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Study for diastereoselective aldol reaction in flow: synthesis of (*E*)-(*S*)-3-hydroxy-7-tritylthio-4-heptenoic acid, a key component of cyclodepsipeptide HDAC inhibitors

Takayuki Doi *, Hiroyuki Otaka, Koji Umeda, Masahito Yoshida

Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aza-Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

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This paper is dedicated to Honorary Professor Jiro Tsuji on the occasion of his Tetrahedron Prize

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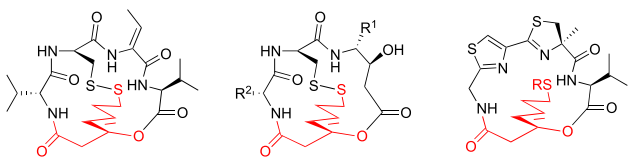
ABSTRACT

Flow synthesis of (*E*)-(*S*)-3-hydroxy-7-tritylthio-4-heptenoic acid (**5**), a key component of cyclodepsipeptide histone deacetylase inhibitors was achieved. An efficient flow system for the synthesis of α, β-unsaturated ester **8** was established using a flow reactor column packed with polymer-supported 1,4-diazabicyclo[2.2.2]octane and a fast mixing accessible flow reactor (Comet X-01). Enal **9** was efficiently prepared by a partial reduction of the α, β-unsaturated ester **8** using diisobutylaluminium hydride in the flow system, and the continuous-flow diastereoselective aldol reaction was performed at low temperature, giving a good yield and diastereoselectivity of the desired aldol **10**.

1. Introduction

The use of flow synthesis in the current organic synthesis has been investigated extensively in recent decades because of the advantages flow synthesis offers over the conventional batch synthesis. These advantages include the ability to strictly control the reaction temperature through an efficient heat transfer and the ability to mix reactants quickly using miniaturized flow devices.[1] Flow systems can also allow a synthesis to be performed reproducibly at different scales with a specified reaction time, and this can be achieved using a continuous-flow system without the need to further optimize the reaction conditions though it is necessary in batch systems. The potential for using flow systems to perform reactions that are difficult to regulate in the batch systems has been investigated by several research groups, i.e., metalation of haloarenes,[2] photochemical reactions,[3] and the multi-step processes such as natural product synthesis have also been attempted utilizing the flow reactor.[4] We have focused on developing a flow system for reproducibly synthesizing (*E*)-(*S*)-3-hydroxy-7-tritylthio-4-heptenoic acid (**5**), which is a key component of the natural product histone deacetylase (HDAC) inhibitors, FK228 (**1**),[5] spiruchostatins (**2**),[6] burkholdacs (**3**)[7] and largazole (**4**)[8] (Fig. 1). HDAC inhibitors have been found to be novel anticancer drug candidates, because the inhibition of HDACs causes apoptosis to be induced in cancer cells.[9] The naturally occurring cyclodepsipeptide FK228 (**1**) has recently been approved for treating human cutaneous T-cell lymphoma. Synthetic analogues of **1** containing the β-



FK228 (**1**)

Spiruchostatin A (**2a**: R^1=*i*Pr, R^2=Me)
Spiruchostatin B (**2b**: R^1=*s*-Bu, R^2=Me)
Spiruchostatin C (**2c**: R^1=*i*Bu, R^2=Me)
Spiruchostatin D (**2d**: R^1=R^2=*i*Pr)
Burkholdac A (**3a**: R^1=*i*Pr, R^2=Me)
Burkholdac B (**3b**: R^1=*s*-Bu, R^2=Me)

Largazole (**4**)
R = $Me(CH_2)_6CO$

Fig. 1. Naturally occurring cyclodepsipeptide HDAC inhibitors containing a 3-hydroxy-7-thio-4-heptenoic acid moiety.

* Corresponding author. E-mail address: doi_taka@mail.pharm.tohoku.ac.jp (T. Doi).

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hydroxy acid derivative **5** described above could therefore also be attractive for discovering anticancer agents. The synthesis of a variety of cyclodepsipeptide analogues described above would require an efficient method for supplying sufficient quantities of **5**.

The synthesis of the desired β-hydroxy acid derivative **5** has previously been reported by several groups,[10] and we have also established the solution-phase synthesis of **5** from acrolein (**6**) and trityl thiol as shown in Fig. 2.[11] The method involves (1) 1,4-addition of thiol, (2) Horner–Wadsworth–Emmons (HWE) reaction, (3) reduction of α, β-unsaturated ester, (4) oxidation to the enal, (5) diastereoselective aldol reaction and (6) removal of the chiral auxiliary.

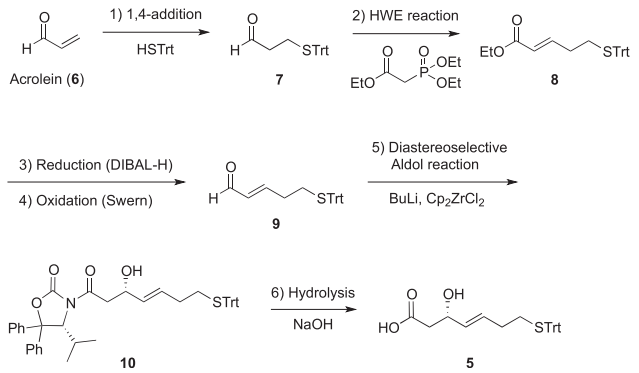


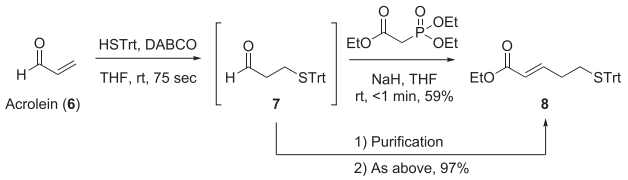
Fig. 2. Current synthesis of (*E*)-(*S*)-3-hydroxy-7-tritylthio-heptenoic acid (**5**).

We believed that our synthetic scheme could be improved to produce **5** more reproducibly by developing it for use in one-pot synthesis or the flow synthesis methods. For instance, we recently succeeded in improving the synthesis of enal **9** by a partial reduction of α, β-unsaturated esters **8** using commercially available diisobutylaluminium hydride (DIBAL-H) in flow, providing some hundreds of milligrams of enal **9**.[12] The desired β-hydroxy acid derivative **5** can be produced by basic hydrolysis of **10**, followed by removal of the resulting chiral auxiliary by simple filtration. Therefore, we subsequently aimed to establish an integrated flow system for synthesizing the α, β-unsaturated ester **8** and the aldol **10** as a step toward reliably producing sufficient quantities of **5**.[1d,e] Herein, we describe the development of the method for synthesizing the β-hydroxy acid derivative **5** using an integrated flow system involving a polymer-supported reagent-packed column reactor and a fast mixing accessible flow reactor Comet X-01.[13]

2. Results and discussion

2.1. Continuous synthesis of α, β-unsaturated ester by sequential 1,4-addition–HWE reaction

Before attempting to develop a flow synthesis, we initially investigated a one-pot method for synthesizing α, β-unsaturated ester **8** through the 1,4-addition of trityl thiol to acrolein (**6**), followed by Horner–Wadsworth–Emmons reaction in a conventional batch system (Scheme 1). The 1,4-addition of thiol to **6** smoothly occurred within 75 sec in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO),[14] and the HWE reaction was subsequently performed on the resulting aldehyde **7** using deprotonated triethyl phosphonoacetate. However, the yield of the α, β-unsaturated ester **8** was only moderate (59%), whereas HWE reaction of the isolated aldehyde **7** smoothly proceeded to provide the corresponding ester **8** in 97% yield. These observations led us to conclude that the presence of DABCO in the reaction mixture could inhibit the HWE reaction and decreased the yield of the corresponding α, β-unsaturated ester **8**.



Scheme 1. Initial attempt of the one-pot synthesis of **8** in a batch system.

We therefore planned to synthesize **8** using a flow reactor, described in Fig. 3. The first step in the planned synthesis was the 1,4-addition of thiol to acrolein (**6**), performing by passing through a column containing polymer-supported DABCO.[15] The resulting aldehyde **7** could be combined with deprotonated phosphonoacetate in the flow reactor (Comet X-01-T) to afford the desired α, β-unsaturated ester **8**. The solutions of the substrates and phosphonoacetate were to be independently introduced to the flow reactor using syringe pumps, and the resulting reaction mixture was to be poured directly into aqueous HCl to terminate the reaction.

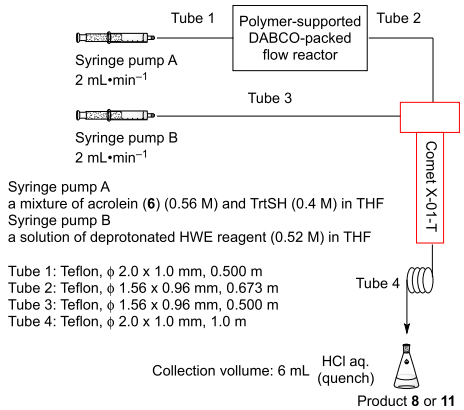


Fig. 3. Flow system for the synthesis of α, β-unsaturated esters **8** and **11**.

The synthesis of α, β-unsaturated esters **8** using the above designed flow system was investigated, and the results are shown in Table 1. A mixture of trityl thiol (1 equiv, 0.4 M) and acrolein (**6**) (1.4 equiv, 0.56 M) in THF was pumped at a flow rate of 2 mL min^{-1} through the polymer-supported DABCO using a syringe pump, and 1,4-addition of the thiol to **6** was complete within 75 sec to give the aldehyde **7**. The resulting **7** generated in situ was subsequently introduced into the reactor and mixed with a solution of the deprotonated HWE reagent (1.3 equiv, 0.52 M) in THF, supplied by another syringe pump, at room temperature to afford α, β-unsaturated ester **8** in the short residence time (12 sec) (69%, entry 1). With the good reaction conditions in hand, we further scoped the HWE reagents in the continuous-flow synthesis of the esters **11**. Reactions using α-bromo and α-chloro-substituted HWE reagents in flow occurred smoothly to provide the corresponding α, β-unsaturated esters **11a** and **11b**, respectively, in moderate yields (entries 2 and 3), whereas the yield of the fluoro-substituted **11c**[16] was low because the high viscosity of the deprotonated α-fluoro HWE reagent led to mixing occurring slowly and the reaction not reaching completion (entry 4). Moderate yields of the α-alkyl-substituted **11d** and **11e** were found using the reaction conditions described above. This is because that nucleophilic addition to the

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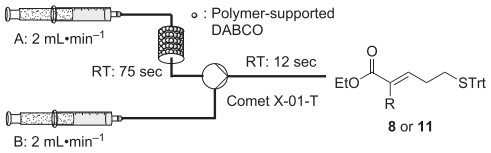
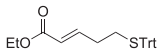
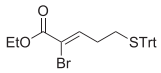
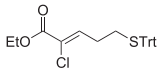
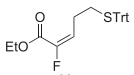
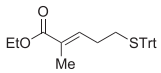
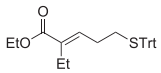
Table 1
Synthesis of the α, β-unsaturated esters **8** and **11** using the integrated flow system



Entry	Product	Yield[a]	Ratio of E/Z[b]
1	 **8**	69%	>95:5
2	 **11a**	72%	19:81
3	 **11b**	74%	19:81
4	 **11c**	36%	91:9
5	 **11d**	55%	87:13
6	 **11e**	54%	56:44

Conditions: A: a mixture of 0.4 M TrtSH and 0.56 M acrolein (**6**) in THF. B: a 0.52 M solution of the deprotonated HWE reagent in THF.
[a] Isolated yield.
[b] The ratio was determined by crude ^{1}H NMR.

aldehyde **7** would occur slowly because of steric hindrance of the α-alkyl-substituted HWE reagents. It would therefore be necessary to adjust the residence time for the HWE reaction in the flow synthesis of α-substituted α, β-unsaturated esters **11**.

2.2. A partial reduction of the α, β-unsaturated ester 8 to the enal 9 in flow

We next performed a partial reduction of **8** to give the enal **9** once the flow synthesis of α, β-unsaturated ester **8** had been achieved.[12] The flow system we used to achieve this partial reduction is shown in Fig. 4.[17] The flow reactor (Comet X-01-SS) and tubing, made of stainless steel, were used because of its good thermal conductivity. Solutions of the substrate and DIBAL-H in toluene were prepared and independently introduced into the reactor at the desired flow rate using rotary piston pumps. The reaction mixture was subsequently quenched with EtOH in a T-shaped mixer connected to the outlet of the flow reactor. The reaction was performed at −97 °C, which was achieved by immersing the system in a liquid N_2/MeOH cooling bath.

As we have previously reported,[12] α, β-unsaturated ester **8** was partially reduced by DIBAL-H in the flow system in a ratio of 89:11, and the desired enal **9** was afforded in 82% isolated yield (Table 2, entry 1). On the other hand, the yield of **9** was moderate using conventional methods such as slow addition of DIBAL-H and two-step procedure (entries 2 and 3). In addition, 264 mg of the desired enal **9** per minute was afforded in a single step; therefore we concluded that the method we developed is an efficient and redox-economical[18] for synthesizing a desired enal from the corresponding α, β-unsaturated ester **8** in the gram scale.

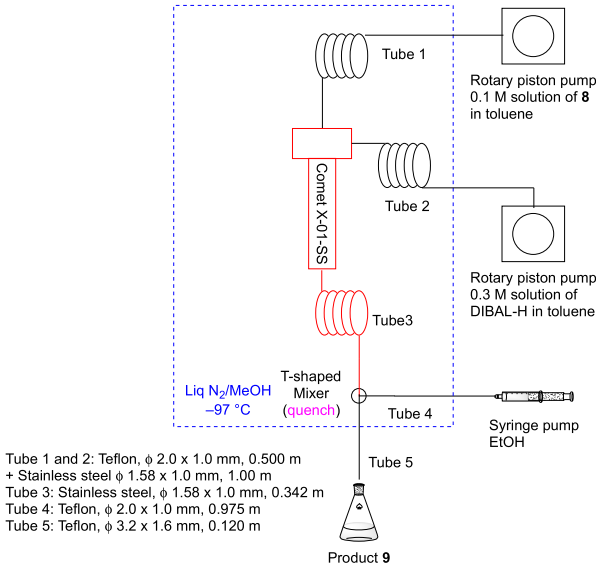
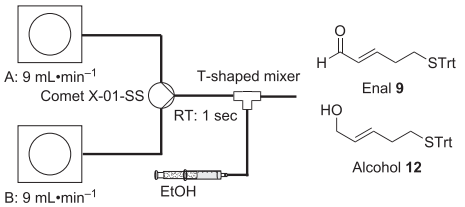


Fig. 4. Flow system for a partial DIBAL-H reduction of α, β-unsaturated ester **8**.

Table 2
Selective synthesis of enal **9** by a partial reduction of **8** in flow



Entry	Conditions	Conv. (%)[a]	Ratio of **9**:**12**[a]	Yield of **9** (%)[b]
1	Flow (−97 °C, 18 nL/min, RT=1 sec)	>95	89:11	82
2	Batch slow addition (1.1 equiv)	75	45:55	33
3	Batch 2 steps 1) DIBAL-H, 2) Swern.	—	—	67[c]

Conditions: A: a 0.1 M solution of α, β-unsaturated ester **8** in toluene. B: a 0.3 M solution of DIBAL-H in toluene.
[a] The ratio of **9**:**12** was determined by crude ^{1}H NMR.
[b] Isolated yield.
[c] see Ref. 10a.

2.3. A continuous-flow diastereoselctive aldol reaction with the enal 9

The continuous-flow diastereoselective aldol reaction of an acetate derivative with **9** was next attempted.[19] The key to achieving the diastereoselective aldol reaction was rapidly generating the enolate in the flow reactor and achieving high conversion efficiency and a high stereoselectivity. We have previously reported the synthesis of β-hydroxy acid derivative **10** through a diastereoselective aldol reaction using the Zr-enolate of acetyloxazolidinone **13**,[20] but it is conceivable that it could be difficult to prepare the Zr-enolate for the large-scale synthesis of **10** because of the poor solubility of the zirconium salt in organic solvents. On the other hand, we have previously reported the aldol reaction using Li-enolate of **13** afforded good yield and moderate diastereoselectivity in the aldol reaction (89%, *S*:*R*=77:23).[11a] Therefore, we investigated the diastereoselective aldol reaction in flow using soluble and

commercially available LiHMDS. The details of the flow system used for the aldol reaction are shown in Fig. 5. A Comet X-01-T (Teflon) flow reactor was used for the enolate formation and a Comet X-01-SS (Stainless steel) was used for the aldol reaction, respectively. Syringe pumps were used to independently deliver the substrate **13**, and LiHMDS dissolved in THF into the first flow reactor at the specified flow rate and at the appropriate temperature. The resulting enolate was directly introduced into the next reactor, in which the aldol reaction was performed by treatment with the enal **9** pumped by another syringe pump. Finally, the resulting reaction mixture was then poured into saturated aqueous NH_4Cl to terminate the reaction, and allow the desired aldol adduct **10** to be afforded.

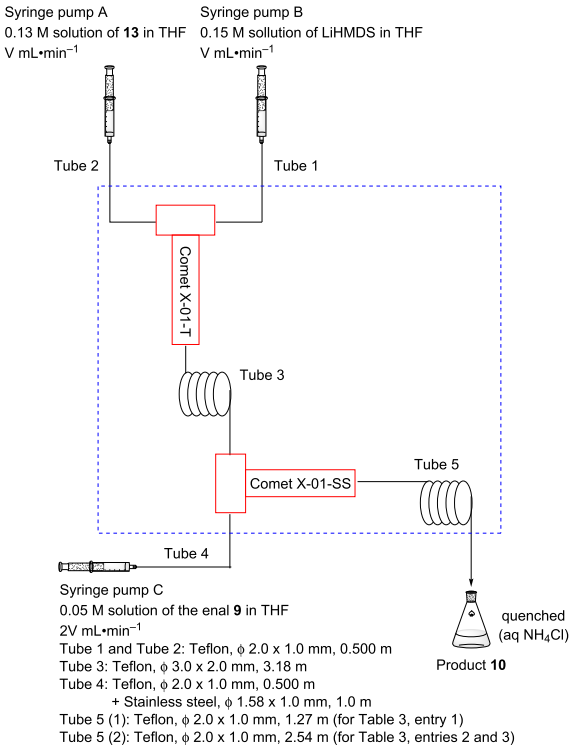
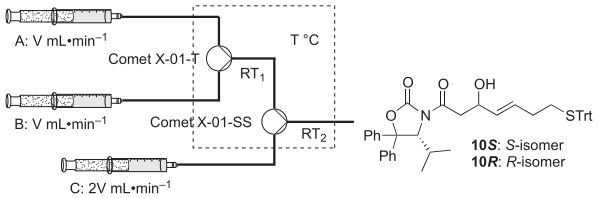


Fig. 5. Flow system for a diastereoselective aldol reaction of **13** with the enal **9**.

We initially investigated the aldol reaction of the enal **9** in the flow system at different temperatures, and the results are summarized in Table 3. The enolate formation and the aldol reaction were performed at −40 °C by immersing the flow reactor into dry ice/acetone cryogenic bath.[21] A 0.13 M solution of acetyloxazolidinone **13** in THF was combined with a 0.15 M solution of LiHMDS in THF in the flow reactor Comet X-01-T, both solutions being delivered at a flow rate of 2 mL min^{-1}. The enolate formation was allowed to proceed for 150 sec, and then the resulting enolate was subsequently introduced into the next reactor Comet X-01-SS and mixed with a 0.05 M solution of the enal **9** in THF, dispensed at 4 mL min^{-1} by a syringe pump, to perform the aldol reaction at the same temperature. Enal **9** was completely consumed within a shorter residence time (7.5 sec), and the desired aldol product **10** was obtained in 85% yield with a moderate diastereoselectivity (**10*S***:**10*R***=78:22, entry 1). We next performed the reaction at a lower temperature to improve a diastereoselectivity in the aldol reaction, and the residence time allowed for the enolate formation and the aldol reaction were extended using a lower flow rate (1 mL min^{-1}). It was found that a diastereomeric ratio was increased to 91:9 when the reaction was performed at −60 °C, but

Table 3
Investigation of diastereoselective aldol reaction with the enal **9** in flow



Entry	Flow rate (V mL·min^{-1})	Residence time (sec)		Temp (°C)	Conv. (%)[a]	Ratio of **10*S***:**10*R***[a]	Yield of **10** (%)
		RT_1	RT_2				
1	2	150	7.5	−40	>95	78:22	85[b]
2	1	300	30	−60	82	91:9	51[b]
3	1	300	30	−78	65	>95:5	33[c]

Conditions: A: a 0.13 M solution of acetyl oxazolidinone **13** in THF. B: a 0.15 M solution of LiHMDS in THF. C: a 0.05 M solution of the enal **9** in THF.
[a] Determined by crude ^1H NMR.
[b] Combined yield of a mixture of *S*- and *R*-isomers.
[c] Isolated yield.

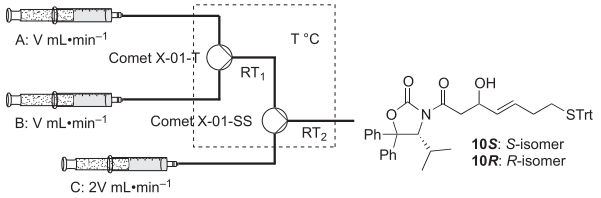
conversion of the enal **9** was decreased to 82%, conceivably because the reaction temperature was slightly lower to allow for the sufficient enolate formation (entry 2). On the other hand, excellent diastereomeric ratio was observed at −78 °C (**10*S***:**10*R***= >95:5), and the desired *S*-isomer was afforded in 33% yield as a sole product (entry 3). Note that this observation is a first example of the aldol reaction being performed using the lithium enolate of non-substituted-acetyl oxazolidinone derivatives and giving **10** with excellent diastereoselectivity. The aldol product **10** obtained using these conditions was easily converted into the desired β-hydroxy acid derivative **5** by hydrolysis under basic condition and by simple purification using a short pad silica gel column chromatography.[11]

As can be seen from the descriptions above, we found that performing the reaction at the lower temperature such as −78 °C was required to improve the diastereoselectivity of the reaction, but a higher conversion was achieved when the reaction was conducted at a higher temperature (up to −40 °C). We therefore expected that a high conversion and good diastereoselectivity could be achieved by performing the enolate formation and the aldol reaction under different conditions; therefore, we redesigned the flow system used for the aldol reaction. In the redesigned system, two flow reactors were immersed in separate cryogenic baths, at −40 °C for the enolate formation and −78 °C for the aldol reaction, and the reagents including **13** and LiHMDS were both dispensed at a flow rate of 1 mL min^{-1}. The enolate formation of **13** proceeded at −40 °C by mixing with LiHMDS in the reactor, and the resulting enolate was immediately introduced into the next flow reactor, in which the aldol reaction with enal **9** was performed at −78 °C. The aldol reaction smoothly proceeded with good conversion as same as the reaction in the batch system, and the desired product **10** was afforded in 73% yield with acceptably high diastereoselectivity (Table 4, entry 1, **10*S***:**10*R***=86:14). We also found that the reaction reached completion with a shorter residence time when a higher flow rate (e.g., 3 mL min^{-1}) was used, affording the desired **9** without decreasing the yield and the diastereoselectivity (entry 2). Therefore, it is conceivable that the flow system we established could be used in the scalable synthesis of **10**, because the system allows the reaction temperature to be controlled, which is difficult to achieve in a large scale batch system.

3. Conclusion

We have developed a flow synthesis method for producing β-hydroxy acid derivative **5**, which is a key component of the natural product HDAC inhibitors, FK228 (**1**), spiruchostatins (**2**),

Table 4
Investigation of diastereoselective aldol reaction of **13** with the enal **9** in flow



Entry	Flow rate (V mL·min^{-1})	Residence time (sec)		Conv. (%)[a]	Ratio of **10*S***:**10*R***[a]	Yield of **10** (%)[b]
		RT_1	RT_2			
1	1	300	30	91	86:14	73
2	3	100	10	91	83:17	76

Conditions: A: a 0.13 M solution of acetyl oxazolidinone **13** in THF.B: a 0.15 M solution of LiHMDS in THF. C: a 0.05 M solution of the enal **9** in THF.
[a] Determined by crude ^{1}H NMR.
[b] Combined yield of a mixture of *S*- and *R*-isomers.

burkholdacs (**3**) and largazole (**4**). An integrated flow system involving 1,4-addition of thiol and HWE reaction was established for synthesizing the α, β-unsaturated ester **8**. In the system, 1,4-addition of trityl thiol to acrolein (**6**) was achieved with a high efficiency using polymer-supported DABCO, and the subsequent HWE reaction smoothly proceeded at ambient temperature to afford the corresponding esters **8** in moderate yield (scalability: 209 mg min^{-1}), not less than the yield by one-pot synthesis in solution-phase. Partial reduction of the resulting α, β-unsaturated ester **8** was achieved in the flow system by strictly controlling the flow rate, the residence time and the reagent concentration. The scalable synthesis of desired enal **9** was also achieved, and it is noteworthy that the flow system we developed efficiently provided some hundreds milligram of enal **9** per minute (scalability: 264 mg min^{-1}). A continuous-flow diastereoselective aldol reaction with the above enal **9** was then attempted, and excellent diastereoselectivity was observed when the reaction was performed at −78 °C. The scalable synthesis of **10** could also be achieved using the flow system when a high flow rate (3 mL min^{-1}) was used with controlling the reaction temperature (scalability: 155 mg min^{-1}). The methods we developed together offer a simple, reproducible and reliable way of synthesizing β-hydroxy acid derivative **5**. We are currently investigating the application of these methods to multi-step processes, such as natural product synthesis, and the results of our investigations will be reported in due course.

4. Experimental section

4.1. General techniques

All commercially available reagents were used as received. Dry THF (Kanto Chemical Co.) was obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. MeOH was distilled from iodine and magnesium turnings. Toluene was distilled from sodium. DMF was purchased from Wako. All reactions in solution-phase were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light, and visualized with anisaldehyde, 10% ethanolic phosphomolybdic acid. Silica gel 60N (Kanto Chemical Co. 100–210 μm) was used for column chromatography. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on a JEOL JNM-AL400 spectrometer. Chemical shifts (δ) are reported in units parts per million (ppm) relative to signal for internal tetramethylsilane (0 ppm for ^{1}H) for solutions in $CDCl_3$. NMR spectral data are reported as follows: chloroform (7.26 ppm for ^{1}H) or chloroform-*d* (77.0 ppm for ^{13}C) when internal standard is not indicated. Multiplicities are reported by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) dd (double doublet), dt (double triplet), ddt (double double triplet), brs (broad singlet), *J* (coupling constants in Herts). Mass spectra and high-resolution mass spectra were measured with JEOL JMS-DX303 (EI), MS-AX500 (FAB), or BRUKER microTOF-II (ESI) instruments. IR spectra were recorded with a Shimadzu FTIR-8400, and data are given in cm^{-1}. Only the strongest and/or structurally important absorptions are reported. Melting points were measured using a Round Science Inc. RFS-10 instrument and are not corrected.

4.2. Synthesis of ethyl (*E*)-5-(triphenylmethylthio)-2-pentenoate (8)[11] by one-pot procedure in the batch system

To a solution of HSTrt (442 mg, 1.60 mmol, 1.0 equiv) and DABCO (246 μL, 2.24 mmol, 1.4 equiv) in THF (3.6 mL, 2.25 mL/mmol) was added acrolein (**6**) (150 μL, 2.24 mmol, 1.4 equiv) at room temperature, and the mixture was stirred at the same temperature for 75 sec. To the reaction mixture was added a solution of deprotonated triethyl phosphonoacetate (580 μL, 2.91 mmol, 1.3 equiv) in THF (3.6 mL, 2.25 mL/mmol) at room temperature. After the aldehyde **6** was completely consumed (<1 min), the reaction mixture was quenched with H_2O, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc=98:2) to give the α, β-unsaturated ester **8** as a white solid (59%, 381 mg, 0.946 mmol). Mp 81–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.19 (m, 15H), 6.75 (dt, 1H, *J*=16.0, 6.8 Hz), 5.69 (d, 1H, *J*=16.0 Hz), 4.15 (q, 2H, *J*=7.6 Hz), 2.28 (t, 2H, *J*=7.2 Hz), 2.18 (dt, 2H, *J*=7.2, 6.8 Hz), 1.26 (t, 3H, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 146.5, 144.6, 129.5, 127.9, 126.6, 122.3, 66.8, 60.2, 31.3, 30.2, 14.2; FTIR (Neat): 3056, 3030, 2980, 1719, 1654, 1594, 1489, 1444, 1367, 1335, 1309, 1270, 1196, 1143, 1035, 743, 701, 622 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}NaOS$ $[M+Na]^+$ 425.1551, found 425.1526.

4.3. HWE reaction of the isolated aldehyde 7 with triethyl phosphonoacetate

To a solution of a suspension of NaH (60% in mineral oil, 16 mg, 0.389 mmol, 1.3 equiv) in THF (0.75 mL, 2.5 mL/mmol) was added triethyl phosphonoacetate (89 μL, 0.449 mmol, 1.5 equiv) at 0 °C under argon, and the mixture was stirred at the same temperature for 30 min. To the reaction mixture was added a solution of aldehyde **6** (99 mg, 0.299 mmol, 1 equiv) in THF (0.75 mL, 2.5 mL/mmol) dropwise at 0 °C. After being stirred at room temperature, the reaction mixture was quenched with H_2O and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc=98:2) to give the α, β-unsaturated ester **8** as a white solid (97%, 117 mg, 0.290 mmol).

4.4. General procedure for the synthesis of α, β-unsaturated ester 8 and 11a–e in flow

The flow system was established with a syringe pumps (HII–10B, Techno applications®), Teflon tube, the flow reactor (Comet X-01-T, Techno applications®), polymer-supported DABCO (2.2 g, 2.3 mmol) packed column flow reactor (20 mm bore×38 mm length). Before use, the flow system was flushed with THF and dried under vacuum. A solution of the trityl thiol (0.4 M) and acrolein (**6**) (0.56 M) in THF was then loaded into a Teflon sample loop (Tube 1), and a solution of deprotonated HWE reagents (0.52 M) in THF was loaded into another Teflon sample loop (Tube 3). Both two solutions were pumped at flow rate of 2 mL min^{-1}, and mixed in the reactor

(Comet X-01-T and Tube 4) at the room temperature. The resulting mixture was quenched by 1 M aqueous HCl, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc=98:2) to give the α, β-unsaturated esters **8** and **11a**–**e**.

*4.4.1. Ethyl (E)-5-(triphenylmethylthio)-2-pentenoate (**8**).* Collection volume: 6 mL; colorless oil 334 mg, 0.83 mmol, 69%, *E*/*Z*=>95:5).

*4.4.2. Ethyl (Z)-2-bromo-5-(triphenylmethylthio)-2-pentenoate (**11a**).* Collection volume: 6 mL; colorless oil (417 mg, 0.866 mmol, 72%, *E*/*Z*=19:81). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.38 (m, 6H), 7.32–7.26 (m, 6H), 7.24–7.18 (m, 3H), 7.14 (t, 1H, *J*=6.8 Hz), 4.25 (q, 2H, *J*=7.2 Hz), 2.40–2.31 (m, 4H), 1.31 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 144.5, 143.6, 129.5, 127.9, 126.7, 117.4, 66.9, 62.4, 31.2, 29.6, 14.1; FTIR (Neat) 3083, 3056, 3030, 2980, 2928, 1727, 1489, 1444, 1254, 1045, 743, 701 cm^{-1}; HRMS (ESI): calcd for $C_{26}H_{25}{}^{79}BrNaO_2S$ $[M+Na]^+$ 503.0656, found 503.0650.

*4.4.3. Ethyl (Z)-2-chloro-5-(triphenylmethylthio)-2-pentenoate (**11b**).* Collection volume: 6 mL; colorless oil (386 mg, 0.883 mmol, 74%, *E*/*Z*=19:81). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.36 (m, 6H), 7.32–7.24 (m, 6H), 7.23–7.16 (m, 3H), 6.91 (t, 1H, *J*=6.8 Hz), 4.23 (q, 2H, *J*=7.0 Hz), 2.40–2.28 (m, 4H), 1.29 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 144.5, 139.7, 129.4, 127.8, 126.6, 125.6, 66.8, 62.1, 29.7, 28.5, 14.0; FTIR (Neat): 3056, 3030, 2981, 2627, 1731, 1489, 1444, 1259, 1049, 743, 701 cm^{-1}; HRMS (ESI): calcd for $C_{26}H_{25}ClNaO_2S$ $[M+Na]^+$ 459.1161, found 459.1157.

*4.4.4. Ethyl (E)-2-fluoro-5-(triphenylmethylthio)-2-pentenoate (**11c**).* Collection volume: 6 mL; colorless oil (175 mg, 0.416 mmol, 36%, *E*/*Z*=91:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (m, 6H), 7.22–7.15 (m, 6H), 7.14–7.06 (m, 3H), 5.67 (dt, 1H, *J*=20.4, 7.4 Hz), 4.15 (q, 2H, *J*=7.2 Hz), 2.48 (ddt, 2H, *J*=7.6, 7.4, 1.6 Hz), 2.17 (t, 2H, *J*=7.6 Hz), 1.21 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6 (d, *J*=35.9 Hz), 147.4 (d, *J*=252.4 Hz), 144.6, 129.4, 127.8, 126.6, 121.3 (d, *J*=19.8 Hz), 66.7, 61.3, 31.3 (d, *J*=2.5 Hz), 24.5 (d, *J*=5.3 Hz), 14.0; FTIR (Neat): 3056, 2981, 1728, 1489, 1444, 1375, 1320, 1241, 743, 701 cm^{-1}; HRMS (ESI): calcd for $C_{26}H_{25}FNaO_2S$ $[M+Na]^+$ 443.1452, found 443.1460.

*4.4.5. Ethyl (E)-2-methyl-5-(triphenylmethylthio)-2-pentenoate (**11d**).* Collection volume: 6 mL; colorless oil (275 mg, 0.66 mmol, 55%, *E*/*Z*=87:13). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.39 (m, 6H), 7.32–7.25 (m, *J*=8.8 Hz, 2H), 7.23–7.18 (m, 3H), 6.57 (dt, 1H, *J*=6.8, 1.0 Hz), 4.16 (q, 2H, *J*=7.0 Hz), 2.31–2.27 (m, 2H), 2.21–2.17 (m, 2H), 1.71 (d, 3H, *J*=1.0 Hz), 1.27 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 144.7, 139.4, 129.5, 129.0, 127.8, 126.6, 66.7, 60.4, 30.7, 27.9, 14.2, 12.4; FTIR (Neat): 3056, 3030, 2979, 2927, 1709, 1489, 1444, 1259, 1108, 743, 701 cm^{-1}. HRMS (ESI): calcd for $C_{27}H_{28}NaO_2S$ $[M+Na]^+$ 439.1708, found 439.1707.

*4.4.6. Ethyl (E)-2-ethyl-5-(triphenylmethylthio)-2-pentenoate (**11e**).* Collection volume: 6 mL; colorless oil (278 mg, 0.645 mmol, 54%, *E*/*Z*=56:44). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.38 (m, 6H), 7.32–7.25 (m, 6H), 7.24–7.17 (m, 3H), 6.52 (t, 1H, *J*=7.2 Hz), 4.16 (q, 2H, *J*=7.0 Hz), 2.30–2.14 (m, 6H), 1.27 (t, 3H, *J*=7.0 Hz), 0.92 (t, 3H, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 144.7, 139.0, 135.2, 129.5, 127.8, 126.6, 66.7, 60.3, 30.9, 27.6, 20.0, 14.2, 13.8; FTIR (Neat): 3057, 2975, 2933, 2873, 1709, 1489, 1444, 1288, 1288, 1244, 743, 701 cm^{-1}; HRMS (ESI): calcd for $C_{28}H_{30}NaO_2S$ $[M+Na]^+$ 453.1864, found 453.1857.

4.5. General procedure for the synthesis of enal 9 in flow

The flow system was established with two rotary piston pumps (Reglo-CPF Digital/ISM 321 and RH0.CKC-LF/FMI013, ISMATEC®), a syringe pump (HII–10B, Techno applications®), stainless steel tube, Teflon tube, the flow reactor (Comet X-01-SS, Techno applications®) and a methanol/liquid N_2 cryogenic bath. Before use, the flow system was flushed with dry toluene. A solution of the substrate in toluene (0.1 M) was then loaded into a stainless steel sample loop (Tube 1), and a solution of DIBAL-H in toluene (0.3 M) was loaded into another stainless steel sample loop (Tube 2). The two sample solutions were pumped at a combined flow rate of 18.0 mL min^{-1}, and mixed in the reactor (Comet and Tube 3) at −97 °C. The output of the reactor was connected with a T-shaped mixer to quench the reaction with EtOH (2 mL min^{-1}). The resulting mixture was collected for 4.5 min, and the collected mixture was diluted with water, and the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc=96:4) to give **9** (82%, 1.19 g, 3.32 mmol) as a white solid.

*4.5.1. (E)-5-(Triphenylmethylthio)-2-pentenal (**9**).*[11] Mp 141–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (d, 1H, *J*=8.0 Hz), 7.47–7.38 (m, 6H), 7.32–7.19 (m, 9H), 6.61 (dt, 1H, *J*=16.0, 6.4 Hz), 6.13 (dd, 1H, *J*=16.0, 8.0 Hz), 2.34–2.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 155.6, 144.5, 133.5, 129.4, 127.9, 126.7, 66.9, 31.6, 29.9; FTIR (Neat) 3056, 3030, 2980, 2929, 1719, 1444, 1269, 1195, 743, 700 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{22}NaOS$ $[M+Na]^+$ 381.1289, found 381.1275.

4.6. Procedure for the synthesis of aldol 10 in flow at −78 °C (Table 3, entry 3)

The flow system was established with two syringe pumps (HII–10B, Techno applications®), Teflon tube, the flow reactor (Comet X-01-T, Techno applications®), stainless steel flow reactor (Comet X-01-SS, Techno applications®) and an acetone/dry-ice bath. Before use, the flow system was flushed with THF and dried under vacuum. A solution of the acetyloxazolidinone **13** in THF (0.13 M) was then loaded into a Teflon sample loop (Tube 1), and a solution of LiHMDS in THF (0.15 M) was loaded into an another Teflon sample loop (Tube 2). Both two solutions were pumped at a combined flow rate of 2 mL min^{-1}, and mixed in the reactor (Comet X-01-T and Tube 3) at −78 °C. The output of the reactor was connected with another reactor (Comet X-01-SS) and Tube 5 to mix the reaction mixture with a solution of the enal **9** in THF (0.05 M, 2 mL min^{-1}, Tube 4). The reaction mixture was collected for 60 sec, and the resulting mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc=91:9) to give **10** as a white solid (22.4 mg, 33%, *S*/*R*=>95:5).

*4.6.1. (E)-(S)-3-Hydroxyl-1-[(R)-4-isopropyl-5,5-diphenyl-2-oxazolidinone-3-yl]-7-trityl-4-thiohepten-1-one (**10S**).*[11] $[\alpha]_D^{19}$ +89.9 (*c* 0.745, $CHCl_3$); mp 61–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.10 (m, 25H), 5.50 (dt, 1H, *J*=15.6, 7.2 Hz), 5.36 (d, 1H, *J*=3.2 Hz), 5.35 (dd, 1H, *J*=15.6, 6.0 Hz), 4.46 (m, 1H), 3.15 (dd, 1H, *J*=16.8, 3.2 Hz), 2.82 (dd, 2H, *J*=16.8, 8.8 Hz), 2.74 (d, 1H, *J*=4.0 Hz),

2.17 (t, 2H, J=7.2 Hz), 2.06–1.90 (m, 2H), 0.876 (d, 3H, J=6.8 Hz), 0.74 (d, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 152.8, 144.8, 142.0, 137.9, 131.6, 130.1, 129.5, 128.9, 128.7, 128.3, 127.9, 127.8, 126.5, 125.8, 125.4, 89.5, 68.5, 66.5, 64.5, 42.1, 31.3, 29.8, 21.7, 16.2; FTIR (Neat): 3518, 3058, 3029, 2965, 1784, 1700, 1492, 1449, 1366, 1319, 1212, 1175, 1035, 1001, 983, 752, 701 cm^{-1}; HRMS (ESI): calcd for $C_{44}H_{43}NNaO_4S$ $[M+Na]^+$ 704.2810, found 704.2787.

4.7. Procedure for the synthesis of aldol 10 in flow using a high flow rate (Table 4, entry 2)

The flow system was established with two syringe pumps (HII–10B, Techno applications®), Teflon tube, the flow reactor (Comet X-01-T, Techno applications®), stainless steel flow reactor (Comet X-01-SS, Techno applications®) and an acetone/dry-ice bath. Before use, the flow system was flushed with THF and dried under vacuum. A solution of the acetyloxazolidinone **13** in THF (0.13 M) was then loaded into a Teflon sample loop (Tube 1), and a solution of LiHMDS in THF (0.15 M) was loaded into an another Teflon sample loop (Tube 2). Both two solutions were pumped at a combined flow rate of 3 mL min^{-1}, and mixed in the reactor (Comet X-01-T and Tube 3) at −40 °C. The output of the reactor was connected with another reactor (Comet X-01-SS) and Tube 5 to mix the reaction mixture with a solution of the enal **9** in THF (0.05 M, 6 mL min^{-1}, Tube 4) at −78 °C. The reaction mixture was collected for 60 sec, and the resulting mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc=91:9) to give **10** as a white solid (155 mg, 76%, S/R=83:17).

4.8. (*E*)-(*S*)-3-Hydroxyl-7-tritylthio-4-heptenoic acid (5).[11]

To a solution of **10*S*** (22 mg, 0.032 mmol, 1 equiv) in MeOH (1.0 mL, 30 mL/mmol) was added 2 M aqueous NaOH (32 μL, 0.064 mmol, 2 equiv) at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was quenched with 1 M aqueous HCl. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc=1:1) to give **5** (58%, 7.8 mg, 0.019 mmol) as a white solid. $[\alpha]_D^{23}$ −3.11 (*c* 0.388 $CHCl_3$); mp 133–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.18 (m, 15H), 5.58 (dt, 1H, J=15.2, 6.8 Hz), 5.41 (dd, 1H, J=15.2, 6.4 Hz), 4.45 (dd, 1H, J=12.0, 6.4 Hz), 2.52 (d, 2H, J=12.0 Hz), 2.19 (dt, 2H, J=15.2, 6.8 Hz), 2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 144.8, 131.6, 130.7, 129.6, 127.8, 126.6, 68.5, 66.6, 41.1, 31.4; FTIR (Neat) 3379, 3056, 2924, 1714, 1489, 1443, 1261, 1181, 1083, 1034, 742, 700 cm^{-1}; HRMS (ESI): calcd for $C_{26}H_{26}NaO_3S$ $[M+Na]^+$ 441.1503, found 441.1495.

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Supplementary data

Supplementary data (Copies of ^{1}H and ^{13}C NMR spectra for **11a**–**e**. This material is available free of charge via the internet) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.05.051.

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