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DOI: 10.1039/C4RA10503F

Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Reversal of Regioselectivity in Acetylation and Deacetylation of Aryl-Naphthalene Diols and Diacetates by Amano Lipase

Arpita Panja, Deb Ranjan Banerjee and Amit Basak*

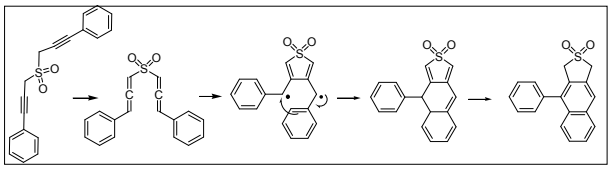
Department of Chemistry, Indian Institute of Technology Kharagpur 721 302 India

Received (in XXX, XXX) XthXXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Abstract— The regioselectivity of hydrolysis by Amano Lipase (AK Lipase) from *Pseudomonas fluorescens* of aryl naphthalene 4',7-diacetates **1a-c** prepared by Garratt-Braverman Cyclization of bis-propargyl sulfones, ethers and sulfonamides and acetylation of the corresponding diol **2a-c** were studied. In all these cases selectivity of hydrolysis and acetylation were both excellent. However, the pattern of selectivity was found to be dependent upon the nature of the fused heterocyclic ring, namely dihydrothiophene dioxide (sulfolene), dihydrofuran (phthalan) or dihydro isoindole (indoline). For the isoindole system, the hydrolysis as well as acetylation occurred at C-7 while for the furan derivative, the reaction took place entirely at the C-4'. Interestingly, for dihydrothiophene dioxide, reversal of selectivity was observed in hydrolysis and acetylation. The results are in contrast with those reported for similar reactions on aryl naphthalene 2', 5-diacetates and corresponding diols. The observed results can be explained by molecular docking using PCL crystal structure representing the *Pseudomonas* lipase family.

1. Introduction

Aryl naphthalene is regarded as a privileged skeleton because of its presence in natural products like the justicidin class of lignans[1] as well as in several unnatural products with the diverse array of optical and electronic properties.[2] Several methods have been reported for the synthesis of such skeletons which include intramolecular Friedel-Crafts and Diels-Alder reactions.[3] In recent years use of Garratt-Braverman (GB) cyclization[4] **(Scheme 1)** for efficient construction of aryl naphthalenes has been reported along with several mechanistic details.[5]



Scheme 1: Garratt-Braverman Cyclization

The usual starting materials for GB cyclization are bis-propargyl sulfones, ethers or sulfonamides. The symmetrical starting materials lead to aryl naphthalenes with the same functional groups at different locations. Unsymmetrical bispropargyl systems with different functionalities at the two ends upon GB cyclization often lead to a mixture of isomers. Thus there is a need to regiochemically differentiate similar functional groups in arylnaphthalenes obtained via GB cyclization of symmetrical systems. In a recent paper,[6] we had reported an enzymatic acetylation/deacetylation route to differentially protected aryl naphthalenes where the functional groups were at C2' and C5 positions. The binding mode was the same for acetylation and for deacetylation reactions (**Scheme 2**). We were curious to know whether similar regioselectivity would be observed for substrates having the acetoxymethyl or hydroxymethyl groups at other positions. With this in mind, we studied the hydrolysis of aryl naphthalene sulfones/ethers/sulfonamide 4',7-diacetates by Amano lipase (AK lipase)[7] *Pseudomonas fluorescens* and acetylation of the corresponding diols. In all cases, the reactions are highly regioselective. However, the pattern of selectivity was found to be dependent upon the nature of the fused heterocyclic ring, namely dihydrothiophene dioxide (sulfolene), dihydrofuran (phthalan) or isoindole (indoline). For the isoindole system, the hydrolysis as well as acetylation occurred at the C-7 while for the furan derivative, the reactions took place entirely at the C4'. For sulfones, reversal of selectivity for hydrolysis and acetylation was observed. The hydrolysis occurred selectively at C-7 while C-4' was the preferred position for acetylation. The results are in contrast with those reported for similar reactions on 2', 5 -disubstituted aryl naphthalenes where hydrolysis/ acetylation both occurred at C-5. The observed results have been explained by molecular docking using the

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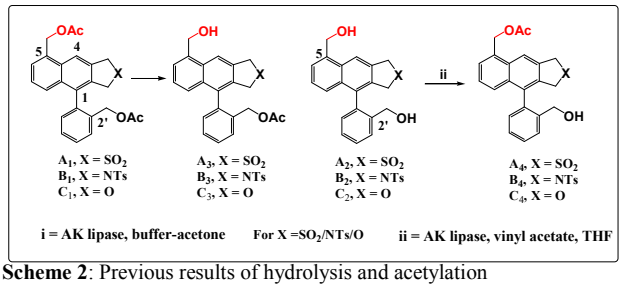
Pseudomonas cepacia lipase crystal structure[8] as the representative class of lipases of the *Pseudomonas* family.



Scheme 2: Previous results of hydrolysis and acetylation

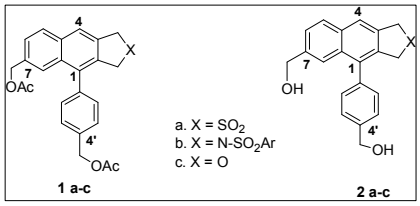
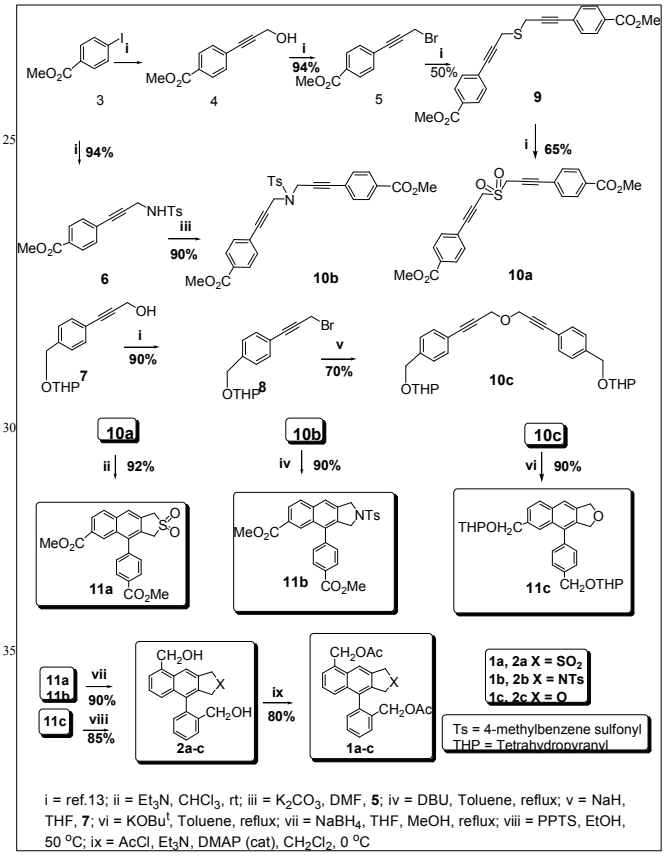


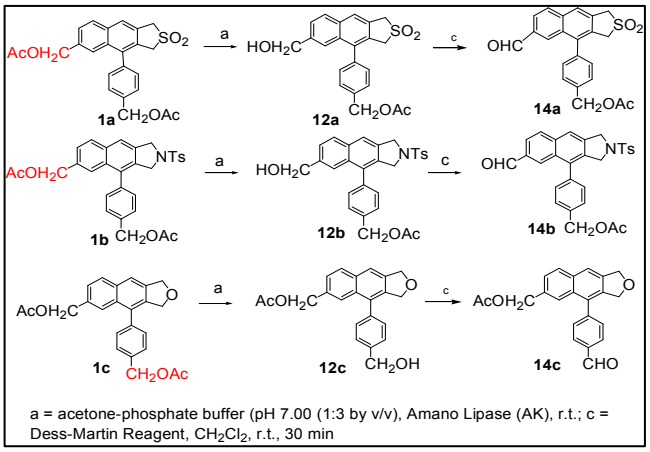
Figure 1: Aryl naphthalene diacetates and diols used for enzymatic hydrolysis and acetylation respectively

The starting diols **2a-b** were prepared by $NaBH_4$ reduction of the corresponding diesters**11a-b**[9]; the other diol **2c** by deprotection of the THP protected diol **11c**. The diesters and the diol, in turn, were obtained from the bis-propargyl sulfone, ether and sulfonamide by Garratt-Braverman cyclization. The diols were then bis-acetylated with acetyl chloride in the presence of triethylamine (**Scheme 3**).



Scheme 3: Synthesis of naphthalene derivatives **1** and **2**

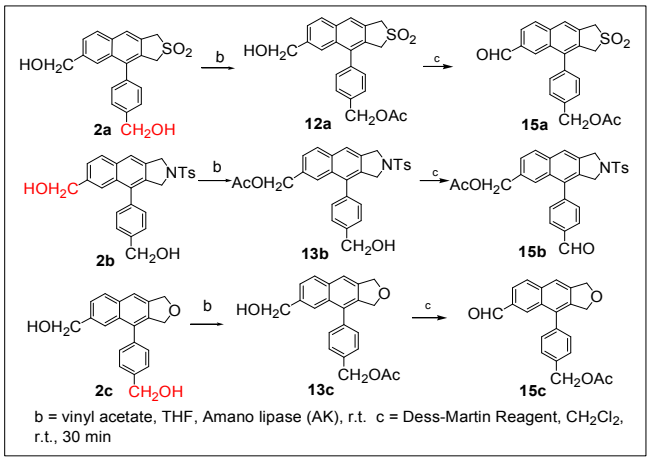
The hydrolytic behavior of the aryl naphthalene bis-acetates **1a-c** was then studied. Attempted chemical hydrolysis, even under mild conditions (LiOH, THF),[10] produced a mixture of monoacetates thereby demonstrating lack of selectivity. Enzymatic hydrolysis was attempted next using various hydrolytic enzymes. While Candida cylindracea (CCL)[11] and Porcine pancreatic lipase (PPL)[12] failed to induce hydrolysis of the diacetates or acetylation of the diols, Amano Lipase AK was able to hydrolyze the diacetates **1a-c** to the monoacetates **12a-c** in a regioselective manner (**Scheme 4**). The products of hydrolysis from the diacetates are shown in **Table 1**.



Scheme 4: Hydrolysis of diacetates and subsequent oxidation

Substrate	Product	Enzyme	Yield(%)
1a	**12a**	Amano Lipase AK	75
1b	**12b**	Amano Lipase AK	68
1c	**12c**	Amano Lipase AK	72

Table 1: Enzymatic hydrolysis of the diacetates



Scheme 5: Acetylation of diols and subsequent oxidation

The acetylation was next carried out using vinyl acetate and Amano Lipase AK **(Scheme 5).** Again the reaction

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proceeded with a high degree of selectivity and the various monoacetates were isolated in high yields (**Table 2**).

Substrate	Product	Enzyme	Yield(%)
2a	**13a**	Amano Lipase AK	82
2b	**13b**	Amano Lipase AK	75
2c	**13c**	Amano Lipase AK	75

Table 2: Enzymatic acetylation of the diols

The structure of the various monoacetates obtained upon hydrolysis/esterification could not be confirmed by X-ray crystallography as we failed to obtain good quality crystals. The ^{1}H NMR also failed to reveal the location of the acetate. Finally the structures could be confirmed by studying the shift of aryl hydrogens upon oxidation to the aldehydes which exerted deshielding effect on the aryl hydrogens to which the aldehyde functionality is attached. As an example, the aldehyde **14c** obtained from **12c**, the hydrogens in the pendant aryl ring experienced downfield shift. For the other aldehyde **15c** derived from **13c**, the aryl hydrogens in ring A of the naphthalene moiety underwent downfield shift (**Figure 2**).

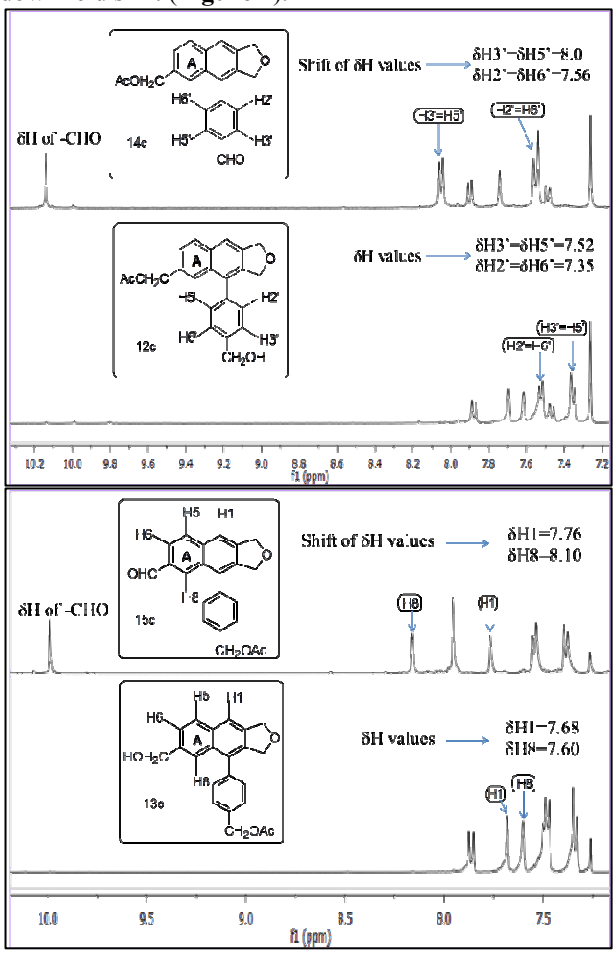
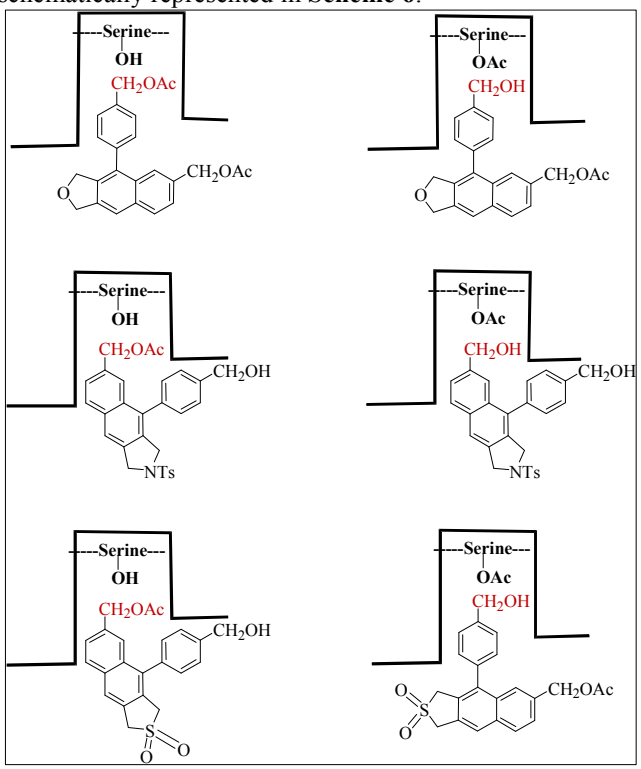


Figure 2: ^{1}H NMR of alcohol and corresponding aldehyde

Inspection of the results shown in **Tables 1** and **2** revealed many important attributes to these enzyme catalyzed reactions. Although all the hydrolysis/acetylation reactions were highly regioselective, the pattern of selectivity is dependent upon the nature of heterocyclic ring. Normally the orientation of substrate binding to the active site of the enzyme for hydrolysis or acetylation is expected to be similar. This is indeed found to be true in case of the furan or isoindole derivative. However, for furan, the substrate binding takes place in such a way that the C4'-acetate or hydroxymethyl is near the active site serine/acetylated serine. For the sulfonamide **(1a and 2a)** it is the other acetate/hydroxymethyl at C5 that is placed near to the active site serine/acetylated serine upon binding. The hydrolytic/acetylation behaviour of the sulfones is interesting. The orientation of binding for hydrolysis is different from that of acetylation. The hydrolysis is taking place preferentially at C5'-acetate while the acetylation has occurred at the C4'-hydroxy methyl. All these aspects are schematically represented in **Scheme 6**.



Scheme 6: Mode of binding of acetate/hydroxymethyl functionality based on the experimental results.

Docking Studies: Explanation of the results

Docking studies have been performed to find insight on binding of our synthesized compounds. The structure of *Pseudomonas fluorescens* lipase (PFL) is yet to be solved; therefore, we have performed these docking studies with *Pseudomonas cepacia* lipase (PCL). PCL is homologous to

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the PFL and has 22% sequence identity.[14]The active site of PCL is constituted by Ser87, His286 and Asp264, while the Leu17 and Gln88 residues also take part in catalysis.[15, 16] PCL have two binding pockets; one is large hydrophobic binding pocket which lies above the active site Ser87 and an "alternate binding pocket" lying below the Ser87. This alternate binding pocket is lined with hydrophobic amino acids Tyr23, Leu27, Tyr29, Phe146, Ile290, and Leu293 (**Figure 3**). Researchers have shown that "extra hydrogen bonds" with Tyr29 or Tyr 23 residues helped the binding of ligand in this alternate groove and play crucial role in the selective catalysis.[15] Lang *et al.*[17] also suggested that Tyr29 remain hydrogen bonded with active site residues in native state and during catalysis. Although crystal structure of PFL is not known, alignment of sequence of PFL with PCL suggests a tyrosine (Tyr50) in same position and indicates the presence of 'alternate binding site' in PFL.[15]

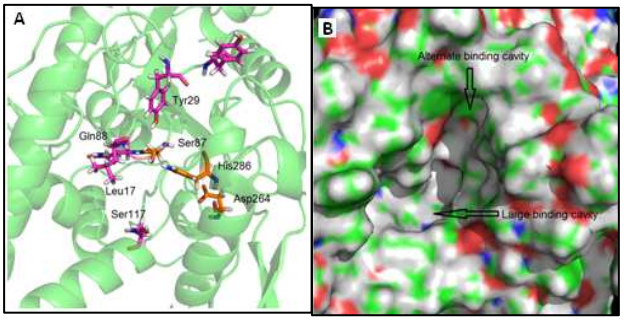

Figure 3: A. PCL active site (PDB ID: 3LIP) with catalytic triad and other crucial residues; **B.** Surface representation of PCL representing the main large binding cavity and alternate binding cavity.

The pattern of selectivity was found to be dependent upon the nature of the fused heterocyclic ring; hence, the differences in their electronic natures, sizes and position of substituent should have effect in their binding modes at lipase's active site cavity.

Before proceeding with the docking study, it would be worth to explore the hydrolysis/acetylation behaviour of some of the representative substrates with PCL and find out whether similar selectivity is followed. Thus the substrates were treated with Lipase, immobilized in Sol-Gel-AK from *Pseudomonas cepacia*. Although the reactions were very sluggish, the hydrolysis of diacetate $\mathbf{B_1}$ and acetylation of diols $\mathbf{C_2}$ and **2a** followed similar regioselectivity as revealed by ^{1}H NMR (**Figure 4**)

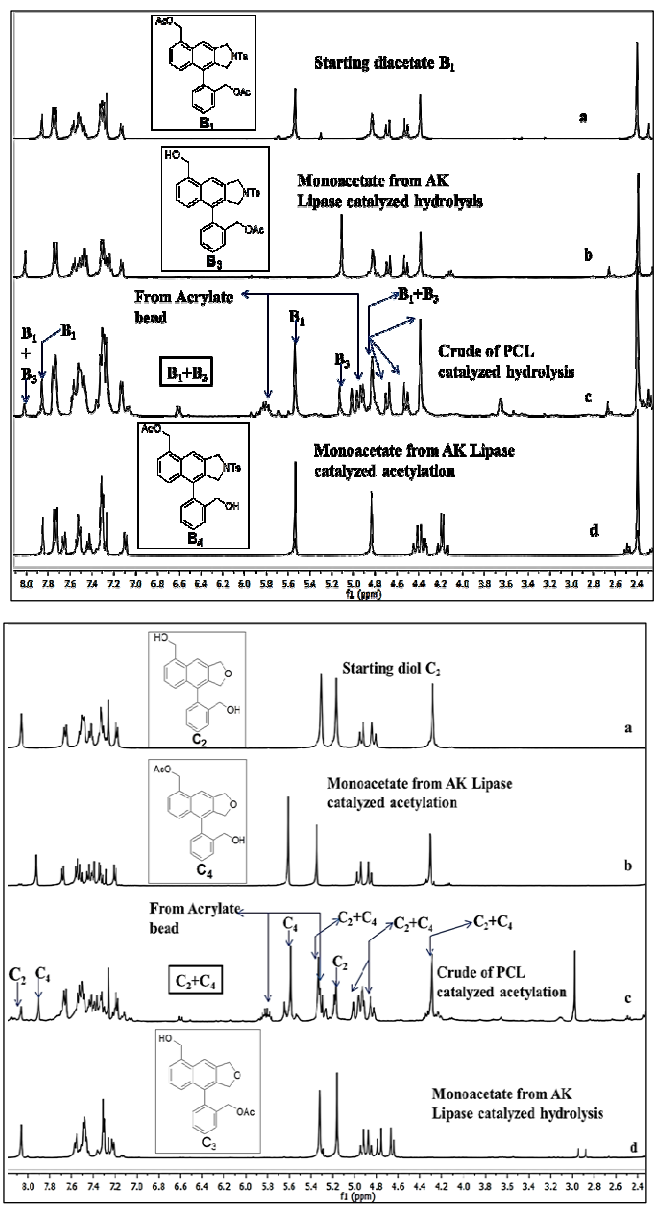

Figure 4: Comparative ^{1}H NMR of PFL and PCL catalyzed reactions; **a:** Starting diacetate or diol**; b**, **d:** Regio-isomeric monoacetate from PFL catalyzed acetylation and hydrolysis; **c:** PCL catalyzed reactions (acetylation or hydrolysis).

Based on these rationales, we have performed the docking studies. Regio-selective catalysis of similar type of aryl-naphthalenes has been reported previously from this group. As PCL has limited homology with PFL, we have tried to standardize and validate current *in silico* approach by using previously reported compounds. Interaction or proximity of ligand part with active site residue Ser87 has been noted with priority because Ser87 is the most crucial residue and involved in the first step of the catalysis.

Compounds with fused dihydrofuran ring: In case of previously reported compounds, the hydrolysis as well as acetylation occurred at C-5 position of naphthalene ring.

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This previous finding has been supported by current docking study (Details are included in SI). Substituent at C-5 position of naphthalene ring is more exposed than sterically crowded C-2' position of aryl ring. In case of both the hydrolysis and acetylation reactions, the respective compound docked at main binding cavity. The acetate/alcohol linked to C-5 has been found to interact with crucial residues line Tyr29/Ser117 and remain in close proximity to the Ser87/acylated-Ser87. Interactions of the substituent with lipase have been found to be major driving force behind region-selectivity of this class compounds.

In case of current compounds, the hydrolysis as well as acetylation occurred at C-4' position of aryl ring. The substituent linked to C-4' position of aryl ring is more exposed than C-2' position of the previous cases. Docking studies indicate that the naphthalene ring docked at main binding cavity; while the acetate/alcohol linked to C-4' drag the aryl ring towards active site *via* interacting with crucial residues like Tyr29 and leu17 (**Figure 5** and **6**).

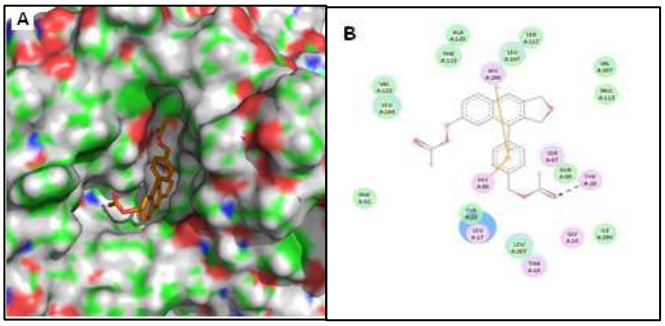

Figure 5: Docked image of **1c** with PCL; **A.** PCL represented as surface, naphthalene docked at main binding cavity while aryl drag near to active site *via* alternate cavity. **B.** 2D diagram of PCl-**1c** interaction, Acetate linked to C-4' interacts with Tyr29 while aryl ring form π-cation interaction with active site residue His286.

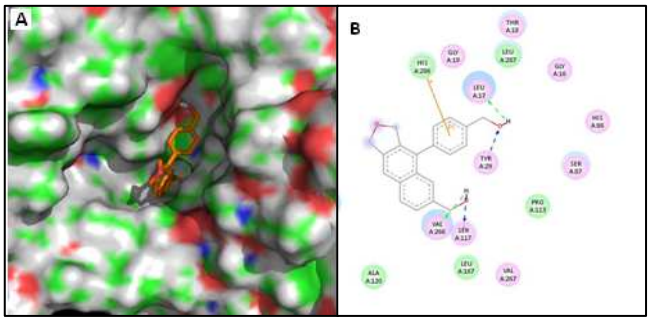

Figure 6: Docked image of **2c** with PCL; **A.** PCL represented as surface, naphthalene docked at main binding cavity while aryl drag near to active site *via* alternate cavity. **B.** 2D diagram of PCl-**2c** interaction, Alcohol linked to C-4' interacts with Tyr29 and Leu17 while aryl ring form π-cation interaction with active site residue His286.

Compounds with fused dihydroisoindole ring: In case of previously reported compounds, the hydrolysis as well as acetylation occurred at C-5 position of naphthalene ring. We have studied these previous finding as model study. Docking study suggests that the region-selectivity of these class compounds has been guided by the positioning of N-tosyl group at binding cavity of lipase. The large and hydrophobic N-tosylgoup always acquires the "alternate binding cavity and force the naphthalene ring pointing towards the active site cavity. Hence, the reaction takes place at C-5 position. (Details are included in SI)

In case of current compounds, the hydrolysis as well as acetylation occurred at C-7 position of naphthalene ring. From docking study, we have found similar results as of model study. The bulky and hydrophobic N-tosyl unit position in an alternate binding cavity and force the naphthalene ring to point towards active site cavity. Hence, reactions take place at C-7 position regio-selectively (**Figure 7** and **8**).

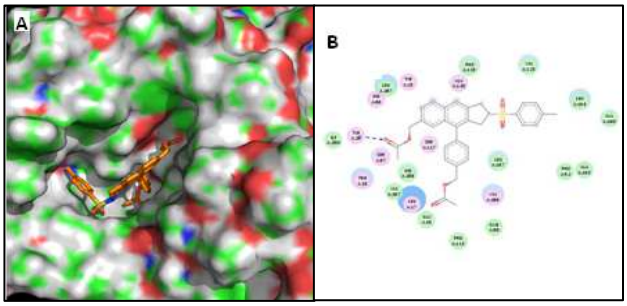

Figure 7: Docked image of **1b** with PCL; **A.** PCL represented as surface, N-tosyl ring docked in another binding cavity; force the naphthalene ring to point towards active site cavity. **B.** 2D diagram of PCl-**1b** interaction, Acetate linked to C-7 interacts with Tyr29 and remain in close proximity to active site residue Ser87.

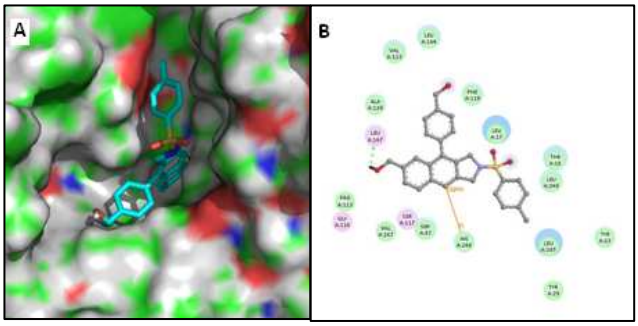

Figure 8: Docked image of **2b** with PCL; **A.** PCL represented as surface, N-tosyl ring docked in alternate binding cavity; force the naphthalene ring to point towards active site cavity. **B.** 2D diagram of PCl-**2b** interaction, Alcohol linked to C-7 interacts with Leu167 and remain in close proximity to active site residue acylated-Ser87.

Compounds with dihydrothiophene dioxide ring: Docking study of this class of compounds is intriguing. Docking study suggests that both the sulfone group and substituent present at ligand molecule can cause sufficient interaction with lipase receptor which can govern the regioselectivity. In case of previously reported compounds, the hydrolysis as well as acetylation occurred at C-5 position of naphthalene ring. But docking study predicts that the reactions should occur at C-2' position (Details are

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included in SI). We have got same trend of regio-selectivity with alternate positioning. This is may be due to the fact that we have preformed this computational study with PCL and we have done experiments with PFL. Sulfone group itself can cause strong interaction with protein residues unlike furan/tosyl, hence small change in sequences or cavity size between PCL and PFL can trigger the position alternation. If we take this result as a model study, then we should get similar result in case of current sulfones too.

In case of current compounds, reversal of selectivity for hydrolysis and acetylation was observed experimentally. Docking study supports this reversal of selectivity with alternate positioning like our model study. The hydrolysis reaction takes place at C-7 position; while docking study predicts the reaction to take place at C-4' position. The sulfone group strongly interacts with Tyr29 and drag the aryl ring towards active site cavity (**Figure 9**). The acetylation reaction takes place at C-4' position; while docking study suggests the reaction to take place at C-7 position. In acetylation process, sulfone group does not interact with lipase, but alcohol group at C-7 position interacts directly with acylated Ser87 residue and governs the reaction (**Figure 10**).

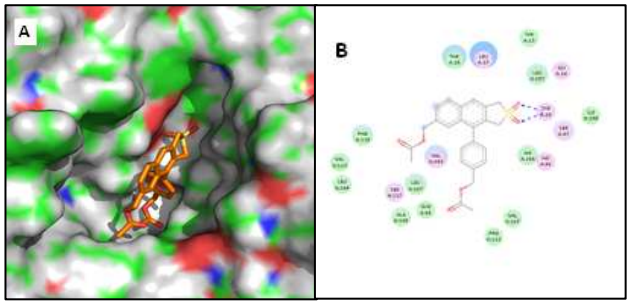

Figure 9: Docked image of **1a** with PCL; **A.** PCL represented as surface, Aryl ring point towards the active site cavity. **B.** 2D diagram of PCl-**1a** interaction, Sulfone causes driving force *via* interacting with Tyr29 and drags the aryl ring towards active site cavity.

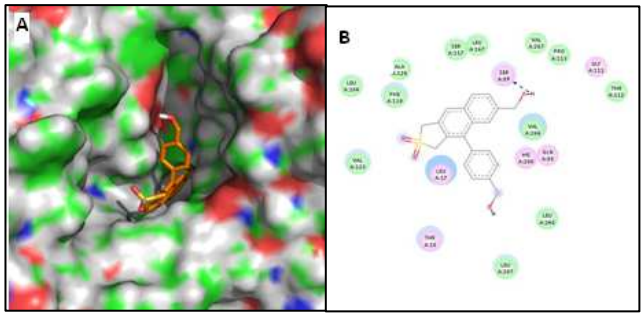

Figure 10: Docked image of **2a** with PCL; **A.** PCL is represented as surface. Sulfone docked away from active site; naphthalene enters into active site cavity; **B.** 2D diagram of PCL-**2a** interaction. Sulfone does not interacts with PCL residues. Alcohol linked to C-7 of naphthalene ring causes the driving force *via* interacting directly with Ser87.

From the above exercise, it is clear that the docking can successfully explain the observed regioselectivity in the case of the isoindole and furan derivatives. While interaction of the substituent with lipase has been the major driving force for furans, the positioning of the bulky N-tosyl group drives the selectivity in case of isoindole derivatives. The docking results of sulfone derivatives are more intriguing. The study has suggested that the combined interactions of the sulfone group and the substituent may be the probable reason behind reversal of selectivity for hydrolysis and acetylation. In case of hydrolysis, the polar sulfone is the main binding force unlike furan/tosyl, while in acetylation, free alcohol group is involved is the major interaction. Though docking studies could not explain the position alternation, it is likely that the sulfone group itself can cause strong interaction with protein residues. A small change between PCL and PFL structures can cause the position alternation. This was observed in acetylation of diol **2a** catalysed by AK lipase and PCL (**Figure 10**).

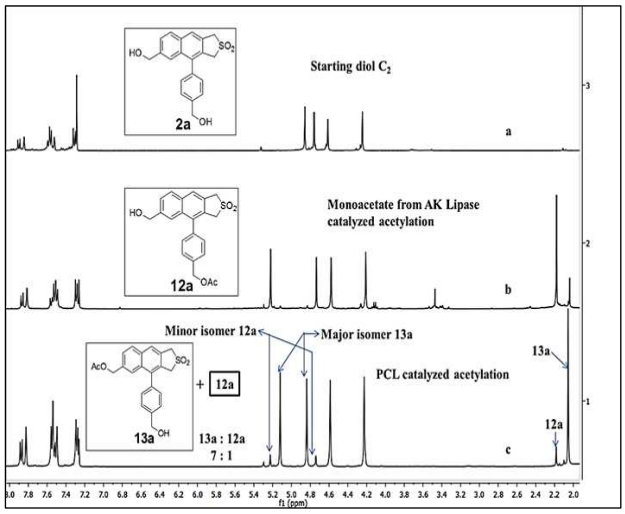

Figure 10: Comparative ^{1}H NMR of PFL and PCL catalyzed acetylation; **a:** Starting diol**; b**, **d:** Regio-isomeric monoacetate from PFL catalyzed acetylation; **c:** PCL catalyzed reactions acetylation.

In conclusion, we have shown that differently functionalized aryl naphthalenes can be prepared by Amino Lipase AK catalyzed hydrolysis or acetylation of the corresponding diacetates or diols respectively. It has also been demonstrated that a change in the fused heterocycle can affect the nature of binding to the active site. Future work will address the issue of axial chirality during the enzyme catalyzed hydrolysis/acetylation of substrates capable of showing atropisomerism.

Acknowledgement

The author AB is grateful to DST, Govt. of India, for research funding and the JC Bose fellowship. AP and DB thanks CSIR, Govt. of India for a research fellowship

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(NET). DST is also thanked for the funds for a 400 MHz NMR facility under the IRPHA programme.

EXPERIMENTAL SECTION

DOCKING DETAILS

Advanced and widely used molecular grid-based docking program Autodock4.2 was used to predict the binding modes and approximate binding free energies of all the designed inhibitors in lead library. The X-ray crystal coordinates of PCL was obtained from the Protein Data Bank (http://www.rcsb.org), PDB ID 3LIP. Receptor structure had been edited and hydrogen atoms added prior to docking. AutoDock Tools was used to assign Gasteiger charges to the receptor. Ligand structures were built up using Accelrys Discovery studio 3.1 client. Energy minimization of ligand structures was performed by applying CHARMM force field. The conformer with best binding energy was evaluated for designing purpose.

CHEMISTRY DETAILS

All reactions were conducted with oven-dried glassware under nitrogen. All common reagents were commercial grade reagents and used without further purification. The solvents were dried by standard methods and purified by distillation before use. Silica gel (60–120 and 230–400 mesh) was used for column chromatography. TLC was performed on aluminum-backed plates coated with Silica gel 60 with F254 indicator. Locally available UV-lamp chamber and I_2-blower were used as the TLC spot indicator. For solid compounds melting point (MP) was measured in melting point apparatus twice and reported without further calibration. The NMR spectra were recorded using 200 MHz and 400 MHz The following abbreviations are used to describe peak patterns: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, ABq = AB quartet.

Procedure for Garratt-Braverman Cyclization:

Synthesis of 11a

To the solution of bis-propargylsulfone**10a** (1.4 mmol) in dry $CHCl_3$, Et_3N (2.8 mmol) was added and stirred for 1 h. at room temperature. The reaction mixture was partitioned between water-dichloromethane. The organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the solvent the crude product was purified by column chromatography over Si gel, using petroleum ether: ethyl acetate (2:1) as eluent. **State:** Sticky mass; **Yield:** 92%;δ_H (400 MHz, $CDCl_3$) 8.28- 8.24 (3H, m), 8.14 (1H, d, J = 8.8 Hz), 7.95 (2H, d, J = 8.4 Hz), 7.43 (2H, d, J = 8 4Hz), 4.63 (2H, s), 4.25 (2H, s), 4.02 (3H, s), 3.89 (3H, S); δ_C (100 MHz, $CDCl_3$) 166.7, 166.5, 137.3, 137.0, 134.0, 132.4, 131.3, 131.0, 130.7, 130.5, 129.9, 129.7, 129.4, 128.6, 126.7, 126.6, 126.4, 57.0, 56.4, 52.5.

Synthesis of 11b

DBU (1.4 mmol) was added to the solution of bis-propargyl tosyl amine **10b** (0.7 mmol) in dry toluene, and refluxed for 48 h. After completion of the reaction, toluene was removed under *vacuo*. The crude was extracted with ethyl acetate and after removing the solvent, it was purified by column chromatography using petroleum ether: ethyl acetate (3:1) as eluent. **State:** Sticky mass; **Yield:** 90%;δ_H (400 MHz, $CDCl_3$) 8.25-8.23(3H, m), 8.07 (1H, d, J = 8.4 Hz), 7.89 (1H, d, J = 8.4 Hz), 7.77-7.73 (3H, m), 7.38 (2H, d, J = 8.4 Hz), 7.33 (2H, d, J= 8.4 Hz), 4.83 (2H, s), 4.47 (2H, s), 4.03 (3H, s), 3.88 (3H, s), 2.41 (3H, s); δ_C (100 MHz, $CDCl_3$) 167.0, 166.8, 144.0, 141.6, 137.0, 135.7, 134.8, 134.5, 133.3, 130.7, 130.3, 130.2, 130.0, 129.6, 128.4, 128.3, 128.0, 127.7, 125.7, 121.2, 53.6, 52.9, 52.5, 52.4, 21.6.

Synthesis of 11c

To the solution of bis-propargyl ether (0.6 mmol) in toluene, potassium *t*-butoxide (1.2 mmol) was added and was allowed to reflux for 6 h. After completion of the reaction, toluene was removed under *vacuo*. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography over Si gel, using petroleum ether: ethyl acetate (3:1) as eluent. **State:** Gummy liquid; **Yield:** 90%; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, d, J = 8.4 Hz), 7.69 (2H, s), 7.53 (3H, d, J = 8.1 Hz), 7.37 (2H, d, J = 6.6 Hz), 5.30 (2H, s), 5.05 (2H, s), 4.94 (1H, d, J = 12 Hz), 4.88-4.84 (2H, m), 4.72-4.70 (1H, m), 4.64-4.57 (2H, m), 3.99-3.89 (2H, m), 3.66-3.52 (2H, m), 1.68-1.52 (12 H, m); δ_C (100 MHz, $CDCl_3$) 138.0, 137.8, 137.4, 137.3, 136.0, 133.4, 132.6, 131.9, 129.7, 128.5, 128.1, 126.0, 124.6, 118.8, 98.3, 98.0, 73.6, 73.2, 69.2, 68.9, 62.4, 30.8, 25.7, 20.0, 19.6.

General procedure for the reduction of diester

To the solution of diesters **11a** and **11b** in THF (15 mL), finely powdered $NaBH_4$ (2 eq) was added and stirred for 15 min at 65°C. Methanol (2 mL) was then added drop wise and stirred at 65°C for 5 h. The reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl. The organic layer was extracted with ethyl acetate (40 mL) and dried over Na_2SO_4. After evaporation of the solvent, diols **2a** and **2b** was purified by column chromatography over Si gel, using petroleum ether: ethyl acetate.

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Compound 2a: State: White solid; **Yield:** 90%; **mp**: 200 °C; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, d, *J* = 8.5 Hz), 7.85 (1H, s), 7.59-7.52 (4H, m), 7.29 (2H, d, *J* = 8.0 Hz), 4.83 (2H, s), 4.73 (2H, s), 4.59 (2H, s), 4.22 (2H, s); δ_C (100 MHz, $CDCl_3$) 141.2, 139.8, 138.0, 136.9, 133.0, 132.3, 130.0, 128.7, 128.7, 128.6, 127.8, 127.7, 126.5, 125.0, 123.9, 65.5, 65.2.

Compound 2b: State: White solid; **Yield:** 90%;**mp:** 220 °C; δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, *J* = 8.4 Hz), 7.73 (2H, d, *J* = 8.0 Hz), 7.63 (1H, s), 7.52-7.47 (4H, m), 7.31-7.24 (4H, m), 4.83 (2H, s), 4.78 (2H, s), 4.69 (2H, s), 4.45 (2H, s), 2.39 (3H, s); δ_C (100 MHz, $CDCl_3$) 143.7, 140.5, 138.6, 136.7, 134.3, 134.0, 133.8, 133.0, 131.7, 129.8, 129.5, 128.4, 127.6, 127.4, 125.4, 123.3, 120.5, 65.4, 65.0, 53.5, 53.1, 22.4.

Procedure for the synthesis of 2c: To the solution of **11c** in ethanol PPTS and drop of water were added and allowed to stir at 50 °C for 8 h. Ethanol was removed under *vacuo*. The mixture was partitioned between water-ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. After removing the solvent, the pure product was obtained by column chromatography over Si gel, petroleum ether: ethyl acetate (1:2) as eluent.

State: Sticky mass; **Yield:** 85%**;** δ_H (400 MHz, $CDCl_3$) 7.89 (1H, d, *J* = 8.4 Hz), 7.71 (1H, s), 7.63 (1H, s), 7.51 (3H, d, *J* = 8.0 Hz), 7.34 (2H, d, *J* = 7.6 Hz), 5.31 (2H, s), 5.0 (2H, s), 4.81 (2H, s), 4.73 (2H, s); δ_C (100 MHz, $CDCl_3$) 140.5, 138.5, 137.8, 137.5, 137.4, 133.4, 132.5, 131.9, 129.8, 128.8, 127.5,125.4,123.5,118.9, 73.5, 73.1, 65.7, 65.3.

General procedure for di-acetylation: Et_3N (6 eq), DMAP (catalytic amount), AcCl (3 eq) were added successively to the solution of diol **2a-c** in CH_2Cl_2 (20 mL) at 0 °C and stirred at room temperature for 1 h. The reaction mixture was partitioned between water-dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4. After evaporation of the solvent the pure diacetate was isolated by column chromatography.

Compound 1a: State: Sticky yellow mass**; Yield:**80%**;** δ_H (400 MHz, $CDCl_3$) 7.90 (1H, d, *J* = 8.4 Hz), 7.85 (1H, s), 7.57-7.54 (3H, m), 7.50 (1H, s), 7.33-7.29 (2H, m), 5.25 (2H, s), 5.15 (2H, s), 4.61 (2H, s), 4.25 (2H, s), 2.20 (3H, s), 2.08 (3H, s); δ_C (100 MHz, $CDCl_3$) 171.0, 170.8, 137.7, 137.2, 136.4, 134.8, 133.0, 131.9, 129.8, 129.1, 128.9, 128.6, 127.0, 125.6, 124.9, 66.3, 65.9, 57.2, 56.5, 21.2, 21.0.

Compound 1b: State: Sticky mass**; Yield:** 70%**;** δ_H (400 MHz, $CDCl_3$) 7.84 (1H, d, *J* = 8.4 Hz), 7.77 (2H, d, *J* = 8.0 Hz), 7.66 (1H, s), 7.55-7.46 (4H, m), 7.33 (2H, d, *J* = 7.6 Hz), 7.28 (2H, d, *J* = 7.6 Hz),5.26 (2H, s), 5.13 (2H, s), 4.81 (2H, s), 4.49 (2H, s), 2.42 (3H, s), 2.23 (3H, s), 2.06 (3H, s); δ_C (100 MHz, $CDCl_3$) 171.2, 171.0, 144.0, 137.4, 136.0, 135.0, 134.3, 134.1, 133.9, 133.6, 133.4, 131.7, 130.1, 129.8, 129.0, 128.7, 127.9, 126.3, 125.3, 120.9, 66.6, 66.2, 53.7, 53.3, 21.7, 21.3, 21.2.

Compound 1c: State: Gummy liquid**; Yield:** 70%**;** δ_H (400 MHz, $CDCl_3$) 7.87 (1H, d, *J* = 8.4 Hz), 7.69 (1H, s), 7.61 (1H, s), 7.51-7.46 (3H, m), 7.35 (2H, d, *J* = 8.0 Hz), 5.28 (2H, s), 5.22 (2H, s), 5.14 (2H, s), 5.01 (2H, s), 2.18 (3H, s), 2.06 (3H, s); δ_C (100 MHz, $CDCl_3$) 171.1, 171.0, 138.3, 137.9, 137.6, 135.6, 133.5, 133.5, 132.3, 131.6, 129.8, 129.0, 128.8, 128.7, 126.0, 125.3, 119.0, 73.5, 73.0, 66.6, 66.2, 21.2, 21.1.

General procedure for enzymatic catalysis

General procedure for hydrolysis of the diacetate: To the solution of diacetates **1a-c** (0.14 mmol) in acetone-phosphate buffer (1:3 v/v, pH 7), the enzyme Amano lipase (18 mg) was added and stirred at room temperature for 6 h. The reaction mixture was filtered and acetone was removed under *vacuo*. The crude was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent the crude was purified by column chromatography over Si gel, using petroleum ether and ethyl acetate (2:1) as eluent to get the pure monoacetates**12a-c**.

State: Sticky mass; **Yield:** 75%; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, d, *J* = 8.4 Hz), 7.83 (1H, s), 7.58-7.51 (4H, m), 7.31-7.29 (2H, m), 5.24 (2H, s), 4.75 (2H, s), 4.59 (2H, s), 4.23 (2H, s), 2.19 (3H, s); δ_C (100 MHz, $CDCl_3$) 171.1, 139.8, 137.6, 137.4, 136.3,132.8, 132.0, 129.8, 128.9, 128.6, 128.5, 128.4, 127.6, 126.4, 124.9, 123.7, 65.9,65.3, 57.2,56.6, 21.2.

State: Semi solid; **Yield**: 68%; δ_H (400 MHz, $CDCl_3$) 7.82 (1H, d, *J* = 8.9 Hz), 7.74 (2H, d, *J* = 8.0 Hz), 7.64 (1H, s), 7.50 (4H, d, *J* = 9.4 Hz), 7.31 (4H, d, *J* = 8.1 Hz), 5.23 (2H, s), 4.78 (2H, s), 4.71 (2H, s), 4.46 (2H, s), 2.39 (3H, s), 2.21 (3H, s); δ_C (100 MHz, $CDCl_3$) 171.2, 144.0, 138.9, 137.6, 135.9, 134.5, 133.5, 134.1, 133.2, 131.8, 130.1, 129.8, 129.0, 128.7, 127.9, 125.7, 123.5, 120.9, 66.2, 65.7, 53.7, 53.3, 21.8, 21.4.

State: Sticky mass**; Yield:** 72%; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, d, *J* = 8.4 Hz), 7.69 (1H, s), 7.62 (1H, s), 7.52 (2H, d, *J* = 7.8 Hz), 7.47 (1H, d, *J* = 8.4 Hz), 7.35 (2H, d, *J* = 7.7 Hz), 5.29 (2H, s), 5.14 (2H, s), 5.01 (2H, s), 4.83 (2H, s), 2.06 (3H, s); δ_C (100 MHz, $CDCl_3$) 171.1, 140.5, 138.4, 137.6, 137.4, 133.5, 132.6, 131.8, 129.9, 128.9, 127.6, 126.0, 125.6, 124.7, 124.2, 119.3, 118.9, 73.6, 73.1, 66.9, 65.4, 21.2.

General procedure for the acetylation of the diol: Vinyl acetate (0.68 mmol) and Amano lipase (44 mg) was added

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DOI: 10.1039/C4RA10503F

to the THF solution of diol **2a-c** (0.34 mmol). The reaction mixture was allowed to stir at room temperature until the reaction was complete (6 h for **2a**; 4 h for **2b** and **2c**). It was then filtered and THF was removed under *vacuo*. The pure monoacetates **12a** and **13b-c** were isolated by column chromatography of the crude residue over Si gel, using petroleum ether and ethyl acetate (2:1) as eluent.

State: Sticky mass; **Yield:** 82%;δ_H (400 MHz, $CDCl_3$) 7.87 (1H, d, J = 8.4 Hz), 7.81 (1H, s), 7.56-7.49 (4H, m), 7.29-7.28 (2H, m) 5.22 (2H, s), 4.73 (2H, s), 4.58 (2H, s), 4.21 (2H, s), 2.18 (3H, s); δ_C (100 MHz, $CDCl_3$) 171.2, 139.9, 137.7, 137.5, 136.4, 132.9, 132.2, 129.9, 129.0, 128.7, 128.6, 128.5, 126.5, 125.1, 123.8, 66.1, 65.4, 57.3, 56.7, 21.3.

State: Semi solid; **Yield:** 75%;δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, J = 9.6 Hz), 7.73 (2H, d, J = 8.0 Hz), 7.63 (1H, s), 7.53-7.49 (3H, m), 7.43 (1H, d, J = 8.0 Hz), 7.29 (3H, d, J = 8.0 Hz), 7.23 (1H, s), 5.09 (2H, s), 4.83 (2H, s), 4.78 (2H, s), 4.46 (2H, s), 2.39 (3H, s), 2.04 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.8, 143.7, 140.6, 136.4, 134.7, 134.1, 134.0, 133.6, 133.4, 133.1, 131.5, 129.8, 129.5, 128.4, 127.6, 127.4, 126.0, 125.2, 120.5, 65.0, 64.4, 53.5, 53.0, 21.5, 20.9.

State: Sticky mass; **Yield:** 75%; δ_H (400 MHz, $CDCl_3$) 7.86 (1H, d, J = 8.4 Hz), 7.68 (1H, s), 7.60 (1H, s), 7.50-7.47 (3H, m), 7.35-7.33 (2H, m), 5.27 (2H, s), 5.21 (2H, s), 4.99 (2H, s), 4.73 (2H, s), 2.17 (3H, s); δ_C (100 MHz, $CDCl_3$) 171.0, 138.5, 138.0, 137.7, 137.3, 135.4, 133.2, 132.1, 131.7, 129.7, 128.6, 128.5, 125.2, 123.3, 118.8, 73.3, 72.9, 66.0, 65.5, 21.1.

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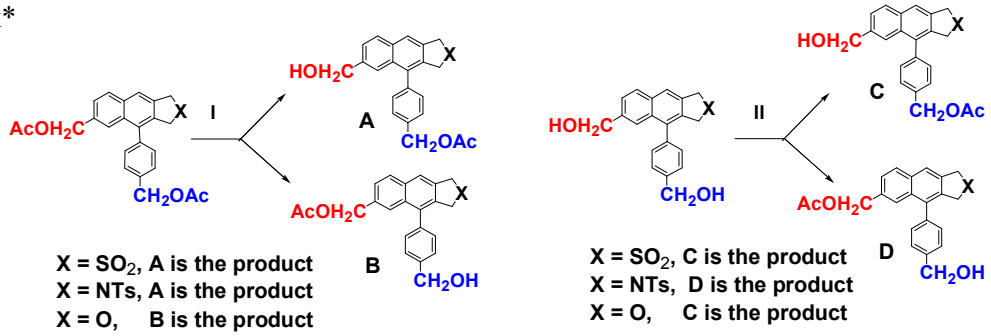
DOI: 10.1039/C4RA10503F

Graphical Abstract

Reversal of Regioselectivity in Acetylation and Deacetylation of Aryl-Naphthalene Diols and Diacetates by Amano Lipase Arpita Panja, Deb Ranjan Banerjee and Amit Basak*



X = SO_2, A is the product
X = NTs, A is the product
X = O, B is the product

X = SO_2, C is the product
X = NTs, D is the product
X = O, C is the product

I = acetone-phosphate buffer (pH 7.00 (1:3 by v/v), Amano Lipase (AK), r.t.; II = vinyl acetate, THF, Amano lipase (AK), r.t.

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DOI: 10.1039/C4RA10503F