

HIGHLY ENANTIOSELECTIVE REDUCTION OF MESO-CYCLIC-1,2-DICARBOXIMIDES. ASYMMETRIC SYNTHESIS OF BICYCLIC 2-PYRROLIDINONE AND ITS 5-HYDROXY CONGENER

Kenji Matsuki, * Hirozumi Inoue, Akihiko Ishida, and Mikio Takeda

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., 2-2-50
Kawagishi, Toda, Saitama 335, Japan

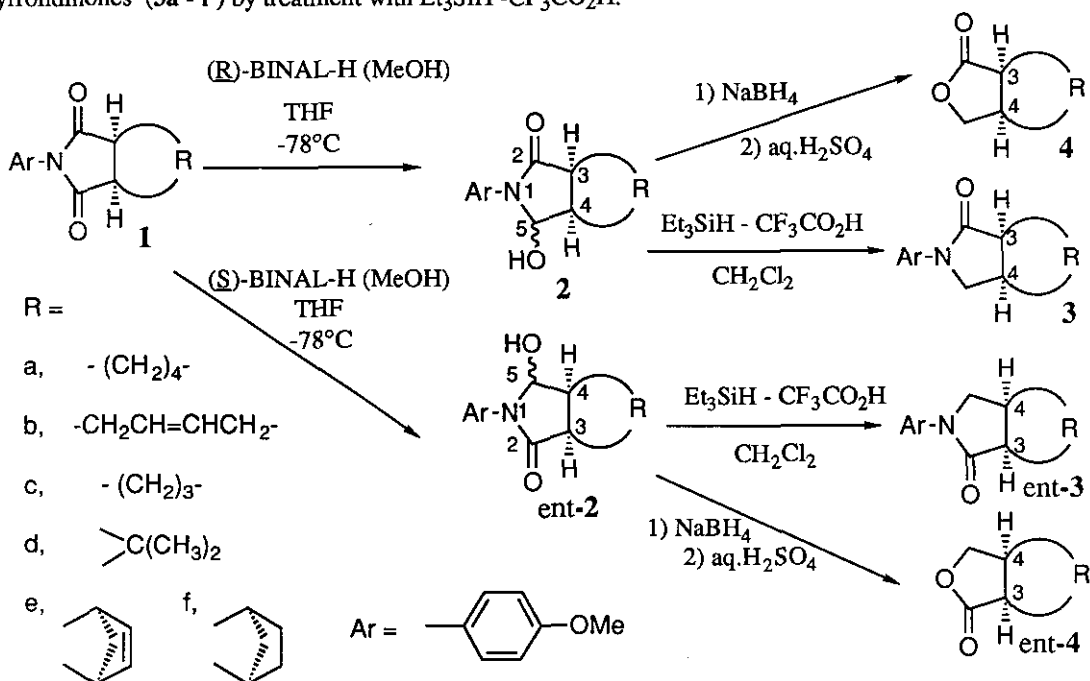
Masako Nakagawa and Tohru Hino

Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho,
Inage-ku, Chiba-shi 263, Japan

Abstract ---- Bicyclic 5-hydroxy-2-pyrrolidinones (**2a - f**) were synthesized with high enantioselectivity by the reduction of meso-cyclic-1,2-dicarboximides (**1a - f**) with lithium aluminum hydride (LiAlH₄)- methanol (MeOH)- 1,1'-bi-2-naphthol complex (BINAL-H). Treatment of **2a - f** with triethylsilane (Et₃SiH) and trifluoroacetic acid (CF₃CO₂H) gave optically active 2-pyrrolidinones (**3a - f**) in quantitative yields. For the absolute configuration correlation, **2a - d** were converted into known lactones (**4a - d**).

Enantioselective synthesis of bicyclic 5-hydroxy-2-pyrrolidinones (**2**), versatile intermediates for synthesis of natural products,¹ can be provided by enantioselective reduction of a carbonyl group in meso-1,2-dicarboximides (**1**) with two carbon centers of opposite chirality. Concerning asymmetric reduction of meso-1,2-dicarboximide (**1**), Mukaiyama and his colleagues have described diastereoselective reduction of meso-imides derived from R-(-)-2-amino-2-phenylethanol and meso-1,2-dicarboxylic anhydrides.² Miller and Chamberlin also reported enantioselective reduction of meso-cyclohexylidene-N-benzyl tartramide with chiral reducing reagents, had been found to afford up to 56%ee of the corresponding 5-hydroxy-2-pyrrolidinone and

the imide moiety was intact for LiAlH_4 and (*R*)-(+)-1,1'-bi-2-naphthol reduction.³ In this communication, we wish to report enantioselective reduction of *meso*-cyclic-1,2-dicarboximides (**1a-f**) into optically active 5-hydroxy-2-pyrrolidinones (**2a-f**) using (*R*)- or (*S*)-BINAL-H, and conversion of **2a-f** to chiral bicyclic 2-pyrrolidinones (**3a-f**) by treatment with $\text{Et}_3\text{SiH} \cdot \text{CF}_3\text{CO}_2\text{H}$.



Scheme 1

At first, we examined the reduction of *N*-(4-methoxyphenyl)-*cis*-1,2-cyclohexanedicarboximide (**1a**)⁴ with (*R*)-BINAL-H, prepared from LiAlH_4 , MeOH and (*R*)-1,1'-bi-2-naphthol (1:1:1 mol ratio) according to the Noyori's Method.⁵ After experiments under various conditions, it was found that the reduction proceeded enantioselectively when the reduction was carried out using 3.5 molar amounts of (*R*)-BINAL-H at -78°C for 20 h. The isolated product was, however, a mixture of C5 α - and C5 β -hydroxy-2-pyrrolidinones (**2a**),⁶ whose ratio depended on the conditions for work-up.⁷ To confirm the enantioselectivity of the BINAL-H reduction, this mixture **2a** was converted into bicyclic 2-pyrrolidinone (**3a**). Treatment of **2a** with $\text{Et}_3\text{SiH} \cdot \text{CF}_3\text{CO}_2\text{H}$ in CH_2Cl_2 gave **3a** in a quantitative yield. The enantiomeric excess (ee) was determined to be 88% by chiral hplc analysis.⁸ The absolute configuration was determined by converting **2a** to bicyclic lactone (**4a**).⁹ NaBH_4 reduction of **2a** and subsequent acid hydrolysis gave the known lactone (**4a**) (94% ee; **3S,4R**) in 78% yield.^{2,10} Under similar conditions for (**3S,4R**) **3a** and (**3S,4R**) **4a**, 5-hydroxy-2-pyrrolidinone (**2a**), prepared

by reduction with (*S*)-BINAL-H, was converted into the lactone(**4a**)(89% ee; **3R**, **4S**)¹⁰ and the lactam **3a** (87% ee; **3R**, **4S**) in high yields, respectively. Similarly, reduction of dicarboximides (**1b** - **f**) with (*R*)- or (*S*)-BINAL-H afforded 5-hydroxy-2-pyrrolidinones (**2b** - **f**) with high enantioselectivity (84 - 91% ee), which were readily converted into the corresponding 2-pyrrolidinones (**3b** - **f**) and lactones (**4b** - **d**) without significant loss of optical purity. Results are summarized in Table 1. Conversion of **2e**, **f** to lactones (**4e**, **f**) was unsuccessful under the above conditions. As regards the absolute configurations of **2e**, **f** and **3e**, **f**, we postulate their configurations are assigned as shown in Scheme 1 by the analogy of the mode of reduction.

Table 1 Enantioselective reduction of *meso*-cyclic-1,2-dicarboximides **1** using BINAL-H.

Entry	Starting Material	BINAL-H (MeOH) Config.	Yield of 2 (%)	3 ^{a)} % ee ^{b)}	4			
					Yield(%)	$[\alpha]_D^{25}$ (c 1.0)	% ee	Config.
1	1a	<i>R</i>	86	88	78	+45.8° (CHCl ₃)	94 ^{c)}	(3S , 4R)
2		<i>S</i>	91	87	82	-43.2° (CHCl ₃)	89 ^{c)}	(3R , 4S)
3	1b	<i>R</i>	79	88	84	-73.5° (acetone) ^{d)}	86 ^{e)}	(3S , 4R)
4		<i>S</i>	77	87	81	+71.5° (acetone) ^{d)}	84 ^{e)}	(3R , 4S)
5	1c	<i>R</i>	78	85	80	+81.7° (CHCl ₃)	84 ^{f)}	(3S , 4R)
6	1d	<i>R</i>	94	91	86	-82.1° (CHCl ₃)	91 ^{g)}	(3R , 4S)
7	1e	<i>R</i>	86	84				
8	1f	<i>R</i>	55	91				

a) Obtained in a quantitative yield. b) Determined by hplc analysis.⁷ c) Based on $[\alpha]_D^{25} +48.8^\circ$ (c 0.5, CHCl₃).¹⁰ d) Measured at 20 °C. e) Based on $[\alpha]_D^{20} -85.4^\circ$ (c 2.63, acetone).¹¹ f) Based on $[\alpha]_D^{25} +96.9^\circ$ (c 1, CHCl₃).¹⁰ g) Based on $[\alpha]_D^{25} -72.8^\circ$ (c 1.4, CHCl₃), 81% ee.²

Although the chiral recognition mechanism is not clear, the mechanism proposed by Noyori *et al.*,^{5b} could be applicable. The reduction would proceed through the preferential attack of (*R*)-BINAL-H to the carbonyl group attached to the *R* center of dicarboximide (**1**) from the convex face¹² to afford 5 β -hydroxy-2-pyrrolidinone, epimerizing easily to 5 α -isomer during work-up. The transition state(**5**) might be more favorable by the n/π^* attractive orbital interaction between the oxygen non-bonding orbital and the LUMO of the imide moiety (Figure 1).

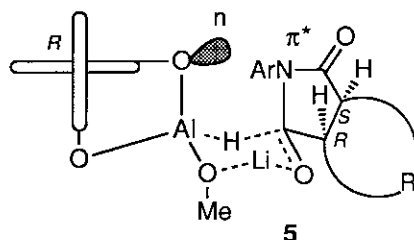


Figure 1

Removal of 4-methoxyphenyl group of lactam and further studies on the chiral recognition mechanism are now under progress.

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4. The starting dicarboxamides (**1a-f**) were readily prepared from *meso*-cyclic-1,2-dicarboxylic anhydrides and 4-methoxyaniline according to the known method.²
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6. The ratio of α and β isomer was found from the ¹H-nmr spectra to be approximately 1:9; C₅ α -OH, 5.06 ppm ($J < 1$ Hz); C₅ β -OH, 5.51 ppm ($J = 5.5$ Hz). For assignment, see; B. P. Wijnberg, H. E. Schoemaker, and W. N. Speckamp, *Tetrahedron*, 1978, **34**, 179.
7. The reduction was quenched by adding 10% HCl solution. Treatment of **2a** ($\alpha/\beta \approx 1/9$) with 10% HCl gave **2a** ($\alpha/\beta \approx 1/1.4$) at 0 °C for 10 min.
8. Hplc analysis was carried out under the following conditions: column, Opti-Pak XC (3.9 x 300 mm); mobile phase, hexane - 2-propanol (80 : 20), 1 ml / min; detector, 254 nm; retention time, (3*S*, 4*R*) **3a** (6.9 min), (3*R*, 4*S*) **3a** (10.3 min).
9. Cyclic lactones (**4**) are also important precursors for synthesis of Trandolapril,^{9a} Brefeldin A,^{9b} and so on.^{2,9c,11}; a) F. Brion, C. Marie, P. Mackiewicz, J. M. Roul, and J. Buendia, *Tetrahedron Lett.*, 1992, **33**, 4889. b) H. -J. Gais and T. Lied, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 145. c) H. -J. Gais and K. L. Lukas, *ibid.*, 1984, **23**, 142.
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