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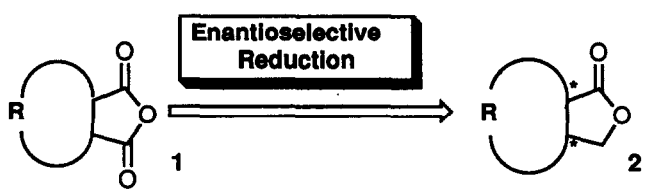
Highly Enantioselective Reduction of *Meso*-1,2-Dicarboxylic Anhydrides

Kenji Matsuki,* Hirozumi Inoue, and Mikio Takeda

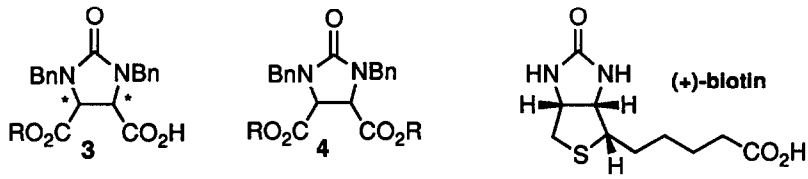
Organic Chemistry Reseach Laboratory, Tanabe Seiyaku Co., Ltd., 2-2-50 Kawagishi, Toda, Saitama 335, Japan.

Abstract: Optically active lactones (**2a-2g**) were synthesized by highly enantioselective reduction of readily available *meso*-1,2-dicarboxylic anhydrides (**1a-1g**) using lithium aluminum hydride -ethanol - 1,1'-bi-2-naphthol complex (BINAL-H).

Enantioselective differentiation of prochiral functional groups in a symmetrical bifunctional compound such as *meso* compounds is an important strategy for creating new chiral centers.[1] Enantioselective synthesis of chiral lactones **2** can be provided by enantioselective reduction of a carbonyl group in *meso*-1,2-dicarboxylic anhydrides **1** with two carbon centers of opposite chirality. However enantioselective reduction of *meso*-1,2-dicarboxylic anhydrides **1** has scarcely been reported. Osakada and his colleagues [2] reported the asymmetric synthesis of γ-lactones **2** by the hydrogenation of **1** using a Ru(II) complex with chiral phosphine ligand as a catalyst, but the enantioselectivity was very low. On the other hand, the excellent chiral recognition ability of lithium aluminum hydride - ethanol - 1,1'-bi-2-naphthol complex (BINAL-H) in the reduction of carbonyl groups has been reported by Noyori and his colleagues.[3] Their reported substrates, however, were restricted to unsaturated ketones.

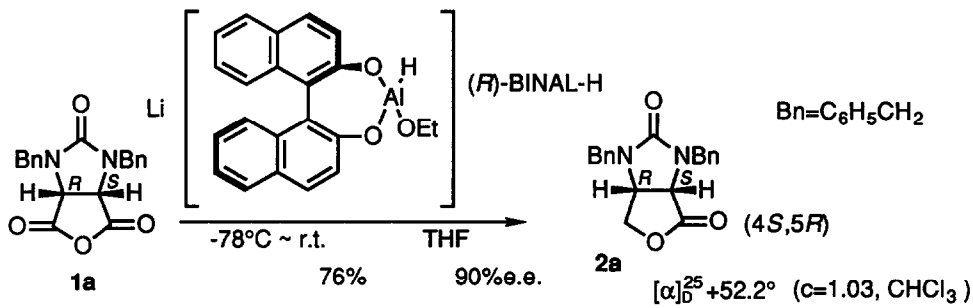


In this paper we wish to report the efficient enantioselective reduction of the anhydrides (**1a-1g**) using BINAL-H to produce the corresponding chiral lactones (**2a-2g**) in high yield.

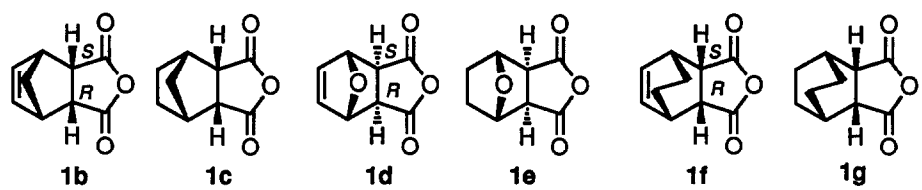


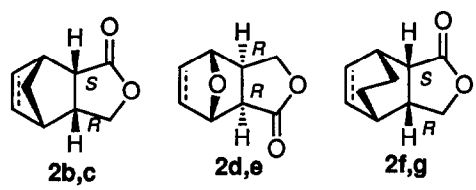
(4*S*,5*R*)-1,3-Dibenzyl-5-hydroxymethyl-2-oxoimidazolidine-4-carboxylic acid lactone **2a**, a key intermediate for the synthesis of (+)-biotin,[4] has been synthesized by chemoselective reduction of the optically active half-ester **3**.[5]

As an alternative method for the synthesis of (+)-biotin, we attempted to prepare (4*S*,5*R*)-**2a** by enantioselective reduction of *meso*-anhydride **1a**. The reduction of **1a** using (*R*)-BINAL-H in THF at -78°C and then warming gradually to room temperature followed by treatment with acid gave the lactone **2a** with 90% e.e. in 76% yield which was enriched to 95% e.e. by recrystallization from benzene-cyclohexane (Scheme 1).



Scheme 1





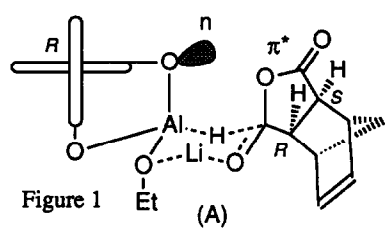


Figure 1 (A)

Chiral bicyclo[2.2.1]heptane lactones **2b,c** can be utilized as building blocks for the synthesis of prostanoids,[6] prostaglandin,[7] boschnialactone and the potent thromboxane A_2 (TXA_2)/prostaglandin H_2 (PGH_2) receptor antagonist,[8,9] and β-santalene.[10] The 7-oxabicyclo[2.2.1]heptane derivatives **2d,e** also can serve as versatile building blocks in the synthesis of PGH_1 analogues,[12a] TXA_2/PGH_2 analogues[12b] as a thromboxane-receptor agonist and antagonist, cyclooxygenase inhibitors,[13] and others.

Application of the (*R*)-BINAL-H reduction to various anhydrides (**1b-g**) which were commercially available or easily prepared afforded the (+)-lactones (**2b-g**) with high enantioselectivity (83 - 99%ee). The results are summarized in Table 1. The enantiomeric excess of the lactones (**2b-g**) were determined on the basis of their optical rotation in comparison with the value reported in the literature.

The reduction of anhydrides (**1a-c,f, g**) was enantiotopically selective for the carbonyl group attached to the chiral center with *R*-configuration, while the reduction of anhydrides (**1d,e**) was selective for that attached to the *S* centers. Increase of steric bulkiness in concave face improved the enantioselectivity (entry 1 and 2), while increase of steric bulkiness in convex face lowered the enantioselectivity (entry 3 and 4). When (*S*)-BINAL-H was used, the (-)-lactone was obtained with high enantioselectivity (entry 6). Since the both enantiomers of 1,1'-bi-2-naphthol are commercially available, the lactone of the desired configuration can be synthesized by use of an appropriate enantiomer of binaphthol. Although the chiral recognition mechanism is not clear, the mechanism proposed by Noyori et.al.[3a] can be applied.This reduction probably proceeds by the preferential attack of (*R*)-BINAL-H to the carbonyl group attached to the *R* center of anhydride **1b** from the convex face to afford (2*S*,3*R*)-hydroxylactone[17] intermediate in the first stage and then leads to hydroxycarboxylate or lactone **2b** by further reduction with excess of (*R*)-BINAL-H at the second stage. By the n/π* attractive orbital interaction between the oxygen non-bonding orbital and the LUMO of the anhydride moiety, the transition state (A) might be more favorable (Figure 1).

Table 1. The Enantioselective Reduction of 1b-g Using $LiAlH_4$ -EtOH -(*R*)-(+)-1,1'-Bi-2-naphthol

Entry	Anhydride	Lactone	Yield(%)	e.e. (%)[a]	$[\alpha]_D^{25}(CHCl_3)$	Reported$[\alpha]_D^{25}$	Ref.
1	**1b**	**2b** (2*S*,3*R*)	69	84 [16]	+120.7°	+143.2°	11)
2	**1c**	**2c** (2*S*,3*R*)	66	88	+134.5°	+153.28°	10)
3	**1d**	**2d**(3a*R*,7a*R*)	63	99	+153.5°	+155.0°	15)
4	**1e**	**2e** (3a*R*,7a*R*)	72	83	+95.1°	+114.2°	14)
5	**1f**	**2f** (2*S*,3*R*)	68	99	+92.6°	+92.0°	11)
6	**1f**[b]	**2f** (2*R*,3*S*)	72	94	-86.8°		
7	**1g**	**2g** (2*S*,3*R*)	65	95	+107.1°	+113.0°	11)

a) Determined on the basis of $[\alpha]_D^{25}$ value in comparison with the reported value.

b) (*S*)-BINAL-H was used.

A typical procedure: Under Ar atmosphere to a stirred suspension of $LiAlH_4$ (270 mg, 7mmol) in THF (10 ml) was added ethanol (320 mg, 6.94mmol) in THF (10 ml) at 0°C. Then, (*R*)-(+)-1,1'-bi-2-naphthol (2.00 g, 6.98mmol) in THF (30 ml) was added dropwise at 0°C. The white-cloudy mixture was stirred at an ambient temperature for 2 hr. The mixture was cooled to -78°C and **1f** (270 mg, 1.52mmol) in THF (10 ml) was added to the mixture during a period of 10 min. After being stirring at -78°C for 5hr, the reaction mixture was gradually warmed up to room temperature. After acidic work up and removal of (*R*)-binaphthol by recrystallization (recovered 1.74 g, 84%), the filtrates were concentrated and chromatographed on aluminum oxide(eluent; $CHCl_3$-*n*-hexane). **2f** was obtained as a colorless solid (Table 1, entry 5).

In conclusion, the reduction of *meso*-1,2-dicarboxylic anhydrides using BINAL-H efficiently proceeds to give lactones in a highly enantioselective manner.

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5. The optically active **3** was prepared by optical resolution of racemic **3** or by enzymatic hydrolysis of diester **4** using pig liver esterase.;Iriuchijima, S.; Hasegawa, K.; Tsuchihashi, G. *Agric. Biol. Chem.*, **1982**, *46*, 1907.
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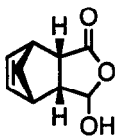
16. 84.5%e.e. This value was determined by HPLC analysis using a 4.6 x 150mm CHIRALCEL OB-H (DAICEL Chemical Industries,Ltd.) and the mobile phase composed of n-hexane and ethanol in a ratio of 250:1 (v/v). The flow rate was maintained at 1.0 ml/min, and the procedure was carried out at ambient temperature. The effluent was monitored at 210nm. The retention time of (+)-isomer was 37.6 min. and (-)-isomer was 45.3min.
17. The hydroxylactone intermediate.



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