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Enzyme Catalysed Lactonization of 3,5 Dihydroxy Esters: Enantioselective Synthesis of Naturally Occurring 3-Hydroxy-5-decanolide, (-)-Massoialactone, and 3-Hydroxy-5-icosanolide.

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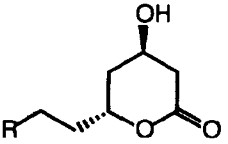
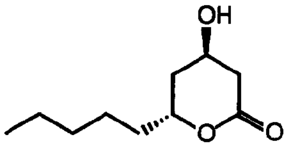
Abstract: *Synthesis of optically active (+)-3-hydroxy-5-decanolide, (-)-massoialactone and of the recently isolated 3-hydroxy-5-icosanolide was achieved by enzyme-catalysed lactonization of racemic 3,5 dihydroxy esters with PPL in dry* Et_2O *. Ees vary from 86% up to >98%.*

The δ- lactone system is a common feature of several natural products[2]. Many of these lactones are either β–hydroxy substituted or α,β-unsaturated and show interesting biological activities: the hypocholesterolemic property of compactin and mevinolin[3], well known inhibitors of HMGCoA-reductase, has been extensively studied.

The enantioselective synthesis of two analogues of the mevinic acids **1** and **2**[4], based on the lipase-catalysed lactonization of the corresponding racemic open chain 3,5 *syn* dihydroxy esters, has recently been described by the authors. The enzyme used (PPL, porcine pancreatic lipase, in anhydrous Et_2O) discriminated between the two enantiomers up to 98% thus producing the corresponding (3R,5R) lactones **1** and **2** with the same absolute configuration as the lactone moiety of the natural mevinic acids.



1 R= Ph
2 R= Cyclohexyl



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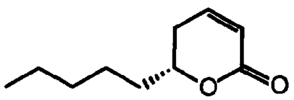

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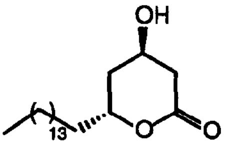

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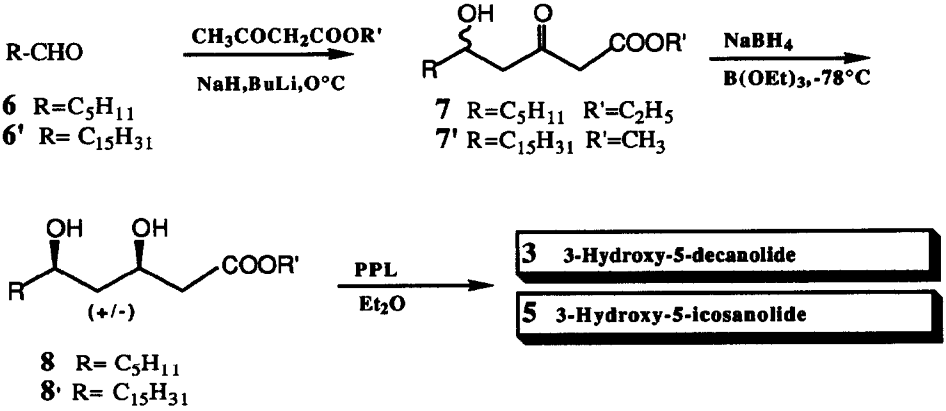
In order to verify the application of the described methodology to analogous systems, we devoted our attention to the synthesis of the naturally occurring (3R,5R)-(+)-3-hydroxy-5-decanolide **3**, (5R)-(-)-massoialactone **4** and 3-hydroxy-5-icosanolide **5**, following the synthetic route outlined in scheme 1.

The dianion of ethyl (or methyl) acetoacetate[5] was added to the aldehydes **6** and **6'** to obtain the aldols **7** and **7'**, which were diastereoselectively reduced[6] to the *syn* 1,3 diol esters **8** and **8'**. The unoptimized overall yields of the synthetic sequence were 51% for **8** and 47% for **8'** (for a complete experimental procedure see ref. 4).

Scheme 1

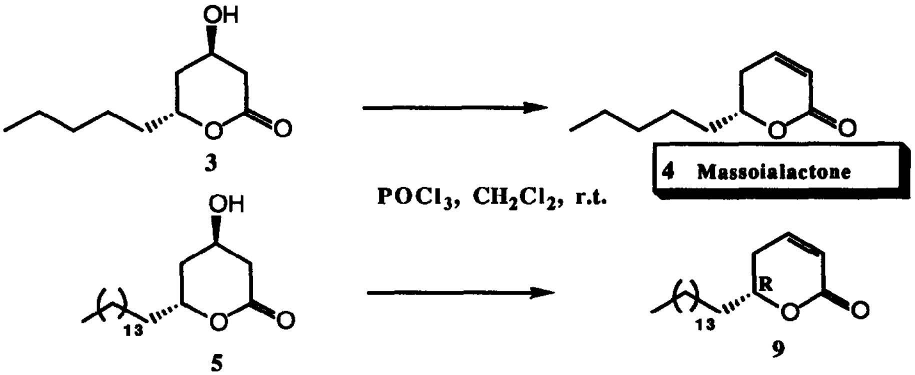


The enzymatic lactonization of **8** and **8'** should allow, as in the case of compounds **1** and **2**, kinetic enantioselective resolution to the naturally occurring **3** and **5**.

Compound **3**, isolated from the fungus *Cephalosporium recifei*[7] has already been synthesized starting from a yeast-reduction product[8] or from chiral metabolites[9]. We obtained **3** from the enzymatic lactonization of **8** in dry Et_2O in presence of crude PPL[9] to afford **3** after 12 days, with a chemical yield of 25% and an ee of 86%[11]. Attempts to improve the chemical yield increasing the reaction times were unsuccessfull, probably because of the retroinhibition on the enzyme by the formed products (studies on this effect are in progress and will be reported).

Synthetic compound **3** shows spectral properties identical to the natural one[8,9] and an $[\alpha]_D= +26$ (c=1.2 in $CHCl_3$; natural, $[\alpha]_D= 27.4$)[8,9]. **3** was then quantitatively dehydrated (CH_2Cl_2, $POCl_3$, r.t., see scheme 2) to (-)-massoialactone **4**, a natural lactone isolated from various sources, among them the bark oil of *Criptocarya massoia*[12], jasmine flowers[13], and the defence secretion of the two species of formicin ants of the genus *Camponotus*[14]. Beyond the perfect agreement with the spectroscopic data[8,9], the synthetic compound **4** shows an $[\alpha]_D= -84$ (c= 1.8 in $CHCl_3$; natural product $[\alpha]_D= -91$)[8].

Scheme 2



Compound **5** was recently isolated and identified from Texas bitterweed *Hymenoxys odorata*[15]: its relative 3,5 *syn* configuration was estabilished by ^{1}H-NMR, but unfortunately its absolute configuration is still unknown and no optical rotation is so far available.

Following our procedure the lactonization of **8'** with PPL in Et$_2$O dry yielded **5**, after 3 days with a chemical yield of 15% and ee>98%. Synthetic compound **5** shows spectroscopic data in complete agreement with the data reported[15], thus unambiguously demostrating the structure of 3β-hydroxyicosan-1,5-β-olide for the isolated lactone 5. On the other hand synthetic 5 shows a positive specific rotation ($[\alpha]_D$= +18, c=1 in CHCl$_3$), as was for all the other natural and synthetic (3R,5R)-3-hydroxy-δ-lactones.

The subsequent dehydration of **5** afforded the α,β-unsaturated lactone **9** which showed a negative optical rotation ($[\alpha]_D$= -42, c=0.5 in CHCl$_3$. Furthermore **9** shows a negative Cotton curve on its CD spectrum. The negative sign of the specific rotation[16] and the negative Cotton effect in its CD spectrum[17] are a known demonstration of the 5R absolute configuration of **9** : therefore the absolute configuration of synthetic **5** is 3R,5R. When the specific rotation of the natural **5** is available it will thus be possible to assign its absolute configuration.

In conclusion the described protocol can be considered a rapid way to synthesize optically active β-hydroxy δ-lactones and related compounds: the enzymatic lactonization shows high preference for the R,R enantiomer, as demonstrated for all the prepared compounds. Further studies are in progress to improve reaction times, chemical yields and e.e.s for the biocatalytic reaction as well as its extension to *anti* 3,5 dihydroxyesters and related meso compounds.

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5. The reported esters, with different alcoholic residue (OMe, OEt), gave best results for the e.e. of the final products. More details on the experiments with different OR groups will be reported.

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11. The enantiomeric excess (ee) for the synthetic lactones **3** and **5** has been determined by esterification with (-) camphanic acid chloride (for the experimental procedure see ref. 4). In the obtained derivate the geminal methyls of the camphanil residue, which in ^{1}H-NMR spectrum (300 MHz) occurs in the 0.9-1.2 chemical shift range, are valuable for the determination of ee. ^{1}H-NMR chemical shifts of geminal methyls in the camphanic derivative: (3S, 5S) **3**, 1.03 and 0.93 ppm; (3R, 5R) **3**, 1.02 and 0.92 ppm; (3S,5S) **5**, 1.06 and 0.96 ppm; (3R, 5R) **5**, 1.05 and 0.95 ppm.

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