

Selective One-Pot Synthesis of Allenyl and Alkynyl Esters from β -Ketoesters

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Supporting Information

Table of Contents	Page
General information	S1
General procedure for conjugate alkyne synthesis	S2
Spectral data for conjugate alkynyl esters 2d and 2e	S2
Procedure for synthesis of alkynyl ester 8 and spectral data	S2 - S3
General procedure for deconjugated alkyne/conjugated allene isomers via monoanionic enyne enolate	S3
Spectral data for deconjugated alkyne/conjugated allenes 9b – 9d and for mixtures 9e/10e thru 9h/10h	S3 - S4
General procedures for silylated deconjugated alkyne/conjugated allene isomers via dianionic enolate	S5
Spectral data for mixture 9c/18a and pure 18b	S5 –S6
^1H and ^{13}C spectra	S7 – S32

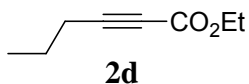
General Information. All the reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring. THF was dried using a double alumina column. LDA and LiHMDS were purchased from Aldrich as 1.0 M solutions in THF. β -Ketoesters, triflic anhydride, and chloro silanes were purchased from Acros and TCI America and used without further purification. Purification of reaction products was carried out by flash column chromatography using Flash Silica gel 40-63 μ . Analytical thin layer chromatography was performed on 0.25mm silica gel 60-F plates. Visualization was accomplished with UV light and aqueous potassium permanganate solution staining followed by air heating.

^1H NMR and ^{13}C NMR were recorded on a 400 MHz NMR spectrometer and are reported in ppm using solvent as internal standard. Data are reported as: (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet; coupling constant(s) in Hz, integration).

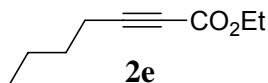
General procedure for conjugate alkyne synthesis

To a round bottom flask (50 mL) under argon was added dry THF (7 mL) and LiHMDS (4 mL, 1.0 M in THF). The solution was then cooled to $-78\text{ }^{\circ}\text{C}$ (acetone-dry ice bath) followed by the addition of β -keto ester (2 mmol). After stirring for 45 min, triflic anhydride (2 mmol) was added slowly over 15 min. The reaction was then stirred overnight slowly warming to room temperature and quenched with saturated NH_4Cl solution. The organic layer was separated, the aqueous fraction was extracted with ether, and the organic layers were combined and dried with anhydrous Na_2SO_4 . The product was purified by silica gel chromatography in the usual manner using 1-2% EtOAc in hexanes. Products **2a**,¹ **2b**,² and **2c**³ are reported in the literature and compared favorably with our own NMR spectra of these compounds.

Ethyl hex-2-ynoate (2d) ^1H NMR (400MHz, CDCl_3) δ 4.22 (q, $J = 7.14$ Hz, 2H), 2.31 (t, $J = 7.1$ Hz, 2H), 1.66-1.57 (m, 2H), 1.31 (t, $J = 7.14$ Hz, 3H), 1.02 (t, $J = 7.38$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.8, 89.2, 73.2, 61.7, 21.0, 20.5, 14.0, 13.4; HRMS calc. for $\text{C}_8\text{H}_{12}\text{O}_2$ $[\text{M}+\text{H}]^+$: 141.0910. Found: 141.0899.



Ethyl hept-2-ynoate (2e) ^1H NMR (400MHz, CDCl_3) δ 4.21 (q, $J = 7.05$ Hz, 2H), 2.34 (t, $J = 7.06$ Hz, 2H), 1.61-1.53 (m, 2H), 1.49-1.39 (m, 2H), 1.31 (t, $J = 7.05$ Hz, 3H), 0.92 (t, $J = 7.41$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.9, 89.4, 73.1, 61.7, 29.5, 21.9, 18.3, 14.0, 13.5; HRMS calc. for $\text{C}_9\text{H}_{14}\text{O}_2$ $[\text{M}+\text{H}]^+$: 155.1067. Found: 155.1061.



Procedure for synthesis of alkynyl ester **8**

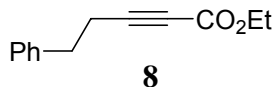
To a round bottom flask (50 mL) under argon was added dry THF (7 mL) and LiHMDS (4 mL, 1.0 M in THF). The solution was then cooled to $-78\text{ }^{\circ}\text{C}$ (acetone-dry ice bath) followed by the addition of β -keto ester (2 mmol). After stirring for 45 min, BnBr (2 mmol) was added dropwise followed by warming slowly to room temperature over the course of 6 h. The reaction mixture was then cooled to $-78\text{ }^{\circ}\text{C}$ and charged with LiHMDS (2 mL, 1.0 M in THF). After for 45 min, Tf_2O (2 mmol) was added slowly over 15 min and the reaction was stirred overnight slowly warming to room temperature and quenched with saturated NH_4Cl solution. The organic layer was separated, the aqueous fraction was extracted with ether, and the organic layers were combined and dried with anhydrous Na_2SO_4 . The product was purified by silica gel chromatography in the usual manner using 1-2% EtOAc in hexanes.

¹ Fisher D. F.; Xin, Z.; Peters, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 7704.

² Tokuda, M.; Nishio, O. *J. Org. Chem.* **1985**, *50*, 1592.

³ Frimer, A. A.; Antebi, A. *J. Org. Chem.* **1980**, *45*, 2334.

Ethyl 5-phenyl-pent-2-ynoate (8) ^1H NMR (400MHz, CDCl_3) δ 7.40-7.22 (m, 5H), 4.21 (q, $J = 7.2$ Hz, 2H), 2.89 (t, $J = 7.6$ Hz, 2H), 2.61 (t, $J = 7.6$ Hz, 2H), 1.30 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.0, 139.9, 128.8, 128.6, 126.9, 88.5, 73.9, 62.1, 34.1, 21.1, 14.3; HRMS calc. for $\text{C}_{13}\text{H}_{14}\text{O}_2$ $[\text{M}+\text{H}]^+$: 203.1067. Found: 203.1059.



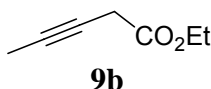
General procedure for deconjugated alkyne/conjugated allene isomers via monoanionic enyne enolate

To a round bottom flask (50 mL) under argon was added dry THF (7 mL) and LiHMDS (4 mL, 1.0 M in THF). The solution was then cooled to -78 °C (acetone-dry ice bath) followed by the addition of β -keto ester (2 mmol). After stirring for 45 min, triflic anhydride (2 mmol) was added slowly over 15 min. The reaction was maintained at -78 °C with stirring for an additional 1 h followed by the addition of LiHMDS (2 mmol). The mixture was stirred at -78 °C for an additional 30 min followed by the addition of HMPA (7 mmol). After an additional 30 min at -78 °C, the reaction was quenched by pouring into an ice-cold stirring biphasic mixture of ether and saturated aqueous NH_4Cl .

Depending on the substrate, the reaction may lead to mixtures of deconjugated alkyne and conjugated allene which are inseparable by ordinary flash chromatography. Furthermore, deconjugated alkynes **9e** – **9h** isomerize rapidly to conjugated allenes on silica gel. In such cases, compounds were analyzed as crude mixtures to determine product ratios and then chromatographed to obtain combined isolated yields.

Products **9a**, **10a**,⁴ **10e**,⁵ **10f**,⁶ **10g**,⁷ **10i**,⁸ and **10j**⁹ are reported in the literature and compared favorably with our own NMR spectra of these compounds.

Ethyl pent-3-ynoate (9b) ^1H NMR (400MHz, CDCl_3) δ 4.19 (q, $J = 7.13$ Hz, 2H), 3.22 (q, $J = 2.58$ Hz, 2H), 1.83 (t, $J = 2.58$ Hz, 3H), 1.28 (t, $J = 7.13$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.8, 78.9, 70.4, 61.2, 25.8, 20.8, 3.3; HRMS calc. for $\text{C}_7\text{H}_{10}\text{O}_2$ $[\text{M}+\text{H}]^+$: 127.0754. Found: 127.0742.



⁴ Commercially available

⁵ Jung, E. M.; Nishimura, N. *Org. Lett.* **2001**, *3*, 2113.

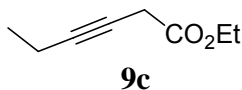
⁶ Jones, E. R. H.; Whitham, G. H.; Whiting, M. C. *J. Chem. Soc.* **1957**, 4628.

⁷ Bloshchista, F. A.; Burmakov, A. I.; Kunshenko, B. V.; Alekseeva, L. A.; Yagupolskii, L. M. *Zhurnal Organicheskoi Khimii* **1982**, *18*, 782.

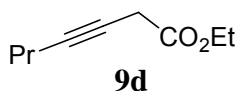
⁸ Himbert, G.; Fink, D.; Diehl, K. *Chemische Berichte* **1988**, *121*, 431.

⁹ Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836.

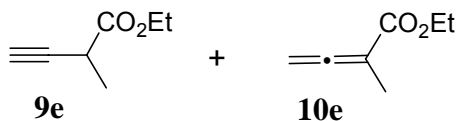
Ethyl hex-3-ynoate (9c) ^1H NMR (400MHz, CDCl_3) δ 4.19 (q, $J = 7.12$ Hz, 2H), 3.25 (t, $J = 2.43$ Hz, 2H), 2.21 (tt, $J = 7.51, 2.46$ Hz, 2H), 1.28 (t, $J = 7.12$ Hz, 3H), 1.14 (t, $J = 7.50$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.9, 85.0, 70.7, 61.3, 26.0, 20.3, 14.0, 12.4; HRMS calc. for $\text{C}_8\text{H}_{12}\text{O}_2$ $[\text{M}+\text{H}]^+$: 141.0910. Found: 141.0907.



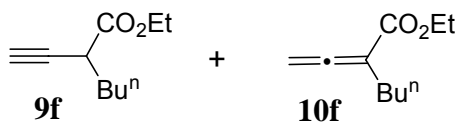
Ethyl hept-3-ynoate (9d) ^1H NMR (400MHz, CDCl_3) δ 4.18 (q, $J = 7.23$ Hz, 2H), 3.25 (t, $J = 2.51$ Hz, 2H), 2.18 (tt, $J = 7.09, 2.51$ Hz, 2H), 1.57-1.48 (m, 2H), 1.28 (t, $J = 7.23$ Hz, 3H), 0.98 (t, $J = 7.39$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.9, 83.6, 71.5, 61.3, 26.0, 22.6, 22.1, 14.0, 13.3; HRMS calc. for $\text{C}_9\text{H}_{14}\text{O}_2$ $[\text{M}+\text{H}]^+$: 155.1067. Found: 155.1061.



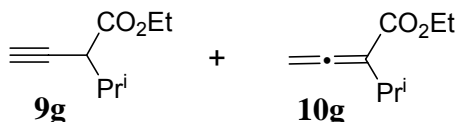
Ethyl-2-methyl-3-butynoate (9e) and Ethyl-2-methylallenylester (10e) ^1H NMR (400MHz, CDCl_3) δ 5.06 (q, $J = 3.16$ Hz, 2H), 4.25-4.16 (m, 3H), 3.40 (q, $J = 7.23$ Hz, 1H), 1.88 (t, $J = 3.15$ Hz, 3H), 1.82 (d, $J = 3.55$ Hz, 1H), 1.42 (d, $J = 7.20$ Hz, 3H).



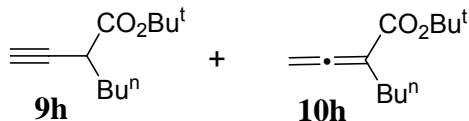
Ethyl-2-n-butyl-3-butynoate (9f) and Ethyl-2-n-butylallenylester (10f) ^1H NMR (400MHz, CDCl_3) δ 4.96 (t, $J = 3.1$ Hz, 2H), 4.10-4.00 (m, 3H), 3.16 (dd, $J = 7.95, 6.56$ Hz, 1H), 2.10-1.96 (m, 3H), 1.70-1.55 (m, 3H), 1.3-1.15 (m, 3H), 1.14-1.06 (m, 6H), 0.78-0.70 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 212.7, 170.8, 168.9, 103.4, 88.7, 87.2, 79.6, 62.1, 61.7, 39.9, 32.9, 31.5, 30.9, 30.0, 28.5, 28.0, 23.2, 23.0, 15.1, 15.0, 14.9, 14.7.



Ethyl-2-iso-propyl-3-butynoate (9g) and Ethyl-2-iso-propylallenylester (10g) ^1H NMR (400MHz, CDCl_3) δ 5.13 (d, $J = 2.35$ Hz, 2H), 4.21-4.16 (q, $J = 7.12$ Hz, 1H), 4.13-4.06 (q, $J = 7.13$ Hz, 2H), 3.14 (d, $J = 6.62$ Hz, 0.5H), 2.73-2.58 (m, 1.5H), 1.30-1.20 (m, 5H), 1.03 (d, $J = 6.88$ Hz, 6H), 0.94 (d, $J = 6.62, 1.5\text{H}$); ^{13}C NMR (100 MHz, CDCl_3) δ 212.6, 171.0, 166.9, 107.0, 101.1, 88.9, 87.8, 20.7, 20.6, 14.2, 14.1, 14.1.



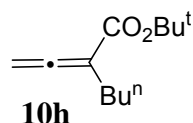
tert-Butyl-2-n-butyl-3-butynoate (9h) and tert-Butyl -2-n-butylallenylester (10h) ¹H NMR (400MHz, CDCl₃) δ 5.05 (t, *J* = 3.03 Hz, 2H), 3.28 (t, *J* = 7.33 Hz, 0.4H), 2.29-2.24 (m, 0.8H), 2.18 (m, 2H), 1.47 (s, 9H), 1.44 (s, 3.6H), 1.45-1.30 (m, 5.6H), 0.91-0.85 (m, 4.5H).



General procedure for deconjugated alkyne/conjugated allene isomers via monoanionic enyne enolate with ZnCl₂ additive

To a round bottom flask (50 mL) under argon was added dry THF (7 mL) and LiHMDS (4 mL, 1.0 M in THF). The solution was then cooled to -78 °C (acetone-dry ice bath) followed by the addition of β-keto ester (2 mmol). After stirring for 45 min, triflic anhydride (2 mmol) was added slowly over 15 min. The reaction was maintained at -78 °C with stirring for an additional 1 h followed by the addition of LiHMDS (2 mmol). The mixture was stirred at -78 °C for an additional 30 min followed by the addition of HMPA (7 mmol). After stirring for stirring at -78 °C for an additional 30 min, ZnCl₂ (2.4 mmol) was added as an ether solution. The reaction was quenched after an additional 30 min by pouring into an ice-cold stirring biphasic mixture of ether and saturated aqueous NH₄Cl. NMR spectra were recorded after workup for each reaction confirming the formation of only conjugated allene which were compared with literature references (except for **10h**).

tert-Butyl-2-n-butylallenylester (10h) ¹H NMR (400MHz, CDCl₃) δ 5.05 (t, *J* = 3.03 Hz, 2H), 2.18 (m, 2H), 1.47 (s, 9H), 1.45-1.30 (m, 4H), 0.91 (t, *J* = 7.19 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 213.6, 166.6, 101.7, 80.7, 30.2, 28.0, 27.7, 22.3, 13.9; HRMS calc. for C₁₂H₂₀O₂ [M+H]⁺: 197.1542. Found: 197.1543.



General procedures for silylated deconjugated alkyne/conjugated allene isomers via dianionic enolate

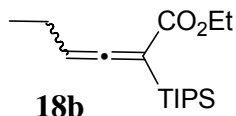
To a round bottom flask (50 mL) under argon was added dry THF (7 mL) and LiHMDS (4 mL, 1.0 M in THF). The solution was then cooled to -95 °C (methanol-liquid N₂ bath) followed by addition of β-keto ester (2 mmol). After stirring for 1 h, triflic anhydride (2 mmol) was added slowly over 15 min. Since Tf₂O is a solid at this reaction temperature, the slow addition should be accompanied by vigorous stirring. Alternatively, Tf₂O can be added as ether solution (not in THF since this solvent reacts to form polymer at room temperature). The reaction mixture was stirred for an additional 1 h at -95 °C followed by the addition of LiHMDS (4 mL, 1.0 M in THF). After an additional 1 h at -95 °C,

R₃SiCl (6 mmol) was added dropwise followed by warming to room temperature over 1 hour and quenching with saturated NH₄Cl solution. The organic layer was separated, the aqueous fraction was extracted with ether, and the organic layers were combined and dried with anhydrous Na₂SO₄. The product was purified by silica gel chromatography in the usual manner using 1-2% EtOAc in hexanes.

Ethyl-2-trimethylsilylhexa-2,3-dienoate (18a) and Ethyl hex-3-ynoate (9c): ¹H NMR (400MHz, CDCl₃) δ 5.33 (t, *J* = 6.4 Hz, 1H), 4.22-4.15 (m, 6H), 3.25 (t, *J* = 2.42 Hz, 4H), 2.21 (qt, *J* = 7.51, 2.44 Hz, 4H), 2.15-2.07 (m, 2H), 12.8 (t, *J* = 7.11 Hz, 9H), 1.14 (t, *J* = 7.49 Hz, 6H), 1.05 (t, *J* = 7.35 Hz, 3H), 0.18 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 215.0, 168.9, 167.9, 90.1, 88.8, 85.0, 70.7, 61.3, 60.5, 26.0, 20.3, 14.1, 14.0, 13.7, 13.4, 12.4, -1.2; HRMS calc. for C₁₁H₂₀O₂Si [M+H]⁺: 213.1305. Found: 213.1313.



Ethyl-2-triisopropylsilylhexa-2,3-dienoate (18b): ¹H NMR (400MHz, CDCl₃) δ 5.24 (t, *J* = 6.61 Hz, 1H), 4.16 (q, *J* = 7.05 Hz, 3H), 2.20-1.05 (m, 2H), 1.34-1.18 (m, 9H), 1.07 (d, *J* = 7.40 Hz, 18H); ¹³C NMR (100 MHz, CDCl₃) δ 216.2, 168.6, 91.5, 89.6, 60.7, 20.9, 18.6, 17.7, 14.2, 12.2; HRMS calc. for C₁₇H₃₂O₂Si [M+H]⁺: 297.2244. Found: 297.2236.



Product **19**¹⁰ is reported in the literature and compared favorably with our own NMR spectra of this compound.

¹⁰ Lepore, S.D.; He, Y.J.; Damisse, P. *J. Org. Chem.*, **2004**, *69*, 9171.

