Asymmetric Transformation of (*RS*)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic Acid via Salt Formation with (1*S*)-10-Camphorsulfonic Acid

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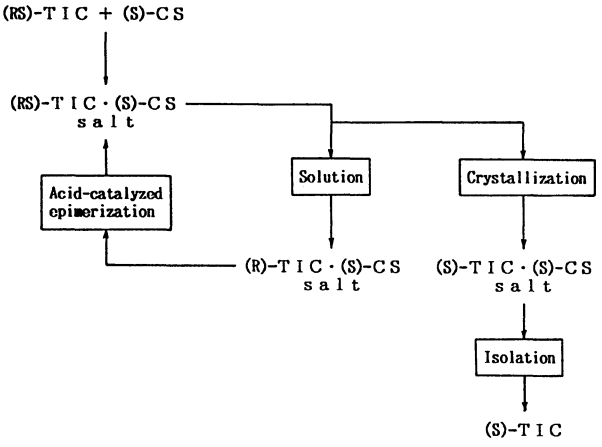
Synopsis. Asymmetric transformation of (*RS*)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid [(*RS*)-TIC] by use of (1*S*)-10-camphorsulfonic acid [(*S*)-CS] as a resolving agent gave a salt of (*S*)-TIC with (*S*)-CS with 90% optical purity in hexanoic acid. The TIC obtained from the salt was purified to give optically pure (*S*)-TIC in 80% yield based on the starting (*RS*)-TIC.

(*S*)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid [abbreviated as (*S*)-TIC] is a useful intermadiate for synthesizing antihypertensive agents such as (*S*)-2-(3-mercapt-1-oxopropyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid derivatives.[1–3] Although (*S*)-TIC has been obtained by condensation of L-phenylalanine [L-Phe] with formaldehyde in concentrated hydrochloric acid,[4,5] this reaction gives partially racemized (*S*)-TIC. Acquisition of optically pure (*S*)-TIC, therefore, seems to require a tedious procedure.[4,5]

We found that optically active TIC was apt to racemize only on heating in carboxylic acids and that optical resolution of (*RS*)-TIC by use of (1*S*)-10-camphorsulfonic acid [(*S*)-CS] as a resolving agent gave a salt of (*S*)-TIC with (*S*)-CS as the less soluble diastereomeric salt. In view of this, an asymmetric transformation of (*RS*)-TIC was attempted here via salt formation with (*S*)-CS on heating in a carboxylic acid to convert (*RS*)-TIC efficiently into (*S*)-TIC, as illustrated in Scheme 1.

In what follows, (*S*)·(*S*) salt denotes the salt of (*S*)-TIC with (*S*)-CS, (*R*)·(*S*) salt that of (*R*)-TIC with (*S*)-CS, and (*S*)·(*R*) salt that of (*S*)-TIC with (*R*)-CS.



Scheme. 1. Illustration of asymmetric transformation of (*RS*)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid.
TIC: 1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid.
(S)-CS: (1*S*)-10-Camphorsulfonic acid.

Experimental

Materials. L-Phe was purchased from Kokusan Chemical Works, Ltd., DL-Phe from Sigma Chemicals Co., and (*S*)- and (*RS*)-CS and (*R*)-CS monohydrate from Wako Pure Chemicals Ind.

(*RS*)- and (*S*)-TIC were prepared by a reaction of the corresponding Phe with formaldehyde in concentrated hydrohchloric acid.[4,5] (*RS*)-TIC was obtained in 69% yield and (*S*)-TIC ($[\alpha]_D^{20}$ −143° (*c* 1.00, 1 mol dm^{-3} aqueous sodium hydroxide)) in 78% yield. (*S*)-TIC was purified via formation of a salt with (*S*)-CS as described below.

Preparation of Standard Salts. (*S*)-TIC (4.43 g, 25.0 mmol) was added to a 10 cm^3 methanol solution containing 25.0 mmol of (*S*)-CS (5.81 g) or (*R*)-CS monohydrate (6.26 g). After stirring for 30 min in an ice bath, the mixture was allowed to stand overnight at 5 °C. The precipitated salt was collected by filtration, washed with diethyl ether, and dried. (*S*)·(*S*) salt: Mp 268—269 °C; $[\alpha]_D^{20}$ −41.3° (*c* 1.00, methanol). Found: C, 58.54; H, 6.58; N, 3.45%. Calcd for $C_{20}H_{27}NO_6S$: C, 58.66; H, 6.65; N, 3.42%). (*S*)·(*R*) salt: Mp 249—250 °C; $[\alpha]_D^{20}$ −85.1° (*c* 1.00, methanol). Found: C, 58.61; H, 6.62; N, 3.33%.

Asymmetric Transformation. A mixture of 1.77 g (10.0 mmol) of (*RS*)-TIC and 2.09 g (9.00 mmol) of (*S*)-CS in 15 cm^3 of butanoic acid or hexanoic acid was stirred for 2—25 h at 120 °C. After further addition of 0.23 g (1.0 mmol) of (*S*)-CS, the mixture was stirred for 5 min and then for 0.5 h in an ice bath. The (*S*)·(*S*) salt formed was collected by filtration, thoroughly washed with diethyl ether, and dried; the optical purity of the salt obtained was determined on the basis of the specific rotations of the standard salts.

After adding an equivalent of triethylamine to a solution of the salt obtained in methanol (25 cm^3 g^{-1}), the mixture was stirred for 1 h in an ice bath. The precipitated (*S*)-TIC was collected by filtration, washed with methanol, and dried. The optical purity was determined on the basis of the specific rotation of (*S*)-TIC; lit,[5] $[\alpha]_D^{19}$ −177.4° (*c* 1.00, 1 mol dm^{-3} aqueous sodium hydroxide).

The (*S*)-TIC (2.00 g) obtained by reaction for 12 h in butanoic acid and those for 20 and 25 h in hexanoic acid were added to a solution containing an equivalent of (*S*)-CS in 17 cm^3 of methanol. After stirring the mixture for 20 min at 20 °C, the (*S*)·(*S*) salt formed was collected by filtration, washed with diethyl ether, and dried. The (*S*)·(*S*) salt was treated with triethylamine in methanol to give optically pure (*S*)-TIC.

Optical Resolution. (*RS*)-TIC (1.77 g, 10.0 mmol) was added to a solution of 2.32 g (10.0 mmol) of (*S*)-CS in 10 cm^3 of methanol. After stirring the mixture for 0.5 h at 20 °C, the formed (*S*)·(*S*) salt of 74.7% optical purity was collected by filtration, washed with diethyl ether, and dried; yield, 40.6% (1.66 g) based on 4.09 g of the salt; $[\alpha]_D^{20}$ −25.3° (*c* 1.00, methanol). The filtrate was dried under reduced pressure to give the (*R*)·(*S*) salt of 57.3% optical purity in 51.1% (2.10 g) yield; $[\alpha]_D^{20}$ +58.1° (*c* 1.00, methanol). The (*S*)·(*S*) and

(*R*)·(*S*) salts obtained were treated with triethylamine in methanol to give (*S*)- and (*R*)-TIC; (*R*)-TIC of 56.1% optical purity was obtained in 49.0% (0.867 g) yield; $[\alpha]_D^{20}$ +99.6° (*c* 1.00, 1 mol dm^{-3} aqueous sodium hydroxide). The (*S*)-TIC obtained was purified via salt formation with (*S*)-CS to obtain (*S*)-TIC of 99.2% optical purity in 33.3% (0.590 g) yield; $[\alpha]_D^{20}$ −176° (*c* 1.00, 1 mol dm^{-3} aqueous sodium hydroxide).

Rate Constant for Racemization. (*S*)-TIC (1.00 mmol) and 0.900, 0.950, or 1.00 mmol of (*RS*)-CS were immediately dissolved in 50 cm^3 of acetic acid, propanoic acid, or butanoic acid at 120 °C, respectively. Portions of the solution were pipetted out at appropriate time intervals and the optical rotation at 589 nm was measured with a Union Giken PM-101 digital polarimeter equipped with a quartz cell of 0.500 dm path length. The rate constant for racemization (k_R/s^{-1}) was calculated by least-squares fitting to the equation

$$\ln \alpha_0/\alpha_t = k_R \cdot t, \quad (1)$$

where α_t is the optical rotation at time t and α_0 that extrapolated to zero time.

Results and Discussion

Racemization of (*S*)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic Acid. The racemization of (*S*)-TIC could be regarded as a pseudo first-order reaction because a linear relationship was found between ln α_0/α_t and time t. The rate constant (k_R/s^{-1}) and half-life period ($t_{1/2}$/s) are listed in Table 1.

The racemization of (*S*)-TIC seems to start with the protonation to the carbonyl oxygen atom by the carboxylic acid used as solvent, followed by the formation of an enol and the concomitant α-proton abstraction by the resulting carboxylate anion, and hence should be influenced by the acidity of the carboxylic acid.[6,7] The acidity constant (pK_a) of acetic acid, propanoic acid, and butanoic acid at 120 °C were estimated from the data at 0—60 °C[8] to be 5.07, 5.21, and 5.27, respectively. Since the k_R value paralells the pK_a value, the rate-determining step seems to be the enol formation.[7] In addition, the k_R value increased with a decrease in the amount of (*RS*)-CS, as seen in Table 1.

Asymmetric Transformation of (*RS*)-1,2,3,4,-Tetrahydro-3-isoquinolinecarboxylic Acid. In the optical resolution by use of (*S*)-CS, the (*S*)·(*S*) salt was obtained as the less soluble diastereomeric salt, as mentioned in the Experimental section. The asymmetric transformation, based on the results of the optical resolution and racemization, gave the (*S*)·(*S*) salt of 75—79% optical purity in 87—90% yield by reaction for 10—14 h in butanoic acid at 120 °C, as shown in Table 2. The (*S*)-TIC obtained from the (*S*)·(*S*) salt of 79% optical purity was purified to give (*S*)-TIC of 98% optical purity in 74% yield, based on the starting (*RS*)-TIC.

The epimerized salt seems to have a relatively high solubility in butanoic acid at 120 °C, and hence cooling of the reaction mixture would lower the optical purity of the resulting (*S*)·(*S*) salt. The (*S*)·(*S*) and (*R*)·(*S*) salts seem to be less soluble in higher carboxylic acids. Although the rates of racemization in the higher carboxylic acids could not be measured because of a poor solubility of (*S*)-TIC, the estimated pK_a value (5.26)[9] of hexanoic acid at 120 °C would suggest that the rate in hexanoic acid is approximately equal to that in butanoic acid. The asymmetric transformation, therefore, was carried out in hexanoic acid and gave the (*S*)·(*S*) salt of 90% optical purity in 86% yield by reaction for 20 and 25 h. Optically pure (*S*)-TIC was obtained in 80% yield by purification of the (*S*)-TIC obtained from these salts.

To summarize, the present results demonstrate that

Table 1. Rate Constant and Half-Life Period for Racemization[a]

Conditions		k_R[c]	$t_{1/2}$[d]
Carboxylic acid	(*RS*)-CS[b] mmol	10^{-4} s^{-1}	10^3 s
AcA[e]	0.900	4.19	1.65
PrA[f]	0.900	4.82	1.44
BuA[g]	0.900	7.75	0.894
	0.950	5.71	1.21
	1.00	2.77	2.50

a) (*S*)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid 1.00 mmol; carboxylic acid 50 cm^3; temperature 120 °C. b) (*RS*)-CS: (1*RS*,4*SR*)-10-Camphorsulfonic acid. c) k_R: Rate constant for racemization. d) $t_{1/2}$: Half-life period. e) Acetic acid. f) Propanoic acid. g) Butanoic acid.

Table 2. Asymmetric Transformation of (*RS*)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic Acid[a]

Carboxylic acid	Reaction time	(*S*)·(*S*) Salt[b] Yield	(*S*)·(*S*) Salt[b] Optical purity	(*S*)-TIC Yield[d]	(*S*)-TIC Optical purity
	h	g [%[c]]	%	%	%
BuA[e]	2	3.79 [92.7]	22.7	89.2	21.6
	4	3.73 [91.2]	42.5	87.0	36.9
	6	3.71 [90.7]	56.9	87.5	55.1
	8	3.68 [90.0]	64.8	84.5	65.9
	10	3.58 [87.5]	74.9	83.2	74.4
	12	3.60 [88.0]	78.7	86.1	76.6
				73.6[g]	98.0
	14	3.56 [87.0]	76.6	85.6	75.6
HxA[f]	2	3.79 [92.7]	11.7	89.6	10.1
	4	3.69 [90.2]	16.4	88.0	14.2
	6	3.56 [87.0]	42.4	84.7	42.3
	8	3.55 [86.8]	55.8	85.1	54.7
	10	3.75 [91.7]	65.2	88.6	63.1
	15	3.57 [87.3]	80.4	83.3	80.8
	20	3.59 [87.8]	90.1	86.5	90.2
				80.0[g]	100
	25	3.57 [87.3]	89.9	86.1	90.0
				79.4[g]	100

a) Conditions: (*RS*)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid [(*RS*)-TIC] 10.0 mmol; (1*S*)-10-camphorsulfonic acid [(*S*)-CS] 9.00 mmol; carboxylic acid 15 cm^3; temperature 120 °C. b) (*S*)·(*S*) Salt: Salt of (*S*)-TIC with (*S*)-CS. c) The yield was calculated on the basis of 4.09 g (10.0 mmol) of the (*S*)·(*S*) salt. d) The yield was calculated on the basis of 1.77 g (10.0 mmol) of (*S*)-TIC. e) Butanoic acid. f) Hexanoic acid. g) The (*S*)-TIC obtained was purified by formation of a salt with (*S*)-CS.

the asymmetric transformation of (*RS*)-TIC is an efficient means to obtain optically pure (*S*)-TIC.

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