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

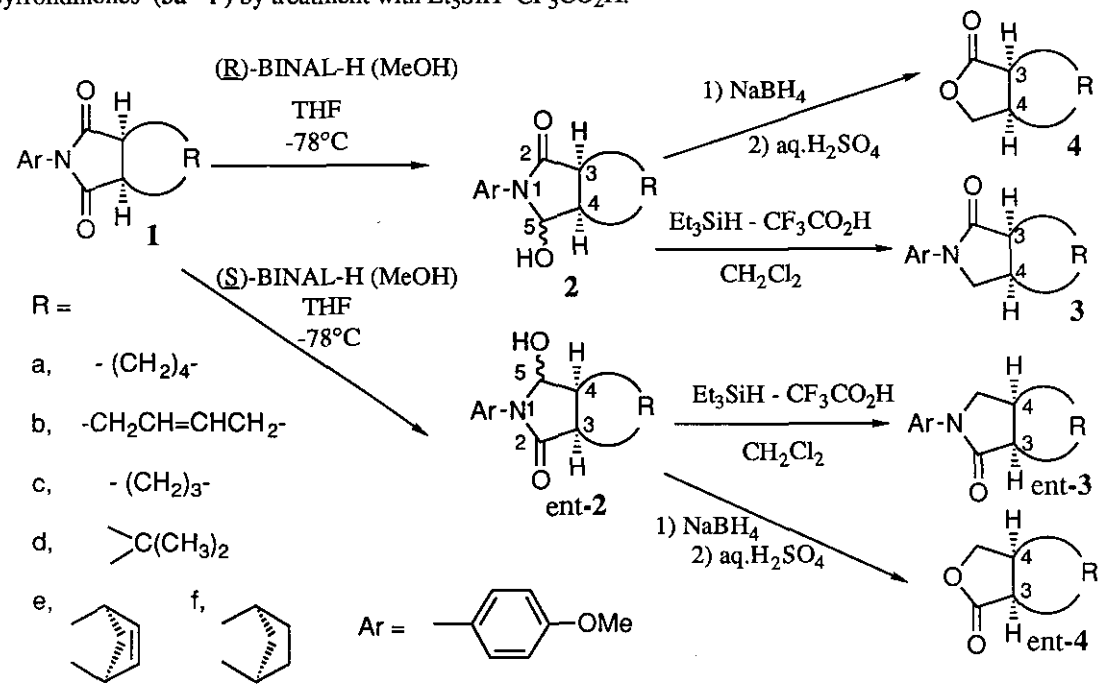
Masako Nakagawa and Tohru Hino

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 ($LiAlH_4$)- methanol (MeOH)- 1,1'-bi-2-naphthol complex (BINAL-H). Treatment of **2a - f** with triethylsilane (Et_3SiH) and trifluoroacetic acid(CF_3CO_2H) 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 tartrimide 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 Et_3SiH -CF_3CO_2H.



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 C_5 α– and C_5 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 Et_3SiH-CF_3CO_2H 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

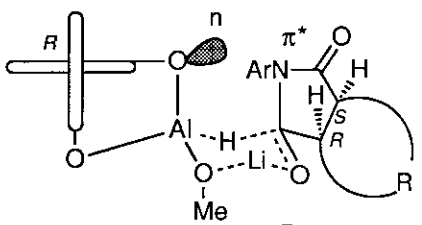
by reduction with (S)-BINAL-H, was converted into the lactone(**4a**)(89% ee; 3R, 4S)[10] and the lactam **3a** (87% ee; 3R,4S) in high yields, respectively. Similarly, reduction of dicarboximides (**1b - f**) with (R)- or (S)-BINAL-H afforded 5-hydroxy-2-pyrrolidinones (**2b - f**) with high enantioselectivity (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(%)	**4** $[\alpha]_D^{25}$ (c 1.0)	**4** % ee	**4** Config.
1	**1a**	R	86	88	78	+45.8° ($CHCl_3$)	94[c]	(3S, 4R)
2		S	91	87	82	-43.2° ($CHCl_3$)	89[c]	(3R, 4S)
3	**1b**	R	79	88	84	-73.5° (acetone)[d]	86[e]	(3S, 4R)
4		S	77	87	81	+71.5° (acetone)[d]	84[e]	(3R, 4S)
5	**1c**	R	78	85	80	+81.7° ($CHCl_3$)	84[f]	(3S, 4R)
6	**1d**	R	94	91	86	-82.1° ($CHCl_3$)	91[g]	(3R, 4S)
7	**1e**	R	86	84				
8	**1f**	R	55	91				

a) Obtained in a quantitative yield. b) Determined by hplc analysis.[7] c) Based on $[\alpha]_D^{25}$ +48.8°(c 0.5,$CHCl_3$).[10] d) Measured at 20 °C. e) Based on $[\alpha]_D^{20}$ -85.4°(c 2.63, acetone).[11] f) Based on $[\alpha]_D^{25}$ +96.9°(c 1, $CHCl_3$).[10] g) Based on $[\alpha]_D^{25}$ -72.8°(c 1.4, $CHCl_3$), 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 face[12] to afford 5β-hydroxy-2-pyrrolidinone, epimerizing easily to 5α-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).



5

Figure 1

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

REFERENCES AND NOTES

1. Some representative reports:a) Y. Arai, T. Kontani, and T. Koizumi, Tetrahedron: Asymmetry, 1992, **3**, 535. b) W. N. Speckamp and H. Hiemstra, Tetrahedron, 1985, **41**, 4367.
2. T. Mukaiyama, H. Yamashita, and M. Asami, Chem. Lett., 1983, 385. For a related strategy, see; S. A. Miller and A. R. Chamberlin, J. Org. Chem., 1989, **54**, 2502.
3. S. A. Miller and A. R. Chamberlin, J. Am. Chem. Soc., 1990, **112**, 8100.
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]
5. a)R. Noyori, I. Tomino, and Y. Tanimoto, J. Am. Chem. Soc., 1979, **101**, 3129. b)R. Noyori, I. Tomino, Y. Tanimoto, and M. Nishizawa, J. Am. Chem. Soc., 1984, **106**, 6709.
6. The ratio of α and β isomer was found from the ^{1}H-nmr spectra to be approximately 1:9 ; C5α-OH, 5.06 ppm (J < 1 Hz) ; C5β-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** (α/β ≒ 1/9) with 10% HCl gave **2a** (α/β ≒ 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, (3S, 4R) **3a** (6.9 min), (3R, 4S) **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.
10. I. J. Jakovac, H. B. Goodbrand, K. P. Lok, and J. B. Jones, J. Am. Chem. Soc., 1982, **104**, 4659.
11. H. -J. Gais, K. L. Lukas, W. A. Ball, S. Braun, and H. J. Lindner, Liebigs Ann. Chem., 1986, 687.
12. cis-1,2,3,6-Tetrahydrophthalic anhydride was suggested to exist preferentially as a folded conformer. R. M. Larter, R. E. R. Craig, A. C. Craig, and B. P. Mundy, J. Org. Chem., 1977, **42**, 1259.

Received, 30th November, 1992