

AN ASYMMETRIC SYNTHESIS OF BICYCLIC LACTONES AND
ITS APPLICATION TO THE ASYMMETRIC SYNTHESIS OF (1R,3S)-CIS-CHRYSANTHEMIC ACID

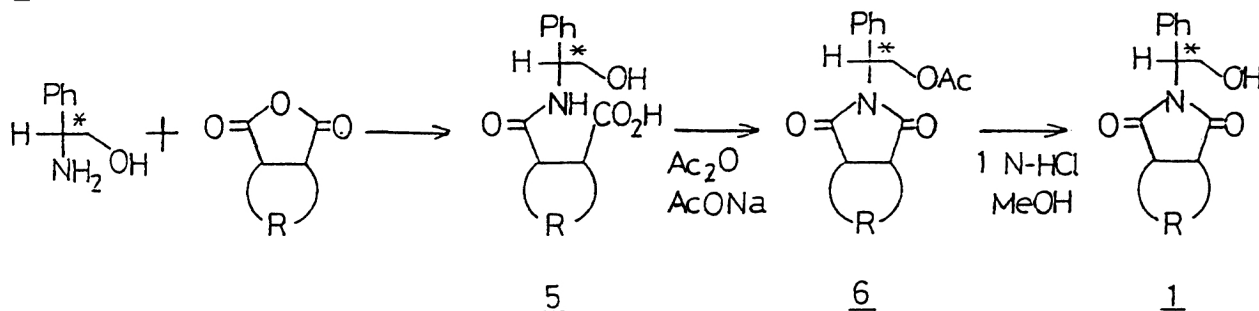
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Optically active bicyclic lactones are synthesized from imides, derived from (R)-(-)-2-amino-2-phenylethanol and meso-cyclic-1,2-cis-dicarboxylic acids, by successive treatment with sodium bis(2-methoxyethoxy)aluminum hydride and sodium borohydride, followed by acid hydrolysis. This reaction is successfully applied to the asymmetric synthesis of (1R,3S)-cis-chrysanthemic acid.

Among various types of asymmetric synthesis, it would become one of the effective methods to prepare optically active compounds starting from symmetrical compounds by finding out the hidden symmetry in the desired chiral compounds.^{1,2,3)} As a chemical method to synthesize optically active compounds from meso-dicarboxylic acids, an asymmetric synthesis using the corresponding diamide with two equivalents of a chiral source, (R)-4-methoxycarbonyl-1,3-thiazolidine-2-thione, has been reported.³⁾

Theoretically, it is possible to explore an efficient method to distinguish one of the enantiotopic carbonyl groups of a meso-dicarboxylic acid from another by employing only one chiral source. In this communication, we wish to describe an efficient method for an asymmetric synthesis of bicyclic lactones starting from optically active imides (1), derived from meso-cyclic-1,2-cis-dicarboxylic acids⁴⁾ and (R)-(-)-2-amino-2-phenylethanol.⁵⁾ By treating the imide (1) with a suitable aluminum hydride, one of the carbonyl groups of the imide (1) was selectively reduced to give the corresponding hydroxypyrrolidone derivative (2), which in turn was reductively cleaved to the corresponding amide (3) with sodium borohydride. Bicyclic lactone (4) was obtained in good optical yield after acid hydrolysis of (3).



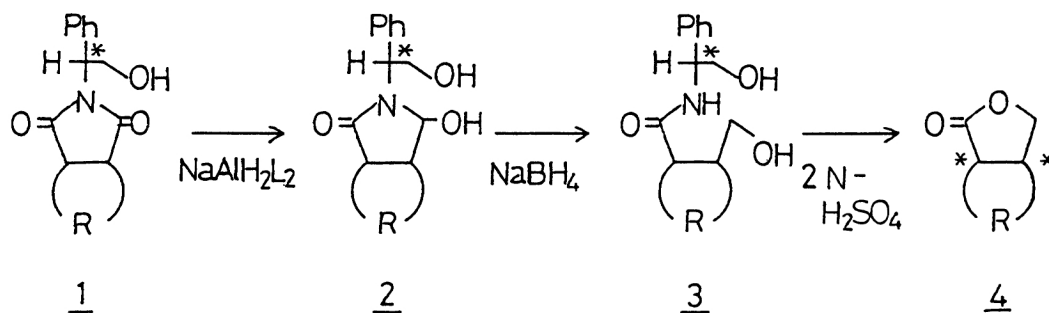
Optically active imides (1) were synthesized by the following general procedure; to a suspension of (R)-(-)-2-amino-2-phenylethanol (30 mmol) in 50 ml of THF was added a THF (20 ml) solution of meso-cyclic-1,2-cis-dicarboxylic acid anhydride (30 mmol) over 15 min at 0°C. After stirring the mixture for an additional hour at room temperature, THF was removed in vacuo. Then, the resulting amide (5) and 0.5 g of sodium acetate in acetic anhydride (30 ml) were stirred at 100°C for 3 h. After removal of excess acetic anhydride, the residue was purified by silica-gel column chromatography to afford the imide (6). The acetyl group of (6) was removed by refluxing in 50 ml of 1 N methanolic solution of hydrochloric acid for 2 h. After concentration under reduced pressure, the residue was purified by silica-gel column chromatography to afford the imide (1) in good overall yield. The results are summarized in Table I.

Table I. The Synthesis of Cyclic Imide (1)

	R	Overall Yield (%) ^{a)}	$[\alpha]_D^{22}$ (c 10.0, MeOH)	M.p.(°C)
<u>1a</u>	-(CH ₂) ₄ -	68.4	+2.11	104 - 106
<u>1b</u>	-(CH ₂) ₃ -	78.0	-5.62	109 - 111
<u>1c</u>	-(CH ₂) ₂ -	82.4	-20.3	105 - 107
<u>1d</u>	-(CH ₂)-	89.6	+3.06	107 - 109
<u>1e</u>	-(CMe ₂)-	67.2	+11.6	91 - 93

a) All products gave satisfactory NMR and IR spectra.

Among various reducing reagents screened for the selective reduction of one of the diastereotopic carbonyl groups of the imide (1), modified aluminum hydride reagents containing two active hydrides, such as, sodium bis(2-methoxyethoxy)aluminum hydride and sodium diethylaluminum hydride were found to give good results.



The general procedure leading to optically active lactones is as follows; to a THF (10 ml) solution of (1) (3 mmol) was added the modified aluminum hydride reagent (3 mmol) at -42°C ~ -100°C. After stirring for 0.5 ~ 8 h, 10 ml of ethyl acetate and 10 ml of 30% potassium tartrate solution were added. Then, the reaction temperature was raised to room temperature and the organic layer was separated. The aqueous layer was extracted with 15 ml of ethyl acetate, and the combined extracts were dried over Na₂SO₄ and concentrated. The resulting oily substance was purified by silica-gel column chromatography to give the hydroxypyrrolidone derivative (2). Then, (2) in 60% ethanol (10 ml) was treated with sodium borohydride

(6 mmol) at 50 °C for about 4 h. After addition of 20 ml of ethyl acetate, 10 ml of 5% hydrochloric acid was added slowly with cooling, and the separated organic layer was dried over Na_2SO_4 and concentrated. The resulting oily substance was purified by silica-gel column chromatography to give the amide (3). A suspension of (3) in 5 ml of 2 N sulfuric acid was stirred at 80°C for 2 h, then, after cooling, the reaction mixture was extracted with 10 ml of methylene chloride three times. The combined extracts were dried over Na_2SO_4 and concentrated. Pure optically active lactone (4) was obtained by Kugelrohr distillation. From the aqueous layer, 2-amino-2-phenylethanol could be recovered without racemization. The results are summarized in Table II.

Table II. Synthesis of Optically Active Lactone (4)

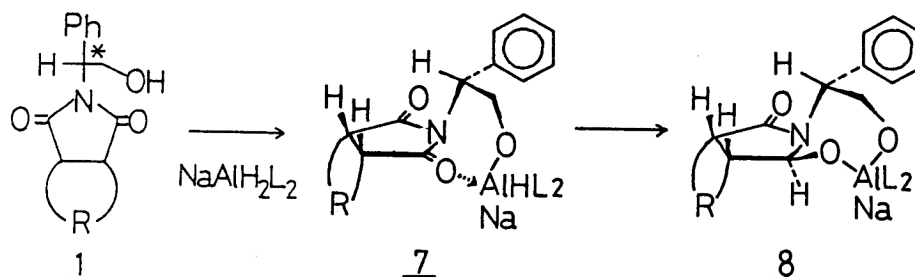
Starting material	<u>2</u>				<u>3</u>				<u>4</u>			
	a)	Temp.(°C)	Time(h)	Yield(%)	Yield(%)	Yield(%) ^{d)}	$[\alpha]_D^{25}$ (CHCl_3)	Config. ^{b)}	%ee ^{c)}			
<u>1a</u>	A	-78	2	95			+43.0(c 0.50)		88			
	B	-100	1	90			+38.4		76			
	B	-78	0.5	96	97	81	+32.8	(<u>1S</u> , <u>2R</u>)	67			
	C	-78	0.5	92			+7.8		16			
<u>1b</u>	A	-78	4	94	96	79	+66.9(c 1.0)	(<u>1S</u> , <u>2R</u>)	69			
	B	-78	3	92			+62.3		64			
<u>1c</u>	A	-78	6	89			+80.7(c 10.0)		68			
	B	-100	8	93	98	77	+82.1	(<u>1S</u> , <u>2R</u>)	69			
	B	-78	2	97			+60.5		51			
<u>1d</u>	A	-78	8	85			-36.0(c 6.0)		58			
	B	-78	4	88	91	77	-34.3	(<u>1S</u> , <u>2R</u>)	56			
<u>1e</u>	A	-42	8	89			-72.8(c 1.4)		81			
	B	-42	8	87	95	76	-68.2	(<u>1R</u> , <u>3S</u>)	76			
	C	-78	1.5	92			-15.8		17			

a) Reducing reagents. A= $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ (70 wt% toluene solution)
 B= $\text{NaAlH}_2\text{Et}_2$ (27 wt% toluene solution)
 C= $\text{AlH}(\text{CH}_2\text{CHMe}_2)_2$ (Two equivalents were used)

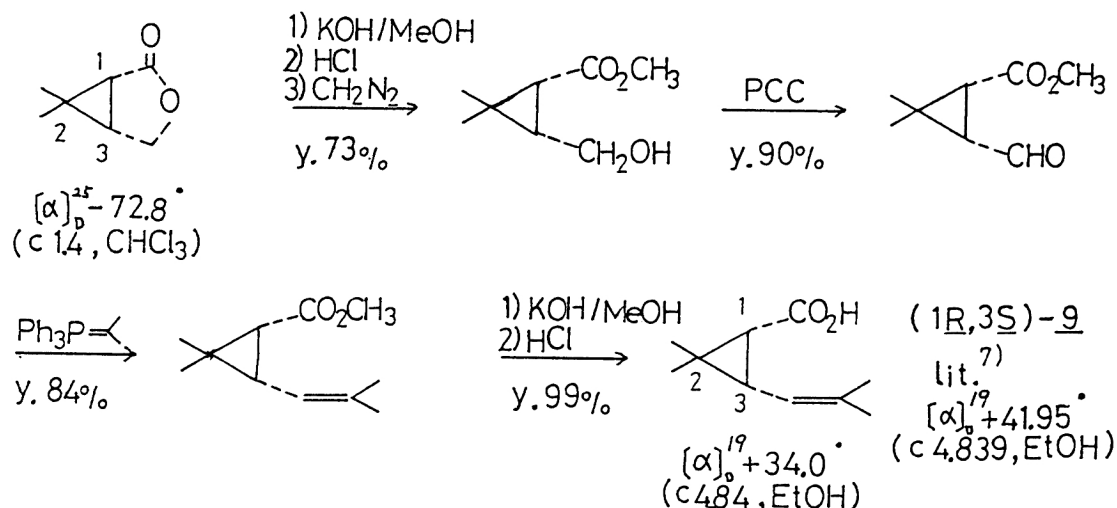
b) Absolute configurations have been reported in ref. 1. c) Enantiomeric excess was determined by comparison with the optical rotation value of lactone (4) reported in ref. 1 except (4e) whose enantiomeric excess was determined by transformation to cis-chrysanthemic acid. d) Isolated yield by Kugelrohr distillation (100°C/5 mm). Spectral properties were identical with those reported in ref. 1.

Based on the result that (1S,2R)-lactones were obtained in all cases, we assume the following possible mechanism for the selective reduction of the imide (1); the modified aluminum hydride reagent would react with (1) to form the intermediate (7). A consideration of the conformation of (7) by molecular models suggests that the N-substituting phenylethoxyaluminum moiety would locate against the cyclic R-substituent by the steric repulsion, and the phenyl group would also keep away from the bulky bicyclic imide moiety. Further, one of the diastereotopic carbonyl groups of (7) is able to coordinate intramolecularly to the aluminum, and the reduced product (8) having a favorable cis-anti-cis-fused tricyclic structure would

be formed.



Next, an application of the present method to the asymmetric synthesis of (1R,3S)-*cis*-chrysanthemic acid (9) was tried according to the reported procedure⁶⁾ for the racemic compound. The optically active lactone (4e) (81 %ee) was transformed to (9) without any racemization as shown in the following scheme.



It is noted that the present method enables to prepare various bicyclic lactones in good optical purities by a simple procedure. And, it was demonstrated that these lactones would be useful synthetic intermediates for the synthesis of optically active natural products as shown in the synthesis of (1R,3S)-*cis*-chrysanthemic acid.

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