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Stereochemical Studies. XIV.[1] Studies on the Neighboring Aryl Group Participation in Nitrous Acid Deaminations of L-Phenylalanine Ethyl Ester and Its *p*-Nitro and *p*-Methoxy Derivatives[2]

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Detailed examinations on nitrous acid deaminations of L-phenylalanine ethyl ester (Ib) and its *p*-nitro (Ia) and *p*-methoxy (Ic) derivatives in 1N sulfuric acid, acetic acid, and trifluoroacetic acid have shown that the reactions are highly dependent both on the solvent employed and on the substituent attached to the aromatic ring. Results may be rationalized by evaluating the changes in nucleophilicities of both the solvent and the aryl group. We clearly demonstrated that aryl groups exhibit strong neighboring group participation in deamination in trifluoroacetic acid.

Deamination of optically active α-amino acid having a hydrogen and no aryl group at the asymmetric α-carbon atom is generally recognized to lead to the α-substituted acid with retention, due to participation of the neighboring carboxylate group,[4] while deamination of the corresponding α-amino acid ester leads to the α-substituted ester with inversion accompanied by much racemization.[4] Although deamination is one of the oldest and most extensively used reactions in organic chemistry, there has been much research activity on it in recent years[5]; usually with primary emphasis on determining the reaction mechanism.

Detailed examinations of nitrous acid deamination of L-phenylalanine ethyl ester (Ib) in acetic acid[6] have shown, however, that phenyl migration (IIIb, X=OAc), hydrogen migration (IVb, X=OAc) and elimination (Vb) products are also obtained along with the substitution product (IIb, X=OAc). Their stereochemical consequences have also been clarified. Application of this reaction to DL-phenylalanine 3α-tropanyl ester in 2N sulfuric acid was successful for the one-step synthesis of atropine and other related tropane alkaloids.[7]

The present study was undertaken to find the factors that control the reaction patterns (yields of products and their stereochemical results) in deaminations of optically active α-amino acid derivatives. L-Phenylalanine ethyl ester (Ib) and its *p*-nitro (Ia) and *p*-methoxy (Ic) derivatives were selected as substrates. Detailed examinations were carried out on

1) Part XIII: Y. Murakami, K. Koga, H. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 543 (1972).
2) A preliminary report has been published: K. Koga, C.C. Wu, and S. Yamada, *Tetrahedron Letters*, **1971**, 2283.
3) Location: *Hongo, Bunkyo-ku, Tokyo.*
4) *a*) A Neuberger, "Advances in Protein Chemistry," Vol. 4, ed. by M.L. Anson and J.T. Edsall, Academic Press, New York, 1948, pp. 327—338; *b*) P. Brewster, F. Hiron, E.D. Hughes, C.K. Ingold, and P.A.D.S. Rao, *Nature*, **166**, 179 (1950); *c*) N. Izumiya, *Bull, Chem. Soc. Japan*, **72**, 26 (1951).
5) *a*) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957); *b*) H. Zollinger, "Azo and Diazo Chemistry," Interscience Publ., New York, 1961, pp. 93—137; *c*) R.A. More O'Ferrall, "Advances in Physical Organic Chemistry," Vol. 5, ed. by V. Gold, Academic Press, New York, 1967, pp. 331—339; *d*) E.H. White and D.J. Woodcock, "The Chemistry of the Amino Group," ed. by S. Patai, Interscience Publ., New York, 1968, pp. 407—497; *e*) L. Friedman, "Carbonium Ions," Vol. 2, ed. by G.A. Olah and P. von R. Schleyer, Wiley-Interscience, New York, 1970, pp. 655—713.
6) S. Yamada, T. Kitagawa, and K. Achiwa, *Tetrahedron Letters*, **1967**, 3007.
7) Y. Takeuchi, K. Koga, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **19**, 2603(1971).

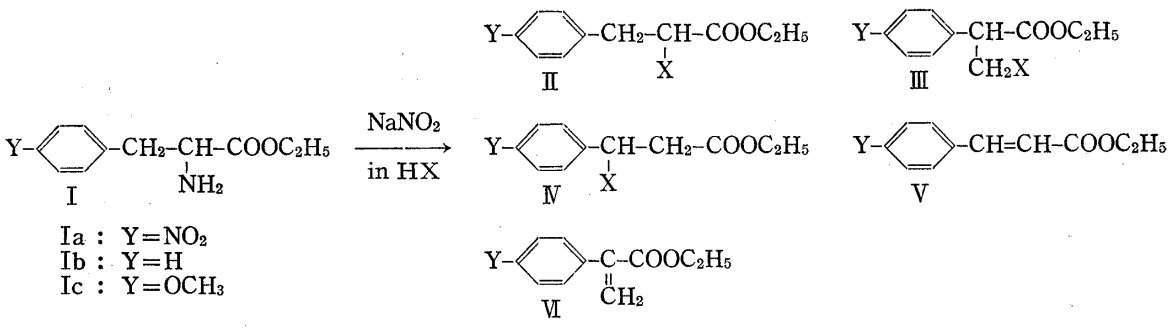


Chart 1

the effects of the method of diazotization, on the effects of the solvent used, and on the effects of the neighboring aryl group.

Result and Discussion

Starting Materials and Products

Optically pure L-amino acid ethyl esters (Ia,[8] Ib,[6] and Ic[9]) were prepared according to the usual methods. Determinations of product ratios were made by gas liquid chromatography (GLC) or nuclear magnetic resonance (NMR). Determinations of the stereochemical

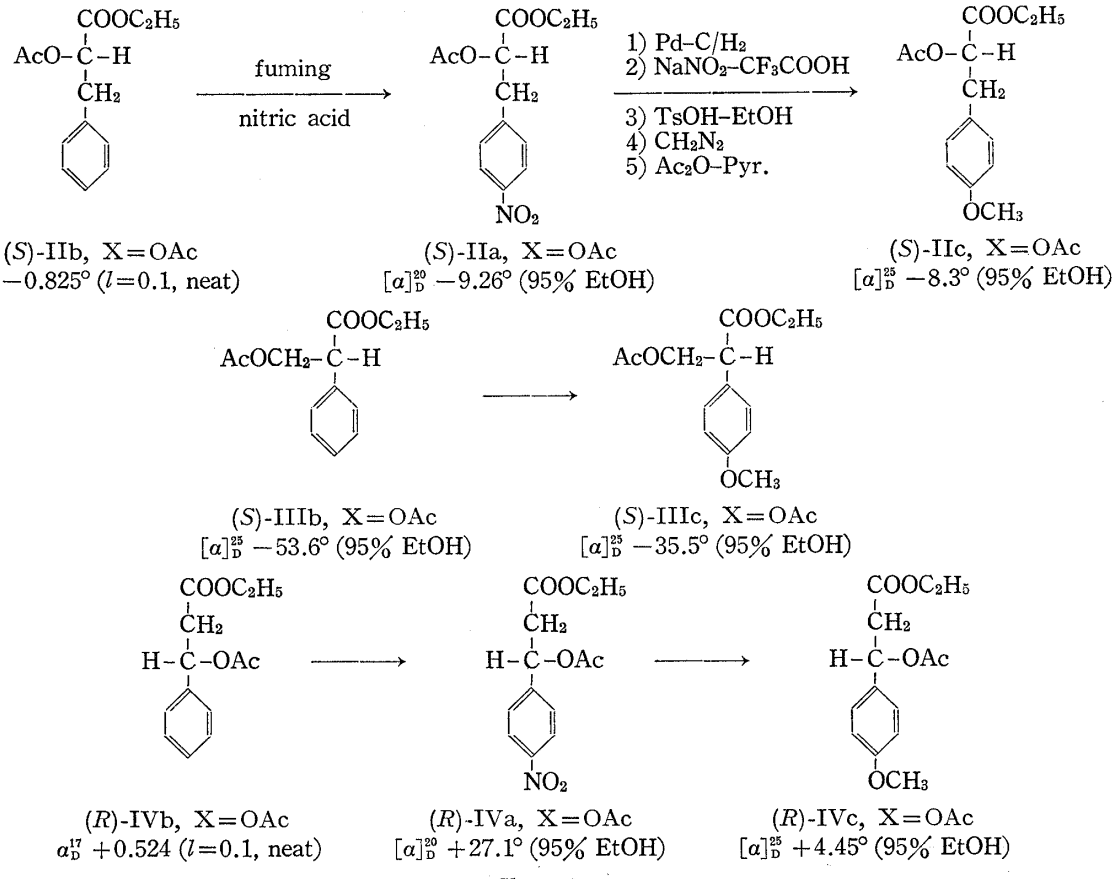


Chart 2

8) F. Bergel and J.A. Stack, *J. Chem. Soc.*, **1954**, 2409.
9) *a*) L.D. Behr and H.T. Clark, *J. Am. Chem. Soc.*, **54**, 1630 (1932); *b*) N. Izumiya and A. Nagamatsu, *Bull. Chem. Soc. Japan*, **25**, 263 (1952).

results of non-olefinic products were made polarimetrically, after derivation to their corresponding acetates followed by separation. Optically pure authentic acetates were prepared as follows. Ethyl (*S*)-2-acetoxy-3-phenylpropionate[10] ((*S*)-IIb, X=OAc) was nitrated to give ethyl (*S*)-2-acetoxy-3-(*p*-nitrophenyl)propionate ((*S*)-IIa, X=OAc), which was converted to ethyl (*S*)-2-acetoxy-3-(*p*-methoxyphenyl)propionate ((*S*)-IIc, X=OAc) by a reaction sequence involving reduction of the nitro group to the amino group, diazotization of the amino group in trifluoroacetic acid, hydrolysis of the trifluoroacetyl and acetyl groups, methylation of the phenolic hydroxyl group, and acetylation of the alcoholic hydroxyl group. Similarly, determinations of absolute configurations and maximum rotations of ethyl (*S*)-3-acetoxy-2-(*p*-methoxyphenyl)propionate ((*S*)-IIIc, X=OAc), ethyl (*R*)-3-acetoxy-3-(*p*-nitrophenyl)propionate ((*R*)-IVa, X=OAc), and ethyl (*R*)-3-acetoxy-3-(*p*-methoxyphenyl) propionate ((*R*)-IVc, X=OAc) were made by preparing them from ethyl (*S*)-3-acetoxy-2-phenylpropionate (Ethyl (*S*)-O-acetyltropate)[11] ((*S*)-IIIb, X=OAc) or ethyl (*R*)-3-acetoxy-3-phenylpropionate[12] ((*R*)-IVb, X=OAc) as shown in Chart 2.

Effects of the Method of Diazotization on the Reaction

Results of nitrous acid deamination of L-phenylalanine ethyl ester (Ib) in acetic acid (method a) reported previously[6] were compared with results obtained by the following three methods (Chart 3): (1) Pyrolysis of N-acetyl-N-nitroso-L-phenylalanine ethyl ester (VIII) in acetic acid[13] (method b). (2) The reaction of N-(*p*-tolylazo)-L-phenylalanine ethyl ester (IX) with acetic acid[14] (method c), and (3) The reaction of ethyl 2-diazo-3-phenylpropionate (X) with acetic acid[5c] (method d). These three methods are expected to give products containing the same components as the products from method a.

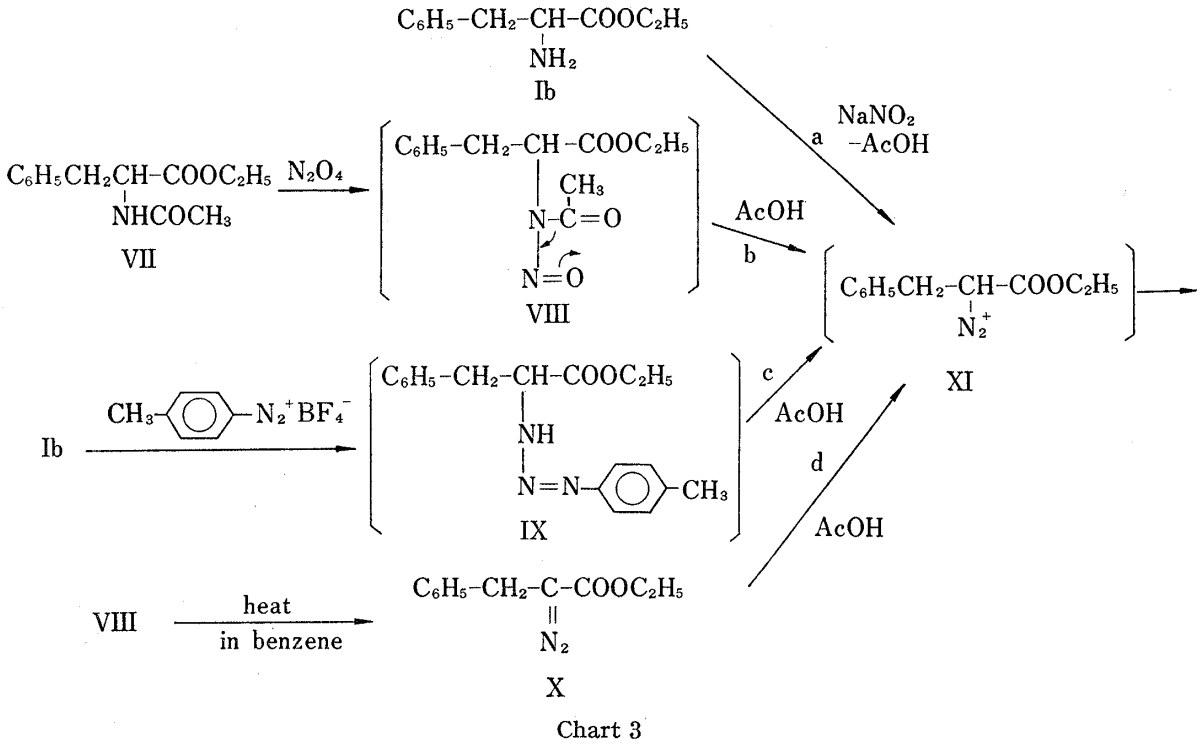
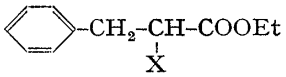
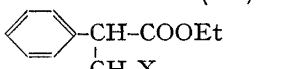
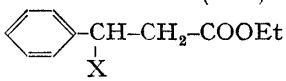
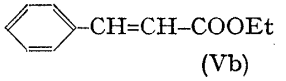


Chart 3

10) S.G. Cohen and S.Y. Weinstein, *J. Am. Chem. Soc.*, **86**, 5326 (1964).
11) *cf.* A. McKenzie and J.K. Wood, *J. Chem. Soc.*, **115**, 828 (1919).
12) J. Kenyon, H. Phillips, and G.R. Shutte, *J. Chem. Soc.*, **1935**, 1663.
13) *cf.* E.H. White and C.A. Aufdermarsh, *J. Am. Chem. Soc.*, **83**, 1174, 1179 (1961).
14) *cf. a*) E.H. White and H. Scherrer, *Tetrahedron Letters*, **1961**, 738; *b*) H. Mashill, R.M. Southam, and M.C. Whiting, *Chem. Commun.*, **1965**, 496.

As shown in Table I, the reaction pattern does not change significantly due to differences in the method of generation of the diazonium ion. Thus, the four methods afforded similar patterns in their product compositions; in which the hydrogen migration product (IVb, X=OAc) was predominant. Stereochemical results were also roughly similar in the two methods examined. However, a relatively large amount of elimination product (Vb) was obtained in method d; probably due to partial commitment of the carbene intermediate.[15]

Table I. Reaction Patterns from Various Methods of Diazotization

Product (X=OAc)	Method a[a] Yield (%)	Method a[a] Stereochemistry[b]	Method b Yield (%)	Method b Stereochemistry[b]	Method c[c] Yield (%)	Method d Yield (%)
 (IIb)	26	11 inv	18	9 inv	23	17
 (IIIb)	24	35 inv	26	60 inv	25	20
 (IVb)	35	70 (*S*)	28	65 (*S*)	33	27
 (Vb)	14—16	—	16	—	19	26

a) Data taken from ref. 6.
b) Values represent optical purity in net. inv=inversion, ret=retention, (*R*) and (*S*) represent absolute configuration.
c) Stereochemical examination was not performed.

Effects of Solvent (HX) and *p*-Substituent (Y) on the Reaction

Nitrous acid deaminations of Ia, Ib, and Ic in 1N sulfuric acid, acetic acid, and trifluoroacetic acid were undertaken to examine whether the reaction pattern would be influenced by the character of the solvent and of the aryl group. Results are shown in Table II.

It is apparent that the reaction patterns differ considerably. The following points are particularly interesting: (1) The reaction pattern changes with a change of solvent. Thus, stereochemical results for the substitution products, IIa, IIb, and IIc, are relatively high net retention in trifluoroacetic acid, in contrast to net inversion in 1N sulfuric acid and in acetic acid. This phenomenon is at variance with the general observation[4] that substitution reactions in deaminations of α-amino acid esters proceed with net inversion. On the other hand, both the yields and the degree of inversion of aryl migration products (IIIb and IIIc) in trifluoroacetic acid are higher than those in the other solvents. (2) The pattern of the reaction changes with the change of substituent attached to the aromatic *p*-position. Introduction of an electron-donating substituent raises both the yields and the degree of inversion of aryl migration products. Thus, among the three α-amino acid esters, *p*-methoxy derivative (Ic) gave aryl migration products (IIIc and VIc) in the highest yield. Moreover, the degree of inversion of aryl migration product (IIIc) was high in all solvents. The aryl migration reaction also occurred extensively (over 90%) in the reaction of Ic in trifluoroacetic acid.

15) *cf.* Y. Yamamoto and I. Moritani, *Tetrahedron Letters*, **1969**, 3087.

Table II. Patterns of Reactions of Ia, Ib, and Ic in 1N H_2SO_4, AcOH, and CF_3COOH

Starting Material (Y)	Product	Solvent (HX): 1N H_2SO_4 (X=OH) Yield (%)	1N H_2SO_4 (X=OH) Stereochemistry[a]	CH_3COOH (X=$OCOCH_3$) Yield (%)	CH_3COOH (X=$OCOCH_3$) Stereochemistry[a]	CF_3COOH (X=$OCOCF_3$) Yield (%)	CF_3COOH (X=$OCOCF_3$) Stereochemistry[a]
Ia (NO_2)	IIa	39	40 inv	35	13 inv	25	48 ret
	IIIa	trace		8		9	
	IVa	16	~0	19	8 (*S*)	27	~0
	Va	32		30		18	
Ib (H)[b]	IIb	24	43 inv	26	11 inv	11	66 ret
	IIIb	26	72 inv	24	35 inv	50	87 inv
	IVb	33	22 (*S*)	35	70 (*S*)	28	6 (*R*)
	Vb	18		14—16		3	
Ic (OCH_3)	IIc	15	37 inv	21	8 inv	8	80 ret
	IIIc	54	76 inv	31	61 inv	52	88 inv
	IVc	25	5 (*S*)	21	23 (*S*)		
	Vc	5		21			
	VIc			5		39	

a) Values represent optical purities in net. inv=inversion. ret=retention. (*R*) and (*S*) represent absolute configuration.
b) Data on the reaction in CH_3COOH are from ref. 6.

The mechanism for the deamination of Ia in acetic acid has already been discussed.[6] The striking differences in the reaction pattern in the present deaminations must come from two factors; the solvent and *p*-substituent.

Trifluoroacetic acid is recognized as a unique solvent due to its very low nucleophilicity and relatively high ionizing power.[16] However, the substituent at *p*-position in the aromatic ring is remote from the reaction site, and is thought to have few effects sterically, but to have considerable effects electronically in changing the nucleophilic character of the aryl group.

The two points stated above are rationalized by evaluating changes in the nucleophilicities of the solvent and the aryl group. Thus, both the solvent and the aryl group are considered to be nucleophiles in the present deamination reactions. The generation of cation in a solvent of very low nucleophilicity is expected to cause the attack of a neighboring aryl group to the cationic center; preferentially from the backside of the leaving group to produce an unsymmetrical phenonium ion (XII) or its stereochemically equivalent equilibrating pair of cations (XIII). The reaction of solvent (HX) at α-position of XII or XIII is expected to give the substitution product ((*S*)-II) with retention, while the reaction of solvent (HX) at β-position is expected to give the aryl migration product ((*R*)-III) with inversion. The increase in nucleophilicity of the aryl group is also expected to enhance aryl group participation. This mechanism seems to be predominantly operative in the present deaminations in trifluoroacetic acid, as shown in Table II.

The stereochemical results of hydrogen migration products (IV) are, however, quite puzzling. Stereospecificity of the reaction to produce IV should be decreased by an increase in the stability of the benzylic carbonium ion, that is considered to be influenced both by the electronic effect of the aryl group and the nucleophilicity of the solvent. It was shown that this concept was oversimplification. Solving this problem requires further investigation.

16) *a*) J.E. Nordlander and W.G. Deadman, *J. Am. Chem. Soc.*, **90**, 1590 (1968); *b*) I. Lazdins Reich, A. Diaz, and S. Winstein, *ibid.*, **91**, 5635 (1969); *c*) J.A. Thompson and D.J. Cram, *ibid.*, **91**, 1778 (1969).

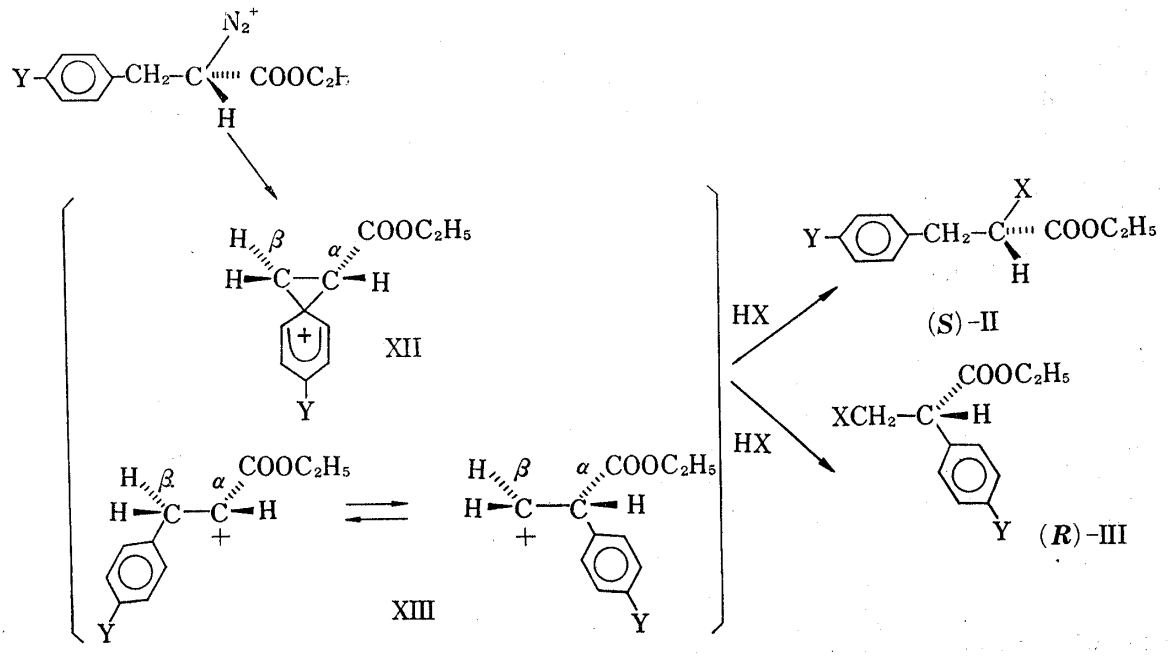


Chart 4

Results of the present study clearly demonstrate that aryl groups situated at β-position to the amino group exhibit such strong neighboring group participation in deaminations in solvents of low nucleophilicity as to overcome the expected control of conformational populations of the ground state,[17] especially in the reaction of L-(*p*-methoxy-phenyl)alanine ethyl ester (Ic) in trifluoroacetic acid.

Experimental[18]

L-(*p*-Nitrophenyl)alanine Ethyl Ester (Ia)——This compound was prepared from L-(*p*-nitrophenyl)-alanine ethyl ester hydrochloride of mp 208° (decomp.), $[\alpha]_D^{25}$ +12.5° (*c*=2.0, H_2O) (reported[8] mp 207—208° (decomp.), $[\alpha]_D^{25}$ +12.7±3° (*c*=2.24, H_2O)), as a liquid of bp 158° (0.01 mmHg), α_D^{24} +1.272° (*l*=0.1, neat). IR ν_{max}^{film} cm^{-1}: 3035 (amino), 1730 (ester), 1516, 1348 (nitro). *Anal.* Calcd. for $C_{11}H_{14}O_4N_2$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.53; H, 5.96; N, 11.93.

L-Phenylalanine Ethyl Ester (Ib)——This compound was prepared, as described previously,[6] as a colorless liquid of bp 125° (5 mmHg), $[\alpha]_D^{22}$ +23.6° (*c*=4.52, EtOH) (reported[19] $[\alpha]_D$ +23±1° (*c*=3.1, EtOH)). IR ν_{max}^{film} cm^{-1}: 3350 (amino), 1735 (ester).

L-(*p*-Methoxyphenyl)alanine Ethyl Ester (Ic)——This compound was prepared from L-(*p*-methoxyphenyl)-alanine[9] of mp 265° (decomp.), $[\alpha]_D^{23}$ −5.7° (*c*=2, 1N HCl) in the usual manner as a colorless liquid of bp 137° (0.04 mmHg), $[\alpha]_D^{25}$ +18.2° (*c*=2.0, EtOH), α_D^{25} +1.290° (*l*=0.1, neat). IR ν_{max}^{film} cm^{-1}: 3035 (amino), 2820 (methoxy), 1730 (ester). *Anal.* Calcd. for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.25: H, 7.74; N, 6.46.

Ethyl (*S*)-2-Acetoxy-3-phenylpropionate ((*S*)-IIb, X=OAc)——This compound was prepared, according to the reported method,[10] as a colorless liquid of bp 138° (4 mmHg), α_D^{23} −0.825° (*l*=0.1 neat) $[\alpha]_D^{23}$ −8.75° (*c*=7.08, $CHCl_3$) (reported[10] bp 85—87° (0.2 mmHg), $[\alpha]_D^{23}$ −8.7° (*c*=6.65, $CHCl_3$)). IR ν_{max}^{film} cm^{-1}: 1751 (ester), 1233 (acetoxy). This sample was identical with one obtained previously.[6]

17) D.J. Cram and J.E. McCarthy, *J. Am. Chem. Soc.*, **79**, 2866 (1957).

18) All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded with a Koken DS-402G Spectrometer. NMR spectra were recorded with a JNM 3H-60 Spectrometer operating at 60 MHz or with a JNM-PS-100 Spectrometer operating at 100 MHz using tetramethylsilane as an internal standard. Optical rotations were measured with a Yanaco OR-50 Automatic Polarimeter or with a JASCO ORD/UV-5 Spectrometer. Separations of compounds by GLC were carried out with a Perkin-Elmer F-21 Preparative gas chromatograph equipped with columns containing 20% Carbowax 20M on Chromosorb WAW. Microanalyses and spectral measurements were performed by members of the Central Analysis Room of this faculty.

19) F. Bergel, G.E. Lewis, S.W.D. Drr, and J. Butler, *J. Chem. Soc.*, **1959**, 1431.

Ethyl (*S*)-2-Acetoxy-3-(*p*-nitrophenyl)propionate ((*S*)-IIa, X=OAc)——(*S*)-IIb (X=OAc) (72.0 g) was added to fuming nitric acid (700 ml) portionwise at 0°. After stirring at the same temperature for 1.5 hr, the resulting solution was poured into ice-water, then the whole was extracted with AcOEt. Extracts were combined, washed successively with H_2O, sat. $NaHCO_3$, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the AcOEt *in vacuo* left a pale yellow liquid (72.0 g), which partially solidified on standing in a refrigerator in the presence of AcOEt–hexane. Recrystallization of the solid from EtOH afforded pale yellow pillars (10.0 g, 12% yield) of mp 50—51°, $[\alpha]_D^{20}$ −9.26° (c=2.31, 95% EtOH), $[\alpha]_{450}$ −13.5° (c=2.816, 95% EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (ester), 1525. 1350 (nitro), 1230 (acetoxy). NMR (in CCl_4, 100 MHz) τ: 8.78 (3H, t, J=7 Hz, -CH_2-C$\underline{H}_3$), 7.97 (3H, s, -OCOC$\underline{H}_3$), 6.86—6.74 (2H, m, -C$\underline{H}_2$-CH-), 5.88 (2H, q, J=7 Hz, -O-C$\underline{H}_2$-CH_3), 4.94—4.79 (1H, m, -C$\underline{H}_2$-CH-), 2.13, 1.95 (4H, d-d, J=9 Hz, -$C_6\underline{H}_4$-). *Anal.* Calcd. for $C_{13}H_{15}O_6N$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.36; H, 5.43; N, 4.98.

Ethyl (*S*)-2-Acetoxy-3-(*p*-methoxyphenyl)propionate ((*S*)-IIc, X=OAc)——A suspension of (*S*)-IIa (X=OAc) (1.97 g, 7 mmoles) and 5% Pd-C (200 mg) in EtOH (20 ml) was shaken vigorouly at room temperature, under the atmospheric pressure of H_2, until absorption of H_2 ceased (20 min). The catalyst was filtered off, and the filtrate was evaporated to dryness *in vacuo* to give a colorless liquid. $NaNO_2$ (560 mg, 8 mmoles) was added to a solution of this liquid in CF_3COOH (14 ml) portionwise, then the whole was heated at 60° for 1.5 hr. The red-colored reaction mixture was evaporated *in vacuo* and the residue was dissolved in EtOH (40 ml). A trace of TsOH was added to this solution, then the whole was refluxed for 1.5 hr. After evaporation of the solvent, the residue was taken up in AcOEt, the AcOEt solution was washed successively with H_2O, dil. HCl, H_2O, dil. $NaHCO_3$, sat. NaCl, and dried over anhyd. Na_2SO_4. Evaporation of the AcOEt *in vacuo* gave a reddish brown oil (1.78 g), which was dissolved in EtOH (50 ml). A solution of CH_2N_2 (generated from nitrosomethylurea (5.0 g, 35 mmoles)) in ether (50 ml) was mixed with the EtOH solution, then the whole was allowed to stand at room temperature for 14 hr. After decomposing excess CH_2N_2 with formic acid, the reaction mixture was evaporated to dryness *in vacuo* and the residue was dissolved in AcOEt. This AcOEt solution was washed successively with H_2O, dil. HCl, H_2O, dil. $NaHCO_3$, sat. NaCl, then dried over anhyd. Na_2SO_4. Evaporation of the AcOEt left a liquid, which was treated with Ac_2O–pyridine in the usual manner to give a liquid (1.51 g). This liquid was chromatographed on silica gel (80 g) with $CHCl_3$ to give (*S*)-IIc (X=OAc) as a pale yellow liquid (620 mg, 33% yield) of bp 131° (0.04 mmHg), mp 44—46.5° $[\alpha]_D^{25}$ −8.3° (c=1.502, 95% EtOH), $[\alpha]_{29}^{450}$ −12.8° (c=1.502, 95% EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2845 (methoxy), 1744 (ester), 1243 (acetoxy). NMR (in CCl_4, 60 MHz) τ: 8.80 (3H, t, J=7 Hz, -CH_2-C$\underline{H}_3$), 8.00 (3H, s, -OCOC$\underline{H}_3$), 7.37—6.73 (2H, m, -C$\underline{H}_2$-CH-), 6.26 (3H, s, -OC$\underline{H}_3$), 5.90 (2H, q, J=7 Hz, -O-C$\underline{H}_2$-CH_3), 5.10—4.89 (1H, m, -CH_2-C$\underline{H}$-), 2.98, 3.28 (4H, d-d, J=9 Hz, -$C_6\underline{H}_4$-). *Anal.* Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.17; H, 6.76.

Ethyl (*S*)-3-Acetoxy-2-phenylpropionate (Ethyl (*S*)-O-Acetyltropate ((*S*)-IIIb, X=OAc)——This compound was prepared from (*S*)-tropic acid (obtained by hydrolysis of scopolamine) with a mp of 125.5—127.5°, $[\alpha]_D^{20}$ −76.3° (c=1.52, H_2O) (reported[11] mp 128—129°, $[\alpha]_D^{15}$ −79.0° (c=1.538, H_2O)) according to the reported method[6] as a colorless liquid of bp 136° (3 mmHg), α_D^{28} −6.185° (l=0.1, neat), $[\alpha]_D^{25}$ −53.1° (c=2.094, EtOH), $[\alpha]_D^{25}$ −53.6° (c=2.258, 95% EtOH) (reported[6] α_D^{28} −5.984° (l=0.1, neat), $[\alpha]_D^{25}$ −54.4° (c=2.2, EtOH). IR ν_{max}^{film} cm^{-1}: 1742 (ester), 1234 (acetoxy). *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.23; H, 6.86.

Ethyl (*S*)-3-Acetoxy-2-(*p*-methoxyphenyl)propionate ((*S*)-IIIc, X=OAc)——This compound was prepared from (*S*)-IIIb (X=OAc), in a manner similar to that for the conversion of (*S*)-IIb (X=OAc) to (*S*)-IIc (X=OAc) described above, as a colorless liquid of bp 132° (0.03 mmHg), $[\alpha]_D^{25}$ −35.5° (c=1.28, 95% EtOH), $[\alpha]_{400}^{25}$ −101.6° (c=1.28, 95% EtOH). IR ν_{max}^{film} cm^{-1}: 2850 (methoxy), 1740 (ester), 1242 (acetoxy). NMR (in CCl_4, 60 MHz) τ: 8.80 (3H, t, J=7 Hz, -CH_2-C$\underline{H}_3$), 8.01 (3H, s, -OCOC$\underline{H}_3$), 6.25 (3H, s, -OC$\underline{H}_3$), 5.89 (2H, q, J=7 Hz, -C$\underline{H}_2$-CH_3), 6.48—5.38 (3H, m, -C$\underline{H}_2$-C$\underline{H}$-), 3.21 2.83 (4H, d-d, J=9 Hz, -$C_6\underline{H}_4$-). *Anal.* Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.88; H, 6.66.

Ethyl (*R*)-3-Acetoxy-3-phenylpropionate ((*R*)-IVb, X=OAc)——This compound was prepared according to the reported method[12] as a colorless liquid of bp 127° (5 mmHg), α_D^{17} +0.524° (l=0.1, neat) (reported[12] bp 102—103° (0.1 mmHg), α_D^{17} +1.32° (l=0.25, neat)). IR ν_{max}^{film} cm^{-1}: 1741 (ester), 1224 (acetoxy). *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.15; H, 6.90.

Ethyl DL-3-Acetoxy-3-(*p*-nitrophenyl)propionate (DL-IVa, X=OAc)——Ethyl DL-3-acetoxy-3-phenylpropionate[6] (10.1 g) (obtained from ethyl 3-hydroxy-3-phenylpropionate[20]) was added to fuming nitric acid (100 ml) dropwise at 0°. After stirring at a constant temperature for 0.5 hr, the resulting solution was poured into ice-water, then the whole was extracted with AcOEt. Extracts were combined, washed successively with H_2O, sat. $NaHCO_3$, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the AcOEt *in vacuo* left a pale yellow oil, which partially solidified on standing. Recrystallizations of the solid from EtOH afforded pale yellow pillars (1.5 g, 14% yield) of mp 50—51°. IR $\nu_{max}^{CS_2}$ cm^{-1}: 1747 (ester), 1347 (nitro), 1222 (acetoxy). IR ν_{max}^{Nujol} cm^{-1}: 1745 (ester), 1525, 1351 (nitro), 1224 (acetoxy). NMR (in $CDCl_3$, 100 MHz)

20) C.R. Hauser and D.S. Breslow, "Organic Syntheses," Coll. Vol. III, ed. by E.C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 408.

τ: 8.79 (3H, t, J=7 Hz, -CH_2-C$\underline{H}_3$), 7.96 (3H, s, -OCOC$\underline{H}_3$), 7.45—6.98 (2H, m, -CH_2-C$\underline{H}$-), 5.93 (2H, q, J=7 Hz, -C$\underline{H}_2$-CH_3), 3.99—3.85 (1H, m, -CH_2-C$\underline{H}$-), 2.52, 1.92 (4H, d-d, J=9 Hz, -$C_6\underline{H}_4$-). *Anal.* Calcd. for $C_{13}H_{15}O_6N$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.47; H, 5.21; N, 5.06.

Ethyl (*R*)-3-Acetoxy-3-(*p*-nitrophenyl)propionate ((*R*)-IVa, X=OAc)——The reaction of (*R*)-IVb (X=OAc) (8.0 g) with fuming nitric acid (80 ml) and separation of the product were carried out similar to the synthesis of DL-IVa (X=OAc), described above, to give a pale yellow liquid (9.5 g), which was chromatographed on silica gel (200 g) with a mixture of benzene and AcOEt. The last fractions (3.0 g) which did not contain olefinic impurities were chromatographed twice more on silica gel (200 g and 100 g) with benzene–$CHCl_3$ (10:1) to give a colorless liquid (100 mg) of $[\alpha]_D^{20}$ +27.1° (c=1.728, 95% EtOH), $[\alpha]_{450}$ +51.5° (c=1.728, 95% EtOH). IR (in CS_2) and NMR (in $CDCl_3$) spectra of this sample were superimposable with those of DL-IVa (X=OAc) described above.

Ethyl (*R*)-3-Acetoxy-3-(*p*-methoxyphenyl)propionate ((*R*)-IVc, X=OAc)——This compound was prepared from (*R*)-IVb (X=OAc), in a manner similar to that for the conversion of (*S*)-IIb (X=OAc) to (*S*)-IIc (X=OAc), described above, as a colorless liquid of bp 127° (0.02 mmHg), $[\alpha]_D^{25}$ +4.45° (c=2.946, 95% EtOH), $[\alpha]_{450}^{28}$ +6.8° (c=2.946, 95% EtOH). IR ν_{max}^{film} cm^{-1}: 2840 (methoxy), 1742 (ester), 1238 (acetoxy). NMR (in CCl_4, 60 MHz) τ: 8.80 (3H, t, J=7 Hz, -CH_2-C$\underline{H}_3$), 8.03 (3H, s, -OCOC$\underline{H}_3$), 7.65—6.90 (2H, m, -C$\underline{H}_2$-CH-), 6.23 (3H, s, -OC$\underline{H}_3$), 5.94 (2H, q, J=7 Hz, -O-CH_2-CH_3), 4.12—3.88 (1H, m, -CH_2-C$\underline{H}$-), 3.21, 2.76 (4H, d-d, J=9 Hz, -$C_6\underline{H}_4$-). *Anal.* Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.89; H, 6.80.

N-Acetyl-N-nitroso-L-phenylalanine Ethyl Ester (VIII)——This compound was prepared according to White's method[13] with modifications as follows: Anhydrous AcONa (37.0 g, 0.450 mole) was added to a solution of N_2O_4[21] (20.8 g, 0.226 mole) in CCl_4 (304 ml) at −60°. N-Acetyl-L-phenylanine ethyl ester (VII) (mp 90—91°, $[\alpha]_D^{25}$ +14.0° (c=2.0, MeOH), 70% optical purity based on the reported value[22]) (35.3 g, 0.150 mole) was added portionwise to the stirred solution warmed at 0°, then the whole was stirred at a constant temperature for 20 min. The reaction mixture was poured into ice-water, and the whole was extracted with ether. Ethereal extracts were combined, washed successively with H_2O, 5% $NaHCO_3$, H_2O, and dried over anhydrous Na_2SO_4. Evaporation of the ether *in vacuo* left a pale yellow liquid (40.0 g), which was used without purification. IR ν_{max}^{film} cm^{-1}: 1518 (nitroso).

Pyrolysis of N-Acetyl-N-nitroso-L-phenylalanine Ethyl Ester (VIII) in AcOH——*a*) Determination of the Yields of Products: A solution of VIII (250 mg) in AcOH (2.5 ml) was heated at 85° for 45 min, then was evaporated *in vacuo* to dryness. The residue was analyzed by GLC[23] using methyl β-naphthyl ether as an internal standard. The result is shown in Table I.

b) Determination of Stereochemical Results: A solution of VIII (40.0 g) in AcOH (400 ml) was heated at 85° for 45 min, then was evaporated *in vacuo* to dryness. The residue was dissolved in ether. The ethereal solution was washed successively with H_2O, 10% HCl, H_2O, sat. $NaHCO_3$, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the ether *in vacuo* left a pale yellow liquid (24.2 g), which was chromatographed repeatedly on silica gel with benzene to give the following three compounds. These compounds were identified spectrally with their corresponding authentic samples as described above. i) IIb (X=OAc): bp 133—134° (7 mmHg). α_D^{23} +0.059° (l=0.1, neat), corresponding to be 9%[24] net inversion. ii) IIIb (X=OAc): bp 140—141° (7 mmHg). α_D^{25} +2.514° (l=0.1, neat), corresponding to be 60%[24] net inversion. iii) IVb (X=OAc): bp 145° (7 mmHg). α_D^{17} −0.239° (l=0.1, neat), corresponding to be 65%[24] (*S*).

N-(*p*-Tolylazo)-L-phenylalanine Ethyl Ester (IX)——A solution of *p*-tolyldiazonium fluoroborate[25] (4.90 g, 0.026 mole) in DMF (20 ml) was added dropwise to a stirred mixture of Ib (4.56 g, 0.0236 mole) and Na_2CO_3 (35.4 g, 0.334 mole) in DMF (70 ml) cooled at −5°, then the whole was stirred at 0° for 30 min. The reaction mixture was mixed with ether then filtered. The ethereal filtrate was washed with H_2O. Evaporation of the dried ethereal solution *in vacuo* left a dark-red liquid (7.32 g) of IX, which was used without purification. IR ν_{max}^{film} cm^{-1}: 3350 (NH), 1735 (ester).

The Reaction of N-(*p*-Tolylazo)-L-phenylalanine Ethyl Ester (IX) with AcOH——A solution of IX (4.08 g) in AcOH (40.8 ml) was refluxed for 2 hr, then was evaporated to dryness *in vacuo* to give a residue, which was analyzed by GLC.[23] The result is shown in Table I.

Ethyl 2-Diazo-3-phenylpropionate (X)——A solution of VIII (3.68 g) in benzene (50 ml) was refluxed for 2 hr, then was evaporated *in vacuo* to dryness. The residual pale yellow oil was chromatographed on alumina with benzene–hexane (1:1) to give X as a chromatographycally pure liquid (270 mg, 9% yield), which was used without further purification. IR ν_{max}^{film} cm^{-1}: 2080 (diazo), 1690 (ester).

21) A. Pedler and F.H. Pollard, "Inorganic Syntheses," Vol. V, ed. by T. Moeller, McGraw-Hill, New York, 1957, p. 87.
22) B. Zenner, R.P.M. Bond, and M. Bender, *J. Am. Chem. Soc.*, **86**, 3674 (1964).
23) GLC response ratios were established by analyzing known mixtures under the same conditions under which the actual analyses were performed.
24) A corrected value based on the fact that the starting material (VII) is 70% optically pure.
25) G. Barlz and G. Schiemann, *Ber.*, **60**, 1186 (1927).

The Reaction of Ethyl 2-Diazo-3-phenylpropionate (X) with AcOH——A solution of X (270 mg) in AcOH (2.7 ml) was stirred at 25° for 12 hr, then was evaporated to dryness *in vacuo*. The residue was analyzed by GLC[23] using methyl β-naphthyl ether as an internal standard. The result is shown in Table I.

General Procedure of Nitrous Acid Deamination——1.1 molar equivalents of $NaNO_2$ were added in portions for about 5 hr at room temperature to a stirred solution of L-amino acid ethyl ether (Ia, Ib, or Ic) in tenfold volume of 1N H_2SO_4, AcOH, or CF_3COOH then the whole was stirred at the same temperature overnight. In cases where AcOH or CF_3COOH was used, the solvent was evaporated *in vacuo* to dryness and the residue was mixed with H_2O. The aqueous reaction mixture was extracted several times with ether. Ethereal extracts were washed successively with sat. NaCl, sat. $NaHCO_3$, sat. NaCl, then dried over anhydrous Na_2SO_4. A mixture of reaction products was obtained as a liquid on evaporation of the solvent.

a) Determination of Product Yields: The mixture of reaction products was analyzed; by NMR[26] directly in the reaction of Ia in AcOH, by NMR[26] after conversion of reaction products to their corresponding acetates in the reaction of Ia in 1N H_2SO_4 and CF_3COOH, by GLC[23,27] directly in the reaction of Ic in AcOH, and by GLC[23,27] after reduction with $LiAlH_4$ followed by acetylation with Ac_2O and pyridine in the reactions of Ib and Ic in 1N H_2SO_4 and CF_3COOH. Results are shown in Table II.

b) Determination of Stereochemical Results: Stereochemical results were determined polarimetrically. For this purpose, a mixture of reaction products was separated directly in the reactions of Ia and Ic in AcOH, and after conversion to their corresponding acetates in the reactions of Ia, Ib, and Ic in 1N H_2SO_4 and CF_3COOH. Compounds separated were identified with their corresponding authentic samples described above by spectral comparisons. Results are shown partly in Table II. The data obtained on separated compounds, whith three typical examples of separation, are as follows.

i) The reaction of Ia in AcOH: A mixture of reaction products obtained from Ia in AcOH according to the general procedure was chromatographed repeatedly on silica gel with benzene to give two compounds. IIa (X=OAc): pale yellow solid of mp 67—68°, $[\alpha]_D^{31.5}$ +1.23° (c=2.028, 95% EtOH), corresponding to 13% net inversion; IVa (X=OAc): pale yellow solid of mp 50—51°, $[\alpha]_D^{20}$ −1.28° (c=2.344, 95% EtOH), $[\alpha]_{450}^{31}$ −4.10° (c=2.344, 95% EtOH), corresponding to 8% (*S*).

ii) The reaction of Ib in CF_3COOH: A mixture of reaction products obtained from Ib in CF_3COOH accroding to the general procedure was dissolved in AcOEt. The AcOEt solution was washed well with 10% aq. NaOH, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the solvent left an oily residue, which was treated with Ac_2O in pyridine in the usual manner. After evaporation of the reaction mixture *in vacuo*, the residue was chromatographed repeatedly on silica gel with benzene to give the following three compounds. IIb (X=OAc): colorless liquid of 134° (4 mmHg), α_D^{25} −0.545° (l=0.1, neat) corresponding to 66% net retention; IIIb (X=OAc): colorless liquid of bp 140—141° (7 mmHg), α_D^{23} +5.360 (l=0.1, neat), corresponding to 87% net inversion; IVb (X=OAc): bp 135—136° (7 mmHg), α_D^{17} +0.030° (l=0.1, neat), corresponding to 6% (*R*).

iii) The reaction of Ic in 1N H_2SO_4: A mixture of reaction products obtained from Ic in 1N H_2SO_4 according to the general procedure was treated with Ac_2O in pyridine in the usual manner. After evaporation of the reaction mixture *in vacuo*, the residue was chromatographed on silica gel with $CHCl_3$ to give IIc (X=OAc) and IIIc (X=OAc) as a mixture, and IVc (X=OAc) as a pure form. Preparative GLC of this mixture completely separated the two components, which were purified once again by chromatography on silica gel with Benzene–$CHCl_3$ (10:1). IIc (X=OAc): colorless liquid of bp 132° (0.1 mmHg), $[\alpha]_D^{25}$ +3.1° (c=2.0, 95% EtOH), corresponding to 37% net inversion; IIIc (X=OAc): colorless liquid of bp 133° (0.1 mmHg), $[\alpha]_D^{25}$ +13.5° (c=2.052, 95% EtOH), $[\alpha]_{400}^{33}$ +75.9° (c=2.052, 95% EtOH), corresponding to 76% net inversion; IVc (X=OAc): colorless liquid of bp 112° (0.01 mmHg), $[\alpha]_D^{25}$ −0.11° (c=5.634, 95% EtOH), $[\alpha]_{400}^{31}$ −0.32° (c=5.634, 95% EtOH), corresponding to 5% (*S*).

iv) The reaction of Ia in 1N H_2SO_4: IIa (X=OAc): pale yellow solid of mp 66—68°, $[\alpha]_D^{32}$ +3.7° (c=2.14, 95% EtOH), corresponding to 40% net inversion; IVa (X=OAc): pale yellow solid of mp 46—48°, showing a quite small optical rotation ($[\alpha]_{450}^{30}$ +0.88° (c=3.312, 95% EtOH)).

v) The reaction of Ia in CF_3COOH: IIa (X=OAc): pale yellow solid of mp 44—46°, $[\alpha]_D^{32.5}$ −4.5° (c=2.17, 95% EtOH), corresponding to 48% net retention; IVa (X=OAc): pale yellow soldi of mp 46—48°, showing a quite small optical rotation ($[\alpha]_{450}^{32}$ −0.64° (c=5.502, 95% EtOH).

vi) The reaction of Ib in 1N H_2SO_4: IIb (X=OAc): colorless liquid of bp 133° (7 mmHg), α_D^{23} +0.352° (l=0.1, neat), corresponding to 43% net inversion; IIIb (X=OAc): colorless liquid of bp 140—141° (7 mmHg), α_D^{23} +4.444° (l=0.1, neat), corresponding to 72% net inversion; IVb (X=OAc): colorless liquid of bp 135—136° (7 mmHg), α_D^{17} −0.115° (l=0.1, neat), corresponding to 22% (*S*).

vii) The reaction of Ic in AcOH: IIc (X=OAc): colorless liquid of bp 132° (0.03 mmHg), $[\alpha]_{450}^{27.5}$ +0.98° (c=2.04, 95% EtOH), corresponding to 8% net inversion; IIIc (X=OAc): colorless liquid of bp 133° (0.02 mmHg), $[\alpha]_D^{25}$ +22.6° (c=2.4, 95% EtOH), $[\alpha]_{400}^{29}$ +62.1° (c=2.4, 95% EtOH), corresponding to 61% net

26) *p*-Nitroanisole was used as an internal standard.
27) Methyl β-naphthyl ether was used as an internal standard.

inversion; IVc (X=OAc): colorless liquid of bp 132° (0.03 mmHg), $[\alpha]_D^{25}$ −1.1° (c=2.00, 95% EtOH), $[\alpha]_{400}^{28}$ −1.54° (c=4.536, 95% EtOH), corresponding to 23% (*S*).

viii) The reaction of Ic in CF_3COOH: IIc (X=OAc): colorless liquid of bp 132° (0.03 mmHg), $[\alpha]_D^{25}$ −7.26° (c=1.132, 95% EtOH), $[\alpha]_{450}^{30}$ −10.2 (c=1.132, 95% EtOH), corresponding to 80% net retention; IIIc (X=OAc): colorless liquid of bp 132° (0.02 mmHg), $[\alpha]_D^{25}$ +31.3° (c=2.592, 95% EtOH), $[\alpha]_{400}^{29.5}$ +89.5° (c=2.592, 95% EtOH), corresponding to 88% net inversion.