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3; IIc, 124266-64-4; IIId, 124266-65-5; IIE, 124266-66-6; IIIa, 124266-67-7; IIIb, 124266-68-8; IIIc, 124266-69-9; IIId, 124266-70-2; IIIe, 124266-71-3; IVa, 124266-72-4; IVb, 124266-73-5; IVc, 124266-74-6; IVd, 124266-75-7; IVe, 124266-76-8; Va, 124266-77-9; Vb, 124266-78-0; Vc, 124266-79-1; Vd, 124266-80-4; Ve, 124266-81-5; VIa, 124266-82-6; VIb, 124266-83-7; VIc, 124266-84-8; VIId, 124266-85-9; VIE, 124266-86-0; VIIa, 124266-87-1; VIIb, 124266-88-2; VIIc, 124266-89-3; VIId, 124266-90-6; VIIe, 124266-91-7; 2-aminothiophenol, 137-07-5; 2-aminophenol, 95-55-6; *o*-phenylenediamine, 95-54-5; ethanolamine, 141-43-5; ethylene-diamine, 107-15-3.

## Ethyl 2(*R*)-[4-[[3-Chloro-5-(difluoromethoxy)-2-pyridyl]oxy]phenoxy]propanoate. A New Selective Postemergent Herbicide<sup>†</sup>

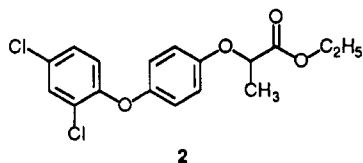
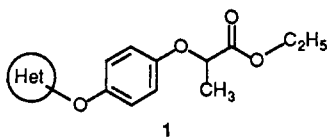
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The two-step synthesis of ethyl 2(*R*)-[4-[[3-chloro-5-(difluoromethoxy)-2-pyridyl]oxy]phenoxy]propanoate starting from 2,3-chloro-5-(difluoromethoxy)pyridine, hydroquinone, and ethyl (2*S*)-*O*-tosyl-lactate is described, and its herbicidal properties are compared to those of known herbicides.

[4-[(Heteroaryl)oxy]phenoxy]propanoic acid derivatives 1 are highly active and selective herbicides for the control of gramineous weeds in broadleaf crops and tolerant cereals.

All these compounds can be regarded as heterocyclic analogues of the wild oat herbicide diclofop-methyl (2) (Nestler et al., 1978) in which the halogen-substituted



phenyl ring is replaced by a heterocycle, e.g., pyridine (Nishiyama et al., 1977; Plowman et al., 1980; Johnston et al., 1977), quinoline (Ura et al., 1979), quinoxaline (Ura et al., 1979; Sakata et al., 1983), benzothiazole (Handte et al., 1982a), or benzoxazole (Handte et al., 1982b). Compounds 1 exhibit a marked difference in crop selectivity with respect to the heterocyclic moiety and its substitution pattern.

<sup>†</sup> Dedicated to Prof. Hilger on the occasion of his 60th birthday.

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### SYNTHESIS

During our investigations in this field we found a new selective herbicide, 1a (Koch et al., 1985), which was synthesized in a two-step sequence as outlined in Scheme I. Reaction of 2,3-dichloro-5-(difluoromethoxy)pyridine (3) (Koch et al., 1985; Koch and Fuss, 1990) with hydroquinone (4) in the presence of 2 equiv of sodium hydroxide yielded (pyridyloxy)phenol 5. Compound 5 was further O-alkylated with ethyl 2(*S*)-*O*-tosyllactate (Kenyon et al., 1924) to give by inversion of configuration the target compound ethyl 2(*R*)-[4-[[3-chloro-5-(difluoromethoxy)-2-pyridyl]oxy]phenoxy]propanoate (1a).

**4-[[3-Chloro-5-(difluoromethoxy)-2-pyridyl]oxy]phenol (5).** Hydroquinone (4; 66.10 g, 0.6 mol) is dissolved in DMSO (100 mL), dibenzo-18-crown-6 (1.8 g, 5 mmol) and 50% KOH (90 mL) are added, and the mixture is warmed to 80 °C. 2,3-Dichloro-5-(difluoromethoxy)pyridine (3; 42.8 g, 0.2 mol) (Koch et al., 1985; Koch and Fuss, 1990) in DMSO (110 mL) is added dropwise, and the solution is stirred for 3 h. To the cooled mixture is added water (70 mL), and pH is adjusted to 5 with acetic acid. The mixture is extracted with toluene (3 × 400 mL), the organic layer washed with water (2 × 400 mL) and dried with MgSO<sub>4</sub>, the solvent evaporated, and the residue dried under vacuum; yield 53.0 g (92%) of crude product; mp 73-76 °C. Recrystallization from cyclohexane/toluene (20:1, v/v) gave 5 as a white solid; yield 41.0 g (71%); purity 95% (HPLC); mp 82-84 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, TMS) δ 6.78 (d, 2 H, *J* = 9.5 Hz), 6.97 (d, 2 H, *J* = 9.5 Hz), 7.22 (t, 1 H, *J* = 72.5 Hz, OCHF<sub>2</sub>), 8.01 (d, 1 H, *J* = 2.5 Hz), 8.08 (d, 1 H, *J* = 2.5 Hz), 9.43 (s, 1 H, OH). Anal. Calcd for C<sub>12</sub>H<sub>9</sub>ClF<sub>2</sub>NO<sub>3</sub> (287.65): C, 50.11; H, 2.80; Cl, 12.32; F, 13.21; N, 4.87. Found: C, 49.9; H, 2.9; Cl, 12.4; F, 13.0; N, 4.6.

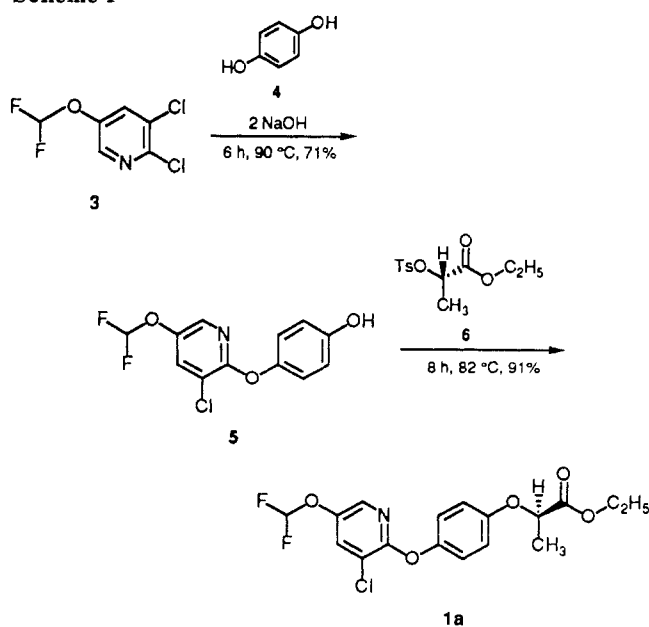
**Ethyl 2(*R*)-[4-[[3-Chloro-5-(difluoromethoxy)-2-pyridyl]oxy]phenoxy]propanoate (1a).** 4-[[3-Chloro-5-(difluoromethoxy)-2-pyridyl]oxy]phenol (5; 14.4 g, 0.05 mol), ethyl (2*S*)-

**Table I. Herbicidal Activity and Crop Tolerance of 1a, 7, and 8 Applied Preemergence**

	mortality, % (at rate, g AI/ha)					
	1a (600)	7 (600)	8 (600)	1a (150)	7 (150)	8 (150)
	Grassy Weeds					
<i>Aleopecurus myosuroides</i>	100	100	100	98	98	90
<i>Avena fatua</i>	100	95	92	98	60	60
<i>Digitaria sanguinalis</i>	100	100	98	99	98	60
<i>Echinochloa crus galli</i>	100	100	80	95	99	40
<i>Setaria viridis</i>	100	100	80	98	99	50
<i>Sorghum halepense</i>	100	100	70	90	95	30
	Crops					
<i>Triticum aestivum</i> (wheat)	99	100	50	90	70	10
<i>Hordeum vulgare</i> (barley)	85	98	60	30	40	40
<i>Zea mays</i> (corn)	98	98	80	95	90	50
<i>Oryza sativa</i> (rice)	100	100	30	90	99	0
<i>Brassica oleracea</i> (rapeseed)	0	0	0	0	0	0
<i>Beta vulgaris</i> (sugarbeet)	0	0	0	0	0	0
<i>Glycine max</i> (soybean)	0	0	0	0	0	0
<i>Gossypium hirsutum</i> (cotton)	0	0	0	0	0	0

**Table II. Herbicidal Activity and Crop Tolerance of 1a, 7, and 8 Applied Postemergence at 3-4-Leave Growth Stage**

	mortality, % (at rate, g AI/ha)					
	1a (600)	7 (600)	8 (600)	1a (150)	7 (150)	8 (150)
	Grassy Weeds, Perennial					
<i>Agropyron repens</i>	99	90	60	92	60	25
<i>Cynodon dactylon</i>	98	90	95	95	65	80
<i>Sorghum halepense</i>	100	100	60	85	85	20
<i>Paspalum distichon</i>	98	90	90	90	70	65
	Grassy Weeds, Annual					
<i>Aleopecurus myosuroides</i>	100	100	100	100	100	95
<i>Avena fatua</i>	100	100	100	100	100	95
<i>Digitaria sanguinalis</i>	100	90	100	98	85	90
<i>Echinochloa crus galli</i>	100	100	100	100	100	100
<i>Setaria viridis</i>	100	100	100	100	95	100
<i>Sorghum halepense</i>	100	99	99	100	99	95
	Crops					
<i>Triticum aestivum</i> (wheat)	100	100	95	100	95	70
<i>Zea mays</i> (corn)	100	100	100	100	100	100
<i>Oryza sativa</i> (rice)	50	90	95	40	40	70
<i>Brassica oleracea</i> (rapeseed)	20	20	20	0	0	0
<i>Beta vulgaris</i> (sugarbeet)	25	25	25	0	0	5
<i>Glycine max</i> (soybean)	10	10	20	0	0	0
<i>Gossypium hirsutum</i> (cotton)	5	10	20	0	0	0

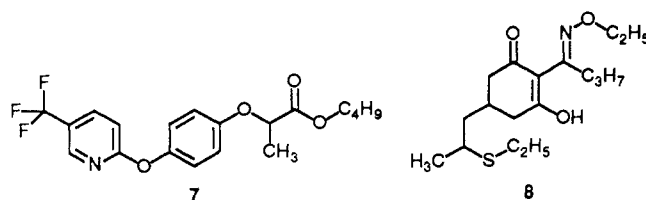
**Scheme I**

O-tosyllactate (6; 13.6 g, 0.05 mol), and  $K_2CO_3$  (13.8 g, 0.1 mol) are refluxed in acetonitrile (200 mL) for 8 h. After filtration

the solvent is evaporated and the residue dissolved in  $CH_2Cl_2$  (200 mL) and washed with ice-cold 2.5% NaOH (3 × 50 mL) and brine (2 × 50 mL), and the organic layer is dried with  $Na_2SO_4$ . Evaporation of the solvent left 1a as an oily product: yield 17.7 g (91%); purity >97% (HPLC); ee 84% (HPLC);  $n_D^{20/4}$  1.5970;  $[\alpha]_D^{20} +29.2^\circ$  (c 1.8,  $CHCl_3$ );  $^1H$  NMR ( $CDCl_3$ , TMS)  $\delta$  1.25 (t, 3 H,  $J = 6.9$  Hz), 1.62 (d, 3 H,  $J = 6.9$  Hz), 4.23 (q, 2 H,  $J = 6.9$  Hz), 4.72 (q, 1 H,  $J = 6.9$  Hz), 6.49 (t, 1 H,  $J = 72.5$  Hz,  $OCHF_2$ ), 6.95 (m, 4 H), 7.68 (d, 1 H,  $J = 2.5$  Hz), 7.92 (d, 1 H,  $J = 2.5$  Hz). Anal. Calcd for  $C_{17}H_{16}ClF_2NO_5$  (387.8): C, 52.61; H, 4.12; Cl, 9.15; N, 3.61. Found: C, 52.1; H, 4.1; Cl, 9.0; N, 3.5.

**HERBICIDAL ACTIVITY**

Compound 1a was formulated as emulsifiable concentrate containing 10% active ingredient and applied to grassy weeds and various crops to investigate the herbicidal activity and tolerance of crops. Commercial herbicides fluzifop-butyl (7) and sethoxydim (8) were used for comparison. Trials were con-



ducted in the greenhouse in pots with two replicates. Visual

ratings were taken 4 weeks after application. Plants were kept at good growing conditions at a temperature regime of 24 °C/18 °C (day/night).

## RESULTS

As results of preemergence applications indicate (Table I), compound **1a** very effectively controlled grassy weeds at a rate of 150 g of AI/ha. **1a** is very well tolerated by broadleaf crops like rapeseed, beets, soybean, or cotton at high rates of 600 g of AI/ha. Broadleaf crops were not controlled at all. Graminaceous crops proved to be very susceptible even at low dosage rates of 150 g of AI/ha. Herbicidal activity of compound **1a** is superior to that of sethoxydim and comparable to that of fluazifop-butyl.

Following postemergence application (Table II) compound **1a** showed excellent activity against annual and perennial grassy weeds at a rate of 150 g of AI/ha. Broadleaf crops demonstrated high tolerance to the herbicide, while graminaceous crops were rather susceptible. Broadleaf weeds were not controlled. In comparison with commercial herbicides 7 and 8, compound **1a** showed superior herbicidal activity particularly with respect to perennial grassy weeds.

In summary, compound **1a** may be considered a very effective herbicide that can be used to selectively control a broad range of annual and perennial grassy weeds in broadleaf crops, such as sugarbeet, soybean, or cotton.

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# Improved Synthesis of [3',5'-<sup>2</sup>H<sub>2</sub>]Folic Acid: Extent and Specificity of Deuterium Labeling<sup>†</sup>

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As an extension of research concerning stable-isotopic labeling of folates, this report describes a modification of our previous procedure for the preparation of folic acid labeled with deuterium at the 3',5'-positions. The major procedural changes were (a) preliminary removal of exchangeable protons from the substrate, 3',5'-dibromofolate, and (b) the catalytic dehalogenation reaction conducted in an aprotic solvent of NaOD in D<sub>2</sub>O. Proton NMR examination of the resulting [3',5'-<sup>2</sup>H<sub>2</sub>]folic acid indicated complete labeling of the 3',5'-positions. Labeling of other positions of the folate molecule was not detected.

The development of stable-isotopic methods has greatly facilitated research concerning the absorption, metabolism, and turnover of many nutrients in humans. Application of stable isotopes permits in vivo isotopic studies with no radiation hazard to human subjects and pro-

vides useful options in experimental design and analysis (Hachey et al., 1987; Bier, 1987). We have recently developed methods for the synthesis of deuterium-labeled forms of folic acid and related folates and have devised mass spectral methods for analysis of urinary folates (Gregory and Toth, 1988a,b, 1989).

To permit studies of dual-label design, methods were developed for synthesizing folates in either [3',5'-<sup>2</sup>H<sub>2</sub>]-

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