An Efficient Synthesis of an Apoptosis Inducer, F-3-2-5 by Using Octanol-Accelerated Baylis-Hillman Reaction

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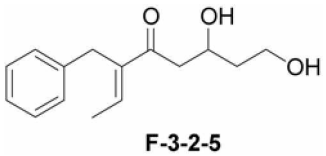
F-3-2-5 (Fig. 1) is a novel apoptosis inducer which was recently isolated from *Streptomyces* sp., of which potent anticancer activity warrants further preclinical investigation as well as extensive structure-activity relationship study.[1]

Thus, there has been an urgent need to devise an efficient synthetic method of **F-3-2-5** which has a synthetically challenging trisubstituted $\alpha\beta$-unsaturated ketone moiety as an integral part. Herein, we report an efficient synthesis of the title compound by using Baylis-Hillman reaction as the key step.

A synthetic plan for the title compound is shown in Figure 2. The Baylis-Hillman reaction[2a,2b] of methyl vinyl ketone (MVK, **1**) with acetaldehyde would provide 3-(1-hydroxy-ethyl)-but-3-en-2-one (**2**), which can be transformed into the key intermediate **4** by acetylation followed by 1,4-addition by phenylmagnesium bromide. Aldol condensation of the key intermediate **4** with protected propionaldehyde followed by deprotection would provide the title compound, **F-3-2-5**.

The condensation of MVK and acetaldehyde under Baylis-Hillman conditions was reported to give the desired compound in 81% yield.[2c] However, in our hands, the reaction was too slow to be used as a synthetic method. Also, the reaction always gave a complex mixture among which only a trace amount of the desired compound could be identified by ^{1}H NMR. Usually, the Baylis-Hillman reaction is a slow reaction requiring a few days to a few weeks for completion depending upon the reactivities of both the activated alkene and electrophile. Therefore, several efforts were directed to surmount the problem of a slow reaction rate including application of reactive activated alkenes,[3] reactive electrophiles,[4] microwave irradiation,[5] use of excess catalyst or co-catalyst,[6] use of various proton donors (additives, solvents and catalysts),[7] and high pressure.[8]

In our preliminary research, by thorough investigation of the solvent effect on the rate of the Baylis-Hillman reaction, we observed that the yield of the reaction gradually increases as the aliphatic chain length of the protic solvents increases from methanol to 1-octanol (Entries 1-4, Table 1). Additionally, we investigated if octanol could be used as an additive to the normal Baylis-Hillman conditions because it was difficult to remove octanol during work-up process (Entries 5-7, Table 1). The use of octanol as an additive in aprotic (THF) or protic (MeOH) solvent systems did not produce any rate acceleration (Entries 5-6 Table 1). However, to our surprise, even more remarkable rate acceleration was observed by addition of 2 eq. of octanol into the mixture of acetaldehyde, MVK and DABCO in the absence of solvent (90% yield, Entry 7, Table 1). Acceleration of the Baylis-



F-3-2-5

Figure 1. Structure of **F-3-2-5**.

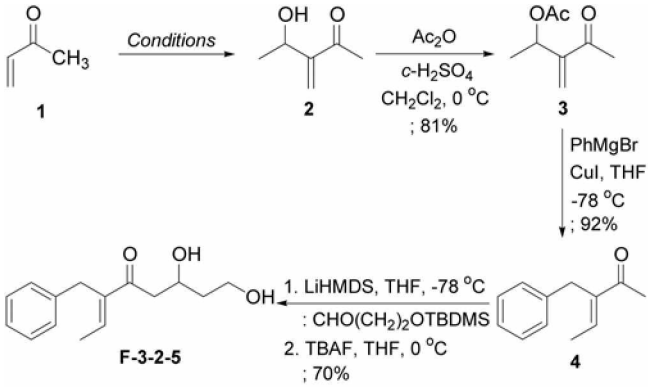


Figure 2. Synthetic route for F-3-2-5.

Table 1. Baylis-Hillman reaction of acetaldehyde with MVK

Entry	Solvent	Additive (equivalent)	Yield (%)
1	CH_3OH	–	28
2	$(CH_3)_2CHOH$	–	31
3	$CH_3(CH_2)_4OH$	–	52
4	$CH_3(CH_2)_7OH$	–	65
5	THF	$CH_3(CH_2)_7OH$ (2.0)[a]	12
6	CH_3OH	$CH_3(CH_2)_7OH$ (3.0)	10
7	None	$CH_3(CH_2)_7OH$ (2.0)	90[b]

[a]2.0 equivalent is minimum amount of octanol needed to dissolve the starting materials and DABCO. [b]Improved yield compared with entry 4 is presumably due to the efficient intermolecular condensation reaction under more concentrated reaction conditions.

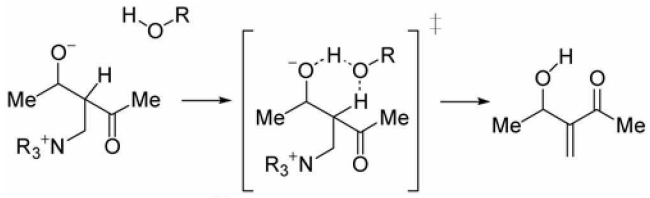


Figure 3. Proton transfer mechanism of the Baylis-Hillman reaction.

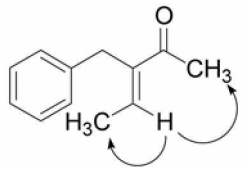


Figure 4. NOE between vinyl proton and two methyl groups.

Hillman reaction by octanol additive might be related with efficient proton transfer[9] by octanol (Fig. 3) but, at this point, it is not clear how the long aliphatic chain of the protic solvents promotes proton transfer and why octanol has the optimum chain length.

Thus, the Baylis-Hillman reaction of acetaldehyde with MVK was optimized by addition of octanol (2 eq.) to a mixture of acetaldehyde, MVK and DABCO in the absence of a solvent. Also, we tested if these reaction conditions could be applied to the large scale (11 g) synthesis of **2**, which smoothly proceeded in 85% yield in 12 h.[10] The *trans*-configuration of the double bond was confirmed by NOESY experiment, which showed strong correlation between the vinyl peak and two methyl peaks (Fig. 4). No correlation was observed between the vinyl peak and benzylic protons (Fig. 4).

Ensuing acetylation followed by 1,4-addition of phenylmagnesium bromide was performed by adapting the literature procedures[11] to give the key intermediate **4** in 75% yield in two steps (Fig. 2). The title compound was obtained by aldol condensation of **4** with protected propionaldehyde by using LiHMDS in THF at −78 °C followed by the final deprotection of the silyl group (70% yield, two steps, Fig. 2). The ^{1}H as well as ^{13}C NMR spectra of the title compound **F-3-2-5** matched well with that of the authentic sample.[12]

In summary, we devised an efficient synthetic method to prepare a novel apoptosis inducer, **F-3-2-5** by using octanol-accelerated Baylis-Hillman reaction as the key step. Particularly, as the reaction conditions were confirmed to provide the title compound in large quantity, this method opens a door for extensive structure-activity relationship study as well as preclinical study of the title compound.

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10. To a mixture of **1** (17.4 g, 248 mmol), acetaldehyde (11.0 g, 250 mmol), and DABCO (4.17 g, 37.1 mmol) was added 1-octanol (78 mL, 494 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was directly purified by column chromatography on silica gel (Hex:EtOAc = 4:1) to give the desired product **2** (24.1 g, 210.8 mmol, 85%) as oil.
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12. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.25-7.21 (m, 2H), 7.16-7.07 (m, 3H), 7.10 (q, J = 7.0 Hz, 1H), 4.27-4.21 (m, 1H), 3.72 (s, 2H), 3.70 (t, J = 6.5 Hz, 2H), 3.34 (br s, 1H), 2.96 (dd, J = 16.0, 7.9 Hz, 1H), 2.81 (dd, J = 16.0, 4.6 Hz, 1H), 1.95 (d, J = 7.0 Hz, 3H), 1.71-1.63 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 201.9, 143.2, 142.1, 129.3, 129.3, 126.8, 67.2, 60.7, 46.0, 40.6, 31.5, 15.4; ESIMS *m/z* 248.1 (M^+).