (m, 2H), 1.30 – 1.28 (m, 8H), 0.88 (t, 3H, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 153.95, 88.62, 75.89, 61.86, 52.75, 36.67, 64.29, 24.85, 22.51, 13.97. HRMS (MNH_4^+) for $\text{C}_{12}\text{H}_{24}\text{NO}_3$ Calcd: 230.1756; Found: 230.1754

Methyl 4-hydroxy-oct-2-ynoate. 76 % isolated yield. 89% *ee* determined by analyzing the ^1H NMR spectrum of its (*R*)-mandalate ester. $[\alpha]_{\text{D}} = 0.81$ ($c = 1.0$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 4.47 (t, 1H, $J = 6.6$ Hz), 3.76 (s, 3H), 2.54 (bs, 1H), 1.78 – 1.71 (m, 2H), 1.48 – 1.29 (m, 4H), 0.89 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 153.89, 88.44, 76.04, 61.98, 52.80, 36.47, 26.97, 22.20, 13.84. HRMS (MNH_4^+) for $\text{C}_9\text{H}_{18}\text{NO}_3$ Calcd: 188.1286; Found: 188.1282

Methyl 4-hydroxy-6-methyl-hep-2-ynoate. 73% isolated yield.. 83% *ee* determined by analyzing the ^1H NMR spectrum of its (*R*)-mandalate ester. $[\alpha]_{\text{D}} = 3.3$ ($c = 1.02$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 4.51 (t, 1H, $J = 7.2$ Hz), 3.75 (s, 3H), 2.79 (bs, 1H), 1.83 (hep, 1H), 1.72 – 1.53 (m, 2H), 0.92 (d, 3H, $J = 2.7$ Hz), 0.881 (d, 2H, $J = 2.7$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 153.94, 88.71, 75.96, 60.44, 52.78, 45.62, 24.45, 22.41, 22.15. HRMS (MNH_4^+) for $\text{C}_9\text{H}_{18}\text{NO}_3$ Calcd: 188.1286; Found : 188.1286

Methyl 4-hydroxy-4-cyclohexyl-but-2-ynoate. 60% isolated yield. 81% *ee* determined by analyzing the ^1H NMR spectrum of its (*R*)-mandalate ester. $[\alpha]_{\text{D}} = -2.20$ ($c = 1.02$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 4.27 (t, 1H, $J = 6.3$ Hz), 3.77 (s, 3H), 2.10 (d, 1H, $J = 6.0$ Hz), 1.88 – 1.75 (m, 4H), 1.69 – 1.62 (m, 2H), 1.27 – 1.11 (m, 5H).

^{13}C NMR (75 MHz, CDCl_3) δ 153.79, 87.51, 77.07, 66.84, 52.79, 43.56, 28.32, 28.03, 26.10, 25.67. HRMS (MNH_4^+) for $\text{C}_{11}\text{H}_{20}\text{NO}_3$ Calcd: 214.1443. Found: 214.1445.

Methyl 4-hydroxy-5-methyl-hept-5-ene-2-ynoate. 38% isolated yield. 90% *ee* determined by analyzing the ^1H NMR spectrum of its (R)-mandalate ester. ^1H NMR (300 MHz, CDCl_3) δ 5.72 – 5.66 (m, 1H), 4.84 (s, 1H), 3.75 (s, 3H), 2.75 (bs, 1H), 1.72 (d, 3H, $J = 0.9$ Hz), 1.62 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 153.84, 133.05, 124.14, 86.70, 76.77, 67.42, 52.77, 13.24, 11.92..

5-Heptyl-4-hydroxy-5H-furan-2-one. 55 % yield. m.p. 81 -82° C. $[\alpha]_D = 12.2$ ($c = 0.175$, CHCl_3). enol: keto = 1.0:3.5. ^1H NMR (300 MHz, CDCl_3) δ 10.66 (bs, 1H), 5.01 (s, 1H), 4.82 (dd, 1H, $J = 3.9$ Hz, $J = 3.9$ Hz), 4.74 (dd, 1H, $J = 4.5$, 4.8 Hz), 3.18 (s, 1H), 3.17 (d, 1H, $J = 0.9$ Hz), 1.97 – 1.63 (m, 2H), 1.48 – 1.41 (m, 2H), 1.36 – 1.25 (m, 8H), 0.87 (t, 3H, $J = 6.6$ Hz). *ee* of the acetate derivative = 80%. GC conditions: 160 °C-isothermal-60 minutes, 20 °C per minute to 220 °C hold 10 minutes. Flow rate: 2 mL per minutes. Retention time: 45.84 (major), 47.19 (minor). ^1H NMR (300 MHz, CDCl_3) δ 6.09 (d, 1H, $J = 1.2$ Hz), 4.88 – 4.84 (m, 1H), 2.31 (s, 3H), 1.97 (m, 1H), 1.65 – 1.53 (m, 1H), 1.49 – 1.44 (m, 2H), 1.39 – 1.25 (m, 8H), 0.87 (t, 3H, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 172.08, 17.01, 165.52, 101.24, 79.27, 31.64, 29.10, 28.97, 24.25, 22.55, 21.09, 14.03. HRMS (MH^+) for $\text{C}_{13}\text{H}_{21}\text{O}_4$ Calcd: 241.1439. Found: 241.1443.

5-Butyl-4-hydroxy-5H-furan-2-one. 66% yield. m.p. 78 – 79° C. $[\alpha]_D = -16.1^\circ$ ($c = 0.96$, CHCl_3). enol:keto = 1.13:0.37. ^1H NMR (300 MHz, CDCl_3) δ 11.72 (bs, 1H), 5.06 (s, 1H), 4.82 (dd, 1H, $J = 3.6$, 3.6 Hz), 4.74 (dd, 1H, $J = 4.8$, 4.5 Hz), 3.19 (s, 1H), 3.18 (d, 1H, $J = 0.9$ Hz), 1.99 – 1.92 (m, 1H), 1.69 – 1.62 (m, 1H), 1.46 – 1.24 (m, 4H), 0.88 (t, 3H, $J = 6.9$ Hz). *ee* of the acetate derivative = 83%. GC conditions: 160 °C-isothermal-60 minutes, 20 °C per minute to 220 °C hold 10 minutes. Flow rate: 2 mL per minutes. Retention time: 12.83 (major), 13.27 (minor). ^1H NMR (300 MHz, CDCl_3) δ 6.09 (d, 1H, $J = 1.2$ Hz), 4.88 – 4.84 (m, 1H), 2.32 (s, 3H), 1.99 – 1.87 (m, 1H), 1.65 – 1.53 (m, 1H), 1.47 – 1.28 (m, 4H), 0.90 (t, 3H, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 172.11, 170.09, 165.53, 101.20, 79.25, 31.31, 26.31, 22.25, 22.25, 21.10, 13.78. HRMS (MH^+) for $\text{C}_{10}\text{H}_{15}\text{O}_4$ Calcd: 199.0970. Found: 199.0963

5-(2-methyl)propyl-4-hydroxy-5H-furan-2-one. 60% yield. m.p. 90 – 92° C. $[\alpha]_D = -47.5$ ($c = 0.45$, CHCl_3). enol:keto = 1.0:0.36. ^1H NMR (300 MHz, CDCl_3) δ 11.76 (bs, 1H), 4.84 (dd, $J = 2.7$, 2.7 Hz), 4.78 (dd, $J = 4.2$, 4.2 Hz), 3.20 (s, 1H), 1.96 – 1.46 (m, 3H), 0.097 (d, 6H, $J = 6.3$ Hz). *ee* of the acetate derivative = 74%. GC conditions: 160 °C-isothermal-60 minutes, 20 °C per minute to 220 °C hold 10 minutes. Flow rate: 2 mL per minutes. Retention time: 10.17 (major), 10.31 (minor). ^1H NMR (300 MHz, CDCl_3) δ 4.08 (d, 1H, $J = 1.5$ Hz), 4.91 - 4.86 (m, 1H), 2.31 (s, 3H), 1.99 – 1.90 (m, 1H), 1.71 – 1.62 (m, 1H), 1.52 – 1.42 (m, 1H), 1.00 - 0.96 (dd, 6H, $J = 4.8$, 5.1 Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 172.08, 170.74, 165.52, 100.87, 78.033, 41.03, 24.94, 23.24, 21.61, 21.10. HRMS (MH^+) for $\text{C}_{10}\text{H}_{15}\text{O}_4$ Calcd: 199.0970; Found: 199.0975.

5-Cyclohexyl-4-hydroxy-5H-furan-2-one. 78% yield. m.p. 154 – 156° C. $[\alpha]_D = -22.8$ ($c = 1.0$, CH_3COCH_3). enol:keto = 1.0:0.31. ^1H NMR (300 MHz, CD_3COCD_3) δ 11.18 (bs, 1H), 4.94 (d, 1H, $J = 0.9$ Hz), 4.66 (d, 1H, $J = 2.7$ Hz), 4.62 (d, 1H, $J = 4.5$ Hz), 3.2 (s, 2H), 1.84 – 1.49 (m, 6H), 1.34 – 1.07 (m, 5H). *ee* of the acetate derivative = 82%. GC conditions: 160 °C-isothermal-65 minutes, 20 °C per minute to 220 °C hold 10 minutes. Flow rate: 2 mL per minutes. Retention time: 43.63(minor), 44.69(major). ^1H NMR (300 MHz, CDCl_3) δ 6.17 (d, 1H, $J = 1.2$ Hz), 4.74 (q, 1H), 2.32 (s, 3H), 1.83 – 1.65 (m, 5H), 1.44 – 1.08 (m, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ 172.38, 169.0, 165.52, 101.99, 83.12, 39.10, 26.21, 25.82, 25.70, 25.60, 24.85, 21.21. HRMS (MH^+) for $\text{C}_{12}\text{H}_{17}\text{O}_4$ Calcd: 225.1126; Found: 225.1133.

1-Methyl-1-propenyl-4-hydroxy-5H-furan-2-one. 46% yield. $[\alpha]_D = -2.9$ ($c = 1.15$, CHCl_3). ee of the acetate derivative = 90%. GC conditions: 150 °C-isothermal-60 minutes, 20 °C per minute to 220 °C hold 10 minutes. Flow rate: 2 mL per minutes. Retention time: 18.92 (major), 19.74 (minor). ^1H NMR (300 MHz, CDCl_3) δ 6.16 (d, 1H, $J = 1.5$ Hz), 5.78 – 5.71(m, 1H), 5.18 (d, 1H, $J = 0.9$ Hz), 2.28 (s, 3H), 1.71 (dd, 3H, $J = 0.9\text{Hz}$, 0.9Hz), 1.47 (t, 3H, $J = 1.2\text{Hz}$).

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5-(2-methylphenyl)-4-hydroxy-5H-furan-2-one. 41% yield. m.p. 156 – 157 °C. $[\alpha]_D = -35.3^\circ$ ($c = 0.865$, EtOH). enoll:keto = 0.78:0.3. ^1H NMR (300 MHz, CD_3CN) δ 9.40 (bs, 1H), 7.30 – 7.14 (m, 5H), 6.03 (d, 1H, $J = 0.9\text{Hz}$), 5.19 (d, 1H, $J = 0.9$ Hz), 3.38 (s, 3H), 2.42 (s, 3H). ee of the acetate derivative = 92%. GC conditions: 170 °C-isothermal-55 minutes, 20 °C per minute to 220 °C hold 10 minutes. Flow rate: 1.5 mL per minutes. Retention time: 56.89 (major), 57.05 (minor). ^1H NMR (300 MHz, CDCl_3) δ 7.23 – 7.15 (m, 4H), 7.03 (d, 1H, $J = 7.8\text{Hz}$), 6.19 (d, 1H, $J = 0.9$ Hz), 6.05 (d, 1H, $J = 1.2$ Hz), 2.40 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 172.06, 169.59, 165.50, 137.11, 131.38, 131.25, 131.01, 129.56, 126.63, 126.07, 101.72, 77.92, 21.07, 19.16. HRMS (MH^+) for $\text{C}_{13}\text{H}_{13}\text{O}_4$ Calcd: 233.0813; Found: 233.0808.

General Procedure for the Preparation of Racemic Propargylic Alcohols. All the racemic propargylic alcohols are prepared for the HPLC analysis according to the following procedure. A solution of an alkyne (3 mmol) in tetrahydrofuran (25 mL) in a 100 mL flask under N_2 is cooled to -78 °C with dryice/acetone bath. n-BuLi in hexanes (1.6 M, 2.8 mmol) is added. The reaction mixture is stirred for 1 h at this temperature. An aldehyde (2 mmol) is added and the mixture is stirred for additional 1 h. The reaction is quenched with ice, and the resulting mixture is extracted with methylene chloride. After dried over magnesium sulfate, the volatile solvent is removed by roto-evaporation and the residue is passed through a short silica gel column to afford the product.

153.897

88.446

77.424

77.000

76.574

76.048

61.984

52.803

36.472

26.970

22.202

13.841

153.897

88.446

77.424

77.000

76.574

76.048

61.984

52.803

36.472

26.970

22.202

13.841

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