Tetrahedron: Asymmetry Vol. 3, No. 4, pp. 521-524, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

Enzyme Assisted Preparation of Enantiomerically Pure β-Adrenergic Blockers III. Optically Active Chlorohydrin Derivatives and Their Conversion

Ulrich Ader and Manfred P. Schneider*

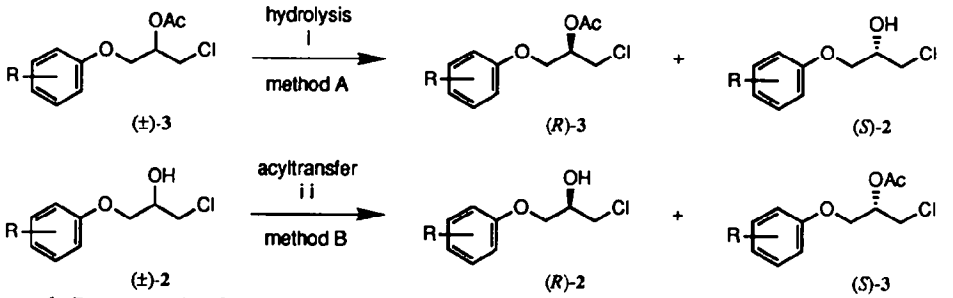
Fb. 9 Bergische Universität-GH-Wuppertal, D-5600 Wuppertal 1, Germany

(*Received* 24 *February* 1992)

Abstract: Optical active chlorohydrin derivatives **2a-m** and **3a-m** of both enantiomeric series were prepared via both enzymatic hydrolyses and acyltransfer reactions catalysed by a highly selective lipase from *Pseudomonas sp.*. The resulting building blocks were further transformed into the corresponding β-blockers of high enantiomeric purity.

β-Adrenergic blocking agents of the 1-alkylamino-3-aryloxy-2-propanol type **1** are widely used for the treatment of angina pectoris, hypertension and other cardiac diseases. It is well established that the desirable therapeutic activities reside mainly in the (*S*)-enantiomers of these molecules[1]. It seem also to be known that some of the opposite enantiomers (*R*)-**1** display undesireable side effects[2]. Although many of these pharmaceuticals are still marketed as racemates, considerable efforts have been made in recent years for the preparation in enantiomerically pure form, e.g. by asymmetric syntheses[3] or biotransformations[4]. Previous work[5] resulted in: a) the identification of α-chlorohydrin derivatives as suitable building blocks for these target molecules and b) suitable enzymatic methods for their preparation in high optical purity.

Based on these initial results the substituted (±)-1-aryloxy-3-chloro-2-propanol [(±)-**2a–m**][6] and the corresponding (±)-2-acetoxy-1-aryloxy-3-chloropropan [(±)-**3a–m**][7] were synthesized and resolved both by enzyme mediated acyltransfer (method B) and hydrolysis (method A), respectively (Scheme 1).



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

All these bioconversions were carried out as previously described[5]. The results are summarized in Tables 1 and 2. With the exception of **2h, l** and **3h, l** whose optical purities had to be determined via ^{1}H-NMR spectroscopy or HPLC of the corresponding "Mosher" [methoxy-(trifluormethyl)phenylacetyl-, MTPA-] esters[8], the enantiomeric purities of all products were again obtained *via* HPLC analysis on chiral supports[9] [Chiralcel OB, OD and Chiralpak OT(+)].

As outlined in Scheme 1 and further documented in Table 1 enzymatic hydrolyses of the acetates [(±)-3a-m] in presence of the lipase from *Pseudomonas sp.* led to the corresponding (*S*)-alcohols **2** and (*R*)-acetates **3**. All substrates with the exception of (±)-**3l**, a crystalline compound, were converted under the conditions employed[10].

Table 1

		(*R*)-3		(*S*)-2					
substrate	R	% ee[a]	% yield	% ee[b]	% yield	*t*(25%) [h][d]	conv.	*E*[11]	
(±)-**3a**	H	97.2	42	92.3	31	1.6	0.51	>100	(107)
b	2-CH_3	77.5	44	81[c]	33	6.2	0.49	22	
c	3-CH_3	95.1	42	96	42	1.5	0.5	184	(184)
d	4-CH_3	96.2	42	90.5	44	1.2	0.52	80	
e	2-OCH_3	49	39	39.4	51	21	0.55	4	
f	3-OCH_3	87.9	42	99	37	3.3	0.47	>>100	(583)
g	4-OCH_3	99	31	74.3	31	3.2	0.58	34	
h	2,3-C_4H_4	76[c]	52	96[c]	40	22.5	0.44	>100	(113)
i	2-$CH_2CH{=}CH_2$	97.3	45	95	41	26	0.51	>100	(169)
j	2-*cyclo*-C_5H_{11}	80.7	51	98.8	37	34.4	0.45	>100	(414)
k	4-CH_2CN	99.5	34	66.7	54	2.6	0.6	28	
l	4-NO_2	–	–	–	–	–	–	–	
m	2-$OCH_2CH{=}CH_2$	84.6	41	92.6	41	5.3	0.48	73	

a) Chiralcel OB, Chiralpak OT(+), b) Chiralcel OD, c) MTPA-ester d) time required for 25% conversion

A comparative analysis of the results summarized in Table 1 clearly reflects the considerable influence of the substitution pattern on both the specific activities and the enantioselectivities. In comparison to the parent compound (±)-**3a** *ortho*-substition as in (±)-**3b, e, h, i, j, m** causes a strong decrease in specific activity resulting in rather long reaction times. A less marked relationship is observed between substitution pattern and enantioselectivity. While substrates (±)-**3h, j** were hydrolyzed with high selectivities [$E > 100$] only low or moderate optical purities were observed in the transformations of (±)-**3b** and **3e**, respectively. In summary, with only four exceptions remarkably high enantioselectivities were observed.

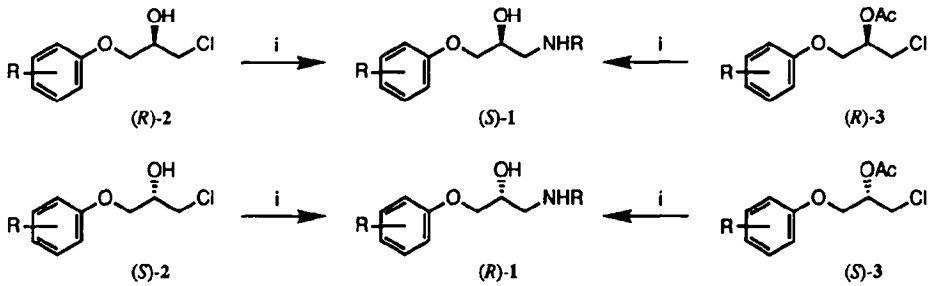
Complementary to the hydrolytic experiments, the corresponding esterifications of (±)-**2a-m** under the conditions of irreversible acyltransfer produces the (*R*)-alcohols **2** and (*S*)-acetates **3**. As documented in Table 2 these esterifications generally proceed with considerably higher enantioselectivities than the corresponding hydrolyses. Again the *ortho*-substituted derivatives [**2b, e, h, i, j, m**] display considerable lower specific activities as compared to the *m*- and *p*-substituted derivatives. This effect is clearly reflected in the considerable reaction times required for the conversion of these *ortho*-substituted compounds.

The thus prepared building blocks of both enantiomeric series can be converted into β-andrenergic blockers of both absolute configurations as outlined in Scheme 2. Base catalyzed conversions of either the α-chlorohydrins **2** or their acetates **3** resulted in the corresponding oxiranes, respectively. Without isolation, these were further converted into the corresponding β-adrenergic blocking agents by nucleophilic ring opening reaction with isopropylamine or *tert.*-butylamine, respectively. Reaction of the free bases with HCl in ether, produces the corresponding hydrochlorides, which upon recrystallisation led to the actual pharmaceuticals in optically pure form. The enantiomeric purities of all drugs were again determined by HPLC on a chiral support (Chiralcel OD)[12].

Table 2

		(*R*)-2		(*S*)-3					
substrate	R	% ee[a]	% yield	% ee[b]	% yield	t(25%) [h][d]	conv.	*E*[11]	
(±)-2a	H	95.6	42	96.6	44	16	0.5	>100	(223)
b	2-CH_3	98.6[c]	38	86.6	43	136	0.53	68	
c	3-CH_3	96.3	47	96	49	17	0.50	>100	(197)
d	4-CH_3	86.6	47	96.7	36	16	0.47	>100	(169)
e	2-OCH_3	83.6	47	83.1	51	16	0.52	32	
f	3-OCH_3	98.6	39	98.6	46	14	0.5	>>100	(706)
g	4-OCH_3	94	45	93.6	47	11	0.5	>100	(108)
h	2,3-C_4H_4	83[c]	44	92[c]	46	66	0.53	35	
i	2-$CH_2CH{=}CH_2$	93.8	41	92	55	75	0.51	85	
j	2-*cyclo*-C_5H_{11}	85.7	46	97.2	47	208	0.47	>100	(195)
k	4-CH_2CN	97	45	99.5	53	9	0.49	>>100	(1694)
l	4-NO_2	87[c]	47	92[c]	48	21	0.49	68	
m	2-$OCH_2CH{=}CH_2$	88.7	48	93.7	46	50	0.49	92	

a) Chiralcel OD, b) Chiralcel OB, Chiralpak OT(+) c) MTPA-ester d) time required for 25% conversion



Scheme 2 *Reagents*: i, 2 mmol substrate, 2.2 mol or 4.4 mol KO^{t}Bu, 10 ml THF, 0°C, 1 h;without isolation of epoxide 5 ml isopropylamine or *tert.*-butylamine, 5 ml ethanol, 12 h rf., ether/HCl

Using propranolol **[1h]**[13] as a model system both enantiomeric forms were prepared from all available enantiomers [(*R*)-, (*S*)-**2h**, (*R*)-, (*S*)-**3h**]. Both the free base and the hydrochloride were synthesized (Table 3).

In case of other β-blockers, e.g. Toliprolol **[1c]**[14], Moprolol **[1e]**[15], Alprenolol **[1i]**[16], Penbutenol **[1j]**[15,17], Atenolol **[1k]**[18], Practolol **[1l]**[19] and Oxprenolol **[1m]**[20] only the biologically active (*S*)-enantiomers were prepared as free bases (Table 4).

Table 3

educt		propranolol (free base)			propranolol (hydrochloride)		
config.	% ee	config.	% ee[a]	% yield	config.	% ee[a]	% yield
(*R*)-(–)-**2h**	92	(*S*)-(–)-**1h**	94.5	79	(*S*)-(–)-**1h**	>99.5	74
(*R*)-(–)-**3h**	96	(*S*)-(–)-**1h**	82.1	71	(*S*)-(–)-**1h**	99	68
(*S*)-(+)-**2h**	96	(*R*)-(+)-**1h**	>99.5	79	(*R*)-(+)-**1h**	>99.5	79
(*S*)-(+)-**3h**	83	(*R*)-(+)-**1h**	89	69	(*R*)-(+)-**1h**	>99.5	69

a) determined by HPLC on Chiralcel OD

Table 4

educt		β-blocker		
config.	% ee	config.	% ee[a]	% yield
(*R*)-(–)-**2c**	96.3	(*S*)-(–)-**1c**	>99.5	79
(*R*)-(–)-**2e**	96	(*S*)-(–)-**1e**	>98	60
(*R*)-(–)-**2i**	93.8	(*S*)-(–)-**1i**	77.6	35
(*R*)-(–)-**2j**	80.8	(*S*)-(–)-**1j**	90.8	45
(*R*)-(–)-**3k**	>99.5	(*S*)-(–)-**1k**	>99	46
(*R*)-(–)-**2l**	87	(*S*)-(–)-**1l**	>99	30
(*R*)-(–)-**2m**	88.7	(*S*)-(–)-**1m**	90.4	66

a) determined by HPLC on Chiralcel OD

REFERENCES

1. R. Howe and R.G. Shanks, *Nature* 1966, 1336
2. F. Jamali, R. Mehvar and F. M. Pasutto, *J. Pharm. Sci.*, **1989**, *78*, 695; J. R. Powell, I. W. Wainer and D.E. Drayer (ed.), *Drug Stereochemistry Analytical Methods and Pharmacology*, Marcel Dekker Inc., 1988, p. 245ff, 317ff
3. H. Takahashi, S. Sakuraba, H. Takeda and K. Achiwa, *J. Am. Chem. Soc.*, 1990, **112**, 5876; J.M. Klunder, T. Onami and K. B. Sharpless, *J. Org. Chem.*, 1989, **54**, 1295; Y. Tsuda, K. Yoshimoto and T. Nishikawa, *Chem. Pharm. Bull.*, 1981, **29**, 3593; D. E. McClure, B. H. Arison and J. J. Baldwin, *J. Am. Chem. Soc.*, 1979, **101**, 3666; W. L. Nelson, J. E. Wennerstrom and S. R. Sankar, *J. Org. Chem.*, 1977, **42**, 1006
4. H. S. Bevinakatti and A. A. Banerji, *J. Org. Chem.*, 1991, **56**, 5372; A. Kamal and M. V. Rao, *Tetrahedron: Asymmetry*, 1991, 2, 751; S.-H. Hsu, S.-S. Wu, Y.F. Wang and C.H. Wong, *Tetrahedron Lett.* 1990, 31, 6406; Y.-F. Wang, S. T. Chen, K. K.-C. Liu and C.-H. Wong, *Tetrahedron Lett.*, 1989, **30**, 1917; Y. Terao, M. Murata and K. Achiwa, *Tetrahedron Lett.*, 1988, **29**, 5173; M. Kloosterman, V. H. M. Elferink, J. v. Iersel, J.-H. Roskam, E. M. Meijer, L. A. Hulshof and R. A. Sheldon, *TIBTECH*, 1988, **6**, 251; S. Hamaguchi, T. Ohashi and K. Watanabe, *Agric. Biol. Chem.*, 1986, **50**, 375; S. L. Johnstone, G. T. Phillips, B. W. Robertson, P. D. Watts, M. A. Bertola, H. S. Koger and A. F. Marx, *Biocatalysis in Organic Media*, C. Laane, J. Tramper and M. D. Lilly (ed.), Proceedings of an International Symposium, Wageningen (NL), 1986; N. Matsuo and N. Ohno, *Tetrahedron Lett.*, 1985, **26**, 5533; K. Kan, A. Miyama, S. Hamaguchi, T. Ohashi and K. Watanabe, *Agric. Biol. Chem.*, 1985, **49**, 1669; S. Iriushijima, A. Keiyu and N. Kojima, *Agric. Biol. Chem.*, 1982, **46**, 1593; S. Iriushijima and N. Kojima, *Agric. Biol. Chem.*, 1982, **46**, 1153
5. U. Ader and M. P. Schneider, *Tetrahedron: Asymmetry*, 1992, **3**, 201, 205
6. O. Stephenson, *J. Chem. Soc.*, **1954**, 1571
7. obtained by reaction of alcohol with Ac_2O in CH_2Cl_2 and DMAP as catalyst
8. J.A. Dale and H.S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512
9. supplied by Diacel Chemical Industries, Ltd. or Baker Chemikalien, D-6080 Groß-Gerau, Germany
10. The difficulties in the enzymatic hydrolysis of water insoluble, crystalline esters like (±)-**3l** have been encountered in numerous cases during our work. Frequently cosolvents can be added to act as mediators. In this particular case all attemps of this nature were unsuccessful. That the substructure of (±)-**3l** is in fact accepted by the enzyme is documented by the fact that the esterification of corresponding alcohol (±)-**2l**, carried out in an organic solvent (Scheme 2, Table 2) proceeds with high enantioselectivity.
11. C.-S. Chen, Y. Fujimoto, G. Girdaukas and C.-J. Sih, *J. Am. Chem. Soc.* 1982, **104**, 7294
    Due to the large errors associated with the detection of *E*-values, all numbers $E > 100$ are of little significance. For all reaction with high enantiomeric ratio therefore $E > 100$ was listed. For comparison the actually calculated vaues are included in brackets.
12. Y. Okamoto, M. Kawashima, R. Aburatani, K. Hatada, T. Nishiyama and M. Masuda, *Chem. Lett.*, **1986**, 1237
13. J. M. Klunder, S. Y. Ko and K. B. Sharpless, *J. Org. Chem.* 1986, **51**, 3710
14. R. Howe and B.S. Rao, *J. Med. Chem.*, **1968**, *11*, 1118
15. K. Kan, A. Miyama, S. Hamaguchi, T. Ohashi and K. Watanabe, *Agric. Biol. Chem.* 1985, **49**, 207
16. A. Brändström, H. Corrodi, Ulf Junggren and T.-E. Jönsson, *Acta Pharma Suecica*, 1966, **3**, 303
17. J. M. Klunder, T. Onami and K.B. Sharpless, *J. Org. Chem.* 1989, **54**, 1295
18. S. L. Johnstone, G. T. Phillips, B. W. Robertson, P. D. Watts, M. A. Bertola, H. S. Koger and A. F. Marx, *Biocatalysis in Organic Media*, C. Laane, J. Tramper and M. D. Lilly (ed.), Proceedings of an International Symposium held at Wageningen, NL, 1987, Elsevier Science Publishers, p. 387
    (*S*)-(–)-**1k** was prepared from (*R*)-(–)-**3k** according to A. M. Barrett, J. Carter, R. Hull, D. J. Le Count and C. J. Squire, (ICI), *U.S. Pat. Appl.* 3836671 (1974)
19. J. C. Danilewicz and J. E. G. Kemp, *J. Med. Chem.*, 1973, **16**, 168
    (*S*)-(–)-**1l** was prepared from (*R*)-(–)-**2l** by reduction of nitro-function with Pd/C in AcOH/Ac_2O and following by refluxing with *iso*-propylamine
20. M. Meier, P. R. Hedwall, P. Imhof, M. Wilhelm and H. Brunner, *Arzneimittel-Forsch. (Drug Res.)*, 1970, **20**, 1890