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Enzyme Assisted Preparation of Enantiomerically Pure β-Adrenergic Blockers II. Building Blocks of High Optical Purity and their Synthetic Conversion

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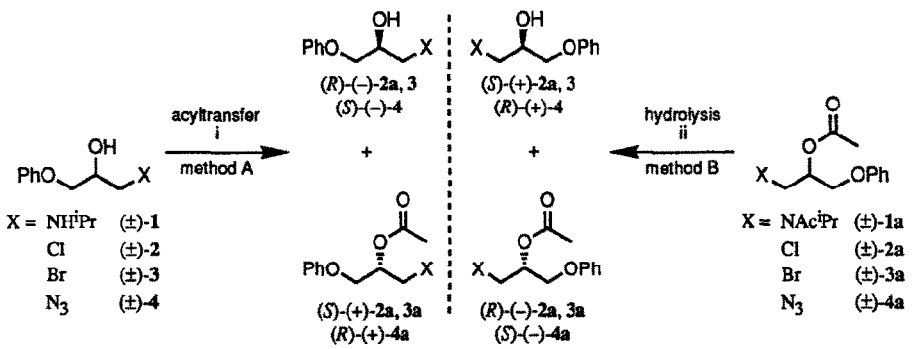
Abstract: Based on previous screening results a series of potential building blocks **2-4** for β-adrenergic blockers were prepared both by enzymatic hydrolysis and acyltransfer and further transformed into the corresponding oxiranes and aminoalcohols of defined absolute configurations.

In the preceding paper[1] we reported screening experiments resulting in the identification of a highly enantioselective lipase from *Pseudomonas sp.* for the preparation of potential precursors of title compounds in the optically pure form. By retrosynthetic analysis[1] α-aminoalcohols [(±)-**1**], α-chlorohydrins [(±)-**2**][2], α-bromohydrins [(±)-**3**][3] and α-azidohydrins [(±)-**4**][4] were identified as potential building blocks for β-blockers and consequently chosen for further synthetic studies.

Esterhydrolases (esterases, lipases) are well known to catalyze both the enantioselective synthesis of esters, e.g. by irreversible acyltransfer (method A) and their hydrolysis (method B). Based on our previous experience[5] in this area and literature data[6] both methods were employed for the corresponding bioconversions of the above intermediates, leading to products of complementary stereochemistry (Scheme 1).



Scheme 1 *Reagents*: i, 10 mmol substrate, 30 mmol vinylacetate, 10 ml ^{t}BuOMe, 400 mg lipase, rt.; ii, 10 mmol substrate, 20 ml phosphate buffer pH 7.0, 400 mg lipase, 20°C

In typical experiments (method A) alcohols [(±)-**1**, **2**, **3**, **4**] (10 mmol) were dissolved in ^{t}BuOMe (10 ml) containing vinylacetate (30 mmol). After addition of the crude lipase from *Pseudomonas sp.* (400 mg, 3200 u; standard: tributyrin) the resulting mixtures were stirred at room temperature, the reaction progress being monitored by HPLC. After the desired conversions (ca. 50 %) were reached, the enzyme was simply removed by filtration. Evaporation of the volatile components (^{t}BuOMe and vinylacetate) led to product mixtures of the corresponding alcohols [(*R*)-(–)-**2**, **3**, (*S*)-(–)-**4**] and acetates [(*S*)-(+)-**2a**, **3a**, (*R*)-(+)-**4a**].

Alternatively, the corresponding acetates [(±)-**1a**, **2a**, **3a**, **4a**] were mixed with 0.1 M phosphate buffer (20 ml, pH 7.0, 20°C) and enzymatically hydrolysed in the presence of the same lipase (400 mg, 3200 u; standard: tributyrin). The decreasing pH was kept constant throughout the reaction by continous addition of 1 M NaOH solution from an autoburette. The reactions were terminated after ca. 50 % consumption of base by extraction of the reaction mixture with CH_2Cl_2. After removal of the solvent, product mixtures containing the corresponding alcohols [(*S*)-(+)-**2**, **3**, (*R*)-(+)-**4**] and acetates [(*R*)-(–)-**2a**, **3a**, (*S*)-(–)-**4a**] of complementary stereochemistry, were obtained.

The products resulting from both series of experiments were separated by flash chromatography on SiO_2 (hexane/ethylacetate 1:4). With exception of (*R*)- and (*S*)-**3a**, which had to be hydrolyzed to the alcohols prior to their analysis on Chiralcel OD, the enantiomeric purities of all products were determined conveniently by enantioselective HPLC on commerically available colums [Chiralcel OD (alcohols), Chiralpak OT(+) and Chiralcel OB (acetates)][7].

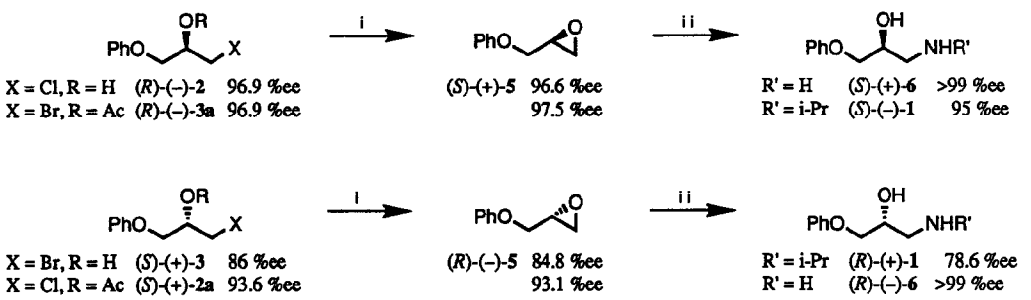
Table 1

substrate	method	t(25%) [h][a]	products	% e.e.[b]	% yield	conv.[8]	E[8]
(±)-**1**	A	–	(±)-**1**	–	–	–	–
(±)-**2**	A	16	(*R*)-(–)-**2**	95.6	42	0.5	223
			(*S*)-(+)-**2a**	96.6	44		
(±)-**3**	A	26	(*R*)-(–)-**3**	98.3	33	0.54	56
			(*S*)-(+)-**3a**	84.6[c]	56		
(±)-**4**	A	68	(*R*)-(–)-**4**	82.7	41	0.51	21
			(*S*)-(+)-**4a**	78.7	41		
(±)-**1a**	B	–	(±)-**1a**	–	–	–	–
(±)-**2a**	B	<2	(*S*)-(+)-**2**	92.3	31	0.51	107
			(*R*)-(–)-**2a**	97.2	41		
(±)-**3a**	B	<2	(*S*)-(+)-**3**	86	46	0.53	55
			(*R*)-(–)-**3a**	96.9[c]	41		
(±)-**4a**	B	8	(*S*)-(+)-**4**	90.8	48	0.48	55
			(*R*)-(–)-**4a**	84	48		

a) time required for 25 % conversion
b) alcohols determined by HPLC on Chiralcel OD, acetates on Chiralcel OB and Chiralpak OT(+)
c) analyzed as alcohol on Chiralcel OD

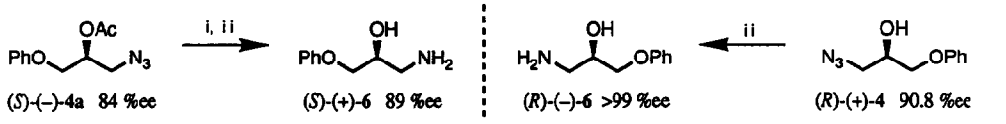
From Table 1 it is obvious that the α-chloro-derivatives [(±)-**2**, **2a**] are the best suited intermediates for our purpose. This is clearly reflected in the high *E*-values determined for the corresponding transformations. With all substrates of higher steric demand, e.g. (±)-**3**, **3a**, **4**, **4a** the observed enantioselectivities are considerable lower in presence of the chosen biocatalyst. Under the conditions employed none of the α-amino-substituted deriviatives [(±)-**1**, **1a**] were transformed in presence of the lipase used.

In order to confirm the absolute configurations of the obtained products, alcohols [(*R*)-**2**, (*S*)-**3**] and acetates [(*S*)-**2a**, (*R*)-**3a**] were converted under basic conditions into the known epoxides (*R*)- and (*S*)-**5**[9]. Regioselective ring opening of (*R*)- and (*S*)-**5** using ammonia or isopropylamine leads to the previously undescribed aminoalcohols **1a** and **6** in both enantiomeric forms, constituting the parent substructures of β-adrenergic blockers (Scheme 2).



Scheme 2 *Reagents*: i, KO^{t}Bu, THF, 0°C; ii, NH_3 or ^{i}PrNH$_2$, EtOH, 50°C

Alternative routes to optically pure (*R*)- and (*S*)-**6** are provided by the catalytic hydrogenation of the optically active α-azido derivatives [(*R*)-**4** or (*S*)-**4a**] (Scheme 3). By comparison with the products of known absolute configuration obtained earlier (Scheme 2), these transformations thus also secured the absolute configurations of (*S*)-**4a** and (*R*)-**4**.



Scheme 3 *Reagents*: i, MeOH/HCl; ii, H_2, Pd/C, MeOH, recryst.

Based on the highly enantioselective preparation of α-chlorohydrin derivatives both by enzymatic esterification and hydrolysis, the above experiments provide a general route to numerous intermediates for β-adrenergic blocking agents in optically pure forms and in synthetically useful quantities[10].

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