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Lipase-mediated asymmetric acetylation of prochiral diols directed towards total syntheses of biologically active molecules

Kozo Shishido *, Toshikazu Bando

Institute for Medicinal Resources, University of Tokushima, Sho-machi 1, Tokushima 770, Japan

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Abstract

Lipase mediated asymmetric acetylation of σ-symmetrical 2-aryl-1,3-propanediols (**1a–f**), which were prepared conveniently via sequential Heck coupling between (**5a–f**) and (**6**), ozonolysis and reductive workup, provided the enantiomerically enriched monoacetates (**2a–f**) in good chemical and optical yields. These monoacetates (**2a–f**) were successfully converted into the biologically and pharmacologically interesting molecules, Baclofen (**10**), *ar*-turmerone (**13**), α-cuparenone (**19**), *ent*-aflatoxin B_2 (**24**), ibuprofen (**26**), naproxen (**28**), and indolmycin (**32**) as optically active forms, respectively.

Keywords: Lipase; Asymmetric acetylation; Heck reaction; Prochiral diol; Total synthesis

Tertiary and quaternary carbon centers at benzylic position are found in a wide range of natural and unnatural compounds which possess biological and pharmacological activities, and these structural features present a number of synthetic challenges. In this paper, we present an efficient strategy for asymmetric constructions of the benzylic tertiary and quaternary stereogenic centers and its application to enantiocontrolled syntheses of some natural and unnatural molecules. We envisaged that the benzylic asymmetric tertiary carbon (e.g., in **2**) can be constructed by a lipase-mediated asymmetric acetylation of the prochiral diol (**1**) [1,2], while the quaternary center (e.g., in **4**) might be assembled by employing the diastereoselective [1,5] C–H insertion reaction of alkylidene carbene (**3**) which would readily be derived from **2**. [1] (Scheme 1)

A variety of prochiral diols (**1a–f**), [2] substrates for the key chemoenzymatic transformation, were prepared efficiently by sequential Heck reaction [10–12] between the corresponding aryl iodides (**5a–f**) and 2-*tert*-butyl-4,7-dihydro-1,3-dioxepine (**6**) [10], ozonolysis and reductive treatment with $NaBH_4$ as shown in Scheme 2.

With the substrate for a key conversion in hand, we next turned to the search for optimum

* Corresponding author.

[1] Representative references for cyclopentene annulation: [6–8].
[2] For a conventional method: see Ref. [9].

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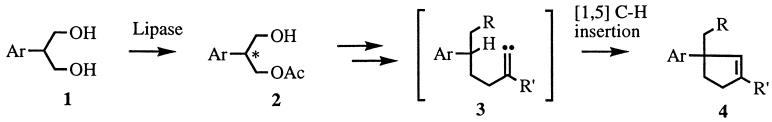
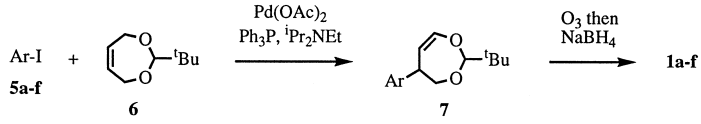


Scheme 1.



Scheme 2.

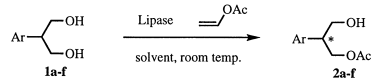
conditions for the lipase-mediated asymmetric acetylation of prochiral diols (**1a–f**) using vinyl acetate as an acyl donor in organic solvents. The results are shown in Table 1. The enantiomerically enriched monoacetates (**2a–f**) were obtained in good chemical yields. The enantiomeric excesses were 85–99% as determined by ^{1}H NMR analyses of their MTPA ester derivatives or HPLC analyses. The absolute configurations of newly generated tertiary stereogenic centers in **2a–f** were established by the empirical rule based on the chemical shifts of the corresponding MTPA esters [3–5] or by comparison of the sign of specific rotation with that of authentic materials. (Table 1)

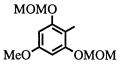
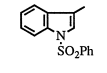
Chiral monoacetates (**2a–f**) with a tertiary stereogenic center at the benzylic position thus obtained were then transformed into biologically interesting natural and unnatural molecules as follows. *R*-3-Acetoxy-2-(4-chlorophenyl)-1-propanol (**2a**) (99% ee) was converted via a six-step sequence into Baclofen (**10**), an analog of the inhibitory neurotransmitter γ-aminobutyric acid [13–16]. (Scheme 3)

R-3-Acetoxy-2-tolyl-1-propanol (**2b**) (99% ee) was initially converted into the biologically promising aromatic bisabolene type sesquiterpene *ar*-turmerone (**13**). [3] For the construction of benzylic quaternary center and its application, the intermediate cyanide (**12**) was then led to the in situ formation of alkylidene carbene species (**16**) via the iodonium salt (**15**) according to the procedure developed by Ochiai et al. [7]. The [1,5] C–H insertion reaction gave rise to the cyclized product (**17**), which was converted into the known enone (**18**) [18] and the formal synthesis of α-cuparenone (**19**) was completed [19]. (Scheme 4)

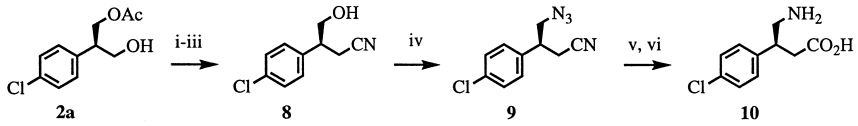
Synthesis of the unnatural enantiomer (**24**) of a mycotoxin aflatoxin B_2 was formally completed by converting *S*-**2c** (89% ee) into the tetrahydro[2,3-*b*]benzofuran (**23**) [20,21], a penultimate intermediate in the synthesis of optically active **24**, as shown in Scheme 5 [22].

Table 1
Lipase mediated asymmetric acetylation of prochiral diols **1a–f**

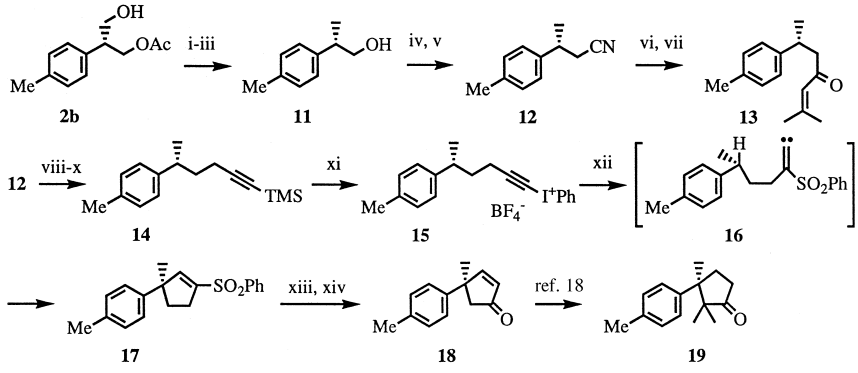


	Ar	Lipase	solvent	yield of **2**, %	ee, %	abs. config.
a		PPL	Et_2O	92	99	*R*
b		PPL	Et_2O	90	99	*R*
c		AL	Et_2O	72	89	*S*
d		PPL	Et_2O	76	99	*R*
e		PPL	Et_2O	80	89	*R*
f		AK	benzene	82	85	*S*

[3] For the first asymmetric synthesis: see Ref. [17].

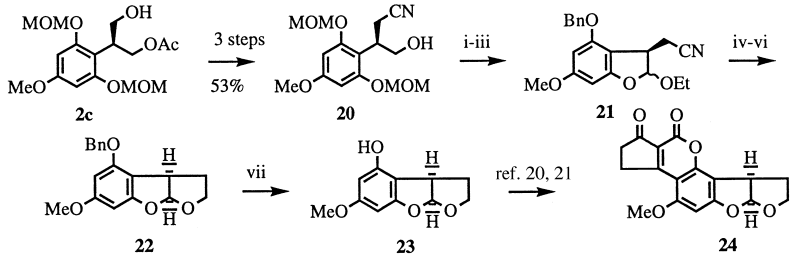


Scheme 3. Reagents: (i) MsCl, $^{i}Pr_2NEt$, 4-DMAP; (ii) KCN, 18-Crown-6; (iii) LiOH, 61% from **2a**; (iv) DEAD, Ph_3P, $(PhO)_2PON_3$, 75%; (v) aq. HCl; (vi), H_2, PtO_2.

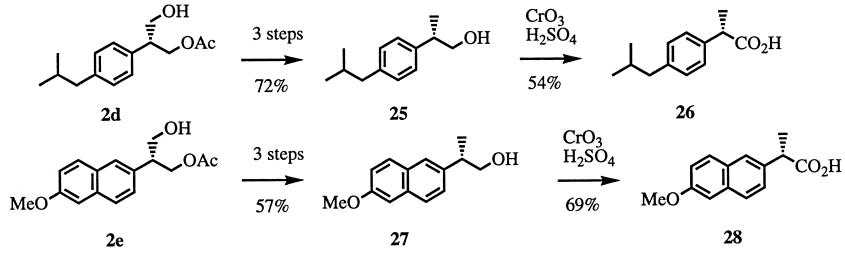


Scheme 4. Reagents: (i) TsCl, Et_3N; (ii) $NaBH_4$, DMSO, 60°C; (iii) $LiAlH_4$, 73% from **2b**; (iv) MsCl, $^{i}Pr_2NEt$, 4-DMAP; (v) KCN, 18-Crown-6, 79% from **11**; (vi) KOH, 88%; (vii) methallylmagnesium chloride; (viii) DIBAL-H, H_3O^+ then $NaBH_4$, 75%; (ix) Ph_3P, CBr_4, 94%; (x), $^{n}BuLi$, trimethylsilylacetylene, 69%; (xi) $(PhIO)_n$, $BF_3 \cdot OEt_2$; (xii) $PhSO_2Na$, H_2O, 83% from **14**; (xiii) Na–Hg, 70%; (xiv) PDC, $^{t}BuOOH$, Celite, 72%.

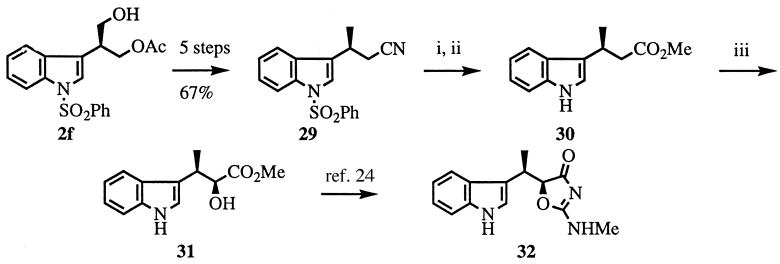
2-Arylpropionic acids are known as an important class of non-steroidal anti-inflammatory agents. Two representative members of this class are ibuprofen (**26**) and naproxen (**28**). Since the pharmacological activities of the *S*-isomers of both have been reported to be stronger than



Scheme 5. Reagents: (i), TPAP, NMO; (ii), $(EtO)_3CH$, HCl; (iii) BnCl, K_2CO_3, 50% from **20**; (iv) KOH; (v) $BH_3 \cdot SMe_2$, (vi) *p*-TsOH, 43% from **21**; (vii) Pd–C, 1,4-cyclohexadiene, 100%.



Scheme 6.



Scheme 7. Reagents: (i) KOH; (ii) CH_2N_2, 83% from **29**; (iii) LDA, O_2, $P(OEt)_3$, HMPA, 67%.

those of the *R*-isomers, development of an efficient and enantioselective synthetic route to *S*-isomers has received considerable attention. *R*-3-Acetoxy-2-(4-isobutylphenyl)-1-propanol (**2d**) (99% ee) and *R*-3-acetoxy-2-(6-methoxynaphth-2-yl)-1-propanol (**2e**) (89% ee) were easily converted into ibuprofen (**26**) and naproxen (**28**), respectively [23]. (Scheme 6)

Finally, *S*-**2f** (85% ee) was elaborated to the Mukaiyama's intermediate (**31**) [24] for the asymmetric total synthesis of antibacterial indolmycin (**32**) via an eight-step sequence of reactions [25]. (Scheme 7)

In conclusion, we have developed an efficient strategy for the construction of tertiary and quaternary asymmetric stereogenic centers at benzylic position by employing a lipase-mediated asymmetric acetylation of σ-symmetrical 2-aryl-1,3-propanediols as the key step. The versatility of enantiomerically enriched monoacetates thus obtained has been demonstrated by their successful conversion into some biologically important molecules.

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