Monatsh Chem (2012) 143:951–953
DOI 10.1007/s00706-011-0688-y

ORIGINAL PAPER

A biocatalytic approach for regioselective monoacetylation of 3-aryloxy-1,2-propanediols by porcine pancreatic lipase

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Received: 11 September 2011 / Accepted: 6 November 2011 / Published online: 29 November 2011
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Abstract Among the various lipases screened for the regioselective monoacetylation of 3-aryloxy-1,2-propanediols, porcine pancreatic lipase was found to afford a higher yield. The selectivity for the monoacetylation process was maximized by using different organic solvents and diisopropyl ether gave the highest conversion to monoacetylated product (ca. 98%). The optimized reaction afforded excellent yields of the monoacetylated product with regioselectivity at the terminal hydroxyl group in the presence of various aryl substituents in the starting material.

Keywords Lipases · Monoacetylation · Regioselectivity · 3-Aryloxy-1,2-propanediol · Biocatalysis

Introduction

Optically pure 3-aryloxy-1,2-propanediols are valuable precursors for the synthesis of important pharmaceuticals such as centrally acting muscle relaxants [1], antifungal agents [2], β-blockers [3], drugs for treating arthritis and osteoporosis [4], and antibacterial agents [5]. Other extensive applications include preservatives in cosmetics and foods [5], gene therapy [6], optics [7], pigmented ink [8], polyesters [9], resins [10], dyes [11], and nonspreading lubricants [12]. 3-Aryloxy-1,2-propanediols are also often used as intermediates in the synthesis of chiral ligands for transition metal complexes or building blocks for crown ethers and many other synthetic sequences [13, 14]. It is necessary to synthesize these molecules in optically pure form as chirality governs the major biological interactions.

One of the existing methods employed for obtaining the optically pure diols is the kinetic resolution of their monoacetylated derivatives; therefore regioselective monoacetylation of diols becomes crucial [15, 16]. The chemical methods for monoacetylation using active acyl donors and amine base or complex catalysts suffer from the disadvantages of poor regioselectivity, longer reaction time, low yield, harsh reaction conditions, and formation of side products [17–20]. Biocatalysis provides an alternative for the regioselective monoacetylation by lipases which have additional advantages of their easy availability, simple workup and handling, low cost, mild reaction conditions, avoidance of side reactions, and ability to work without requiring cofactors [21–30]. Regioselective monoacetylation of 3-aryloxy-1,2-propanediols by porcine pancreatic lipase has not been reported so far. We tried to develop a new enzymatic method by screening various lipases for the regioselective monoacetylation of 3-aryloxy-1,2-propanediols that can allow the product formation in a short period of time with high regioselectivity and yield.

Results and discussion

Herein we report a regioselective monoacetylation of 3-aryloxy-1,2-propanediol derivatives using porcine pancreatic lipase (PPL) that afforded the product in excellent yield by transesterification from vinyl acetate over a short period of time. As a model reaction, 3-phenoxy-1,2-propanediol was treated with vinyl acetate in the presence of Amano "AY" lipase using toluene as the solvent. The reaction was continued for 8 h and the conversion of the

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Table 1 Screening of lipase for regioselective monoacetylation

Entry	Lipase	Conversion/%		
		MA	DA	Diol
1	Amano "AY"	69	31	0
2	*Candida rugosa*	59	41	0
3	Pancreatic porcine	93	7	0
4	*Candida cylindracea*	51	49	0
5	*Aspergillus niger*	92	5	3
6	*Candida antarctica* (acrylic resin)	39	57	4
7	*Candida antarctica* (CLEA)	8	92	0
8	*Mucor miehei*	83	13	4
9	*Pseudomonas cepaceia* (sol gel)	87	13	0

MA monoacetate, *DA* diacetate

diol to the acetylated products was monitored by HPLC at different time intervals. The reaction formed both the mono- and diacetylated products in quantitative yield. Comparison of the ^{1}H NMR spectra of the monoacetylated product with those of standard compounds revealed that the monoacetylation had taken place at the terminal position. Although the reaction afforded good product yield, lipases from various sources were also screened for the transesterification as shown in Table 1.

As expected, most of the lipases afforded the monoesters but the best results were obtained with porcine pancreatic and *Aspergillus niger* lipase. PPL showed the best activity as compared with lipases from other sources. Previous findings are in accordance with this observation. The higher stability of PPL is attributed to its tight binding of water molecules that cannot be stripped out even by hydrophilic organic solvents. These inherent water molecules are essential for enzyme activity [31]. Recent findings support similar observations whereby higher conversions have been achieved in lipase-mediated monoacetylation in organic solvents [32]. Both the enzymes directed the acetylation to the terminal hydroxyl group with the formation of the diacetylated product in trace amounts. As the solvent plays an important role in the course of the reaction, various solvents were screened for the transesterification of the diols with vinyl acetate using PPL and the results are shown in Table 2.

It is evident from Table 2 that maximum conversion was obtained with the nonpolar solvents such as toluene, cyclohexane, isooctane, diethyl ether, but diisopropyl ether showed the best results with 98% conversion. An increase in the polarity of the solvent led to a sluggish reaction with poor yields. Therefore, diisopropyl ether was used as the solvent for further optimization. Further, we tried to study the reaction kinetics by taking aliquots from the reaction mixture over a period of 3 h and the relative ratio of the diol and the monoacetylated product formed was determined by HPLC with a C_{18} column. The time course of

Table 2 Screening of solvents for regioselective monoacetylation

Entry	Solvent	log *P* value	Conversion/%		
			MA	DA	Diol
1	Dichloromethane	0.60	34	8	58
2	Hexane	3.50	90	9	1
3	Acetone	−0.23	22	23	55
4	1,4-Dioxane	−1.10	47	0	53
5	Acetonitrile	−0.33	28	8	64
6	Toluene	2.50	93	7	0
7	Heptane	4.1	89	10	1
8	Diisopropyl ether	2.3	98	2	0
9	Tetrahydrofuran	0.49	42	2	55
10	Diethyl ether	–	93	1	6
11	Pyridine	0.65	33	10	57
12	Isobutyl alcohol	–	26	0	74
13	Isooctane	4.5	91	8	1
14	Xylene	3.10	31	39	30
15	Cyclohexane	3.20	93	4	3

MA monoacetate, *DA* diacetate

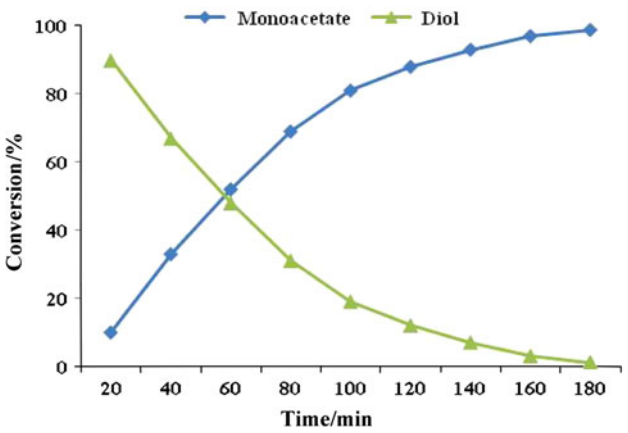
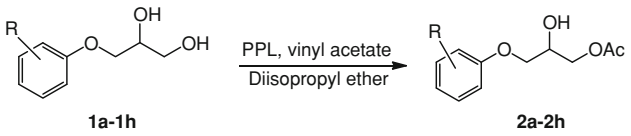


Fig. 1 Course of reaction of regioselective monoacetylation of 3-aryloxy-1,2-propanediols

reaction in Fig. 1 shows that the concentration of monoacetate increased gradually and the complete conversion of the diol to the monoacetylated product was achieved within 3 h.

After optimizing the reaction conditions, we tried to generalize the reaction with 3-aryloxy-1,2-propanediols (Scheme 1). It has been observed that the reaction is compatible with a range of substrates leading to the monoacetylation at the primary hydroxyl group and the products were obtained in excellent yield in a short period of time as shown in Table 3. When the reaction was continued for a prolonged time, diacetylated products were formed in trace amount as observed in the HPLC chromatogram.



1a-1h 2a-2h

Scheme 1

Table 3 Generalization of the reaction with substituted 3-aryloxy-1,2-propanediols

Entry	Substrate	R	Yield/%	Product	Ref
1	**1a**	H	98	**2a**	[24, 34]
2	**1b**	2-Cl	97	**2b**	[24, 34]
3	**1c**	3-Cl	98	**2c**	[24, 34]
4	**1d**	4-Cl	98	**2d**	[24, 34]
5	**1e**	2-Me	97	**2e**	[33, 34]
6	**1f**	3-Me	98	**2f**	[24, 34]
7	**1g**	4-Me	98	**2g**	[24, 34]
8	**1h**	3-NO_2	97	**2h**	[34]

Experimental

The ^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$. Mass spectra were recorded on a Finnigan Mat LCQ LCMS. The reactions were monitored by TLC (Merck). Solvents were evaporated under reduced pressure using a Büchi rotary evaporator.

General procedure for the regioselective monoacetylation of 3-aryloxy-1,2-propanediols

To a round-bottom flask containing 3-aryloxy-1,2-propanediols (1 mmol) was added 5 cm^3 diisopropyl ether followed by the addition of lipase (100 mg) and 200 mm^3 vinyl acetate. The reaction mixture was stirred for 3 h at room temperature. The product was extracted with ethyl acetate, which was evaporated under reduced pressure to afford the crude product. The reaction progress was monitored using reversed-phase HPLC.

Quantification of product by HPLC analysis

The amount of product formed and the remaining substrate was quantified by HPLC (Shimadzu 10AD VP, Kyoto, Japan) using a Phenomenex C_{18} column (250 × 4.6 mm, 5 μm, Madrid Ave, USA) at a flow rate of 1 cm^3/min with a solvent system of water/acetonitrile (35:65, v/v). The absorbance was monitored at 254 nm.

Acknowledgments VSM gratefully acknowledges the Department of Biotechnology, Government of India, New Delhi for providing the Senior Research Fellowship during the entire period of study.

References

1. Moussou P, Archelas A, Baratti J, Furstoss R (1998) Tetrahedron Asymmetry 9:1539
2. Yale HJ, Pribyl EJ, Braker W, Bergeim FH, Lott WA (1950) J Am Chem Soc 72:3710
3. Kloosterman M, Elferink VHM, Lersel JV, Roskam J, Meijer EM, Hulshof LA, Sheldon RA (1988) Trends Biotechnol 6:251
4. Lo YS, Nolan JC, Walsh DA, Welstead W (1990) Eur Pat Appl EP 403185A2, 19901219
5. Kaminuma M, Suetsugu M, Ogawa S, Yokota E, Hara E (2004) PCT Int Appl WO 2004089087A1, 20041021
6. Wang Y, Li Y, Shao R, Ren K, He H, Wang J, Bai X, Xu L, Wu X, Li B (2010) CN 101921292A:20101222
7. Gao J, Cui Y, Yu J, Lin W, Wang Z, Qian G (2010) Dyes Pigm 87:204
8. Valentini JE, Morris GP (2010) PCT Int Appl WO 2010111343A1, 20100930
9. Shimizu T, Maeda S, Hotta Y (2000) JP 2000128966A, 20000509
10. Smits JJT, Walhof JJB (1998) PCT Int Appl WO 9834930A1, 19980813
11. Maier K (1973) DE 1644451A, 19710408
12. Martin JS Jr (1957) US 2794037, 19570528
13. Turgut Y, Aral T, Hosgoren H (2009) Tetrahedron Asymmetry 20:2293
14. Turgut Y, Aral T, Karakaplan M, Deniz P, Hosgoren H (2010) Synthetic Commun 40:3365
15. Theil F, Weidner J, Ballschuh S, Kunath A, Schick H (1993) Tetrahedron Lett 34:305
16. Zelaszczyk D, Kiec-Kononowicz K (2007) Curr Med Chem 14:53
17. Sigthor P (2009) Tetrahedron Asymmetry 20:887
18. Natsumi W, Shoji H (2010) Tetrahedron 66:7939
19. Yamada S (1992) J Org Chem 57:1591
20. Ishihara K, Kurihara H, Yamamoto H (1993) J Org Chem 58:3791
21. Patti A, Nicolosi G (1999) Tetrahedron Asymmetry 10:2651
22. Borreguero I, Sanchez-Montero JM, Sinisterra JV, Rumbero A, Hermoso JA, Alcantara AR (2001) J Mol Catal B Enzym 11:1013
23. Egri G, Baitz-Gács E, Poppe L (1996) Tetrahedron Asymmetry 7:1437
24. Theil F, Weidner J, Ballschuh S, Kunath A, Schick H (1994) J Org Chem 59:388
25. Theil F, Lemke K, Ballschuh S, Kunath A, Schick H (1995) Tetrahedron Asymmetry 6:1323
26. Kamal A, Chouhan G (2004) Tetrahedron Lett 45:8801
27. Tahmina Y, Tao J, Buxing H (2007) Catal Lett 116:46
28. Klibanov AM (1990) Acc Chem Res 23:114
29. Jaeger KE, Eggert T (2002) Curr Opin Biotech 13:390
30. Vicente GF, Rosario B, Vicente GJ (2006) Mol Catal B: Enzym 40:111
31. Zaks A, Klibanov AM (1985) Proc Natl Acad Sci 82:3192
32. Sun J, Jing K, Lu Y (2011) Afr J Biotechnol 10:11990
33. Theil F, Ballschuh S, Kunath A, Schick H (1991) Tetrahedron Asymmetry 2:1031
34. Egri G, Kolbert A, Bálint J, Fogassy E, Novák L, Poppe L (1998) Tetrahedron Asymmetry 9:271