Accepted Manuscript

Submission Date: 2024-05-19
Accepted Date: 2024-06-14
Accepted Manuscript online: 2024-06-17

Synlett

Synthesis of Methyl 2-[Bis(benzylthio)phosphoryl]acetate as a Novel Horner–Wadsworth–Emmons-Type Reagent and Its Application to the Diastereodivergent Synthesis of (E)- and (Z)-α,β-Unsaturated Esters

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DOI: 10.1055/a-2347-1027

Please cite this article as: Sano S, Yamada S, Ihara T et al. Synthesis of Methyl 2-[Bis(benzylthio)phosphoryl]acetate as a Novel Horner–Wadsworth–Emmons-Type Reagent and Its Application to the Diastereodivergent Synthesis of (E)- and (Z)-α,β-Unsaturated Esters. Synlett 2024. doi: 10.1055/a-2347-1027

Conflict of Interest: The authors declare that they have no conflict of interest.

This study was supported by Japan Society for the Promotion of Science (http://dx.doi.org/10.13039/501100001691), JP20K06966,JP23K06026

Abstract:
Methyl 2-[bis(benzylthio)phosphoryl]acetate has proven to be an efficient Horner–Wadsworth–Emmons (HWE)-type reagent for the diastereodivergent synthesis of (E)- and (Z)-α,β-unsaturated esters. Under the condition of excess NaHMDS relative to the HWE-type reagent, the HWE-type reactions of methyl 2-[bis(benzylthio)phosphoryl]acetate with various aldehydes afforded the corresponding α,β-unsaturated esters in an E-selective manner in up to 100:0 E/Z ratio. However, when an excess of the HWE-type reagent was used relative to NaHMDS, the stereoselectivity of the HWE-type reactions was dramatically changed from E to Z, yielding an E/Z ratio up to 2:98.

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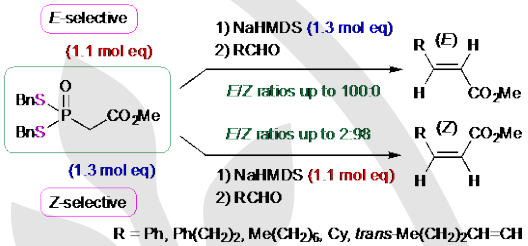
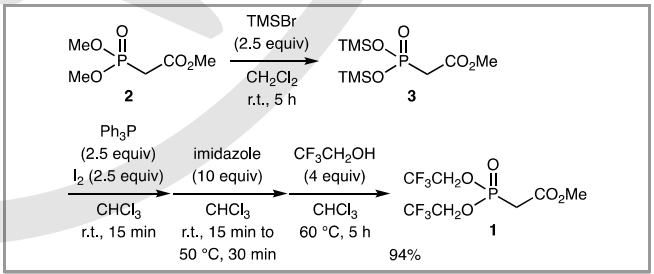


Received:
Accepted:
Published online:
DOI:

Abstract Methyl 2-[bis(benzylthio)phosphoryl]acetate has proven to be an efficient Horner–Wadsworth–Emmons (HWE)-type reagent for the diastereodivergent synthesis of (*E*)- and (*Z*)-α,β-unsaturated esters. Under the condition of excess NaHMDS relative to the HWE-type reagent, the HWE-type reactions of methyl 2-[bis(benzylthio)phosphoryl]acetate with various aldehydes afforded the corresponding α,β-unsaturated esters in an *E*-selective manner in up to 100:0 *E*/*Z* ratio. However, when an excess of the HWE-type reagent was used relative to NaHMDS, the stereoselectivity of the HWE-type reactions was dramatically changed from *E* to *Z*, yielding an *E*/*Z* ratio up to 2:98.

Key words Horner–Wadsworth–Emmons-type reagents, phosphorus–sulfur single bonds, α,β-unsaturated esters, diastereodivergent olefination, methyl 2-[bis(benzylthio)phosphoryl]acetate, Garegg–Samuelsson reaction conditions, aldehydes

One of the most extensively utilized reactions for the stereoselective construction of carbon–carbon double bonds is the reaction of aldehydes or ketones with stabilized phosphonate carbanions. This reaction is called the Horner–Wadsworth–Emmons (HWE) reaction, and various phosphonate derivatives have been developed as useful HWE reagents over the last half century.[1] On the other hand, the importance of organic compounds such as phosphorothioates, phosphonothioates, phosphinothioates, and phosphonodithioates containing phosphorus–sulfur single bonds has increased over the same period, especially in the fields of agrochemicals, medicinal chemistry, and materials chemistry.[2] To the best of our knowledge, however, the synthesis of HWE-type reagents in which both the phosphorus–oxygen single bonds of HWE reagents are replaced with phosphorus–sulfur single bonds, has not yet been achieved. Since oxygen and sulfur are in the same group of the periodic table, but sulfur is in the same period as phosphorus, the above structural conversion from the HWE reagents to HWE-type reagents was expected to result in a significant change in their reactivity. We recently reported an efficient two-step synthesis of methyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (Still–Gennari reagent, **1**) based on Garegg–Samuelsson reaction conditions (triphenylphosphine, iodine, and imidazole) from methyl 2-(dimethoxyphosphoryl)acetate (**2**) via methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate (**3**) as an intermediate (Scheme 1).[3,4] This procedure has been found to be applicable not only to the synthesis of Still–Gennari reagent (**1**) but also to the synthesis of other HWE-type reagents that have phosphorus–sulfur or phosphorus–nitrogen single bonds instead of phosphorus–oxygen single bonds. Herein, we report the efficient synthesis of methyl 2-[bis(benzylthio)phosphoryl]acetate (**4a**) as a novel HWE-type reagent and its application to the diastereoselective synthesis of (*E*)- and (*Z*)-α,β-unsaturated esters by the HWE-type reaction of **4a** with various aldehydes.

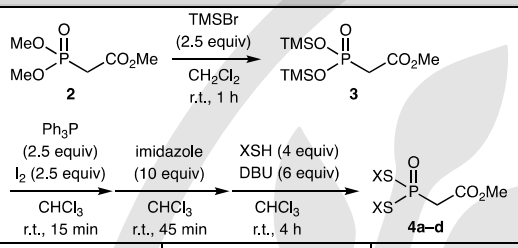


Scheme 1 Two-step synthesis of Still–Gennari reagent (**1**) from methyl 2-(dimethoxyphosphoryl)acetate (**2**)

Based on our previous work on the synthesis of **1**, we first investigated the two-step conversion of **2** into some methyl 2-

[bis(organothio)phosphory]acetates **4a–d**. As a result, four kinds of **4a–d** were obtained in 87–95% yields from **2** by employing 2.5 equiv of triphenylphosphine, 2.5 equiv of iodine, 10 equiv of imidazole, 4 equiv of thiol, and 6 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the second step as shown in Table 1.[5]

Table 1 Synthesis of methyl 2-[bis(organothio)phosphoryl]acetates **4a–d**

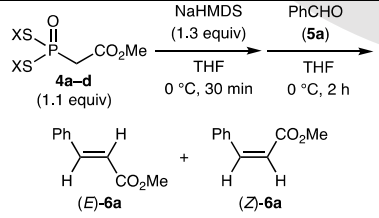


Entry	X	Yield of **4** (%)[a]
1	Bn	95 (**4a**)
2	Ph	90 (**4b**)
3	$Ph(CH_2)_2$	88 (**4c**)
4	n-$C_{12}H_{25}$	87 (**4d**)

[a] Isolated yield.

The HWE-type reaction was investigated using 1.1 equiv of methyl 2-[bis(benzylthio)phosphoryl]acetate (**4a**) and 1.1 equiv of sodium hexamethyldisilazide (NaHMDS) to benzaldehyde (**5a**) at 0 °C in THF. α,β-Unsaturated esters **6a** were obtained in good yield, but it was difficult to obtain reproducible results in *E*/*Z* selectivity. However, when the amount of NaHMDS was increased to 1.3 equiv, only the (*E*)-α,β-unsaturated ester (*E*)-**6a** was formed reproducibly, as shown in Table 2 (entry 1).[6] The use of NaHMDS was slightly preferable to lithium hexamethyldisilazide (LiHMDS) and potassium hexamethyldisilazide (KHMDS) in terms of yield and/or selectivity (entries 2 and 3). The HWE reaction of aldehydes under isopropylmagnesium bromide (*i*-PrMgBr) conditions generally tends to proceed with high *E*-selectivity,[7] while the reaction of **4a** and **5a** under *i*-PrMgBr conditions gave (*E*)-**6a** in a slightly lower *E*-selective manner (entry 4) than those under other basic conditions. In the HWE-type reaction using other HWE-type reagents **4b–d**, the (*E*)-α,β-unsaturated ester (*E*)-**6a** was also obtained with 100% stereoselectivity (entries 5–7). The geometries of **6a** were confirmed based on the coupling constants between the olefinic protons, and the *E*/*Z* ratios of **6a** were calculated by integration of the appropriate proton absorptions determined by ^{1}H NMR analysis.

Table 2 HWE-type reaction of methyl 2-[bis(organothio)phosphoryl]acetate (**4a–d**) with benzaldehyde (**5a**) under excess NaHMDS conditions

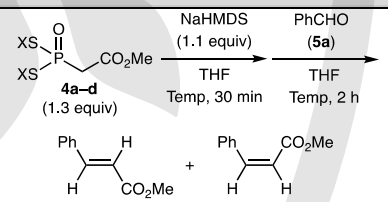


Entry	HWE-type reagents **4a–d**	Yield of **6a** (%)[a]	*E*/*Z*[b]
1	**4a** (X = Bn)	99	100:0
2[c]	**4a** (X = Bn)	97	99:1
3[d]	**4a** (X = Bn)	86	100:0
4[e]	**4a** (X = Bn)	90	96:4
5	**4b** (X = Ph)	78	100:0
6	**4c** [X = $Ph(CH_2)_2$]	90	100:0
7	**4d** (X = n-$C_{12}H_{25}$)	86	100:0

[a] Isolated yield.
[b] Determined by ^{1}H NMR (400 MHz, $CDCl_3$) analysis.
[c] LiHMDS was used instead of NaHMDS.
[d] KHMDS was used instead of NaHMDS.
[e] *i*-PrMgBr was used instead of NaHMDS.

Surprisingly, (*Z*)-α,β-unsaturated ester (*Z*)-**6a** was found to be the major product when the quantity relationship between HWE-type reagents **4a–d** and NaHMDS was reversed as shown in Table 3 (entries 1–4). Furthermore, the *Z*-selectivity was improved when the reaction was carried out at –78 °C, and the highest selectivity (*E*/*Z* = 2:98) was obtained by the reaction of the HWE-type reagent **4a** (entry 5).[8] In other words, the newly developed HWE-type reagents **4a–d** can diastereoselectively synthesize α,β-unsaturated esters **6a** from the same reagent by changing the amount ratio of the HWE-type reagents **4a–d** to NaHMDS. For the reaction of **4a**, the use of NaHMDS gave slightly favorable results in yield and selectivity compared to LiHMDS and KHMDS (entries 6 and 7). Notably, the reaction of **4a** and **5a** under *i*-PrMgBr conditions showed *E*-selectivity (entry 8).[7] When benzaldehyde (**5a**) was reacted with **4d** having dodecylthio groups at –78 °C, the yield was remarkably low (entry 11).

Table 3 HWE-type reaction of methyl 2-[bis(organothio)phosphoryl]acetate (**4a–d**) with benzaldehyde (**5a**) under excess HWE-type reagent conditions

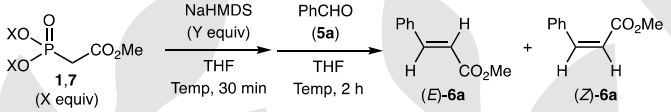


Entry	HWE-type reagents **4a–d**	Temp (°C)	Yield of **6a** (%)[a]	*E*/*Z*[b]
1	**4a** (X = Bn)	0	99	14:86
2	**4b** (X = Ph)	0	84	34:66
3	**4c** [X = $Ph(CH_2)_2$]	0	94	25:75
4	**4d** (X = n-$C_{12}H_{25}$)	0	81	31:69
5	**4a** (X = Bn)	–78	94	2:98
6[c]	**4a** (X = Bn)	–78	90	5:95
7[d]	**4a** (X = Bn)	–78	80	6:94
8[e]	**4a** (X = Bn)	–78	18	85:15
9	**4b** (X = Ph)	–78	87	7:93
10	**4c** [X = $Ph(CH_2)_2$]	–78	96	4:96
11	**4d** (X = n-$C_{12}H_{25}$)	–78	7	46:54

[a] Isolated yield.
[b] Determined by ^{1}H NMR (400 MHz, $CDCl_3$) analysis.
[c] LiHMDS was used instead of NaHMDS.
[d] KHMDS was used instead of NaHMDS.
[e] *i*-PrMgBr was used instead of NaHMDS.

To clarify the differences between the HWE-type reagents **4a–d** capable of diastereodivergent synthesis of α,β-unsaturated ester **6a** and the more commonly used HWE reagents, we examined the results of HWE reactions of Still–Gennari reagent (**1**) and methyl 2-[bis(benzyloxy)phosphoryl]acetate (**7**) under the same conditions as in Tables 2 and 3. The results showed that regardless of the amount ratio of each HWE reagent to NaHMDS, HWE reagent **1** exhibited moderate *Z*-selectivity, and HWE reagent **7** exhibited high *E*-selectivity (Table 4). There was no reversal of stereoselectivity depending on the amount ratio of reagents for either of the HWE reagents **1** or **7**. The novel HWE-type reagent **4a** has a characteristic chemical structure in which the two phosphorus–oxygen single bonds of HWE reagent **7** are replaced by phosphorus–sulfur single bonds, and its reactivity was found to be significantly different from that of ordinary HWE reagents such as **1** and **7**.

Table 4 HWE reaction of Still-Gennari reagent (**1**) and methyl 2-[bis(benzyloxy)phosphoryl]acetate (**7**) with benzaldehyde (**5a**)

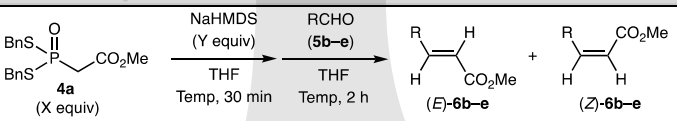


Entry	HWE reagents **1** and **7**	X (equiv)	Y (equiv)	Temp (°C)	Yield of **6a** (%)[a]	*E*/*Z*[b]
1	**1** (X = CF_3CH_2)	1.1	1.3	0	91	34:66
2	**1** (X = CF_3CH_2)	1.3	1.1	0	89	32:68
3	**1** (X = CF_3CH_2)	1.3	1.1	–78	95	17:83
4	**7** (X = Bn)	1.1	1.3	0	94	97:3
5	**7** (X = Bn)	1.3	1.1	0	99	97:3
6	**7** (X = Bn)	1.3	1.1	–78	95	96:4

[a] Isolated yield.
[b] Determined by ^{1}H NMR (400 MHz, $CDCl_3$) analysis.

Based on the results of Tables 2 and 3, we investigated the HWE-type reaction with various aldehydes using HWE-type reagent **4a**. The results of the *E*-selective HWE-type reaction using 1.1 equiv of HWE-type reagent **4a** and 1.3 equiv of NaHMDS to aldehydes **5b–e**, and the *Z*-selective HWE-type reaction using the reverse ratio of the amounts of HWE-type reagent **4a** and NaHMDS are shown in Table 5. When aldehydes **5b**, **5c**, and **5e** were used under excess NaHMDS conditions, the reaction proceeded in an *E*-selective manner as for aldehyde **5a**; the exception was aldehyde **5d**, which afforded (*Z*)-α,β-unsaturated ester (*Z*)-**6c** as the main product (entries 1–4). However, when the reaction of aldehyde **5d** was carried out at –40 °C, the selectivity was reversed, and (*Z*)-α,β-unsaturated ester (*Z*)-**6c** was obtained as the major product (88%, *E*/*Z* = 95:5). On the other hand, under the excess HWE-type reagent conditions, all the HWE-type reactions of **4a** and aldehydes **5b–e** proceeded in a *Z*-selective manner (entries 5–8).

Table 5 Diastereodivergent synthesis of α,β-unsaturated esters (*E*)- and (*Z*)-**6b–e** by HWE-type reaction of methyl 2-[bis(benzylthio)phosphoryl]acetate (**4a**) with various aldehydes **5b–e**

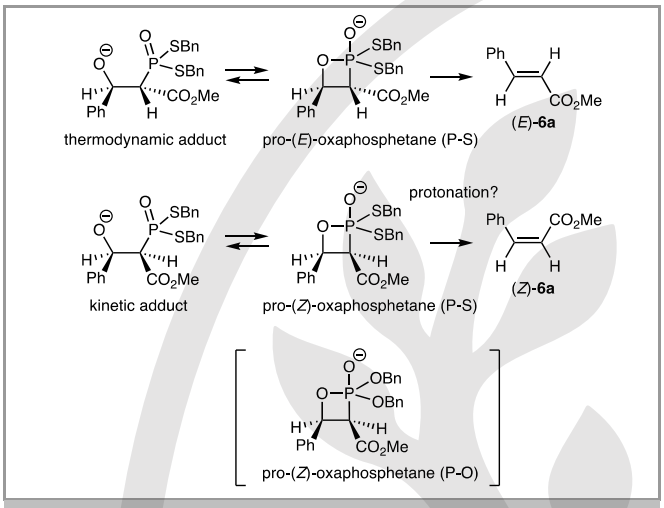


Entry	Aldehydes **5b–e**	X (equiv)	Y (equiv)	Temp (°C)	Yield of **6b–e** (%)[a]	*E*/*Z*[b]
1	**5b** [R = $Ph(CH_2)_2$]	1.1	1.3	0	86 (**6b**)	89:11
2	**5c** [R = $Me(CH_2)_6$]	1.1	1.3	0	77 (**6c**)	96:4
3	**5d** (R = C_y)	1.1	1.3	0	96 (**6d**)	10:90
4	**5e** [R = *trans*-$Me(CH_2)_2CH{=}CH$]	1.1	1.3	0	80 (**6e**)	79:21
5	**5b** [R = $Ph(CH_2)_2$]	1.3	1.1	–78	82 (**6b**)	6:94
6	**5c** [R = $Me(CH_2)_6$]	1.3	1.1	–78	82 (**6c**)	5:95
7	**5d** (R = C_y)	1.3	1.1	–78	78 (**6d**)	2:98
8	**5e** [R = *trans*-$Me(CH_2)_2CH{=}CH$]	1.3	1.1	–78	67 (**6e**)	5:95

[a] Isolated yield.
[b] Determined by ^{1}H NMR (400 MHz, $CDCl_3$) analysis.

Assuming that the pro-(*Z*)-oxaphosphetane (P-S) kinetically generated from the novel HWE-type reagent **4a** and benzaldehyde (**5a**) was more stable than the conventional pro-(*Z*)-oxaphosphetane (P-O), an equilibrium occurs between pro-(*Z*)-oxaphosphetane (P-S) and pro-(*E*)-oxaphosphetane (P-S) under excess NaHMDS conditions. As a result, it is considered that (*E*)-**6a** was obtained via the thermodynamically favorable pro-(*E*)-oxaphosphetane (P-S). If pro-(*Z*)-oxaphosphetane (P-S) was protonated and destabilized under excess HWE-type reagent

conditions, (*Z*)-**6a** was obtained via the kinetically favorable pro-(*Z*)-oxaphosphetane (P-S). Although the reaction mechanism is currently unknown, a similar HWE-type reaction of **4a** and **5a** under aqueous conditions (**5a**/**4a**/NaHMDS/H_2O = 1:1.1:1.1:1.1) gave α,β-unsaturated ester **6a** in a *Z*-selective manner (*E*/*Z* = 1:99) in 82% yield. Therefore, the excess HWE-type reagent **4a** is considered to be acting as some kind of proton source.



Scheme 2 Plausible intermediates in HWE-type reaction of methyl 2-[bis(benzylthio)phosphoryl]acetate (**4a**) with benzaldehyde (**5a**)

In conclusion, we efficiently synthesized novel HWE-type reagents **4a–d** from methyl 2-(dimethoxyphosphoryl)acetate (**2**) using Garegg–Samuelsson reaction conditions. Novel HWE-type reagent **4a** was found to diastereodivergently afford α,β-unsaturated esters **6a–e** in the HWE-type reactions depending on the reaction conditions. Conditions using 1.1 equiv of **4a** and 1.3 equiv of NaHMDS to aldehydes **5a–e** are suitable for the preparation of (*E*)-α,β-unsaturated esters (*E*)-**6a–e**, and conditions using 1.3 equiv of **4a** and 1.1 equiv of NaHMDS to aldehydes **5a–e** are suitable for the preparation of (*Z*)-α,β-unsaturated esters (*Z*)-**6a–d**. It is to be noted that the HWE-type reagents **4a–d** in which both the phosphorus–oxygen single bonds of HWE reagents are replaced with phosphorus–sulfur single bonds were not reported previously, and we have succeeded for the first time in synthesis of **4a–d** and in diastereodivergent HWE-type reaction of **4a–d** with aldehydes **5a–e**. The reaction mechanism of the diastereodivergent HWE-type reactions of methyl 2-[bis(organothio)phosphoryl]acetates **4a–d** with aldehydes **5a–e** remains unclear at present, but efforts towards the elucidation of the reaction mechanism are currently under way in our laboratory.

Funding Information

This work was supported by JSPS KAKENHI Grant Number JP20K06966 and JP23K06026.

Acknowledgment

Click here to insert acknowledgment text. Funding sources and grant numbers should be given above in the Funding Information section.

Supporting Information

YES.

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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(5) **Preparation of Methyl 2-[Bis(benzylthio)phosphorylacetate (4a)**
Bromotrimethylsilane (1.67 mL, 12.8 mmol) was added to a solution of methyl 2-(dimethoxyphosphoryl)acetate (**2**; 929 mg, 5.10 mmol) in anhydrous CH_2Cl_2 (15 mL) at r.t. under argon. After stirring at r.t. for 1 h under argon, evaporation of the reaction mixture in vacuo gave methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate (**3**), which was used without further purification. Triphenylphosphine (3.38 g, 12.8 mmol) and iodine (3.25 g, 12.8 mmol) were added to a solution of **3** in anhydrous $CHCl_3$ (20 mL) at r.t. under argon. After stirring at r.t. for 15 min under argon, imidazole (3.47 g, 51.0 mmol) was added. The reaction mixture was stirred at r.t. for 45 min. Afterwards, a solution of phenylmethanethiol (2.40 mL, 20.4 mmol) and DBU (4.60 mL, 30.6 mmol) in anhydrous $CHCl_3$ (10 mL) was added and the reaction mixture was stirred at r.t. for 4 h. The reaction mixture was purified by flash column chromatography [Silica Gel PSQ 60B (Fuji Silysia Chemical): *n*-hexane–EtOAc (1:1)] to afford **4a** (1.78 g, 95%).
Colorless needles ($CHCl_3$–*n*-pentane); mp 36.0–36.8 °C; IR (KBr): 3029, 2967, 2913, 1733, 1496, 1454, 1438, 1418, 1257, 1205, 1191, 1114 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 10H), 4.27–4.13 (m, 4H), 3.72 (s, 3H), 3.22 (d, $^2J_{H,P}$ = 16.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2 (d, $^2J_{C,P}$ = 5.4 Hz), 136.4 (d, $^3J_{C,P}$ = 5.5 Hz), 129.2, 128.8, 127.9, 52.8, 45.4 (d, $^1J_{C,P}$ = 63.6 Hz), 35.0 (d, $^2J_{C,P}$ = 3.2 Hz). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}O_3PS_2Na$: 389.0411; found: 389.0407. Anal. Calcd for $C_{17}H_{19}O_3PS_2$: C, 55.72; H, 5.23. Found: C, 55.74; H, 5.21.

(6) ***E*-Selective HWE-Type Reaction of Methyl 2-[Bis(benzylthio)phosphoryl]acetate (4a) with Benzaldehyde (5a) under Excess NaHMDS Conditions**
To a solution of methyl 2-[bis(benzylthio)phosphoryl]acetate (**4a**) (150 mg, 0.409 mmol) in anhydrous THF (2.5 mL) was added NaHMDS (1.0 mol/L in THF, 484 μL, 0.484 mmol), and the solution was stirred at 0 °C for 30 min under argon. After adding benzaldehyde (**5a**) (38.0 μL, 0.372 mmol), the mixture was stirred at 0 °C for 2 h under argon. The reaction mixture was treated with 1N HCl (2.5 mL) and then extracted with $CHCl_3$ (10 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N (Kanto Chemical): *n*-hexane–

EtOAc (20:1)] to afford (*E*)-α,β-unsaturated ester (*E*)-**6a** (59.9 mg, 99%, *E*/*Z* = 100:0).

Methyl (*E*)-3-Phenylacrylate [(*E*)-6a][7c]

Colorless needles (*n*-hexane); mp 30.0–30.2 °C; IR (KBr): 2947, 2846, 1718, 1638, 1495, 1452, 1315, 1172 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 16.0 Hz, 1H), 7.55–7.51 (m, 2H), 7.41–7.37 (m, 3H), 6.45 (d, *J* = 16.0 Hz, 1H) 3.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.5 144.9, 134.3, 130.3, 128.9, 128.1, 117.8, 51.7. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{10}O_2Na$: 185.0578; found: 185.0588. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.22. Found: C, 74.04; H, 6.30.

(7) (a) Sano, S.; Ando, T.; Yokoyama, K.; Nagao, Y. *Synlett* **1998**, 777. (b) Sano, S.; Teranishi, R.; Nagao, Y. *Tetrahedron Lett.* **2002**, *43*, 9183. (c) Sano, S.; Takemoto, Y.; Nagao, Y. *Arkivoc* **2003**, (viii), 93. (d) Sano, S.; Takemoto, Y.; Nagao, Y. *Tetrahedron Lett.* **2003**, *44*, 8853. (e) Claridge, T. D. W..; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437. (f) Sano, S.; Matsumoto, T.; Nanataki, H.; Tempaku, S.; Nakao, M. *Tetrahedron Lett.* **2014**, *55*, 6248.

(8) ***Z*-Selective HWE-Type Reaction of Methyl 2-[Bis(benzylthio)phosphoryl]acetate (4a) with Benzaldehyde (5a) under Excess HWE-Type Reagent Conditions**

To a solution of methyl 2-[bis(benzylthio)phosphoryl]acetate (**4a**) (177 mg, 0.484 mmol) in anhydrous THF (2.5 mL) was added NaHMDS (1.0 mol/L in THF, 409 μL, 0.409 mmol), and the solution was stirred at –78 °C for 30 min under argon. After adding benzaldehyde (**5a**) (38.0 μL, 0.372 mmol), the mixture was stirred at –78 °C for 2 h under argon. The reaction mixture was treated with 1N HCl (2.5 mL) and then extracted with $CHCl_3$ (10 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N (Kanto Chemical): *n*-hexane–EtOAc (20:1)] to afford a mixture of α,β-unsaturated ester (*E*)- and (*Z*)-**6a** (56.9 mg, 94%, *E*/*Z* = 2:98).

Methyl (*Z*)-3-Phenylacrylate [(*Z*)-6a][9]

Colorless oil; IR (neat): 2950, 1725, 1632, 1495, 1436, 1200, 1169 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.57 (m, 2H), 7.39–7.31 (m, 3H), 6.96 (d, *J* = 12.6 Hz, 1H), 5.96 (d, *J* = 12.6 Hz, 1H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 143.5, 134.7, 129.7, 129.1, 128.0, 119.2, 51.4. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{10}O_2Na$: 185.0578; found: 185.0577.

(9) Akkarasamiyo, S.; Chitsomkhuan, S.; Buakaew, S.; Samec, J. S. M.; Chuawong, P.; Kuntiyong, P. *Synlett* **2022**, *33*, 1353.

Supporting Information

for

Synthesis of Methyl 2-[Bis(benzylthio)phosphoryl]acetate as a Novel Horner-Wadsworth-Emmons-Type Reagent and Its Application to the Diastereodivergent Synthesis of (*E*)- and (*Z*)-α,β-Unsaturated Esters

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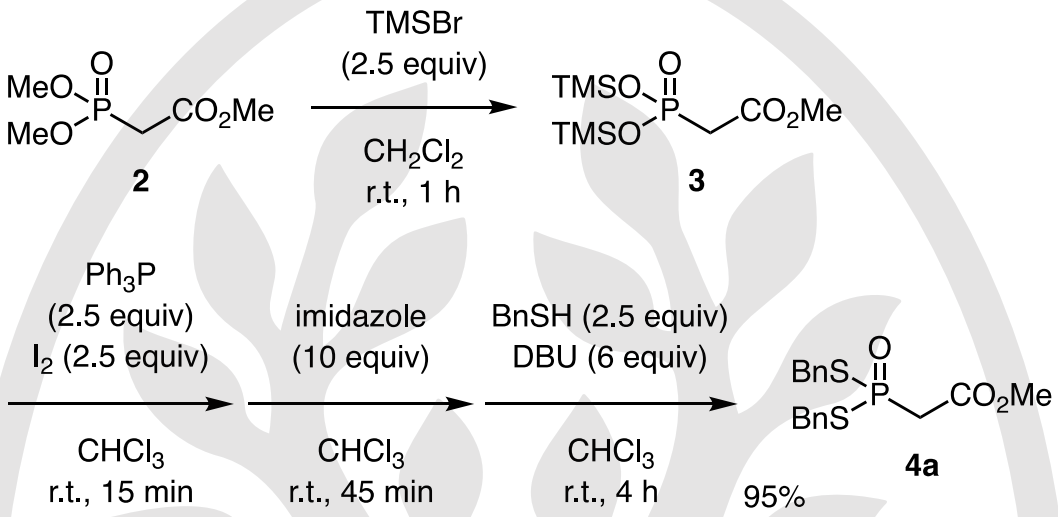
1. General Information

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained with a JASCO FT/IR-6200 IR Fourier transform spectrometer. ^{1}H NMR (400 MHz) spectra were recorded with a Bruker AV400N and Bruker AV400NEO spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded with a Bruker AV500 and JEOL JNM-ECZL500R spectrometer. Chemical shifts are given in δ values (ppm) using TMS as an internal standard. HRMS (ESI) were recorded with a Waters LCT Premier spectrometer. Elemental combustion analyses were performed with a J-SCIENCE LAB JM10. All reactions were monitored by TLC employing 0.25 mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Silica Gel PSQ 60B (Fuji Silysia Chemical) or Silica Gel 60N (Kanto Chemical)]. Anhydrous CH_2Cl_2, $CHCl_3$, and THF were used as purchased from Kanto Chemical. All other reagents were used as purchased.

2. Experimental Procedures and Compound Characterizations

2.1 General Procedure for the Preparation of Methyl 2-[Bis(organothio)phosphoryl]acetates 4a–d



Bromotrimethylsilane (1.67 mL, 12.8 mmol) was added to a solution of methyl 2-(dimethoxyphosphoryl)acetate (**2**; 929 mg, 5.10 mmol) in anhydrous CH_2Cl_2 (15 mL) at r.t. under argon. After stirring at r.t. for 1 h under argon, evaporation of the reaction mixture in vacuo gave methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate (**3**), which was used without further purification. Triphenylphosphine (3.38 g, 12.8 mmol) and iodine (3.25 g, 12.8 mmol) were added to a solution of **3** in anhydrous $CHCl_3$ (20 mL) at r.t. under argon. After stirring at r.t. for 15 min under argon, imidazole (3.47 g, 51.0 mmol) was added. The reaction mixture was stirred at r.t. for 45 min. Afterwards, a solution of phenylmethanethiol (2.40 mL, 20.4 mmol) and DBU (4.60 mL, 30.6 mmol) in anhydrous $CHCl_3$ (10 mL) was added and the reaction mixture was stirred at r.t. for 4 h. The reaction mixture was purified by flash column chromatography [Silica Gel PSQ 60B (Fuji Silysia Chemical): *n*-hexane–EtOAc (1:1)] to afford **4a** (1.78 g, 95%).

Methyl 2-[Bis(benzylthio)phosphoryl]acetate (**4a**)

Colorless needles ($CHCl_3$–*n*-pentane); mp 36.0–36.8 °C; IR (KBr): 3029, 2967, 2913, 1733, 1496, 1454, 1438, 1418, 1257, 1205, 1191, 1114 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 10H), 4.27–4.13 (m, 4H), 3.72 (s, 3H), 3.22 (d, $^2J_{H,P}$ = 16.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2 (d, $^2J_{C,P}$ = 5.4 Hz), 136.4 (d, $^3J_{C,P}$ = 5.5 Hz), 129.2, 128.8, 127.9, 52.8, 45.4 (d, $^1J_{C,P}$ = 63.6 Hz), 35.0 (d, $^2J_{C,P}$ = 3.2 Hz). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{19}O_3PS_2Na$: 389.0411; found: 389.0407. Anal. Calcd for $C_{17}H_{19}O_3PS_2$: C, 55.72; H, 5.23. Found: C, 55.74; H, 5.21.

Methyl 2-[Bis(phenylthio)phosphoryl]acetate (**4b**)

Colorless oil; yield: 1.68 g (90%). IR (neat) 3059, 2952, 1736, 1473, 1440, 1269, 1222, 1108, 1023, 1002 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.63–7.59 (m, 4H), 7.45–7.36 (m, 6H), 3.77 (s, 3H), 3.31 (d, $^2J_{H,P}$ = 16.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.1 (d, $^2J_{C,P}$ = 4.7 Hz), 136.0 (d, $^3J_{C,P}$ = 4.4 Hz), 129.9 (d, $^5J_{C,P}$ = 3.0 Hz), 129.5 (d, $^4J_{C,P}$ = 2.4 Hz), 125.1 (d, $^2J_{C,P}$ = 6.6 Hz), 52.8, 42.5 (d, $^1J_{C,P}$ = 61.3 Hz). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{15}O_3PS_2Na$: 361.0098; found: 361.0084. Anal. Calcd for $C_{15}H_{15}O_3PS_2$: C, 53.24; H, 4.47. Found: C, 53.15; H, 4.52.

Methyl 2-[Bis(phenetylthio)phosphoryl]acetate (**4c**)

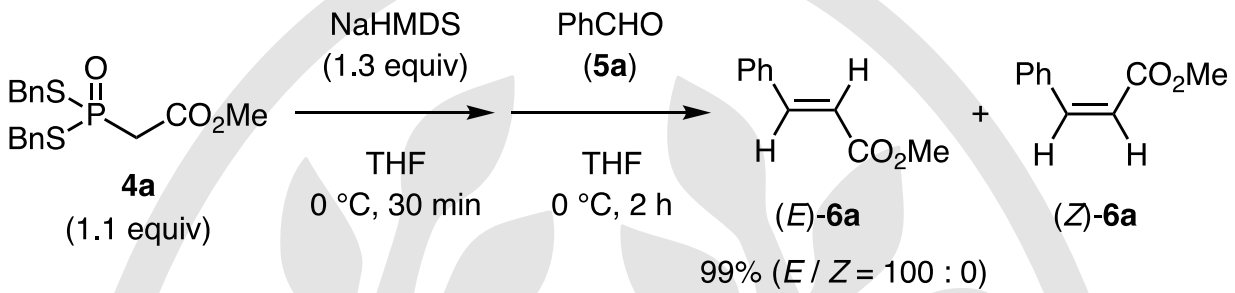
Colorless oil; yield: 1.91 g (88%). IR (neat) 3027, 2950, 1738, 1496, 1454, 1435, 1270, 1234, 1207, 1108 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.32–7.28 (m, 4H), 7.25–7.19 (m, 6H), 3.74 (s, 3H), 3.32 (d, $^2J_{H,P}$ = 16.0 Hz, 2H), 3.27–3.18 (m, 4H), 3.08–2.98 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.2 (d, $^2J_{C,P}$ = 5.4 Hz), 139.1, 128.7, 128.5, 126.7, 52.8, 45.6 (d, $^1J_{C,P}$ = 64.2 Hz), 36.9 (d, $^2J_{C,P}$ = 4.8 Hz), 32.1 (d, $^3J_{C,P}$ = 3.4 Hz). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{23}O_3PS_2Na$: 417.0724; found: 417.0718. Anal. Calcd for $C_{19}H_{23}O_3PS_2$: C, 57.85; H, 5.88. Found: C, 57.55; H, 5.86.

Methyl 2-[Bis(dodecylthio)phosphoryl]acetate (**4d**)

Colorless needles (*n*-hexane); mp < 30.0 °C; yield: 2.51 g (87%). IR (KBr) 2914, 2848, 1737, 1470, 1437, 1263, 1206, 1117, 1003 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.77 (s, 3H), 3.40 (d, $^{2}J_{H,P}$ = 16.2 Hz, 2H), 3.04–2.92 (m, 4H), 1.76–1.69 (m, 4H), 1.45–1.35 (m, 4H), 1.34–1.22 (m, 32H), 0.88 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.5 (d, $^{2}J_{C,P}$ = 5.4 Hz), 52.8, 45.7 (d, $^{1}J_{C,P}$ = 63.7 Hz), 31.9, 31.1 (d, $^{2}J_{C,P}$ or $^{3}J_{C,P}$ = 3.4 Hz), 30.7 (d, $^{2}J_{C,P}$ or $^{3}J_{C,P}$ = 5.2 Hz), 29.65, 29.64, 29.58, 29.5, 29.4, 29.0, 28.7, 22.7, 14.1. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{55}O_3PS_2Na$: 545.3228; found: 545.3241. Anal. Calcd for $C_{27}H_{55}O_3PS_2$: C, 62.03; H, 10.60. Found: C, 62.08; H, 10.51.

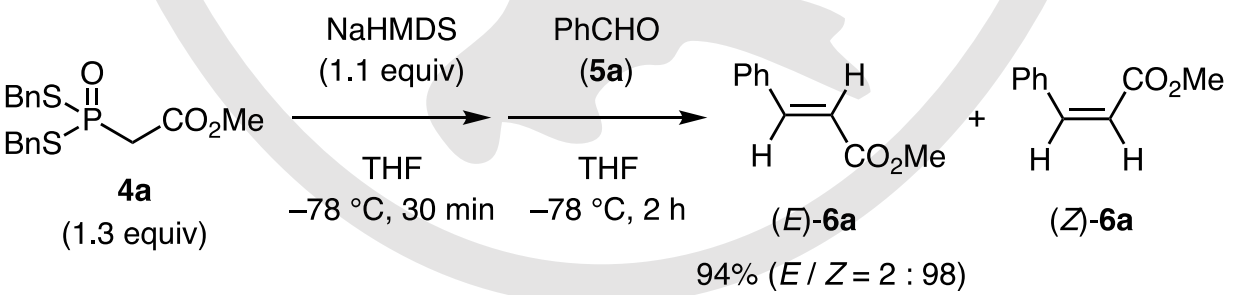
2.2 General Procedure for the HWE-Type Reaction of Methyl 2-[Bis(benzylthio)phosphoryl]acetate (4a) with Aldehydes 5a–e

E-Selective HWE-Type Reaction under Excess NaHMDS Conditions



To a solution of methyl 2-[bis(benzylthio)phosphoryl]acetate (**4a**) (150 mg, 0.409 mmol) in anhydrous THF (2.5 mL) was added NaHMDS (1.0 mol/L in THF, 484 μL, 0.484 mmol), and the solution was stirred at 0 °C for 30 min under argon. After adding benzaldehyde (**5a**) (38.0 μL, 0.372 mmol), the mixture was stirred at 0 °C for 2 h under argon. The reaction mixture was treated with 1N HCl (2.5 mL) and then extracted with $CHCl_3$ (10 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N (Kanto Chemical): *n*-hexane–EtOAc (20:1)] to afford (*E*)-α,β-unsaturated ester (*E*)-**6a** (59.9 mg, 99%, *E*/*Z* = 100:0).

Z-Selective HWE-Type Reaction under Excess HWE-Type Reagent Conditions



To a solution of methyl 2-[bis(benzylthio)phosphoryl]acetate (**4a**) (177 mg, 0.484 mmol) in anhydrous THF (2.5 mL) was added NaHMDS (1.0 mol/L in THF, 409 μL, 0.409 mmol), and the

solution was stirred at –78 °C for 30 min under argon. After adding benzaldehyde (**5a**) (38.0 μL, 0.372 mmol), the mixture was stirred at –78 °C for 2 h under argon. The reaction mixture was treated with 1N HCl (2.5 mL) and then extracted with $CHCl_3$ (10 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N (Kanto Chemical): *n*-hexane–EtOAc (20:1)] to afford a mixture of α,β-unsaturated ester (*E*)- and (*Z*)-**6a** (56.9 mg, 94%, *E*/*Z* = 2:98).

Methyl (*E*)-3-Phenylacrylate [(*E*)-**6a**]

Colorless needles (*n*-hexane); mp 30.0–30.2 °C; IR (KBr) 2947, 2846, 1718, 1638, 1495, 1452, 1315, 1172 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 16.0 Hz, 1H), 7.55–7.51 (m, 2H), 7.41–7.37 (m, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.5, 144.9, 134.3, 130.3, 128.9, 128.1, 117.8, 51.7. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{10}O_2Na$: 185.0578; found: 185.0588. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.22. Found: C, 74.04; H, 6.30.

Methyl (*Z*)-3-Phenylacrylate [(*Z*)-**6a**]

Colorless oil; IR (neat) 2950, 1725, 1632, 1495, 1436, 1200, 1169 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.60–7.57 (m, 2H), 7.39–7.31 (m, 3H), 6.96 (d, *J* = 12.6 Hz, 1H), 5.96 (d, *J* = 12.6 Hz, 1H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.6, 143.5, 134.7, 129.7, 129.1, 128.0, 119.2, 51.4. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{10}O_2Na$: 185.0578; found: 185.0577.

Methyl (*E*)-5-Phenylpent-2-enoate [(*E*)-**6b**]

Colorless oil; IR (neat) 2949, 1724, 1657, 1436, 1319, 1273, 1202 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.32–7.27 (m, 2H), 7.23–7.16 (m, 3H), 7.01 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.6 Hz, 1H), 3.72 (s, 3H), 2.78 (brt, 2H), 2.56–2.50 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.0, 148.4, 140.7, 128.5, 128.3, 126.2, 121.4, 51.5, 34.3, 33.9. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd

for $C_{12}H_{14}O_2Na$: 213.0891; found: 213.0894.

Methyl (*Z*)-5-Phenylpent-2-enoate [(*Z*)-**6b**]

Colorless oil; IR (neat) 2950, 1720, 1646, 1455, 1438, 1407, 1175 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.31–7.27 (m, 2H), 7.23–7.17 (m, 3H), 6.25 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.79 (dt, *J* = 11.5, 1.7 Hz, 1H), 3.70 (s, 3H), 3.02–2.96 (m, 2H), 2.77 (brt, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.7, 149.4, 141.1, 128.5, 128.4, 126.0, 119.8, 51.1, 35.0, 30.5. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{14}O_2Na$: 213.0891; found: 213.0880.

Methyl (*E*)-Dec-2-enoate [(*E*)-**6c**]

Colorless oil; IR (neat) 2928, 2856, 1728, 1658, 1436, 1271, 1198, 1171 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.98 (dt, *J* = 15.6, 7.0 Hz, 1H), 5.82 (dt, *J* = 15.6, 1.6 Hz, 1H), 3.73 (s, 3H), 2.20 (brqd, 2H), 1.50–1.40 (m, 2H), 1.35–1.21 (m, 8H), 0.88 (brt, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.2, 149.8, 120.8, 51.4, 32.2, 31.8, 29.11, 29.07, 28.0, 22.6, 14.1.

Methyl (*Z*)-Dec-2-enoate [(*Z*)-**6c**]

Colorless oil; IR (neat) 2926, 2856, 1726, 1645, 1438, 1407, 1197, 1173 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.24 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.77 (dt, *J* = 11.5, 1.7 Hz, 1H), 3.71 (s, 3H), 2.65 (qd, *J* = 7.5, 1.7 Hz, 2H), 1.48–1.39 (m, 2H), 1.36–1.21 (m, 8H), 0.88 (brt, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.9, 151.1, 119.1, 51.0, 31.8, 29.3, 29.1, 29.05, 29.04, 22.7, 14.1.

Methyl (*E*)-3-Cyclohexylacrylate [(*E*)-**6d**]

Colorless oil; IR (neat) 2927, 2853, 1726, 1655, 1436, 1275, 1227, 1196, 1170, 1139 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.93 (dd, *J* = 15.8, 6.8 Hz, 1H), 5.77 (dd, *J* = 15.8, 1.4 Hz, 1H), 3.73 (s, 3H), 2.18–2.08 (m, 1H), 1.80–1.72 (m, 4H), 1.71–1.64 (m, 1H), 1.36–1.08 (m, 5H). ^{13}C NMR (125 MHz,

$CDCl_3$) δ = 167.6, 154.7, 118.4, 51.4, 40.4, 31.7, 25.9, 25.7.

Methyl (*Z*)-3-Cyclohexylacrylate [(*Z*)-**6d**]

Colorless oil; IR (neat) 2926, 2852, 1725, 1646, 1437, 1409, 1223, 1194, 1175, 1135 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.05 (brt, 1H), 5.67 (d, *J* = 11.5 Hz, 1H), 3.71 (s, 3H), 3.36–3.25 (m, 1H), 1.77–1.63 (m, 5H), 1.41–1.27 (m, 2H), 1.24–1.02 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.8, 156.1, 117.1, 51.0, 37.3, 32.3, 25.9, 25.5.

Methyl (2*E*,4*E*)-Octa-2,4-dienoate [(*E*)-**6e**]

Colorless oil; IR (neat) 2959, 2932, 2872, 1719, 1645, 1617, 1435, 1266, 1143 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.28 (dd, *J* = 15.4, 10.0 Hz, 1H), 6.22–6.09 (m, 2H), 5.79 (d, *J* = 15.4 Hz, 1H), 3.74 (s, 3H), 2.15 (brq, 2H), 1.46 (sext, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.7, 145.4, 144.7, 128.5, 118.7, 51.4, 35.0, 21.9, 13.7.

Methyl (2*Z*,4*E*)-Octa-2,4-dienoate [(*Z*)-**6e**]

Colorless oil; IR (neat) 2960, 2932, 2873, 1718, 1639, 1603, 1438, 1413, 1175 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.40–7.32 (m, 1H), 6.56 (t, *J* = 11.3 Hz, 1H), 6.12–6.04 (m, 1H), 5.57 (d, *J* = 11.3 Hz, 1H), 3.73 (s, 3H), 2.19 (brq, 2H), 1.47 (sext, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.0, 145.8, 145.7, 127.0, 115.0, 51.1 35.0, 22.0, 13.8.

3. NMR spectra