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An Optical Resolution of Pyridyl and Bipyridylethanols and A Facile Preparation of Optically Pure Oligopyridines

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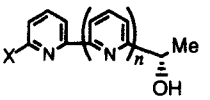
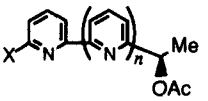
Abstracts: A kinetic resolution of racemic pyridyl and bipyridylethanols was performed by *Candida antarctica* lipase with vinyl acetate in diisopropyl ether, in which (*R*)-alcohol was acetylated stereoselectively, and both the acetate **2** and the remaining (*S*)-alcohol **1** were obtained with high enantiomeric excesses. (*S*)-Oligopyridylethanols, **7** and **8** were prepared by a coupling reaction of (*S*)-**1b** and (*S*)-**1e** with ethyl bipyridyl sulfoxide.

Oligopyridines have become more important not only for ligands in catalyst chemistry[1] but also for key functions in molecular recognition chemistry.[2] Particularly, chiral pyridines and bipyridines have recently been received increasing attentions as a chiral ligand[3] and used for enantioselective reactions, e.g. asymmetric hydrosilylation,[4] asymmetric aldol addition,[5] asymmetric Michael addition,[6] and asymmetric cyclopropanation.[7] We have reported preparation of unsymmetrical oligopyridines,[8] and oligopyridino-azacrown ethers, and their unique characteristic features in transportation and extraction of metal ions and amino acid esters.[9] In an extension of these studies for a chiral recognition chemistry, we have required optically pure oligopyridines. In this communication, we describe a practical preparation of substituted pyridyl and bipyridylethanols, (*S*)-**1a~f** and their acetates, **2a~f** by lipase catalyzed kinetic resolution and a facile synthesis of oligopyridines, **7** and **8** by a coupling reaction of pyridyllithium and pyridyl sulfoxide.

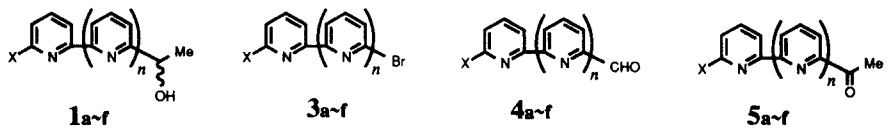


(*S*)-**1a~f**



2a~f

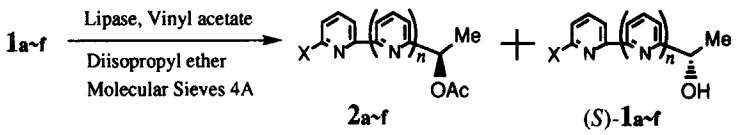
a; $n = 0$, X = H
b; $n = 0$, X = Br
c; $n = 0$, X = $Bu^tMe_2SiOCH_2$
d; $n = 1$, X = H
e; $n = 1$, X = Br
f; $n = 1$, X = $Bu^tMe_2SiOCH_2$



1a~f **3a~f** **4a~f** **5a~f**

Racemic pyridyl and bipyridylethanols **1a~f** were prepared in 68~90% yields from the corresponding bromopyridines, **3a~f** in two steps; i) lithium-bromine exchange by Bu^nLi and formylation by N,N-dimethylformamide ii) Grignard reaction of the formate **4a~f**, with methylmagnesiun bromide. Alternatively, after the lithium-bromine exchange, the produced pyridyllithium was once lead to acetyl-pyridine, **5a~f** by the reaction with N,N-dimethylacetoamide, then reduction with sodium borohydride afforded 65~89% yields of **1a~f** in two steps.

Optically active pyridines have been prepared by assembling of pyridyl part with chiral auxiliary part[3,4] or by asymmetric reduction of pyridyl ketones.[10] Initially, we attempted an asymmetric reduction of **5a~f**, by the Corey-Itsuno method.[11] The reduction was employed by the original method and some modified methods using a combination of (*R*)-prolinol and BH_3. The chemical yields were excellent in 85 to 98% yields and (*R*)-alcohols were formed in preference. However, the enantiomeric excess values determined by HPLC[12] and/or Mosher's ester analysis[13] were found to be 55 to 96%. The selectivities were depended on the substrates and could not be obtained constantly. These disappointing results led us to try enzymatic resolution. Although lipase catalyzed kinetic resolutions of aryl alcohols have well investigated,[14] pyridyl alcohols have not examined except simple pyridylethanols.[15] We have examined several kinds of lipases[16] in acetylation of pyridyl and bipyridyl ethanols, **1a~f**. The reaction was carried



2a~f (*S*)-**1a~f**

$n = 0$ or 1

out in diisopropyl ether with vinyl acetate in the presence of lipase and molecular sieves 4A.[17] Among the lipases, CAL(*Candida antarctica* lipase) presented the best enantioselectivity as well as chemical yield for both the acetates **2** and the recovered alcohols (*S*)-**1**. The results are summarized in Table. The recovered alcohols of (*S*)-**1a** and (*S*)-**1b**, have an (*S*)-chiral center identified by the optical rotation data in literature,[18] which show opposite signs to those obtained in the above asymmetric reduction. Other recovered alcohols, **1c**, **1d**, **1e**, and **1f** were assumed to possess the same (*S*)-chiral center in comparison of their CD spectra with those of (*S*)-**1a** and (*S*)-**1b**. Namely, the CD spectra of the recovered alcohols including (*S*)-**1a** and (*S*)-**1b** indicated the same patterns of a positive Cotton effect. In all the cases, the enantiomeric excess values of the acetates and the recovered alcohols were excellent, and the efficiency factor, E-values[19] were extremely good (~100) even in a practical scale. Consequently, the kinetic resolution for substituted pyridyl and bipyridyl ethanols works very well and gives an (*R*)-acetate and an (*S*)-alcohol, which is the same selectivity as usually observed in lipase mediated resolution of aryl alcohols.[14] It is emphasized that this

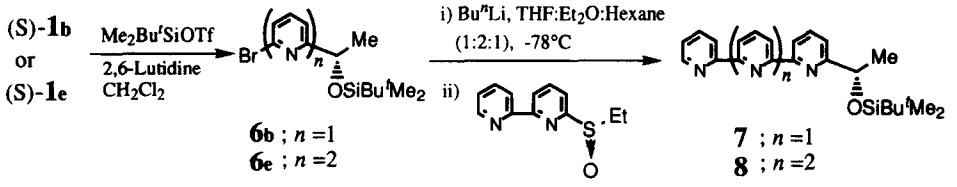
Table. Enantioselective Acetylation of Pyridyl and Bipyridylethanols Catalyzed by *Candida antarctica* lipase[a)]

Entry	Starting Alcohol	X	*n*	Reaction Time (hr)	Acetate	Yield (%)[b)]	e. e. (%)	Recovered Alcohol	Yield (%)[b)]	e. e. (%)
1	**1a**	H	0	4	**2a**	47	99 [c)]	(*S*)-**1a**	46	97 [c)]
2	**1b**	Br	0	6	**2b**	46	97 [c)]	(*S*)-**1b**	49	93 [c)]
3	**1c**	$Bu^tMe_2SiOCH_2$	0	60	**2c**	43	99 [c, d)]	(*S*)-**1c**	46	95 [c, d)]
4	**1d**	H	1	5	**2d**	47	98 [c)]	(*S*)-**1d**	43	94 [c)]
5	**1e**	Br	1	10	**2e**	48	99 [c)]	(*S*)-**1e**	49	92 [c)]
6	**1f**	$Bu^tMe_2SiOCH_2$	1	7	**2f**	42	97 [c, e)]	(*S*)-**1f**	49	90 [c, e)]

a) The reaction was carried out in 300 mg scale. *b*) Isolated yields. *c*) Determined by ^1H NMR after deriving the MTPA ester. *d*) Determined by HPLC after leading to an acetate of 1-[2-(6-hydroxymethylpyridyl)]ethanol. *e*) Determined by HPLC directly for the alcohol and after hydrolysis for the acetate.

method offers several advantages in the following points; i) very simple protocol without any special conditions such as anhydrous solvent or high purity of catalyst, ii) clean reaction, iii) good chemical yield, iv) reliable reproducibility, v) large scale preparation, vi) both (*R*)- and (*S*)-isomers are available at one time, and vii) lipase can be recovered in large scale reaction and recycled.

We have reported that bromopyridines and bromobipyridines can multiply the pyridyl units by a cross coupling reaction with pyridyl sulfoxide.[8)] Thus, the chiral bromopyridines and bipyridines, (*S*)-**1b**, (*S*)-**1e**, **2b**, and **2e**, could become a good candidate for chiral oligopyridine synthesis. Optically pure terpyridine **7**, and quaterpyridine **8** were prepared in reasonable yields along this methodology. Bromopyridine **6b** derived from (*S*)-**1b** by silylation in 95% yield was treated with butyllithium, then the formed lithio pyridine was reacted with ethyl bipyridyl sulfoxide to give **7** in 65% yield. In the same manner, starting from (*S*)-**1e**, quaterpyridine **8** was obtained in 61% yield.



Meanwhile, it should also be noted that optically pure pyridines and bipyridines, (*S*)-**1c**, (*S*)-**1f**, **2c**, and **2f** possess a functional carbon unit at the terminal C-6' carbon, which allows to extend a further carbon chain. Syntheses of more complex chiral oligopyridino molecules are in progress at this laboratory.

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16) We have tested the following lipases; Lipozyme (*Rhizomucor miehei*), AK (*Pseudomonas sp.*), PS (*Pseudomonas cepacia*), CAL (*Candida antarctica*), LPL (*Pseudomonas aeruginosa*), and Pancreatin F (*Porcine pancreas*).
17) CAL catalyzed acetylation for the case of **1f**; A mixture of **1f** (1.2 g), CAL (420 mg), powdered molecular sieves 4A (1 g) and vinyl acetate (2.4 mL) in diisopropyl ether (240 mL) was stirred for 9 hr at room temperature. The whole was filtered through extrelut pad (3 g) and the pad was washed with dichloromethane (8 ml X 2). The filtrate was condensed and purified by silica gel clomun chromatography eluted with 10% ethyl acetate in hexane for **2f** and then with 80% ethyl acetate in hexane for (S)-**1f**. **2f**; 44% yield and 97% e. e. determined by HPLC on Chiralcel OJ after hydrolysis of the acetate, $[\alpha]_D^{24}$ +50.6° (c 8.87, chloroform), ^{1}H NMR($CDCl_3$) δ 0.15 (6H, s), 0.98 (9H, s), 1.66 (3H, d, J=6.7 Hz), 2.15 (3H, s), 4.91 (2H, s), 6.02 (1H, q, J=6.7 Hz), 7.34 (1H, d, J=7.7 Hz), 7.52 (1H, d, J=7.7 Hz), 7.78 (1H, t, J=7.8 Hz), 7.82 (1H, t, J=7.8 Hz), 8.29 (1H, d, J=7.1 Hz), 8.31 (1H, d, J=6.6 Hz); (S)-**1f**; 48% yield and 93% e. e. determined by HPLC on Chiralcel OJ, $[\alpha]_D^{24}$ +10.1° (c 7.80, chloroform), ^{1}H NMR($CDCl_3$) δ 0.15 (6H, s), 0.99 (9H, s), 1.56 (3H, d, J=6.6 Hz), 4.92 (2H, s), 4.96 (1H, q, J=6.5 Hz), 7.26 (1H, d, J=7.6 Hz), 7.54 (1H, dd, J=7.8 and 0.9 Hz), 7.81 (1H, t, J=7.8 Hz), 7.85 (1H, t, J=7.8 Hz), 8.28 (1H, d, J=7.9 Hz), 8.31 (1H, d, J=7.9 Hz).
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