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Lipase-Catalyzed Resolution of 2-Substituted 3-Cyclopenten-1-ol Derivatives

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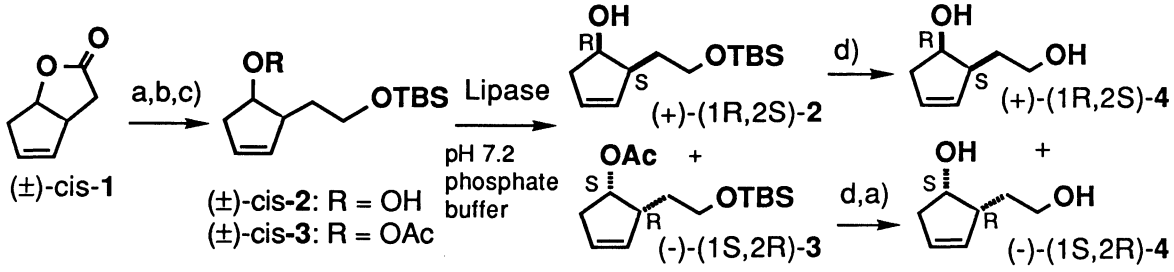
2-Oxabicyclo[3.3.0]oct-6-en-3-one, the key intermediate in the prostaglandin synthsis, was subjected to the optical resolution effectively by use of lipase after conversion to 2-[2-(t-butyldimetylsilyloxy)ethyl]-3-cyclopenten-1-yl acetate and 2-[2-(N,N-dimethylcarbamoyl)methyl]-3-cylopenten-1-yl acetate.

Much attention has been focussed on the preparative methods for optically active 2-oxabicyclo[3.3.0]oct-6-en-3-one (**1**) and its derivatives[1a-f] because of the importance especially in the prostaglandin synthesis. The reported methods involve critically controlled asymmetric syntheses with chiral organometallic reagents,[1a,b] enzyme-catalyzed resolutions,[1c-e] and bakers' yeast reduction with lengthy conversion steps.[1f] We recently encountered to need the chiral lactone **1** for our promoting natural product synthesis and felt that the reported prescriptions are insufficient in a viewpoint of the simple, laboratory-scale preparative method. Lately, the optical resolution with lipase, which is readily accessible and easy to handle, has become to be widely utillized as one of the straightforward methods to obtain chiral compounds.[2] We report here a successful application of lipase to the resolution of the lactone (±)-**1** after conversion to 2-[2-(t-butyldimetyl-silyloxy)ethyl]-3-cyclopenten-1-yl acetate (±)-cis-(**3**) and 2-[2-(N,N-dimethylcarbamoyl)methyl]-3-cylopenten-1-yl acetate (±)-(**6**) to obtain the corresponding acetates and the alcohols with high optical purities.

Preparation of the substrate (±)-cis-**3**[3] from (±)-**1** and the subsequent optical resolution is outlined below. The resolution procedure with lipase is as follows: A mixture of (±)-cis-**3** (600 mg, 11 mmol), lipase (Amano P, 480 mg), and pH 7.2, 0.1 M phosphate buffer solution (20 ml) was stirred at 35 °C for 5-7 h. The reaction progress was monitored by both TLC (silica gel) and GLC (Apiezone Grease L). The incubation was stopped at the 50% conversion. The extract with ethyl acetate was fractionated by column chromatography (silica gel, n-hexane:ethyl acetate = 20:1) to give (+)-**2** (37% yield) and (-)-**3** (39% yield). Optical purity (% ee) was determined as >99% ee for (+)-**2** [(HPLC with Chiralcel OB of Daicel, n-hexane:i-PrOH 9:1), $[\alpha]_D$ +47.7° (c 2.5, $CHCl_3$)] and 92% ee for (-)-**3** [(200 MHz ^1H NMR analysis with 50 mol% of Eu(hfc)$_3$), $[\alpha]_D$ -18.6°



a) $LiAlH_4$/THF (97%); b) TBS-Cl/Imidazole/THF (76%); c) AcCl/DMAP/THF (97%); d) n-Bu_4NF/THF (59%).

(c 3.0, $CHCl_3$, 92 % ee)]. The absolute configurations of (+)-**2** and (-)-**3** were assigned by transformation to the diols (+)-(1R,2S)-**4** ([α]$_D$ +63.0° (c 1.5, MeOH)) and (-)-(1S,2R)-**4** [[α]$_D$ -63.0° (c 1.4, MeOH), (lit.[4]) for (1S,2R)-**4** [α]$_D$ -60.0° (MeOH)], respectively.

The advantage to choose the N,N-dimethylamide derivative (±)-**6** as the substrate is of the convenience to transform into the chiral lactone **1**. The compound (±)-**6** was prepared from (±)-**1** in two steps [a) excess of $HNMe_2$, THF-H_2O (55% yield); b) AcCl, DMAP in CH_2Cl_2 (80% yield)] . The results by use of three types of lipases are shown in Table 1. The procedure for the resolution is similar to that described above, excepting the ratio of the lipase/substrate. As compared with (±)-**3**, the amide (±)-**6** markedly retarded the hydrolysis. In the case of lipase Amano P, the reaction time of 7.5 day is required for the 50% conversion. The optical purities (ee) of the resulting (+)-**5** and (-)-**6** did not exceed 84%. The lipase Amano A12 much more shortened the reaction time to 7 h, while decreasing the ee(s) of the products. The last choice of the lipase Amano PS favorably raised the ee(s) of both (+)-**5** (93%) and (-)-**6** (90%). One of the reasons of the unsatisfactory yields may due to the water-solubility of the amides. The configuration of (-)-**6** was assigned by correlation ($HClO_4$, H_2O-CH_2Cl_2, 78%) to that of (+)-(1R,5S)-**1** [[α]$_D$ +94° (c 1.4, MeOH), (lit.[1a] [α]$_D$ -106° (MeOH) for (1S,5R)-**1**)].

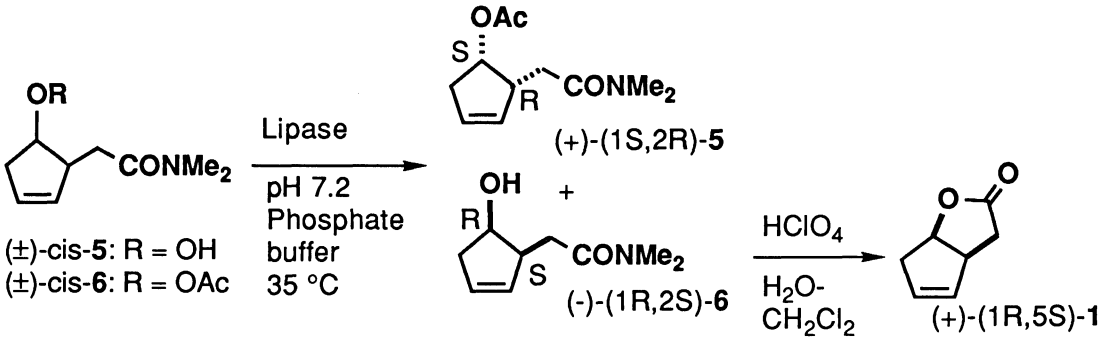


Table 1. Lipase-Catalysed Optical Resolution of N,N-Dimethylamide Derivative (±)-**6**

Lipase	Lipase/Substrate (w/w)	Time d	(-)-(1S,2R)-**5**			(+)-(1R,2S)-**6**		
			Yield/%	ee/%[a]	[α]$_D$/[b]	Yield/%	ee/%[a]	[α]$_D$/[b]
Amano P	2/1	7.5	29	56	-32	14	84	+18
AmanoA12	1/1	7 (h)	25	77	-44	45	26	+6
Amano PS	2/1	4.0	20	93	-48	17	90	+20

a) Determined by HPLC analysis (Daicel, Chiralcel OB). b) In chloroform.

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