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One-Pot Synthesis of α-Substituted Acrylates

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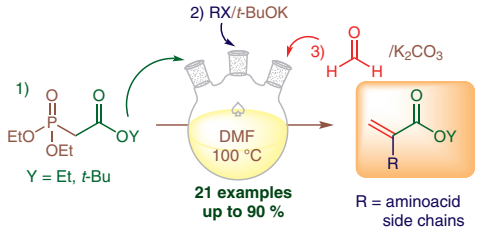

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Abstract A simple and efficient synthetic method towards α-substituted acrylic esters has been developed using the Horner–Wadsworth–Emmons (HWE) reaction with HCHO after alkylation of phosphonoacetates in a one-pot reaction. This method allows the smooth introduction of various side-chains, such as natural amino acids and other biologically relevant substituents. The use of mild conditions, inexpensive reagents, short reaction times and simple work-up and purification steps provides an effective and general alternative to cumbersome multistep and low-yielding procedures described to date.

Key words acrylates, Horner–Wadsworth–Emmons reaction, amino-acid analogues, one-pot synthesis, β-amino acids

α-Substituted acrylic esters are important intermediates in organic synthesis for C–C and C–heteroatom bond formation.[2] Acrylates are also widely used in many other areas of chemistry, such as materials science,[3] biotechnology,[4] and nanotechnology,[5] and they are key intermediates for the synthesis of biologically active compounds, such as β-amino-acids, phosphinic peptide analogues,[6] and natural products.[7]

Efficiency and economy in a sequence of reactions are of great importance in the development of new synthetic methods. The combination of two or more synthetic steps in a single-pot reaction has always been of great interest in organic transformations because such an approach saves time and reagents, avoids purification steps, and leads to increased overall yields.[8]

In the course of our studies regarding rapid access[9] and diversification[10] of phosphinic peptide protease inhibitors, we became interested in the development of an expedient approach that would lead to α-substituted acrylates incorporating all of the natural amino acid side-chains, preferably in a one-pot reaction. To achieve enhanced recognition by proteases, the resemblance of the peptide core with natural substrates is of critical importance for inhibitory potency and selectivity.[11] Use of α-aminophosphinic acids and acrylates is essential. Although several synthetic methods have been reported and reviewed[12] towards the synthesis of the α-aminophosphinic analogues of almost all amino acids, this is not the case for the amino acid acrylate analogues.

The commonly used methods for acrylate synthesis (Figure 1) involve multistep procedures such as the Mannich reaction,[13] catalytic coupling,[14] HWE,[15] Baylis–Hillman,[16] use of Meldrum's acid and aldehydes, or a reductive coupling reaction followed by Eschenmoser methylenation.[17] Using these methods the acrylate analogues of His, Leu, Nle, Phe, ψPro, Thr, Tyr, and Val (Figure 2) have been synthesized in overall yields ranging from 10 to 45%.[18] Except very few commercially available acrylates such as Ala,

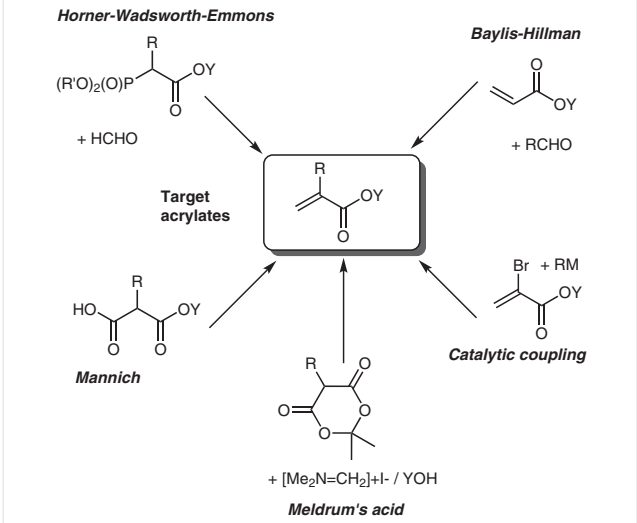
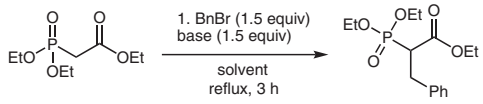


Figure 1 General methods for acrylate synthesis

Gly, and Ser, most of them have never been synthesized including Arg, Asn, Cys, Gln, Ile, Lys, Met, Orn and Trp. Some were unsuccessful by-products that were not investigated thoroughly, such as His and Met.[19] Acidic acrylates Asp and Glu have been reported, but not in orthogonally protected form.[20]

The lack of a general synthetic methodology to acquire all amino acid analogues of acrylates, the low overall yields leading to some of them by using multistep procedures, and the fact that some of these acrylates have not been synthesized before, prompted us to examine the matter in detail by using, as a method of choice, the Horner–Wadsworth–Emmons (HWE) reaction. The HWE reaction is a powerful tool for the formation of conjugated alkenes, which has been used in numerous cases for diversely substituted α,β-unsaturated carbonyl units. It offers a wide tolerance of various functional groups, availability and low price of starting materials, simplicity of reaction conditions, and most importantly, the possibility to perform both alkylation and methylenation steps in a single-pot reaction. Towards this end, a series of experiments was performed firstly to optimize the alkylation step,[21] secondly the methylenation step, and thirdly the effect of performing the two steps in one pot.

In the first optimization round (Scheme 1) benzyl bromide was chosen as the alkylating agent for a number of combinations of solvents and bases. All reactions were performed both at room temperature and reflux temperature of the solvent, with various reaction times and equivalents of base; the optimal results are shown in Table 1. According to these data, use of NaH/THF (entry 2) and *t*-BuOK/DMF (entry 5) provided superior results with respect to yield and purity of the alkylated product. All yields reported correspond to isolated products.



Scheme 1 Alkylation conditions optimization

Table 1 Effect of the Base and Solvent for the Alkylation Step

Entry	Base	Solvent	Yield (%)
1	NaH	DMF	65
2	NaH	THF	82
3	LDA	THF	57
4	*t*-BuLi	THF	29
5	*t* -BuOK	DMF	86
6	*t* -BuOK	THF	81
7	*t* -BuOK	DMSO	40
8	K_2CO_3	THF	0
9	K_2CO_3/LiCl	CH_3CN	0
10	DBU	CH_3CN	0
11	DBU/LiCl	CH_3CN	22

For the second optimization round of the HWE methylenation step (Scheme 2), a series of experiments was performed by using either paraformaldehyde or aqueous formaldehyde and a combination of solvents and bases, retaining those that showed optimal results in the alkylation step and/or adding K_2CO_3 or Cs_2CO_3 for the second step (Table 2). The use of weak bases in the second step provided cleaner reactions and higher yields compared with strong bases, with the latter affording the product as a complex mixture. In the first step, NaH (entries 1 and 2) proved to be less suit-

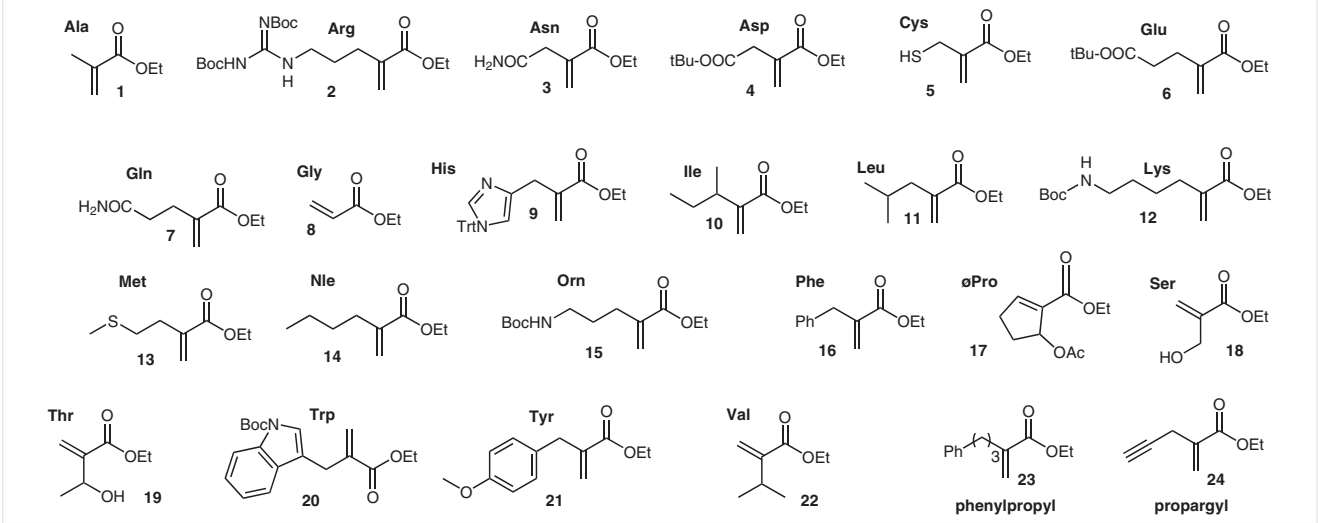
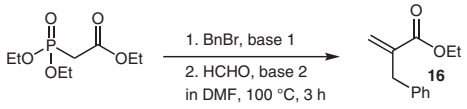


Figure 2 Target acrylate structures



Scheme 2 HWE reaction optimization

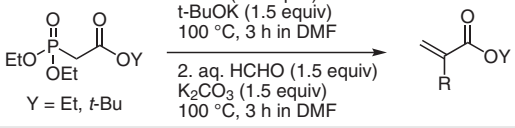
able than *t*-BuOK; therefore, further experiments were conducted by retaining *t*-BuOK as the base of choice for the first step and K_2CO_3 for the second step (entry 4). Adding a phase-transfer catalyst (entry 5) did not improve the results significantly, nor did a change from K_2CO_3 to the more DMF-soluble Cs_2CO_3 (entry 6). Using aq. HCHO (entry 7) led to a 10% yield increase and to a 73% overall yield for the isolated product over the two-step process.

Table 2 Effect of the Bases and Solvent on the One-Pot Two-Step Reaction

Entry	Base	HCHO	Yield (%)
1	NaH	$(HCHO)_n$	0
2	NaH	$(HCHO)_n$	25
3	*t*-BuOK	$(HCHO)_n$	48
4	*t*-BuOK/K_2CO_3	$(HCHO)_n$	62
5	*t*-BuOK/K_2CO_3 *n*-Bu_4I	$(HCHO)_n$	68
6	*t*-BuOK/Cs_2CO_3	$(HCHO)_n$	60
7	*t*-BuOK/K_2CO_3	aq. HCHO	73

The two steps were subsequently repeated separately, isolating the alkylated product, which was subsequently subjected to the methylenation reaction using identical reaction conditions as for the one-pot reaction without observing an increase in the overall yield, proving thus that the two steps can be effectively performed in one-pot without cost to the overall yield and purity of the final acrylate product.

Using these optimal conditions (Scheme 3), a series of acrylates has been synthesized in good to excellent yields as shown in Table 3. For the purpose of broadening the scope of the reaction, *t*-butyl diethylphosphonoacetate has also been used in selected examples and led to the smooth formation of acrylates protected with the *t*-butyl group at the carboxylic acid functionality. The yields for these compounds are given in parentheses in Table 3.



Scheme 3 General synthesis of target acrylates

In most cases the alkylating agents were commercially available, except for Lys and Orn, where the corresponding Boc- and Cbz- protected bromides were synthesized by using known procedures.[22] Surprisingly, the Lys analogue could not be isolated, although it was formed as judged by NMR experiments. Several attempts were made using Boc- and Cbz- protecting groups, for both the ethyl ester and the *tert*-butyl ester analogues but with no success. The allylic acetate ψPro was synthesized instead of the acrylate analogue of Pro, because of the lack of reactivity of the acrylate towards conjugate additions.[23] Attempts to synthesize Arg from Orn failed, probably due to the presence of the electrophilic conjugated system.[24] Cys and Met were not possible to make by using this method because of the unavailability of the corresponding alkylation agents. However, Cys

Table 3 Alkylating Agents and Yields

Acrylate	Alkylating agent	Corresponding amino acid	Yield (%)[a]
4	*t*-butyl chloroacetate/(ethyl bromoacetate)	Asp	68 (72)
6	*t*-butyl 3- bromopropionate	Glu	65
10	2-bromobutane	Ile	53 (58)
11	1-bromo-2-methylpropane	Leu	67 (63)
14	1-bromobutane	Nle	84 (78)
15	*t*-butyl (3-bromopropyl) carbamate	Orn	43
16	benzylbromide	Phe	73 (78)
17	2,5-dimethoxytetrahydrofuran, then acetylation	ψPro	68
20	*t*-butyl 3-bromomethyl-indole-1-carboxylate	Trp	78
21	1-(chloromethyl)-4-methoxybenzene	Tyr	84 (89)
22	2-bromopropane	Val	76
23	1-bromo-3-phenylpropane	phenylpropyl	89 (84)
24	3-bromopropyne	propargyl	64 (62)

[a] The yield obtained with *t*-butyl diethylphosphonoacetate are given in parentheses.

analogues can be easily accessed otherwise.[10a] The terminal amides Asn and Gln provided complex mixtures of by-products but, again, these acrylates are accessible by other methods.[25] His was also not possible to synthesize using this one-pot reaction, and the Mannich reaction remains the only method to access this analogue.[26] Finally, Thr is easily made by a Baylis–Hillman reaction with acetaldehyde,[27] therefore its synthesis was not attempted by using this method.

In conclusion, we present here a new and general synthetic methodology towards acrylate analogues of most amino acids, with some of them reported for the first time. Alkylation of triethyl and *t*-butyl diethyl phosphonoacetates followed by HWE methylenation is a general and effective synthetic approach towards α-substituted acrylate ethyl and *t*-butyl esters. By thorough investigation of the reaction conditions, this new method has been developed that provides access to most of the natural amino acid substituted acrylates in good to excellent yields in a two-step, one-pot reaction.

Compounds for which analytical and spectroscopic data are quoted were homogenous by TLC. TLC analyses were performed using silica gel plates (E. Merck silica gel 60 F-254) and components were visualized by the following methods: UV light absorbance, iodine vapour and charring after staining with phosphomolybdic acid (PMA), using as eluents (A) petroleum ether 30–60 °C/EtOAc, 95:5, and (B) hexanes/CH_2Cl_2, 2:1, unless otherwise stated. Column chromatography was carried out on silica gel (0.060–0.200mm 40A). All the compounds were characterized by ^1H and ^{13}C NMR spectroscopy and spectra were recorded in $CDCl_3$ with a Bruker Avance III 400 spectrometer at r.t. Chemical shifts (δ) are reported in parts per million (ppm) using residual $CHCl_3$ as internal reference (7.26 ppm in ^1H spectra and 77.36 ppm in ^{13}C spectra) and *J* values are given in Hz. The following abbreviations are used to indicate the multiplicity: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), and multiplet (m). Splitting patterns that could not be easily interpreted are designated as multiplet (m). HRMS were obtained with a Bruker Daltonics – micrOTOF - Q II – ESI – Qq - TOF mass spectrometer. All commercially available reagents, solvents and starting materials were used without further purification.

Typical Procedure

Phosphonoacetate (5 mmol) and KO*t*Bu (1.5 equiv, 7.5 mmol) were dissolved in anhydrous DMF (25 mL) in a round-bottom flask and stirred at 100 °C for 10 min under an argon atmosphere. The alkylation agent (1.5 equiv, 7.5 mmol) was added slowly and the reaction mixture was stirred for 3 h at 100 °C (except for low b.p. alkylating agents where heating 15–20 °C below the b.p. was applied). Then K_2CO_3 (3 equiv, 15 mmol) and 37 wt.% aqueous HCHO (3 equiv, 15 mmol) were added and the resulting mixture was stirred for another 3 h at 100 °C. The reaction was quenched with 0.5 M HCl to ca. pH 5 and the mixture was extracted with Et_2O (2 × 40 mL). The combined extracts were washed with water (50 mL), dried over Na_2SO_4, filtered, and concentrated. The target compounds were obtained as colourless liquids by column chromatography purification on silica gel using hexanes/CH_2Cl_2 as eluent.

4-*tert*-Butyl 1-Ethyl 2-Methylenesuccinate (4)

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and *t*-butyl chloroacetate (1.13 g, 7.5 mmol) at r.t. for 12 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 2:1) in 68% yield (0.73 g, 3.4 mmol) as a colourless liquid. R_f (A) = 0.40, R_f (B) = 0.11.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.28 (s, 1 H), 5.63 (s, 1 H), 4.21 (q, *J* = 7.12 Hz, 2 H), 3.24 (s, 2 H), 1.44 (s, 9 H), 1.29 (t, *J* = 7.12 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.98, 166.37, 134.64, 127.62, 80.94, 60.91, 39.05, 27.99, 14.16.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{11}H_{19}O_4$: 215.1205; found: 215.1264.

5-*tert*-Butyl 1-Ethyl 2-Methylenepentanedioate (6)

[CAS Reg. No. 127678–93–7]

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and *t*-butyl-3-bromopropionate (1.57 g, 7.5 mmol) at r.t. for 12 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 2:1) in 65% yield (0.74 g, 3.4 mmol) as a colourless liquid. R_f (A) = 0.38, R_f (B) = 0.10.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.17 (s, 1 H), 5.56 (s, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 2.59 (t, *J* = 7.5 Hz, 2 H), 2.42 (t, *J* = 7.5 Hz, 2 H), 1.43 (s, 9 H), 1.30 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.10, 166.80, 139.38, 125.27, 80.42, 60.72, 34.24, 28.11, 27.42, 14.21.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{12}H_{21}O_4$: 229.1362; found: 229.1350.

Ethyl 3-Methyl-2-methylenepentanoate (10)

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and 2-bromobutane (1.03 g, 7.5 mmol) at 70 °C for 6 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 3:1) in 53% yield (0.41 g, 2.65 mmol) as a colourless liquid. R_f (A) = 0.62, R_f (B) = 0.35.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.15 (s, 1 H), 5.48 (s, 1 H), 4.20 (q, *J* = 7.12 Hz, 2 H), 2.68–2.56 (m, 1 H), 1.50–1.35 (m, 2 H), 1.38 (t, *J* = 7.12 Hz, 3 H), 1.08 (d, *J* = 6.92 Hz, 3 H), 0.87 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.60, 146.15, 122.45, 60.49, 36.13, 28.66, 19.32, 14.22, 11.65.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_9H_{17}O_2$: 157.1150; found: 157.1106.

Ethyl 4-Methyl-2-methylenepentanoate (11)

[CAS Reg. No. 87438–94–6]

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and 1-bromo-2-methylpropane (1.03 g, 7.5 mmol) at 70 °C for 6 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 3:1) in 67% yield (0.52 g, 3.35 mmol) as a colourless liquid. R_f (A) = 0.60, R_f (B) = 0.32.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.15 (s, 1 H), 5.47 (s, 1 H), 4.18 (q, *J* = 7.12 Hz, 2 H), 2.16 (d, *J* = 7.0 Hz, 2 H), 1.86–1.72 (m, 1 H), 1.30 (t, *J* = 7.12 Hz, 3 H), 0.89 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.53, 139.99, 125.45, 60.52, 41.31, 27.20, 22.27, 14.20.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_9H_{17}O_2$: 157.1150; found: 157.1200.

Ethyl 2-Methylenehexanoate (14)

[CAS Reg. No. 3618–37–9]

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and 1-bromobutane (1.03 g, 7.5 mmol) at 80 °C for 5 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 3:1) in 84% yield (0.66 g, 4.2 mmol) as a colourless liquid. R_f (A) = 0.75, R_f (B) = 0.42.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.12 (s, 1 H), 5.50 (s, 1 H), 4.20 (q, *J* = 7.12 Hz, 2 H), 2.30 (t, *J* = 7.5 Hz, 2 H), 1.50–1.41 (m, 2 H), 1.39–1.28 (m, 2 H), 1.30 (t, *J* = 7.12 Hz, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.45, 141.17, 124.09, 60.53, 31.55, 30.59, 22.30, 14.22, 13.89.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for: 157.1150; found: 157.1124.

Ethyl 5-((*tert*-Butoxycarbonyl)amino)-2-methylenepentanoate (15)

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and *t*-butyl (3-bromopropyl) carbamate (1.78 g, 7.5 mmol) at r.t. for 24 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 2:1) in 43% yield (0.55 g, 2.15 mmol) as a colourless liquid. R_f (A) = 0.33, R_f (B) = 0.05.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (s, 1 H), 5.56 (s, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 3.15–3.10 (m, 2 H), 2.38–2.27 (m, 2 H), 1.75–1.62 (m, 2 H), 1.44 (s, 9 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.12, 155.98, 140.02, 125.06, 79.13, 60.67, 40.04, 29.01, 28.92, 28.39, 14.17.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{13}H_{24}NO_4$: 258.1627; found: 258.1624.

Ethyl 2-Benzylacrylate (16)

[CAS Reg. No. 20593–63–9]

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and benzyl bromide (1.28 g, 7.5 mmol). The product was isolated by column chromatography (hexanes/CH_2Cl_2, 2:1) in 73% yield (0.69 g, 3.65 mmol) as a colourless liquid. R_f (A) = 0.57, R_f (B) = 0.23.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.17 (m, 5 H), 6.23 (s, 1 H), 5.45 (s, 1 H), 4.18 (q, *J* = 7.12 Hz, 2 H), 3.63 (s, 2 H), 1.26 (t, *J* = 7.12 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.94, 140.42, 138.82, 129.06, 128.39, 126.30, 125.96, 60.74, 38.08, 14.14.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{12}H_{15}O_2$: 191.0994; found 191.1028.

***tert*-Butyl 3-(2-(Ethoxycarbonyl)allyl)-1*H*-indole-1-carboxylate (20)**

[CAS Reg. No. 645396–50–5]

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and *t*-butyl 3-bromomethylindole-1-carboxylate (2.3 g, 7.5 mmol) at r.t. for 24 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 2:1) in 78% yield (1.28 g, 3.9 mmol) as a colourless liquid. R_f (A) = 0.37, R_f (B) = 0.19.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.18 (m, 5 H), 6.24 (s, 1 H), 5.50 (s, 1 H), 4.23 (q, *J* = 7.12 Hz, 2 H), 3.71 (s, 2 H), 1.67 (s, 9 H), 1.31 (t, *J* = 7.12 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.99, 149.70, 138.68, 130.31, 126.56, 125.91, 124.33, 124.04, 122.41, 119.30, 117.65, 115.26, 83.50, 60.84, 28.24, 27.29, 14.20.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{19}H_{24}NO_4$: 330.1627; found: 330.1682.

Ethyl 2-(4-Methoxybenzyl)acrylate (21)

[CAS Reg. No. 20566–48–7]

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and 1-(chloromethyl)-4-methoxybenzene (1.17 g, 7.5 mmol). The product was isolated by column chromatography (hexanes/CH_2Cl_2, 2:1) in 84% yield (0.93 g, 4.2 mmol) as a colourless liquid. R_f (A) = 0.53, R_f (B) = 0.22.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.54 Hz, 2 H), 6.82 (d, *J* = 8.54 Hz, 2 H), 6.19 (s, 1 H), 5.42 (s, 1 H), 4.17 (q, *J* = 7.12 Hz, 2 H), 3.78 (s, 3 H), 3.56 (s, 2 H), 1.26 (t, *J* = 7.12 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.01, 158.15, 140.83, 130.84, 128.89, 125.60, 113.83, 63.79, 60.70, 55.28, 37.24, 27.75, 14.17.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{13}H_{17}O_3$: 221.1099; found: 221.1089.

Ethyl 3-Methyl-2-methylenebutanoate (22)

[CAS Reg. No. 68834–46–8]

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and 2-bromopropane (0.92 g, 7.5 mmol) at r.t. for 24 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 3:1) in 76% yield (0.54 g, 3.8 mmol) as a colourless liquid. R_f (A) = 0.58, R_f (B) = 0.39.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (s, 1 H), 5.49 (s, 1 H), 4.21 (q, *J* = 7.12 Hz, 2 H), 2.85–2.80 (m, 2 H), 1.29 (t, *J* = 7.12 Hz, 3 H), 0.88 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.22, 147.37, 121.18, 60.31, 31.56, 22.60, 21.67, 14.06.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_8H_{15}O_2$: 143.0994; found: 143.0894.

Ethyl 2-Methylene-5-phenylpentanoate (23)

[CAS Reg. No. 27356–88–3]

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and 1-bromo-3-phenylpropane (1.49 g, 7.5 mmol). The product was isolated by column chromatography (hexanes/CH_2Cl_2, 2:1) in 89% yield (0.97 g, 4.45 mmol) as a colourless liquid. R_f (A) = 0.72, R_f (B) = 0.33.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.14 (m, 5 H), 6.14 (s, 1 H), 5.51 (s, 1 H), 4.19 (q, *J* = 7.12 Hz, 2 H), 2.64 (t, *J* = 7.66 Hz, 2 H), 2.34 (t, *J* = 7.66 Hz, 2 H), 1.84–1.76 (m, 2 H), 1.29 (t, *J* = 7.12 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.29, 142.14, 140.73, 128.43, 128.32, 125.78, 124.54, 60.60, 35.43, 31.54, 30.10, 14.22.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for: 219.1307; found: 219.1335.

Ethyl 2-Methylenepent-4-ynoate (24)

[CAS Reg. No. 54109–54–5]

The title compound was obtained according to the typical procedure from triethyl phosphonoacetate (1.12 g, 5 mmol) and 3-bromopropyne (0.89 g, 7.5 mmol) at 70 °C for 6 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 3:1) in 64% yield (0.44 g, 3.2 mmol) as a colourless liquid. R_f (A) = 0.61, R_f (B) = 0.39.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 (s, 1 H), 6.04 (s, 1 H), 4.22 (q, *J* = 7.12 Hz, 2 H), 3.24 (s, 2 H), 2.20 (s, 1 H), 1.31 (t, *J* = 7.12 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.05, 135.23, 126.07, 80.18, 71.92, 61.01, 21.51, 14.18.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_8H_{11}O_2$: 139.0681; found: 139.0642.

1-(*tert*-Butyl) 4-Ethyl 2-Methylenesuccinate (4a)

The title compound was obtained according to the typical procedure from *tert*-butyl diethyl phosphonoacetate (1.26 g, 5 mmol) and ethyl bromooacetate (1.25 g, 7.5 mmol). The product was isolated by column chromatography (hexanes/CH_2Cl_2, 2:1) in 72% yield (0.77 g, 3.6 mmol) as a colourless liquid. R_f (A) = 0.45, R_f (B) = 0.16.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.25 (s, 1 H), 5.62 (s, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 3.30 (s, 2 H), 1.50 (s, 9 H), 1.28 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.87, 165.33, 135.53, 127.21, 81.08, 60.79, 38.07, 27.96, 14.16.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{11}H_{19}O_4$: 215.1205; found: 215.1198.

***tert*-Butyl 3-Methyl-2-methylenepentanoate (10a)**

The title compound was obtained according to the typical procedure *tert*-butyl diethyl phosphonoacetate (1.26 g, 5 mmol) and 2-bromobutane (1.03 g, 7.5 mmol) at 70 °C for 6 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 3:1) in 58% yield (0.53 g, 2.9 mmol) as a colourless liquid. R_f (A) = 0.73, R_f (B) = 0.58.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06 (s, 1 H), 5.40 (s, 1 H), 2.60–2.55 (m, 1 H), 1.58–1.31 (m, 11 H), 1.06 (d, *J* = 7.00 Hz, 3 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.93, 147.57, 121.39, 80.28, 36.09, 28.79, 27.42, 19.21, 11.71.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for: 185.1463; found: 185.1502.

***tert*-Butyl 4-Methyl-2-methylenepentanoate (11a)**

[CAS Reg. No. 1146623–12–2]

The title compound was obtained according to the typical procedure from *tert*-butyl diethyl phosphonoacetate (1.26 g, 5 mmol) and 1-bromo-2-methylpropane (1.03 g, 7.5 mmol) at 70 °C for 6 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 3:1) in 63% yield (0.58 g, 3.15 mmol) as a colourless liquid. R_f (A) = 0.70, R_f (B) = 0.42.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06 (s, 1 H), 5.40 (s, 1 H), 2.14 (d, *J* = 6.9 Hz, 2 H), 1.80–1.75 (m, 1 H), 1.49 (s, 9 H), 0.89 (d, *J* = 7.0 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.78, 141.38, 124.54, 80.23, 41.38, 28.03, 27.37, 22.28.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{11}H_{21}O_2$: 185.1463; found: 185.1422.

***tert*-Butyl 2-Methylenehexanoate (14a)**

The title compound was obtained according to the typical procedure from *tert*-butyl diethyl phosphonoacetate (1.26 g, 5 mmol) and 1-bromobutane (1.03 g, 7.5 mmol) at 80 °C for 5 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 3:1) in 78% yield (0.72 g, 3.9 mmol) as a colourless liquid. R_f (A) = 0.80, R_f (B) = 0.54.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03 (s, 1 H), 5.43 (s, 1 H), 2.26 (t, *J* = 7.4 Hz, 2 H), 1.44 (s, 9 H), 1.37–1.35 (m, 2 H), 1.34–1.31 (m, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.72, 142.58, 123.17, 80.27, 31.63, 30.71, 28.04, 22.35, 13.89.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for: 185.1463; found: 185.1478.

***tert*-Butyl 2-Benzylacrylate (16a)**

[CAS Reg. No. 111832–40–7]

The title compound was obtained according to the typical procedure from *tert*-butyl diethyl phosphonoacetate (1.26 g, 5 mmol) and benzyl bromide (1.28 g, 7.5 mmol). The product was isolated by column chromatography (hexanes/CH_2Cl_2, 2:1) in 78% yield (0.85 g, 3.9 mmol) as a colourless liquid. R_f (A) = 0.68, R_f (B) = 0.31.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5 H), 6.19 (s, 1 H), 5.41 (s, 1 H), 3.63 (s, 2 H), 1.48 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.22, 141.78, 139.14, 129.00, 128.34, 126.21, 125.19, 80.70, 38.24, 28.00.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{14}H_{19}O_2$: 219.1307; found: 219.1350.

***tert*-Butyl 2-(4-Methoxybenzyl)acrylate (21a)**

[CAS Reg. No. 942298–92–2]

The title compound was obtained according to the typical procedure from *tert*-butyl diethyl phosphonoacetate (1.26 g, 5 mmol) and 1-(chloromethyl)-4-methoxybenzene (1.17 g, 7.5 mmol). The product was isolated by column chromatography (hexanes/CH_2Cl_2, 2:1) in 89% yield (1.10 g, 4.45 mmol) as a colourless liquid. R_f (A) = 0.65, R_f (B) = 0.28.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 8.48 Hz, 2 H), 6.86 (d, *J* = 8.48 Hz, 2 H), 6.14 (s, 1 H), 5.37 (s, 1 H), 3.81 (s, 3 H), 3.56 (s, 2 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.30, 158.07, 142.16, 131.14, 129.96, 124.79, 113.75, 80.62, 55.22, 37.34, 28.02.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for: 249.1412; found: 249.1450.

***tert*-Butyl 2-Methylene-5-phenylpentanoate (23a)**

The title compound was obtained according to the typical procedure from *tert*-butyl diethyl phosphonoacetate (1.26 g, 5 mmol) and 1-bromo-3-phenylpropane (1.49 g, 7.5 mmol). The product was isolated by column chromatography (hexanes/CH_2Cl_2, 3:1) in 84% yield (1.03 g, 4.2 mmol) as a colourless liquid. R_f (A) = 0.84, R_f (B) = 0.43.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.22 (m, 5 H), 6.08 (s, 1 H), 5.47 (s, 1 H), 2.66 (t, *J* = 7.76 Hz, 2 H), 2.34 (t, *J* = 7.56 Hz, 2 H), 1.78–1.83 (m, 2 H), 1.51 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.59, 142.25, 142.15, 128.43, 128.31, 125.75, 123.64, 80.45, 35.54, 31.66, 30.28, 28.08.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{16}H_{23}O_2$: 247.1620; found: 247.1688.

***tert*-Butyl 2-Methylenepent-4-ynoate (24a)**

The title compound was obtained according to the typical procedure from *tert*-butyl diethyl phosphonoacetate (1.26 g, 5 mmol) and 3-bromopropyne (0.89 g, 7.5 mmol) at 70 °C for 6 h. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 3:1) in 62% yield (0.52 g, 3.1 mmol) as a colourless liquid. R_f (A) = 0.72, R_f (B) = 0.50.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.24 (s, 1 H), 5.96 (s, 1 H), 3.19 (s, 2 H), 2.19 (s, 1 H), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.19, 136.55, 125.14, 81.06, 80.43, 71.72, 27.99, 21.48.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd for $C_{10}H_{15}O_2$: 167.0994; found: 167.0903.

Ethyl 5-Acetoxycyclopent-1-ene-1-carboxylate (17)

[CAS Reg. No 115413–74–6]

A solution of 2,5-dimethoxytetrahydrofuran (1.06 g, 8 mmol) and HCl 0.6 M (6.5 mL) was heated to 70 °C for 2.5 h under vigorous stirring. After cooling to 0 °C, the mixture was neutralized with aq. $KHCO_3$ (10%, 4.5 mL), and triethyl phosphonoacetate (1.8 g, 8.1 mmol) and K_2CO_3 (6.4 M, 3.5 mL) were added. The reaction mixture was stirred for 24 h at r.t. Extraction with EtOAc (3 × 20 mL), washing with brine (10 mL), drying over Na_2SO_4, filtration and concentration, and purification by column chromatography using hexane/EtOAc, 3:1 as eluent afforded ethyl 5-hydroxycyclopent-1-ene-1-carboxylate in 80% yield (1 g, 6.4 mmol) as a colourless liquid.

To a solution of ethyl 5-hydroxycyclopent-1-ene-1-carboxylate (1 g, 6.4 mmol) and pyridine (3.04 g, 38.4 mmol) in CH_2Cl_2 (3 mL), acetyl chloride (3.02 g, 38.4 mmol) was added dropwise at 0 °C. The reaction mixture was stirred overnight at r.t.. Solvent removal, dissolution in EtOAc (50 mL), washing with HCl 1 M to ca. pH 3, washing with aq. $NaHCO_3$ (5%, 30 mL), brine (20 mL) drying over Na_2SO_4, filtration and concentration, and purification by column chromatography using CH_2Cl_2 as eluent afforded the product in 85% yield (1.08 g, 5.44 mmol) as a pale-yellow liquid. R_f (hexanes/EtOAc, 3:1) = 0.55.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (s, 1 H), 5.97–5.92 (m, 1 H), 4.20–4.13 (m, 2 H), 2.68–2.61 (m, 1 H), 2.48–2.33 (m, 2 H), 1.99 (s, 3 H), 1.90–1.84 (m, 1 H), 1.26–1.22 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.47, 163.52, 149.63, 135.10, 77.21, 60.28, 31.20, 31.05, 21.11, 14.15.

HRMS (ESI): *m*/*z* [M + 1]$^+$ calcd $C_{10}H_{14}O_4$: 199.0892; found: 199.0924.

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Supporting Information

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