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Aryl Propargylic Alcohols Of High Enantiomeric Purity *via* Lipase Catalyzed Resolutions

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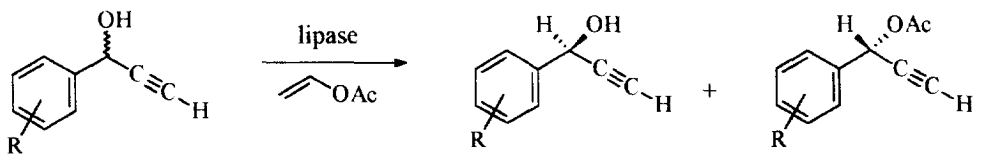
Abstract: A variety of substituted aryl propargylic alcohols were prepared *via* lipase catalyzed resolutions, the enantioselective hydrolysis of the corresponding esters being the method of choice.

The title compounds are useful starting materials for the synthesis of chiral allenes[1], benzo[b]furan(1-benzofuran) and indole derivatives[2]. An enantiospecific route to the latter class of compounds *via* transition metal mediated cyclisation of propargylic alcohols is described in the following paper of this issue[3]. In an attempt to provide a general and facile route to the required molecules and based on our previous experience in this area[4] we decided to explore the possibility of obtaining these materials *via* lipase catalyzed synthesis or hydrolysis of the corresponding esters[5].

The racemic starting materials were prepared in >80% yield by addition of bromomagnesium acetylide to the corresponding aryl aldehydes at temperatures ranging from -78 °C to 0 °C. Acetates and chloroacetates were synthesized by reaction of the alcohols with either acetylchloride or chloroacetic anhydride in the presence of triethylamine using dichloromethane as solvent.

Lipases are known to catalyze both the enantioselective esterification of racemic alcohols and/or the hydrolysis of their corresponding esters. Both reaction modes have previously been employed in our laboratory for that purpose using different substrates[4]. In order to identify the most desirable mode of transformation and the best suited enzyme for the present class of compounds a series of screening experiments were carried out.



(±)-1 (*S*)-1 (*R*)-2

Scheme 1: Enzymatic esterification of racemic propargylic alcohols

Studies aimed at the esterification of these target molecules in the presence of various lipases [from Hog Pankreas, Porcine Pankreas, *Aspergillus niger*, *Mucor javanicus*, *Candida cylindracea*, *Candida lipolytica*, *Penicillium roquefortii*, *Mucor miehei* (Lipozyme), SAM I and SAM II], carried out under the conditions of irreversible acyl transfer [100 mg alcohol, 176 µl vinylacetate, 5 ml *t*-BuOMe, 50 mg of the lipase] revealed

that only the two lipases derived from *Pseudomonas species* [SAM-I, II] were able to catalyze these reactions, albeit with rather low enantioselectivities and in preparatively unsatisfactory reaction times (Scheme 1, Table 1).

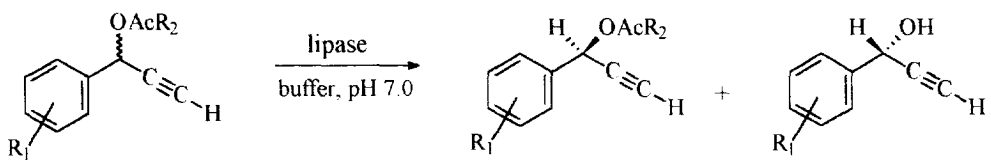
Table 1: Lipase catalyzed esterification of racemic propargylic alcohols.

Educt	Product	R	Reaction time [d][a]	Con-version	Yield [%][c]	Configu-ration[b]	$[\alpha]_D^{20}$ = [c]	ee [%][d]	E
(±)-1a[g]	**(*S*)-1a**	H	5.5	46	25	*S*	+20.0 (c=1.13)	72	26.5
	(*R*)-2a	H			39	*R*	+3.4 (c=1.07)	85	
(±)-1b[g]	**1b**	o-OMe			no conversion				
(±)-1c[g]	**1c**	m-OMe			no conversion				
(±)-1d[g]	**(*S*)-1d**	p-OMe	2.7	38.5	42	*S*	+5.3 (c=3.05)	10	1.5
	(*R*)-2d	p-OMe			38	*R*	+2.7 (c=1.01)	16	
(±)-1f[f]	**(*S*)-1f**	p-CN	6.0	23	n.d.	*S*	n.d.	<30	
	(*R*)-2f	p-CN			n.d	*R*	n.d.	<30	
(±)-1f[g]	**(*S*)-1f**	p-CN	6.0	40	n.d.	*S*	n.d.	37	5.1
	(*R*)-2f	p-CN			n.d.	*R*	n.d.	56	

a) 25% conversion. b) determined by method of Horeau[6] c) solvent: $CHCl_3$. d) determined as MTPA-Esters, NMR[7] e) Isolated and purified materials, f) SAM I, g) SAM II . n.d.: not determined.

From the results summarized in Table 1 it became immediately clear that enantioselective esterificatitions - both due the extremely long reaction times and the observed low enantioselectivities - would not allow the preparation of the title compounds on a satisfactory scale and with the required enantiomeric purities.

The corresponding hydrolyses of the acetates and chloroacetates derived from the title compounds proved to be much more successful (Scheme 2).



(±)-2 **(*S*)-2** **(*R*)-1**

Scheme 2: Enzyme catalyzed hydrolyses of esters derived from propargylic alcohols

While in this reaction mode several of the screened enzymes (see above) displayed hydrolytic activity, again only the two lipases from *Pseudomonas species* showed enantioselectivities which looked promising for preparative applications (Table 2). The observed enantioselectivities, expressed as E-values[8] in Table 2 proved to be strongly dependent on the substitution pattern of the benzene moiety, regarding both the type of substituent and its position on the aromatic ring. While in some cases products with very high enantiomeric purities could thus be obtained directly from the reaction mixtures [**1,2a**; **1,2h**; **1,2l**] or with extended conversions[8] [**1,2e**; **1,2g**; **1,2i**; **1,2k**; **1,2m**], in selected cases [**1,2f** ; **1,2d** ; **1,2b**; **1,2 c**] extremely low E-values were observed.

Table 2: Enzymatic hydrolyses of esters derived from propargylic alcohols

Educt	Product[b]	R_1, R_2	Time [h][a]	c [%]	Yield [%][f]	$[\alpha]_D^{20}$= [h]	ee [%][d]	E
(±)-2a	**(*S*)-2a**	H, H	4.8	47.3	45.2	-4.1 (c= 3.04)	87	>100
	(*R*)-1a	H, -			30.1	-26.8 (c= 3.18)	97	
(±)-2b	**(*S*)-2b**	o-OMe, H	2.4	85	13	+1.96 (c= 1.02	<5	1.05
	(*R*)-1b	o-OMe, -			28	-0.31 (c= 2.58)	<5	
(±)-2c	**(*S*)-2c**	m-OMe, H	2.4	76.4	45	-6.1 (c= 1.85)	38	5.7
	(*R*)-1c	m-OMe, -			31	-10.5 (c= 2.11)	95	
(±)-2d	**(*S*)-2d**	p-OMe, H	2.4	58.7	12	-6.6 (c= 1.02)	24	2.2
	(*R*)-1d	p-OMe, -			25	-13.1 (c= 3.22)	34	
(±)-2e	**(*S*)-2e**	p-Me, H	144	60.7	e)	n.d.	64.8	35
	(*R*)-1e	p-Me, -					<99.5	
(±)-2f	**(*S*)-2f**	p-CN, H	52	67.8	e)	n.d.	86.6	6
	(*R*)-1f	p-CN, -					41.2	
(±)-2g	**(*S*)-2g**	p-Me, Cl	10	56.4	40.7	-23.3 (c= 1.12)	97.8	36
	(*R*)-1g	p-Me, -			51.0	-27.9 (c= 3.05)	75.7	
	(*S*)-1g[g]	p-Me, -			98.9	+28.3 (c= 3.01)	97.7	
(±)-2h	**(*S*)-2h**	m-Me, Cl	4.5	51.8	43.5	-13.9 (c= 0.84)	99.2	>140
	(*R*)-1h	m-Me, -			46.1	-27.5 (c= 0.65)	92.1	
	(*S*)-1h[g]	m-Me, -			99.6	+27.7 (c= 0.74)	99.2	
(±)-2i	**(*S*)-2i**	o-Me, Cl	22	53.9	45.1	+16.2 (c= 1.25)	94.0	39
	(*R*)-1i	o-Me, -			46.9	-18.1 (c= 2.58)	80.4	
	(*S*)-1i[g]	o-Me, -			98.5	+21.8 (c= 1.30)	94.0	
(±)-2k	**(*S*)-2k**	p-F, Cl	11	53.8	44.9	-11.8 (c= 1.01)	96.8	45
	(*R*)-1k	p-F, -			53.1	-24.9 (c= 2.11)	83.2	
	(*S*)-1k[g]	p-F, -			98.9	+28.6 (c= 1.01)	98.8	
(±)-2l	**(*S*)-2l**	m-F, Cl	2.8	52.1	46.2	-5.3 (c= 1.33)	99.4	127
	(*R*)-1l	m-F, -			46.3	-21.1 (c= 1.44)	91.5	
	(*S*)-1l[g]	m-F, -			98.7	+23.1 (c= 1.13)	99.3	
(±)-2m	**(*S*)-2m**	p-CN, Cl	5.5	53.0	44.5	-31.3 (c= 0.98)	96.6	50
	(*R*)-1m	p-CN, -			49.5	-20.8 (c= 0.60)	85.5	
	(*S*)-1m[g]	p-CN, -			97.9	+21.1 (c= 0.54)	95.9	

a) 25% conversion. b) configuration determined by the method of Horeau[6]. c) conversion. d) determined by GC on a β-cyclodextrine column. e) product not isolated: ee-values and conversion determined directly in the reaction mixture. f) Isolated and purified materials. n.d.: not determined. g) Hydrolysis of (S)-2-Esters into the corresponding alcohols by treatment with saturated solution of potassiom carbonate in methanol at 0°C for 30 min MeOH. h) solvent: $CHCl_3$.

Table 3: Enzymatic hydrolyses of propargylic alcohol esters - effect of temperature and added cosolvents

Educt	R_1, R_2	Product	Co-solvent	Temperature [°C]	c [%]	Reaction time [h]	ee [%]	E
(±)-2e	p-Me, H	**(*S*)-2e**	None	RT	60.7	144	100	35
	p-Me, -	**(*R*)-1e**					64.8	
(±)-2e	p-Me, H	**(*S*)-2e**	None	35	50.4	134	80.8	22
	p-Me, -	**(*R*)-1e**					79.7	
(±)-2e	p-Me, H	**(*S*)-2e**	None	55	58.1	32	89.7	14
	p-Me, -	**(*R*)-1e**					64.8	
(±)-2e	p-Me, H	**(*S*)-2e**	MTBE (10%)	RT	38.1	47	47.3	12
	p-Me, -	**(*R*)-1e**					77.0	
(±)-2e	p-Me, H	**(*S*)-2e**	MTBE (25%)	RT	41.2	40	38.4	5
	p-Me, -	**(*R*)-1e**					54.7	
(±)-2e	p-Me, H	**(*S*)-2e**	Acetone (5%)	RT	48.2	76	79.5	31
	p-Me, -	**(*R*)-1e**					85.4	
(±)-2f	p-CN, H	**(*S*)-2f**	None	RT	67.8	52	86.6	6
	p-CN, -	**(*R*)-1f**					41.2	
(±)-2f	p-CN, H	**(*S*)-2f**	MTBE (10%)	RT	67.7	36	86.6	6
	p-CN, -	**(*R*)-1f**					41.2	
(±)-2f	p-CN, H	**(*S*)-2f**	MTBE (30%)	RT	66.0	36	86.8	7
	p-CN, -	**(*R*)-1f**					44.7	

c) conversion, MTBE: Methyl-tert. Butyl-Ether

In order to achieve higher enantioselectivities in these cases the influence of both added cosolvents and elevated temperatures was studied (Table 3). All attempts of this nature were unsuccessful; they resulted in fact in a reduction of the E-values.

Based on the experiments described above it became obvious that the following reaction conditions are best suited for the preparation of the title compounds.

Experimental:

10 mmol of the corresponding ester (acetate or chloroacetate) were suspended in 0.1M phosphate buffer (10 ml, pH 7.0) and the mixture was stirred at room temperature for ca. 10 min in order to test for non catalyzed hydrolysis. After that the crude lipase preparation of *Pseudomonas species* (SAM II) was added to the mixture (10% by weight of the ester). The reaction mixture was stirred at room temperature, while the pH of the reaction was kept at 7.0 by continuous addition of 1 N NaOH from an autoburette. The reaction progress was monitored by GC (β-cyclodextrine column) allowing the simultaneous determination of conversion and enantiomeric purities of both educt and product. After the desired or required conversion was achieved the reaction mixture was diluted with diethylether and water and the resulting phases were separated. The organic phase was washed with water and dried. After removal of the solvent the resulting products were separated and purified by chromatography on silica gel (eluent hexane / diethyl acetate 9 / 1, 500 ml, column: 3 x 30 cm, silica gel 200 mesh). The enantiomeric purities of purified products were determined by GC on the above mentioned chiral column. The determined e.e.' s of both the purified alcohols and esters were identical with those obtained directly from the reaction mixture. In none of the cases there were indications for racemisations during work up.

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