Tetrahedron: Asymmetry Vol. 4, No. 2, pp. 153-156, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Enzyme-catalyzed Lactonization of Methyl (±)-(*E*)-3,5-Dihydroxy-7-phenyl-6-heptenoates. - A Comparison of the Behaviour of *syn*- and *anti*-Compounds[1]

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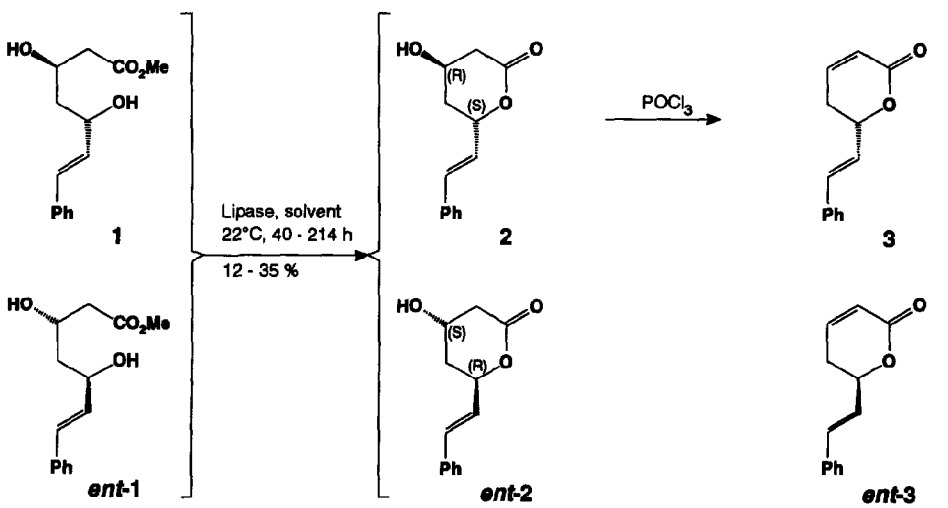
(*Received in UK* 30 *November* 1992)

Abstract: 3-Hydroxy lactones with a high enantiomeric excess were obtained by the lipase-catalyzed enantioselective lactonization of racemic *syn*- and *anti*-3,5-dihydroxy carboxylic esters. The (5*S*)-lactones were formed predominantly from both diols with pancreatin as enzyme. The lipase from *Candida sp. 382*, however, catalyzed the preferential formation of the (5*S*)-lactone only from the *syn*-diol. From the *anti*-diol the (5*R*)-lactone was formed as the main enantiomer.

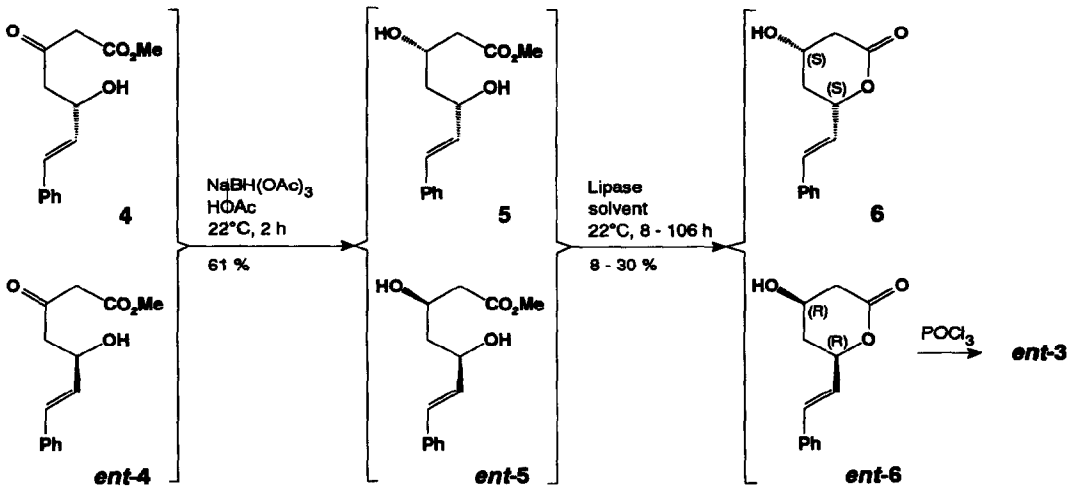
The enantioselective enzyme-catalyzed lactonization of several alkyl *syn*-3,5-dihydroxyalkanoates[2] and -alkenoates[3] recently has been investigated, as the resulting 5-substituted (3*R*,5*S*)-3-hydroxy-5-pentanolides exhibit the structure of the lactone part of compactin[4] and mevinolin,[5] which are known as potent inhibitors of the hydroxymethylglutaryl coenzyme A reductase.[6] Continuing our efforts directed towards the use of enzymes in enantioselective lactonizations of alkyl 3,5-dihydroxy carboxylates, we now concentrated our interest on the influence of the configuration of the hydroxy groups on the stereochemical outcome of a lipase-catalyzed intramolecular transesterification. The compounds ***rac*-1** and ***rac*-5** have been chosen as substrates for a comparison between a *syn*- and an *anti*-diol.



The *syn*-diol ***rac*-1** and the *anti*-diol ***rac*-5** were obtained as pure diastereomers by reduction of the keto ester ***rac*-4**[3] with sodium borohydride/ethoxydimethylborane in THF/hexane[7] and sodium triacetoxyborohydride in acetic acid,[8] respectively.

Both racemic diols were subjected to lactonization in the presence of pancreatin and the lipase from *Candida sp. 382* in various ethers at 22°C. The reaction was monitored by TLC and terminated after the time given in the Table. The enantiomeric excess (e.e.) of the lactones **2**/***ent*-2** and **6**/***ent*-6**, which were isolated from the reaction mixture by column chromatography, was determined by HPLC on a chiral phase. The absolute configuration of the lactones **6** and ***ent*-6** was established by dehydration with phosphoryl chloride in pyridine to (-)-(*S*)-goniothalamin[9] (**3**) and (+)-(*R*)-goniothalamin[9] (***ent*-3**), as already described for the lactones **2** and ***ent*-2**[3]. The results are compiled in the Table.

The pancreatin-catalyzed lactonization of the *syn*-diol ***rac*-1** in diethyl ether afforded the (3*R*,5*S*)-lactone **2** in a yield of 33 % with an enantiomeric excess (e.e.) of 80 % (Table, entry 1). Assuming that this relatively low conversion was caused by an equilibrium between the methyl esters **1**/***ent*-1**, the lactone **2**/***ent*-2**, and the formed methanol, this experiment was repeated in the presence of molecular sieve 4Å. Indeed, by this procedure the rate of the lactonization could be increased. A conversion of 33 % could be reached in one third of the time and the e.e. could be enhanced up to 92 % (entry 2). A repetition of this experiment with the diol **1**/***ent*-1** with an e.e. of 92 % yielded the lactone **2** with an e.e. of >99 % (entry 3).



The pancreatin-catalyzed lactonization of the *anti*-diol ***rac*-5** provided the lactone **6** in a yield of 13 % with an e.e. of 31% (entry 1). Addition of molecular sieve 4Å accelerated the lactonization and increased the yield, but dropped the e.e. of the predominantly formed lactone **6** to 17 % (entry 2).

The use of diisopropyl ether, tert-butyl methyl ether, or tetrahydrofuran as solvent for the pancreatin-catalyzed lactonization of the *syn*- and *anti*-diols ***rac*-1** and ***rac*-5** did not improve the outcome of the reaction (entries 4-6).

Table. Enantioselective Formation of the Lactones **2**/***ent*-2** and **6**/***ent*-6** by an Enzyme-catalyzed Lactonization of the *syn*-Diol ***rac*-1** and the *anti*-Diol ***rac*-5**

			Lactone **2**/***ent*-2**			Lactone **6**/***ent*-6**		
Entry	Enzyme[a]	Solvent	Time (h)	Yield (%)	E.e.[b] (%)	Time (h)	Yield (%)	E.e. (%)
1	Panc.	Et_2O	214	33	80	106	13	31[c]
2	Panc.	Et_2O[d]	71	33	92	80	26	17[c]
3	Panc.	Et_2O[d,e]	117	35	99	-	-	-
4	Panc.	*t*BuOMe	40	34	72	80	14	36[c]
5	Panc.	iPr_2O	40	27	73	80	15	36[c]
6	Panc.	THF	200	12	69	106	8	22[c]
7	Cand.	Et_2O	100	29	53	30	29	73[f]
8	Cand.	Et_2O[d]	-	-	-	8	30	74[f]
9	Cand.	Et_2O[g]	-	-	-	30	28	96[f]
10	Cand.	*t*BuOMe	45	31	54	30	31	58[f]
11	Cand.	iPr_2O	45	22	66	30	25	64[f]
12	Cand.	THF	192	12	38	80	14	29[f]

[a] Panc.: pancreatin; Cand.: lipase from *Candida sp. 382*. [b] E.e. of lactone **2**. [c] E.e. of lactone **6**. [d] Lactonization in the presence of molecular sieve 4Å (200 mg). [e] Starting from *syn*-diol **1** with an e.e. of 92 %. [f] E.e. of lactone ***ent*-6**. [g] Starting from *anti*-diol ***ent*-5** with an e.e. of 73 %.

With the lipase from *Candida sp. 382* as enzyme and diethyl ether as solvent, the *syn*-diol ***rac*-1** afforded the lactone **2** with only 53 % e.e. in a yield of 29 % (entry 7). That means that this lipase is not superior to pancreatin in respect to the enantioselective lactonization of ***rac*-1**. However, under the same conditions, the *anti*-diol ***rac*-5** afforded the lactone ***ent*-6** with an e.e. of 73 % (entry 7). The use of molecular sieve 4Å again accelerated the reaction, but the e.e. was not increased (entry 8). Lactone ***ent*-6** with an e.e. of 96 % was obtained when enantiomerically enriched *anti*-diol ***ent*-5/5**, prepared by esterification with methanol in the presence of triethylamine from ***ent*-6/6** with an e.e. of 73 %, was once more subjected to a lactonization catalyzed by the lipase from *Candida sp. 382* (entry 9). Recrystallization from diisopropyl ether provided enantiomerically pure ***ent*-6**.

As well, in the case of the lipase from *Candida sp. 382*, diethyl ether was superior to the other investigated ethers (entries 10-12).

In conclusion, in the presence of pancreatin, *syn*-diol ***rac*-1**, as well as *anti*-diol ***rac*-5**, were lactonized preferentially to the lactones with (5*S*)-configuration, i. e. **2** and **6**. The enantioselectivity was higher in the case of the *syn*-diol.

In the presence of the lipase from *Candida sp. 382*, the *syn*-diol ***rac*-1** again was predominantly lactonized to the lactone **2** with (5*S*)-configuration. The *anti*-diol ***rac*-5**, however, afforded preferentially the lactone ***ent*-6** with (5*R*)-configuration. For this enzyme the enantioselectivity was higher in the case of the *anti*-diol.

Methyl (±)-(3*R,5*R**,6*E*)-3,5-Dihydroxy-7-phenyl-6-heptenoate (*rac*-5):** Sodium borohydride (1.1 g, 29.2 mmol) was added under argon at 18°C in small portions to acetic acid (35 ml) and stirred for 5 min until the hydrogen formation ceased. Then the keto ester **rac-4**[3] (1.83 g, 7.4 mmol) dissolved in acetic acid (8 ml) was added and stirring was continued at 22°C for 2 h. Acetic acid was removed under reduced pressure. The residue was distributed between water (50 ml) and dichloromethane (50 ml). After separation the aqueous phase was extracted with dichloromethane (3 x 40 ml). The organic phase and the combined extracts were dried with sodium sulfate and concentrated under reduced pressure. Flash chromatography of the residue on silica gel with hexane/ethyl acetate (1:2) as eluant afforded a 88:12 mixture (1.56 g, 85 %) of the *anti*-diol ***rac*-5** and the *syn*-diol ***rac*-1**. Pure ***rac*-5** (1.1 g; 61 %) was obtained by recrystallization from diisopropyl ether in the form of yellow needles: M.p. 52-54°C; ^{13}C NMR ($CDCl_3$): δ = 41.15, 42.16, 51.92, 65.69, 70.07, 126.69, 127.86, 128.80, 130.26, 131.97, 136.88, 173.45; Anal. calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.95; H, 7.21.

Enzyme-catalyzed Lactonization of the *syn*-Diol *rac*-1 and the *anti*-Diol *rac*-5. - General Procedure: Pancreatin[10] (400 mg) or lipase from *Candida sp. 382*[11] (80 mg) were added to a solution of ***rac*-1** and ***rac*-5**, respectively, (200 mg, 0.8 mmol) in the solvent (10 ml) given in the Table. The mixture was stirred at 22°C for 8-214 h. Then the enzyme was filtered off and the filtrate was concentrated under reduced pressure. Column chromatography of the residue with ethyl acetate/diethyl ether (1:1) as eluant afforded the lactones **2**/***ent*-2** and **6**/***ent*-6**. The e.e. were determined by HPLC with hexane/2-propanol (80:20, v:v) as eluant. At a flow rate of 2 ml/min the retention times were 6.3 min for ***ent*-2** and 8.7 min for **2** on Chiralcel OF. The corresponding values for **6** and ***ent*-6** were 24.7 and 22. 2 min at a flow rate of 0.5 ml/min on Chiralcel OD. Yields and e.e.'s are given in the Table.

(3R,5S,6E)-3-Hydroxy-7-phenyl-6-hepten-5-olide **(2)***:* M.p. 103-105°C (Et_2O) (Ref.[3]: M.p. 103-105°C); $[\alpha]_D^{20}$ = 12 (c = 0.95, CH_2Cl_2), e.e. = >99 %.

(3R,5R,6E)-3-Hydroxy-7-phenyl-6-hepten-5-olide **(*ent*-6):** M.p. 89-91°C (iPr_2O); $[\alpha]_D^{20}$ = -16 (c = 0.75, methanol), e.e. = 96 %; ^{13}C NMR ($CDCl_3$): δ = 38.32, 39.57, 63.93, 77.70, 126.22, 126.94, 128.59, 128.92, 133.09, 135.95, 170.61; Anal. calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.12; H. 6.43.

Acknowledgement. The authors are grateful to Mrs. Karin Schiche for skilful technical assistance. Financial support by the Fonds der Chemischen Industrie is gratefully acknowledged.

References and Notes

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10. Pancreatin (6 x NF, 360 U/g, triolein as substrate, 5.4% H_2O) was purchased from Fa. Belger, Kleinmachnow, Germany.
11. Lipase from *Candida sp. 382* (40 BIU/g, 2 % H_2O) was a generous gift of Novo Industri A/S, Copenhagen, Denmark.