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A Facile Lipase-Catalyzed Resolution of 2-Azabicyclo[2.2.1]hept-5-en-3-ones

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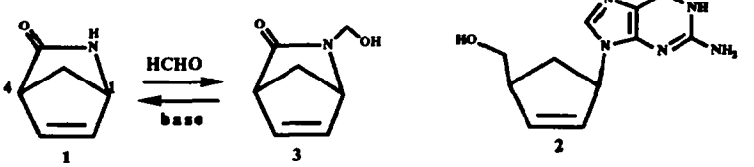
Abstracts: The lipase-catalyzed asymmetric synthesis of optically active 2-azabicyclo[2.2.1]hept-5-en-3-ones is reported. Chiral 2-azabicyclo[2.2.1]hept-5-en-3-ones were obtained conveniently by lipase-catalyzed enantioselective transesterification of 2-hydroxymethyl-2-azabicyclo-[2.2.1]-hept-5-en-3-one.

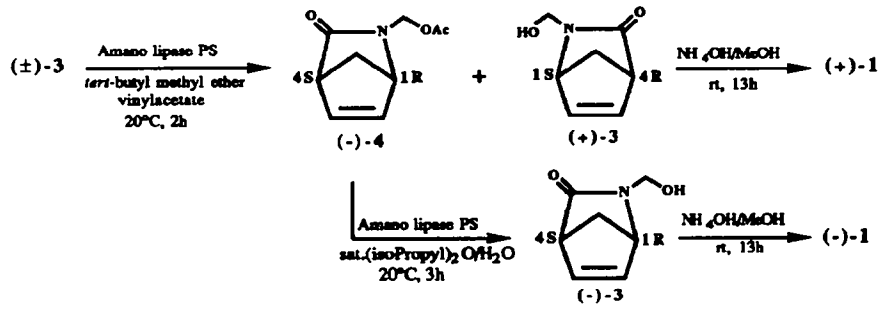
Racemic 2-azabicyclo[2.2.1]hept-5-en-3-one **1** has great potential as a synthetic interemediate. Thus, bicyclic lactam **1** may become a synthon of carbocyclic sugar amines,[1] carbonucleosides,[2] and carbocyclic dinucleotide analogues.[3] Particularly , the synthetic potential of **1** is proved as an useful synthon for the synthesis of (-)-carbovir **2** , which is shown to have similar activity to AZT(zidovudine) against HIV.[4] In contrast to the substantial amount of experimental work on synthesis and application of racemate **1**,[2,5] little attention has been focused on those of the chiral bicycloamide **1**, except for the chemoenzymatic synthesis by Roberts *et al.*[4] A lipase is a typical enzyme to be accepted into routine use in organic synthesis, because it requires no coenzymes and is commercially available and inexpensive. We wish to report the facile synthesis of chiral bicycloamide **1** by lipase-catalyzed enantioselective transesterification of 2-hydroxymethyl-2-azabicyclo[2.2.1]hept-5-en-3-one **3** with no production of the amino acid. The *N*-hydroxymethyl group[6] is easily removed under the basic reaction conditions.



1 **3** **2**

Racemic **3** was prepared easily from racemate **1** and paraformaldehyde. The transesterification of (±)-**3** with vinyl acetate by the three lipases (PS, AK, and AY)[7] was examained in *tert*-butyl methyl ether (Table 1), and high enantioselective transesterification of (±)-**3** with lipase PS proceeded to give acetate (-)-**4**, 38%, 94%ee and recover (+)-**3**, 40%, 89%ee. The (+)-**3** was purified by recrystallization (diisopropyl ether) to extremely high optical purity (20%, >99%ee), mp 60-62°C, $[\alpha]_D^{20}$+344 (c2.1, $CHCl_3$). Furthermore, the hydrolysis[8] of acetate (-)-**4**, viscous oil, 94%ee, $[\alpha]_D$ -104 (c2.5, $CHCl_3$) using lipase PS under the mild conditions gave the *N*-hydroxymethyl form (-)-**3**, 80%, >99%ee, mp 58-59°C, $[\alpha]_D$-343 (c2.1, $CHCl_3$) in excellent chemical and optical yields. The (+)- and (-)-**3** obtained were converted conveniently into the (+)-**1**, 38%, >99%ee, mp 89-90°C, $[\alpha]_D$+554 (c 1.2, $CHCl_3$), lit.[4]: $[\alpha]_D$ +555±15 and (-)-**1**, 51%, >99%ee, mp86-88°C, $[\alpha]_D$-556 (c

1.1, $CHCl_3$), lit.[4]: $[\alpha]_D$-568±15, respectively, by the treatments with ammonium hydroxide in methanol. The absolute configurations of bicyclic lactams [(+)-3 (1S,4R), (-)-4 (1R,4S) and (-)-3 (1R,4S)] were confirmed by the conversion into (+)-1 (1S,4R) and (-)-1 (1R,4S), respectively. The enantiomeric excesses of



the chiral compounds **1**, **3** and **4** were determined by HPLC analysis using a chiral column [Chiralpack AS (Daicel,Japan)] and these structures were characterized by IR, ^{1}H-NMR spectroscopy, mass and high-resolution mass spectrometry.

Table 1. Lipase-catalyzed transesterification[a] of (±)-3

				Product (-)-4		Recovery (+)-3	
Lipase	Time(h)	Temp(°C)	Convn(%)[b]	C. Y.(%)	e.e(%)	C. Y.(%)	e.e(%)
PS	2	20	49	38	94	40	89
AK	5	20	51	31	89	40	91
AY	10	20	0	5	26	40	rac

a. Conditions: (±)-3 (1.44mmol, 200mg), lipases PS, AK and AY (200mg), vinyl acetate (6.97mmol, 600mg), tert-butyl methyl ether (100ml). b. Conversion: ref. 9.

References and notes

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7. We are grateful to Amano Pharmaceutical Co., Ltd. for the generous gift of lipases [PS (*Pseudomonas cepacia*), AK(*Pseudomonas fluorescens*) and AY (*Candida rugosa*)].
8. Conditions: acetate (-)-4 (0.55mmol, 100mg), lipase PS (100mg), diisopropyl ether saturated with water (100ml).
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