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ENZYMATIC HYDROLYSIS OF PROCHIRAL CIS-1,4-DIACYL-2-CYCLOPENTENEDIOLS: PREPARATION OF (1S,4R)-AND (1R,4S)-4-HYDROXY-2-CYCLOPENTENYLDERIVATIVES, VERSATILE BUILDING BLOCKS FOR CYCLOPENTANOID NATURAL PRODUCTS [1].

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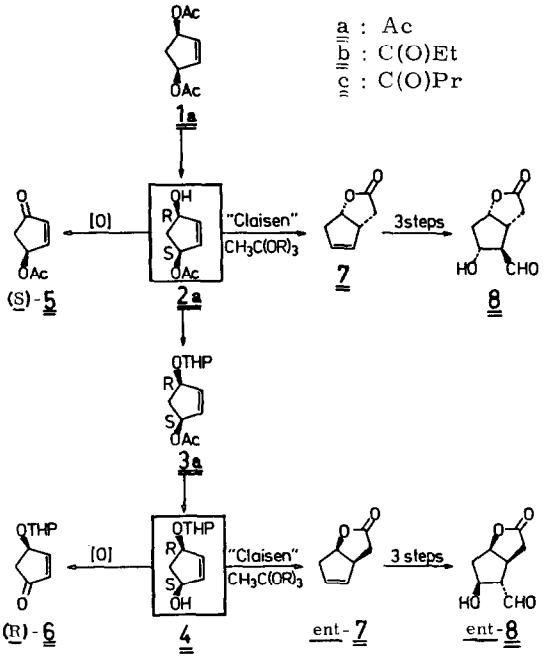
Summary : The enzymatic hydrolysis of prochiral diesters 1 was studied in presence of seven enzymatic systems, resulting in the enantioselective preparation of both enantiomeric series of chiral building blocks 2 - 4 and ent- 2 - 4 on a preparative scale .

4-Oxo-2-cyclopentenylderivatives (e.g. (R)-/(S)- 5 or 6) are useful building blocks for numerous cyclopentanoid natural products [2] . (R)- 6 and the "Corey lactone " 8 are important starting materials for the enantioselective preparation of prostaglandins[3], and therefore attractive targets in organic synthesis. Enantioselective transformation of the prochiral title compounds 1a - c , readily accessible in large quantities from cheap starting materials [4], would lead to the chiral monoesters 2a - c (or ent-2a-c) , from which , by choice , both enantiomeric series of the above molecules are available by selective functional group manipulation (Scheme) . Applications of the "meso-trick" to this effect[5]



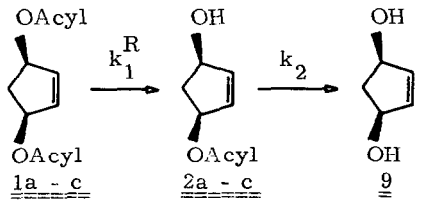
SCHEME

are involving (often tedious) separations of diastereomers, yielding maximal 50% (in practice usually 20-25%)[5b] of each enantiomer.

Enzymes, in contrast, are capable of converting prochiral substrates (like 1) enantioselectively and quantitatively (100% in theory, often ca. 90%, see below) into one enantiomer by enantiotopous group differentiation. In view of the synthetic value of the above molecules it is not surprising that the enzymatic hydrolysis of 1a has been studied before[6]. The obtained chemical and optical yields (15-35% e.e.) were, however, unsuitable for a practical application in organic synthesis[7]. We report here :

(1) a practical method for the synthesis of both 2a and ent-2a on a preparative scale ;

(2) a systematic study of the hydrolysis of 1a-c in presence of seven different, commercially available, enzymatic systems and the dependence of (a) chemical yields ;(b) enantiomeric purity ;(c) absolute configuration;(d) reaction times from the nature of the acylgroup and the enzyme (equ. 1) .



a : Ac
b : C(O)Et
c : C(O)Pr (1)

In a series of experiments 1a - c (10 mmol) were suspended in 0.1 M phosphate buffer (20 ml, pH 7 , T= 32°C) and treated with the appropriate enzyme preparation . The beginning hydrolysis was indicated by the decrease of the pH , which was maintained constant at pH 7 by continous addition of 1N NaOH - solution from an autoburette , the time dependence of the reactions being recorded automatically. In contrast to prochiral dicarboxylic esters these reactions (with one exception, entry 3, table) do not terminate after saponification of one ester function. The optimal point for termination is therefore controlled by the relative rates for hydrolysis of the first (k_1) and second (k_2) ester group in 1a - c . Only if $k_1 > k_2$ high chemical, and if $k_1^R > k_1^S$ high optical, yields can be expected [8] .

The results are listed in the table and can be summarized as follows :

(a) Chemical yields : They are best in all cases for 1a and are decreasing for 1b, c ;

(b) Enantiomeric purities: The highest values are obtained for the esterase from porcine liver (PLE) , followed by bakers yeast and the lipases from Rhizopus sp. and Candida cylindracea . Although both acetylesterases (entries 2, 3) are producing high chemical yields of products in a very short time , 2a is formed nearly racemic.

(c) Absolute configurations : The (R)- acyl group is preferentially hydrolized by α-Chymotrypsin , bakers yeast and PLE (entries 1, 4, 5) , whereas the lipases showing a preference for the (S)- acyl groups (entries 8-10) .

(d) Reaction times : The fastest reactions were observed with the acetyl esterases, followed by PLE and the lipase from Candida cylindracea . Too slow for practical applications were the reactions with α -Chymotrypsin and Rhizopus sp. The slowest reaction was ob-

TABLE . ENZYMATIC HYDROLYSIS OF CIS-1,4-DIACYL-2-CYCLOPENTENE DIOLS (1a - c).

ENTRY	SUBSTRATE	ENZYME	ABS. CONFIG. [a]	CHEM. YIELD(%) [b]	R:S (% e.e.) [c]	REACT. TIME [d] (h u^{-1} $mmol^{-1}$)
1	1a	α-CHYMOTRYPSIN (E.C. 3.4.21.1)	R	73	71:29 (42)	6×10^3
2	1a	ACETYLESTERASE (E.C. 3.1.1.6)	R	79	52:48 (4)	0.73
3	1a	ACETYLESTERASE(bacillus subt.) [e]	R	93	53:47 (6)	0.05 [f]
4	1a	SACCHAROMYCES CEREVISIAE (BAKERS YEAST)	R	87	87:13 (74)	very slow
5	1a	ESTERASE (PORCINE LIVER)PLE (E.C. 3.1.1.1)	R	86	93: 7 (86) [g]	1
6	1b	dto	R	52	83:17(66)	-
7	1c	dto	R	trace	65:35 (30)	-
8	1a	LIPASE(CANDIDA CYLINDRACEA) (E.C. 3.1.1.3)	S	82	25:75 (50)	555
9	1b	dto	S	60	46:54 (8)	-
10	1a	LIPASE (RHIZOPUS SP.)	S	83	17:83 (66)	6×10^5

a) hydrolized acyl group ; b) isolated ; c) cap. GLC of the diastereomeric (-)-MTPA-("Mosher")-esters (ref. 14); d) relative to PLE = 1.0 ; e) whole organism ; f) estimated ; g) after one recrystallisation .

served with baker's yeast (entry 4). In view of the high chemical and optical yields and the low cost of the catalyst, we are presently investigating this reaction in more detail .

Taking into account factors (a) - (d) and the cost of the enzymes , the following two procedures for the preparation of both 2a and ent- 2a were chosen for optimisation on a preparative scale :

(-)-(1S,4R)-4-Hydroxy-2-cyclopentenylacetate (2a) : 12.9 g (70 mmol) of 1a were suspended in 0.1 M phosphate buffer (140 ml , pH 7 , T=32 °C) and treated with 10 mg (1000 units) of PLE (Boehringer) . By continous addition of 1N NaOH-solution the pH was kept constant during the hydrolysis. After consumption of 74 ml (1.05 equ.) of NaOH (8 h) the mixture was extracted with Et_2O to yield, after work up and fract. distillation 8.6 g(86%) of 2a , b.p.$_{0.2}$ = 82 °C ; $[\alpha]_D^{20}$ - 49.7 °(c 0.86, $CHCl_3$) . One recrystallisation from Et_2O/PE (2:1) produced crystalline 2a , m.p. 40-40.5 °C ; $[\alpha]_D^{20}$ -60.4 °(c 0.27, $CHCl_3$) [9] .

(+)-(1R,4S)-4-Hydroxy-2-cyclopentenylacetate (ent- 2a) : 9.2 g (50 mmol) of 1a were suspended in 0.1 M phosphate buffer (70 ml, pH 7 , T=30 °C) and treated with 250 mg of lipase (Candida cylindracea , Sigma) . The pH was kept constant as shown above . After addition of 51.7 ml of 1N NaOH (27 h) the reaction mixture was worked up as above to yield 5.85 g (82%) of ent- 2a , $[\alpha]_D^{20}$ 28.6 ° (c 1.3 , $CHCl_3$) .

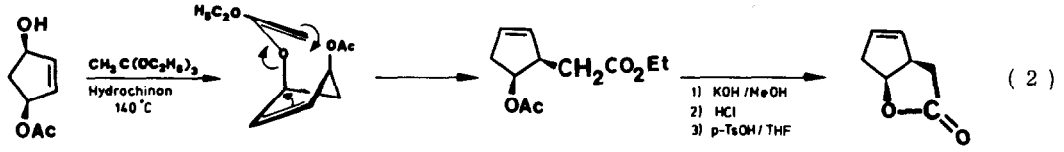
As shown before in other cases [10], the enantioselectivity, although not 100% , is frequently sufficient for purification by simple recrystallisation. 2a can thus be obtained optically pure (> 96% e.e. , $[\alpha]_D^{20}$ - 68 °) by further recrystallisation ; we are confident to purify also ent- 2a during the further progress of this work .

Regardless of this, both enantiomeric series can be interconverted by simple functional group manipulation as demonstrated for 2a (Scheme) :

(1) Conversion of 2a (DHP, p-TsOH, 95%) into (-)-(1S,4R)-4- tetrahydropyranoxy-2-cyclopentenylacetate (3a) [5a,9] ;

(2) Removal of the acetate function (enzymatically or NaOH/THF/H_2O, RT, 95%) leading to (+)-(1S,4R)-4- tetrahydropyranoxy-2-cyclopentenol (4) [9].

Oxidation of 2a and 4 (MnO_2 , PCC) [5a,6a] leads to (S)- 5 and (R)-6, respectively. Claisen rearrangement of 2a and 4 ($CH_3C(OEt)_3$, hydroquinone, 140 °C , 80%, eq. 2) [11]



2a 7 (2)

produces the lactones 7 and ent-7 , respectively , again useful intermediates in prostaglandin synthesis [12] . 7 and ent- 7 can be converted [13] in 3 steps via the " Prins"-reaction into the "Corey lactone " (8) and its "unnatural" enantiomer ent- 8 .

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8. Since the reactions are not completely enantioselective, four rate constants have to be considered. A full mathematical treatment of this will be published in the full paper .
9. 2a : ^{1}H-NMR($CDCl_3$) δ=1. 62(1H, dt, J=4,15 Hz) , 2. 03(3H, s, CH_3), 2. 50(1H, bd, J=6,5Hz, OH), 2. 79(1H, dt, J=7,15Hz), 4. 71(1H, m), 5. 50(1H, m), 6. 05(2H, AB, J=7. 5Hz) ; 3a : ^{1}H-NMR($CDCl_3$) δ = 1. 45-1. 90 (7H, m), 2. 07(3H, s, CH_3), 2. 75-2. 94(1H, ddt), 3. 48-3. 58 (1H, m) , 3. 84-4. 07(1H, m), 4. 64-4. 78(2H, m), 5. 45-5. 52(1H, m), 5. 94-6. 0(1H, m), 6. 09-6. 18(1H, m), 1:1 mixture of diastereomers $[\alpha]_D^{20}$ - 8. 0° (c 1. 65, $CHCl_3$) ; 4 : ^{1}H-NMR ($CDCl_3$) δ = 1. 46-1. 90 (7H, m), 2. 68(0. 5H, dt, J=7, 14 Hz), 2. 75(0. 5H, dt, J=7, 14 Hz), 3. 14 (1H, bs, OH), 3. 48-3. 59(1H, m), 3. 72-3. 82(1H, m), 4. 59-4. 68(2H, m), 4. 72-4. 79(1H, m), 5. 97-6. 05(2H, m);1:1 mixture of diastereomers; $[\alpha]_D^{20}$ 21. 5° (c 3. 12, $CHCl_3$) .
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