Pergamon

Tetrahedron Letters 43 (2002) 1449–1451

TETRAHEDRON LETTERS

Synthesis of acaterin via a new application of the Baylis–Hillman reaction

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Received 4 January 2002

Abstract—Acaterin **1** was synthesized by condensation of a chiral α,β-unsaturated γ-lactone with octanal via a DABCO-mediated Baylis–Hillman reaction. This is the first application of the Baylis–Hillman reaction to α,β-unsaturated lactones. © 2002 Published by Elsevier Science Ltd.

Acaterin **1**, isolated in 1992 from *Pseudomonas* sp.,[1] is an inhibitor of acyl-CoA:cholesterol acyltransferase (ACAT). The absolute configurations of the chiral centres of **1** have been determined by the synthesis of the four possible diastereomers and it has been shown that its butenolide moiety has the opposite absolute configuration of the one of Annonaceous acetogenins (Fig. 1).[2]

The Baylis–Hillman reaction has been extensively studied[3] recently and major contributions have led to an increase in both yields and kinetics. The most studied substrates are acrylate derivatives followed by acrylonitriles. In some cases, enones or crotonates have been used as the Michael acceptors but they require either longer reaction times,[4] high pressures[5] or the use of a Lewis acid.[6] We thought that acaterin **1** could be prepared by using an α,β-unsaturated lactone instead of an α,β-unsaturated ester although this extension of the Baylis–Hillman reaction has never been described (Fig. 2).

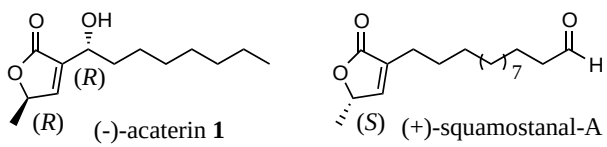

Figure 1.

In the case of α, β-unsaturated lactones, an expected side reaction is the aldolization because of the basicity of DABCO. This has been confirmed by the aldolization rate when the reaction has been performed with the unsubstituted 2(5*H*)-furanone after treatment with DABCO in a water/dioxane mixture: 50% of aldol was obtained along with 17% of the desired Baylis–Hillman adduct (results not shown). We thought that the pres-

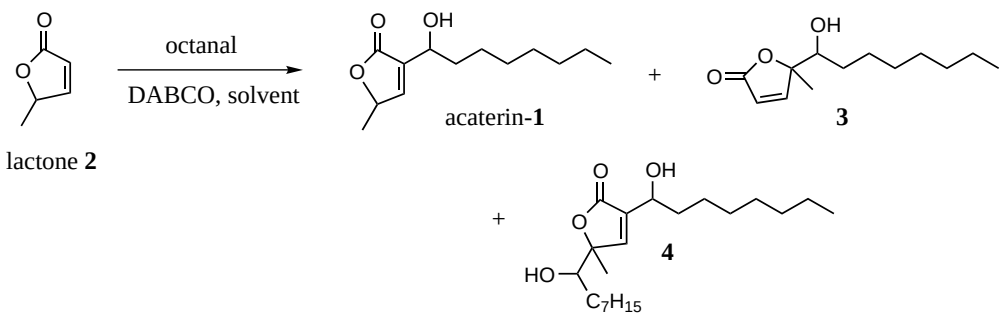

Figure 2.

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PII: S0040-4039(02)00058-8

ence of a methyl at the 5-position of the lactone could reduce the aldolization process and therefore increase the Baylis–Hillman adduct. Two by-products are still expected: aldols **3** and **4**, the latter resulting from further aldolization of the Baylis–Hillman adduct (Fig. 2).

We first tried to find the best conditions for the Baylis–Hillman reaction using the racemic lactone **2** prepared in three steps from pent-3-ene-nitrile after hydrolysis, bromolactonization and basic treatment. We studied different anhydrous conditions (THF, NMP, ethyleneglycol/dioxane, NMP/ethyleneglycol) and aqueous mixtures (H_2O/dioxane) with several nucleophiles (TMG, sparteine) or additives in the presence of DABCO ($ZnBr_2$, phosphate buffer, ADOGEN 464) but were not able to obtain any product in interesting yields. One of the best results was obtained by using 1 equiv. of DABCO in a 1:1 mixture of water and dioxane[7] after 17 h (41% of *rac*-acaterin **1**, 11% of aldol **3** and 3% of aldol **4**) (Table 1). Use of NMP instead of dioxane yielded less of the Baylis–Hillman adduct. Performing the reaction with additives such as LiI,[8] or $LiClO_4$,[9] resulted in an increase of the reaction rate but also in an increase of the aldols/acaterin ratio. However, the use of $Mg(ClO_4)_2$[9] resulted only in a slight increase of the yield without increasing the **3**/**1** ratio, and thus was not pursued because of these dangerous conditions.[9]

It should be noted that the diastereoselectivity of the reaction is low as a mixture of acaterin (*R**,*R**) and pseudo-acaterin (*R**,*S**) is obtained in a 60/40 ratio, respectively (two broad singlets at δ 5.05 and 5.09 ppm were observed for H-5 after irradiation of the two methyl signals at 1.23 and 1.29 ppm, in deuterated pyridine).[2]

Table 1. Optimisation of the experimental conditions for the obtention of *rac*-acaterin **1**

Entry	Solvent[a] (time[b])	Additive	**1**/**3**/**4** (%)[e]
1	Dioxane/H_2O (17)	–	41/11/3
2	NMP/H_2O (17)	–	31/6/5
3	Dioxane/H_2O[c] (6)	$LiClO_4$	41/20/8
4	Dioxane/H_2O[c] (6)	LiI	34/17/9
5	Dioxane/H_2O[c] (6)	LiI	23/12/10[d]
6	Dioxane/H_2O[c] (6)	$Mg(ClO_4)_2$	32/7/5
7	Dioxane/H_2O[c] (17)	$Mg(ClO_4)_2$	47/11/10
8	NMP/H_2O[c] (17)	$Mg(ClO_4)_2$	37/9/12

[a] As a 1/1 mixture.
[b] In hours.
[c] As a 4 M solution of additive in water.
[d] With 50% of DABCO.
[e] Isolated yields, **1** and **3** as an unseparable mixture, easily distinguishable by NMR.

We then performed the Baylis–Hillman reaction with enantiomerically pure (e.e. 99%) lactone **2-(*S*)** prepared by asymmetric reduction of the required α-chlorinated ketone with baker's yeast.[10] Two different conditions[11] were tested: with or without $Mg(ClO_4)_2$.[9] It was found that the e.e.'s of acaterin[12] were low in both cases (around 15%) but it is not clear whether racemization occurs after the Baylis–Hillmann reaction or if the mecanism goes through enolization then α-aldolization (Fig. 3). Indeed, on the one hand (path a), Michael addition of DABCO followed by aldolization and β-elimination gives acaterin **1** which can be racemized by the presence of DABCO. On the other hand (path b), lactone **2** can be first racemized by DABCO to generate racemic lactone **2** (which gives rise to racemic acaterin **1** via a Baylis–Hillman reaction) which can also give through γ-aldolization compound **3**. The formation of **4**

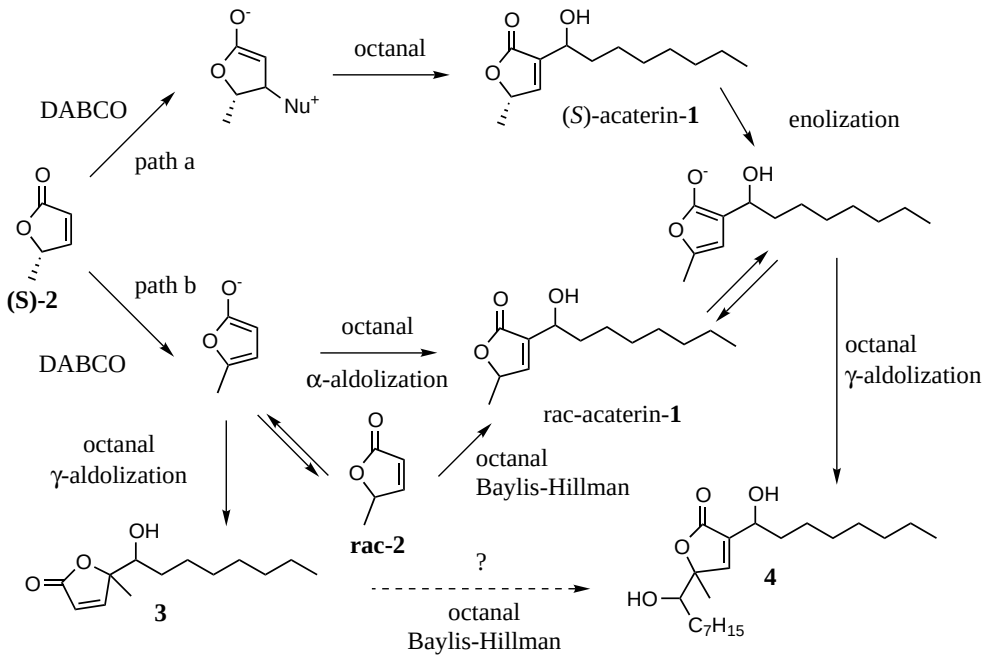

Figure 3.

can be explained by enolization of chiral or racemic acaterin **1** followed by γ-aldolization with octanal, its formation by Baylis–Hillman reaction on aldol **3** seems less probable due to steric hindrance.

In conclusion we report the first Baylis–Hillman reaction with an α,β-unsaturated γ-methyl-γ-lactone to give acaterin **1** in a straightforward manner. This reaction will certainly find applications in the synthesis of other natural products due to the high degree of functionality of such synthons.

Acknowledgements

We gratefully acknowledge J.-C. Jullian for NMR experiments, Dr. M. Pichon for preliminary studies and Professor R. Hocquemiller for his interest in these studies.

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9. **WARNING**: the use of perchlorates may be extremly dangerous (explosive), and should be avoided when possible.
10. Tsuboi, S.; Sakamoto, J.; Kawano, T.; Utaka, M.; Takeda, A. *J. Org. Chem*. **1991**, *56*, 7177–7179.
11. Typical procedure: To a mixture of lactone **2** (1 mmol) in 5 ml of dioxane/water (1/1) is added octanal (0.5 mmol) followed by DABCO (1 mmol). The reaction is stirred at room temperature for 17 h then extracted with diethyl ether. The combined organic layers are washed with water then dried over $Mg(SO_4)_2$ before concentration. The crude material is purified by flash-chromatography using cyclohexane/ethyl acetate 6/4 as solvent.
12. The enantiomeric excesses were calculated after measurement of the optical rotation of the mixture of acaterin and pseudo-acaterin (see Ref. 2)