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**Optical Enrichment in Enzyme-catalyzed Resolution of
1-Aryl-2,2-dimethyl-1,3-propanediols**

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Draft

Abstract: Novozym® 435 efficiently catalyzed the chemo-, regio-, and enantioselective transesterification of 1-aryl-2,2-dimethyl-1,3-propanediols in different organic solvents with

vinyl acetate as the acetyl donor at room temperature. This enzyme-catalyzed chemical transformation method provides an efficient route for optically-enriched propanediol derivatives.

Key words: 1-Aryl-2,2-dimethyl-1,3-propanediols, kinetic resolution, Novozym® 435, enantioselection, optical enrichment, biocatalysis, enzyme-assisted organic synthesis.

Introduction

Several mono and dicarbamate derivatives of 1,3-propanediols such as mebutamate, meprobamate, tybamate, carisprodol, felbamate and methocarbamol (Fig. 1) are clinically used as sedatives, tranquilizers, anxiolytic and muscle relaxing drugs.¹⁻³ Mephenesin (Fig. 1), a clinical muscle relaxant, has marked structural resemblance to methocarbamol but it is a diol rather than a carbamate.⁴ Bronopol, 2-bromo-2-nitro-1,3-propanediol, is an antimicrobial agent and used as a preservative in cosmetics.⁵ In addition to the pharmacological profile, propanediols such as 2,2-bis(bromomethyl)-1,3-propanediol is widely used as a flame retardant.⁶ Recently, 1,3-propanediol has also emerged as an interesting polyester raw material similar to homologs ethylene glycol and butanediol.⁷

For particular relevance to the current investigations are 1-aryl-2,2-dimethyl-1,3-propanediols **1** (Figure 1). Monocarbamate derivatives of these compounds (**2** and **3**) have been studied for sedative and tranquilizing activity.^{8,9} The esters, acetals, and ketals of 1-aryl-2,2-dimethyl-1,3-propanediols possess good aroma; hence, they have the potential to be used as essential oils in perfume industries.¹⁰

Figure 1. Biologically active propanediol carbamates and related propanediols.

The significance of propanediol in different aspects of life has promoted the need to develop efficient routes for their synthesis. The most common synthetic method involves the hydroformylation of epoxides, which is generally accompanied with numerous side products, thus resulting in a poor yield. Efforts to improve the yield have led to the evolution of several metal catalysts and promoters.^{7,11,12} However, the present research is focused on developing on developing enantiomerically pure 1-aryl-2,2-dimethyl-1,3-propanediols (**1**) from its aldol-crossed Cannizzaro reaction-derived racemic mixture using enzyme catalysis based bioengineering techniques. It should be noted that all clinically used chiral drugs shown in Fig. 1 are marketed in racemic form. The pharmacological activity of a pair of enantiomers often differs from each other, and one enantiomer is often responsible for the desired activity when racemic drug is administered. The unwanted enantiomer may have toxic properties.¹³ This has triggered the need for obtaining a drug molecule in an optically pure form. Optically enriched 1,3-propanediol derivatives have been synthesized using the enzymatic

desymmetrization of prochiral diols.^{14–16} Similar enantiomerically pure substrates, namely, 1-(4-phenyl)-2,2-dimethyl-1,3-propanediol and 1-(4-chlorophenyl)-2,2-dimethyl-1,3-propanediol, have been obtained as their chiral cyclic phosphonates from the corresponding phosphoric acid derivatives. These chiral cyclic phosphonates have been used as the chiral derivatizing agents for the enantiomeric excess (*ee*) determination of amines, alcohols, and unprotected amino acids.^{17–21} However, none of the methods used green catalysts—enzymes—for obtaining enantiomerically pure 1-aryl-2,2-dimethyl-1,3-propanediols in an eco-friendly manner.

Novozym® 435 is a commercially available heterogeneous biocatalyst that consists of *Candida antarctica* lipase B physically immobilized within a macroporous resin of poly(methyl methacrylate) and is marketed by Novozymes and other chemical vendors.²² Owing to its in vitro transesterification potential, Novozym® 435 has been extensively utilized for synthesizing esters from alcohols and phenols using an acyl group donor.^{23–25}

In continuation of our interest in enzyme-assisted synthesis of chemical building blocks and potential drug intermediates,^{24–28} we herein report Novozym® 435-catalyzed enantioselective acetylation of a series of racemic 1-aryl-2,2-dimethyl-1,3-propanediols (**1**).

Results and Discussion

The compound of this investigation, namely, 1-aryl-2,2-dimethyl-1,3-propanediols **1**, was synthesized chemically as a racemic mixture by following a literature method involving an aldol-crossed Cannizzaro reaction between 1 equivalent of an aromatic aldehyde, 2 equivalent of isobutyraldehyde, and 1 equivalent of KOH in ethanol.¹⁷

To check the feasibility of the enzyme-catalyzed enantioselective transesterification process, three reactions on a model substrate 2,2-dimethyl-1-phenyl-1,3-propanediol **1a** were

carried out with vinyl acetate as acetyl group donor at room temperature in diisopropyl ether (DIPE) as the solvent: a) in the absence of any enzyme (blank), b) in the presence of Novozym® 435, and c) in the presence of Amano PS lipase. A nonpolar solvent (diisopropyl ether) was selected as the solvent because both the starting material and product are soluble in this solvent. No reaction was observed in the blank reaction and in presence of Amano PS lipase even after 72 h of reaction time. However, in the presence of Novozyme® 435, it took 36 h to consume ~50% of the starting material and to form a new relatively non-polar product as visualized qualitatively on TLC (Scheme 1). The reaction was quenched by filtering the enzyme and the reaction mixture was purified by performing column chromatography on silica gel to isolate unreacted starting material **1a** and the product which was characterized as 2,2-dimethyl-1-phenyl-propane-3-acetate-1-ol (**4a**) on the basis of ^1H & ^{13}C NMR and HRMS data. Thus, the reaction clearly displayed regio- and chemoselectivity in the sense that primary –OH group was exclusively acetylated. To ascertain the extent of enantioselectivity, if any, optical rotation of the unreacted diol **1a** and the corresponding monoacetylated product **4a** were measure in chloroform at room temperature. To our delight, a non-zero optical rotation of these compounds (-15.38° and $+1.48^\circ$ for unreacted **1a** and monoacetylated product **4a**, respectively) were observed confirming some degree of enantioselection. Encouraged by these results, optimization of the effect of solvent was carried out for the kinetic resolution of the model substrate **1a** was screened using Novozym® 435 in several solvents of varying polarities. The variation in optical rotation values, time required for 50% conversion, and chemical yields are listed in Table 1. As expected, the Novozym® 435-catalyzed selective acetylation of **1a** was found to be enantioselective as well as regio and chemoselective in the case of all the solvents used for

the reaction. The extent of optical enrichment measured as enantiomeric excess (*ee*) in the lipase-catalyzed reactions was determined by ^1H NMR experimental studies using $\text{Eu}(\text{hfc})_3$ as the chiral lanthanide shift reagent (CLSR) in CDCl_3 as the solvent. The ^1H NMR peaks for the diastereomeric mixtures were successfully separated, and the *ee* was calculated from the integration of the peaks of respective acetoxy group singlets. This data is presented in Table 1. The addition of $\text{Eu}(\text{hfc})_3$ caused a downfield shift of all the protons in the ^1H NMR spectra. The absolute configuration assigned to the products in the scheme under Table 1 was based on comparison of the sign of optical rotation of previously characterized optically pure compounds reported in the literature.¹⁸

Scheme 1. Kinetic resolution of racemic 2,2-dimethyl-1-phenyl-1,3-propanediol **1a**.

Table 1 Stereoselective acetylation of *racemic* 1-(4-methoxyphenyl)-2,2-dimethyl-1,3-propanediol **1a** in different solvents

Solvents	Time (h)	Monoacetate (4a)			Unreacted Diol (1a)		
		% yield ^b	$[\alpha]_D$	% <i>ee</i>	% yield ^b	$[\alpha]_D$	% <i>ee</i>
DIPE	36	49	+1.48	21	39	−15.38	57
Chloroform	96	13	+2.85	41	70	−2.72	19
THF	12	47	+12.0	52	49	−27.0	66

Toluene	23	43	+2.0	19	25	-7.33	30
Acetone	22	21	+1.0	47	48	-5.5	26
Acetonitrile	23	29	+1.18	39	49	-6.2	61
Dioxane	26	41	+2.2	37	46	-7.5	28
Ethyl acetate ^a	96	11	+2.66	38	71	-3.0	7

^a No vinyl acetate was added in the ethyl acetate reaction.

^b Isolated yield.

The effect of solvent polarity on enantioselective acylation of **1a** is clearly evident in the data presented in Table 1. In the case of THF as the reaction medium, best enantioselection was obtained for unreacted diol **1a** as well as the primary monoacylated product **4a**, 66% and 52% *ee*, respectively. However, the time required for enzymatic reactions for ~50% conversion of racemic **1a** to monoacetate **4a** varied significantly from 12 to 96 h by changing the solvent. The reaction in THF again, was found to be the fastest; ~50% conversion of racemic **1a** to **4a** was achieved in ~12 h. The reactions in toluene, acetone, acetonitrile, and dioxane needed 22-26 h for ~50% conversion. The reaction in diisopropyl ether (DIPE) was comparatively slower; ~50% conversion was achieved in 36 h. The reaction in chloroform attained only ~20% conversion even after four days (96 h). The reaction in ethyl acetate, which also acted as acetyl group donor, was also found to be equally slow. Isomeric secondary acetoxy product (**5a**) was isolated in the THF reaction in trace amounts. Optical activity of **5a** was not recorded. The structure of the major acetylated products **4a**, where the acetate is at the C-3 position, was confirmed from the appearance of a chiral center proton, namely, C-1H at δ 4.6 ppm compared to δ 5.8 ppm in the case of C-1-acetylated product (**5a**).

Having optimized the Novozyme® 435 catalyzed chemo-, regio-, and enantioselective transesterification of model compound **1a** in THF at room temperature with vinyl acetate as the acyl donor, the enzyme reactions were carried out on a series of differently phenyl-substituted 1,3-propanediols **1b–j** under identical conditions (Scheme 2). As the customary, these reactions were stopped at the 50% conversion (qualitative, by tlc) by filtering off the enzyme. The unreacted propanediols **1b–j** and product monoacetates **4b–j** were separated by performing flash column chromatography over silica gel. The optical rotation values, observed chemical yields, and time required for the half acetylation of propanediols **1a–j** to the corresponding acetates **4a–j** are listed in Table 2. The enantiomeric ratios (E-values) of the reactions were calculated using Eq. 1 and are reported in Table 2.

$$E = \frac{\ln [1-c (1+ee)]}{\ln [1-c (1-ee)]} \quad \text{Eq. 1}$$

where *c* is the conversion of the reaction, and *ee* is the enantiomeric excess of the product.

Scheme 2. Kinetic resolution of racemic 1-aryl-2,2-dimethyl-1,3-propanediols **1a–j**.

Table 2 Stereoselective acetylation of 1-aryl-2,2-dimethyl-1,3-propanediols **1a–j** in THF.

		Monoacetate (4a–j)				Unreacted Diol (1a–j)			
#	Ar	% yield	$[\alpha_D]$	% ee	E	% yield	$[\alpha_D]$	% ee	E
a	Phenyl	47	+12.0	52	1	49	–27.0	66	1

b	4-Cl-phenyl	35	+1.2	23	1	54	-15.6	71	1
c	4-F-phenyl	41	+6.4	25	1	20	-15.87	53	1
d	4-OMe-phenyl	42	+8.0	19	1	35	-4.0	30	1
e	4-NO ₂ -phenyl	37	+12.4	57	1	50	-1.2	51	1
f	3,4-OCH ₂ O-phenyl	41	+0.73	43	1	29	-2.77	51	1
g	3,4-diOMe-phenyl	66	+10.0	8	1	20	-4.0	5	1
h	Pyridin-4-yl	41	+1.60	- ^a	-	20	-5.30	- ^a	-
-i	Pyridin-2-yl	44	+1.20	- ^a	-	20	-18.4	- ^a	-
j	Furan-2-yl	28	+1.83	25	1	24	-4.33	40	1

^a The *ee* could not be calculated owing to peak broadening in the ¹H NMR experiments with CLSR.

Enantioselection was evident from the opposite signs and comparable values of specific rotation for each pair of unreacted diols and the corresponding acetates. All the unreacted diols showed a negative sign of rotation, whereas the acetates showed a positive sign of rotation (Tables 1 and 2). Enantiopure **1a** with *R* absolute stereochemistry has a negative optical rotation (conc. 1g/100 mL of CHCl₃, [α]_D = -49.9°).¹⁸ This indicates that the unreacted diols **1a–j** with negative optical rotations are optically enriched in favor of the *R* isomers, whereas monoacetates **4a–j** are optically enriched in favor of the *S* isomers.

The *ee* values were determined by ¹H NMR experiments using Eu(hfc)₃ as the chiral lanthanide shift reagent in CDCl₃ as the solvent (*vide supra*). The ¹H NMR peaks for the diastereomeric mixtures were successfully separated, and the *ee* was calculated from the integration of the peaks of acetate, methyl, methoxy, or chiral center proton, whichever worked the best in particular case. In the case of pyridine-substituted propanediols (**1i** and

1j), addition of Eu(hfc)_3 led to broadening of peaks in the respective ^1H NMR spectra and therefore, the *ee* could not be determined. Use of another chiral shift reagent, Eu(tfc)_3 , also led to the same unfortunate outcome. In all these cases again, chemo- and regioselectivity of the transesterification reaction turned out to be nearly exclusive in the favor of primary acetoxy products **4b-j**. The isomeric secondary acetoxy product was isolated in trace amounts (<5% yield) when the starting material was **1d** (4-MeO- substituted phenyl). The enantioselectivity, however, ranged from 19-57% for **4a-j** and 5-71% for unreacted recovered **1a-j**.

The stereoselective deacetylation of one representative compound 1-(4-methoxyphenyl)-2,2-dimethyl-1,3-propanediacetate **6** was also studied using Novozym® 435 in different organic solvents for kinetic resolution using *n*-butanol as the acetyl scavenger. When monitored in anhydrous organic solvents, no deacetylation was observed. Subsequently, water-saturated organic solvents were used to screen the catalytic activity of Novozym® 435 as enzymes show better catalytic activity in aqueous medium. However, no deacetylation of **6** was observed.

Conclusion

The Novozym® 435-catalyzed transesterification of 1-aryl-2,2-dimethyl-1,3-propanediols using vinyl acetate as the acetyl donor in organic solvents exhibited nearly exclusive regio-, and chemoselectivity in favor of acetylating the primary hydroxyl group when the reaction was allowed to proceed until ~50% conversion. However, this resulted in varying degrees of enantioselectivity. The rate of the acetylation was found to be fastest in tetrahydrofuran.

Experimental General

The melting points are reported in degrees Celsius, measured using a MEL-TEMP II capillary melting point apparatus, and are uncorrected. The H^1 and C^{13} NMR spectra were recorded using a Bruker AV-300 spectrometer at 300 and 75.5 MHz, respectively. The chemical shifts are reported in parts per million (ppm, δ scale), downfield from internal standard tetramethylsilane, and the coupling constants (J) are reported in Hz. The UV-visible spectra were recorded using a LKB Biochrom Ultrospec Plus 4054 UV-visible spectrophotometer. The optical rotations were recorded on ADP220 Polarimeter (Bellingham Stanley Ltd.) using $CHCl_3$ as the solvent. Precoated fluorescent silica gel thin-layer chromatography plates were used to monitor the progress of the reactions and determine the R_f values. The progress of enzyme-catalyzed reactions was monitored both by UV light visibility and using methanolic $FeCl_3$ reagent. Novozym® 435 (*Candida antarctica* lipase B immobilized on acrylic acid resin) was purchased from Aldrich. All the solvents were dried prior to use in the enzyme-catalyzed reactions.

General procedure for synthesis of 1a–j

2,2-Dimethyl-3-aryl-1,3-propanediols were prepared following a modified literature procedure starting from isobutyraldehyde (20 mmol), an appropriate aromatic aldehyde (10 mmol), and KOH (10 mmol) in ethanol (150 mL).¹⁶ The pure products were obtained in 41–69 % yields after column chromatography using a mixture of 20–30% EtOAc/hexane as the eluent.

214 **1-Phenyl-2,2-dimethyl-1,3-propanediol (1a):** It was obtained as a solid in 69% yield; m.p.
215 71–73 °C (lit. m.p.²⁹ 78–79 °C). Its ¹H spectrum was found to be identical to the literature
216 report.²⁹ ¹³C NMR (75.5 MHz, CDCl₃): δ 19.4, 23.2, 39.4, 72.4, 82.5, 127.9, 128.0, 128.1,
217 141.8. UV (MeOH) λ_{max}: 215, 257 nm. HRMS (ESI) *m/z*: Found 203.1040 [M+Na]⁺; calcd.
218 for [C₁₁H₁₆O₂+Na]⁺: 203.1048.

219 **1-(4-Chlorophenyl)-2,2-dimethylpropane-1,3-diol (1b):** It was obtained as a solid in 68%
220 yield; m.p. 93–95 °C; lit. m.p.¹⁰ 89–90 °C. Its ¹H spectrum was found to be identical to the
221 literature report.¹⁷ ¹³C NMR (75.5 MHz, CDCl₃): δ 19.4, 23.2, 39.4, 72.4, 82.5, 127.9, 128.0,
222 128.1, 141.8. UV (MeOH) λ_{max}: 215, 257 nm. HRMS (ESI) *m/z*: Found 237.0662 [M+Na]⁺;
223 calcd. for [C₁₁H₁₅ClO₂+Na]⁺: 237.0658.

224 **1-(4-Fluorophenyl)-2,2-dimethylpropane-1,3-diol (1c):** It was obtained as a solid in 54%
225 yield; m.p. 70–72 °C; ¹H NMR (300 MHz, CDCl₃) δ 0.79 and 0.82 (6H, s, 2 × CH₃), 3.49–
226 3.52 (3H, m, CH₂ and OH), 3.94 (1H, d, *J* = 2.7 Hz, OH), 4.58 (1H, d, *J* = 1.8 Hz, CH), 7.01
227 (2H, t, *J* = 8.7 Hz, ArH), 7.24–7.29 (2H, m, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ 19.2,
228 23.1, 39.4, 72.4, 81.8, 114.9 (d, 2C, *J* = 21.8 Hz), 129.5 (d, 2C, *J* = 8.3 Hz), 137.5, 162.6 (d,
229 2C, *J* = 245.4 Hz); UV (MeOH) λ_{max}: 213, 264, 271 nm. HRMS (ESI) *m/z*: Found 221.0945
230 [M+Na]⁺; calcd. for [C₁₁H₁₅FO₂+Na]⁺: 221.0954.

231 **1-(4-Methoxyphenyl)-2,2-dimethylpropane-1,3-diol (1d):** It was obtained as a solid in
232 62% yield; m.p. 77–78 °C (lit. m.p.³⁰ 78–79 °C). Its ¹H and ¹³C NMR spectra were found to
233 be identical to the literature report.³⁰

234 **1-(4-Nitrophenyl)-2,2-dimethylpropane-1,3-diol (1e):** It was obtained as a solid in 54%
235 yield; m.p. 43–44 °C (lit. m.p.²⁹ 36–38 °C). Its ¹H NMR spectrum was found to be identical
236 to the literature report.²⁹ ¹³C NMR (75.5 MHz, CDCl₃) δ 19.1, 22.9, 39.6, 72.4, 81.3, 123.2,

128.9, 147.7, 149.4; UV (MeOH) λ_{max} : 203, 214, 275 nm. HRMS (ESI) m/z : Found 248.0905
[M+Na]⁺; calcd. for [C₁₁H₁₅NO₄+Na]⁺: 248.0899.

1-(Benzol[d][1,3]dioxol-5-yl)-2,2-dimethylpropane-1,3-diol (1f): It was obtained as a solid
in 41% yield; m.p. 70–72 °C. Its ¹H NMR spectrum was found to be identical to the literature
report.¹⁷ ¹³C NMR (75.5 MHz, CDCl₃) δ 19.4, 23.1, 39.6, 72.5, 82.3, 101.3, 107.9, 108.4,
121.3, 135.9, 147.2, 147.6; UV (MeOH) λ_{max} : 209, 235, 285 nm. HRMS (ESI) m/z : Found
247.0940 [M+Na]⁺; calcd. for [C₁₂H₁₆O₄+Na]⁺: 247.0946.

1-(3,4-Dimethoxyphenyl)-2,2-dimethylpropane-1,3-diol (1g): It was obtained as a red
liquid in 45% yield; ¹H NMR (300 MHz, CDCl₃) δ 0.79 (6H, s, 2 × CH₃), 3.45 (2H, q, J =
13.5 Hz, CH₂), 3.70 (1H, br s, OH), 3.83 (6H, s, 2 × OCH₃), 3.90 (1H, br s, OH), 4.50 (1H, s,
CH), 6.77 (2H, s, ArH), 6.84 (1H, s, ArH); ¹³C NMR (75.5 MHz, CDCl₃) δ 19.3, 23.1, 39.4,
56.2 (2C), 72.4, 82.2, 110.8, 111.3, 120.3, 134.6, 148.6 (2C); UV (MeOH) λ_{max} : 208, 229,
277 nm. HRMS (ESI) m/z : Found 263.1264 [M+Na]⁺; Calcd. for [C₁₃H₂₀O₄+Na]⁺: 263.1260.

1-(Furan-2-yl)-2,2-dimethylpropane-1,3-diol (1h): It was obtained as a solid in 45.12%
yield; m.p. 53–55 °C. Its ¹H and ¹³C NMR spectra were found to be identical to the literature
report.¹⁷

1-(Pyridin-4-yl)-2,2-dimethylpropane-1,3-diol (1i): It was obtained as a solid in 43% yield;
m.p. 120–122 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 0.64 and 0.78 (3H each, s, 2 × CH₃),
3.08 and 3.34 (1H each, d, J = 10.5 Hz each, CH₂), 4.51 (1H, s, CH), 4.80 and 5.51 (1H each,
br s, OH), 7.28 (2H, d, J = 4.8 Hz, pyridyl-H), 8.47 (2H, d, J = 4.2 Hz, pyridyl-H); ¹³C NMR
(75.5 MHz, DMSO-d₆) δ 20.3, 21.6, 40.1, 68.8, 75.8, 123.8 (2C), 149.3 (2C), 152.9; UV
(MeOH) λ_{max} : 206, 257 nm. HRMS (ESI) m/z : Found 204.0997 [M+Na]⁺; calcd. for
[C₁₀H₁₅NO₂+Na]⁺: 204.1001.

1-(Pyridin-2-yl)-2,2-dimethylpropane-1,3-diol (1j): It was obtained as a solid in 52% yield; m.p. 52–55 °C; ^1H NMR (300 MHz, CDCl_3) δ 0.85 (6H, s, $2 \times \text{CH}_3$), 3.41 (2H, s, CH_2), 4.20 (1H, br s, OH), 4.68 (2H, br s, CH and OH), 7.19 (1H, d, $J = 1.2$ Hz, pyridyl-H), 7.33 (1H, d, $J = 7.8$ Hz, pyridyl-H), 7.67 (1H, br s, pyridyl-H), 8.47 (1H, d, $J = 4.5$ Hz, pyridyl-H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 20.4, 21.7, 40.5, 71.5, 79.8, 122.9 (2C), 136.6, 148.3, 160.7; UV (MeOH) λ_{max} : 211, 261 nm. HRMS (ESI) m/z : Found 204.1008 $[\text{M}+\text{Na}]^+$; calcd. for $[\text{C}_{10}\text{H}_{15}\text{NO}_2+\text{Na}]^+$: 204.1001.

General procedure for the synthesis of enantiomerically-enriched 1-aryl-2,2-dimethylpropane-3-acetate-1-ols (4a–j)

To a solution of propanediol (5 mmol) and vinyl acetate (5 mmol) in an appropriate organic solvent (20 mL), Novozym® 435 (1 g) was added, and the resulting mixture was shaken at room temperature. The reaction was stopped by filtering off the enzyme after approximately 50% conversion (qualitatively based on TLC) of the diol into the monoacetate. The solvent was removed under vacuum, and the unreacted diol and acetate were separated by column chromatography over silica gel (230–400 mesh) using a mixture of 10–25% EtOAc/hexane as the eluent. In the case of **1a** and **1d** as starting materials, very small amounts of monoacetates formed after transesterification of secondary hydroxyl groups (**5a** and **5d**) were also isolated.

1-Phenyl-2,2-dimethylpropane-3-acetate-1-ol (4a): It was obtained as a solid in 50% yield; m.p. 62–64 °C; ^1H NMR (300 MHz, CDCl_3) δ 0.87 and 0.95 (3H each, s, $2 \times \text{CH}_3$), 2.12 (3H, s, OCOCH_3), 2.40 (1H, d, $J = 3.3$ Hz, OH), 3.80 and 4.20 (1H each, d, $J = 10.8$ Hz each, CH_2), 4.59 (1H, d, $J = 3.3$ Hz, CH), 7.28–7.36 (5H, m, ArH); ^{13}C NMR (75.5 MHz, CDCl_3) δ

19.7, 21.3, 21.8, 39.4, 71.2, 78.2, 127.9 (2C), 128.0 (2C), 128.1, 141.5, 171.6; UV (MeOH)
 λ_{max} : 213, 257 nm. HRMS (ESI) m/z : Found 245.1148 $[\text{M}+\text{Na}]^+$; calcd. for $[\text{C}_{13}\text{H}_{18}\text{O}_3+\text{Na}]^+$:
245.1154.

1-(4-Chlorophenyl)-2,2-dimethylpropane-3-acetate-1-ol (4b): It was obtained as a solid in
35% yield; mp 88–90 °C (lit. m.p.⁹ 78.5–80 °C). ^1H NMR (300 MHz, CDCl_3) δ 0.83 and
0.89 (3H each, s, $2 \times \text{CH}_3$), 2.10 (3H, s, OCOCH_3), 2.69 (1H, brs, OH), 3.73 and 4.18 (1H
each, d, $J = 11.1$ Hz each, CH_2), 4.53 (1H, s, CH), 7.23 and 7.29 (2H each, d, $J = 7.2$ Hz,
ArH); ^{13}C NMR (75.5 MHz, CDCl_3) δ 19.4, 21.3, 21.8, 39.4, 71.1, 128.2, 129.4, 133.6,
139.9, 171.7; UV (MeOH) λ_{max} : 220 nm. HRMS (ESI) m/z : Found 279.0769 $[\text{M}+\text{Na}]^+$; calcd.
for $[\text{C}_{13}\text{H}_{17}\text{ClO}_3+\text{Na}]^+$: 279.0764.

1-(4-Fluorophenyl)-2,2-dimethylpropane-3-acetate-1-ol (4c): It was obtained as a solid in
62% yield; mp 80–83 °C; ^1H NMR (300 MHz, CDCl_3) δ 0.84 and 0.91 (3H each, s, $2 \times$
 CH_3), 2.11 (3H, s, OCOCH_3), 2.55 (1H, d, $J = 2.4$ Hz, OH), 3.76 and 4.20 (1H each, d, $J =$
11.1 Hz each, CH_2), 4.56 (1H, d, $J = 2.1$ Hz, CH), 7.01 (2H, t, $J = 8.4$ Hz, ArH), 7.27 (2H, t, J
 $= 8.1$ Hz, ArH); ^{13}C NMR (75.5 MHz, CDCl_3) δ 19.5, 21.3, 21.9, 39.5, 71.1, 77.6, 114.9 (2C,
d, $J = 21.1$ Hz), 129.5 (2C, d, $J = 7.5$ Hz), 137.14, 162.6 (2C, d, $J = 245.4$ Hz), 171.72; UV
(MeOH) λ_{max} : 212, 264, 270 nm. HRMS (ESI) m/z : Found 263.1055 $[\text{M}+\text{Na}]^+$; calcd. for
 $[\text{C}_{13}\text{H}_{17}\text{FO}_3+\text{Na}]^+$: 263.1059.

1-(4-Methoxyphenyl)-2,2-dimethylpropane-3-acetate-1-ol (4d): It was obtained as a solid
in 43% yield; m.p. 63–65 °C. ^1H NMR (300 MHz, CDCl_3) δ 0.84 and 0.93 (3H each, s, $2 \times$
 CH_3), 2.10 (3H, s, OCOCH_3), 2.40 (1H, d, $J = 3.0$ Hz, OH), 3.80 (3H, s, OCH_3), 3.78 (1H, d,
 $J = 12.3$ Hz, $\text{CH}_\alpha\text{H}_\beta$), 4.16 (1H, d, $J = 10.8$ Hz, $\text{CH}_\alpha\text{H}_\beta$), 4.53 (1H, d, $J = 3.0$ Hz, CH), 6.86
(2H, d, $J = 8.4$ Hz, ArH), 7.22 (2H, d, $J = 8.4$ Hz, ArH); ^{13}C NMR (75.5 MHz, CDCl_3) δ

19.7, 21.3, 21.8, 39.5, 55.6, 71.2, 77.8, 113.5 (2C), 129.0 (2C), 133.6, 159.4, 171.6; UV (MeOH) λ_{max} : 225, 274, 281 nm. HRMS (ESI) m/z : Found 275.1260 $[\text{M}+\text{Na}]^+$; calcd. for $[\text{C}_{14}\text{H}_{20}\text{O}_4+\text{Na}]^+$: 275.1259.

1-(4-Nitrophenyl)-2,2-dimethylpropane-3-acetate-1-ol (4e): It was obtained as a solid in 37.13% yield; m.p. 90–92 °C. ^1H NMR (300 MHz, CDCl_3) δ 0.86 and 0.89 (6H, 2s, $2 \times \text{CH}_3$), 2.12 (3H, s, OCOCH_3), 2.93 (1H, d, $J = 3.3$ Hz, OH), 3.73 and 4.29 (1H each, d, $J = 11.1$ Hz each, CH_2), 4.66 (1H, d, $J = 3.3$ Hz, CH), 7.49 (2H, d, $J = 8.4$ Hz, ArH), 8.17 (2H, d, $J = 8.4$ Hz, ArH). ^{13}C NMR (75.5 MHz, CDCl_3) δ 19.2, 21.2, 22.0, 39.7, 70.9, 77.0, 123.2 (2C), 128.9 (2C), 147.7, 148.8, 171.8. UV (MeOH) λ_{max} : 273 nm. HRMS (ESI) m/z : 290.0999 $[\text{M}+\text{Na}]^+$; Calcd. for $[\text{C}_{13}\text{H}_{17}\text{NO}_5+\text{Na}]^+$: 290.1005.

1-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-dimethylpropane-3-acetate-1-ol (3f): It was obtained as a solid in 40.5% yield; mp 75–77 °C; ^1H NMR (300 MHz, CDCl_3) δ 0.85 and 0.93 (3H each, s, $2 \times \text{CH}_3$), 2.04 (1H, s, OH), 2.11 (3H, s, OCOCH_3), 3.77 and 4.17 (1H each, d, $J = 10.8$ Hz, CH_2), 4.51 (1H, s, CH), 5.95 (2H, s, OCH_2O), 6.75 (2H, s, ArH), 6.84 (1H, s, ArH); ^{13}C NMR (75.5 MHz, CDCl_3) δ 19.7, 21.3, 21.8, 39.5, 71.2, 78.0, 101.3, 107.8, 108.4, 121.3, 135.4, 147.2, 147.6, 171.7; UV (MeOH) λ_{max} : 209, 234, 285 nm. HRMS (ESI) m/z 289.1048 $[\text{M}+\text{Na}]^+$; Calcd. for $[\text{C}_{14}\text{H}_{18}\text{O}_5+\text{Na}]^+$: 289.1052.

1-(3,4-Dimethoxyphenyl)-2,2-dimethylpropane-3-acetate-1-ol (4g): It was obtained as a liquid in 55.4% yield; ^1H NMR (300 MHz, CDCl_3) δ 0.86 and 0.95 (3H each, s, $2 \times \text{CH}_3$), 2.12 (3H, s, OCOCH_3), 2.37 (1H, br s, OH), 3.79 and 4.18 (1H each, d, $J = 11.1$ Hz, CH_2), 3.88 (6H, s, $2 \times \text{OCH}_3$), 4.54 (1H, s, CH), 6.82 (2H, br s, ArH), 6.88 (1H, br s, ArH); ^{13}C NMR (75.5 MHz, CDCl_3) δ 19.8, 21.4, 21.9, 39.5, 56.2 (2C), 71.3, 78.0, 110.7, 111.1, 120.3,

134.0, 148.7 (2C), 171.7; UV (MeOH) λ_{max} : 204, 228, 274, 379 nm. HRMS (ESI) m/z : 305.1361 $[M+Na]^+$; Calcd. for $[C_{15}H_{22}O_5+Na]^+$: 305.1365.

1-(Furan-2-yl)-2,2-dimethylpropane-3-acetate-1-ol (4h): It was obtained as a liquid in 28.11% yield. ^1H NMR (300 MHz, CDCl_3) δ 0.93 and 1.01 (3H each, s, $2 \times \text{CH}_3$), 2.10 (3H, s, OCOCH_3), 2.44 (1H, d, $J = 4.2$ Hz, OH), 3.84 and 4.12 (1H each, d, $J = 11.1$ Hz each, CH_2), 4.58 (1H, d, $J = 5.1$ Hz, CH), 6.25 (1H, d, $J = 3.0$ Hz, furyl-H), 6.34 (1H, d, $J = 1.8$ Hz, furyl-H), 7.37 (1H, s, furyl-H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 20.1, 21.3, 21.6, 39.5, 70.8, 72.7, 107.9, 110.5, 142.1, 155.0, 171.6; UV (MeOH) λ_{max} : 217, 317 nm. HRMS (ESI) m/z : 235.0942 $[M+Na]^+$; Calcd. for $[C_{11}H_{16}O_4+Na]^+$: 235.0947.

1-(Pyridin-4-yl)-2,2-dimethylpropane-3-acetate-1-ol (4i): It was obtained as a solid in 40% yield; mp 69–71 °C; ^1H NMR (300 MHz, CDCl_3) δ 0.83 and 0.88 (6H, 2s, $2 \times \text{CH}_3$), 2.01 (1H, s, OH), 2.06 (3H, s, OCOCH_3), 3.75 (1H, d, $J = 10.8$ Hz, $\text{CH}\alpha\text{H}\beta$), 4.19 (1H, d, $J = 11.1$ Hz, $\text{CH}\alpha\text{H}\beta$), 4.53 (1H, s, CH), 7.22 (2H, d, $J = 5.1$ Hz, ArH), 8.38 (2H, d, $J = 5.1$ Hz, ArH); ^{13}C NMR (75.5 MHz, CDCl_3) δ 19.3, 21.3, 21.8, 39.3, 70.8, 76.3, 123.4 (2C), 149.1 (2C), 151.2, 171.7; UV (MeOH) λ_{max} : 257 nm. HRMS (ESI) m/z 246.1099 $[M+Na]^+$; Calcd. for $[C_{12}H_{17}NO_3+Na]^+$: 246.1106.

1-(Pyridin-2-yl)-2,2-dimethylpropane-3-acetate-1-ol (4j): It was obtained as a solid in 41% yield; mp 54–55 °C; ^1H NMR (300 MHz, CDCl_3) δ 0.88 and 0.93 (3H each, s, $2 \times \text{CH}_3$), 2.07 (3H, s, OCOCH_3), 3.88 (1H, d, $J = 10.8$ Hz, $\text{CH}\alpha\text{H}\beta$), 4.14 (1H, d, $J = 10.5$ Hz, $\text{CH}\alpha\text{H}\beta$), 4.40 (1H, d, $J = 9.0$ Hz, OH), 4.62 (1H, d, $J = 6.6$ Hz, CH), 7.23 (2H, t, $J = 7.5$ Hz, pyridyl-H), 7.66 (1H, t, $J = 6.0$ Hz, pyridyl-H), 8.57 (1H, d, $J = 4.8$ Hz, pyridyl-H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 20.0, 21.3, 21.7, 39.9, 70.6, 76.5, 122.9, 123.0, 136.1, 148.4, 159.4,

171.4; UV (MeOH) λ_{max} : 261 nm. HRMS (ESI) m/z 246.1098 $[\text{M}+\text{Na}]^+$; Calcd. for $[\text{C}_{12}\text{H}_{17}\text{NO}_3+\text{Na}]^+$: 246.1106.

1-Phenyl-2,2-dimethylpropane-1-acetate-3-ol (5a): It was obtained as a liquid in 5% yield; ^1H NMR (300 MHz, CDCl_3) δ 0.90 and 0.95 (6H, s, $2 \times \text{CH}_3$), 2.14 (3H, s, OCOCH_3), 2.32 (1H, br s, OH), 3.26 and 3.46 (1H each, d, $J = 11.4$ Hz, CH_2), 5.82 (1H, s, CH), 7.28–7.33 (5H, m, ArH); ^{13}C NMR (75.5 MHz, CDCl_3) δ 19.7, 21.5, 21.8, 40.3, 69.4, 79.3, 128.2 (5C), 137.9, 171.2; UV (MeOH) λ_{max} : 207, 258 nm. HRMS (ESI) m/z 245.1150 $[\text{M}+\text{Na}]^+$; Calcd. for $[\text{C}_{13}\text{H}_{18}\text{O}_3+\text{Na}]^+$: 245.1154.

1-(4-Methoxyphenyl)-2,2-dimethylpropane-1-acetate-3-ol (5d): It was obtained as a liquid in 2% yield; ^1H NMR (300 MHz, CDCl_3) δ 0.87 and 0.88 (6H, s, $2 \times \text{CH}_3$), 2.12 (3H, s, OCOCH_3), 3.24 and 3.44 (1H each, d, $J = 12.0$ Hz, CH_2), 3.81 (3H, s, OCH_3), 5.77 (1H, s, CH), 6.87 (2H, d, $J = 8.7$ Hz, ArH), 7.24 (2H, d, $J = 8.4$ Hz, ArH); ^{13}C NMR (75.5 MHz, CDCl_3) δ 19.8, 21.6, 21.8, 40.4, 55.6, 69.4, 79.1; UV (MeOH) λ_{max} : 225, 274, 281 nm. HRMS (ESI) m/z 275.1262 $[\text{M}+\text{Na}]^+$; Calcd. for $[\text{C}_{14}\text{H}_{20}\text{O}_4+\text{Na}]^+$: 275.1260.

Synthesis of 1-(4-methoxyphenyl)-2,2-dimethylpropane-1,3-diacetate (6):

To a stirred solution of 1-(4-methoxyphenyl)-2,2-dimethyl-1,3-propanediol (80 mmol) in acetic anhydride (160 mmol), DMAP (catalytic amount) was added, and the resulting mixture was stirred at room temperature for 48 h. Water was added to the reaction mixture and extracted with ethyl acetate (3×100 mL). The organic layer was dried and concentrated to afford a crude product which was purified by column chromatography (8% EtOAc/hexane as the eluent). It was obtained as a colorless solid in 84% yield; mp 35–38 °C; ^1H NMR (300 MHz, CDCl_3) δ 0.91 and 0.99 (3H each, s, $2 \times \text{CH}_3$), 2.08 and 2.10 (6H, 2s, 2

373 × OCOCH₃), 3.69 and 4.05 (1H each, d, J = 10.8 Hz, CH₂), 3.80 (3H, s, OCOCH₃), 5.68 (1H,
374 s, CH), 6.85 (2H d, J = 8.7 Hz, ArH), 7.20 (2H, d, J = 8.7 Hz, ArH); ¹³C NMR (75.5 MHz,
375 CDCl₃) δ 20.7, 21.3, 21.5 (2C), 38.7, 55.6, 70.1, 78.7, 113.7 (2C), 129.2 (2C), 129.9, 159.5,
376 170.3, 171.4; UV (MeOH) λ_{max}: 222, 274, 280 nm. HRMS (ESI) m/z 317.1357 [M+Na]⁺;
377 Calcd. for [C₁₆H₂₂O₅+Na]⁺: 317.1365.

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442 **Tables and Figure Captions:**

443 **Figure 1.** Biologically active propanediol carbamates and related propanediols.

444 **Table 1.** Stereoselective acetylation of *racemic* 1-(4-methoxyphenyl)-2,2-dimethyl-1,3-
445 propanediol **1a** in different solvents

446 **Table 2.** Stereoselective acetylation of 1-aryl-2,2-dimethyl-1,3-propanediols **1a-j** in THF.

447 **Scheme 1.** Attempted Novozym® 435-catalyzed deacetylation reaction of racemic diacetate
448 **6**.

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Draft

451 Graphical Abstract:

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453 **Optical Enrichment in Enzyme-Catalyzed Resolution of 1-Aryl-2,2-Dimethyl-1,3-**

454 **Propanediols**

455 Chandrani Mukherjee, Prabhu P. Mohapatra, Dani Youssef, Amitabh Jha*

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