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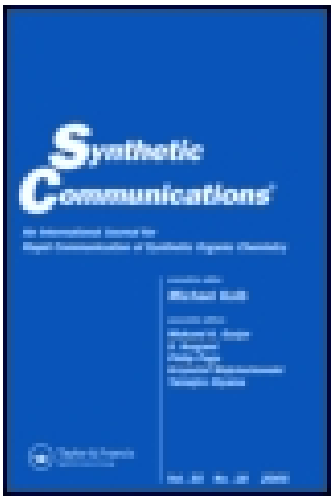

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A Simple Access to a Forskolin Precursor

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SYNTHETIC COMMUNICATIONS, 23(13), 1923-1927 (1993)

A SIMPLE ACCESS TO A FORSKOLIN PRECURSOR.

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Abstract *: Cyclization of acetoacetate of hydroxy-ionone* ***1*** *into lactone* ***2****, a precursor of forskolin, is shown to occur in excellent yield using* Cs_2CO_3 *or* Cs_2CO_3/K_2CO_3 *mixture.*

Considerable effort has been directed towards the synthesis of the labdane diterpene compound forskolin [1], owing to its remarkable activity [2] and its challenging structure. Our work towards the same target has prompted us to reinvestigate a reaction reported by Koft describing a very elegant and simple access to a valuable intermediate, lactone **2**, by treatment of acetoacetate **1** with a catalytic amount of Cs_2CO_3 [3].

This multistep reaction involves an internal Michael addition, followed by an aldol condensation, deacylation and double bond isomerization (route a, figure 1). Koft's paper [3] briefly demonstrated that a propionylacetate derivative of **1** also led

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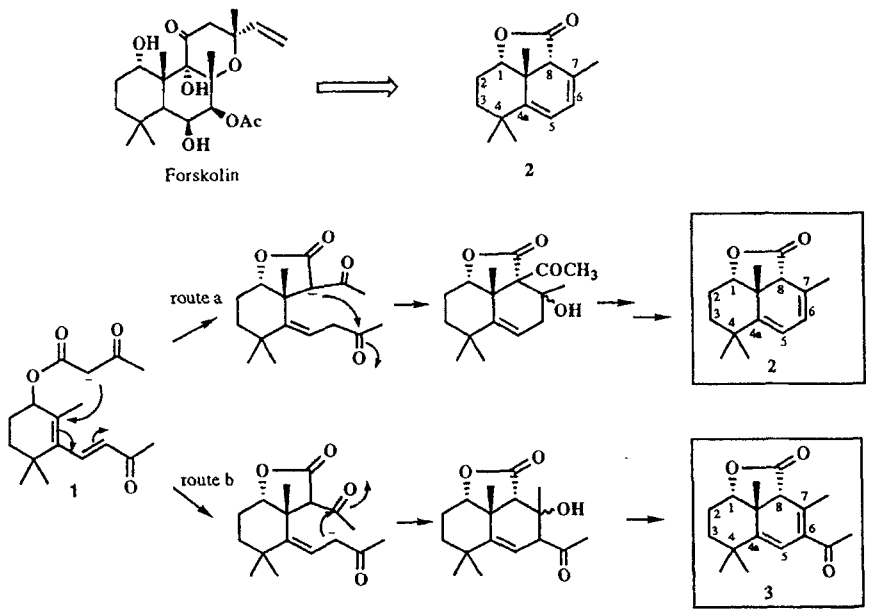

Figure 1

to lactone **2**, and pointed out that the cleaved acyl group arose on the β-ketoester moiety.

Moderate yield of **2** (50 %) was reported using a catalytic amount (0,2 eq.) of Cs_2CO_3. Despite several attemps to reproduce this result, we have not been able to obtain a yield better than 18 % after a lengthy and careful chromatographic purification. Among the byproducts, compound **3** was isolated and its structure was elucidated on the basis of its NMR spectra [4]. This allowed for a better understanding and eventual improvement of the reaction. In its normal course (route a), the deacylation step leading to lactone **2**, produces one equivalent of acetic acid which neutralizes the corresponding amount of Cs_2CO_3. A break-down

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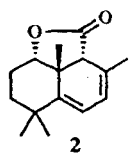
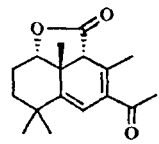
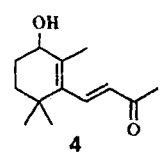
Table 1

		 2	 3	 4
Cs_2CO_3, 1.1 eq.,	8 hrs	90%		trace
K_2CO_3, 1.4 eq.,	30hrs	62%	25%	13%
K_2CO_3, 2.5 eq.,	26 hrs	68%	24%	8%
K_2CO_3, 1.2 eq., Cs_2CO_3, 0.3 eq.,	9 hrs	95%	trace	trace

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of the reaction course is consequently expected after consumption of the base. A complete conversion of the starting material to **2** would require one equivalent of Cs_2CO_3. Formation of **3** (route b) clearly involves a cyclization of the enolate obtained after a Michael addition on the carbonyl of the acetoacetic moiety, followed by H_2O elimination. This process which requires only a catalytic amount of base, becomes predominant and leads to **3** when the Cs_2CO_3 has been consumed by the formation of lactone **2**.

From these observations it was clear that the use of at least 1 equivalent of base was necessary to carry out the reaction. Indeed the use of 1.1 equivalents of Cs_2CO_3 enhanced the yield of lactone **2** up to 90 %. Preparation of the starting material **1** was easily achieved by reaction of hydroxy-ionone **4** and acetylated Meldrum's acid according to the procedure used by Ruveda in a similar case [5].

As Cs_2CO_3 is an expensive reagent we have investigated the possibility of replacement of this salt by K_2CO_3. The reaction proved relatively sluggish but led to lactone **2** and byproduct **3** in roughly equal amounts accompanied by hydroxy-ionone **4**. This demonstrated that Cs_2CO_3 modifies at least the kinetics of various

steps of routes a and b. Finally the use of mixtures of K_2CO_3 and Cs_2CO_3 was found to be very efficient as reported in table 1, and suitable for preparative scale reactions.

Typical experimental procedure : to a mixture of 0.650 g (2 mmol) Cs_2CO_3 and 1.120 g (8 mmol) K_2CO_3 dried under vacuum (120 °C, 12 hrs) were added at r.t. 2 g (6.8 mmol) of **1** in 500 ml of dry CH_3CN. The mixture was refluxed for 9 hrs and extracted, giving 1.5 g (95 % yield) of lactone **2** recristallized from ether/pentane (m.p. 82-84 °C, lit. [3] : 80-82 °C).

These results confirm the outstanding ability of Cs_2CO_3 to promote Michael type reactions[6] and also reveal the possibility of partial substitution of Cs_2CO_3 by a less costly salt such as K_2CO_3 when stoechiometric conditions are required. The reaction provides an efficient and simple access to an interesting intermediate in forskolin or related terpene synthesis. Transformation of **2** into forskolin has been published by Corey [7] and our efforts towards this objective will be reported soon.

References and Notes.

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(4) ^1H NMR (200 MHz, $CDCl_3$) ppm : 6.12, (s, H-5), 4.35 (t, H-1), 2.75(s, H-8), 2.28 (s,$\underline{CH_3}$-CO-), 2.18 (s, $\underline{CH_3}$-C=C), 1.16 (s, $\underline{CH_3}$), 1.08 (s, 2 $\underline{CH_3}$).

^{13}C NMR (50.3 MHz, $CDCl_3$) ppm : 200.0 (conjugated C=O), 174,5 (lactone C=O), 143.5, 134.3, 133.1, 118.7 (sp^2 carbons), 84.5 (C-1),

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58.9 (C-8), 42.8, 34.8 (C-4 and C-8a), 33.1 (CH_2), 30.4 (double intensity), 28.0, 22.1 (CH_2), 21.7, 21.4..

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