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A chemo-enzymatic route to differentially protected aryl-naphthalenes

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ABSTRACT

Aryl-naphthalene diacetates prepared from bispropargyl sulfones, ethers and amines via Garratt–Braverman Cyclization have been selectively hydrolysed by AK lipase to the monoacetates **12a–c** in high yields. The regioisomeric mono acetates **13a–c** have been prepared by acetylation of the corresponding diols using the same enzyme. In both cases, the more exposed acetoxymethyl or hydroxy methyl attached to the naphthalene ring binds to the active site of the enzyme and underwent hydrolysis/acetylation. The method provides easy access to differentially protected aryl-naphthalenes which should allow further modifications.

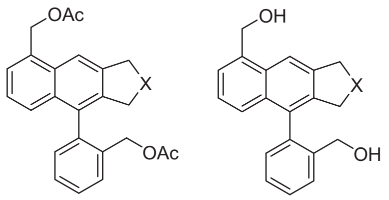
Aryl-naphthalene systems have assumed significant importance in view of their presence in natural biologically active lignans[1] as well as their derivatives possessing wide range of optical and electronic properties.[2] Various methods have been reported for the synthesis of such skeletons; the most widely used of these is the intramolecular Friedel–Crafts reaction.[3] Recently[4] we have reported a Garratt–Braverman Cyclization route to aryl naphthalene lignans starting from a simple substrate, a bispropargyl ether. In this Letter, we report an enzymatic route to differentially protected aryl-naphthalenes. The synthesis allows one to attach functional group on the naphthalene moiety or on the pendant aryl moiety. In the process, a novel highly regioselective hydrolysis of aryl-naphthalene diacetates **1a–c** and acetylation of corresponding aryl-naphthalene diols **2a–c** (Fig. 1) have been developed. The results are described in this Letter.

The starting diols **2a–c** were prepared by $NaBH_4$ reduction of the corresponding diesters **11a–b**[5] and by deprotection of the THP protected diol **11c**.[6] The latter, in turn, were obtained from the bispropargyl sulfone, amine and ether by Garratt–Braverman Cyclization.[7] The diols were then bis acetylated with acetyl chloride (Scheme 1).

The hydrolytic behavior of the aryl-naphthalene bis-acetates **1a–c** was then studied. Chemical hydrolysis, even under mild conditions (LiOH, THF),[8] produced a mixture of monoacetates and continued hydrolysis led to the formation of the diol. Enzymatic hydrolysis using various hydrolytic enzymes, namely Candida cylindracea (CCL),[9] Porcine pancreatic lipase (PPL)[10] and AK Lipase[11] was then attempted. While PPL and CCL did not accept the diacetates as substrates, AK Lipase was able to hydrolyze the diacetates to the monoacetates **12a–c** having the acetate group attached to the pendant aryl ring. The reaction, which was monitored by tlc and by recording ^1H NMR at different time points, was usually stopped after 15 h.

Continuation of the reaction even for 48 h did not produce any trace of the diols. Thus the enzyme hydrolysed only the more exposed acetate which is attached to the naphthalene ring. The results which are similar for all the substrates **1a–c**, are shown in Table 1.

To access the other set of regioisomeric acetates **13a–c**, acetylation was attempted. In this case, the alcohol attached to the naphthalene ring should be able to bind to the active site of the



1 a-c **2 a-c**
a. X = SO_2
b. X = NTs
c. X = O

Figure 1. Aryl-naphthalene diacetates and diols used for enzymatic hydrolysis and acetylation.

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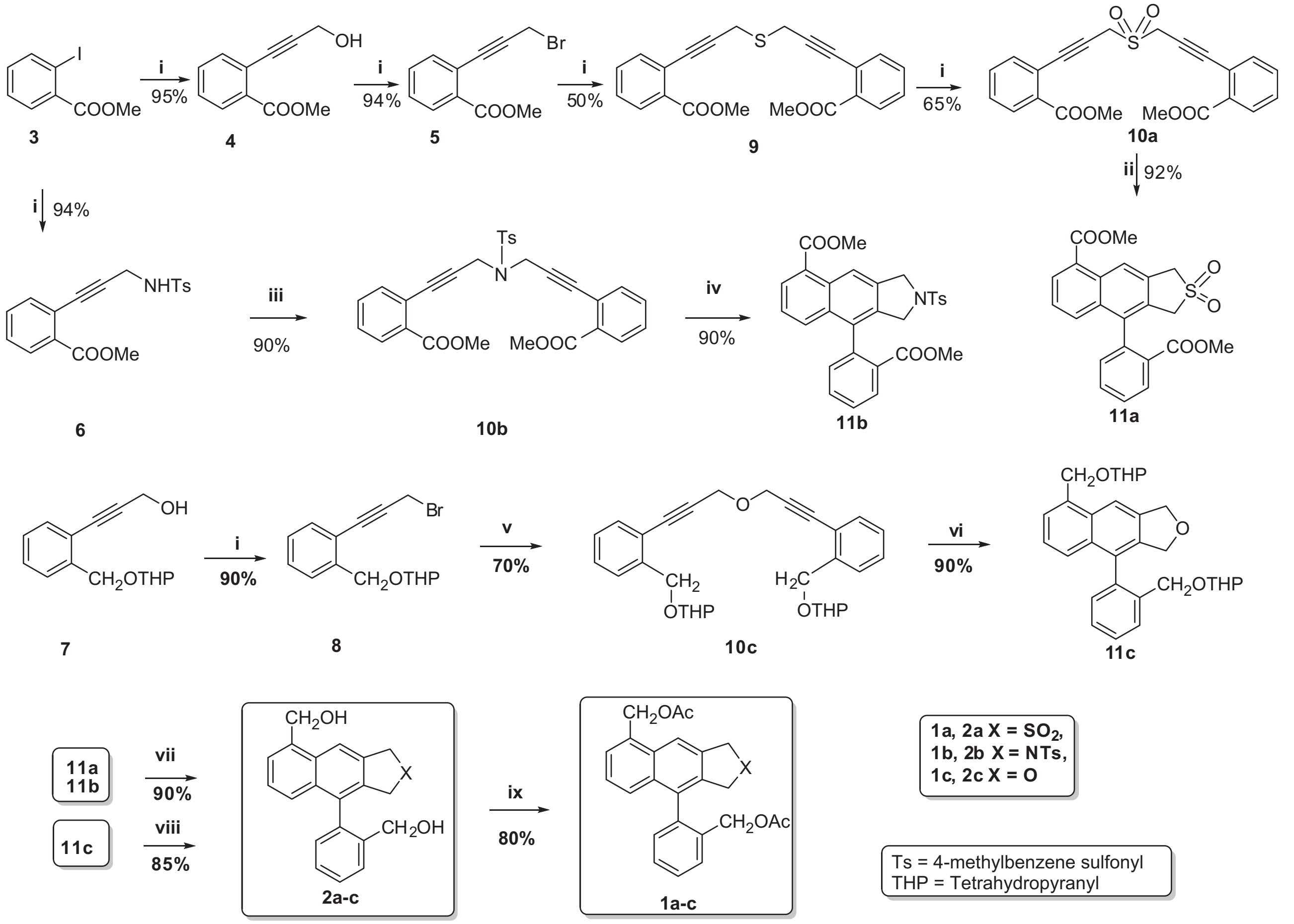
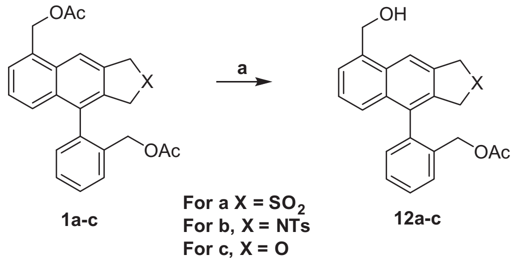


Scheme 1. Synthesis of aryl-naphthalene derivativs **1** and **2**. (i) ref. 13; (ii) Et3N, CHCl3, rt; (iii) K_2CO_3, DMF, 5; (iv) DBU, toluene, reflux; (v) NaH, THF, **7**; (vi) KOBu^t, toluene, reflux; (vii) $NaBH_4$, THF, MeOH, reflux; (viii) PPTS, EtOH, 50 °C; (ix) AcCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C

Table 1

Enzymatic hydrolysis of diacetates **1a–c** catalyzed by AK lipase in acetone/phosphate buffer



a = acetone-phosphate buffer (pH 7.00 (1:3 by v/v), A. K. Lipase, r.t., 15 h

Substrate	Product	Enzyme	Yield[a] (%)
1a	**12a**	AK lipase	95
1b	**12b**	AK lipase	96
1c	**12c**	AK lipase	95

[a] Isolated yields after flash chromatography; detection limit at least 95% by NMR.

acyl-enzyme which should then lead to selective acetylation leaving the other hydroxyl group intact. This was found to be the case when the diols **2a**–**c** were separately treated with vinyl acetate in presence of AK lipase for ~10 h. The monoacetates **13a–c** were isolated in high yield. Again the result is same for the sulfone, ether and for the amine. As expected, the enzymes CCL or PPL did not show any acetylation activity. The results are shown in Table 2.

The structures of the regioisomeric monoacetates were determined by ^{1}H NMR. Thus the acetate attached to the pendant phenyl ring, being in the shielded region of the ring current generated in the naphthalene ring, appeared at a higher field as compared to the deshielded acetate attached to the naphthalene. X-ray crystal structure of two of the monoacetates of each category **12a** and **13b** could be determined which confirmed its structure (ORTEP shown in Fig. 2).

AK lipase has been shown[12] to be effective for hydrolysis/acetylation of molecules with near planar structural features surrounding the reactive functionality, namely the acetate or the alcohol. The enzyme is not suitable for substrates with relatively bulky moieties close to the acetoxymethyl or hydroxyl methyl centre and for those which are unable to adopt a planar conformation around the acetate/hydroxyl group. For the aryl-naphthalenes, the acetoxy or hydroxyl methyl group attached to the naphthalene moiety is free of steric constraints and a relatively large portion of the structure is planar near to this reactive functionality. On the other hand, the acetate or hydroxyl methyl attached to the phenyl ring has the near-orthogonal naphthalene moiety nearby and hence cannot adopt a planar structure suitable for binding. This can possibly explain the very high regioselectivity shown by the enzyme to these substrates. The preferred mode of binding to the active site is shown in Figure 3.

In conclusion, we have achieved a high yielding chemoenzymatic route to aryl-naphthalenes, differentially protected as acetates. In future, a plethora of aryl-naphthalenes will be prepared