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Easy access to an optically pure precursor of forskolin.

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***Abstract** : The PLE catalysed resolution of the (±)-1-hydroxy-β-ionone acetoacetate resulted in the (-)-enantiomer 2 with high optical purity (95 % e.e.). Cyclisation of this material gives access to the (-)-lactone 1 in an optically pure form.*

Lactone **1** and related compounds have often been used in the early steps of forskolin total synthesis[1,2]. Our continuing interest in this molecule and our recent progress[3] in the easy preparation of lactone **1** by cyclisation of the acetoacetic ester **2** in the presence of a mixture of Cs_2CO_3 and K_2CO_3, have prompted us to investigate its preparation in enantiomerically pure form. As depicted in figure 1, this reaction simultaneously controls three asymmetric centers from the absolute configuration at C-1 in ester **2**, and we consequently focused all our efforts on investigating a way to prepare **2** with the *S* configuration at C-1.

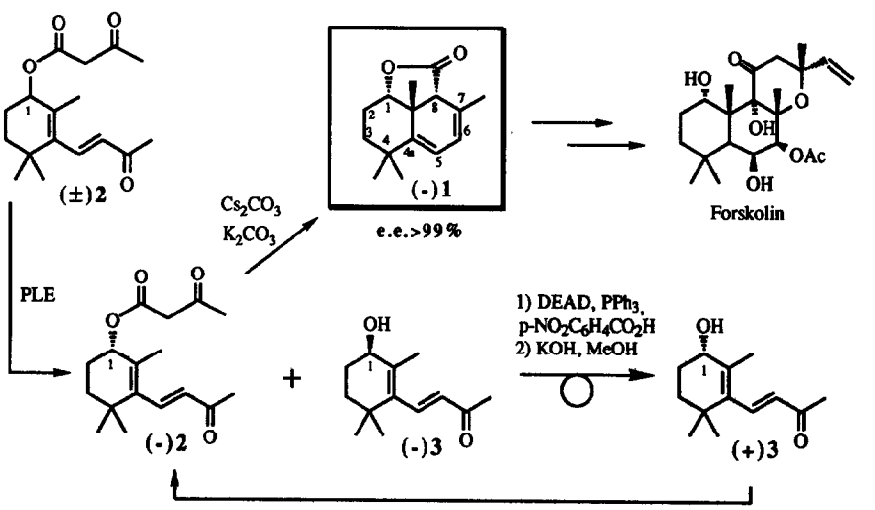

Fig. 1

In their work aimed towards the total synthesis of forskolin, Corey and coworkers[4] have shown the efficiency of the reduction of 1-keto derivatives by chiral boron hydrides. We have found that enzymatic hydrolysis of racemic ester **2** available from (±)1-hydroxy-β-ionone **3**[3] in the presence of pig liver esterase (PLE) is an attractive alternative and can proceed with high enantioselectivity. Various experimental conditions were studied and the results obtained with different samples of PLE are reported in table 1.

Entry	Temperature	Reaction Time	Conversion	3		2	
				$[\alpha]_D$*	% e.e.**	$[\alpha]_D$*	% e.e.**
1	0°C	17 h	45 %	-6.2	93	-45.2	94
2	-10°C	67 h	55 %	-3.2	82	-39.1	88
3	-15°C	116 h	50 %	-1.5	80	-36.4	84
4	0°C	40 h	30 %	-7.0	95	-14.1	
5	0°C	41 h	30 %	-5.8		-51.4	95

* optical rotation measured in methanol, entries 1-3, or ethanol, entries 4-5 (c = 1.5-2.1) on products purified by column chromatography.

** enantiomeric excess from NMR measurements.

Table 1.

Two batches of PLE were used :

- the first sample of PLE (acetone powder, Sigma) led to good yields (≈ 65 % in purified material based on theory) and high enantioselectivity while working at 0° C (entry 1). 45 % conversion was reached after 17 hours. Lowering the temperature from 0° C to -15° C (entries 2-3) resulted in a much longer reaction time and a drop in the enantiomeric selectivity from 93 % to less than 80 %.

- the second sample of PLE (acetone powder, Sigma) was found to be less efficient. Under the same conditions, hydrolysis was sluggish and the enantioselectivity lower. In order to circumvent this difficulty, a procedure involving two consecutive hydrolyses at 0° C was developed. The first hydrolysis (entry 4) led to virtually optically pure alcohol **3** ($[\alpha]_D$= -7.0) with a conversion of 30 % after 40 hours and to a poorly enriched ester **2** ($[\alpha]_D$= -14.1). This ester was in turn submitted to a second hydrolysis (entry 5) leading to an optically pure sample of (-)**2**, $[\alpha]_D$=-51.4. The alcohol **3** recovered after the second hydrolysis was, as expected, a mixture of enantiomers ($[\alpha]_D$ = -5.8).

Enantiomeric purity of the different samples was measured by NMR (400 MHz) using the chiral shift reagent Eu(III) D_3-heptafluorobutyrylcamphorate. Addition of 0.4 eq. of this reagent in dry $CDCl_3$ to the racemic starting ester **2** (≈ 6 mg in 1 ml) induced the splitting of almost all the proton signals. The most sensitive resonances were that of H-1 (5.25 ppm), protons of the allylic methyl (1.69 ppm) and the two olefinic protons of the side chain (6.1 and 7.12 ppm). The spectrum of the recovered (-)-ester **2** showed the presence of only traces of the (+)-enantiomer, corresponding to an enantiomeric excess greater than 94 % in the one step hydrolysis (entry 1) or 95 % in the two steps procedure (entry 5). Similar measurements were performed on (-)-alcohol **3** which showed an e.e. greater than 93 % (entry 1) or 95 % (entry 4).

The absolute *R* configuration of (-)-alcohol **3** (table 1, entry 4) was established by comparison of its $[\alpha]_D$ = -7.0 (c= 2.06, ethanol) with that reported by Eschenmoser[5] : $[\alpha]_D$=-7.0 ± 1(c= 1.04, ethanol). Consequently, the absolute configuration of the recovered (-)-ester **2** was assumed to be *S*. The maximum optical rotation found for this compound was $[\alpha]_D$= -51.4 (entry 5). The *S* configuration was confirmed by chemical hydrolysis (0.5 % KOH, CH_3OH, r.t., 24 h.) on a sample characterized by $[\alpha]_D$ = -45.2 (entry 1) leading to the *(S)*- alcohol **3** with $[\alpha]_D$ =+6.0.

A sample of (-)-ester **2** ($[\alpha]_D$ =-51.4) with an absolute configuration at C-1 corresponding to that of forskolin was then submitted to cyclisation (0.3 eq. Cs_2CO_3,1.2 eq. of K_2CO_3 in refluxing CH_3CN for 8h.). The (-)-lactone **1** was isolated in 70 % yield by crystallization from aqueous methanol[6] (m.p. 124 - 125° C, racemic lactone m.p. 83° C [3]). NMR studies (400 MHz) on this sample ($[\alpha]_D$ = -150) in the presence of chiral shift reagent and GC analysis on a chiral column (Chiraldex®, GTA, g-cyclodextrinetrifluoroacetyl) did not reveal any detectable trace of the enantiomer (e.e. greater than 99 %).

Recycling of (-)-alcohol **3** with the undesired absolute configuration at C-1was explored by Mitsunobu inversion (DEAD, PPh_3, $C_6H_5CO_2H$)[7,8]. Incomplete esterification of (-)**3** was observed when benzoic acid was used as the nucleophile in tetrahydrofuran, but the reaction was completed within one hour using Martin and Dodge's conditions[9] (DEAD, PPh_3, then p-nitrobenzoic acid in benzene). A sample of *(R)*- alcohol **3** displaying an enantiomeric excess of about 80 % ($[\alpha]_D$= -5.7) was easily converted into the *(S)*- p-nitrobenzoate derivative ($[\alpha]_D$=-4.3, 75 % yield) which was submitted to hydrolysis (0.5 % KOH aqueous-methanolic 5/95 solution) giving(+)-alcohol **3** in 88 % yield characterized by $[\alpha]_D$=+5.8. This alcohol was in turn converted into the corresponding (-)-ester **2** by reaction with acetylated Meldrum's acid[3,10] and recycled in the preparation of (-)-lactone **1**

The simplicity of this method strongly favors the approach to forskolin via chiral synthon **1**.

Experimental.

General procedure for the enzymatic hydrolysis of ester 2 : The racemic ester (±)**2** (184 mg, 0.63 mmol) was emulsified by magnetic stirring in a buffered aqueous methanolic medium (20 ml, CH_3OH / 1M phosphate buffer pH=7.4, 1/4) . The enzymatic hydrolysis was initiated by addition of the PLE esterase (74 mg) and carried out at 0° C without control of the pH. The progress of the reaction was followed by TLC (SiO_2, Et_2O/pentane, 60/40) on 0.5 ml aliquots extracted with ethyl acetate. When conversion approached 50 % (after about 17 hours), the mixture was extracted with CH_2Cl_2 (4x100 ml) and ethyl acetate (1x100 ml). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The oily residue (147 mg) was purified by chromatography (SiO_2, Et_2O/cyclohexane) to give, successively, (-)-ester **2** (51 mg ; 27.5 %

yield, 55 % based on theory) and (-)-alcohol **3** (42 mg ; 32.5 % yield, 65 % of transformed material). The starting racemic ester was crystaline (m.p.= 54- 54.5° C from pentane/Et_2O), and the (-)-ester **2** isolated was a colorless oil, $[\alpha]_D$= -45.2.

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