Tetrahedron xxx (2015) 1–8

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

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

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ARTICLE INFO

Article history:
Received 14 March 2015
Received in revised form 14 May 2015
Accepted 15 May 2015
Available online xxx

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

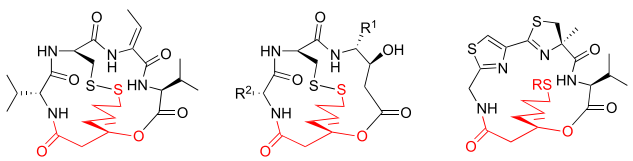
Keywords:
Aldol reaction
Flow synthesis
Diastereoselective
Histone deacetylase inhibitor
Cyclodepsipeptide

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.

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http://dx.doi.org/10.1016/j.tet.2015.05.051
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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.

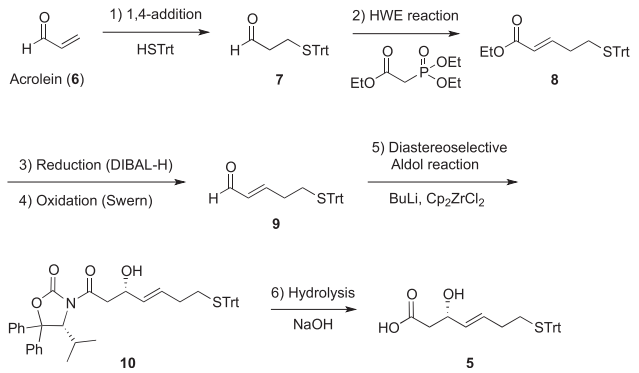


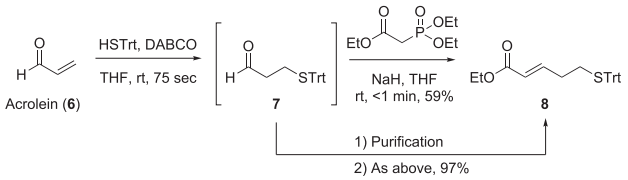
Fig. 2. Current synthesis of (*E*)-(*S*)-3-hydroxy-7-tritylthio-heptenoic acid (**5**).

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.

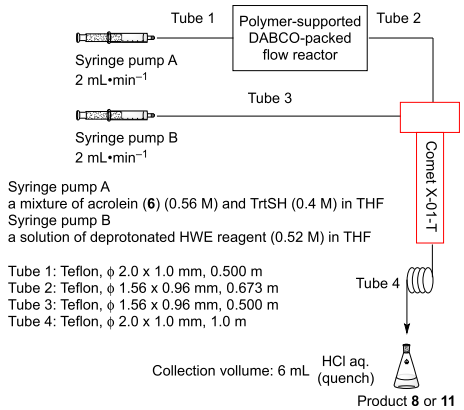


Fig. 3. Flow system for the synthesis of α, β-unsaturated esters **8** and **11**.

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

Please cite this article in press as: Doi, T.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.05.051