

Simplified Chiral Aminolysis
of Prochiral σ -Symmetric Dicarboxylic Anhydrides
with Sodium Salt of 4(S)-IPTT¹⁾

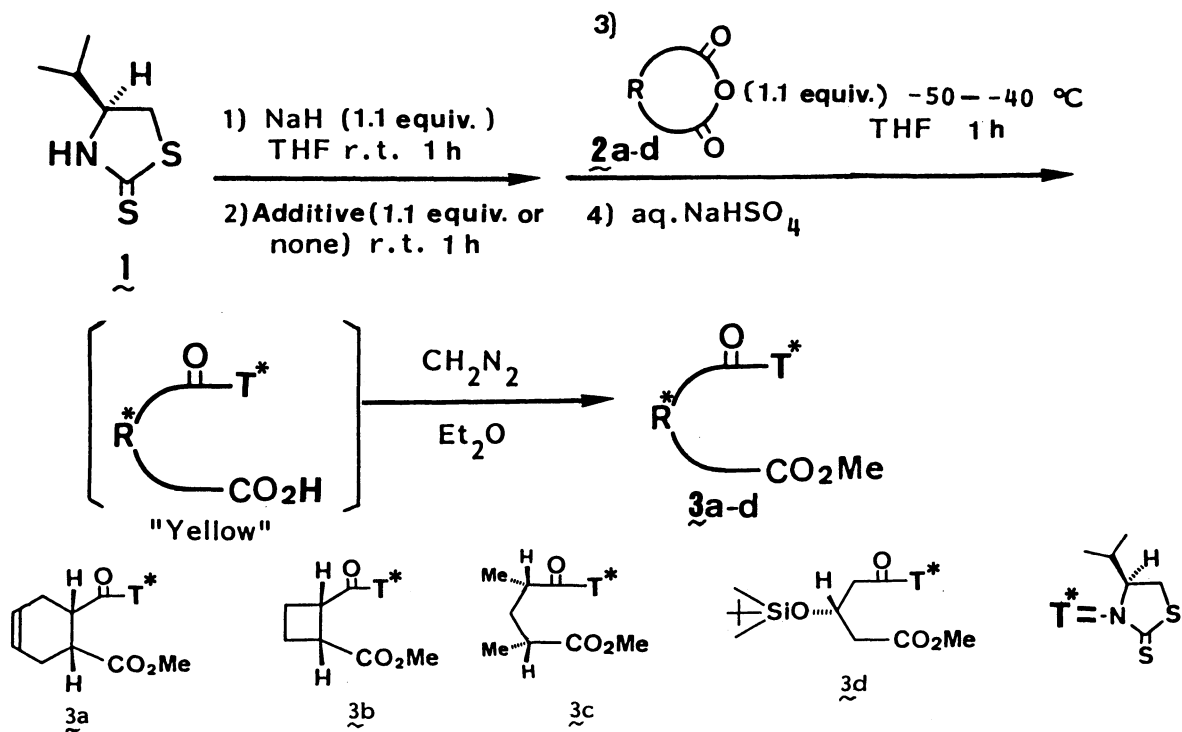
Yoshimitsu NAGAO,* Yuichi HAGIWARA, Yukari HASEGAWA,
Masahito OCHIAI, Takehisa INOUE,^{††} Motoo SHIRO,[†] and Eiichi FUJITA^{†††}
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611
[†]Shionogi Research Laboratories, Shionogi & Co. Ltd., Fukushima-ku, Osaka 553
^{††}Kyoto Pharmaceutical University, Misasagi, Yamashina-ku, Kyoto 607
^{†††}Osaka University of Pharmaceutical Sciences, Kawai, Matsubara, Osaka 580

Highly enantioselective chiral aminolysis of cis-4-cyclohexen-1,2-ylenebis(carboxylic acid) anhydride has been performed by employing sodium salt of 4(R)-isopropyl-1,3-thiazolidine-2-thione in THF-DMSO. Other chiral aminolyses of prochiral σ -symmetric dicarboxylic anhydrides such as cis-cyclobutan-1,2-ylenebis(carboxylic acid) anhydride, meso-2,4-dimethylglutaric anhydride, and 3-[(t-butyldimethylsilyl)oxy]glutaric anhydride were similarly investigated.

Chiral Differentiation between two identical carboxyl groups in prochiral σ -symmetric dicarboxylic acids utilizing enzymatic or nonenzymatic procedure should be a rational strategy for chiral syntheses of biologically active compounds because the resultant chiral product(s) can be available for its (or thier) further "enantioconvergent" transformations on the basis of the latent σ -symmetry.²⁾ Previously, we disclosed a novel nonenzymatic chiral induction into prochiral σ -symmetric dicarboxylic acids employing a functional heterocycle, 4(R or S)-methoxycarbonyl-1,3-thiazolidine-2-thione.²⁻⁵⁾ In the course of our series of studies on the chiral induction utilizing C4-chiral thiazolidines,³⁻⁷⁾ we anticipated that 4(S)-isopropyl-1,3-thiazolidine-2-thione [4(S)-IPTT] (1)⁷⁾ would be available for chiral aminolysis of prochiral dicarboxylic anhydrides 2 [e. g., cis-4-cyclohexen-1,2-ylenebis(carboxylic acid)anhydride (2a)] (See Scheme 1).¹⁾ From the viewpoint that anhydride 2a is regarded as a useful prochiral precursor for the chiral synthesis of carbapenems and (+)-carbacyclin,^{8,9)} we firstly attempted its chiral aminolysis with 4(S)-IPTT(1) as follows.

A solution of 60% NaH (coated type with mineral oil, 220 mg, 5.5 mmol) in THF (6 ml) was added to a solution of 4(S)-IPTT (1) (805 mg, 5 mmol) in THF (5 ml) at 0 °C with stirring. The mixture was stirred at 0 °C for 10 min and then anhydrous DMSO (0.43 ml, 6 mmol) was added at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was added to a solution of 2a (836.8 mg, 5.5 mmol) in THF (6 ml) at -50 °C. The mixture was stirred at

-50 - -40 °C for 1 h, acidified with saturated aqueous NaHSO₄ (20 ml), and extracted with CH₂Cl₂. The usual work-up of the CH₂Cl₂ extract gave a crude carboxylic acid, which was treated with CH₂N₂ in ether affording methyl ester **3a** [1.30 g (80.2% yield); 94% diastereomer excess (de), [α]_D²⁴ +217.9° (c 1.12, CHCl₃)] as a yellow oil after chromatographic purification (Run 5 in Table 1). This simple chiral induction¹⁰⁾ into **2a** can be promised for the big-scale synthesis of the useful chiral synthon for carbapenems and (+)-carbacyclin.^{8,9)}



Scheme 1.

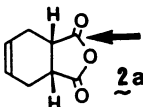
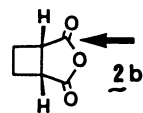
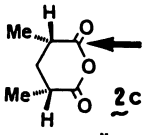
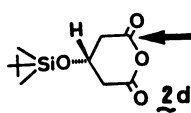
The absolute configuration of the product **3a** was established by its chemical conversion to the antipodal compound **4** [62% overall yield from **3a**; [α]_D²⁵ +78.5° (c 0.7, acetone)] of the known lactone [[α]_D²⁵ - 85.4° (c 2.63, acetone)]⁹⁾ via reduction of **3a** with NaBH₄ in aqueous EtOH followed by lactonization with a catalytic amount of TsOH in toluene at 110 °C for 3 h.

Although similar aminolyses of **2a** with sodium salt of 4(S)-IPTT were carried out in the absence or in the presence of some additives such as HMPA, 18-Crown-6, and TMEDA, their results might be unsatisfactory with respect to the chemical and/or optical yield(s) of **3a** (Runs 1-4 in Table 1).

Based on the result of **2a**, chiral aminolyses of anhydrides **2b** - **2d** with or without 1.2 mol equiv. of DMSO as an effective additive were similarly examined by employing sodium salt of 4(S)-IPTT(**1**). All results were listed in Table 1 (Runs 6 - 11). The product (Run 7) obtained from the chiral aminolysis of *cis*-4-cyclobutan-1,2-ylenebis(carboxylic acid) anhydride (**2b**) proved to be the **3b**-excess compound by its chemical conversion to the antipodal compound **5** [42% overall yield from **3b**; [α]_D²⁴ - 77.9° (c 1.2, CHCl₃)] of the known lactone¹⁰⁾ [[α]_D²⁴ + 118.7° (c 10, CHCl₃)] in the same manner as the case of **3a**. In anhydride **2c** (Run

9), the $\underline{3c}$ - excess product was obtained, which was confirmed by its aminolysis with piperidine (1.0 mol equiv.) in CH_2Cl_2 at 0°C giving the known amide $\underline{6}$ [91% yield; $[\alpha]_D^{20} + 0.92^\circ$ (c 3.5, CHCl_3); lit.⁵⁾ $[\alpha]_D^{25} + 2.45^\circ$ (c 3.26, CHCl_3)]. The stereochemistry of the major aminolysis product (Run 10) of $\underline{2d}^{10)}$ was clarified to be $\underline{3d}$ [38.8% yield; mp $64 - 65^\circ\text{C}$ (ether - hexane); $[\alpha]_D^{20} + 219^\circ$ (c 0.8, CHCl_3)] by its X-ray analysis (Fig. 1) after separation of the major diastereomer on a silica gel column [hexane-AcOEt (4 : 1)].

Table 1. Chiral aminolysis of prochiral dicarboxylic anhydrides $\underline{2a} - \underline{d}$ with sodium salt of 4(S)-IPTT (1)

Run	Anhydride	Additive	Yield/% of $\underline{3a} - \underline{d}$	Diastereomer excess/% ^{a)}
1		None	96 ($\underline{3a}$ excess)	86
2	"	HMPA	48 ($\underline{3a}$ excess)	96
3	"	18-Crown-6	6 ($\underline{3a}$ excess)	76
4	"	TMEDA	68 ($\underline{3a}$ excess)	82
5	"	DMSO	80 ($\underline{3a}$ excess)	94
6		None	81 ($\underline{3b}$ excess)	62
7	"	DMSO	85 ($\underline{3b}$ excess)	68
8		None	87 ($\underline{3c}$ excess)	28 ^{b)}
9	"	DMSO	86 ($\underline{3c}$ excess)	46 ^{b)}
10		None	62 ($\underline{3d}$ excess)	40
11	"	DMSO	46 ($\underline{3d}$ excess)	16

a) Checked by HPLC unless otherwise stated. b) Checked by $^1\text{H-NMR}$.

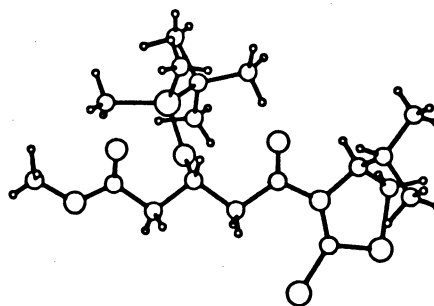
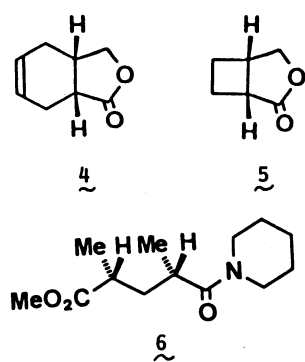


Fig. 1. Perspective view of the crystallographic structure of compound $\underline{3d}$.

We assigned a structure 7 to the sodium salt of 4(S)-IPTT based on its ^{13}C -NMR spectrum (δ 180 ppm : $>\text{C}=\text{S}$)¹²⁾ in d8-THF and X-ray analysis of 3-(p-bromobenzyl)-4(S)-isopropyl-1,3-thiazolidine-2-thione(8) [mp 108 °C (CHCl₃-hexane)] (Fig. 2). Thus, stereochemical outcome of the chiral aminolysis of anhydrides 2a can be rationalized by assuming a transition state (Fig. 3) where the sodium salt 7 attacks the S-site carbonyl carbon from the least hindered convex side. Another transition state where compound 7 may approach the R-site carbonyl carbon on the convex face should be eliminated due to the severe steric hindrance between two axial-like protons of 2a and C4- and C5-protons of 7. In other three cases of 2b - 2d, the similar consideration would also be available for their stereochemical results.

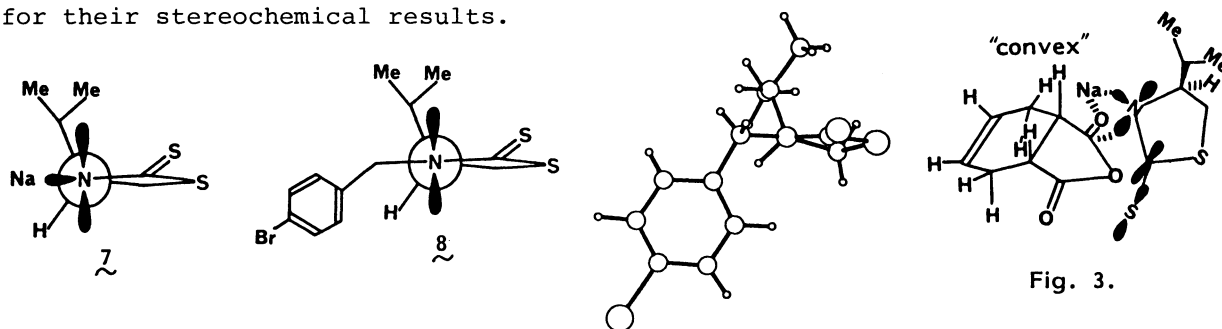


Fig. 2. X-Ray analysis of compound 8.

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