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Stereochemical Studies. XXXVI.[1] Stereoselective Syntheses of *trans*- and *cis*-Cinnamic Acid Esters from the Phenylalanine Derivatives[2]

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α-Diazo-β-phenyl-propionic acid esters (II) prepared from the phenylalanine derivatives (I) were readily decomposed by the alkoxide in tetrahydrofuran to give *trans*-cinnamic acid esters (III) stereoselectively, while the decomposition of II in the presence of boron trifluoride etherate and dicyclohexylcarbodiimide in methylene chloride afforded *cis*-cinnamic acid esters (IV) as sole reaction products.

In previous papers[4] we described a very convenient method for preparation of various α-substituted-α-diazoesters from the corresponding α-amino acids. A variety of reactions of ethyl diazoacetate have been widely studied, most of which involve a carbene as an intermediate. When these α-substituted-α-diazoesters having the methylene group adjacent to the diazo carbon are submitted to a carbene reaction, it is plausible that a hydrogen atom on the methylene group shifts to the carbene formed, affording a mixture of isomeric olefins.[5] It was found that some reactions of this type, such as the Cu-catalyzed or photochemical decomposition of α-diazo-β-phenylpropionic acid ester (II), actually gave a mixture of *trans*- (III) and *cis*- cinnamic acid esters (IV) (Cu-catalyzed: III/IV=65/35, photochemical: III/IV=39/61).

We have been consequently investigating some non-carbene type reactions of α-substituted-α-diazoesters and now wish to report stereoselective syntheses of III and IV from II derived from the phenylalanine derivatives (I).

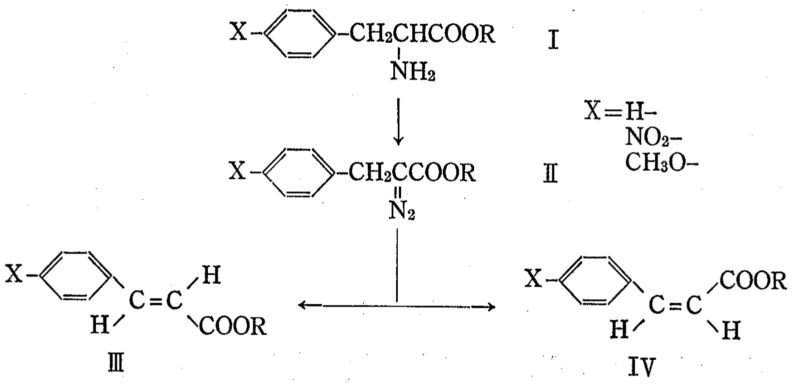

Chart 1

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[1] Part XXXV: M. Shibasaki, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), 23, 279 (1975).

[2] This work was the subject of a preliminary report: N. Takamura, T. Mizoguchi, and S. Yamada, *Tetrahedron Letters*, **1973**, 4267.

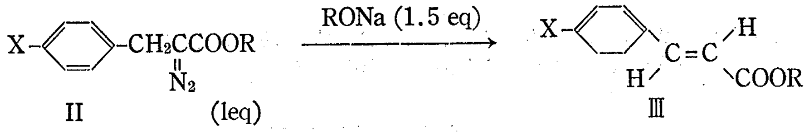
[3] Location: *a) 2-2-50, Kawagishi, Toda-shi, Saitama, 335, Japan*; *b) 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan.*

[4] N. Takamura, T. Mizoguchi, K. Koga, and S. Yamada, *Tetrahedron Letters*, **1971**, 4495; *idem*, *Tetrahedron*, "in press."

[5] W. Kirmse, "Carbene Chemistry," ed. by A.T Blomquist, Academic Press, New York, 1964.

Studies on enzymatic deamination of phenylalanine to *trans*-cinnamic acid are well documented,[6] but chemical deaminations of this amino acid and its ester generally give a variety of products.[7] Our detailed examinations on II, however, showed that II was decomposed with sodium alkoxide to afford III stereoselectively and also that the decomposition of II in the presence of $BF_3O(C_2H_5)_2$ and dicyclohexylcarbodiimide (DCCD) gave IV solely.

TABLE I.



	X	R	Reaction conditions	Yield (%)	Content of IV (%)[a]
IIIa	CH_3O	C_2H_5	50°, 1.5 hr	72	<1
IIIb	H	CH_3	R.temp., 3 hr	72	none
IIIc	NO_2	C_2H_5	−78°→R.temp., 1 hr	59	none

a) measured by VPC, see ref. 15 R. temp. (room temp.)

When II dissolved in tetrahydrofuran was left standing in the presence of the alkoxide, gentle evolution of nitrogen gas took place and the product, after purification on preparative thin-layer chromatography (TLC) (silica gel, benzene), was characterized as III.[8] The yields are given in Table I together with reaction conditions employed in each case. A substituent at the *p*-position of the aromatic ring apparently influences removability of the hydrogen atom from the *β*-carbon, and stronger reaction conditions are required in proportion to the increase of the electron density at the *β*-carbon. This result is tentatively rationalized by the following mechanism. The reaction may be initiated by removal of a molecule of nitrogen to give the intermediate (V), which is subsequently converted into thermodynamically stable III.

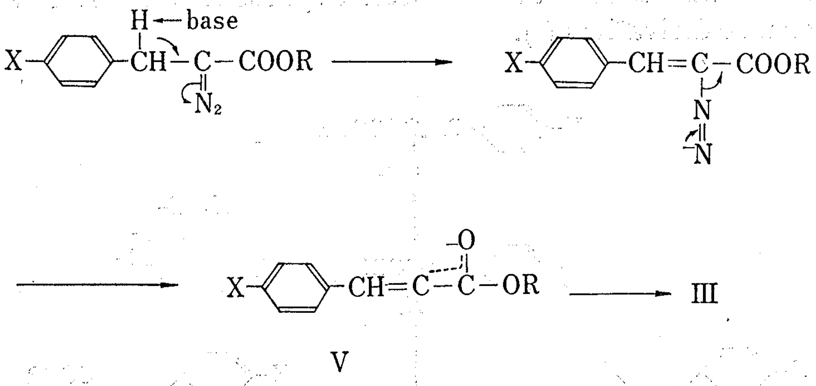


Chart 2

The decomposition of II by sodium bistrimethylsilylamide also gave III stereoselectively, while the product was accompanied with the corresponding *trans*-free acid (VI) in this case. The yields are given as the total yields of VI, after hydrolysis of III, (VIa: X=CH_3O, 52%; VIb: X=H, 51% yield).

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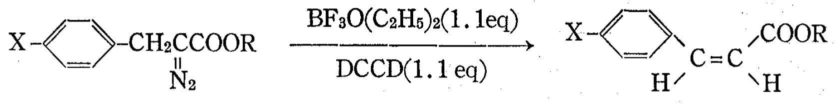
[6] J. Koukal and E.E. Conn, *J. Biol. Chem.*, **236**, 2692 (1961); K.R. Hanson, R.H. Wightman, J. Staunton, and A.R. Battersby, *J. Chem. Soc. D.*, **1971**, 185.

[7] K. Koga, C.C. Wu, and S. Yamada, *Tetrahedron Letters*, **1971**, 2283, 2287; *idem*, *Chem. Pharm. Bull.* (Tokyo), **20**, 1272, 1282 (1972).

[8] The vapar phase chromatography (VPC) of the reaction mixture showed that the content of IV in III was less than 1%.

Although synthetic methods for the thermodynamically more stable *trans*-cinnamic acid are commonly known,[9] only few methods are available for the *cis*-isomer, such as hydrogenation of phenylpropiolic acid using special catalysts (*e.g.* Lindlar catalyst[10,11]) or UV irradiation of the *trans*-cinnamic acid esters.[12]

TABLE II



II (leq) IV

	X	R	Yield (%)	Content of III (%)[a]
IVa	CH_3O	C_2H_5	71	<1
IVb	H	C_2H_5	80	<2
IVc	NO_2	C_2H_5	68	none

a) measured by VPC, see ref. 15

When II was treated with $BF_3O(C_2H_5)_2$ in the presence of DCCD in CH_2Cl_2 at 0—5°, IV was easily obtained in a fairly good yield.[13] The yields, after purification on column chromatography are given in Table II. The oily products, IVa and IVb, were hydrolyzed to the corresponding *cis*-acids (VIIa: X=CH_3O, 88%; VIIb: X=H, 74% yield) and identified. In the absence of DCCD, the reaction occurred even at −78° with vigorous evolution of nitrogen to give a complex mixture of several kinds of products. Assuming that DCCD simply weakened the acidity of BF_3, we attempted to use pyridine, $C_6H_5N{=}CHC_6H_5$ or $(C_6H_5)_3P$ instead of DCCD, but the results obtained were similar to that in the absence of DCCD. Therefore this reaction evidently requires DCCD.

Although the mechanism of this reaction has not been clarified yet, the intermediate of the reaction is presumably a cycloaddition product, 1,2,3-triazoline derivative.[14] Of the three possible comformations, VIIIa, b and c, VIIIa must be most preferable because of the least steric repulsion between the aromatic ring and cyclohexane ring. Concomitant elimination of DCCD (as the BF_3 complex) and nitrogen from VIIIa thus gives IV stereoselectively.

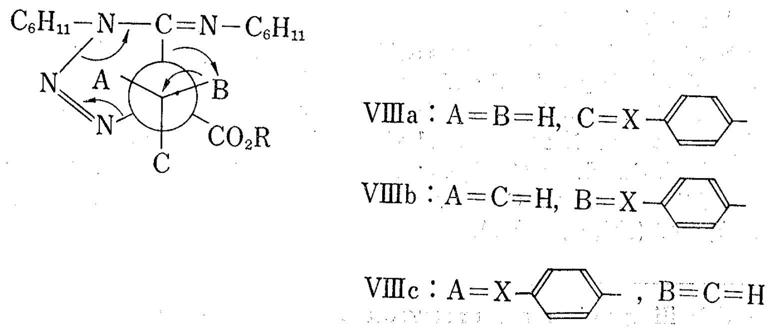


Chart 3

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9) C.S. Marvel and W.B. King, "Org. Syntheses," Coll. Vol. I, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York. 1941, p. 252.

10) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

11) E.A.R. Visscher and E.C. Kooyman, *J. Catalysis*, **2**, 421 (1963).

12) E. Grovenstein, Jr. and S.P. Theophilon, *J. Am. Chem. Soc.*, **77**, 3795 (1955).

13) The VPC of the reaction mixture showed that the content of III in IV was less than 2%.

14) Such a cycloaddition between carbodiimides and diazomethane was alread reportedy by Rotter; *Monatsh. Chem.*, **47**, 353, (1926).

Experimental[15]

trans-*p*-Methoxycinnamic Acid Ethyl Ester (IIIa)——To a suspension of sodium ethoxide (prepared from 0.17 g of Na, 7.5 mmole) in tetrahydrofuran (THF) (85 ml) was added at $-78°$ a solution of α-diazo-β-*p*-methoxyphenylpropionic acid ethyl ester[4] (1.17 g, 5 mmole) in THF (15 ml) and the mixture was kept at 50° for 1.5 hr, neutralized with AcOH and concentrated *in vacuo* to remove THF. The residue was taken up in AcOEt, washed with 2% HCl, H_2O, satd. $NaHCO_3$ and H_2O, and then dried over Na_2SO_4. Filtration and evaporation gave a reddish brown oil[8] (0.86 g), which was purified on preparative TLC (silica gel, eluent: benzene) to afford IIIa (0.74 g, 72%), mp 46—48°. Recrystallization from ethanol afforded colorless prisms, mp 48—49° (lit.,[16] mp 48—49°). *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.51; H, 6.97. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1710, 1633, 1600, 1570, 1515. NMR (in $CDCl_3$) τ: 8.70 (3H, t, 7 Hz), 6.26 (3H, s), 5.84 (2H, q, 7 Hz). 3.80 (1H, d, 16 Hz), 3.22 (2H, d, 8 Hz), 2.63 (2H, d, 8 Hz), 2.45 (1H, d, 16 Hz).

trans-Cinnamic Acid Methyl Ester (IIIb)——To a suspension of sodium methoxide (7.5 mmole) in THF (85 ml) was added at $-78°$ a solution of α-diazo-β-phenylpropionic acid methyl ester[4] (0.95 g, 5 mmole) in THF (15 ml) and the mixture was stirred for 3 hr at room temperature. Working-up of the brown reaction mixture in a similar manner described above for IIIa gave a pale yellow solid[8] (0.68 g), which was purified on preparative TLC (silica gel, eluent: benzene) to give IIIb (0.58 g, 72%), mp 31—33°. Recrystallization from hexane afforded colorless prisms, mp 36° (lit.,[17] mp 33.4°). *Anal.* Calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 73.79; H, 6.32. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1720, 1640. NMR (in $CDCl_3$) τ: 6.30 (3H, s), 3.70 (1H, d, 16 Hz), 2.73 (5H, m), 2.42 (1H, d, 16 Hz).

trans-*p*-Nitrocinnamic Acid Ethyl Ester (IIIc)——To a solution of sodium ethoxide (7.5 mmole) in THF (85 ml) was added at $-78°$ a solution of α-diazo-β-*p*-nitrophenylpropionic acid ethyl ester[4] (1.25 g, 5 mmole) in THF (15 ml). The dark purple mixture was stirred for 1 hr at $-78° \rightarrow 25°$ and treated in a manner similar to that of IIIa to give a yellow solid[8] (0.82 g). Purification of the solid by preparative TLC (silica gel, eluent: benzene) afforded IIIc (0.65 g, 59%), mp 127—130°. Two recrystallizations from ethanol gave slightly yellow leaflets, mp 132—134° (lit.,[18] mp 136°). *Anal.* Calcd. for $C_{11}H_{11}O_4N$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.65; H, 5.11; N, 6.40. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1712, 1645, 1600, 1595, 1520. NMR (in $CDCl_3$) τ: 8.67 (3H, t, 7 Hz), 5.77 (2H, q, 7 Hz), 3.53 (1H, d, 16 Hz), 2.40 (2H, d, 9 Hz), 2.35 (1H, d, 16 Hz), 1.85 (2H, d, 9 Hz).

trans-*p*-Methoxycinnamic Acid (VIa)——To a solution of sodium bistrimethylsilylamide (1.10 g, 6 mmole) in THF (85 ml) was added dropwise over a 60-minutes period a solution of α-diazo-β-*p*-methoxyphenylpropionic acid ethyl ester[4] (1.17 g, 5 mmole) in THF (15 ml) at room temperature, and the resultant dark brown solution was stirred for 20 hr, neutralized with AcOH and concentrated *in vacuo* to remove THF. The residue was dissolved in AcOEt, washed with 1% HCl and H_2O, and then extracted with 10% K_2CO_3. The organic phase was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The reddish brown oil (0.52 g) thus obtained was purified on preparative TLC (silica gel, eluent: benzene–ethyl acetate) to give IIIa[8] (0.25 g), whose IR and NMR spectra were identical with those of an authentic sample. IIIa obtained was hydrolyzed for 4 hr at room temperature in a solution of 2.5 N NaOH (1.25 ml) and MeOH (6 ml). The mixture was diluted with H_2O and washed with AcOEt. The aqueous layer was acidified with conc. HCl and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried and evaporated to dryness to give VIa as colorless crystals (0.19 g), mp 164—165°.

The 10% K_2CO_3 extract mentioned above was acidified with conc. HCl and extracted with AcOEt. The AcOEt solution was washed with H_2O, dried and evaporated to dryness to leave a semisolid, which was triturated with AcOEt–hexane to afford VIa as pale yellow crystals (0.27 g), mp 164—167°, (total 0.46 g, 52%). Recrystallization from AcOEt afforded colorless prisms, mp 170→171°, clarified at 184° (lit.,[19] mp 170°, clarified at 185°). *Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.17; H, 5.53. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1690, 1623, 1598, 1515. NMR (in $CDCl_3$-d_6-DMSO) τ: 6.27 (3H, s), 3.79 (1H, d, 16 Hz) 3.19 (2H, d, 8 Hz), 2.62 (2H, d, 8 Hz), 2.49 (1H, d, 16 Hz).

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15) All the melting and boiling points are uncorrected. Infrared (IR) spectra were taken with Hitachi 215 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded at 60 Mc on Japan Electron Optical Models JNM-60 NMR spectrometer, (Abbreviation; s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet). Gas–liquid chromatography (GLC) analyses were carried out with Shimazu Model GC-1C gaschromatograph (EGA, column length 1.8 m. $X=H$, $R=CH_3$; column temp. 70°, retention time *trans*: 3.4 min. $X=H$, $R=C_2H_5$; 80° *cis*; 3.1 min, *trans*: 6.0 min) and Perkin Elmer Model 800 gaschromatograph (OV-17, 1.1 m. $X=CH_3O$, $R=C_2H_5$; 150°, *cis*: 2.7 min, *trans*: 4.9 min. $X=NO_2$, $R=C_2H_5$; 180°, *cis*: 1.8 min, *trans*: 3.0 min)

16) D. Vorländer, *Ann. Chem.*, **294**, 253 (1897).

17) R. Anschütz and L. Kinnicutt, *Chem. Ber.*, **11**, 1219 (1878).

18) Y. Urushibara and M. Hirota, *Nippon Kagaku Zasshi*, **82**, 351, 358 (1961).

19) Th. Rotarski, *Chem. Ber.*, **41**, 1994 (1908).

***trans*-Cinnamic Acid (VIb)**——To a solution of sodium bistrimethylsilylamide (1.10 g, 6 mmole) in THF (85 ml) was added dropwise a solution of α-diazo-β-phenylpropionic acid methyl ester[4] (0.95 g, 5 mmole) in THF (15 ml). The mixture was stirred for 24 hr at room temperature and treated in the same manner as for VIa described above affording VIb as colorless prisms (0.38 g, yield 51%), mp 130—132° (lit.,[20] mp 133°). *Anal.* Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 73.19; H, 5.54. IR ν_{max}^{Nujol} cm^{-1}: 1685, 1630. NMR (in $CDCl_3$-d_6-DMSO) τ: 3.52 (1H, d, 16 Hz), 2.54 (5H, m), 2.18 (1H, d, 16 Hz).

***cis-p*-Methoxycinnamic Acid Ethyl Ester (IVa)**——A solution of α-diazo-β-*p*-methoxyphenylpropionic acid ethyl ester[4] (2.1 g, 9 mmole) and DCCD (2.04 g, 9.9 mmole) in CH_2Cl_2 (40 ml) was cooled to −78° in a dry ice-acetone bath. To the solution was added a cold solution of $BF_3O(C_2H_5)_2$ (1.40 g, 9.9 mmole) in CH_2Cl_2 (10 ml). The bath was then replaced by ice-water bath. The diazoester began to decompose with gentle evolution of nitrogen gas. After being kept to stand at 0—5° for 22 hr, the reaction mixture was diluted with CH_2Cl_2 (30 ml), washed successively with H_2O, satd. $NaHCO_3$ and H_2O, and then dried over Na_2SO_4. Filtration and evaporation gave a yellow residue,[13] which was chromatographed over silica gel column (80 g, eluent: benzene) to give IVa as a colorless oil (1.31 g, 71%). Distillation gave a pure sample, which was analyzed, bp 110—112° (0.2 mmHg). *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.82; H, 6.66. IR ν_{max}^{liq} cm^{-1}: 1715, 1620, 1600, 1570, 1510. NMR (in $CDCl_3$) τ: 8.76 (3H, t, 7 Hz), 6.25 (3H, s), 5.85 (2H, q, 7 Hz), 4.23 (1H, d, 12 Hz), 3.20 (1H, d, 12 Hz), 3.17 (2H, d, 9 Hz), 2.34 (2H, d, 9 Hz).

***cis-p*-Methoxycinnamic Acid (VIIa)**——A solution of IVa (0.78 g, 3.78 mmole) in 1N NaOH (10 ml) and ethanol (15 ml) was allowed to stand for 3 hr at room temperature, diluted with H_2O (30 ml) and washed with ether. The aqueous layer was acidified with conc. HCl and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to leave VIIa (0.59 g, 88%), mp 65—66°. Recrystallization from benzene–hexane afforded colorless plates, mp 68° (lit.,[18] mp 66.5°). *Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.16; H, 5.54. IR ν_{max}^{Nujol} cm^{-1}: 1685, 1595, 1565, 1510. NMR (in $CDCl_3$) τ: 6.28 (3H, s), 4.22 (1H, d, 13 Hz), 3.20 (2H, d, 9 Hz), 3.11 (1H, d, 13 Hz), 2.33 (2H, d, 9 Hz).

***cis*-Cinnamic Acid Ethyl Ester (IVb)**——To a solution of α-diazo-β-phenylpropionic acid ethyl ester[4] (2.04 g, 10 mmole) and DCCD (2.27 g, 11 mmole) in CH_2Cl_2 (40 ml) was added at −78° a cold solution of $BF_3O(C_2H_5)_2$ (1.56 g, 11 mmole) in CH_2Cl_2 (10 ml). The reaction mixture was allowed to stand at 0—5° for 19 hr and worked up in a similar manner to that described above to give a brown oil,[13] which was submitted to column chromatography on silica gel (120 g, eluent: benzene–hexane) to give IVb (1.41 g, 80%) as a colorless oil, bp 69—71° (0.25 mmHg). IR ν_{max}^{liq} cm^{-1}: 1719, 1630. NMR (in $CDCl_3$) τ: 8.80 (3H, t, 7 Hz), 5.85 (2H, q, 7 Hz), 4.05 (1H, d, 13 Hz), 3.04 (1H, d, 13 Hz), 2.20—2.75 (5H, m).

***cis*-Cinnamic Acid (VIIb)**——A solution of IVb (0.88 g, 5 mmole) and 1N NaOH (10 ml) in ethanol (15 ml) was kept standing for 2.5 hr at room temperature and treated with a method similar to that for VIIa to give VIIb (0.55 g, 74%). Two recrystallizations from hexane afforded colorless elongated prisms, mp 67—68° (lit.,[11] mp 68°). *Anal.* Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.87; H, 5.64. IR ν_{max}^{Nujol} cm^{-1}: 1683, 1625. NMR (in $CDCl_3$) τ: 4.10 (1H, d, 13 Hz), 3.00 (1H, d, 13 Hz), 2.20—2.85 (5H, m).

***cis-p*-Nitrocinnamic Acid Ethyl Ester (IVc)**——To a solution of α-diazo-β-*p*-nitrophenylpropionic acid ethyl ester[4] (0.90 g, 3.6 mmole) and DCCD (0.82 g, 3.96 mmole) in CH_2Cl_2 (20 ml) was added at −78° a cold solution of $BF_3O(C_2H_5)_2$ (0.56 g, 3.96 mmole) in CH_2Cl_2 (10 ml). The whole was kept standing at 0—5° for 20 hr and worked up in a similar manner as for IVa to give a brown oil,[13] which was purified on column chromatography using silica gel (70 g, eluent: benzene) to give IVc (0.54 g, 68%), mp 52—53°. Recrystallization from ether–hexane afforded faint yellow prisms, mp 53—54° (lit.,[18] mp 53°). *Anal.* Calcd. for $C_{11}H_{11}O_4N$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.58; H, 4.98; N, 6.44. IR ν_{max}^{Nujol} cm^{-1}: 1705, 1630, 1600, 1595, 1515. NMR (in $CDCl_3$) τ: 8.78 (3H, t, 7 Hz), 5.86 (2H, q, 7 Hz), 3.94 (2H, d, 12 Hz), 3.01 (2H, d, 12 Hz), 2.36 (2H, d, 9 Hz), 1.84 (2H, d, 9 Hz).

Cu-catalyzed Decomposition of α-Diazo-β-phenylpropionic Acid Ethyl Ester——A mixture of α-diazo-β-phenylpropionic acid ethyl ester[4] (0.51 g, 2.5 mmole) and Cu powder (0.05 g) in benzene (15 ml) was stirred for 78 hr at room temperature. Filtration and evaporation gave an oil (0.43 g), which was purified on column chromatography using silica gel (40 g, eluent: benzene–hexane) to give a mixture of *cis*- and *trans*-cinnamic acid ethyl esters (0.15 g, 34%). The VPC of the mixture showed that the *trans*/*cis* ratio was 65/35.

Photochemical Decomposition of α-Diazo-β-phenylpropionic Acid Ethyl Ester——A yellow solution of α-diazo-β-phenylpropionic acid ethyl ester[4] (0.51 g, 2.5 mmole) in CH_2Cl_2 (30 ml) was irradiated with a 20W low pressure Hg lamp for 25 hr under flowing Argon gas. The resultant colorless solution was evaporated to dryness *in vacuo* to give a pale yellow oil (0.47 g), which was chromatographed over silica gel column (40 g, eluent: benzene–hexane) to afford a mixture of *cis*- and *trans*-cinnamic acid ethyl esters (0.34 g, 77%). The VPC of the mixture showed that the *trans*/*cis* ratio was 39/61.

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20) K. Kraut, *Ann. Chem.*, 133, 87 (1865).