# A Large Scale and Concise Synthesis of γ-Linolenic Acid from 4-Chlorobut-2-yn-1-ol

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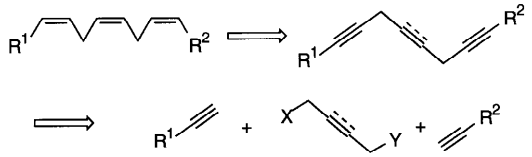
**Abstract:** A large scale and concise synthesis of γ-linolenic acid is described. The key step of the synthesis involves a copper salt mediated cross-coupling of two different alkynes and chlorobutynol.

**Key words:** γ-linolenic acid, skipped diyne, terminal alkynes, copper-catalyzed cross-coupling reactions

Polyunsaturated fatty acids (PUFA) are present in the major part of organisms and are the precursors of numerous types of metabolites such as prostaglandins or leucotrienes.[1] Several human diseases are directly linked to the deficiency of specific desaturase or elongase enzymatic systems.[2] To locate deficient enzymes, probe molecules (labeled compounds) allowing the detection of cumulative metabolites are necessary. Before synthesizing labeled PUFA, we decided to elaborate a valuable route affording a large quantity of γ-linolenic acid.

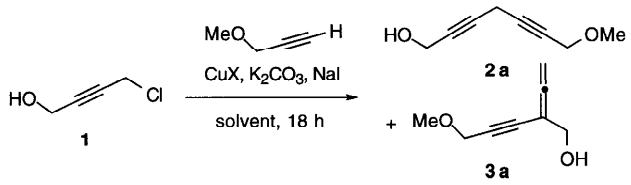
Recently our group proposed a synthesis of arachidonic acid based on a Wittig approach with a C3-homologating agent.[3] This strategy has been applied to the synthesis of pheromones,[4] eicosapentaenoic acid and docosahexaenoic acid.[5] Nevertheless, when we used this approach on a large scale (up to 0.1 mole), numerous difficulties such as the presence of conjugated diene or *E*-isomer impurities, low yields or drastic experimental conditions have emerged. For all these reasons, we planned to study a straightforward method for making *Z,Z,Z*-skipped trienes based on the selective reduction of the appropriate triyne precursor. This approach involves two successive alkylations with different alkynyl derivatives of a difunctional C4-synthon as illustrated retrosynthetically in Scheme 1.



**Scheme 1**

First, we investigated the copper-catalyzed cross-coupling of acetylenic Grignard reagents[6] with (*Z*)-1,4-dichlorobut-2-ene. This reaction initially used by Nicolaou and co-workers in the synthesis of leucotrienes[7] led to an inseparable mixture of the desired skipped chloro-enyne, the $S_N2'$ coupling product and the symmetric skipped enediyne.[8] Under the same experimental conditions, 1,4-dichlorobut-1-yne also led to an inseparable mixture of chloro skipped diyne product and the symmetric skipped triyne.[9]

Attention was next turned to the synthesis of skipped triynes through a copper salt mediated cross-coupling between 4-chlorobut-2-yn-1-ol **(1)** and terminal alkynes under conditions ($Na_2CO_3$, $Bu_4NCl$, CuI, DMF, 18 h) described by Jeffery and co-workers.[10] Cross-coupling of 3-methoxypropyne with chlorobutynol **1** under these conditions occurs with a low conversion rate (32%) (Scheme 2). In order to find better conditions, the cross-coupling of chlorobutynol with methoxypropyne was investigated under potassium carbonate and sodium iodide activation.[11] The nature and the number of equivalents of the copper salt and the nature of the solvent were examined. Special attention was paid to the chemical yields and stereoselectivities in order to evaluate the scope and limitations of the reaction. The results are presented in Table 1.




**Scheme 2**

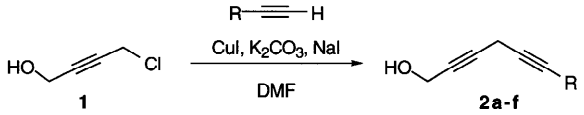
**Table 1.** Copper Salt Catalyzed Cross-Coupling of Chlorobutynol **1**

| Entry | Copper Salt | Equiv | Solvent | Yield (%) **2a** + **3a** | Ratio **2a**/**3a** |
|---|---|---|---|---|---|
| 1 | CuI | 1 | DMF | 93 | 92:8 |
| 2 | CuBr | 1 | DMF | 69 | 92:8 |
| 3 | CuBr•$Me_2S$ | 1 | DMF | 77 | 92:8 |
| 4 | CuCl | 1 | DMF | 75 | 89:11 |
| 5 | CuCN | 1 | DMF | 66 | 86:14 |
| 6 | CuI + $Bu_4NCl$ | 1 | DMF | 88 | 90:10 |
| 7 | CuI | 0.5 | DMF | 86 | 92:8 |
| 8 | CuI | 0.1 | DMF | 58 | 92:8 |
| 9 | CuI | 1 | NMP | 38 | 91:9 |
| 10 | CuI | 1 | MeCN | 33 | 93:7 |
| 11 | CuI | 1 | $MeNO_2$ | 5 | – |
| 12 | CuI | 1 | $H_2O$ | 47 | 92:8 |

The observed regioselectivity (**2a**/**3a** ratio) is relatively independent of the nature of the copper salt, and is above 90:10 when the reaction is performed at 20°C. Attempts to improve the selectivity by lowering (–40°C) or increasing (70°C) the temperature were unsuccessful. Low temperature only induced a lowering of the conversion rate. For this reaction, we found that copper(I) iodide could be used in catalytic quantity, with a decrease in the conversion rate as a drawback. Moreover, DMF use is critically important since its replacement by other solvents led to

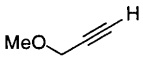
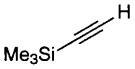
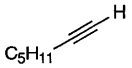
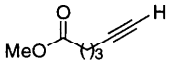
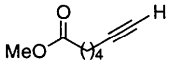
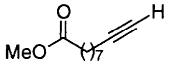
very low conversion rates although with similar selectivities. It should be noted that water does not inhibit the reaction which even occurs in fair yield; nevertheless, attempts done with hept-1-yne in this solvent were unsuccessful. This is certainly due to the very low solubility of heptyne in water.

For practical reasons (easier workup), the experimental conditions used in entry 7 were preferred. According to the results of Table 1, we then applied this reaction to other terminal alkynes (Scheme 3). The substitution reaction seems to have a mild and general character leading to skipped diynols with good yields (cf. Table 2).

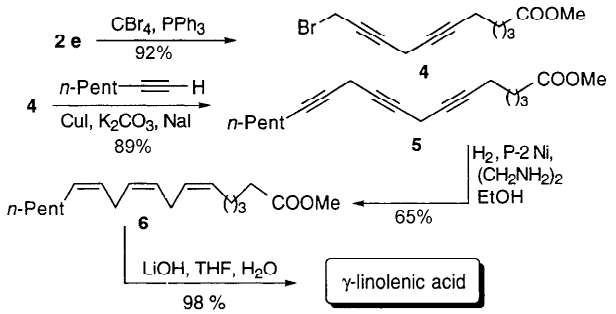



**Scheme 3**

**Table 2.** Copper Salt Catalyzed Alkynylation of Chlorobutynol **1**

| Entry | Alkyne | Products | Yield (%) |
|---|---|---|---|
| 1 |  | **2a** | 86 |
| 2 |  | **2b** | 85 |
| 3 |  | **2c** | 91 |
| 4 |  | **2d** | 86 |
| 5 |  | **2e** | 89 |
| 6 |  | **2f** | 56 |

Attention was next directed to the synthesis of the skipped triyne precursor of $\gamma$-linolenic acid by a second copper(I) iodide mediated cross-coupling as described in Scheme 4.




**Scheme 4**

Compound **2e** was brominated with the complex triphenylphosphene/tetrabromomethane to give **4** in 92% yield.[12] A second copper cross-coupling between hept-1-yne and **4** was then conducted in DMF at 40 °C and afforded the expected skipped triyne **5** in 89% yield. Finally, partial reduction over P-2 Ni catalyst[13] and hydrolysis of the ester function led to $\gamma$-linolenic acid in 46% overall yield from chlorobutynol. It should be noted that this sequence allows the elaboration of approximately 30 g of this acid following a simple procedure.

In conclusion, the above results clearly show that this route constitutes a new, alternative way to obtain large quantities of trienic fatty acids. The copper-catalyzed cross-coupling exhibits a general character to build the carbon skeleton. The mildness of the experimental conditions preserving the skipped diyne moiety shows the versatile and powerful worth of this key reaction. Syntheses of other PUFA and labeled linolenic acids are currently underway.

All reactions were carried out under argon. $CH_2Cl_2$ was dried by distillation over $CaH_2$. DMF was dried by distillation over 4Å molecular sieves. Flash chromatography was carried out with Macherey Nagel silica gel (230–400 mesh). $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AC 200 (NMR) spectrometer. Chemical shifts are given in ppm referring to TMS for $^1$H and $^{13}$C NMR spectra (solvent: $CDCl_3$). MS were obtained on a Hewlett Packard apparatus (5989A) in the GC/MS mode. IR spectra were recorded on an IR-FT Perkin–Elmer 1600 spectrophotometer and principal patterns are given in cm$^{-1}$. Copper salts are commercially available products from Aldrich or Acros. CuI was purified by a standard procedure.[14] Heptyne, methoxypropyne and trimethylsilylacetylene are commercially available products from Aldrich. Chlorobutynol **1** was prepared from thionyl chloride and but-2-yne-1,4-diol.[15] Methyl hept-6-ynoate was prepared from lithium acetylide and bromovaleric acid in ammonia followed by esterification with MeOH under acidic catalysis.[16] Methyl hex-5-ynoate and methyl dec-9-ynoate were prepared as follows: propargyl alcohol in the presence of lithium amide was alkylated by bromopropane or bromoheptane;[17] "Zip" reaction with $NaNH_2$ performed in 1,3-diaminopropane led to terminal alkynols (hex-5-yn-1-ol or dec-9-yn-1-ol)[18] which were oxidized with Jones reagent and esterified with MeOH under sulfonic acid resin catalysis. All new compounds gave satisfactory microanalyses (C, H ± 0.5).

**Skipped Diynols 2a–f; General Procedure:**
A solution of $K_2CO_3$ (34.5 g, 250 mmol), NaI (37.5 g, 250 mmol), CuI (23.8 g, 125 mmol), terminal alkyne (250 mmol) and chlorobutynol **1** (26 g, 250 mmol), in DMF (500 mL), was stirred under argon for 12 h. The mixture was quenched with sat. aq $NH_4Cl$ (200 mL) and extracted with $Et_2O$ (3 × 100 mL). After drying ($MgSO_4$), and concentration, the residue was purified by flash chromatography ($Et_2O$/petroleum ether 2:8 to 6:4).

*7-Methoxyhept-2,5-diyn-1-ol* **(2a)**: $R_f$ 0.12 ($Et_2O$/petroleum ether 4:6).
$^1$H NMR: $\delta$ = 3.24 (2H, quint, $J$ = 2.13 Hz), 3.35 (3H, s), 4.06 (2H, t, $J$ = 2.15 Hz), 4.23 (2H, t, $J$ = 2.07 Hz).
$^{13}$C NMR: $\delta$ = 9.5, 50.2, 57.1, 59.5, 78.6, 78.9, 80.2 (2C).
IR (film): $\nu$ = 3387, 2833, 2213 cm$^{-1}$.
MS (70 eV): *m/z* (%) = 90 (52), 69 (47), 55 (18), 52 (39), 51 (100), 45 (100).

*6-Trimethylsilylhex-2,5-diyn-1-ol* **(2b)**: $R_f$ 0.29 ($Et_2O$/petroleum ether 4:6).
$^1$H NMR: $\delta$ = 0.12 (9H), 3.21 (2H, t, $J$ = 2.1 Hz), 4.22 (2H, t, $J$ = 2.1 Hz).
$^{13}$C NMR: $\delta$ = 1.1, 10.1, 50.6, 78.2, 78.7, 85.2 (2C).
IR (film): $\nu$ = 3443, 2182 cm$^{-1}$.
MS (70 eV): *m/z* (%) = 76 (19), 75 (100), 55 (22), 43 (16).

*Undeca-2,5-diyn-1-ol* **(2c)**: $R_f$ 0.78 ($Et_2O$/petroleum ether 4:6).
$^1H$ NMR: $\delta$ = 0.87 (3H, t, *J* = 4.96 Hz), 1.22–1.59 (6H, m), 2.12 (2H, m), 3.17 (2H, quint, *J* = 2.26 Hz), 4.24 (2H, bs).
$^{13}C$ NMR: $\delta$ = 9.7, 15.3, 18.6, 22.1, 28.3, 31.0, 50.9, 73.3, 78.3, 80.5, 81.1.
IR (film): $\nu$ = 3381, 2860, 2209 $cm^{-1}$.
MS (70 eV): *m/z* (%) = 107 (23), 95 (99), 93 (25), 79 (100), 77 (82), 55 (56), 43 (22).

*Methyl 10-Hydroxydeca-5,8-diynoate* **(2d)**: $R_f$ 0.14 ($Et_2O$/petroleum ether 4:6).
$^1H$ NMR: $\delta$ = 1.79 (2H, quint, *J* = 7.35 Hz), 1.92 (1H, t, *J* = 2.26 Hz), 2.20 (2H, m), 2.42 (2H, t, *J* = 7.39 Hz), 3.16 (2H, quint, *J* = 2.24 Hz), 3.66, (3H, s), 4.24 (2H, bs).
$^{13}C$ NMR: $\delta$ = 9.3, 17.7, 23.5, 32.5, 50.3, 51.3, 74.3, 78.5, 79.3, 79.5, 173.6.
IR (film): $\nu$ = 3444, 2860, 1735, 1215 $cm^{-1}$.
MS (70eV): *m/z* (%) = 69 (85), 51 (21), 41 (100), 37 (10).

*Methyl 11-Hydroxyundeca-6,9-diynoate* **(2e)**: $R_f$ 0.12 ($Et_2O$/petroleum ether 4:6).
$^1H$ NMR: $\delta$ = 1.42–1.82 (4H, m), 2.17 (2H, m), 2.32 (2H, t, *J* = 7.40 Hz), 3.15 (2H, quint, *J* = 2.28 Hz), 3.65 (3H, s), 4.24 (2H, t, *J* = 2.20 Hz).
$^{13}C$ NMR: $\delta$ = 9.2, 17.8, 23.6, 27.6, 33.0, 49.9, 51.1, 78.6 (2C), 79.1, 79.7, 173.6.
IR (film): $\nu$ = 3406, 2878, 1734, 1215 $cm^{-1}$.

*Methyl 14-Hydroxytetradeca-9,12-diynoate* **(2f)**: $R_f$ 0.21 ($Et_2O$/petroleum ether 4:6).
$^1H$ NMR: $\delta$ = 1.21–1.78 (10H, m), 2.18 (2H, m), 2.30 (2H, t, *J* = 7.34 Hz), 3.16 (2H, quint, *J* = 2.30 Hz), 3.61 (3H, s), 4.22 (2H, t, *J* = 2.30 Hz).
$^{13}C$ NMR: $\delta$ = 9.8, 15.1, 24.7, 28.3, 28.5, 28.7 (2C), 28.9, 34.0, 50.5, 51.5, 78.6, 79.0, 80.1, 80.8, 174.5.
IR (film): $\nu$ = 3442, 2931, 2364, 1736 $cm^{-1}$.

*3-Hydroxymethyl-6-methoxyhexa-1,2-dien-4-yne* **(3a)**: $R_f$ 0.14 ($Et_2O$/petroleum ether 4:6).
$^1H$ NMR: $\delta$ = 3.35 (3H, s), 4.06 (2H, t, *J* = 2.15 Hz), 4.27 (2H, bs), 4.75 (2H, t, *J* = 2.81 Hz).
$^{13}C$ NMR: $\delta$ = 57.1, 59.5, 65.9, 77.1, 84.7, 91.1, 91.3, 210.1.
IR (film): $\nu$ = 3288, 2361 2337, 1926 $cm^{-1}$.

**Methyl 11-Bromoundeca-6,9-diynoate (4):**
To a solution of methyl 11-hydroxyundeca-6,9-diynoate **(2e)** (22.3 g, 107.2 mmol) and $CBr_4$ (49.8 g, 150.1 mmol) in $CH_2Cl_2$ (360 mL) at 0 °C was added under argon $PPh_3$ (39.4 g, 150.1 mmol) over a period of 1 h. After 5 min the mixture was brought to r.t. and stirred for 1 h. $CH_2Cl_2$ was evaporated then the residue was diluted with $Et_2O$ and filtered through a pad of Celite and concentrated. Chromatography ($Et_2O$/petroleum ether 1:9 to 4:6) provided the diyne **4** in 92% yield; $R_f$ 0.57 ($Et_2O$/petroleum ether 4:6).
$^1H$ NMR: $\delta$ = 1.46–1.77 (4H, m), 2.17 (2H, m), 2.31 (2H, t, *J* = 7.36 Hz), 3.18 (2H, quint, *J* = 2.33 Hz), 3.65 (3H, s), 3.89 (2H, t, *J* = 2.36 Hz).
$^{13}C$ NMR: $\delta$ = 8.5, 13.5, 16.9, 22.6, 26.6, 32.0, 49.9, 71.9, 73.9, 79.1, 80.5, 172.1.
IR (film): $\nu$ = 2260, 1734, 1215, 750 $cm^{-1}$.

**Methyl Octadeca-6,9,12-triynoate (5):**
This was prepared from methyl 11-bromoundeca-6,9-diynoate **(4)** and hept-1-yne in a similar manner as for the general procedure, but the mixture was stirred overnight at 40 °C. Workup and chromatography ($Et_2O$/petroleum ether 1:9 to 4:6) afforded the triyne in 89% yield; $R_f$ 0.40 ($Et_2O$/petroleum ether 1:9).
$^1H$ NMR: $\delta$ = 0.87 (3H, t, *J* = 6.70 Hz), 1.27–1.69 (10H, m), 2.14 (4H, m), 2.31 (2H, t, *J* = 7.35 Hz), 3.11 (4H, bs), 3.65 (3H, s).
$^{13}C$ NMR: $\delta$ = 9.7, 13.9, 18.2, 18.6, 22.1, 24.1, 24.4, 26.9, 27.2, 36.2, 54.4, 79.3, 79.9 (2C), 80.6 (2C), 80.8, 176.8.
IR (film): $\nu$ = 2260, 1733, 1215 $cm^{-1}$.

**Methyl (6*Z*,9*Z*,12*Z*)-Octadeca-6,9,12-trienoate (6):**
Nickel acetate tetrahydrate (3.0 g, 12 mmol) was dissolved in 95% EtOH (130 mL) and placed under $H_2$. 1 M $NaBH_4$ in abs EtOH (12 mL) was added at r.t., followed, after 30 min, by ethylenediamine (3.2 mL, 48 mmol) and triyne **5** (3.48 g, 12 mmol) diluted in EtOH (20 mL). The reaction was monitored by TLC, and quenched by addition of $Et_2O$ (100 mL) and filtration through a pad of Celite. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue ($Et_2O$/petroleum ether 5:95 to 50:50) afford pure *Z,Z,Z*-triene (65% yield); $R_f$ 0.73 ($Et_2O$/petroleum ether 1:9).
$^1H$ NMR: $\delta$ = 0.81 (3H, t, *J* = 6.79 Hz), 1.18–1.30 (8H, m), 1.55–1.70 (2H, m), 1.98–2.11 (4H, m), 2.29 (2H, t, *J* = 7.26 Hz), 2.78 (4H, t, *J* = 5.34 Hz), 3.65 (3H, s), 5.27–5.41 (6H, m).
$^{13}C$ NMR: $\delta$ = 14.2, 22.6, 24.5, 25.6, 26.8, 27.1, 29.0, 29.4, 29.7, 31.2, 34.2, 50.1, 127.5, 128.1, 128.2, 128.4, 129.4, 130.2, 173.4.
IR (film): $\nu$ = 1738, 1658, 1259 $cm^{-1}$.
MS (70 eV): *m/z* (%) = 116 (12), 113 (27), 112 (14), 101 (30), 87 (66), 84 (17), 74 (45), 67 (39), 59 (100), 57 (32), 56 (16), 55 (77), 44 (20), 43 (71), 42 (21), 41 (62), 39 (28).

**(6*Z*,9*Z*,12*Z*)-Octadeca-6,9,12-trienoic Acid ($\gamma$-Linolenic Acid):**
To a 0 °C solution of methyl ester **6** in THF (80 mL) was added dropwise 0.5 N aq LiOH (134 mL). After 30 min, the mixture was brought to r.t. and stirred for 12 h. The solution was acidified to pH 2 with 1 N HCl, and extracted with $Et_2O$. The combined $Et_2O$ extracts were dried ($MgSO_4$) and concentrated to furnish $\gamma$-linolenic acid (98% yield); $R_f$ 0.43 ($Et_2O$/petroleum ether 4:6).
$^1H$ NMR: $\delta$ = 0.86 (3H, t, *J* = 6.79 Hz), 1.13–1.30 (8H, m), 1.55–1.70 (2H, m), 1.93–2.06 (4H, m), 2.28 (2H, t, *J* = 7.24 Hz), 2.78, (4H, t, *J* = 5.34 Hz), 5.17–5.43 (6H, m).
$^{13}C$ NMR: $\delta$ = 14.1, 22.6, 24.6, 25.6, 26.9, 27.2, 29.1, 29.4, 29.7, 31.6, 34.2, 127.6, 128.1, 128.2, 128.4, 129.6, 130.4, 173.6.
IR (film): $\nu$ = 1725, 1654 $cm^{-1}$.

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