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THE SYNTHESIS OF CHIRAL ISOPROPYLIDENE DERIVATIVES OF 1,2,3-CYCLOHEXANETRIOLS BY ENZYMATIC DIFFERENTIATION

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Abstract : *2,3-O-Isopropylidene-1-cyclohexanol chiral building blocks have been prepared with high enantiomeric purities by enzymatic hydrolysis of their racemic acetates or n.butyrates.*

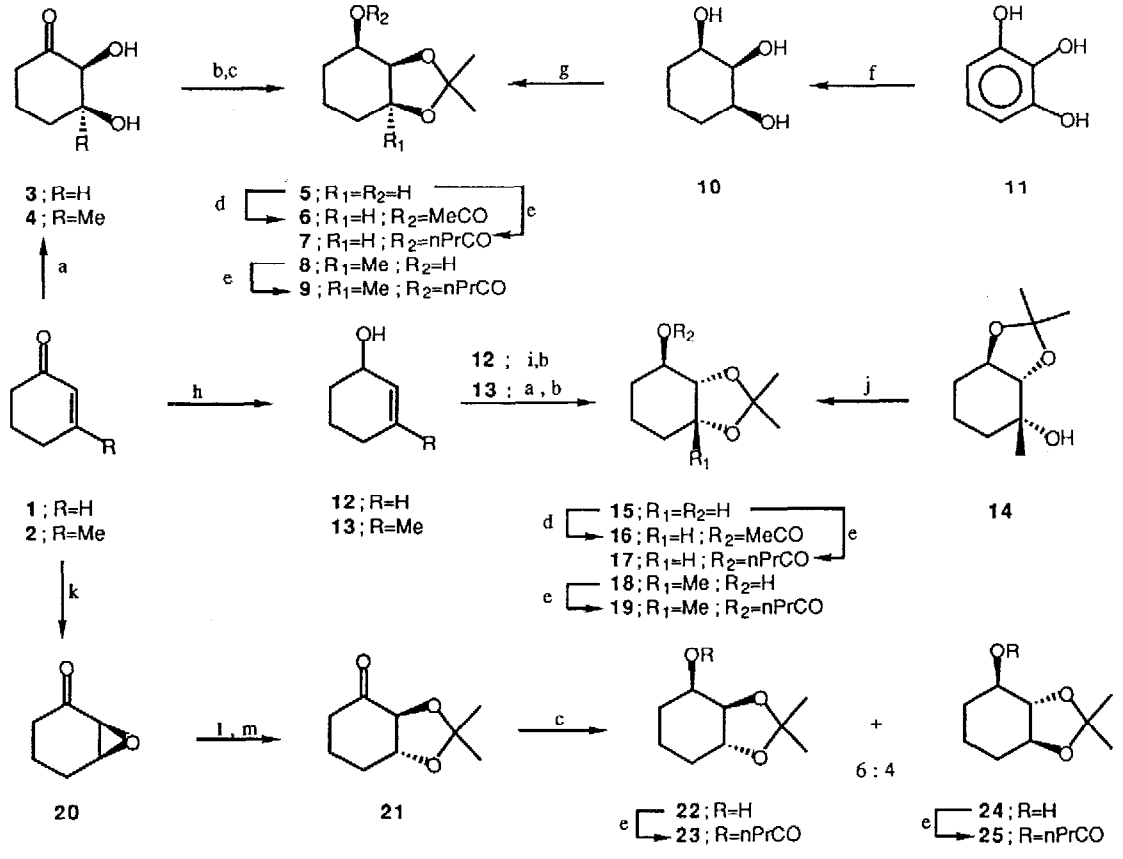
The cyclohexane ring is a pivotal element in a large number of natural products. Recently we have started a study of several potential approaches to suitably functionalized optically active cyclohexanes with potential value in the total synthesis of selected target molecules[1].

In this Letter we want to describe, as part of this program, the preparation of optically active 1,2,3-cyclohexanetriol derivatives by the action of hydrolytic enzymes (esterases, EC 3.1.1.1, and lipases, EC 3.1.1.3) on racemic mono-esters[2]. Tri-esters as substrates were not investigated because of possible acyl migrations in the hydrolyzed products. Therefore, we selected racemic substrates in which two of the three hydroxyl groups are protected as acetonides.

The synthesis of the racemic substrates is summarized in scheme 1. The cis-fused isopropylidene derivatives with an endo oriented acyloxy group **6**, **7** and **9** were obtained via syn-dihydroxylation[3] of **1** or **2** followed by ketalisation, exo-selective reduction of the carbonyl function and esterification. A facile multi-gram scale preparation of **5** consists of catalytic hydrogenation of unexpensive pyrogallol (**11**) in 40 % unoptimized yield and subsequent ketalisation. To the best of our knowledge hydrogenation of **11** has not yet been described in the literature. The exo-isomers **16**, **17** and **19** were obtained via dihydroxylation of 2-cyclohexenols **12** and **13** respectively. Treatment of the diol, obtained from **13**, with pTSA and acetone led to **18**, but the conversion was low (ca 50 %). Surprisingly, substituting acetone for 2,2-dimethoxypropane yielded exclusively the trans-fused isopropylidene derivative **14** (86 % yield) as the kinetic product. Subsequent Amberlyst-15 mediated isomerization of **14** gave quantitatively the desired more stable **18**. The trans-fused substrates **23** and **25** were prepared via initial epoxidation of **1**.[4] After hydrolytic epoxide opening, under neutral conditions, acetonide formation of the trans-diol could only be effected with 2-trimethylsilyloxy-propene (TMSP).[5] Finally reduction of the keto function gave the alcohols **22** and **24** in 6:4 ratio.

The enzymatic saponifications of the substrates were studied in the presence of several hydrolases. The experiments were carried out in a phosphate buffer (0.1 M) at pH 7 and at 35°C, by continuous addition of NaOH (1 M), and monitored by a pH-stat apparatus. After addition of 50 % of the amount of base needed for complete hydrolysis, the reactions were terminated by extraction with ether. The results are summarized in the table where the symbol > for % ee indicates that no enantiomer could be detected by the analytical method used.

It is evident from inspection of the table that, in the cis-fused series, the enantioselectivity is highly dependent on the orientation of the acyloxy group. The exo-esters **16** and **17** (entries 11, 12) are poor substrates compared to the endo-isomers **6**, **7** and **9** (entries 2, 3, 5, 6, 8, 9).



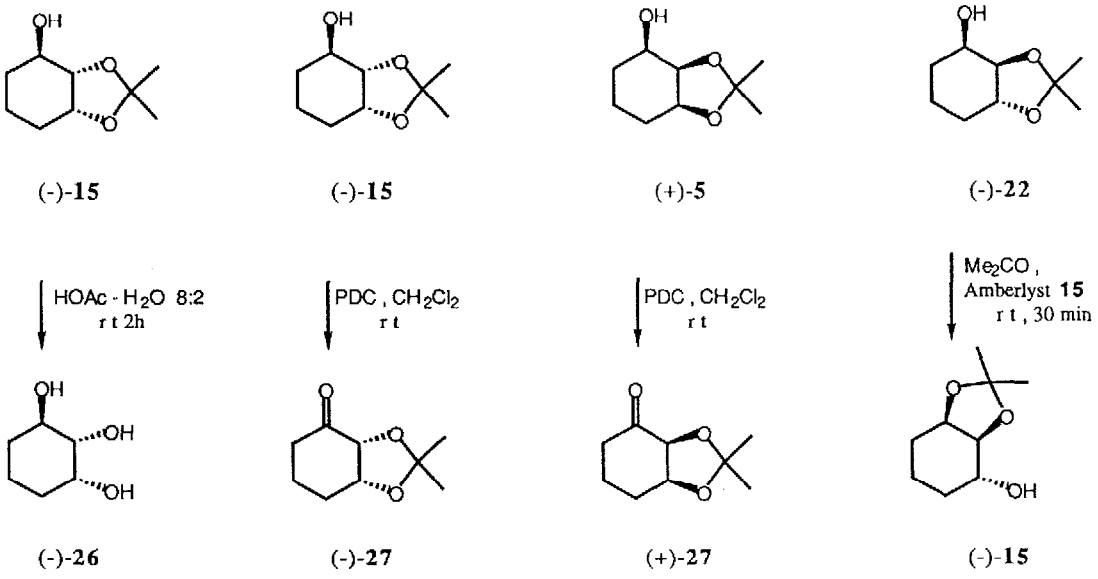
a : OsO_4, $KClO_3$, THF:H_2O 1:1, rt, R=Me : 6 days, R=H : 24 h, (ca 60 %); b : Me_2CO, pTSA, rt 12 h, (50-70 %); c : $NaBH_4$, MeOH, 0°C (1 h), (95 %); d : Ac_2O, pyr, DMAP, rt 2 h; e : nPrCOCl, Et_3N, DMAP, CH_2Cl_2, 0°C 2 h; f : Raney-Ni, H_2, EtOH, 100 atm, 100°C 3 h, (40 %); g : $Me_2C(OMe)_2$, pTSA, rt 12 h, (95 %); h : $NaBH_4$, $CeCl_3$, MeOH, 0°C, 15 min, (86 %); i : $HO_2CCH_2CH_2CO_3H$, H_2O, 2 h, (53 %); j : Me_2CO, Amberlyst 15, rt, 10 min; k : H_2O_2, NaOH (cat.), MeOH, 0°C, 20 min, (94 %); l : H_2O, 70°C, 30 h, (73 %); m: TMSP, HCl(g), CH_2Cl_2, rt, 2h, (95 %).

Scheme 1

However a higher enantioselectivity of Candida cylindracea lipase for the methyl substituted n.butyrate **19** than for **17** is observed. This could be due to a conformational effect, as in **17**, the acyloxygroup is equatorially oriented, while in **19** it occupies an axial position.

On the other hand both racemic butyrates of the trans-fused isomers **23** and **25** (entries 14, 15, 16) are equally excellent substrates as no enantiomer could be detected.

As can be seen from the table (entries 1, 4 and 10) PLE is an unselective enzyme for the substrates studied.



Scheme 2

TABLE : Results of the Enzymatic Hydrolyses

Entry	Substrate	Enzyme[a]	Time (h) (mmol)		% conv.[b]	Alcohol formed chem. yield		% ee [c]	$[\alpha]_D^{20}$ [d]	Ester remaining chem. yield	% ee [e]	$[\alpha]_D^{20}$ [d]
1	(±)-6	PLE	10	(1)	43	44	5	56	+ 6.1° (c=0.8)	48	43	-19.4° (c=0.4)
2	(±)-6	Cand. C	4	(1)	43.5	46	5	>95	+10.2° (c=0.4)	49	73	-38.2° (c=1.1)
3	(±)-6	SAM II	1.25	(1)	50	47	5	>95	+11.1° (c=0.7)	42	>95	-48.8° (c=0.5)
4	(±)-7	PLE	3	(1)	50.5	48	5	38	+ 4.6° (c=0.6)	42	39	-17.0° (c=0.8)
5	(±)-7	Cand. C	0.75	(1)	57	45	5	72	+ 7.3° (c=0.8)	46	>95	-47.7° (c=0.6)
6	(±)-7	SAM II	0.5	(1)	50	43	5	>95	+12.3° (c=0.6)	40	>95	-41.2° (c=0.7)
7	(±)-7	PPL	24	(1)	58	49	5	69	+ 8.2° (c=0.8)	46	>95	-33.3° (c=0.5)
8	(±)-9	Cand. C	2.5	(1)	43	32	8	>99[f]	-13.8° (c=0.5)	45	71	-24.1° (c=0.7)
9	(±)-9	SAM II	10.5	(1)	42	40	8	>99[f]	-13.9° (c=0.8)	44	69	-25.9° (c=0.9)
10	(±)-16	PLE	28	(5)	50	49	15	11	-12.5° (c=3.8)	48	11	+13.2° (c=4.8)
11	(±)-16	Cand. C	113	(5)	50	45	15	25	-31.2° (c=1.8)	49	25	+25.3° (c=1.1)
12	(±)-17	Cand. C	5	(1)	54	48	15	31	-27.2° (c=0.5)	46	36	+29.6° (c=0.5)
13	(±)-19	Cand. C	24	(1)	47	37	18	84[f]	+24.7° (c=1)	46	77[f]	-3.8° (c=1)
14	(±)-23	Cand. C	9	(0.6)	50	35	22	>95	-36.9° (c=0.8)	50	>95	+40.0° (c=1.3)
15	(±)-25	Cand. C	4.5	(0.6)	50	35	24	>95	+9.7° (c=0.7)	48	>95	+17.3° (c=0.6)
16	(±)-25	SAM II	4	(0.6)	50	30	24	>95	+10.7° (c=0.6)	50	>95	+17.4° (c=0.6)

a Pig liver esterase (PLE; Boehringer; 52 units mmole substrate); Pig pancreatic lipase (PPL; Sigma, type II); Cand. cyl. lipase (Sigma, type VII); SAM II (Amano Pharm. Co.) - 50 mg lipase powder/mmole substrate was used.

b Calculated from the % ee-values of product and of remaining ester (after hydrolysis; see e).[6]

c Determined by ^{1}H NMR (360 MHz, $CDCl_3$) in the presence of Eu(hfc)$_3$ except for values marked f).

d All optical rotations were measured in $CHCl_3$ at 20°C.

e Determined on the corresponding alcohol (formed by basic hydrolysis of the ester) by ^{1}H-NMR (360 MHz, $CDCl_3$) in the presence of Eu(hfc)$_3$.

f Determined by GC-analysis of the corresponding N-isopropylcarbamate on a Chirasil-Val capillary column.[7]

The absolute configurations of the alcohols formed were deduced by Horeau's method.[8] In all cases the 1(R)-configuration (as depicted in scheme 1) was found. In a few cases facile chemical correlation was possible because the absolute configuration of (-)-**26** has been established as being the 1(R),3(R)-form[9] (scheme 2). Hydrolysis of R(-)-**15** gave (-)-**26**; on the other hand oxidation of (-)-**15** led to ketone **(-)-27** while (+)-**5** gave the enantiomer (+)-**27**, thus confirming the absolute configuration of (+)-**5**. The absolute configuration of the trans acetonide (-)-**22** was proven by Amberlyst-15 catalyzed isomerisation to the more stable cis-isomer (-)-**15**, together with some (-)-**26** due to concomitant hydrolysis..

Applications of the optically pure products, especially of **5** and ent-**5** are under study.

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