Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

The First Highly Enantioselective Synthesis of g-Hydroxy-a,b-acetylenic Esters by Asymmetric Alkyne Addition to Aldehydes

Ge Gao[†], Qin Wang[†], Xiao-Qi Yu[†*], Ru-Gang Xie[†], and Lin Pu[‡*]

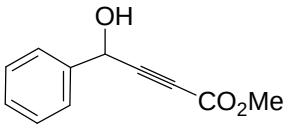
[†] *Department of Chemistry, Key Laboratory of Green Chemistry and Technology (Ministry of Education), Sichuan University, Chengdu 610064, P. R. China*

[‡]*Department of Chemistry, University of Virginia, Charlottesville, VA 22904-4319, USA*

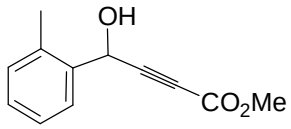
General Data. All reactions were carried out under argon. Unless otherwise specified, all reagents were purchased from Lancaster and used directly. Diethylzinc (1.1 M in toluene) and chloroform-*d* were purchased from Aldrich Chemical Co.

Methylene chloride was dried by heating with calcium hydride at reflux under nitrogen. Tetrahydrofuran was dried by heating with sodium and benzophenone at reflux under nitrogen. Both of the solvents were freshly distilled under nitrogen before use.

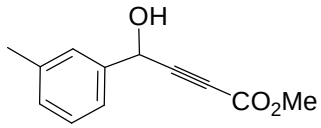
^{1}H NMR spectra and ^{13}C NMR spectra were obtained by using Varian INOVA-400 and Bruker AC-E200 spectrometers respectively at the Sichuan University NMR facility, and TMS was used as the internal standard for the NMR analysis. HPLC analyses were performed on the Agilent 1100 series using Diacel Chiralcel OD column detected at λ = 254 nm, and a mixed solvent of 10% *i*PrOH in hexane was used as the eluent at a flow rate of 2.0 mL/min unless otherwise indicated. The optical rotations were measured on PERKIN ELEMER 241 Polarimeter. Mass spectra were recorded on Agilent 6890-5973 GC-MS system.



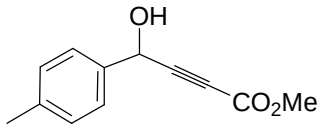
Methyl 4-hydroxy-4-phenylbut-2-ynoate. 69% yield, and. 91% *ee* determined by HPLC analysis; Retention time: t_{major} = 19 min, and t_{minor} = 22.4 min. $[a]_D^{28}$ = –3.56 (c = 0.73, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.52-7.50 (d, J = 6.8 Hz, 2H), 7.42-7.35 (m, 3H), 5.56 (d, J = 4.8 Hz, 1H), 3.79 (s, 3H), 2.71 (d, J = 5.2 Hz, 1H). MS: *m/z* 190 (M^+). HRMS (ESI) calcd for $C_{11}H_{10}O_3$+Na^+: 213.0528; found: 213.0522.



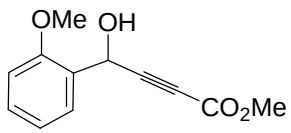
Methyl 4-hydroxy-4-*o*-tolylbut-2-ynoate. 96% yield. 91% *ee* determined by HPLC analysis (10% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 9.6 min, and t_{minor} = 10.7 min. $[a]_D^{12}$ = +7.50 (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.60-7.58 (dd, J = 1.6, 6.4 Hz, 1H), 7.29-7.22 (m, 2H), 7.21-7.19 (m, 1H), 5.71 (d, J = 5.6 Hz, 1H), 3.79 (s, 3H), 2.51 (d, J = 6.0 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) d 153.8, 136.3, 135.9, 130.9, 129.0, 126.6, 126.4, 86.5, 77.5, 62.1, 52.8, 18.9. MS: *m/z* 204 (M^+). HRMS (ESI) calcd for $C_{12}H_{12}O_3$+Na^+: 227.0684; found: 227.0679.



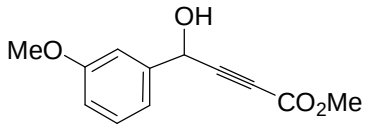
Methyl 4-hydroxy-4-*m*-tolylbut-2-ynoate. 91% yield. 93% *ee* determined by HPLC analysis; Retention time: t_{major} = 4.3 min, and t_{minor} = 5.0 min. $[a]_D^{12}$ = –4.18 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.32-7.28 (m, 3H), 7.17 (d, J = 6.8 Hz, 1H), 5.53 (d, J = 6.0 Hz, 1H), 3.79 (s, 3H), 2.57 (d, J = 6.4 Hz,1H), 2.38 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) d 153.9, 138.6, 138.4, 129.6, 128.7, 127.3, 123.7, 86.9, 77.4, 64.2, 52.9, 21.3. MS: *m/z* 204 (M^+). HRMS (ESI) calcd for $C_{12}H_{12}O_3$+Na^+: 227.0684; found: 227.0679.



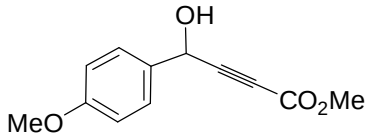
Methyl 4-hydroxy-4-*p*-tolylbut-2-ynoate. 81% yield. 93% *ee* determined by HPLC analysis (Diacel Chiralcel AD-H column, 10% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 11.1 min, and t_{minor} = 13.0 min. $[a]_D^{12}$ = –5.07 (c = 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.39 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 5.52 (s, 1H), 3.78 (s, 3H), 2.62 (br, 1H), 2.36 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) d 153.8, 138.8, 135.6, 129.4, 126.6, 86.8, 77.3, 64.0, 52.8, 21.1. MS: *m/z* 204 (M^+). HRMS (ESI) calcd for $C_{12}H_{12}O_3$+Na^+: 227.0684; found: 227.0679.



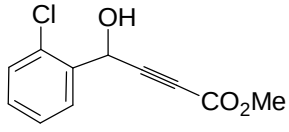
Methyl 4-hydroxy-4-(2-methoxyphenyl)but-2-ynoate. 91% yield. 90% *ee* determined by HPLC analysis (Diacel Chiralcel OJ column, 10% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 51.7 min, and t_{minor} = 41.6 min. $[a]_D^{12}$ = –5.96 (c = 0.97, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.45-7.43 (dd, J = 1.6, 7.6 Hz, 1H), 7.36-7.32 (dt, J = 1.6, 8.0 Hz, 1H), 7.01-6.97 (t, J = 7.6 Hz, 1H), 6.94-6.92 (d, J = 8.0 Hz, 1H), 5.72 (d, J = 5.6 Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.23 (d, J = 6.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) d 156.6, 153.8, 130.1, 127.9, 126.8, 120.1, 111.0, 86.8, 76.4, 60.8, 55.5, 52.6. MS: *m/z* 220 (M^+). HRMS (ESI) calcd for $C_{12}H_{12}O_4$+Na^+: 243.0633; found: 243.0628.



Methyl 4-hydroxy-4-(3-methoxyphenyl)but-2-ynoate. 52% yield. 90% *ee* determined by HPLC analysis; Retention time: t_{major} = 6.1 min, and t_{minor} = 7.7 min. $[a]_D^{12}$ = –7.69 (c = 0.98, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.33-7.29 (t, J = 8.0 Hz, 1H), 7.10-7.06 (m, 2H), 6.91-6.89 (dd, J = 2.4, 8.0 Hz, 1H), 5.55 (br, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.52 (br, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) d 159.8, 153.8, 140.1, 129.8, 118.8, 114.5, 112.1, 86.7, 77.4, 64.0, 55.3, 52.9. MS: *m/z* 220 (M^+). HRMS (ESI) calcd for $C_{12}H_{12}O_4$+Na^+: 243.0633; found: 243.0628.

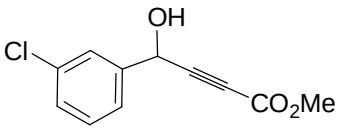


Methyl 4-hydroxy-4-(4-methoxyphenyl)but-2-ynoate. 82% yield. 91% *ee* determined by HPLC analysis (2% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 92.1 min, and t_{minor} = 101.3 min. $[a]_D^{12}$ = –5.41 (c = 1.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.45-7.43 (md, J = 8.8 Hz, 2H), 6.93-6.90 (md, J = 8.8 Hz, 2H), 5.52 (d, J = 5.6 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.45 (d, J = 6.0 Hz, 1H). MS: *m/z* 220 (M^+). HRMS (ESI) calcd for $C_{12}H_{12}O_4$+Na^+: 243.0633; found: 243.0628.

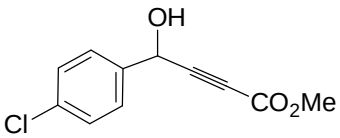


Methyl 4-(2-chlorophenyl)-4-hydroxybut-2-ynoate. 94% yield. 91% *ee* determined by HPLC analysis (10% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 9.0 min, and t_{minor} = 9.8

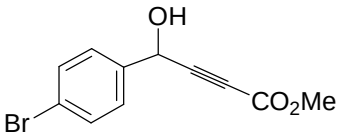
min. $[a]_D^{11}$ = +33.70 (c = 0.99, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) d 7.12-7.69 (dd, J = 2.4, 6.8 Hz, 1H), 7.41-7.39 (m, 1H), 7.36-7.29 (m, 2H), 5.93 (d, J = 5.2 Hz, 1H), 3.80 (s, 3H), 2.81 (d, J = 5.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) d 153.7, 135.9, 132.6, 130.1, 129.8, 128.3, 127.4, 85.6, 77.2, 61.4, 52.9. MS: *m/z* 224 (M^+). HRMS (ESI) calcd for $C_{11}H_9ClO_3$+Na^+: 247.0138; found: 247.0132.



Methyl 4-(3-chlorophenyl)-4-hydroxybut-2-ynoate. 90% yield. 93% *ee* determined by HPLC analysis (10% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 11.4 min, and t_{minor} = 10.0 min. $[a]_D^{11}$ = –9.84 (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) d 7.52 (s, 1H), 7.41-7.38 (m, 1H), 7.36-7.31 (m, 2H), 5.56 (s, 1H), 3.80 (s, 3H), 2.76 (br, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) d 153.7, 140.3, 134.6, 130.1, 129.0, 126.7, 124.7, 85.9, 63.4, 53.0. MS: *m/z* 224 (M^+). HRMS (ESI) calcd for $C_{11}H_9ClO_3$+Na^+: 247.0138; found: 247.0132.

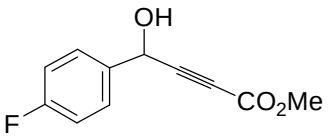


Methyl 4-(4-chlorophenyl)-4-hydroxybut-2-ynoate. 84% yield. 95% *ee* determined by HPLC analysis (5% *i*-PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 19.2 min, and t_{minor} = 18.2 min. $[a]_D^{11}$ = –7.82 (c = 1.02, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) d 7.47-7.44 (md, J = 8.4 Hz, 2H), 7.39-7.35 (md, J = 8.4 Hz, 2H), 5.56 (s, 1H), 3.80 (s, 3H), 2.74 (br, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) d 153.7, 136.9, 134.7, 128.9, 128.0, 86.1, 63.4, 53.0. MS: *m/z* 224 (M^+). HRMS (ESI) calcd for $C_{11}H_9ClO_3$+Na^+: 247.0138; found: 247.0132.

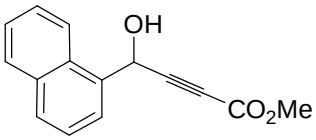


Methyl 4-(4-bromophenyl)-4-hydroxybut-2-ynoate. 82% yield. 93% *ee* determined by HPLC analysis (5% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 22.2 min, and t_{minor} = 20.8 min. $[a]_D^{12}$ = –5.37 (c = 1.01, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) d 7.54-7.52 (md, J = 8.4 Hz, 2H), 7.41-7.39 (d, J = 8.8 Hz, 2H), 5.55 (d, J = 5.2 Hz, 1H), 3.80 (s, 3H), 2.53 (d, J = 6.0 Hz, 1H).

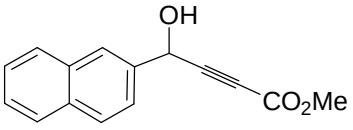
^{13}C NMR (50 MHz, $CDCl_3$) d 153.5, 137.4, 131.9, 128.2, 122.9, 85.8, 77.7, 63.5, 52.9. MS: *m/z* 268 (M^+-1), 270 (M^++1). HRMS (ESI) calcd for $C_{11}H_9BrO_3$+Na^+: 290.9633; found: 290.9627.



Methyl 4-(4-fluorophenyl)-4-hydroxybut-2-ynoate. 76% yield. 85% *ee* determined by HPLC analysis (Diacel Chiralcel AD-H column, 10% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 9.0 min, and t_{minor} = 9.9 min. $[a]_D^{11}$ = –6.49 (c = 1.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.52-7.48 (m, 2H), 7.11-7.06 (t, J = 7.2 Hz, 2H), 5.56 (s, 1H), 3.80 (s, 3H), 2.66 (br, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) d 165.3-160.4 (d, J = 246.45 Hz), 153.7, 134.33-134.27 (d, J = 2.95 Hz), 128.6-128.4 (d, J = 8.45 Hz), 115.9-115.5 (d, J = 21.5 Hz), 86.3, 63.4, 52.9. MS: *m/z* 208 (M^+). HRMS (ESI) calcd for $C_{11}H_9FO_3$+Na^+: 231.0433; found: 231.0428.

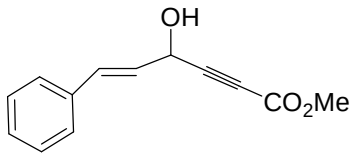


Methyl 4-hydroxy-4-(naphthalen-1-yl)but-2-ynoate. 87% yield. 95% *ee* determined by HPLC analysis (10% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 22.9 min, and t_{minor} = 17.7 min. $[a]_D^{11}$ = +2.82 (c = 1.07, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) d 8.22 (d, J = 8.4 Hz, 1H), 7.90 (t, J = 8.4 Hz, 2H), 7.79 (d, J = 6.8 Hz, 1H), 7.61-7.52 (m, 2H), 7.47 (t, J = 7.2 Hz, 1H), 6.21 (s, 1H), 3.78 (s, 3H), 2.84 (br, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) d 153.8, 133.9, 133.5, 130.2, 129.8, 128.8, 126.7, 126.1, 125.2, 125.0, 123.5, 86.5, 78.1, 62.5, 52.9. MS: *m/z* 240 (M^+). HRMS (ESI) calcd for $C_{15}H_{12}O_3$+Na^+: 263.0684; found: 263.0679.

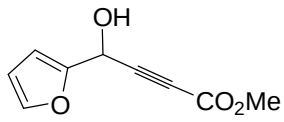


Methyl 4-hydroxy-4-(naphthalen-2-yl)but-2-ynoate. 84% yield. 93% *ee* determined by HPLC analysis (5% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 37.4 min, and t_{minor} = 31.9 min. $[a]_D^{11}$ = +5.30 (c = 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.97 (s, 1H), 7.89-7.84 (m, 3H), 7.62-7.60 (dd, J = 1.6, 8.4 Hz, 1H), 7.53-7.51 (dd, J = 3.2, 6.4 Hz, 2H), 5.74 (br, 1H), 3.80 (s, 3H), 2.69 (br, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) d 153.8, 135.7, 133.3, 133.0 128.8,

128.2, 127.7, 126.6, 126.5, 125.7, 124.2, 86.6, 77.8, 64.3, 52.9. MS: *m/z* 240 (M^+). HRMS (ESI) calcd for $C_{15}H_{12}O_3$+Na^+: 263.0684; found: 263.0679.



(E)-Methyl 4-hydroxy-6-phenylhex-5-en-2-ynoate. 65% yield determined by ^{1}H NMR analysis relative to an internal standard benzimidazole. 91% *ee* determined by HPLC analysis (5% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 51.4 min, and t_{minor} = 56.1 min. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.43-7.40 (md, J = 6.8 Hz, 2H), 7.37-7.30 (m, 3H), 6.83-6.79 (dd, J = 1.2, 16 Hz, 1H), 6.31-6.26 (dd, J = 6.4, 16 Hz, 1H), 5.19 (d, J = 4.8 Hz, 1H), 3.82 (s, 3H). MS: *m/z* 216 (M^+), 215 (M^+-1). HRMS (ESI) calcd for $C_{13}H_{12}O_3$+Na^+: 239.0684; found: 239.0679.



Methyl 4-(furan-2-yl)-4-hydroxybut-2-ynoate. 55% yield determined by ^{1}H NMR analysis relative to an internal standard benzimidazole. 87% *ee* determined by HPLC analysis (10% *i*PrOH in hexane at 1.0 mL/min); Retention time: t_{major} = 12.9 min, and t_{minor} = 11.1 min. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.44 (s, 1H), 6.49 (d, J = 3.2 Hz, 1H), 6.38-6.37 (dd, J = 2.0, 3.2 Hz, 1H), 5.58 (s, 1H), 3.80 (s, 3H), 2.78 (br, 1H). MS: *m/z* 180 (M^+). HRMS (ESI) calcd for $C_9H_8O_4$+Na^+: 203.0320; found: 203.0315.

General Procedure for the Preparation of the Racemic Propargylic Alcohols. All the racemic ?-hydroxy-a,ß-acetylenic esters used for the HPLC analysis were prepared according to the following procedure: Under argon, a solution of methyl propiolate (0.75 mmol) in tetrahydrofuran (3 mL) in a 10 mL round bottom flask was cooled to -78 ^{o}C by a dryice/acetone bath, and *n*BuLi (0.12 mL, 2.5 M in hexane) was added. The mixture was stirred for 15 min. An aldehyde (0.25 mmol) was then added and the reaction mixture was continuously stirred for another 15 min. Ice was added to quench the reaction and methylene chloride was used for extraction. The extract was dried over magnesium sulfate. After the volatile solvent was removed by roto-evaporation, the residue was passed through a short silica gel eluted with petroleum ether/ethyl acetate (9/1) to afford the product.

Preparation of the Mosher Esters: To a 5 mL round-bottom flask, methyl 4-hydroxy-4-phenylbut-2-ynoate [15.2 mg, 0.08 mmol, prepared by using (*R*)-BINOL as the catalyst], DCC (33.0 mg, 0.16 mmol), DMPA (9.8 mg, 0.08 mmol), and (*R*)-Mosher acid or (*S*)-Mosher acid (37.5 mg, 0.16 mmol) were sequentially added. After the solution was stirred at room temperature for 30 min (monitored by TLC), the crude mixture was passed through a short silica gel column to afford the desired (*R*)-Mosher ester or (*S*)-Mosher ester (11.2 mg, 34% yield) as light yellow oil.

Characterization of the Mosher Esters: Proton chemical shifts are referenced to either TMS (d 0.00) or residual $CHCl_3$ (d 7.26); ^{19}FNMR spectra were recorded in $CDCl_3$ with TFA (d -75.77) as an external standard. (*R*)-Mosher ester: ^{1}HNMR (400 MHz, $CDCl_3$) d 7.51-7.49(m, 2H), 7.47-7.45(m, 2H), 7.42-7.35(m, 6H), 6.69(s, 1H), 3.80(s, 3H), 3.47(s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) d -71.76; HRMS calcd for $C_{21}H_{17}F_3Na_1O_5$ (M+Na) 429.0920, found 429.0915. (*S*)-Mosher ester: ^{1}HNMR (400 MHz, $CDCl_3$) d 7.42-7.39(m, 5H), 7.37-7.32(m, 5H), 6.72(s, 1H), 3.80(s, 3H), 3.59(s, 3H); ^{19}FNMR (282 MHz, $CDCl_3$) d -71.62. HRMS calcd for $C_{21}H_{17}F_3Na_1O_5$ (M+Na) 429.0920; found: 429.0925. On the basis of the ^{19}F NMR, the propargylic alcohol methyl 4-hydroxy-4-phenylbut-2-ynoate, prepared by using (*R*)-BINOL as the catalyst, is assigned to have a S configuration. (Ref: Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143-2147.)