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Selective biotransformation reactions on (±)-aryl alkyl ketones, (±)-benzoxazines, and D-*arabino*- and D-*threo*-hydroxyalkyltriazoles*

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Abstract: The capabilities of porcine pancreatic lipase (PPL), *Candida antarctica* lipase (CAL), and *Candida rugosa* lipase (CRL) were evaluated for enantio- and/or regioselective acetylation/deacetylation of (±)-2,4-diacetoxyphenyl alkyl ketones, (±)-4-alkyl-3,4-dihydro-3-hydroxyalkyl-2*H*-1,3-benzoxazines, and D-*arabino* and D-*threo*-polyhydroxyalkyltriazoles in organic solvents. PPL in tetrahydrofuran (THF) exhibited high to moderate enantioselectivity during the deacetylation of (±)-2,4-diacetoxyaryl alkyl ketones and acetylation of (±)-3-hydroxyalkyl-2*H*-1,3-benzoxazines. Together with enantioselectivity, PPL in THF also showed exclusive regioselectivity for the deacetylation of *para*-acetoxy over the *ortho*-acetoxy function, with respect to the nuclear carbonyl group in 2,4-diacetoxyphenyl alkyl ketones. CAL in diisopropyl ether (DIPE) and PPL in THF exhibited exclusive selectivity for the acetylation of primary hydroxyl over secondary hydroxyl group(s) of D-*arabino*- and D-*threo*-polyhydroxyalkyltriazoles.

INTRODUCTION

The search for reactions that show greater selectivity and are environmentally friendly has resulted in the development of enzyme- and microorganism-catalyzed synthetic processes [1,2]. We have earlier demonstrated the capabilities of lipases from porcine pancrease (PPL), *Candida antarctica* (CAL), *Candida rugosa* (CRL), *Pseudomonas* sp. and *Aspergillus* sp. in regio- and enantioselective acetylation/deacetylation of the hydroxy/acetoxy group(s) in different classes of polyphenolic compounds [3–12]. We wish to report herein lipase-catalyzed enantio- and regioselective acetylation/deacetylation of (±)-2,4-diacetoxyphenyl alkyl ketones, (±)-4-alkyl-3,4-dihydro-3-hydroxyalkyl-2*H-1*,3-benzoxazines, and D-*arabino*- and D-*threo*-hydroxyalkyltriazoles, precursors for the synthesis of triazolylacyclonucleosides.

SYNTHESIS AND ENANTIOSELECTIVE RESOLUTION OF (±)-2,4-DIACETOXYPHENYL ALKYL KETONES 9–12

(±)-2,4-Dihydroxyphenyl alkyl ketones **5–8** were prepared by Nencki and Sieber reaction [13] of resorcinol with the corresponding racemic aliphatic acids **1–4** in 50 to 55% yields (Scheme 1). The (±)-diacetates **9–12** of dihydroxy compounds **5–8** were prepared by acetylation using acetic anhydride/DMAP in quantitative yields. All the (±)-dihydroxyphenyl alkyl ketones **5–8** and (±)-diacetoxyphenyl alkyl ketones **9–12** were found to be new in literature and characterized on the basis of their spectral data (IR, UV, ^{1}H NMR, ^{13}C NMR, EI, and HRMS).

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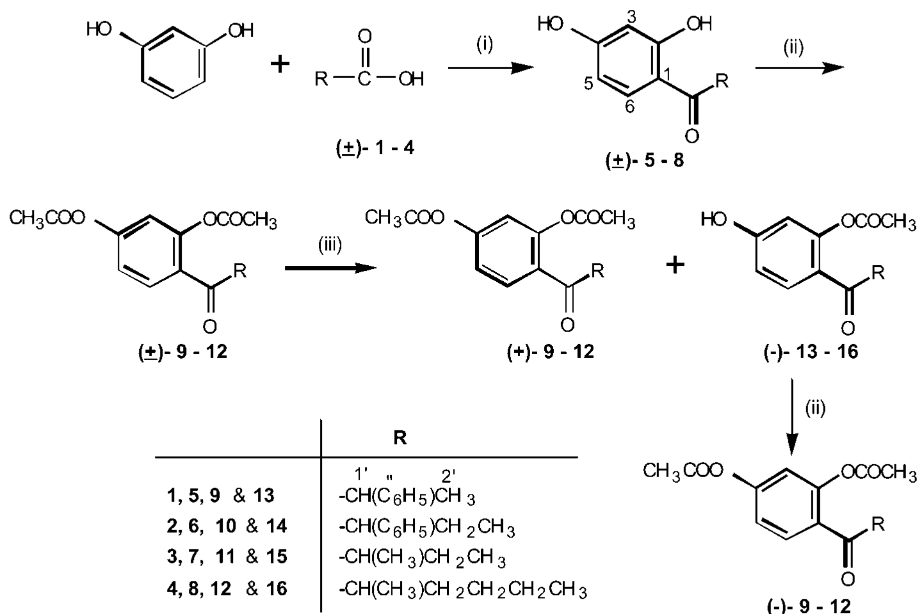
The racemic diacetoxy ketones **9** and **10** were incubated with PPL in THF, and the reaction was stopped by filtering off the enzyme after about 50% conversion of the starting diacetoxyketone to a slow-moving product on TLC. Identification of the deacetylated product revealed that the enzyme selectively deacetylates the *para* acetoxy over the *ortho* acetoxy function with respect to the nuclear carbonyl group in diacetoxyphenyl alkyl ketones **9** and **10**, leading to the formation of **13** and **14** in 55 and 60% yields [14], respectively (Table 1). The result that the *ortho* acetoxy function is inert to PPL-catalyzed deacetylation is in conformity with our earlier findings [11,15]. In addition to the regioselectivity during the deacetylation of (±)-2,4-diacetoxyphenyl alkyl ketones **9** and **10**, the enzyme also showed enantioselectivity and preferentially deacetylated the *para* acetoxy function of one enantiomer over the *para* acetoxy function of the other, leading to the formation of optically enriched (–)-**13** and (–)-**14** (Table 2).



Scheme 1 Reagents and conditions: (i) fused $ZnCl_2$, 150 °C; (ii) acetic anhydride, DMAP, and (iii) PPL, THF, *n*-butanol (5 equivalents), 40–42 °C.

In addition to selective deacetylation study on diacetoxyphenyl alkyl ketones **9** and **10** having phenyl substituent on alkyl moiety, ketones with methyl substituent, i.e., (±)-**11** and (±)-**12** were also incubated with PPL in THF until about 50% conversion of the starting ketone into the product, to investigate the effect of nature of different alkyl moieties on regio- and enantioselective capabilities of the enzyme. It was observed that the enzyme deacetylates the *para* acetoxy group of compounds **11** and **12** exclusively over the *ortho* acetoxy group in the same fashion, leading to the formation of (–)-**15** and (–)-**16** in 72 and 54% yields [14], respectively (Table 1). Again, there was a kinetic resolution during the enzyme-catalyzed deacetylation of (±)-**11** and (±)-**12**, leading to the formation of *laevorotatory* 2-acetoxy-4-hydroxyphenyl alkyl ketones **15** and **16** (Table 2). The time required for about 50% conversion of 2,4-diacetoxyphenyl alkyl ketones **9–12** to 2-acetoxy-4-hydroxyphenyl alkyl ketones **13–16** in the presence of PPL is nearly the same. This result indicates that the nature of alkyl residue in diacetoxyphenyl alkyl ketones does not affect the selectivity of the enzymatic reaction, i.e., the enzyme and alkyl group interaction does not play any crucial role in the deesterification of phenolic acetoxy function. These results are in accordance with our earlier proposed hypothesis on the mechanism of action of PPL in THF involving a dynamic Schiff's base complex formation between the ξ-amino group of the lysine residue present in the active site of the PPL and the keto group directly attached to the benzenoid

Table 1 Selective deacetylation of (±)-2,4-diacetoxyphenyl alkyl ketones mediated by PPL in THF at 40–42 °C in the presence of *n*-butanol[a,b].

Substrate	Time (h)	Products[c] (*% yield*)[d]
(±)-2,4-Diacetoxyphenyl (1-phenyl)-ethyl ketone (**9**)	12	(–)-2-Acetoxy-4-hydroxyphenyl (1-phenyl)ethyl ketone (**13**) (*55*) *and* (+)-2,4-Diacetoxyphenyl (1-phenyl)ethyl ketone (**9**) (*63*)
(±)-2,4-Diacetoxyphenyl (1-phenyl)-propyl ketone (**10**)	12	(–)-2-Acetoxy-4-hydroxyphenyl (1-phenyl)propyl ketone (**14**) (*60*) *and* (+)-2,4-Diacetoxyphenyl (1-phenyl)propyl ketone (**10**) (*75*)
(±)-2,4-Diacetoxyphenyl (1-methyl)-propyl ketone (**11**)	12	(–)-2-Acetoxy-4-hydroxyphenyl (1-methyl)propyl ketone (**15**) (*72*) *and* (+)-2,4-Diacetoxyphenyl (1-methyl)propyl ketone (**11**) (*81*)
(±)-2,4-Diacetoxyphenyl (1-methyl)-pentyl ketone (**12**)	10	(–)-2-Acetoxy-4-hydroxyphenyl(1-methyl)pentyl ketone (**16**) (*54*) *and* (+)-2,4-Diacetoxyphenyl (1-methyl)pentyl ketone (**12**) (*60*)

[a]All these reactions, when performed under identical conditions but without adding porcine pancreatic lipase did not yield any product.
[b]All deacetylation reactions were stopped by filtering off the enzyme after about 50% conversion of the starting racemic diacetate to the product, i.e., monoacetate.
[c]Deacetylated monoacetate and recovered, unreacted diacetate.
[d]See reference 14.

Table 2 Optical rotation values of PPL-catalyzed deacetylation products (–)-**13–16**, recovered, unreacted diacetates (+)-**9–12** and compounds (–)-**9–12** obtained by chemical acetylation of (–)-**13–16.**

Substrate (racemic)	$[\alpha]^{25}_{D}$		
	Monoacetates 13–16	**Recovered diacetates 9–12**	**Diacetates 9–12**[a]
9	**13**: (–) 33.0	**9**: (+) 26.1	**9**: (–) 18.0
10	**14**: (–) 50.8	**10**: (+) 30.0	**10**: (–) 21.8
11	**15**: (–) 41.4	**11**: (+) 32.5	**11**: (–) 23.9
12	**16**: (–) 41.6	**12**: (+) 37.9	**12**: (–) 41.5

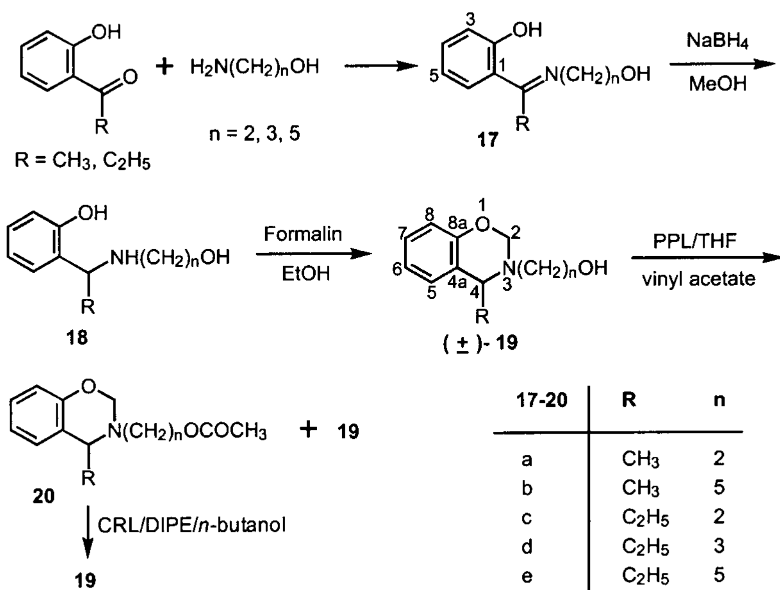
[a]Diacetates **9–12** were prepared by chemical acetylation of enzymatically deacetylatd monoacetates **13–16**.

ring [11]. The products of enzymatic deacetylation reactions (i.e., compounds **13–16**) are new and have been fully characterized on the basis of their spectral data (IR, UV, ^{1}H NMR, ^{13}C NMR, EI, and HRMS). The presence of hydroxyl group at the para position with respect to the nuclear carbonyl group in the compounds **13–16** was supported by the absence of chelated hydroxyl group and presence of only one acetoxy function in their ^{1}H NMR spectra and by the nature of their color reaction with 10% alcoholic $FeCl_3$ solution on TLC. This result was further supported by ^{13}C NMR and other spectral data.

The enantiomeric excess of (–)-2-acetoxy-4-hydroxyphenyl alkyl ketones **13–16** could not be determined either by chiral HPLC or by chiral shift ^{1}H NMR spectroscopy techniques using (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol [(+)-TFAE] shift reagent. However, to show that the lipase exhibits enantioselectivity and yields optically enriched (–)-ketones **13–16**, these monohydroxy ketones were acetylated by acetic anhydride/DMAP method and their optical rotation values measured. The comparison of optical rotation values of the recovered, unreacted (+)-2,4-diacetoxyphenyl alkyl ketones **9–12** with the corresponding (–)-2,4-diacetoxyphenyl alkyl ketones **9–12** obtained by chemical acetylation of (–)-monoacetates **13–16** revealed that they are comparable and had opposite signs of rotation (Table 2). This indicates that the optical enrichment during enzymatic deacetylation is of high order.

SYNTHESIS AND LIPASE-CATALYZED ENANTIOSELECTIVE ACETYLATION OF (±)-4-ALKYL-3,4-DIHYDRO-3-HYDROXYALKYL-2*H*-1,3-BENZOXAZINES 19a–19e

Synthesis of (±)-benzoxazines **19a–19e** has been achieved by Mannich-type condensation of formaldehyde with secondary amines **18a–18e** in 55–62% yields, respectively (Scheme 2). The secondary amines **18a–18e** were prepared in two steps starting from the condensation of *o*-hydroxyacetophenone/*o*-hydroxypropiophenone with hydroxyalkylamines, followed by sodium borohydride reduction of the resulting schiff's bases **17a–17e** (Scheme 2). All the schiff's bases **17a–17e**, secondary amines **18a–18e** and benzoxazines **19a–19e** were found to be new in literature and identified on the basis of their spectral data (UV, IR, ^{1}H NMR, ^{13}C NMR, EI, and HRMS).



17-20	R	n
a	CH_3	2
b	CH_3	5
c	C_2H_5	2
d	C_2H_5	3
e	C_2H_5	5

Scheme 2

PPL and CRL in THF and DIPE, respectively, were screened for enantioselective acetylation of (±)-4-alkyl-3,4-dihydro-3-hydroxyalkyl-2*H*-1,3-benzoxazines **19a–19e** using vinyl acetate as acetylating agent. The acetylation of 3-hydroxyalkylbenzoxazines catalyzed by CRL in DIPE was too slow to be used for any practical purposes, however, the rate of acetylation catalyzed by PPL in THF was satisfactory. In a typical reaction, a mixture of racemic 3-hydroxyalkylbenzoxazine **19a–19e** and vinyl acetate (1.1 eq) was incubated with PPL in THF at 40–42 °C. The reaction was monitored by HPLC and/or TLC and stopped by filtering off the enzyme after about 50% conversion of the 3-hydroxyalkylbenzoxazine into 3-acetoxyalkylbenzoxazine, a fast moving compound on TLC. The enzymatically acetylated benzoxazines and the unreacted hydroxyalkylbenzoxazines were separated by column chromatography on silica gel using a gradient solvent system of petroleum ether–ethyl acetate and their optical rotations were measured (Table 3). Both, acetylated (+)-benzoxazines **20a–20e** and recovered, unreacted (–)/(+)-3-hydroxyalkylbenzoxazines **19a–19e** were found to be optically active, which indicates that the deacetylation reaction is enantioselective. The comparison of optical rotation values of recovered, unreacted (–)/(+)-hydroxyalkylbenzoxazines and (+)/(–)-hydroxyalkylbenzoxazines obtained by deacetylation of enzymatically acetylated benzoxazines **20a–20e** revealed that the enantioselection during PPL-catalyzed acetylation is moderate (Table 4).

Table 3 Enantioselective acetylation of (±)-4-alkyl-3,4-dihydro-3-hydroxyalkyl-2*H*-1,3-benzoxazine **19a–19e** catalyzed by porcine pancreatic lipase in tetrahydrofuran at 40–42 °C[a].

Entry	Substrate	Reaction Time (days)	Products	%Yields[b]
1	(±)-3,4-Dihydro-3-(2'-hydroxyethyl)-4-methyl-2*H*-1,3-benzoxazine (**19a**)	5	(+)-3-(2'-Acetoxyethyl)-3,4-dihydro-4-methyl-2*H*-1,3-benzoxazine (**20a**)	74
			and	
			(–)-3,4-Dihydro-3-(2'-hydroxyethyl)-4-methyl-2*H*-1,3-benzoxazine (**19a**)	63
2	(±)-3,4-Dihydro-3-(5'-hydroxypentyl)-4-methyl-2*H*-1,3-benzoxazine (**19b**)	4	(+)-3-(5'-Acetoxypentyl)-3,4-dihydro-4-methyl-2*H*-1,3-benzoxazine (**20b**)	68
			and	
			(-)-3,4-Dihydro-3-(5'-hydroxypentyl)-4-methyl-2*H*-1,3-benzoxazine (**19b**)	80
3	(±)-3,4-Dihydro-4-ethyl-3-(2'-hydroxyethyl)-2*H*-1,3-benzoxazine (**19c**)	5	(+)-3-(2'-Acetoxyethyl)-3,4-dihydro-4-ethyl-2*H*-1,3-benzoxazine (**20c**)	70
			and	
			(+)-3,4-Dihydro-4-ethyl-3-(2'-hydroxyethyl)-2*H*-1,3-benzoxazine (**19c**)	75
4	(±)-3,4-Dihydro-4-ethyl-3-(3'-hydroxypropyl)-2*H*-1,3-benzoxazine (**19d**)	4.5	(+)-3-(3'-Acetoxypropyl)-3,4-dihydro-4-ethyl-2*H*-1,3-benzoxazine (**20d**)	65
			and	
			(–)-3,4-Dihydro-4-ethyl-3-(3'-hydroxypropyl)-2*H*-1,3-benzoxazine (**19d**)	78
5	(±)-3,4-Dihydro-4-ethyl-3-(5'-hydroxypentyl)-2*H*-1,3-benzoxazine (**19e**)	4	(+)-3-(5'-Acetoxypentyl)-3, 4-dihydro-4-ethyl-2*H*-1,3-benzoxazine (**20e**)	70
			and	
			(-)-3,4-Dihydro-4-ethyl-3-(5'-hydroxypentyl)-2*H*-1,3-benzoxazine (**19e**)	69

[a]All these reactions, when performed under identical conditions, but without adding porcine pancreatic lipase, did not yield any product.
[b]See reference 16.

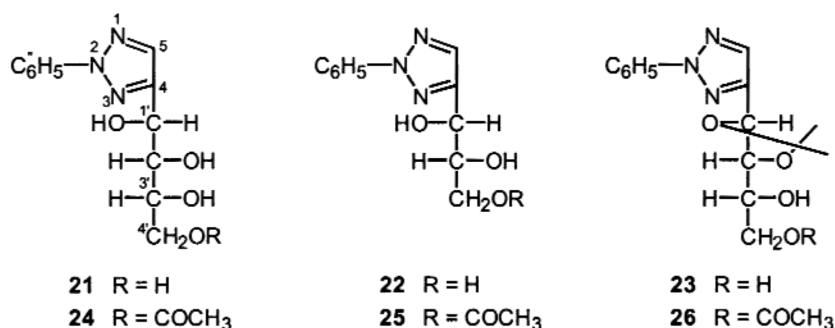
Table 4 Optical rotation values of PPL-catalyzed acetylation products (+)-**20a–20e**, the recovered, unreacted (–)/(+)-benzoxazines **19a–19e**, and (+)/(–)-benzoxazines **19a–19e** obtained by CRL-mediated deacetylation of (+)-**20a–20e.**

Substrate (racemic)	$[\alpha]25_D$		
	(+)-20a–20e	**Recovered, unreacted (–)/(+)-19a–19e**	**(+)/(-)-19a–9e obtained by CRL-catalyzed deacetylation of (+)-20a–20e**
(±)-**19a**	**20a**: (+)38.4	**19a**: (–)06.6	**19a**: (+)11.0
(±)-**19b**	**20b**: (+)08.4	**19b**: (–)06.2	**19b**: (+)11.4
(±)-**19c**	**20c**: (+)06.0	**19c**: (+)09.3	**19c**: (–)13.1
(±)-**19d**	**20d**: (+)14.4	**19d**: (–)10.3	**19d**: (+)15.4
(±)-**19e**	**20e**: (+)10.7	**19e**: (–)08.6	**19e**: (+)13.3

SYNTHESIS AND ENZYME-CATALYZED SELECTIVE ACETYLATION STUDIES ON D-*ARABINO*- AND D-*THREO*- POLYHYDROXYALKYLTRIAZOLES 21–23

The triazolyl sugar **21** was prepared in two steps according to the procedure of Hann and Hudson [17]. *Threo*-trihydroxypropyltriazole **22** was synthesized by $NaIO_4$ oxidation followed by $NaBH_4$ reduction

of tetrahydroxytriazole **21** [18]. The third substrate, i.e., 1',2'-*O*-*iso*propylidene-3',4'-dihydroxytriazole **23** was synthesized from triazole **21** through its diisopropylidene formation by acetone-anhydrous ferric chloride method, followed by the selective removal of the 3',4'-*O*-*iso*propylidene function [19]. The structures of all three compounds (i.e., **21–23**) prepared in our laboratory under a program of synthesis of triazolylacyclonucleosides for antiviral activity evaluation, were unambiguously established on the basis of their spectral analysis. The physical data of two known compounds (i.e., triazolyl sugars **21** and **22**) were found identical with those reported in literature [17,20].



Different lipases, e.g., *Candida antarctica* lipase (CAL) and *Candida rugosa* lipase (CRL) in diisopropyl ether (DIPE), and porcine pancreatic lipase (PPL) in tetrahydrofuran (THF) were screened for the selective acetylation of hydroxyl groups of triazolyl sugars **21–23**. The selection of solvent for different lipases was done on the basis of our earlier experience [3]. No appreciable conversion was observed in the case of acetylation of compounds **21–23** catalyzed by CRL in DIPE even after 34 h of incubation at 42–45 °C. Further, the rate of acetylation of triazolyl sugars **21–23** catalyzed by PPL in THF was quite slow with respect to the acetylation catalyzed by CAL in DIPE (Table 5).

In a typical reaction, a solution of triazolyl sugar (**21, 22,** or **23**, 2 mmol) and vinyl acetate in DIPE/THF was incubated with CAL/PPL in an incubator shaker at 42–45 °C and the progress of the reaction was monitored by HPLC and/or TLC. On completion of the reaction, the enzyme was filtered off, the solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel using a gradient solvent system of petroleum ether–ethyl acetate as eluent. It was observed that both CAL and PPL exclusively acetylate the primary hydroxyl group over the secondary hydroxyl group(s) in all the three triazolyl sugars **21–23**, leading to the formation of 2-phenyl-4-(D-*arabino*-4'-acetoxy-1',2',3'-trihydroxybutyl)-2*H*-1,2,3-triazole (**24**), 2-phenyl-4-(D-*threo*-3'-acetoxy-1',2'-dihydroxypropyl)-2*H*-1,2,3-triazole (**25**), and 2-phenyl-4-(D-*arabino*-4'-acetoxy-*O*-1',2'-*iso*propylidene-3'-hydroxybutyl)-2*H*-1,2,3-triazole (**26**), respectively. All three monoacetylated compounds **24–26** are new in literature and were identified on the basis of their spectral data. As indicated during screening, the rate of acetylation of primary hydroxyl groups of triazolyl sugars **21–23** catalyzed by CAL in DIPE was much faster compared to the rate of acetylation catalyzed by PPL in THF. Thus, acetylation of triazolyl sugar **21** to monoacetate **24** catalyzed by CAL in THF completed in 2h, whereas the conversion was only 72% even after 26h of incubation of **21** with PPL in THF. Similar trend was observed for the other two triazolyl sugars **22** and **23** (Table 5). It is interesting to note that the rate of acetylation of the primary hydroxyl group catalyzed by CAL in DIPE increases on increase in the number of hydroxyl groups in the substrate. Thus, the rate of acetylation of tetrahydroxybutyltriazole **21** catalyzed by CAL in THF was 1.75 and 4 times faster than the rate of acetylation of trihydroxybutyltriazole **22** and monohydroxybutyltriazole **23**, respectively (Table 5). This indicates that the interaction of the secondary hydroxyl groups with the active site of the enzyme facilitates the acetylation of primary hydroxyl group present in the substrate. This is the first report of enzyme-catalyzed selective acetylation studies on triazolyl sugars.

Table 5 Regioselective acetylation of triazolyl sugars **21–23** mediated by lipases at 42–45 °C using vinyl acetate[a].

Entry	Substrate	Lipase-Solvent; (RT in h)	Product (*% yield*)
1	2-Phenyl-4-(D-*arabino*-1',2',3',4'-tetra-hydroxybutyl)-2*H*-1,2,3-triazole (**21**)	CAL-DIPE/ PPL-THF; (2/26)	2-Phenyl-4-(D-*arabino*-4'-acetoxy-1',2',3'-trihydroxybutyl)-2*H*-1,2,3-triazole (**24**) (*98/72*)
2	2-Phenyl-4-(D-*threo*-1',2',3'-trihydroxy-propyl)-2*H*-1,2,3-triazole (**22**)	CAL-DIPE/ PPL-THF; (3.5/48)	2-Phenyl-4-(D-*threo*-3'-acetoxy-1',2'-dihydroxypropyl)-2*H*-1,2,3-triazole (**25**) (*97/68*)
3	2-Phenyl-4-(D-*arabino*-*O*-1',2'- *iso*-propylidene-3',4'-dihydroxybutyl)-2*H*-1,2,3-triazole (**23**)	CAL-DIPE/ PPL-THF; (8/72)	2-Phenyl-4-(D-*arabino*-4'-acetoxy-*O*-1',2'-*iso*propylidene-3'-hydroxybutyl)-2*H*-1,2,3- triazole (**24**) (*95/76*)

[a]All these reactions when performed under identical conditions but without addition of the enzyme did not yield any product.

The above study has revealed that CAL in DIPE exhibits exclusive selectivity for the acetylation of primary hydroxyl group over secondary hydroxyl group(s) in triazolyl sugars. The turn over of the acetylation reaction was very high and 95–98% conversion was observed in 2–8 h. The enzymatic method developed for the selective acetylation of primary hydroxyl group in triazolyl sugars may offer a significant advantage over chemical methods for selective manipulation of different hydroxyl groups *en route* to multistep synthesis of bioactive molecules of this class.

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