Synthesis and Herbicidal Activity of Optically Active Methyl 3-Hydroxy-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoates

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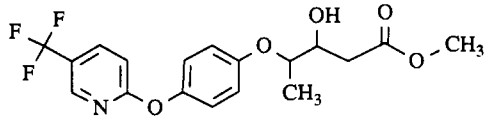
Extensive field testing has shown methyl 3-hydroxy-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate to be a highly active postemergent herbicide. All four diastereomers were prepared separately, and their individual herbicidal activities were evaluated. The two diastereomers of *R* configuration at C-4 were found to be approximately twice as active as the racemic material and 8-fold more active than the corresponding *S* isomers. The absolute stereochemistry at C-3 had no effect on the biological activity. The dependence of the herbicidal activity on the absolute configuration at C-4 can be rationalized if methyl 3-hydroxy-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate is degraded in vivo to a 2-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]propionic acid derivative.

Considerable interest has arisen over the correlation of the stereochemical configuration of 2-(aryloxy)propionic acid derivatives with their biological activities (Matell, 1955; Chan et al., 1975; Cartwright, 1979; Oshumi et al., 1985). Our interest in this area concerned the herbicidal activity of the derivatives of [(pyridinyloxy)phenoxy]alkanoic acids. Methyl 3-hydroxy-4-[4-[[(5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate (1; code number SC-1084; licensed from Zoecon Corp.) was found to have high postemergent graminicidal activity (Lee, 1985). We report the synthesis and separation of the four diastereomers of 1 and their comparative herbicidal activities.



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EXPERIMENTAL SECTION

General Methods. Routine proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM-360 spectrometer using tetramethylsilane as the internal standard in the indicated solvent. The determination of optical purities by ^{1}H NMR using the lanthanide shift reagent was conducted with a Varian XL-400 spectrometer. The mass spectrum of each compound was measured on a Finnigan Model 1020B spectrometer. The infrared spectra were recorded on a Beckman 4250 spectrophotometer. Melting points were determined on a Buchi 510 apparatus and are uncorrected. Optical rotations were determined on a Rudolph Research AutoPol II.

Ethyl (*S*)-2-[[(4-Methylphenyl)sulfonyl]oxy]propionate (3). Propionate 3 was prepared from ethyl (*S*)-2-hydroxypropionate (2; Aldrich Chemical Co.; 90% ee) according to the method described by Chan et al. (1975). The crude product was recrystallized from ether–hexanes (1:1) to give a 97% yield of 3 as white needles: mp 31–34 °C; ^{1}H NMR (δ, $CDCl_3$) 1.18 (3 H, t, J = 7 Hz), 1.49 (3 H, d, J = 7 Hz), 2.43 (3 H, s), 4.10 (2 H, q, J = 7 Hz), 4.92 (1 H, q, J = 7 Hz), 7.35 (2 H, d, J = 8 Hz), 7.81 (2 H, d, J = 8 Hz); IR (film) 2895, 1720, 1600, 1370, 1190, 1175, 1120, 1080, 1025, 940, 885, 815, 780, 660, 550 cm^{-1}; $[\alpha]^{20}_D$ −35.0° ($CHCl_3$, *c* 2.7).

Ethyl (*R*)-2-[4-[[5-(Trifluoromethyl)-2-pyridinyl]oxy]phenoxy]propionate (4). To a stirred solution of 150 g (0.59 mol) of 4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenol and 162 g (0.59 mol) of ethyl (*S*)-2-[[(4-methylphenyl)sulfonyl]oxy]-propionate (3) in 500 mL of DMSO was added 122 g (0.88 mol) of potassium carbonate. The resulting slurry was heated at approximately 40 °C for approximately 2 days, cooled to ambient temperature, and filtered. The filtrate was acidified with 300 mL of 3 N HCl, diluted with 700 mL of water, and extracted twice with 500 mL of ether. The combined organic layers were washed with 500 mL of 3 N HCl, dried over magnesium sulfate, and concentrated under reduced pressure to give 192 g (92% yield) of 4 as a brown oil. Distillation (bulb-to-bulb) afforded 187 g of 4 as a yellow oil: bp 127–145 °C (0.2 mmHg); ^{1}H NMR (δ, $CDCl_3$) 1.13 (3 H, t, J = 7 Hz), 1.50 (3 H, d, J = 7 Hz), 4.06 (2 H, q, J = 7 Hz), 4.63 (1 H, q, J = 7 Hz), 6.67–7.20 (5 H, m), 7.82 (1 H, dd, J = 2.5 Hz, J = 8.5 Hz), 8.39 (1 H, m); IR (film) 2895, 1720, 1640, 1510, 1490, 1330, 1290, 1245, 1200, 1135, 1080 cm^{-1}; MS, *m/e* 355, 336, 282, 254, 238, 227, 146, 141, 126, 119, 91, 75, 69, 63, 45; $[\alpha]^{20}_D$ +34.5° ($CHCl_3$, *c* 2.7). The optical purity of 4 was assessed by addition of the chiral shift reagent, tris[3-[(trifluoromethyl)hydroxymethylene]-*d*-camphorato]-europium(III) (Aldrich), in small increments directly to a sample of 4 in carbon tetrachloride, the ^{1}H NMR spectrum being recorded after each addition. The sample was determined to contain 94% of the major isomer (88% ee).

(*R*)-2-[4-[[5-(Trifluoromethyl)-2-pyridinyl]oxy]phenoxy]propionic Acid (5). To a stirred solution of 10.3 g (0.028 mol) of ethyl (*R*)-2-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]-phenoxy]propionate (4) in 41 mL of methanol was added a solution of 4.64 g (0.083 mol) of potassium hydroxide in 41 mL of water, while the temperature was maintained at 23 °C. After 1 h the reaction mixture was concentrated in vacuo and the residue diluted with 45 mL of toluene and 45 mL of water. Concentrated hydrochloric acid was added to adjust to pH 9, and the mixture was heated to 80 °C. The aqueous phase was separated and cooled to ambient temperature, acidified to pH 1 with concentrated hydrochloric acid, and extracted twice with 50 mL of ether. The combined ethereal extracts were dried over magnesium sulfate and evaporated in vacuo to give 8.93 g (96% yield) of 5 as a nearly colorless resin: ^{1}H NMR (δ, DMSO-d_6) 1.56 (3 H, d, J = 6.5 Hz), 4.62 (1 H, q, J = 6.5 Hz), 6.67–7.10 (5 H, m), 7.78 (1 H, dd, J = 2.5 Hz, J = 8.5 Hz), 8.24 (1 H, m), 11.03 (1 H, br s); IR (film) 2995, 1740, 1620, 1580, 1510, 1490, 1400, 1340, 1290, 1245, 1205, 1135, 1080, 840 cm^{-1}; MS, *m/e* 327, 308, 282, 268, 254, 238, 227, 146, 126, 91; $[\alpha]^{20}_D$ +21.4° ($CHCl_3$, *c* 2.7).

Methyl (*R*)-3-Oxo-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate (6). To a stirred solution of 7.40 g (0.022 mol) of (*R*)-2-[4-[[5-(trifluoromethyl)-2-pyridinyl]-oxy]phenoxy]propionic acid (5) in 37 mL of THF was added 8.62 g (0.053 mol) of 1,1′-carbonyldiimidazole. After the reaction mixture was allowed to stir at ambient temperature under a nitrogen atmosphere overnight, 5.73 g (0.022 mol) of the mag-

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nesium salt of monomethyl malonate [prepared from monomethyl malonate (Strube, 1964) and magnesium in methanol] was added. The reaction mixture was stirred for 4 h and then evaporated to dryness. The residue was partitioned between 35 mL of ether and 50 mL of 3 M HCl. The ethereal layer was washed with 75 mL of saturated sodium bicarbonate solution, dried over magnesium sulfate, and concentrated in vacuo to afford 7.88 g (93% yield) of **6** as an orange oil. Purification of 1.0 g of **6** by radial thin-layer chromatography on silica, eluting with ethyl acetate–hexanes (3:1) gave 0.74 g of a pale yellow oil that solidified upon standing: mp 60–63 °C; ^{1}H NMR (δ, $CDCl_3$) 1.43 (3 H, d, J = 6.5 Hz), 3.58 (5 H, s), 4.74 (1 H, q, J = 6.5 Hz), 6.68–7.22 (5 H, m), 7.78 (1 H, dd, J = 2.5 Hz, J = 8 Hz), 8.32 (1 H, m); IR (film) 3000, 2960, 1755, 1730, 1615, 1505, 1485, 1330, 1290, 1240, 1200, 1165, 1130, 1080, 1010, 835 cm^{-1}; MS, m/e 383, 364, 352, 282, 254, 238, 227, 146, 129, 119, 91; $[\alpha]^{20}_D$ +21.5° ($CHCl_3$, c 2.7). Anal. Calcd for $C_{18}H_{16}F_3NO_5$: C, 56.4; H, 4.2; N, 3.6. Found: C, 56.0; H, 3.8; N, 3.4.

Methyl (4*R*)-3-Hydroxy-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate (7). Methyl (*R*)-3-oxo-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate (**6**; 5.50 g, 0.013 mol) was dissolved in 42 mL of methanol and the resulting solution cooled to 0 °C. Sodium borohydride (0.14 g, 0.004 mol) was added in three portions over 15 min, maintaining the temperature below 5 °C. The reaction mixture was diluted with 25 mL of water and concentrated in vacuo. The residue was partitioned between 25 mL of 0.6 N HCl and 25 mL of ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to afford a pale yellow oil that was purified by chromatography on silica, eluting with ethyl acetate–hexanes (1:2), to give 3.7 g (79% yield) of **7** as a colorless oil: ^{1}H NMR (δ, $CDCl_3$) 1.32 (3 H, d, J = 5.5 Hz), 2.61 (2 H, d, J = 7 Hz), 3.37–3.75 (1 H, m), 3.63 (3 H, s), 3.92–4.58 (2 H, m), 6.68–7.12 (5 H, m), 7.73 (1 H, dd, J = 2.5 Hz, J = 8.5 Hz), 8.29 (1 H, m); IR (film) 3460, 2990, 2955, 1735, 1610, 1580, 1500, 1485, 1330, 1240, 1200, 1130, 1080, 1060, 1010, 890, 835, 755 cm^{-1}; MS, m/e 385, 366, 354, 282, 254, 238, 227, 146, 131, 99, 71, 57, 43; $[\alpha]^{20}_D$ −10.5° ($CHCl_3$, c 2.6). Anal. Calcd for $C_{18}H_{18}F_3NO_5$: C, 56.1; H, 4.7; N, 3.6. Found: C, 55.6; H, 4.5; N, 3.5.

Chromatographic Separation of Esters 7a and 7b. Diastereomers **7a** and **7b** were separated on a Waters Associates M-6000 HPLC system equipped with an Altex 25 cm × 10 mm Lichrosorb Si-60 column (5-μm packing) and a Du Pont Model 842 UV detector set at 254 nm. The mobile phase consisted of a ternary mixture of hexanes–ethyl acetate–acetonitrile (85:12:3). Samples were dissolved in the mobile phase and injected onto the column with use of a 0.85-mL injection loop. Using the combined techniques of peak-shaving and multiple recycles at a flow rate of 9.2 mL/min, 1.0-g portions of **7a** (t_R 35.3 min) and **7b** (t_R 40.3 min) were collected.

Methyl (*R*)-2-[[(4-Methylphenyl)sulfonyl]oxy]propionate (9). Propionate **9** was prepared from methyl (*R*)-2-hydroxypropionate (**8**; CCA Biochem; 85% ee) in a manner analogous to the preparation of ethyl (*S*)-2-[[(4-methylphenyl)-sulfonyl]oxy]propionate (**3**) (vide supra): ^{1}H NMR (δ, $CDCl_3$) 1.48 (3 H, d, J = 7 Hz), 2.40 (3 H, s), 3.58 (3 H, s), 4.87 (1 H, q, J = 7 Hz), 7.18 (2 H, d, J = 8 Hz), 7.65 (2 H, d, J = 8 Hz); IR (KBr) 2880, 1770, 1600, 1455, 1375, 1190, 1180, 1085 cm^{-1}; $[\alpha]^{20}_D$ +34.0° ($CHCl_3$, c 2.7).

Methyl (*S*)-2-[4-[[5-(Trifluoromethyl)-2-pyridinyl]oxy]-phenoxy]propionate (10). Propionate **10** was synthesized from methyl (*R*)-2-[[(4-methylphenyl)sulfonyl]oxy]propionate (**9**) and 4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenol according to the general procedure described for the preparation of ethyl (*R*)-2-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]propionate (**4**) (vide supra): ^{1}H NMR (δ, $CDCl_3$) 1.53 (3 H, d, J = 7 Hz), 3.69 (3 H, s), 4.84 (1 H, q, J = 7 Hz), 6.65–7.08 (5 H, m), 7.78 (1 H, dd, J = 2.5 Hz, J = 8.5 Hz), 8.27 (1 H, m); IR (KBr) 1760, 1615, 1500, 1485, 1330, 1285, 1240, 1195, 1130, 1075 cm^{-1}; MS, m/e 341, 322, 282, 254, 238, 227, 146, 141, 126, 91; $[\alpha]^{20}_D$ −30.0° ($CHCl_3$, c 2.7). Anal. Calcd for $C_{16}H_{14}F_3NO_4$: C, 56.3; H, 4.1; N, 4.1. Found: C, 56.2; H, 3.9; N, 4.0. The optical purity of **10** was assessed by addition of the chiral shift reagent, tris[3-[(trifluoromethyl)hydroxymethylene]-*d*-camphorato]europium-(III) (Aldrich), in small increments directly to a sample of **10** in carbon tetrachloride, the ^{1}H NMR spectrum being recorded after each addition. The sample was determined to contain 91% of the major isomer (82% enantiomeric excess).

(*S*)-2-[4-[[5-(Trifluoromethyl)-2-pyridinyl]oxy]phenoxy]propionic Acid (11). Propionic acid **11** was prepared from methyl (*S*)-2-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]propionate (**10**) in a manner analogous to the preparation of the corresponding *R* isomer **5** (vide supra); $[\alpha]^{20}_D$ −17.2° ($CHCl_3$, c 2.7).

Methyl (*S*)-3-Oxo-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate (12). The preparation of pentanoate **12** is identical with the procedure reported for the synthesis of the corresponding *R* isomer **6** (vide supra); $[\alpha]^{20}_D$ −17.4° ($CHCl_3$, c 2.7). Anal. Calcd for $C_{18}H_{16}F_3NO_5$: C, 56.4; H, 4.2; N, 3.6. Found: C, 56.3; H, 3.7; N, 3.1.

Methyl (4*S*)-3-Hydroxy-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate (13). Pentanoate **13** was prepared by the sodium borohydride reduction of methyl (*S*)-3-oxo-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate (**12**) as described for the analogous synthesis of the 4*R* isomer **7** (vide supra); $[\alpha]^{20}_D$ +9.0° ($CHCl_3$, c 2.7). Anal. Calcd for $C_{18}H_{18}F_3NO_5$: C, 56.1; H, 4.7; N, 3.6. Found: C, 55.5; H, 4.6; N, 3.5.

Chromatographic Separation of Esters 13a and 13b. Diastereomers **13a** and **13b** were separated in the same manner as described for the separation of esters **7** and **7b** (vide supra).

Determination of the Optical Purities of Esters 7 and 13. The optical purities of **7a**, **7b**, **13a**, and **13b** were assessed by chiral-phase HPLC analysis after derivatization of the esters (separately or as mixtures) with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Mosher's reagent) (Dale et al., 1969). HPLC was carried out with a Varian Model 5060 high-performance liquid chromatograph fitted with a 4.6 × 250 mm Pirkle Type 1-A covalent phenylglycine chiral column and a Varian Model UV-100 detector (254 nm). With use of a solvent mixture of hexanes–isopropyl alcohol (98:2) and a flow rate of 0.6 mL/min, retention times of 21.0, 25.5, 27.0, and 29.5 min were obtained for esters **7a**, **13a**, **13b**, and **7b**, respectively.

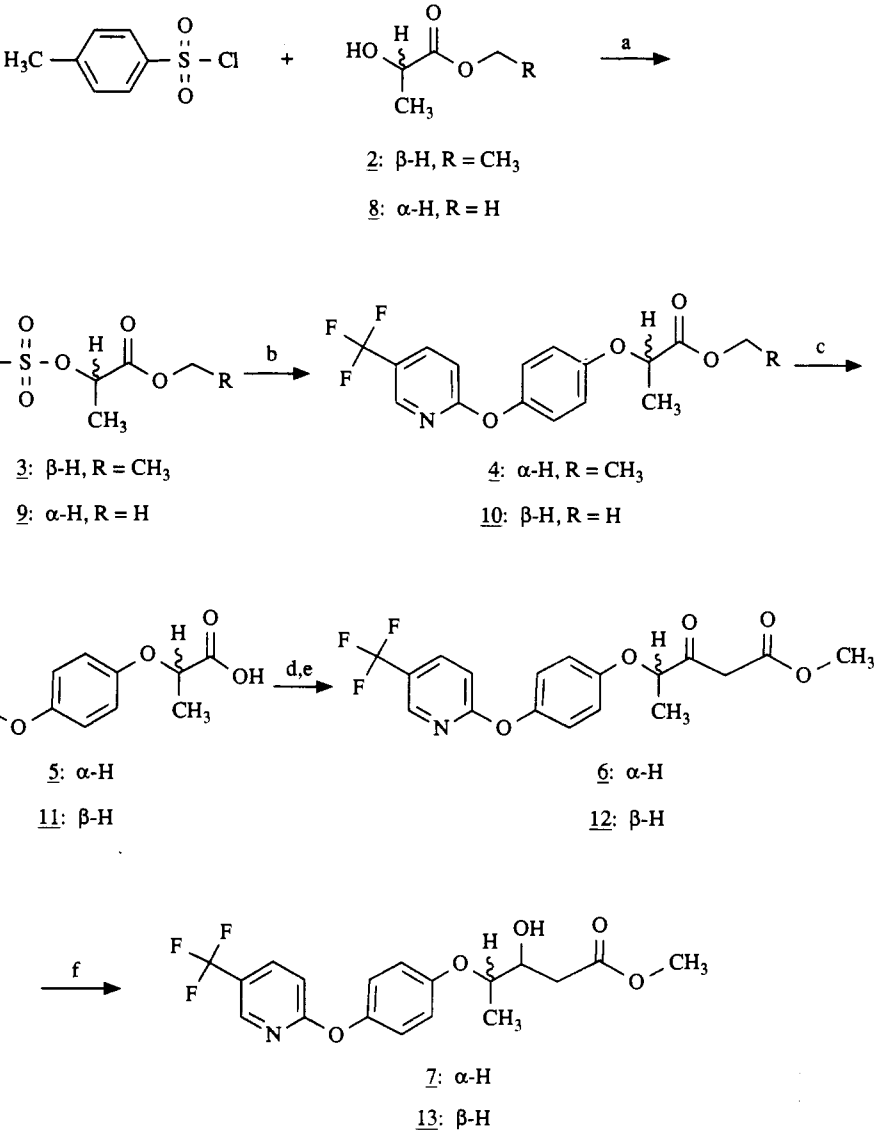
BIOLOGICAL METHOD

Compounds were evaluated as postemergent herbicides on four species of plants: shattercane (SORVU), wild oats (AVEFA), spring wheat-Anza (WH AN), and wild proso millet (PANMIP) in greenhouse tests. Seeds were sowed 0.5 in. deep into a sandy clay loam soil with 100 ppm of Captan and 200 ppm of 17–17–17 fertilizer added. Grass species were sprayed 10–12 days after seeding when the plants were at the 2–3-leaf stage. The test compounds were applied as technical solutions in acetone–water (1:1) containing 0.5% of Tween 20 at the rates indicated in Table II. Species were watered daily, with care being taken not to wet foliage. Two weeks after treatment, the herbicidal activities of the compounds were determined by visual observation of the treated plants in comparison with untreated controls. These observations are reported on a scale of 0–100, where 0 = no effect and 100 = complete control of plant growth.

RESULTS AND DISCUSSION

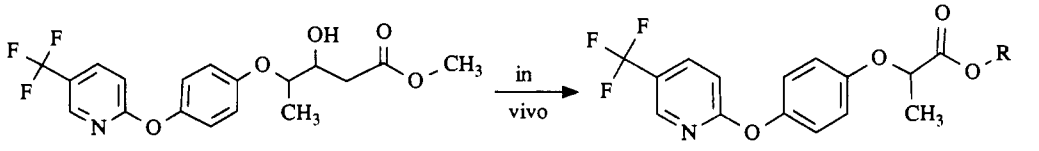
The synthetic routes to (4*R*)- and (4*S*)-methyl 3-hydroxy-2-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate (**7** and **13**) are shown in Scheme I. Ethyl (*S*)-2-[[(4-methylphenyl)sulfonyl]oxy]propionate (**3**), prepared from ethyl (*S*)-2-hydroxypropionate (**2**) and *p*-tolylsulfonyl chloride by the method of Chan et al. (1975), was reacted with 4-[[5-(trifluoromethyl)-2-pyridinyl]-oxy]phenol and potassium carbonate in DMSO to afford ethyl (*R*)-2-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]propionate (**4**). The reaction proceeds with inversion of configuration via an S_N2 mechanism. Mild hydrolysis of ester **4** with dilute sodium hydroxide solution gave (*R*)-2-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]-propionic acid (**5**). Acid **5** was converted to methyl (*R*)-3-oxo-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]-pentanoate (**6**) by the method of Masamune (Brooks et

Scheme I[a]



[a] Key: (a) $(CH_3CH_2)_3N$; (b) 4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenol, K_2CO_3, DMSO; (c) KOH, CH_3OH, H_2O; (d) 1,1′-carbonyldiimidazole, THF; (e) $(CH_3O_2CCH_2CO_2)_2Mg$; (f) $NaBH_4$, CH_3OH.

Scheme II



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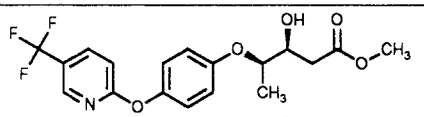
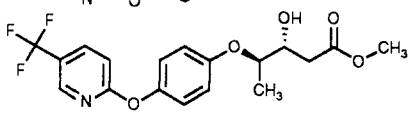
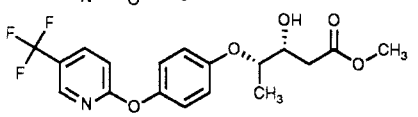
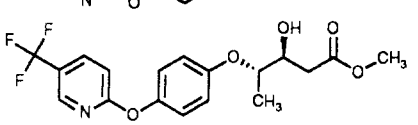
al., 1979). Finally, reduction of ketone **6** with methanolic sodium borohydride afforded methyl (4*R*)-3-hydroxy-4-[4-[[5- (trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate (**7**). Methyl (4*S*)-3-hydroxy-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate (**13**) was prepared in analogous fashion from methyl (*R*)-2-hydroxypropionate (**8**) (Scheme I).

Final separation of the diastereomeric pairs of ester **1** (**7** and **13**) was achieved by preparative HPLC. With an isocratic mixture of ethyl acetate and hexanes with multiple recycles, all four diastereomers of ester **1** were obtained with diastereomeric excesses in the range 70–76% (Table I).

Optical purities for the diastereomers of ester **1** were determined by chiral-phase HPLC. Derivatization of racemic **1** with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Mosher's reagent) afforded four diastereomers that were readily separated by HPLC using a Pirkle Type 1-A covalent phenylglycine chiral column. HPLC analysis of the derivatives of each of the synthetic diastereomers of ester **1** gave the diastereomeric excesses reported in Table I. Underivatized racemic **1** did not separate under similar HPLC conditions.

The absolute configurations of the separated enantiomers of **1** were assigned on the basis of their stereochemical relationships and the results of a microbial reduc-

Table I. Absolute Configuration and Diastereomeric Excess of the Enantiomers of Methyl 3-Hydroxy-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoate

	confign	% de	$[\alpha]^{20}_D$
	**7a** (3*S*, 4*R*)	76	−16.5
	**7b** (3*R*, 4*R*)	76	−1.5
	**13a** (3*R*, 4*S*)	70	16.2
	**13b** (3*S*, 4*S*)	70	1.2

tion of racemic 1. Isomers **7a** and **7b** must have the *R* configuration at C-4 as they were prepared from (*S*)-hydroxypropionic acid; conversely, isomers **13a** and **13b** are of the *S* configuration. On the basis of observed optical rotations, isomers **7a** and **13a** comprise one pair of enantiomers while the other enantiomeric pair consists of isomers **7b** and **13b**. Reduction of racemic **6** with baker's yeast (*Saccharoymes cerevisiae*) afforded, as the major products, isomers **7a** and **13b**. On the basis of work of Sih and Chen (1984), and following Prelog's rule (Prelog, 1964), the products of this reduction would be expected to have the *S* configuration at C-3; therefore, **7a** and **13b** would be the 3*S*,4*R* and 3*S*,4*S* isomers, respectively. The absolute configurations of the other isomers are as shown in Table I. The assumption that products of *S* configuration would result from the microbial reduction may not be correct; however, the absolute configuration at C-3 is not important in understanding the biological activity of 1 (vide infra).

Comparative postemergent herbicidal activities of the four diastereomers and racemic 1 are listed in Table II. Isomers **7a** and **7b** have essentially identical herbicidal activities and are approximately twice as active as racemic 1. Isomers **13a** and **13b** have similar activities and are significantly less active than racemic 1, requiring approximately 4 times the usage rate to achieve equivalent control. The herbicidal activities of the unseparated diastereomeric pairs, (**7a** + **7b**) and (**13a** + **13b**), were also examined. Pair (**7a** + **7b**) has herbicidal activity identical with the activities of either of its separate components, diastereomer **7a** or **7b**. Likewise, the activity of pair (**13a** + **13b**) is essentially the same as the activities of either **13a** or **13b**.

Earlier researchers have shown that the *R* isomers of 2-(aryloxy)propionic acids and their derivatives have far greater herbicidal activity than do the corresponding *S* isomers. The observed activities of the diastereomers of ester 1 are in agreement if one assumes that ester 1 is degraded in vivo to give a 2-(aryloxy)propionic acid (Scheme II). The stereochemistry of ester 1 at C-4 is significant as this center becomes the C-2 center of the corresponding 2-(aryloxy)propionic acid; the stereochemistry at C-3 is unimportant as this carbon becomes planar as a result of the biodegradation.

Table II. Postemergent Herbicidal Activity of Racemic and Optically Active Methyl 3-Hydroxy-4-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]pentanoates

compd	rate, lb/acre	SORVU	AVEFA	WH AN	PANMIP
7a (3*S*, 4*R*)	0.500	100	100	100	
	0.250	100	88	88	
	0.125	100	69	65	
	0.063	100	34	41	
	0.031	96	18	29	
7b (3*R*,4*R*)	0.500	100	100	100	
	0.250	100	83	75	
	0.125	100	69	65	
	0.063	100	44	45	
	0.031	98	19	23	
13a (3*R*,4*S*)	0.500	100	69	69	
	0.250	100	44	53	
	0.125	90	14	30	
	0.063	66	8	23	
	0.031	55	5	14	
13b (3*S*,4*S*)	0.500	100	73	70	
	0.250	99	41	43	
	0.125	93	20	30	
	0.063	79	8	16	
	0.031	35	0	9	
7a + **7b**	0.500	100	100		100
	0.250	100	86		100
	0.125	100	68		100
	0.063	100	41		100
	0.031	96	18		65
13a + **13b**	0.500	85	70		70
	0.250	75	40		50
	0.125	60	17		40
	0.063	43	9		25
	0.031	23	0		23
SC-1084 (racemic)	0.500	100	90	84	100
	0.250	100	75	70	100
	0.125	95	38	45	93
	0.063	95	20	25	68
	0.031	73	9	12	50

ACKNOWLEDGMENT

The technical assistance of Maureen M. McKenna and Steven D. Knight is gratefully acknowledged. I thank Drs. Don Bowler and William Ja for providing analytical support and Dr. Donald Clark for performing the biological assays. Special thanks to Dr. Richard D. Gless for stimulating creative discussions.

Registry No. **3**, 57057-80-4; **4**, 83057-22-1; **5**, 83066-88-0; **6**, 123099-47-8; **7a**, 123164-98-7; **7b**, 123164-99-8; **9**, 109579-04-6; **10**, 123165-02-6; **11**, 95977-30-3; **12**, 123099-48-9; **13a**, 123165-00-4; **13b**, 123165-01-5; 4-[[5-(trifluoromethyl)-2-pyridinyl]-oxy]phenol, 69045-85-8.

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Received for review January 9, 1989. Accepted May 11, 1989.

Pyrethroid-like Carbamates Having Insecticidal Activity

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Carbamate esters have been synthesized from 21 carbamic acids that are nitrogen isoteres of the acid moieties of fenvalerate- and fluvalinate-like pyrethroids. These acid moieties were derived, in the main, from *N*-isopropylaniline and α-(substituted)benzylamine derivatives. The alcohol portions of the carbamate esters were various appropriate pyrethroid alcohols. Preliminary insecticidal activity studies on pyrethroid-susceptible houseflies were conducted; some of the carbamate esters exhibited high toxicity. Conclusions regarding insecticidal activity with respect to the structure and stereochemistry of the carbamate esters have been made. Thus, the *N*-isopropyl substituent decreases insecticidal activity in the benzylamine-derived series of compounds, while the *N*-isopropyl substituent enhances activity in the aniline-derived series of compounds. Also, certain substituents on the phenyl groups of both series, and alkyl substituents on the benzylic carbon of the benzylamine series, can greatly affect insecticidal potency of the carbamate esters.

During the past several years, stereochemical requirements for both acid and alcohol moieties of active pyrethroids have been studied extensively and configurational characteristics have been determined in an effort to relate structure and bioactivity (Anderson et al., 1985; Burt and Goodchild, 1977; Elliott, 1977, 1980; Elliott and Janes, 1978; Plummer et al., 1984; Norton et al., 1985). The configuration at certain chiral centers must be properly oriented for a biological receptor. With stereoisomers of pyrethroid esters, e.g., cypermethrin and decamethrin, the *R* configurations (α-carbon) of the acid moieties are more active than are the *S* isomers (Burt et al., 1974; Elliott et al., 1974, 1978). Similarly, with fenvalerate and related acids, the first potent "pyrethroid" without the cyclopropane ring (Ohno et al., 1974), the (*R*)-isopropyl acetates are much less active than their *S* enantiomers (Miyakado et al., 1975). Again, with fluvalinate, the *R* enantiomer of the α-carbon of the acid moiety shows a higher insecticidal activity than does the *S* enantiomer (Anderson et al., 1985). However, the stereochemical structure in this chiral carbon of fulvalinate is equivalent to that of fenvalerate and the conventional cyclopropanecarboxylate pyrethroids, indicating a similar biological receptor for those structures.

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There has been some work reporting the elimination of certain chiral centers in the acid moieties. With a nitrogen atom in the cyclopropane ring, forming the aziridine group, the carbamic acid esters derived therefrom gave pyrethroid-like compounds but had decreased insecticidal activity (Berteau and Casida, 1969; Sheppard and Norton, 1980). Later reports showed that carbamates bearing the *N*-*tert*-butyl, *N*-benzyl, and *N*-(α-substituted)benzyl groups had some insecticidal activity when esterified with pyrethroid alcohols. (Kirino and Casida, 1985).

It has been reported that the bioactivity of fenvalerate-related pyrethroids is quite sensitive to structural modifications (Ohno et al., 1974, 1976; Elliott et al., 1980). The substitution of a nitrogen atom for the α-carbon atom of the fenvalerate acid moiety would result in the loss of the chiral center of this acid. In the resulting fenvalerate isostere, substituents attached to the nitrogen atom, via a rapid inversion process (Andose et al., 1970), could assume either the *R* or *S* configuration, adapting to a stereospecific receptor site.

In those cases where methylene or substituted methylene has been inserted between a phenyl group and a carbamate function (Kirino and Casida, 1985), the esters with pyrethroid alcohols have produced compounds with intermediate levels of insecticidal activity. These products would closely resemble the stereochemistry of fluvalinate if an isopropyl group were attached to the car-

0021-8561/90/1438-0273$02.50/0