LIPASE-CATALYZED RESOLUTION AND ABSOLUTE CONFIGURATION OF PHOTOPYRIDONES

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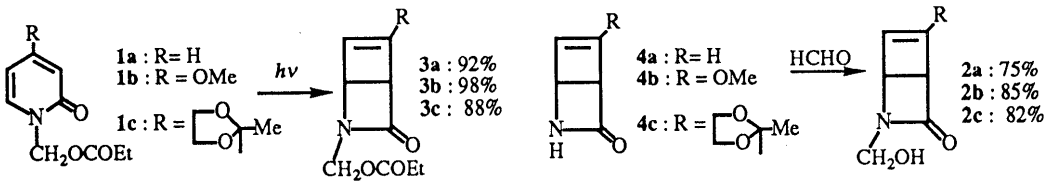
Optically active photopyridones possessing synthetic versatility were obtained conveniently by lipase-catalyzed enantioselective acylation or hydrolysis of racemic photopyridones, and the absolute configurations were determined by chemical correlation, X-ray crystallography and CD spectral analysis.

KEY WORDS lipase-catalyzed resolution; chiral photopyridone; lipasePS; lipaseAK; X-ray analysis; CD spectral analysis

Racemic photoisomers, 3-oxo-2-azabicyclo[2.2.0]hex-5-enes, of 2(1*H*)-pyridones containing β-lactam and cyclobutene moieties have a great potential as synthetic intermediates. Photopyridones would be synthons of carbapenems[1] and also of carbocyclic oxetanocin,[2] which has a similar activity to AZT (zidovudine) against human immunodeficiency virus (HIV). Despite the many synthetic studies of racemic photopyridones,[3] little attention has been focussed on those of chiral photopyridones.[4] Enzymes of a lipase group have been used for syntheses of chiral organic compounds: the enzymatic reaction requires no coenzymes, and lipases are commercially available. Most substrates of the lipase-catalyzed asymmetric resolution have been compounds in which stereogenic carbon atoms were adjacent to the reaction site. We report here the lipase-catalyzed enantioselective acylation or hydrolysis of photopyridones, in which chiral centers are remote from the reactive site. *N*-Hydroxymethyl group of chiral photopyridones obtained is easily removed under the basic conditions.[5] The absolute configurations of chiral photopyridones obtained were determined by chemical correlation, X-ray crystallographic analysis using the anomalous dispersion effect of oxygen atoms, and / or CD spectral analysis.

Racemic *N*-hydroxymethylphotopyridones (**2a-c**) prepared from racemic **4a-c** were subjected to lipase-catalyzed acylation. Racemic *N*-propionyloxymethylphotopyridones (**3a-c**) were synthesized by photoisomerization of 1-propionyloxymethyl-2(1*H*)-pyridones (**1a-c**) in good yields (88-98%), and used for lipase-catalyzed hydrolysis (Chart 1).

Chart 1



The transesterification reaction of (±) **2a-c** with vinyl acetate by lipases (PS and AK)[6] was examined using a *tert*-butyl methyl ether solution. *N*-Acetoxymethylphotopyridones [(-)-**5a-c**] with high optical purity were obtained in spite of the relatively long distance between the reaction site and the asymmetric center (Table 1). Furthermore, the hydrolysis of (±) **3a-c** using two lipases (PS or AK) in isopropyl ether saturated with H_2O gave *N*-hydroxymethylphotopyridones [(-)-**2a-c**] in high optical yields (Table 2). In the case of the lipase-catalyzed transesterification of racemic **2a-c** or hydrolysis of racemic **3a-c**, the two lipases catalyze the reactions in the same absolute stereochemical course, as indicated by the negative sign of optical rotation of the products [(-)-**2a-c** and (-)-**5a-c**].

The absolute configurations of the photopyridones [(-)-**2a-c**] were determined by chemical correlation [(-)-**2b**], X-ray crystallographic analysis [(-)-**2c**)], and CD spectral measurements [(-)-**2a-c**)]. The CD spectra of photopyridones have not been reported yet. The absolute stereochemistry of (-)-[1*S*,4*S*]-**2b** was confirmed by conversion to a synthetic intermediate of chiral carbapenem antibiotics, as shown in Chart 2: β–lactam (-)-**6**, $[\alpha]_D$-308 (c=0.8 in $CHCl_3$); ketone (+)-7[4b], $[\alpha]_D$+325 (c=0.10 in $CHCl_3$), lit.[4b]: $[\alpha]_D$+325 (c=1.05 in $CHCl_3$).

Compound (-)-**2c**, a synthetically enantiomeric intermediate of chiral carbocyclic oxetanocin analog,[2] was unstable, and preparation of proper derivatives was unsuccessful. Therefore, to determine the stereochemistry, X-ray crystallographic analysis[7] of (-)-**2c** was performed. The absolute stereochemistry of (-)-**2c** was determined to be [1*S*,4*R*] using the anomalous dispersive effect of oxygen atoms and the diffraction data measured at 170 K. The

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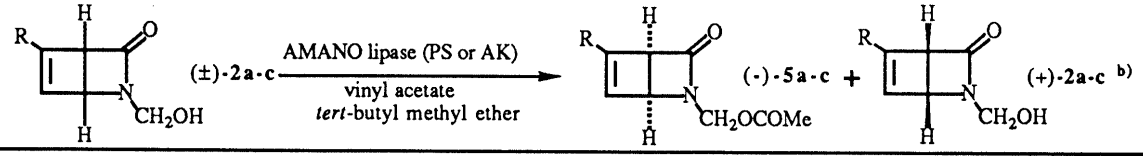
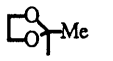
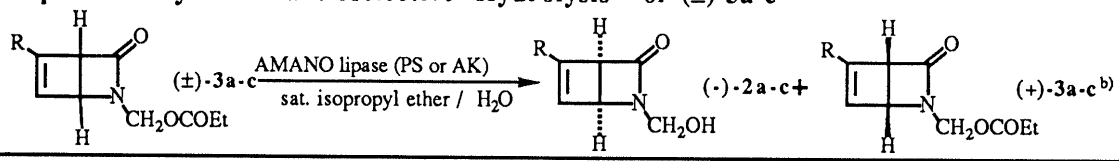
Table 1. Lipase-Catalyzed Enantioselective Acylation[a)] of (±)-2a-c



Substrate	R	Lipase	Time (h)	Temp. (°C)	Product	Chemical Yield(%)[c)]	Optical $[\alpha]_D$[d)]	Optical Yield(%ee)[e)]
2a	H	PS	4	20	(-) - 5a	14	- 94	97
		AK	2	20		26	- 95	98
2b	OMe	PS	0.5	20	(-) - 5b	12	- 36	90
		AK	0.5	20		10	- 41	93
2c		PS	1	20	(-) - 5c	14	- 35	91
		AK	1	20		3	- 33	81

a) Conditions: (±)-2a-c (2.4 mmol), lipase PS (300 mg) and AK (300 mg), vinyl acetate (7.2 mmol), *tert*-butyl methyl ether(100 ml). b) Low optical yields (3-31%ee). c) Isolated yield. d) Optical rotations were taken in chloroform (c=0.06-3.82). e) The optical yields were determined by HPLC on Chiralpack AS (Daicel, Japan) column (hexane/ethanol).

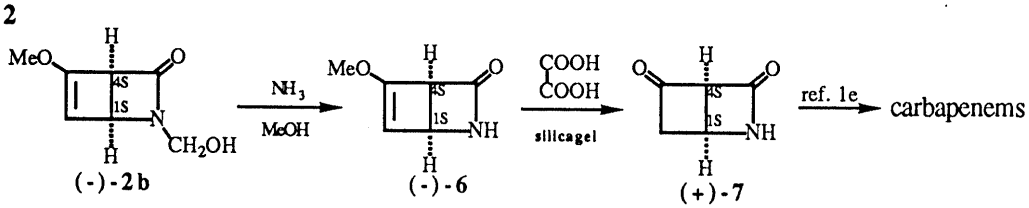
Table 2. Lipase-Catalyzed Enantioselective Hydrolysis[a)] of (±)-3a-c



Substrate	R	Lipase	Time (h)	Temp. (°C)	Product	Chemical Yield(%)[c)]	Optical $[\alpha]_D$[d)]	Optical Yield(%ee)[e)]
3a	H	PS	2	28	(-) - 2a	34	-240	>98
		AK	2	20		25	-275	>98
3b	OMe	PS	35	25	(-) - 2b	28	-135	95
		AK	2	20		27	-135	97
3c		PS	16	25	(-) - 2c	28	- 70	92
		AK	35	25		45	- 52	66

a) Conditions: (±)-3a-c (1.9 mmol), lipase PS (300 mg) and AK (300 mg), sat. isopropyl ether-H_2O (100 ml). b) Low optical yields (18-81%ee). c) Isolated yield. d) Optical rotations were taken in chloroform (c=1.35-2.44). e) The optical yields were determined by HPLC on Chiralpack AS (Daicel, Japan) column (hexane/ethanol).

Chart 2



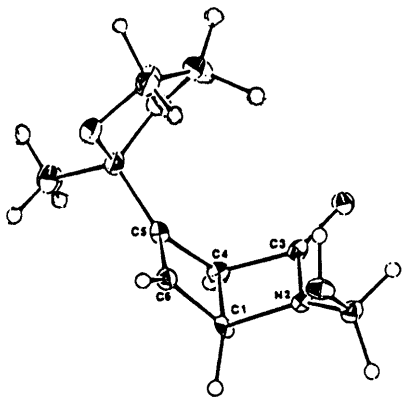


Fig. 1. ORTEP Drawing of (-)-2c

Selected bond lengths (Å) and angles (°): C(1)-N(2) 1.474(6), C(1)-C(4) 1.619(6), C(1)-C(6) 1.534(6), N(2)-C(3) 1.379(5) C(3)-C(4) 1.536(6), C(4)-C(5) 1.527(6), C(5)-C(6) 1.373(6) N(2)-C(1)-C(6) 114.3(3), N(2)-C(1)-C(4) 84.9(3), C(4)-C(1)-C(6) 84.9(3), C(1)-N(2)-C(3) 96.1(3), N(2)-C(3)-C(4) 92.9(3),C(1)-C(4)-C(3) 84.6(2), C(1)-C(4)-C(5) 85.8(2), C(3)-C(4)-C(5) 112.5(3), C(4)-C(5)-C(6) 94.4(3), C(5)-C(6)-C(1) 94.8(3).

molecule [(-)-**2c**] was a strained skeleton which affects the bond lengths and angles. For example, the central C(1)-C(4) bond (1.619Å) and the double bond of C(5)-C(6) (1.373Å) considerably lengthen, and the lengths of other bonds are longer than those of the normal bonds. The dihedral angle between two *cis*-fused four-membered rings is 114.0°.

CD spectra of (-)-**2b** and (-)-**2c** showed strong negative Cotton effects at 217.0 and 224.5 nm, respectively (Fig.2). The absolute configuration of (-)-[1*S*,4*R*]-**2a** was determined by comparing a negative Cotton effect at 228.5 nm with that of (-)-**2b,c** (Fig. 2). Therefore, the absolute configurations of chiral *N*-acetoxymethylphotopyridones [(-)-**5a-c**] were determined to be [1*S*,4*R*]. The structures of all new compounds (**1a-c**, **2a-c**, **3a-c**, **4c**, and **5a-c**) were characterized by IR, ^{1}H-NMR, MS, and HRMS spectroscopic methods.

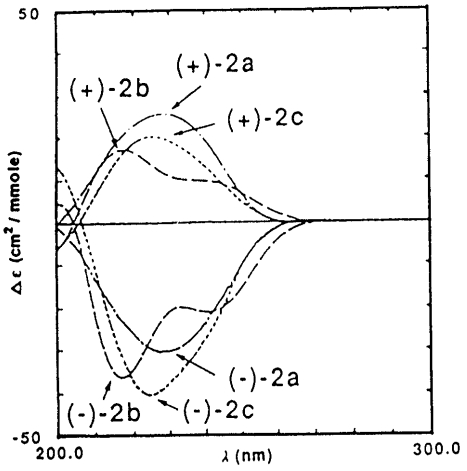


Fig. 2. CD Spectra of (-)-**2a-c** and (+)-**2a-c**

	nm	Δε
(-)-2a (>98%ee)	: 228.5	(-30.2)
(+)-2a (91%ee)	: 228.5	(+27.6)
(-)-2b (>98%ee)	: 217.0	(-36.2)
(+)-2b (48%ee)	: 218.0	(+17.4)
(-)-2c (>98%ee)	: 224.5	(-40.0)
(+)-2c (73%ee)	: 225.5	(+29.3)

We explored the facile lipase-catalyzed resolution of photopyridones, and determined the absolute configuration by CD spectral analysis. The methods reported here should be applicable to the preparation of various chiral photopyridones.

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6) We are grateful to Amano Pharmaceutical Co., Ltd. for the generous gift of lipase PS (*Pseudomonas fluorescens*) and AK (*Pseudomonas cepacia*).

7) X-ray experimental of (-)-**2c**: crystal size=0.20x0.20x0.25 mm, Rigaku AFC5PR diffractometer(45 kV, 200 mA), temperature=170 K, Cu-Kα radiation(λ=1.5418 Å), a=7.687(1), b=19.010(3), c=7.365(1) Å, V=1048.2(2) Å^3, the space group= $P2_12_12_1$, Z=4, Dcalcd=1.10 g/cm^3, μ(CuKα)=5.0 cm^{-1}, 2θ–ω scan mode, scan speed of 6°min^{-1}, measured reflections=2039(two sets of F(h,k,l) and F(-h,-k,-l), reflections used for refinement=1594[Io>3σ(Io)]. The final R values are 0.0584(Rw=0.0697) vs. 0.0589(Rw=0.0705) for two enantiomorphs. Hamilton's ratio test showed the correctness of more than 0.995 probability. More precise re-measurement of eight Bijoet pairs for effective 20 reflections showed all consistency of signs of average Δ Fo vs. Δ Fc. Further details have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

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