Supporting Information

Tandem and mild synthesis of symmetric secondary alcohol toward ionizable lipid analogue to DLin-MC3-DMA

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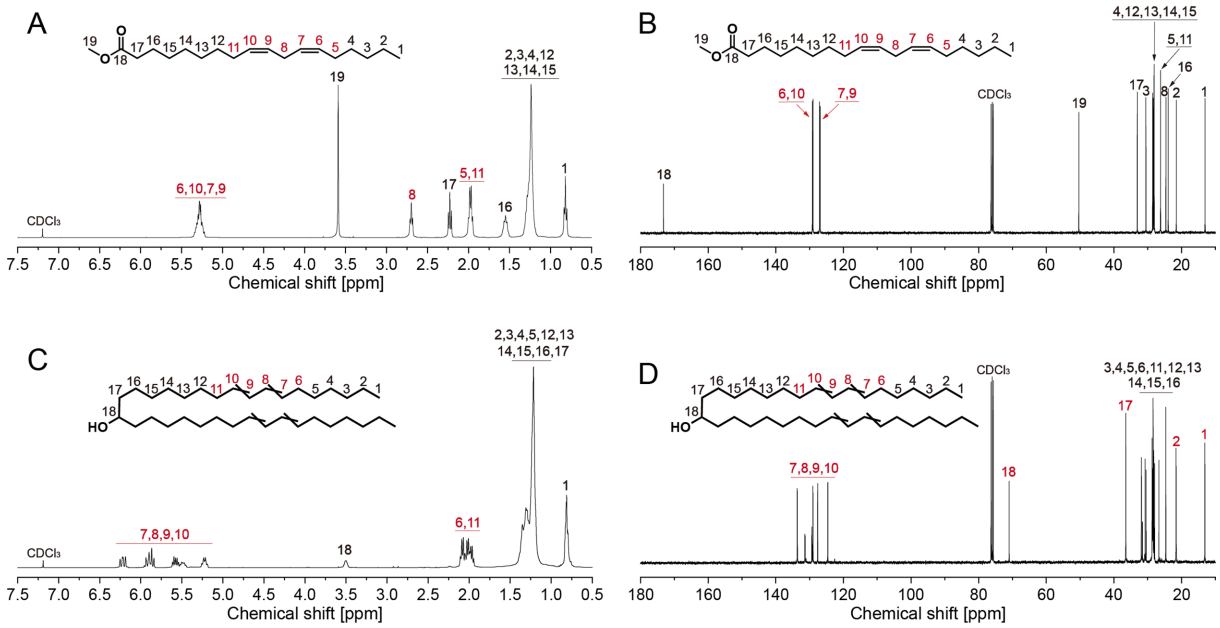

Figure S1. NMR spectra of methyl linoleate and secondary alcohol (A) ^{1}H and (B) ^{13}C NMR spectra of methyl linoleate. (C) ^{1}H and (D) ^{13}C NMR spectra of the secondary alcohol obtained from three-step reaction. First, Claisen condensation reaction mediated by the classical strong base sodium hydride using methyl linoleate as feedstock; subsequent hydrolysis and reduction achieved secondary alcohol.

Table S1. Screening of Lewis acid/base pairs for the self-condensation of methyl linoleate[a].

Entry	Lewis acid	Base	Solvent	yield[b] (%)
1	$TiCl_4$	TEA	Toluene	57
2	$SnCl_4$	TEA	Toluene	0
3	$TiCl_4$	TEA	DCM	61
4	$SnCl_4$	TEA	DCM	0
5	$TiCl_4$	Diisopropylethylamine	DCM	54
6	$TiCl_4$	Imidazole	DCM	Trace
7	$TiCl_4$	Tributylamine	DCM	55
8	$TiCl_4$	TEA	THF	0
9	$TiCl_4$	TEA	Ether	19
10	$TiCl_4$	TEA	1,2-Dichloroethane	47

[a] The Lewis acid (10 mmol) in solvent (30 ml) was added dropwise over a period of 60 min to a solution of methyl linoleate (10 mmol) and base (20 mmol) at 20 °C, followed by 1 h of reaction. [b] Isolated yield of β-ketoester.

Table S2. Screening of conditions for the solvent-free self-Claisen condensation of methyl linoleate.[a]

Entry	$TiCl_4$ (eq.)	TEA (eq.)	Time[b] (min)	Temperature (°C)	Conversion[c] (%)	Yield[d] (%)
1	2	4	60	20	90	34
2	1.5	3	60	20	88	37
3	1	1.5	60	20	65	45
4	1	1.5	80	20	70	53
5	1	1.5	100	20	69	52
6	1	1.5	100	-20	55	43

[a] General procedure: $TiCl_4$ was added dropwise to a mixture of TEA and methyl linoleate. The reaction was stirred for another 1 h after complete addition, where methyl linoleate was used as 1 equivalent (eq). [b] The time taken for the dropwise addition of $TiCl_4$ into the mixture of TEA and methyl linoleate. [c] Conversion of methyl linoleate; determined by recovery. [d] Isolated yield of β-ketoester.

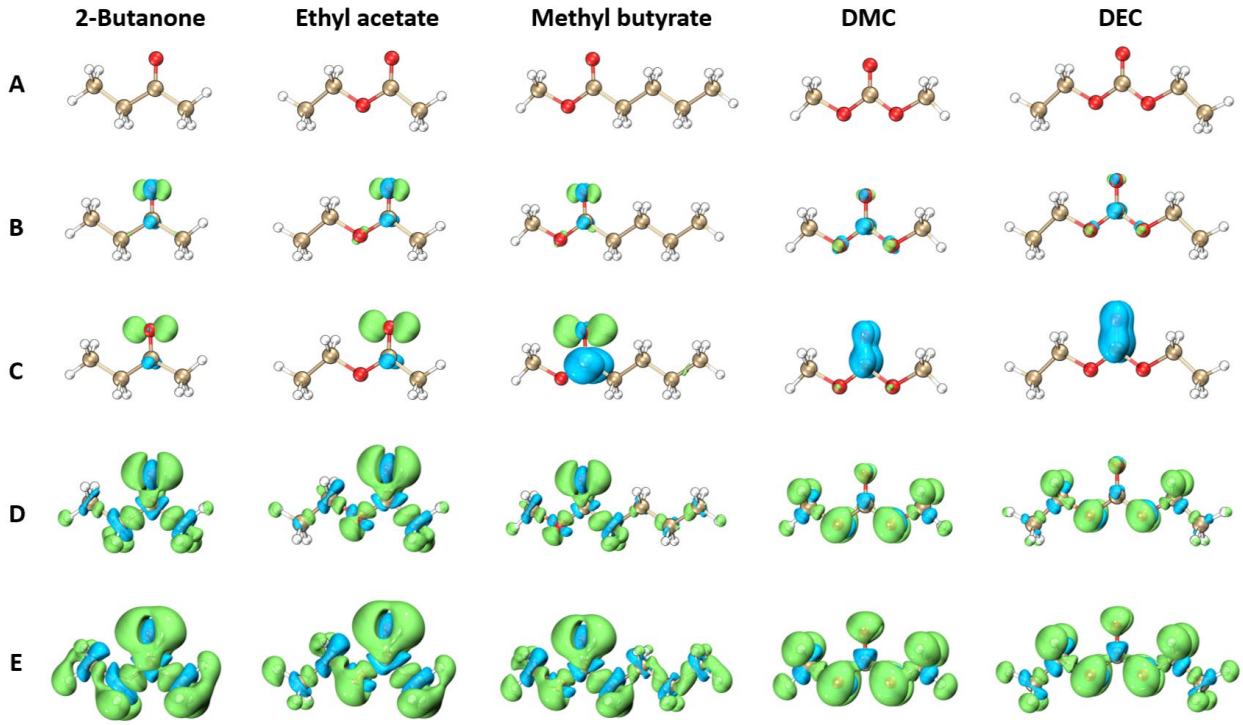

Figure S2. Isosurface diagram of Fukui function for solvents. (A) Molecular structure diagram of the different solvent. (B) Dual descriptor (isosurface = -0.03), (C) dual descriptor potential (isosurface = -0.08), (D) Fukui function f^- (isosurface = 0.05) and (E) Local softness s^- (isosurface = 0.05) of the different solvent. All calculations were producted at the B3LYP/6-31G++ (d,p) level. The blue area represents the electrophilic region susceptible to enolate anion attack.

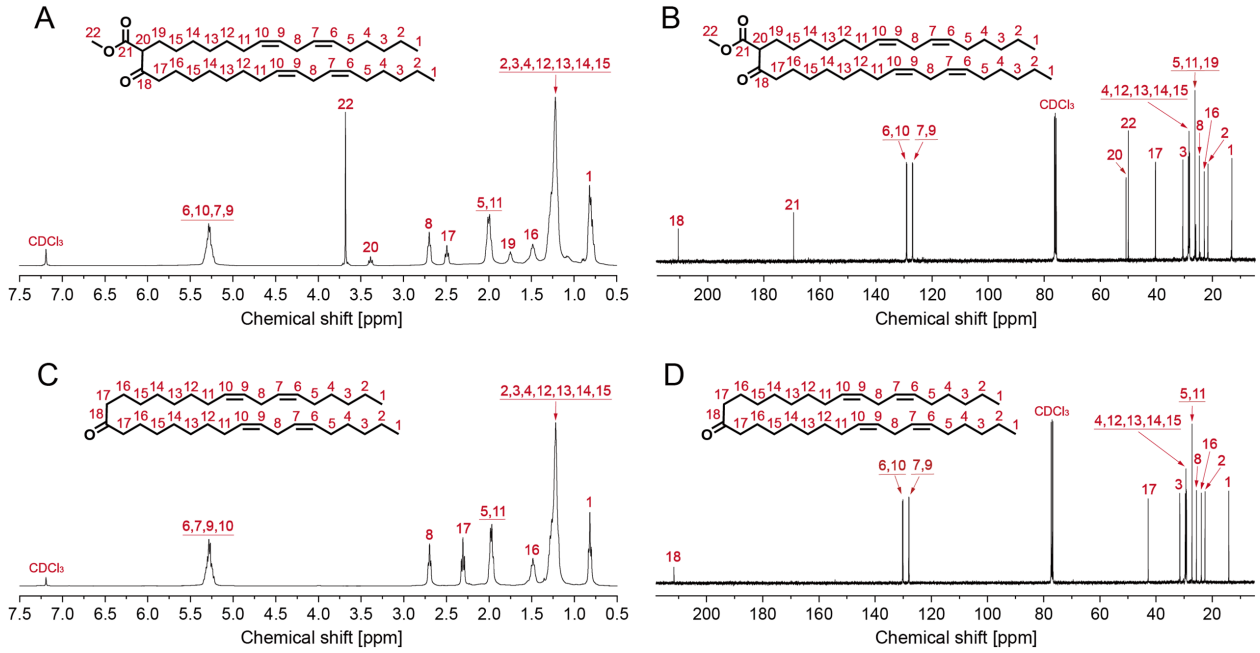

Figure S3. NMR spectra of the tandem reaction intermediates. (A) ^{1}H and (B) ^{13}C NMR spectra of the β-ketoester intermediate obtained from the Claisen condensation; (C) ^{1}H and (D) ^{13}C NMR spectra of the ketone intermediate obtained after hydrolysis.

Table S3. Mass balance for calculating the E-factor of the tandem process present in this work.[a]

Material	Role	Amount (g)
Methyl linoleate	Feedstock	40
TEA	Reagent	23.3
DEC	Solvent	64
$TiCl_4$	Condensation Reagent	33.5
Ethanol	Solvent	550
NaOH	Hydrolysis reagent	32
$NaBH_4$	Reduction reagent	15
NH_4Cl	Quenching reagent	27
Petroleum ether	Extraction solvent	160
Silica gel	Chromatography	130
Ethyl acetate and hexane	Chromatography	1800
Symmetric secondary alcohol	Product	29.2

E-factor for the tandem synthesis of symmetric secondary alcohol was performed according to the following equation:

$$E\text{-}factor = \frac{m_{total\ waste} - m_{product}}{m_{product}} = 98$$

Table S4. Mass balance for calculating the E-factor of the Grignard-based route.[a]

Step	Material	Role	Amount (g)
1	Linoleyl alcohol	Feedstock	40
1	DCM	Solvent	720
1	TEA	Reagent	19.7
1	Mesyl chloride	Reagent	18.9
1	$NaHCO_3$	Washing	27.1
1	NaCl	Washing	52.6
1	Silica gel	Chromatography	150
1	Hexane/Et_2O	Chromatography	3000
2	mesylate	Intermediate product	43.1
2	Et_2O	Solvent	2275
2	MgBr.Et_2O	Reagent	105
2	K_2CO_3	Washing	3.4
2	NaCl	Washing	120
2	Silica gel	Chromatography	150
2	Hexane/Et_2O	Chromatography	3000
3	Bromide	Intermediate product	43.1
3	Magnesium	Reagent	3.9
3	Et_2O	Solvent	697
3	Ethyl formate	Reagent	4.4
3	Acetone	Quenching	13
3	H_2SO_4	Acidification	54
4	Sodium	Reagent	1.6
4	Methanol	Reagent	257.6
4	Hydrochloric acid	Acidification	7.5
4	NaCl	Washing	57
4	Silica gel	Chromatography	150
4	Hexane/Et_2O	Chromatography	3000
4	DLin-MeOH	Product	26.7

[a] Determined by using the minimum practical amounts for these procedures, as these data were not available in the original literature.

E-factor for the Grignard-based route to synthesize DLin-MeOH was performed according to the following equation:

$$E\text{-}factor = \frac{m_{total\ waste} - m_{product}}{m_{product}} = 524$$

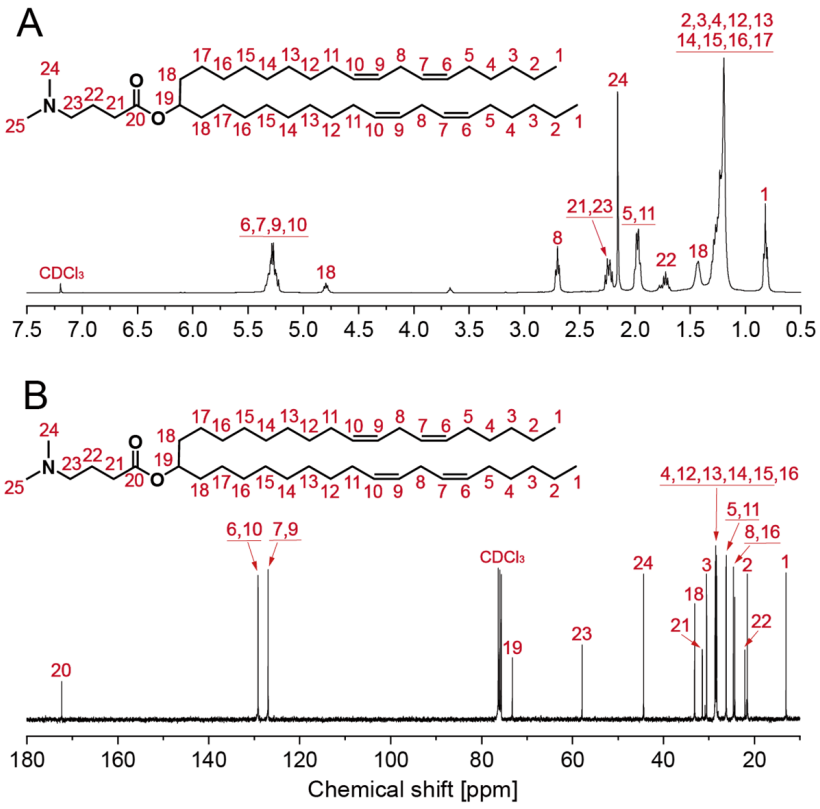

Figure S4. (A) ^{1}H and (B) ^{13}C NMR spectra of DLin-MC3-DMA.

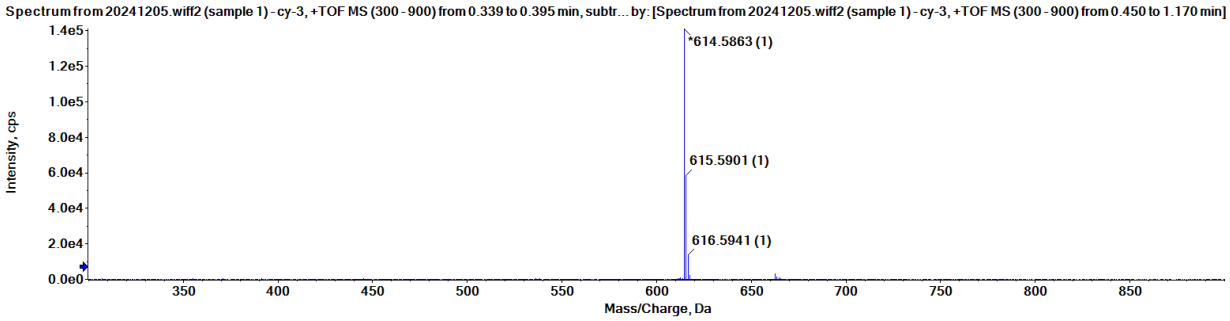

Figure S5. ESI mass spectrum of CLin-17.

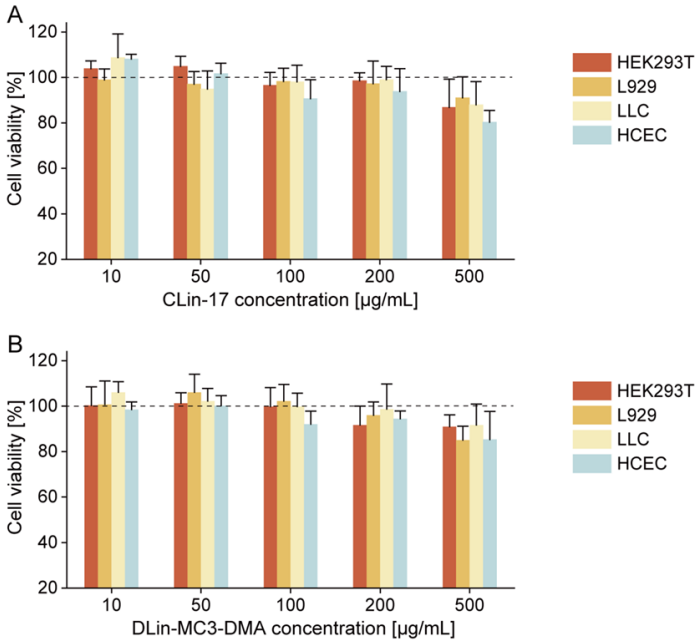

Figure S6. *In vitro* cytotoxicity of (A) CLin-17 and (B) DLin-MC3-DMA measured by CCK8 assay. Data were presented as mean ± S.D. of biological replicates (n = 5).