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STRUCTURE AND DIASTEREOSELECTIVITY OF THE α-HYDROXYLATION OF CHIRAL ESTER ENOLATES BY MOLYBDENUM PEROXO COMPLEX

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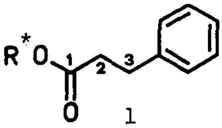
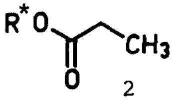
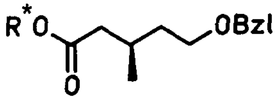
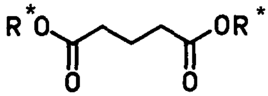
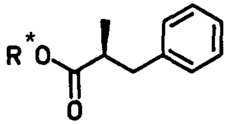
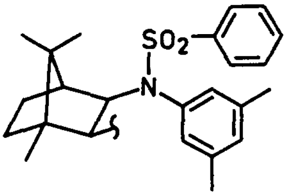
ABSTRACT: Scope and limitations of the diastereoselective α-hydroxylation of chiral ester enolates by $MoO_5 \cdot Py \cdot HMPT$ were investigated. An improved synthesis of natural(-)-verrucarinolactone ((-)-(2S,3R)-2-hydroxy-3-methyl-pentanolide) is described.

In a previous paper we have described results on the α-hydroxylation of esters of 3-phenylpropionic acid with chiral alcohols derived from camphor[1]. Experimental conditions were elaborated which led to a diastereomeric excess of 98% de with a yield of 73% of the isolated products[2]. In order to gain some information about the scope and limitations of the method, we have extended the studies to chiral esters of additional carboxylic acids. The results are summarized in the Table. As expected, the diastereoselection of the α-hydroxylation of propionate 2 (obtained by reacting the chiral alcohol with either propionylchloride in 75% yield or with S-2'-pyridyl-3-phenylthiopropionate[2] in 70% yield) was the same as in the case of 3-phenylpropionate 1 (Exper. 1 and 2). The introduction of a chiral centre at C-3, as shown by the pentanoate 3 (Exper. 3), also did not change the diastereoselection. The esters 1, 2 and 3 were transformed predominantely to the (S)-isomers. It is interesting to note, that the diastereoselection did not decrease upon raising the temperature to -30°C. The results obtained with the esters 1, 2 and 3 are remarkable because so far the structure of the carboxylic acids used to change the diastereoselectivities to a large extent[4]. Experiment 4 represents an interesting case because the diester 4 (obtained by refluxing the chiral alcohol with glutaryl dichloride for 60 h in 88% yield) was only monohydroxylated, even when an excess of the reagents was used in order to allow dihydroxylation (Exper. 4). The presence of the second bulky ester group seems to prevent the dihydroxylation of the dianion. The diastereoselectivity of the monohydroxylation was slightly decreased. The yield of 47% corresponds to that of Exper. 3.

Table

Hydroxylation of Ester Enolates with MoOPH Complex Using 2 equiv. $KN(SiMe_3)_2$ and 8 equiv. K(sec-BuO)[a]

Exper.	Ester[b]	Reaction time	Temp.	(R)/(S)-Ratio	Yield [%][d]
1	 1	40 min	-52° to -46°	1:99[e]	73
2	 2	2 h	-56° to -46°	1:99[e]	74
3	 3	8 h	-56° to -30°	1:99[e]	48
4	 4	1h 40min	-65° to -59°	5:95[f]	47
5	 5	60 h	-50° to -30°	30:70[f]	10

R* = ; Bzl = $CH_2-C_6H_5$

a General procedure[2].

b Synthesis of ester 1 see[2].

c Determined by HPLC (LiChrospher Si 100 5 µm, Merck, solvent ethylacetate-pentane) and by isolation of both diastereoisomers.

d Isolated yield of pure (S)-diastereoisomer.

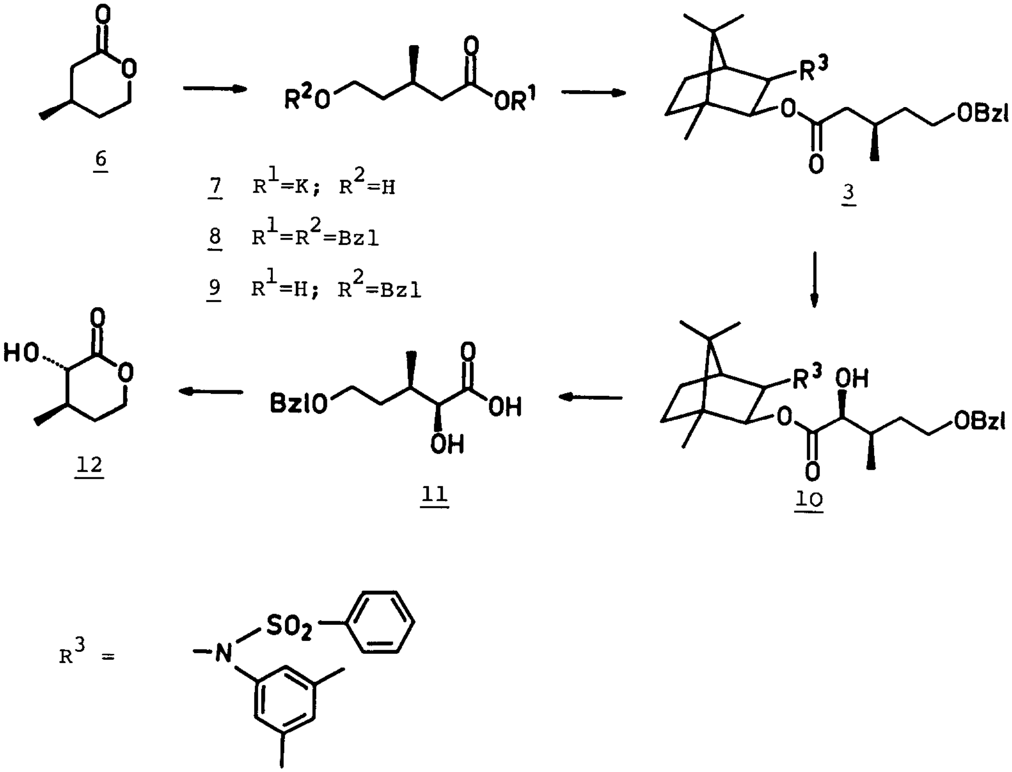
e Determination of the absolute configuration by hydrolysis to the corresponding α-hydroxy-acid.

f Absolute configuration not determined.

In the last example, 2-methyl-3-phenylpropionate 5 (prepared by benzylation of 2 with benzyl bromide[3]), the very low yield of isolated product and the decreased diastereoselectivity indicate that not only the enolate of 5 is not formed selectively but also the oxidation of a tertiary carbon atom by the molybdenum complex is very slow, probably due to steric reasons (Exper. 5).

According to these results it is possible to obtain α-hydroxyesters in very high optical purity if they do not contain substituents in the 2-position.

The excellent diastereoselectivity of the hydroxylation of ester 3 offered the opportunity of a significant improvement of the synthesis of natural (-)-verrucarinic acid ((2S,3R)-2,5-dihydroxy-3-methylpentanoic acid). The



6

7 R^1=K; R^2=H

8 R^1=R^2=Bzl

9 R^1=H; R^2=Bzl

3

10

11

12

δ-lactone 6 served as starting material as in an earlier synthesis[5]. It was transformed to the potassium salt 7. Treatment of the latter with sodium hydride, benzyl chloride and tetrabutyl ammonium iodide led to the benzyl ester 8 (yield 45%). The ester was hydrolysed to the acid 9 by KOH in MeOH (yield 99%). Condensation of 9 with the chiral alcohol (cf. Table), in the presence of carbonyldiimidazole and sodium[6], gave the ester 3 (yield 65%). By subsequent hydroxylation as described above and hydrolysis with KOH in aqueous methanol for several days, the α-hydroxy-acid 11 was obtained (yield 95%). It was converted to (-)-verrucarinolactone ((-)-(2S,3R)-hydroxy-methyl-pentanolide) (12) by hydrogenation using Pd as a catalyst in acetic acid/THF (1:9) (yield 95%). According to GC-MS analysis of 12 the (2R)/(2S)-ratio was 9:91. Thus racemization must have taken place to a slight extent during the base hydrolysis and not in the course of the α-hydroxylation ((2R)/(3S)-ratio was 1:99), although no racemization had been observed in the case of the other α-hydroxy-esters.

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