Highly Enantioselective Synthesis of γ -Hydroxy- α,β -Acetylenic Esters Catalyzed by a β -Sulfonamide Alcohol

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Supporting Information

General initial procedure for addition of alkyne to aldehydes¹.

Method A²: Under argon, the ligand (0.05mmol) and Ti(O^{*i*}Pr)₄ (41 μ L, 0.15mmol) were mixed in dry toluene at room temperature. Then, a solution of Et₂Zn (1.0 M in toluene, 1.5mL), was added. After the mixture was stirred at the room temperature for 1h, phenylacetylene (165 μ L, 1.5mmol) and aldehyde were added together and stirred at room temperature. After the reaction was complete checked by TLC, it was cooled to 0°C and quenched by 5% aqueous HCl. The mixture was extracted with ether. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 12.5% EtOAc in hexane) to give the product.

Method B³: Under argon, the ligand (21.6 mg, 0.06 mmol) and Ti(O^{*i*}Pr)₄ (52.5 μ L, 0.18 mmol) were mixed in dry toluene at room temperature. A solution of ZnEt₂ (1.0m in toluene, 0.6 mL) was then added. After the mixture was stirred at the room temperature for 2 h, alkyne (0.6 mmol) was added and the stirring continued for 1 h. The orange solution was cooled to 0°C and treated with aldehyde (0.2 mmol). The resulting mixture was allowed to warm to room temperature. After the reaction was complete (monitoring with TLC), it was cooled to 0°C and quenched with aqueous HCl (5%) (saturated aqueous of ammonium chloride for methyl propiolate). The mixture was extracted with methylene chloride. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The residue was purified by flash column chromatography to give the product.

General procedure for the asymmetric addition of methyl propiolate to aldehydes.

The β -sulfonamide alcohol **L*** was synthesized according to our previous work.³

To a stirred solution of **L*** (21.6m g, 0.06 mmol, 30 mol %), DME (20.7 μ L, 0.2 mmol) and Et₂Zn (0.6 mL, 0.6 mmol) in toluene (2.4 mL) under Ar, methyl propiolate (53.5 μ L, 0.2 mmol) was added in one portion. After the solution has been stirred at 25°C for 7h, Ti(O^{*i*}Pr)₄ (17.5 μ L, 0.06 mmol, 30mol%) was added and stirred for halfhour. Then, the aldehyde (0.2 mmol) was added in one portion. Ammonium chloride (saturated aq.) was added to quench the reaction until the reaction was complete (monitoring with TLC), and the mixture was extracted with methylene chloride and dried with sodium sulfate. After column chromatography on silica gel eluted with 10% ethyl acetate in hexanes, the optically active γ -hydroxy- α,β -acetylenic ester product was isolated. The enantiomeric purity of the product was determined by using HPLC.

Characterizations of the Products:

Methyl 4-hydroxy-4-phenylbut-2-ynoate.⁴ 79% yield, 91% *ee* determined by HPLC analysis (OD-H column; Hept/*i*-PrOH 80/20, 1mL/min, 223nm); Retention time: *t*_{major} = 9.01 min, *t*_{minor} = 7.83 min. [α]_D²⁰ = +5° (c=1.20, CHCl₃). ¹H NMR (400 MHz): δ 7.52-7.54 (d, *J* = 6.8 Hz, 2H), 7.37-7.44 (m, 3H), 5.59 (s, 1H), 3.80 (s, 3H). ¹³C NMR (100 MHz): δ 153.7, 138.4, 128.9, 128.8, 126.6, 86.5, 77.5, 64.2, 52.9. HRMS-ESI (*m/z*): calcd for C₁₁H₁₀O₃+NH₄⁺.

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(1) Xu, Z. Q.; Lin, L.; Xu, J.K.; Yan, W.J.; Wang, R. *Adv. Synth. Catal.* **2006**, 348, 506-514.

(2) It is Method B mentioned in reference 1.

(3) Xu, Z.Q.; Wang, R.; Xu, J.K.; Da, C.-S.; Yan, W.J.; Chen, C. *Angew. Chem. Int.Ed.* **2003**, 42, 5747-5749.

(4) Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. *Angew. Chem. Int. Ed.* **2005**, 45, 122-125.

208.0968; found: 208.0970, 1.0ppm.

Methyl 4-hydroxy-4-(2-methoxyphenyl)but-2-ynoate.⁴ 77% yield, 90% *ee* determined by HPLC analysis (OJ-H column; Hept/*i*-PrOH 90/10, 1mL/min, 223nm); Retention time: $t_{\text{major}} = 51.27$ min, $t_{\text{minor}} = 63.73$ min. $[\alpha]_D^{25} = +5^\circ$ ($c = 1.34$, CHCl₃). ¹H NMR (200 MHz): δ 7.33-7.47 (m, 2H), 6.91-7.02 (m, 2H), 5.72 (s, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 3.17 (bs, 1H). ¹³C NMR (50 MHz): δ 156.7, 130.2, 128.0, 126.8, 121.0, 111.1, 86.7, 76.7, 61.3, 55.6, 52.7. IR: 3694 (br, OH), 3015, 2921, 2851, 2380, 2232, 1716, 1594, 1433, 1298, 1248, 1161, 1113, 1070, 1018, 749. HRMS-ESI (*m/z*): calcd for C₁₂H₁₂O₄+Na⁺: 243.0628; found: 243.0630, 0.8ppm.

Methyl 4-hydroxy-4-(3-methoxyphenyl)but-2-ynoate.⁴ 78% yield, 92% *ee* determined by HPLC analysis (OD-H column; Hept/*i*-PrOH 90/10, 1mL/min, 223nm); Retention time: $t_{\text{major}} = 27.06$ min, $t_{\text{minor}} = 20.27$ min. $[\alpha]_D^{25} = +8^\circ$ ($c = 1.16$, CHCl₃). ¹H NMR (400 MHz): δ 7.29-7.34 (t, $J = 8$ Hz, 1H), 7.03-7.08 (m, 2H), 6.85-6.90 (m, 1H), 5.51 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.39 (br, 1H). ¹³C NMR (100 MHz): δ 159.8, 153.7, 139.9, 129.9, 118.8, 114.5, 112.0, 86.4, 77.5, 64.1, 55.3, 52.9. IR: 3443 (br, OH), 3013, 2955, 2918, 2849, 2373, 2328, 2236, 1714, 1597, 1486, 1454, 1432, 1254, 1154, 1070, 1027, 785, 745, 694. HRMS-ESI (*m/z*): calcd for C₁₂H₁₂O₄+Na⁺: 243.0628; found: 243.0628, 0ppm.

Methyl 4-hydroxy-4-(4-methoxyphenyl)but-2-ynoate.⁴ 76% yield, 94% *ee* determined by HPLC analysis (OD-H column; Hept/*i*-PrOH 98/2, 1mL/min, 228nm); Retention time: $t_{\text{major}} = 97.17$ min, $t_{\text{minor}} = 120.17$ min. $[\alpha]_D^{25} = +7^\circ$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz): δ 7.42 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J = 8.4$, 2H), 5.50 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 2.25 (bs, 1H). ¹³C NMR (100 MHz): δ 160.1, 153.7, 130.7, 128.2, 114.2, 86.5, 77.5, 63.9, 55.4. IR: 3398 (br, OH), 3012, 2954, 2921, 2850, 2455, 2375, 2328, 2235, 1711, 1608, 1509, 1457, 1433, 1246, 1171, 1110, 1026, 807. HRMS-ESI (*m/z*): calcd for C₁₂H₁₂O₄+Na⁺: 243.0628; found: 243.0624, 1.6ppm.

Methyl 4-(2-chlorophenyl)-4-hydroxybut-2-ynoate.⁴ 77% yield, 93% *ee* determined by HPLC analysis (OD-H column; Hept/*i*-PrOH 90/10, 1mL/min, 223nm); Retention time: $t_{\text{major}} = 9.86$ min, $t_{\text{minor}} = 9.00$ min. $[\alpha]_D^{25} = -30^\circ$ ($c = 1.05$, CHCl₃). ¹H NMR (400 MHz): δ 7.65-7.68 (m, 1H), 7.35-7.37 (m, 1H), 7.24-7.33 (m, 2H), 5.89 (s, 1H), 3.75 (s, 3H), 3.16 (bs, 1H). ¹³C NMR (100 MHz): δ 153.7, 135.8, 132.5, 130.1, 129.8, 128.3, 127.4, 104.1, 85.5, 77.2, 61.4, 52.9. IR: 3420 (br, OH), 3071, 3012, 2954, 2920, 2849, 2239, 1717, 1593, 1575, 1473, 1436, 1257, 1190, 1077, 1054, 1027, 752. HRMS-ESI (*m/z*): calcd for C₁₁H₉ClO₃+Na⁺: 247.0132; found: 247.0138, 2.4ppm.

Methyl 4-(4-bromophenyl)-4-hydroxybut-2-ynoate.⁴ 67% yield, 92% *ee* determined by HPLC analysis (OD-H column; Hept/*i*-PrOH 99/1, 1mL/min, 223nm); Retention time: $t_{\text{major}} = 26.51$ min, $t_{\text{minor}} = 34.19$ min. $[\alpha]_D^{25} = +7^\circ$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz): δ 7.51-7.54 (m, 2H), 7.39 (d, $J = 8.4$, 2H), 5.54 (s, 1H), 3.80 (s, 3H), 2.53 (s, 1H). ¹³C NMR (100 MHz): δ 153.5, 137.4, 132.0, 128.3, 123.1, 85.6, 77.9, 63.6, 52.9. IR: 3403 (br, OH), 3013, 2953, 2921, 2850, 2238, 1715, 1590, 1484, 1435, 1402, 1255, 1185, 1070, 1008, 845. HRMS-ESI (*m/z*): calcd for C₁₁H₉BrO₃+NH₄⁺: 286.0073; found: 286.0071, 0.7ppm.

Methyl 4-hydroxy-4-*p*-tolylbut-2-ynoate.⁴ 76% yield, 94% *ee* determined by HPLC analysis (AD-H column; Hept/*i*-PrOH 90/10, 1mL/min, 223nm); Retention time: $t_{\text{major}} = 14.30$ min, $t_{\text{minor}} = 12.04$ min. $[\alpha]_D^{25} = +7^\circ$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz): δ 7.37 (d, $J = 8$ Hz, 2H), 7.17 (d, $J = 8$, 2H), 5.50 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.78 (br, 1H), 2.43 (s, 1H). ¹³C NMR (100 MHz): δ 153.8, 138.8, 135.6, 129.5, 126.6, 86.8, 77.4, 64.0, 52.8, 21.1. IR: 3415 (br, OH), 3021, 2954, 2921, 2851, 2237, 1716, 1512, 1435, 1253, 1191, 1072, 1025, 815. HRMS-ESI (*m/z*): calcd for C₁₂H₁₂O₃+Na⁺: 227.0679; found: 227.0679, 0ppm.

Methyl 4-hydroxy-4-(naphthalen-1-yl)but-2-ynoate.⁴ 72% yield, 92% *ee* determined by HPLC analysis (OD-H column; Hept/*i*-PrOH 90/10, 1mL/min, 225nm); Retention time: $t_{\text{major}} = 15.14$ min, $t_{\text{minor}} = 19.93$ min. $[\alpha]_D^{25} = -16^\circ$ ($c = 1.21$, CHCl₃). ¹H NMR (400 MHz): δ 8.17 (d, $J = 8.4$ Hz, 1H), 7.85 (t, $J = 8.8$ 2H), 7.76 (d, $J = 8.8$, 1H), 7.48-7.57 (m, 2H), 7.44 (dd, $J = 7.6$, 8 Hz, 1H), 6.17 (s, 1H), 3.77 (s, 3H). ¹³C NMR (100 MHz): δ 153.8, 133.9, 133.5, 130.2, 129.9, 128.8, 126.7, 126.1, 125.2, 125.0, 123.5, 86.3, 78.1, 62.6, 52.9. IR: 3421 (br, OH), 3054, 3017, 2953, 2922, 2850, 2236, 1715, 1625, 1598, 1509, 1435, 1387, 1255, 1164, 1124, 1075, 1017, 803, 780. HRMS-ESI (*m/z*): calcd for C₁₅H₁₂O₃+H⁺: 263.0679; found: 263.0678, 0.4ppm.

Methyl 4-hydroxy-4-(naphthalen-2-yl)but-2-ynoate.⁴ 73% yield, 93% *ee* determined by HPLC analysis (OD-H column; Hept/*i*-PrOH 90/10, 1mL/min, 227nm); Retention time: $t_{\text{major}} = 25.41$ min, $t_{\text{minor}} = 29.43$ min. $[\alpha]_D^{25} = -6^\circ$ ($c = 1.22$, CHCl₃). ¹H NMR (400 MHz): δ 7.92 (s, 1H), 7.80-7.88 (m, 3H), 7.57 (dd, $J = 1.6$, 8.4, 1H), 7.49-7.51 (d, $J = 6.8$ Hz, 2H), 7.43-7.51 (m, 2H), 5.70 (s, 1H), 3.77 (s, 3H), 2.89 (br, 1H). ¹³C NMR (100 MHz): δ 153.8, 135.7, 133.3, 133.0, 128.8, 128.2, 127.7, 126.6, 126.5, 125.7, 124.1, 86.5, 77.7, 64.3, 52.9. IR: 3411 (br, OH), 3050, 3013, 2953, 2918, 2849, 2236, 1714, 1598, 1510, 1434, 1394, 1255, 1163, 1077, 1048, 1035, 1016, 802, 779. HRMS-ESI (*m/z*): calcd for C₁₅H₁₂O₃+Na⁺: 263.0679; found: 263.0676, 1.1ppm.

Methyl 4-(furan-2-yl)-4-hydroxybut-2-ynoate.⁴ 65% yield, 92% *ee* determined by HPLC analysis (OD-H column; Hept/*i*-PrOH 90/10, 1mL/min, 220nm); Retention time: $t_{\text{major}} = 12.61$ min, $t_{\text{minor}} = 16.37$ min. ¹H NMR (400 MHz): δ 7.41 (d, $J = 0.8$ Hz, 1H), 6.47 (d, $J = 3.6$ Hz, 1H), 6.35 (d, $J = 2$ Hz, 1H), 5.55 (d, $J = 6.8$ Hz, 1H), 3.78 (s, 3H), 2.57 (d, $J = 6.8$ Hz, 1H). ¹³C NMR (100 MHz): δ 153.5, 150.6, 143.6, 110.6, 108.7, 83.7, 76.72, 57.9, 52.9. IR: 3436 (br, OH),

3152, 3126, 3013, 2956, 2921, 2850, 2611 (m), 2456, 2374, 2329, 2243, 1715, 1594, 1500, 1435, 1384, 1257, 1188, 1144, 1072, 1011, 819. HRMS-ESI (m/z): calcd for C₁₁H₁₀O₃+NH₄⁺: 208.0968; found: 208.0970, 1.0ppm.

Methyl 4-hydroxy-6-phenylhex-5-en-2-ynoate.⁵ 64% yield, 85% *ee* determined by HPLC analysis (AD-H column; Hept/i-PrOH 90/10, 1mL/min, 250nm); Retention time: *t*_{major} = 21.71 min, *t*_{minor} = 19.14 min. ¹H NMR (400 MHz): δ 7.38 (d, *J*=7.6Hz, 2H), 7.26-7.34 (m, 3H), 6.78 (d, *J*=16Hz, 1H), 6.25 (dd, *J*=6, 9.6Hz, 1H), 5.16 (t, 5.2Hz, 1H), 3.79 (s, 3H), 2.23 (d, *J*=6Hz, 1H). ¹³C NMR (100 MHz): δ 153.7, 135.5, 133.3, 128.6, 128.5, 126.9, 125.6, 109.7, 85.6, 77.4, 62.6, 52.9. IR: 3689, 3176 (m), 3083, 3018, 2953, 2917, 2849, 2453, 2376, 2312, 2283, 2233, 1710, 1595, 1491, 1432, 1385, 1244, 1087, 1060, 1028, 961, 691. HRMS-ESI (m/z): calcd for C₁₄H₁₀O₃+Na⁺: 177.0522; found: 177.0521, 0.6ppm.

Methyl 4-hydroxyhept-5-en-2-ynoate.⁶ 65% yield, 82% *ee* determined by HPLC analysis (AD-H column; Hept/i-PrOH 98/2, 1mL/min, 223nm); Retention time: *t*_{major} = 30.33 min, *t*_{minor} = 27.96 min. ¹H NMR (400 MHz): δ 5.96 (dd, *J*=6.8, 8Hz, 1H), 5.62 (dd, *J*=6, 9.6Hz, 1H), 4.95 (d, *J*=5.6Hz, 1H), 3.80 (s, 3H), 2.18 (s, 1H), 1.75 (d, *J*=6.8Hz, 3H). ¹³C NMR (100 MHz): δ 153.7, 130.6, 128.1, 86.3, 62.5, 52.8, 15.2. IR: 3411 (br, OH), 3032, 2956, 2920, 2857, 2238, 1718, 1436, 1380, 1255, 1120, 1086, 1061, 1035. HRMS-ESI (m/z): calcd for C₁₄H₁₀O₃+Na⁺: 177.0522; found: 177.0521, 0.6ppm.

Methyl 4-hydroxy-4-cyclohexyl-but-2-ynoate.⁷ 80% yield, 79% *ee* determined by HPLC analysis (AD-H column; Hept/i-PrOH 98/2, 1mL/min, 221nm); Retention time: *t*_{major} = 47.25 min, *t*_{minor} = 44.30 min. [α]_D²⁰ = -3° (c=1.38, CHCl₃). ¹H NMR (400 MHz): δ 4.25 (d, *J*=6Hz, 1H), 3.76 (s, 3H), 2.06 (s, 1H), 1.74-1.83 (m, 4H), 1.57-1.67 (m, 2H), 1.02-1.27 (m, 6H). ¹³C NMR (100 MHz): δ 153.8, 87.5, 77.1, 66.8, 52.8, 43.6, 28.3, 28.1, 26.1, 25.7. IR: 3418 (br, OH), 3006, 2928, 2854, 2235, 1718, 1436, 1251, 1083, 1048, 1016. HRMS-ESI (m/z): calcd for C₁₁H₁₆O₃+Na⁺: 219.0992; found: 219.0991, 0.5ppm.

Spectrums of HPLC:

Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1	7.828	552681	4.37	52690	bb			Unknown	
2	9.011	12089113	95.63	850273	bb			Unknown

Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1	51.265	9012151	95.06	86388	bb			Unknown	
2	63.726	468164	4.94	3806	bb			Unknown	

(5) Trost, B.M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, 128, 8-9.

(6) Tejedor, D.; Santos-Exposito, A.; Garcia-Tellado, F. *Synlett.* **2006**, 10, 1607-1609.

(7) Rajaram, A.R.; Pu, L. *Org. Lett.* **2006**, 8, 2019-2021.

Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1	13.858	1889296	7.51	124433	bb			Unknown	
2	15.227	23257909	92.49	1238585	bb			Unknown

Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1	27.957	1447394	8.95	44861	bb			Unknown	
2	30.330	14727545	91.05	329419	bb			Unknown

Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1	44.302	1752378	10.63	37186	bb			Unknown	
2	47.252	14737780	89.37	249825	bb			Unknown

2-MeO

14-2

4-MeO-

4MeO-

7.542
7.538
7.526
7.521
7.515
7.406
7.385
7.263

5.545

3.820
3.800

2.534

1.253

0.000

(2)