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Stereochemical Studies. LX.[1] Neighboring Phenyl Group Participation. I. Stereospecific Transformation of L-Phenylalanine to Optically Active Tropic Acid[2]

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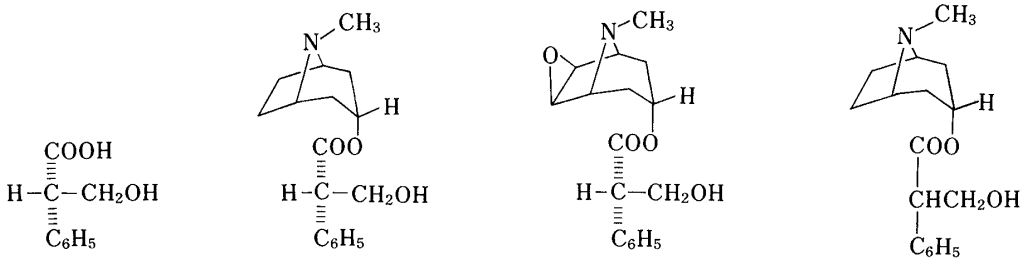
Trifluoroacetolysis of (*S*)-3-phenyllactic acid ester sulfonate((*S*)-**7**), obtained from L-phenylalanine *via* nitrous acid deamination followed by ethanolysis, afforded (*R*)-tropic acid ester ((*R*)-**8**) in good yield by phenyl migration with inversion, while acetolysis followed by ethanolysis afforded (*R*)-phenyllactic acid ester ((*R*)-**6b**) in good yield by substitution with inversion. Mechanistic aspects of these reactions are discussed.

Keywords——neighboring group participation; solvolysis; acetolysis; trifluoroacetolysis; tropic acid; phenonium ion; rearrangement; retention; inversion

Tropic acid (**1**) is the acid moiety of some medicinally useful tropane alkaloids such as hyoscyamine (**2**), scopolamine (**3**) in *S*-form, and atropine (**4**) in racemic form. Phenylalanine is known to be the precursor of this acid in plants.[3]

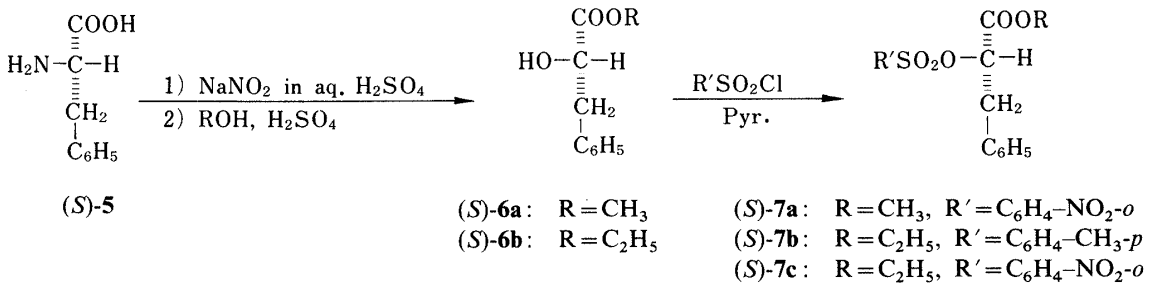


(*S*)-**1** **2** **3** **4**

Chart 1

Chemical transformation of L-phenylalanine and its ester to (*R*)- and (*S*)-tropic acid by phenyl migration during a nitrous acid deamination reaction has been reported,[4] but the chemical and optical yields of tropic acid were not satisfactory and various by-products were obtained. Assuming that solvolysis could be more selective than nitrous acid deamination due to the considerable difference in activation energies between these two reactions,[5] we attempted the chemical transformation of L-phenylalanine ((*S*)-**5**) to optically active tropic acid by solvolysis of sulfonates ((*S*)-**7**) of (*S*)-phenyllactic acid ester ((*S*)-**6**), which is easily available in optically pure form and in good yield from (*S*)-**5** by nitrous acid deamination[6] followed by esterification. Dramatic differences in the products of this solvolysis reaction were observed when different solvents were employed.

Solvolysis of the sulfonate ((*S*)-**7c**) in acetic acid followed by treatment of the reaction mixture with ethanol and acid gave the corresponding substitution product ((*R*)-**6b**) with high



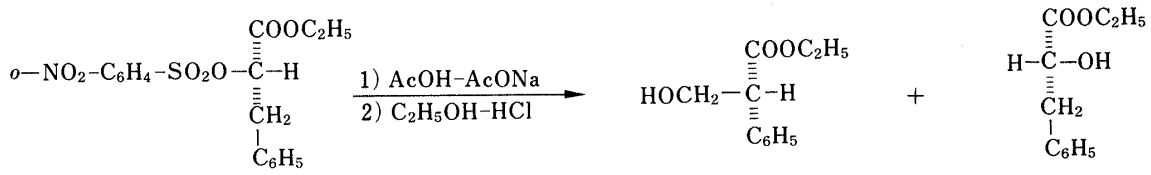
(*S*)-**5**

(*S*)-**6a**: R = CH_3
(*S*)-**6b**: R = C_2H_5

(*S*)-**7a**: R = CH_3, R′ = C_6H_4–NO_2-*o*
(*S*)-**7b**: R = C_2H_5, R′ = C_6H_4–CH_3-*p*
(*S*)-**7c**: R = C_2H_5, R′ = C_6H_4–NO_2-*o*

Chart 2

inversion of configuration as the major product, accompanied by a small amount of the phenyl migration product ((*R*)-**8**) with almost complete inversion of configuration.



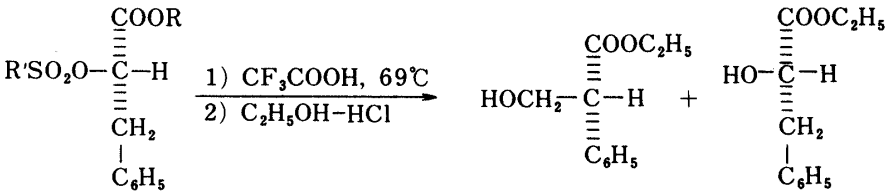
(*S*)-**7c**

(*R*)-**8**
Chem. Y. 2%
(98% Inv.)

(*R*)-**6b**
Chem. Y. 82%
(93% Inv.)

Chart 3

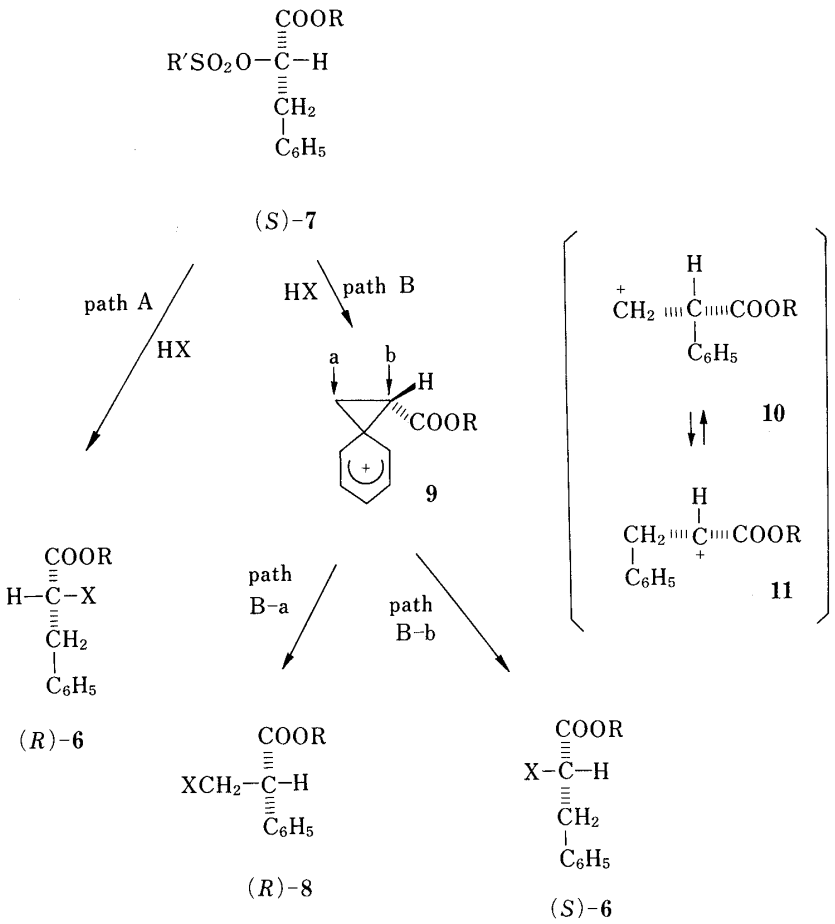
TABLE I. Trifluoroacetolysis of (*S*)-7



(*S*)-7 (*R*)-**8** (*S*)-**6b**

Run	(*S*)-7 Compd. No.	R	R′	Reaction conditions: Salt added (mol eq)	Time (h)	Product: (*R*)-**8** Chem. Y. (%)	(*R*)-**8** Stereochemistry (%ee)	(*R*)-**6b** Chem. Y. (%)	(*R*)-**6b** Stereochemistry (%ee)
1	(*S*)-**7a**	CH_3	C_6H_4–NO_2-*o*	CF_3COONa (1)	45	90	Inv (>98)	3.3	Ret (48)
2	(*S*)-**7a**	CH_3	C_6H_4–NO_2-*o*	None	86	75	Inv (>98)	0.6	—
3	(*S*)-**7b**	C_2H_5	C_6H_4–CH_3-*p*	CF_3COONa (1)	215	86	Inv (>98)	1	
4	(*S*)-**7b**	C_2H_5	C_6H_4–CH_3-*p*	CF_3COONa (5)	160	80	Inv (>98)	—	—
5	(*S*)-**7c**	C_2H_5	C_6H_4–NO_2-*o*	CF_3COONa (1)	36	90	Inv (>98)	4.5	Ret (54)
6	(*S*)-**7c**	C_2H_5	C_6H_4–NO_2-*o*	CF_3COONa (5)	50	87	Inv (>98)	4.8	Ret (63)

On the other hand, the phenyl migration product ((*R*)-**8**) was the major product and the substitution product ((*S*)-**6b**) was a very minor product in the solvolysis of the sulfonates ((*S*)-**7**) in trifluoroacetic acid followed by the same work-up, as shown in Table I. It was again found that phenyl migration had occurred with almost complete inversion, while substitution



XH = CH_3COOH: path A ≫ path B
XH = CF_3COOH: path A ≪ path B, path B-2 ≫ path B-b

Chart 4

had occurred with retention accompanied by partial racemization.

Trifluoroacetic acid is known to be a unique solvent because of its very low nucleophilicity and its relatively high ionizing power, and therefore its high ability to enhance neighboring group participation in solvolysis reactions.[4d,e,7] Based on this characteristic nature of the solvent, the special features of the present solvolysis reactions can be rationalized by evaluating the nucleophilic reactivity of the phenyl group working intramolecularly. Thus, in acetolysis, acetic acid is reasonably nucleophilic, and therefore the major reaction is S_N2 type substitution by the solvent (path A) to give (*R*)-**6** with a high degree of inversion. The reaction *via* neighboring phenyl group participation is very minor.

In trifluoroacetolysis, however, trifluoroacetic acid is not strongly nucleophilic, and the major reaction is considered to be governed by the neighboring phenyl group participation to give the corresponding phenonium ion (**9**) or the corresponding mixture of ions (**10** and **11**) that are equilibrating rapidly (path B). We have no direct evidence for the formation of **9**, but the formation of free carbonium ions is highly unlikely, because no hydrogen migration product formed *via* nucleophilic attack at the benzylic position was found in the reaction mixture,[8] and the optical purity of the phenyl migration product ((*R*)-**8**) was extremely high. Subsequent attack of the solvent at position a will give (*R*)-**8** with inversion (path B-a), while attack at position b will give the substitution product ((*S*)-**6**) with retention. Due to the electron-withdrawing and steric effect of the ethoxycarbonyl group in **9**, the reaction at position b is retarded, and the reaction at position a is considered to be predominant.[9]

Based on the present means of controlling reaction courses by varying the nature of the solvent, it now became possible to synthesize both enantiomers of tropic acid ((*S*)-**1** and (*R*)-**1**) from L-phenylalanine ((*S*)-**5**) in highly optically active form and in reasonably good yield.

Experimental[10]

(*S*)-3-Phenyllactic Acid Methyl Ester *o*-Nitrobenzenesulfonate ((*S*)-7a)——*o*-Nitrobenzenesulfonyl chloride (13.3 g, 60 mmol) was added portionwise to a solution of (*S*)-phenyllactic acid methyl ester ((*S*)-**6a**) (mp 43—45 °C, $[\alpha]_D^{24}$ −11.3 ° (*c*=3.562, benzene)) (reported[11] $[\alpha]_D^{18}$ −12.1 ° (*c*=3.1, benzene)) (4.5 g, 25 mmol) in pyridine (30 ml) at −10 °C and the whole was allowed to stand in a freezer overnight. The reaction mixture was quenched with ice-cooled 10% aq. HCl (100 ml), and the whole was extracted with AcOEt. The AcOEt extracts were combined, washed with 5% aq. $NaHCO_3$ and satd. aq. NaCl, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residual yellow oil was purified by column chromatography (silica gel, benzene) followed by recrystallization from MeOH to give (*S*)-**7a** (5.6 g, 62% yield) as colorless cubes of mp 88.5—89 °C, $[\alpha]_D^{24}$ +27.3 °, IR ν_{max}^{KBr} cm^{-1}: 1759 (–$COOCH_3$), 1545, 1357 (–NO_2), 1382, 1187 (–SO_2–). NMR ($CDCl_3$) δ: 3.2 (2H, m, Ar–C$\underline{H}_2$), 3.72 (3H, s, COOC$\underline{H}_3$), 5.2 (1H, m, Ar–CH_2–C$\underline{H}$), 7.0—7.9 (9H, m, $C_6\underline{H}_5$, $C_6\underline{H}_4$). *Anal.* Calcd for $C_{16}H_{15}NO_7S$: C, 52.60; H, 4.14; N, 3.85. Found: C, 52.68; H, 4.26; N, 3.88.

(*S*)-3-Phenyllactic Acid Ethyl Ester *p*-Toluenesulfonate ((*S*)-7b)——*p*-Toluenesulfonyl chloride (15.25 g, 80 mmol) was added portionwise to a solution of (*S*)-3-phenyllactic acid ethyl ester [(*S*)-**6b**, mp 47—47.5 °C, $[\alpha]_D^{25}$ −22.1 ° (*c*=3.12, benzene); reported[6] mp 46—47 °C, $[\alpha]_D^{24}$ −22.6 ° (*c*=4.33, benzene)] (7.76 g, 40 mmol) in pyridine (40 ml) under ice-cooling, and the whole was allowed to stand in a freezer overnight. The reaction mixture was quenched with ice-cooled 10% aq. HCl (160 ml), and the whole was extracted with AcOEt. The AcOEt extracts were combined, washed with 5% aq. $NaHCO_3$ and satd. aq. NaCl, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residual oil was purified by column chromatography (silica gel, benzene) to give (*S*)-**7b** (13.0 g, 93% yield) as a pale yellow oil of $[\alpha]_D^{25}$ −43.2 ° (*c*=2.74, EtOH). IR ν_{max}^{film} cm^{-1}: 1750 (–$COOC_2H_5$), 1370, 1180 (–SO_2–). NMR ($CDCl_3$) δ: 1.18 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 2.40 (3H, s, C_6H_4–C$\underline{H}_3$), 3.0—3.2 (2H, m, Ar–C$\underline{H}_2$), 4.11 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 4.9 (1H, m, Ar–CH_2C$\underline{H}$), 6.95—7.6 (9H, m, $C_6\underline{H}_5$, $C_6\underline{H}_4$).

(*S*)-3-Phenyllactic Acid Ethyl Ester *o*-Nitrobenzenesulfonate ((*S*)-7c)——(*S*)-3-Phenyllactic acid ethyl ester ((*S*)-**6b**) (4.82 g, 25 mmol) described above was treated with *o*-nitrobenzenesulfonyl chloride (13.22 g, 60 mmol) in pyridine (30 ml) as described for the synthesis of (*S*)-**7a** and the product was purified by column chromatography (silica gel, benzene) to give (*S*)-**7c** (5.4 g, 61% yield) as a pale yellow oil of $[\alpha]_D^{25}$ +17.3 ° (*c*=2.82, EtOH). IR ν_{max}^{film} cm^{-1}: 1760 ($COOC_2H_5$), 1550 (NO_2), 1195 (–SO_2–). NMR ($CDCl_3$) δ: 1.19 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 3.2 (2H, m, Ar–C$\underline{H}_2$), 4.16 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 5.2 (1H, m, Ar–CH_2C$\underline{H}$), 7.0—7.9 (9H, m, $C_6\underline{H}_5$, $C_6\underline{H}_4$).

Acetolysis of (*S*)-3-Phenyllactic Acid Ethyl Ester *o*-Nitrobenzenesulfonate ((*S*)-7c)——A solution of (*S*)-**7c** (1.13 g, 3 mmol) and anhyd. AcONa (1.23 g, 15 mmol) in AcOH (14.6 ml) and Ac_2O (0.6 ml) was heated at 100 °C for 20 h. After evaporation of the solvent *in vacuo*, the residue was taken up in AcOEt, and the whole was washed with satd. aq. NaCl. The AcOEt layer was dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was dissolved in 15% HCl–EtOH (40 ml), and the whole was refluxed for 3 h. Evaporation of the reaction mixture gave a residue, which was dissolved in Et_2O. The ethereal solution was washed with satd. aq. NaCl, dried over anhyd. Na_2SO_4, and then evaporated to dryness. The residue was subjected to column chromatography (silica gel, hexane–Et_2O (1 : 1)). The following two compounds were obtained and were identified by nuclear magnetic resonance (NMR) comparison with authentic samples. (*R*)-**6b**: 431 mg (82% yield), $[\alpha]_D^{25}$ +21.6 ° (*c*=4.21, benzene) corresponding to 93% net inversion.[12] (*R*)-**8**: 10 mg (2% yield), $[\alpha]_D^{25}$ +49.4 ° (*c*=0.17, EtOH) corresponding to 98% net inversion.[12]

Preparation of a Solution of CF_3COONa in CF_3COOH——A solution of NaOH (94% purity) (4.3 g, 0.1 mol) in H_2O (15 ml) and CF_3COOH (15 ml) was evaporated to dryness *in vacuo*. The residual colorless solid was dried over P_2O_5 in an evacuated dessicator overnight, and then dissolved in CF_3COOH (95 ml) and $(CF_3CO)_2O$ (5 ml) to give a total volume of 105 ml. This solution was used as a standard solution (S-solution) of CF_3COONa in CF_3COOH (100 mmol/105 ml).

General Procedure for Trifluoroacetolysis——A solution of (*S*)-**7a**, (*S*)-**7b** or (*S*)-**7c** (6 mmol) in S-solution (6.3 ml) and CF_3COOH (25.7 ml) (for runs 1, 3 and 5 below), in S-solution alone (32 ml) (for runs 4 and 6 below), or in CF_3COOH (32 ml) (for run 2 below) was heated at 69 °C for 36 to 215 h as described in Table I. Evaporation of the solvent *in vacuo* gave a residue, which was taken up in AcOEt. The AcOEt solution was washed with satd. aq. NaCl, dried over anhyd. Na_2SO_4, and then evaporated to dryness. The residue was dissolved in 15% HCl–EtOH (40 ml), and the whole was treated as described in the case of the acetolysis of (*S*)-**7c**. The products were separated similarly by column chromatography (silica gel, hexane–Et_2O (1 : 1)). The following compounds were isolated and their optical purities were calculated polarimetrically.[12]

(a) Run 1: (*R*)-**8**, 90% yield, $[\alpha]_D^{25}$ +50.3 ° (*c*=4.20, EtOH); (*S*)-**6b**, 3.3% yield, $[\alpha]_D^{25}$ −10.6 ° (*c*=0.564, benzene).

(b) Run 2: (*R*)-**8**, 75% yield, $[\alpha]_D^{24}$ +50.3 ° (*c*=3.39, EtOH); **6b**, 0.6% yield.

(c) Run 3: (*R*)-**8**, 83% yield, $[\alpha]_D^{25}$ +50.2° (*c*=3.26, EtOH); **6b**, 1% yield.
(d) Run 4: (*R*)-**8**, 80% yield, $[\alpha]_D^{25}$ +50.1° (*c*=3.32, EtOH).
(e) Run 5: (*R*)-**8**, 90% yield, $[\alpha]_D^{25}$ +50.0° (*c*=3.25, EtOH); (*S*)-**6b**, 4.5% yield, $[\alpha]_D^{25}$ −11.7° (*c*=0.61, benzene).
(f) Run 6: (*R*)-**8**, 87% yield, $[\alpha]_D^{25}$ +50.1° (*c*=3.29, EtOH); (*S*)-**6b**, 4.5% yield, $[\alpha]_D^{25}$ −13.7° (*c*=0.80, benzene).

References and Notes

1) Part LIX: N. Ikota, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, **31**, 887 (1983).
2) Reported in a preliminary form as a communication: S. Yamada, K. Koga, T. M. Juang, and K. Achiwa, *Chem. Lett.*, **1976**, 927.
3) M. L. Louden and E. Leete, *J. Am. Chem. Soc.*, **84**, 4507 (1962).
4) *a*) S. Yamada, T. Kitagawa, and K. Achiwa, *Tetrahedron Lett.*, **1967**, 3007; *b*) K. Koga, C. C. Wu, and S. Yamada, *ibid.*, **1971**, 2283; *c*) *Idem, ibid.*, **1971**, 2287; *d*) *Idem, Chem. Pharm. Bull.*, **20**, 1272 (1972); *e*) *Idem, ibid.*, **20**, 1282 (1972).
5) A. Streitwieser, Jr. and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 2888 (1957).
6) S. G. Cohen and S. Y. Weinstein, *J. Am. Chem. Soc.*, **86**, 5326 (1964).
7) *a*) U. E. Nordlander and W. G. Deadman, *J. Am. Chem. Soc.*, **90**, 1590 (1968); *b*) I. L. Reich, A. Diaz, and S. Winstein, *ibid.*, **91**, 5635 (1969).
8) A hydrogen migration product was actually obtained as one of the products in the nitrous acid deamination reaction of L-phenylalanine ethyl ester in trifluoroacetic acid. See ref. 4*e*.
9) *Cf.* A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw Hill, 1962, p. 119.
10) All melting and boiling points are uncorrected. Infrared spectra were recorded with a JASCO DS-402G or a JASCO IRA-1 spectrometer. NMR spectra were recorded with a JNM PS-100 (100 MHz) or a Hitachi R-24 (60 MHz) spectrometer using tetramethylsilane as an internal standard. Optical rotations were measured with a Yanaco OR-50 automatic polarimeter.
11) A. McKenzie and G. Martin, *J. Chem. Soc.*, **103**, 112 (1913).
12) The values of $[\alpha]_D^{25}$ +50.3° (EtOH) for optically pure (*R*)-**8** (ref. 3) and of $[\alpha]_D^{23}$ +23.2° (benzene) for optically pure (*R*)-**6b** (ref. 5) were used.