Ti-direct, powerful, stereoselective aldol-type additions of esters and thioesters to carbonyl compounds: application to the synthesis and evaluation of lactone analogs of jasmone perfumes†

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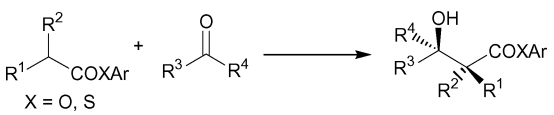
An efficient $TiCl_4$–Et_3N or Bu_3N-promoted aldol-type addition of phenyl and thiophenyl esters or thioaryl esters with aldehydes and ketones was performed (total 46 examples). The present method is advantageous from atom-economical and cost-effective viewpoints; good to excellent yields, moderate to good *syn*-selectivity, substrate variations, reagent availability, and simple procedures. Utilizing the present reaction as the key step, an efficient short synthesis of three lactone [2(5*H*)-furanone] analogs of jasmine perfumes was performed. Among them, the lactone analog of *cis*-jasmone had a unique perfume property (tabac).

Introduction

The aldol-type addition of simple esters with aldehydes and ketones (carbonyl acceptor) has attained an important position in organic syntheses due to its broad utility, that is, a straightforward method to access useful β-hydroxy esters.[1] In general, this reaction is categorized into two types: (i) the direct method of metal enolates generated by strong basic reagents [*e.g.*, LDA and MHMDS (M = Li, Na, K) (metal exchanged enolates are also employable)] to react with the carbonyl acceptor, and (ii) the indirect method of ketene silyl acetals derived from carboxylic esters to react with the carbonyl acceptor promoted by Lewis acids or other catalysts (the Mukaiyama protocol).



Direct aldol-type addition of simple esters with carbonyl acceptors using Lewis acids combined with tertiary amines possesses several advantages because of its simple and atom-economical procedure, high regio- and stereoselectivity, and tolerance to basic labile functionalities. Due to the lower enolization ability of esters ($pK_a \sim 25$) than that of ketones or aldehydes ($pK_a \sim 19$–21), however, there have been only three successful methods to this objective; the use of diazabromoborane (Corey's group),[2] dicyclohexyliodoborane (Brown's group),[3] and boron triflate (Masamune and Abiko's group).[4] From the recently recognized standpoint of process chemistry, readily available, atom-economical, and cost-effective synthetic reagents are increasingly required for the production of fine chemicals. Consistent with our continued studies on Ti-Claisen condensation[5] and relevant Ti-direct aldol-type additions,[6] we report herein the full details of direct, powerful, and stereoselective aldol-type additions of esters and thioesters to aldehydes and ketones promoted by a $TiCl_4$-amine reagent.[7] This paper also describes an application for the short and efficient synthesis of three lactone analogs for dihydrojasmone (known), *cis*- and *trans*-jasmone (novel), with an evaluation of their perfume property.

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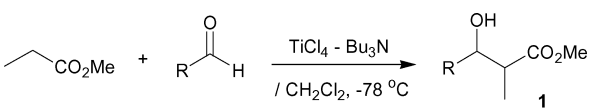
Results and discussion

The salient features of these Ti-mediated reactions are as follows. (i) High reaction velocities and yields. (ii) Higher atom-economy and lower cost than the indirect methods using enol silyl ethers and ketene silyl acetals. (iii) Use of readily available and low toxic metal reagents (*e.g.*, $TiCl_4$, $ZrCl_4$), and use of practical amines (Et_3N, Bu_3N) and solvents (toluene, CH_2Cl_2). (iv) Toleration against basic labile functionalities. (v) Enhanced reactivity using catalytic TMSCl in rare cases.

(A) Basic investigation of Ti-direct aldol-type addition of methyl propanoate to aldehydes

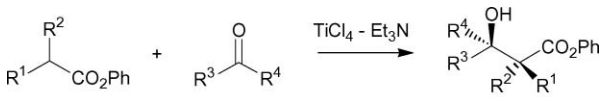
The initial attempt was guided by the reaction between methyl propanoate ($CH_3CH_2CO_2CH_3$) and PhCHO or *t*-BuCHO utilizing a $TiCl_4$–Bu_3N reagent (Scheme 1). The desired β-hydroxy methyl esters **1a**, **1b** were obtained in 75% and 82% yield, respectively. This result is in clear contrast to the method using a $TiCl_2(OTf)_2$–Et_3N reagent, which resists the aldol-type addition and promotes a competitive Ti-Claisen condensation of



1a: R = Ph : 75% (*syn* : *anti* = 65 : 35)
1b: = *t*-Bu : 82% (*syn* : *anti* = 81 : 19)
= *i*-Pr : trace

Scheme 1 Ti-direct aldol-type addition of methyl propanoate to aldehydes.

Table 1 Ti-direct aldol-type addition of phenyl esters **2** to aldehydes and ketones



2 3

Entry	R^1	R^2	R^3	R^4	Product	Yield (%)	*Syn–anti*[b]
1	Me	H	Ph	H	**3a**	80	82 : 18
2[c]					**3a**	75	85 : 15
3	Me	H	*n*-Pr	H	**3b**	84	84 : 16
4[c]					**3b**	76	84 : 16
5	Me	H	i-Pr	H	**3c**	79	89 : 11
6	Me	H	Ph	Et	**3d**	83	64 : 36
7	Me	H	Et	Et	**3e**	77	—
8	Me	H	Ph	CH_2Cl	**3f**	86[d]	68 : 32
9	Bu	H	Ph	H	**3g**	76	84 : 16
10	Bu	H	Ph	Et	**3h**	87	65 : 35
11	Me	Me	Ph	H	**3i**	87	—
12	Me	Me	*n*-Pr	H	**3j**	80	—
13	Me	Me	i-Pr	H	**3k**	80	—
14	Me	Me	Ph	Et	**3l**	81	—
15	Me	Me	Et	Et	**3m**	73	—
16	Me	Me	Ph	CH_2Cl	**3n**	79	—

[a] Carried out in CH_2Cl_2 at −78 °C (entries 1–10) and at 0–5 °C (entries 11–16). Molar ratio **2**–ketone or aldehyde–$TiCl_4$–Et_3N = 1 : 1.2 : 1.2 : 1.4 (entries 1–10) and **2**–ketone or aldehyde–$TiCl_4$–Et_3N = 1 : 1.2 : 1.5 : 2.0 (entries 11–16). [b] Determined by ^1H NMR of the crude product. [c] Use of Bu_3N instead of Et_3N. [d] Yield based on its TMS ether.

$CH_3CH_2CO_2CH_3$, supported by careful cross-over experiments.[5a] Unfortunately, the carbonyl acceptor was limited to aldehydes lacking α-protons, that is, an undesirable side self-aldol addition predominated between two aldehydes such as i-PrCHO, which has α-protons.

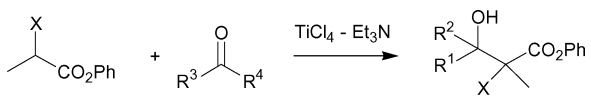
To overcome the problem, we planned to use slightly acidic phenyl esters **2**, because of the higher acidity of phenyl esters than that of alkyl esters.[8] Phenyl esters are readily prepared by several methods and are easily hydrolyzed under milder conditions compared with alkyl esters.[9]

(B) Ti-direct aldol-type addition of phenyl ester to aldehydes and ketones

The aldol-type reaction of phenyl esters **2** with various aldehydes or ketones utilizing $TiCl_4$–Et_3N was examined. Table 1 lists the successful results. The salient features are as follows. (i) Because of the specific character of titanium enolate,[10] the present method is powerful enough to conduct the addition not only to aldehydes but also to less reactive ketones, giving the desired β-hydroxy esters **3**. (ii) Et_3N is somewhat superior to Bu_3N with regard to yield (entries 1–4) in contrast to the Ti-crossed aldol additions[6b] between two different ketones.[11] (iii) Moderate to good *syn*-selectivity was obtained. (iv) This method is applicable to the reaction of less reactive phenyl 2-methylpropanoate under practical temperatures (0–5 °C) (entries 11–16).

Encouraged by this result, we next investigated the aldol-type addition of readily available phenyl 2-chloro and 2-mesyloxypropanoates (**4**; CH_3XCHCO_2Ph, X = Cl, OMs) with aldehydes or ketones. Table 2 lists the successful results. α-Halogenated esters are labile under basic conditions and generally undergo further Darzens-type reactions to form α,β-epoxyesters.[12]

Table 2 Ti-direct aldol-type addition of 2-chloro and 2-mesyloxypropanoates to aldehydes and ketones[a]

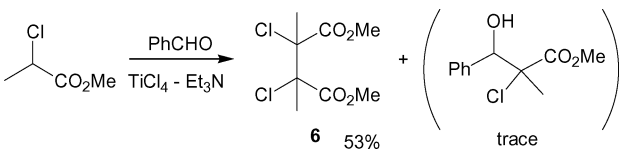


4 X = Cl, OMs 5

Entry	X	R^1	R^2	Product	Yield (%)	Dr[b,c]
1	Cl	Ph	H	**5a**	88	(70 : 30)
2	Cl	i-Pr	H	**5b**	86	(74 : 26)
3	Cl	Et	Et	**5c**	69	—
4	Cl	Ph	Et	**5d**	75	(74 : 26)
5	OMs	Ph	H	**5e**	89	(89 : 11)
6	OMs	Et	Et	**5f**	60	—

[a] Carried out in CH_2Cl_2 at 0–5 °C (entries 1–4) and at −78 °C (entries 5, 6). Molar ratio **4**–ketone or aldehyde–$TiCl_4$–Et_3N = 1 : 1.2 : 1.2 : 1.4. [b] Determined by ^1H NMR of the crude product. [c] *Syn/anti* was not assigned.

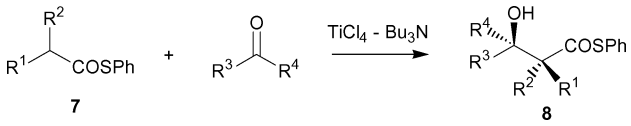
Note that the reaction using $CH_3ClCHCO_2CH_3$ instead of the corresponding phenyl esters **4** resulted in oxidative self-coupling addition at the α-carbon to give dimeric product **6** (Scheme 2), as described by the Kise, Matsumura, and Periasamy groups.[13] Accordingly, from the synthetic view, especially for aldol chemistry, the use of phenyl esters has an advantage over that of methyl esters.



6 53% trace

Scheme 2 Ti-promoted oxidative coupling of methyl 2-chloropropanoate.

Table 3 Ti-direct aldol-type addition of phenylthio esters **7** to aldehydes and ketones[a]



Entry	R^1	R^2	R^3	R^4	Product	Yield (%)	*Syn–anti*[b]
1	Me	H	Ph	H	**8a**	99	86 : 14
2[c]					**8a**	94	86 : 14
3	Me	H	*n*-Pr	H	**8b**	98	82 : 18
4	Me	H	i-Pr	H	**8c**	96	81 : 19
5	Me	H	CH_2CH_2Ph	H	**8d**	99	83 : 17
6	Me	H	Et	Et	**8e**	77	—
6	Me	H	Ph	Et	**8f**	98	77 : 23
7	Bu	H	Ph	H	**8g**	98	77 : 23
8	Bu	H	Et	Et	**8h**	78	—
9	Me	Me	Ph	H	**8i**	80	—
10	Me	Me	*n*-Pr	H	**8j**	76	—
11	Me	Cl	Ph	H	**8k**	97	(70 : 30)[d]
12	Me	Cl	*n*-Pr	H	**8l**	86	(80 : 20)[d]

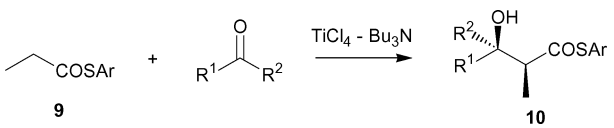
[a] Carried out in CH_2Cl_2 at −78 °C (entries 1–8) and at 0–5 °C (entries 9–12). Molar ratio **7**–aldehyde (ketone)–$TiCl_4$–Bu_3N = 1 : 1.2 (1.5) : 1.2 : 1.4. [b] Determined by ^1H NMR of the crude product. [c] Use of Et_3N instead of Bu_3N. [d] *Syn/anti* was not assigned.

(C) Ti-direct aldol-type addition of phenylthio esters to aldehydes and ketones

The use of phenylthio esters **7** instead of phenyl esters **2** has a notable advantage, because of inherently feasible enolate formation.[14] Table 3 lists the successful results. As anticipated, Ti-enolates of **7** were smoothly generated because of the higher acidity of the α-proton of **7** than that of **2**. The salient features are as follows. (i) With the exception of only a few cases, these reactions proceeded smoothly in excellent yields to afford the desired β-hydroxyl thioesters **8**. (ii) In contrast to the case using phenyl esters **2**, Bu_3N was slightly superior to Et_3N with regard to yield (entries 1, 2). (iii) α,α-Disubstituted phenylthio esters successfully underwent the reaction at 0–5 °C (entries 9–12).

The substituent effect was investigated to improve the yield and stereoselectivity. Table 4 lists the results. Among the aryl thioesters screened, 4-nitrophenyl propanethioate **9** produced better results than phenylthio ester **8a** with PhCHO regarding the *syn*-selectivity (entry 7). The use of *n*-PrCHO, i-PrCHO, and PhCOEt as electrophiles, however, did not notably improve the results (entries 9–12).

Table 4 Ti-direct aldol-type addition of arylthio esters **9** to aldehydes and ketones using $TiCl_4$–Bu_3N[a]



Entry	Ar	R^1	R^2	Product	Yield (%)	*Syn–anti*[b]
1	Ph	Ph	H	**8a**	99	86 : 14
2	(4-OMe)Ph			**10a**	95	80 : 20
3	(4-*t*-Bu)Ph			**10b**	99	82 : 18
4	(2-Cl)Ph			**10c**	92	90 : 10
5	(3-Cl)Ph			**10d**	95	86 : 14
6	(4-Cl)Ph			**10e**	96	86 : 14
7	(4-NO_2)Ph			**10f**	99	94 : 6
8		*n*-Pr	H	**10g**	97	74 : 26
9		i-Pr	H	**10h**	92	67 : 33
10		Ph	Et	**10i**	90	79 : 21

[a] Carried out in CH_2Cl_2 at −78 °C. Molar ratio **9**–aldehyde (ketone)–$TiCl_4$–Bu_3N = 1 : 1.2 (1.5) : 1.2 : 1.4. [b] Determined by ^1H NMR of the crude product.

(D) Synthesis of lactone [2(5*H*)-furanone] analogs for three jasmone perfumes

The present Ti-direct aldol-type addition was successfully applied to the synthesis of three lactone [2(5*H*)-furanone] analogs **11**–**13** of jasmone, which is a typical jasmine perfume (Fig. 1). Lactone analog **12** of *cis*-jasmone is a particularly promising candidate for the synthetic isoster. The Givordan group reported the synthesis of lactone analog **11** of dihydrojasmone utilizing the Reformatsky reaction as the key step.[15] This method, however, is difficult to apply for the synthesis of **12** bearing a double bond in R. Our interest in the practical short synthesis of useful natural perfumes such as *cis*-jasmone and (*R*)-muscone,[5h] (*Z*)-civetone,[5d,f] (*R*)-mintlactone and (*R*)-menthofuran,[6c] utilizing Ti-mediated

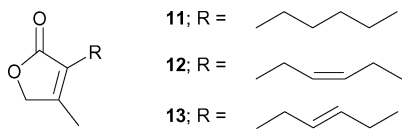
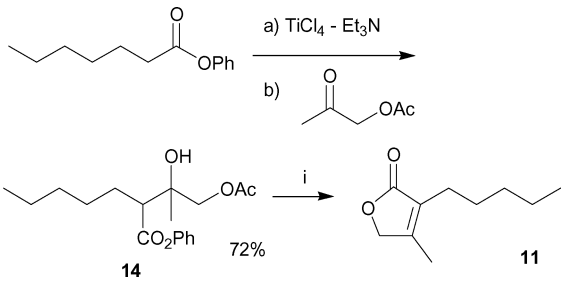


Fig. 1 Three lactone analogs **11–13** of jasmone perfume.

C–C bond forming reactions led us to investigate the general synthesis for lactone analogs **11–13**.

The synthesis of dihydrojasmone lactone analog **11** is shown in Scheme 3. Ti-direct aldol-type addition of phenyl heptanoate with commercially available 1-acetoxy-2-propanone proceeded smoothly to give aldol adduct **14** in 72% yield. The final step was performed through a convenient one-pot deprotection and intramolecular cyclization with dehydration to give **11** in 70%



Scheme 3 Synthesis of dihydrojasmone lactone analog **11**. *Reagents and conditions*: (i) 1.0 M aq KOH, MeOH–THF = 2 : 1, then 1.0 M HCl, 20–25 °C (70%).

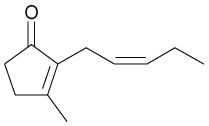
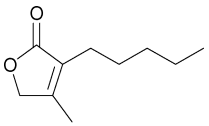
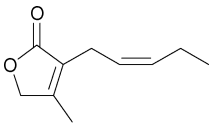
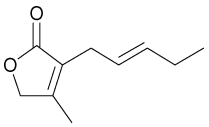
yield. The total yield was increased compared with the reported method[15] utilizing the Reformatsky reaction (34–40% → 50%).

Scheme 4 shows the synthesis of **12** and **13**. Readily available *cis*- and *trans*-2-pentenols (Aoba alcohol analog) **15** and **16** were converted to mesylates **17** and **18**, respectively, using either a conventional method (CH_3SO_2Cl–Et_3N) or an alternative safe and practical sulfonylation for allylic alcohols (CH_3SO_2Cl–Et_3N–Me_3N·HCl).[16] Alkylation using dimethyl malonate with **17** and **18** gave **19** and **20**, which were subjected to hydrolysis and decarboxylation to give acids **21** and **22**, respectively. Acids **21** and **22** were converted to phenyl esters **23** and **24**, by conventional esterification.[17] The key direct Ti-aldol-type addition of **23** and **24** with $AcOCH_2COCH_3$ gave adducts **25** (83%) and **26** (70%), respectively. In a similar one-pot procedure, novel *cis*- and *trans*-lactone analogs **12** (67%) and **13** (65%) was successfully synthesized.

The perfume properties of the lactone analogs **11**, **12**, and **13** were evaluated by the Takasago International Corporation. The results are listed in Table 5. Note that the perfume of **12** showed a unique property for men's fragrance (tabac).

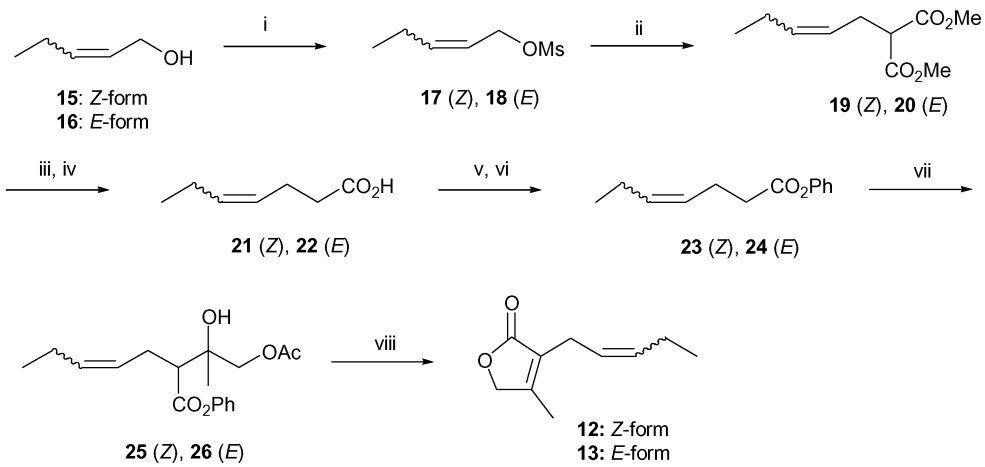
In conclusion, we achieved a simple and efficient Ti-direct aldol-type addition of phenyl and thiophenyl esters with aldehydes and ketones. Application of the present method for synthesizing three lactone analogs **11**, **12**, and **13** was performed. Evaluation of these analogs revealed that *cis*-jasmone analog **12** has a notable perfume property. The present method will provide a new avenue for the aldol-type reaction using esters to obtain a variety of β-hydroxy esters and lactones [2(5*H*)-furanones].

Table 5 Results of odour evaluations of the synthetic compounds

Compounds	Odour description
 ***cis*-jasmone**	Floral, green, jasmine, spicy, fruity
 **11**	Floral, green, fruity, fatty, lactonic
 **12**	Floral, green, tuberose, fruity, tabac, lactonic
 **13**	Floral, green, fruity, jasmine, lactonic

Experimental

Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and were uncorrected. NMR spectra were recorded on a JEOL DELTA 300 spectrometer, operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (=0) for ^{1}H



Scheme 4 Synthesis of *cis*- and *trans*-jasmone lactone analogs **12** and **13**. *Reagents and conditions*: (i) MsCl, Et_3N, Et_2O, 0–5 °C or MsCl, Et_3N–cat. Me_3N·HCl, toluene, 0–5 °C. (ii) Dimethyl malonate, NaH, DMF, 20–25 °C. (iii) 5 M KOH aq, MeOH–THF = 2 : 1, reflux. (iv) Heat at *ca.* 150 °C. (v) $SOCl_2$, cat. DMF, hexane, reflux. (vi) PhOH, Et_3N, MeCN, 0–5 °C. (vii) $TiCl_4$, Et_3N, CH_2Cl_2, then $AcOCH_2COCH_3$, −78 °C. (viii) 1.0 M aq KOH, MeOH–THF = 2 : 1, then 1.0 M aq HCl, 20–25 °C.

NMR. For ^{13}C NMR, chemical shifts were reported on a scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer.

Data of known and new compounds **1a**,[18] **1b**,[19] **3a**,[20] **3b**,[20] **3c**,[20] **3h**, **3i**,[22] **3k**, **3m**, **5d**, **8a**,[23] **8b**,[24] **8c**,[23] **8d**,[23] **8f**, **8h**, **8i**,[25] **8l**, **10a**, **10b**, **10c**, **10d**, **10e**, **10f**, **10g**, **10h**, **10i**, **11**,[15] **20**,[25] **22**, **24**, **19**, **21**[25] and **23** are described in the electronic supporting information.†

Ti-direct aldol-type addition of methyl propanoate to PhCHO or *t*-BuCHO (Scheme 1)

Bu_3N (475 μL, 2.0 mmol) and $TiCl_4$ (165 μL, 1.5 mmol) were successively added to a stirred solution of methyl propanoate (88 mg, 1.0 mmol) and an aldehyde (PhCHO; 127 mg or *t*-BuCHO; 103 mg, 1.2 mmol) in CH_2Cl_2 (2.0 mL) at 0–5 °C under an Ar atmosphere, followed by being stirred at the same temp. for 2 h. The mixture was poured into ice water, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography to give the desired β-hydroxy ester **1a** (146 mg, 75%, *syn–anti* = 65 : 35) or **1b** (143 mg, 82%, *syn–anti* = 81 : 19).

General procedure of Ti-direct aldol-type addition of α-monoalkylated phenyl esters to aldehydes or ketones (Table 1, entries 1–10)

$TiCl_4$ (132 μL, 1.2 mmol) and Et_3N (142 mg, 1.4 mmol) in CH_2Cl_2 (0.5 mL) were successively added to a stirred solution of a phenyl ester (1.0 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C under an Ar atmosphere. After stirring at the same temp. for 30 min, an aldehyde or a ketone (1.2 mmol) was added to the mixture, followed by being stirred at the same temp. for 2 h. The mixture was poured into ice water (reverse quench), which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography to give desired β-hydroxy phenyl esters **3a–3h**.

Phenyl 2-methyl-3-hydroxy-3-phenyl-pentanoate (3d). *syn*-Isomer; colorless crystals; mp 77–78 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (3H, t, J = 7.2 Hz), 1.11 (3H, d, J = 7.2 Hz), 1.93 (1H, dq, J = 7.2 Hz, J_{gem} = 13.8 Hz), 2.07 (1H, dq, J = 7.2 Hz, J_{gem} = 13.8 Hz), 3.12 (1H, q, J = 7.2 Hz), 3.46 (1H, br s), 7.05–7.13 (2H, m), 7.22–7.30 (2H, m), 7.32–7.48 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.86, 12.83, 34.46, 49.12, 77.42, 121.40, 125.57, 126.20, 126.60, 128.07, 129.51, 142.26, 150.20, 176.09; IR (KBr) 3555, 1728, 1493, 1190, 1167, 1136, 1111, 1074, 750, 700 cm^{-1}.

anti-Isomer; colorless crystals; mp 74–75 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (3H, t, J = 7.2 Hz), 1.51 (3H, d, J = 7.2 Hz), 1.73 (1H, dq, J = 7.2 Hz, J_{gem} = 13.8 Hz), 2.02 (1H, dq, J = 7.2 Hz, J_{gem} = 13.8 Hz), 3.32 (1H, q, J = 7.2 Hz), 3.74 (1H, br s), 6.42–6.53 (2H, m), 7.07–7.16 (1H, m), 7.18–7.32 (3H, m), 7.33–7.42 (2H, m), 7.45–7.53 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.53, 11.99, 31.59, 47.92, 77.19, 121.17, 125.72, 125.99, 126.89, 128.09, 129.28, 145.00, 149.85, 175.74; IR (KBr) 3532, 2973, 1725, 1352, 1192, 1154, 1098, 959, 764, 704 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09, found: C, 75.8; H, 6.8%.

Phenyl 3-ethyl-3-hydroxy-2-methylpentanoate (3e). Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.6 Hz), 0.96 (3H, t, J = 7.6 Hz), 1.35 (3H, d, J = 7.2 Hz), 1.45–1.58 (1H, m), 1.59–1.75 (3H, m), 2.56 (1H br s), 2.85 (1H, q, J = 7.2 Hz), 7.04–7.12 (2H, m), 7.21–7.29 (1H, m), 7.34–7.44 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.59, 7.78, 11.91, 26.63, 29.75, 45.20, 74.99, 121.42, 126.10, 129.49, 150.25, 175.80; IR (neat) 3532, 2973, 1736, 1493, 1458, 1194, 1165 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53, found: C, 70.9; H, 8.2%.

Phenyl 4-chloro-2-methyl-3-phenyl-3-trimethylsiloxybutanoate (3f). Because the aldol adduct between phenyl 2-chloropropanoate and phenacyl chloride was relatively unstable, the yield and diastereoselectivity were based on its TMS-ether. This TMS-ether was obtained by nearly neutral trimethylsilylation using BSA–$PyH^+ \cdot OTf^-$.[21] BSA (494 μL, 2.0 mmol) was added to a stirred solution of the obtained crude aldol adduct (334 mg) and $PyH^+ \cdot OTf^-$ (69 mg, 0.3 mmol) in THF (2.0 mL) at 20–25 °C followed by being stirred at the same temp. for 12 h. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography to give the desired product **3f** (323 mg, 86%, *syn–anti* = 68 : 32).

syn- and *anti*-Mixture; colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.18 (*anti*, 9H × 1/3, s), 0.22 (*syn*, 9H × 2/3, s), 1.13 (*syn*, 3H × 2/3, d, J = 7.2 Hz), 1.18 (*anti*, 3H × 1/3, d, J = 7.2 Hz), 3.17 (*syn*, 1H × 2/3, q, J = 7.2 Hz), 3.30 (*anti*, 1H × 1/3, q, J = 7.2 Hz), 4.10 (*syn*, 1H × 2/3, d, J_{gem} = 12.0 Hz), 4.13 (*anti*, 1H × 1/3, d, J_{gem} = 12.0 Hz), 4.26 (*syn*, 1H × 2/3, d, J_{gem} = 12.0 Hz), 4.35 (*anti*, 1H × 1/3, d, J_{gem} = 12.0 Hz), 6.80–6.96 (2H, m), 7.09–7.53 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.33, 12.37, 12.87, 49.92, 50.56, 50.61, 50.92, 81.19, 81.40, 121.34, 125.70, 125.80, 126.16, 126.66, 127.44, 127.65, 127.86, 127.96, 129.28, 129.37, 141.32, 142.15, 150.43, 150.46, 171.77, 171.86; IR (neat) 2957, 1759, 1493, 1252, 1192, 1161, 1084, 845 cm^{-1}. Anal. Calcd for $C_{17}H_{17}ClO_3$: C, 67.00; H, 5.62, found: C, 66.7; H, 5.5%.

Phenyl 2-butyl-3-hydroxy-3-phenylpropanoate (3g). *syn*-Isomer; yellow crystals; mp 44–46 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 6.9 Hz), 1.22–1.53 (4H, m), 1.86–1.93 (2H, m), 2.49 (1H, br s), 2.98 (1H, q, J = 6.9 Hz), 4.98 (1H, d, J = 6.9 Hz), 6.69–6.77 (2H, m), 7.13–7.47 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.92, 22.60, 27.99, 29.77, 53.56, 74.93, 121.40, 125.89, 126.58, 128.13, 128.51, 129.33, 141.61, 150.27, 173.14; IR (KBr) 3426, 2955, 1748, 1493, 1356, 1190, 1144, 1042, 760, 702 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43, found: C, 76.5; H, 7.2%.

General procedure of Ti-direct aldol-type addition of α,α-dimethylated phenyl esters to aldehydes or ketones (Table 1, entries 11–16)

$TiCl_4$ (165 μL, 1.5 mmol) was added to a stirred solution of α,α-disubstituted phenyl esters (1.0 mmol) and Et_3N (202 mg, 2.0 mmol) in CH_2Cl_2 (1.5 mL) at 0–5 °C under an Ar atmosphere. After stirring at the same temp. for 30 min, an aldehyde or ketone (1.2 mmol) was added to the mixture, followed by being stirred at 0–5 °C for 2 h. The mixture was poured into ice water, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by

SiO_2-column chromatography to give desired β-hydroxy phenyl esters **3i–3n**.

Phenyl 3-hydroxy-2,2-dimethylhexanoate (3j). Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, t, $J = 7.2$ Hz), 1.31–1.73 (4H, m), 1.33 (3H, s), 1.35 (3H, s), 3.79 (1H, dd, $J = 2.4$, 10.0 Hz), 7.02–7.08 (2H, m), 7.20–7.27 (1H, m), 7.34–7.42 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.01, 19.82, 20.34, 22.01, 33.96, 47.59, 76.37, 121.46, 125.85, 129.43, 150.71, 176.32; IR (neat) 3526, 2961, 1744, 1595, 1493, 1196, 1109 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53, found: C, 70.9; H, 8.4%.

Phenyl 3-hydroxy-2,2-dimethyl-3-phenylpentanoate (3l). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (3H, t, $J = 7.2$ Hz), 1.31 (3H, s), 1.35 (3H, s), 1.87 (1H, dq, $J = 7.2$ Hz, $J_{gem} = 14.1$ Hz), 2.40 (1H, dq, $J = 7.2$ Hz, $J_{gem} = 14.1$ Hz), 4.06 (1H, br s), 6.90–6.98 (2H, m), 7.18–7.42 (6H, m), 7.44–7.53 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.01, 21.80, 21.99, 28.24, 51.00, 80.00, 121.38, 126.08, 126.87, 127.40, 128.02, 129.43, 140.20, 150.37, 177.58; IR (neat) 3501, 2980, 2940, 1719, 1593, 1493, 1186, 1115, 706 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43, found: C, 76.4; H, 7.4%.

Phenyl 4-chloro-3-hydroxy-2,2-dimethyl-3-phenylbutanoate (3n). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (3H, s), 1.37 (3H, s), 3.56 (1H, br s), 4.36 (1H, d, $J_{gem} = 11.7$ Hz), 4.51 (1H, d, $J_{gem} = 11.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.38, 22.71, 50.54, 51.13, 79.29, 121.34, 125.99, 127.16, 127.81, 127.88, 129.41, 139.76, 150.58, 175.09; IR (neat) 3549, 2984, 1736, 1593, 1493, 1190, 1121, 706 cm^{-1}. Anal. Calcd for $C_{18}H_{19}ClO_3$: C, 67.82; H, 6.01, found: C, 67.6; H, 5.8%.

General procedure of Ti-direct aldol-type addition of α-chloro or α-mesyloxy phenyl esters to aldehydes or ketones (Table 2)

$TiCl_4$ (132 μL, 1.2 mmol) and Et_3N (142 mg, 1.4 mmol) in CH_2Cl_2 (0.5 mL) were successively added to a stirred solution of α-chloro or α-mesyloxy phenyl esters (1.0 mmol) in CH_2Cl_2 (1.5 mL) at 0–5 °C (entries 1–4) or −78 °C (entries 5 and 6) under an Ar atmosphere. After stirring at the same temp. for 30 min, an aldehyde or ketone (1.2 mmol) was added to the mixture, followed by being stirred at the same temp. for 2 h. The mixture was poured into ice water, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography to give desired β-hydroxy phenyl esters **5a–5f**.

Phenyl 2-chloro-3-hydroxy-2-methyl-3-phenylpropanoate (5a). Diastereomixture; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (3H × 3/10, s), 1.78 (3H × 7/10, s), 2.86 (1H, br s), 5.36 (1H × 7/10, s), 5.37 (1H × 3/10, s), 7.04–7.14 (2H, m), 7.22–7.30 (1H, m), 7.34–7.55 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.68, 22.50, 65.81, 69.49, 73.56, 77.75, 121.06, 121.11, 126.31, 126.37, 127.88, 127.94, 128.17, 128.30, 128.63, 128.82, 129.55, 136.96, 137.29, 150.56, 169.51; IR (neat) 3517, 3065, 3036, 1759, 1593, 1493, 1233, 1192, 910, 739 cm^{-1}. Anal. Calcd for $C_{16}H_{15}ClO_3$: C, 66.10; H, 5.20, found: C, 65.9; H, 4.9%.

Phenyl 2-chloro-3-hydroxy-2,4-dimethylpentanoate (5b). Major product; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, d, $J = 6.9$ Hz), 1.10 (3H, d, $J = 6.9$ Hz), 1.93 (3H, s), 2.01–2.15 (1H, m), 2.22 (1H, br s), 3.96 (1H, d, $J = 4.8$ Hz), 7.07–7.16 (2H, m), 7.22–7.30 (1H, m), 7.35–7.46 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.74, 21.66, 24.68, 30.82, 71.82, 79.96, 121.04, 126.33, 129.56, 150.44, 169.78; IR (neat) 3532, 2965, 1752, 1593, 1493, 1238, 1194, 750 cm^{-1}.

Minor product; colorless crystals; mp 40–41 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H d, $J = 6.9$ Hz), 1.10 (3H, d, $J = 6.9$ Hz), 1.87 (3H, s), 1.89–2.01 (1H, m), 2.43 (1H br s), 4.02 (1H, d, $J = 5.9$ Hz), 7.09–7.16 (2H, m), 7.23–7.31 (1H, m), 7.37–7.46 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.62, 20.88, 21.97, 30.76, 74.13, 79.43, 120.98, 126.33, 129.56, 150.44, 169.32; IR (KBr) 3541, 2971, 1745, 1487, 1250, 1194, 1161, 1098, 1046, 752 cm^{-1}. Anal. Calcd for $C_{13}H_{17}ClO_3$: C, 60.82; H, 6.67, found: C, 60.6; H, 6.64%.

Phenyl 2-chloro-3-ethyl-3-hydroxy-2-methylpentanoate (5c). Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, t, $J = 7.6$ Hz), 1.04 (3H, t, $J = 7.6$ Hz), 1.78–1.98 (4H, m), 1.95 (3H, s), 2.97 (1H, br s), 7.09–7.14 (2H, m), 7.24–7.30 (1H, m), 7.37–7.45 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.76, 8.95, 24.76, 27.92, 28.16, 76.75, 77.73, 121.11, 126.45, 129.60, 150.41, 170.62; IR (neat) 3542, 2975, 2946, 1738, 1593, 1491, 1458, 1231, 1090, 756, 727, 689 cm^{-1}. Anal. Calcd for $C_{14}H_{19}ClO_3$: C, 62.10; H, 7.07, found: C, 61.9; H, 6.8%.

Phenyl 3-hydroxy-2-mesyloxy-2-methyl-3-phenylpropanoate (5e). Diastereomixture; brown crystals; mp 78–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (3H × 1/9, s), 1.90 (3H × 8/9, s), 2.92 (1H br s), 3.13 (3H × 1/9, s), 3.19 (3H × 8/9, s), 5.13 (1H × 1/9, s), 5.16 (1H × 8/9, s), 6.92–6.99 (2H, m), 7.20–7.28 (1H, m), 7.32–7.47 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.76, 40.80, 78.22, 91.57, 121.17, 126.43, 127.77, 128.46, 129.09, 129.51, 136.03, 150.08, 168.46; IR (KBr) 3555, 1752, 1348, 1265, 1181, 1113, 1094, 1055, 918, 725 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_6S$: C, 58.27; H, 5.18, found: C, 58.1; H, 5.2%.

Phenyl 3-ethyl-3-hydroxy-2-mesyloxy-2-methylpentanoate (5f). Colorless oil; ^{1}N NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, t, $J = 7.6$ Hz), 1.02 (3H, t, $J = 7.6$ Hz), 1.70–1.87 (4H, m), 2.04 (3H, s), 2.27 (1H br s), 3.15 (3H, s), 7.09–7.18 (2H, m), 7.23–7.31 (1H, m), 7.36–7.45 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.34, 19.85, 26.86, 26.98, 40.57, 77.75, 93.35, 121.27, 126.47, 129.60, 150.27, 169.26; IR (neat) 3528, 2976, 1757, 1348, 1250, 1192, 1086, 976, 937, 914 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_6S$: C, 54.53; H, 6.71, found: C, 54.6; H, 6.8%.

Dimethyl 2,3-dichloro-2,3-dimethylbutanedioate (6). To a stirred solution of methyl 2-chloropropanoate (123 mg, 1.0 mmol) in CH_2Cl_2 (1.0 mL), $TiCl_4$ (139 μL, 1.2 mmol), Bu_3N (259 mg, 1.4 mmol) in CH_2Cl_2 (0.5 mL), and benzaldehyde (122 μL, 1.2 mmol) were successively added at 0–5 °C under an Ar atmosphere and the mixture was stirred at the same temp. for 2 h. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography to give the desired product **6** (129 mg, 53%).

Diastereomixture; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (3H × 1/2, s), 2.07 (3H × 1/2, s), 3.81 (3H × 1/2, s), 3.83 (3H × 1/2, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.11, 26.61, 53.49,

53.57, 73.31, 73.44, 169.03, 169.12; IR (neat) 3005, 2957, 1744, 1449, 1383, 1258, 1094, 976 cm^{-1}.

General procedure of Ti-direct aldol-type addition of phenylthio esters to aldehydes or ketones (Table 3)

$TiCl_4$ (132 μL, 1.2 mmol) and Bu_3N (259 mg, 1.4 mmol) in CH_2Cl_2 (0.5 mL) were successively added to a stirred solution of phenylthio esters (1.0 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C (entries 1–8) or 0–5 °C (entries 9–12) under an Ar atmosphere. After stirring at the same temp. for 30 min, an aldehyde (1.2 mmol) or ketone (1.5 mmol) was added to the mixture, followed by being stirred at the same temp. for 2 h. The mixture was poured into ice water, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography to give desired β-hydroxy phenylthio esters **8a–8l**.

***S*-Phenyl 3-ethyl-3-hydroxy-2-methylpentanethioate (8e).** Colorless crystals; mp 38–40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (3H, t, J = 7.6 Hz), 0.93 (3H, t, J = 7.6 Hz), 1.31 (3H, d, J = 6.9 Hz), 1.36–1.51 (1H, m), 1.54–1.71 (3H, m), 2.88 (1H, q, J = 6.9 Hz), 2.90 (1H, br s), 7.36–7.48 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.59, 7.90, 12.64, 26.46, 29.71, 53.00, 75.99, 127.21, 129.24, 129.62, 134.34, 204.35; IR (KBr) 3532, 2969, 1680, 1445, 1329, 1132, 953, 901, 747, 687 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99, found: C, 66.8; H, 8.05%.

***S*-Phenyl 2-butyl-3-hydroxy-3-phenylpropanethioate (8g).** *syn*- and *anti*-Mixture; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 6.9 Hz), 1.19–1.47 (4H, m), 1.59–1.93 (2H, m), 2.72 (*syn*, 1H × 7/9, br s), 2.81 (*anti*, 1H × 2/9, bt d, J = 5.2 Hz), 2.96 (*syn*, 1H × 7/9, ddd, J = 3.8, 5.9, 10.0 Hz), 3.00–3.07 (*anti*, 1H × 2/9, m), 4.83 (*anti*, 1H × 2/9, dd, J = 5.2, 6.9 Hz), 4.94 (*syn*, 1H × 7/9, d, J = 5.9 Hz), 7.19–7.42 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.73, 13.79, 22.49, 22.66, 27.29, 29.10, 29.58, 29.87, 60.71, 61.32, 74.44, 75.72, 126.31, 127.27, 127.46, 127.73, 127.98, 128.26, 128.44, 129.09, 129.43, 134.25, 134.29, 141.27, 141.86, 201.00, 201.54; IR (neat) 3453, 2957, 2930, 2861, 1698, 1024, 924, 747, 702, 691 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_2S$: C, 72.57; H, 7.05, found: C, 72.3; H, 7.01%.

***S*-Phenyl 3-hydroxy-2,2-dimethylhexanethioate (8j).** Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.2 Hz), 1.25–1.69 (4H, m), 1.32 (3H, s), 1.34 (3H, s), 2.07 (1H, br s), 3.65–3.77 (1H, m), 7.34–7.46 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.96, 19.81, 20.97, 22.45, 33.92, 54.84, 76.89, 127.46, 129.16, 129.35, 134.92, 205.59; IR (neat) 3472, 2961, 1690, 1466, 1441, 959, 928, 747, 689 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99, found: C, 66.5; H, 7.7%.

***S*-Phenyl 2-chloro-3-hydroxy-2-methyl-3-phenylpropanethioate (8k).** Diastereomixture; colorless crystals; mp 81–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (3H × 7/10, s), 1.85 (3H × 3/10), 2.93 (1H br s), 5.12 (1H × 3/10, s), 5.17 (1H × 7/10, s), 7.25–7.47 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.49, 25.99, 77.96, 78.34, 78.95, 80.88, 127.44, 127.75, 127.88, 128.09, 128.19, 128.51, 128.65, 129.26, 129.72, 134.59, 134.65, 137.44, 137.54, 200.07, 200.37; IR (KBr) 3484, 1676, 1441, 1038, 1024, 970, 951, 747, 702, 687 cm^{-1}. Anal. Calcd for $C_{16}H_{15}ClO_2S$: C, 62.64; H, 4.93, found: C, 62.4; H, 4.8%.

General procedure of Ti-direct aldol-type addition of arylthio esters with aldehydes or ketones (Table 4)

$TiCl_4$ (132 mL, 1.2 mmol) and Bu_3N (259 mg, 1.4 mmol) in CH_2Cl_2 (0.5 mL) were successively added to a stirred solution of arylthio esters (1.0 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C under an Ar atmosphere. After stirring at the same temp. for 30 min, an aldehyde (1.2 mmol) or ketone (1.5 mmol) was added to the mixture, followed by being stirred at the same temp. for 2 h. The mixture was poured into ice water, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by Si_2O-column chromatography to give desired β-hydroxy arylthio esters **10a–10i**.

Phenyl 4-acetoxy-3-hydroxy-3-methylheptanoate (14). $TiCl_4$ (396 μL, 3.6 mmol) and Et_3N (425 mg, 4.2 mmol) in CH_2Cl_2 (1.0 mL) were successively added to a stirred solution of phenyl heptanoate (619 mg, 3.0 mmol) in CH_2Cl_2 (10.0 mL) at −78 °C under an Ar atmosphere. After stirring at the same temp. for 30 min, a solution of acetoxy-2-propanone (418 mg, 3.6 mmol) in CH_2Cl_2 (1.0 mL) was added to the mixture, followed by being stirred at the same temp. for 2 h. The mixture was poured into ice water (reverse quench), which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. Obtained crude product was purified by SiO_2-column chromatography (hexane–AcOEt = 10 : 1) to give the desired product **14** (701 mg, 72%).

Diastereomixture; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.97 (3H, m), 1.25–1.54 (6H, m), 1.33 (3H × 7/10, s), 1.37 (3H × 3/10, s), 1.57–1.79 (1H, m), 1.80–1.96 (1H, m), 2.10 (3H × 7/10, s), 2.12 (3H × 3/10, s), 2.38 (1H, br s), 2.82 (1H × 7/10, dd, J = 3.4, 11.7 Hz), 2.83 (1H × 3/10, dd, J = 3.4, 11.7 Hz), 4.09 (1H × 7/10, d, J = 11.4 Hz), 4.10 (1H × 3/10, d, J = 11.4 Hz), 4.13 (1H × 7/10, d, J = 11.4 Hz), 4.20 (1H × 3/10, d, J = 11.4 Hz), 7.05–7.12 (2H, m), 7.21–7.29 (1H, m), 7.35–7.43 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.96, 20.84, 21.49, 22.43, 23.25, 27.00, 27.59, 27.67, 31.57, 51.66, 52.62, 68.95, 70.00, 72.39, 72.64, 121.44, 121.48, 126.08, 126.12, 129.49, 150.27, 150.33, 170.81, 173.68; IR (neat) 3495, 2957, 1748, 1493, 1373, 1233, 1196, 1163, 1113, 1044 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13, found: C, 66.8; H, 8.0%.

Phenyl 4-acetoxy-3-hydroxy-3-methyl-2-[(*Z*)-pent-2-enyl]butanoate (25). Following the procedure of aldol-type addition of phenyl esters to aldehydes or ketones (Table 1, entries 1–10), the reaction of (*Z*)-phenyl hept-4-enoate (**23**; 613 mg, 3.0 mmol) with acetoxy-2-propanone (418 mg, 3.6 mmol) using $TiCl_4$ (396 μL, 3.6 mmol) and Et_3N (425 mg, 4.2 mmol) gave the desired product **25** (798 mg, 83%).

Diastereomixture; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.6 Hz), 1.35 (3H × 7/10, s), 1.40 (3H × 3/10, s), 2.03–2.15 (2H, m), 2.09 (3H × 7/10, s), 2.12 (3H × 3/10, s), 2.34–2.52 (1H, m), 2.63–2.77 (1H, m), 2.82 (1H, br s), 2.87 (1H × 7/10, dd, J = 4.1, 11.0 Hz), 2.89 (1H × 3/10, dd, J = 4.1, 11.4 Hz), 4.09 (1H × 7/10, d, J_{gem} = 11.4 Hz), 4.11 (1H × 3/10, d, J_{gem} = 11.4 Hz), 4.15 (1H × 7/10, d, J_{gem} = 11.4 Hz), 4.20 (1H × 3/10, d, J_{gem} =

11.4 Hz), 5.34–5.47 (1H, m), 5.50–5.62 (1H, m), 7.01–7.10 (2H, m), 7.19–7.28 (1H, m), 7.33–7.42 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.11, 20.55, 20.84, 21.74, 23.27, 24.98, 25.47, 51.51, 52.39, 68.89, 70.04, 72.26, 72.41, 121.51, 124.59, 124.82, 126.08, 129.43, 134.69, 134.78, 150.31, 150.35, 170.73, 173.37; IR (neat) 3491, 2967, 1748, 1493, 1373, 1236, 1194, 1163, 1119, 1046 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55, found: C, 67.2; H, 7.5%.

4-Methyl-3-[(*Z*)-pent-2-enyl]-2(5*H*)-furanone (12). 1.0 M KOH aqueous solution (2.5 mL) was added to a stirred solution of phenyl 4-acetoxy-3-hydroxy-3-methyl-2-[(*Z*)-pent-2-enyl]butanoate (**25**; 320 mg, 1.0 mmol) in MeOH–THF (7.8 mL, v/v = 2/1) at 20–25 °C, and the mixture was stirred at the same temp. for 10 h. 1.0 M HCl aqueous solution (3.0 mL) was added to the mixture, followed by being stirred at the same temp. for 2 h. The mixture was concentrated under reduced pressure, which was extracted twice with Et_2O. The obtained organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane–AcOEt = 8 : 1) to give the desired product **12** (109 mg, 67%).

Pale yellow oil; ^{1}H NMR (300 MHz,$CDCl_3$) δ 1.00 (3H, t, J = 7.6 Hz), 2.04 (3H, s), 2.16 (2H, dq, J = 6.9, 7.6 Hz), 3.03 (2H, d, J = 7.2 Hz), 4.61 (2H, d, J = 1.0 Hz), 5.28–5.39 (1H, m), 5.41–5.52 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.24, 14.03, 20.54, 21.53, 72.43, 123.58, 126.08, 133.41, 156.54, 174.71; IR (neat) 2961, 1740, 1437, 1341, 1231, 1155, 1028, 970 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49; O, 19.25, found: C, 72.1; H, 8.3%.

Phenyl 4-acetoxy-3-hydroxy-3-methyl-2-[(*E*)-pent-2-enyl]-butanoate (26). Following the procedure for the preparation of **24**, the reaction of (*E*)-phenyl hept-4-enoate (**24**; 613 mg, 3.0 mmol) with acetoxy-2-acetone (418 mg, 3.6 mmol) using $TiCl_4$ (396 μL, 3.6 mmol) and Et_3N (425 mg, 4.2 mmol) gave the desired product **26** (677 mg, 70%).

Diastereomixture; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.2 Hz), 1.34 (3H × 7/10, s), 1.38 (3H × 3/10, s), 2.05 (2H, quint., J = 7.2 Hz), 2.10 (3H × 7/10, s) 2.13 (3H × 3/10, s), 2.37–2.61 (2H, m), 2.88 (1H × 7/10, dd, J = 4.5, 11.01 Hz), 2.90 (1H × 3/10, dd, J = 4.8, 9.6 Hz), 3.11 (1H, br s), 4.08 (1H × 7/10, d, J_{gem} = 11.4 Hz), 4.10 (1H × 3/10, d, J_{gem} = 11.4 Hz), 4.14 (1H × 7/10, d, J_{gem} = 11.4 Hz), 4.19 (1H × 3/10, J_{gem} = 11.4 Hz), 5.39–5.53 (1H, m), 5.65 (1H, dt, J = 6.2, 15.5 Hz), 6.99–7.11 (2H, m), 7.19–7.28 (1H, m), 7.32–7.43 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.57, 20.84, 21.74, 23.14, 25.53, 30.32, 30.86, 51.74, 52.62, 68.95, 70.02, 72.20, 72.35, 121.44, 121.48, 124.80, 125.07, 126.07, 129.43, 135.32, 135.45, 150.29, 170.73, 173.20; IR (neat) 3497, 2965, 1734, 1493, 1373, 1238, 1194, 1163, 1047, 970 cm^{-1}.

4-Methyl-3-[(*E*)-pent-2-enyl]-2(5*H*)-furanone (13). Following the procedure for the preparation of **12**, the reaction of phenyl 4-acetoxy-3-hydroxy-3-methyl-2-[(*E*)-pent-2-enyl]butanoate (**26**; 320 mg, 1.0 mmol) gave 4-methyl-3-[(*E*)-pent-2-enyl]-2(5*H*)-furanone (**13**; 108 mg, 65%).

Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.2 Hz), 1.94–2.06 (2H, m), 2.03 (3H, s), 2.97 (2H, d, J = 6.2 Hz), 4.62 (2H, d, J = 1.0 Hz), 5.41 (1H, dtt, J = 1.4, 6.2, 15.1 Hz), 5.55 (1H, dtt, J = 1.4, 6.2, 15.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.14, 13.46, 25.26, 26.39, 72.37, 123.60, 125.68, 133.96, 157.04, 174.69; IR (neat) 3418, 2973, 1740, 1676, 1443, 1389, 1343, 1188, 1101, 1038 cm^{-1}.

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