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Fluorine analogs of dicamba and tricamba herbicides; synthesis and their pesticidal activity

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Abstract: Fluorine analogs of the dicamba and tricamba herbicides were synthesized. Their herbicide activities were compared with the activities of the pattern herbicides dicamba and tricamba.

Keywords: dicamba; fluorine analogs; herbicidal activity; tricamba.

1 Introduction

The investigations of the properties of fluorine analogs of organic molecules are the result of the activity and specific physicochemical properties of compounds containing fluorine atoms.

The fluorine atom is known to imitate a hydrogen atom [1]. Structural similarity and analogous biological effects of two functional groups (known as bioisosterism) are used especially for the replacement of hydrogen by fluorine. Such a replacement is considered as the most popular monovalent bioisosteric substitution [2]. A similar size of both atoms is the most common reason for substituting hydrogen by fluorine [1–4]. The strong inductive electron-withdrawing effect of the fluorine atom can significantly affect the reactivity and stability of functional groups as well as the reactivity of neighboring reaction centers [1]. In one of our previous works, attempts were made to exchange the hydrogen atoms in the methylene group of the phenoxyacetic acid herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2-methyl-4-chlorophenoxyacetic acid (MCPA) with fluorine atoms [5].

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Bogumiła Huras, Krzysztof Żelechowski, Anna Kiełczewska, Maria Krawczyk, Jarosław Hupko and Katarzyna Jaszczuk, Łukasiewicz Research Network, Institute of Industrial Organic Chemistry, Annopol 6, 03-236 Warsaw, Poland

The second popular idea of converting one set of atoms into another one is to examine various atoms belonging to the same group of the periodic table of elements – exchange halogen atoms with other halogens or an oxygen atom with another chalcogen: sulfur, selenium or tellurium.

The exchange of entire fragments can also be seen in the literature. The analogs of phenoxyacetic acids as potential candidates for compounds showing an herbicidal activity were suggested. Instead of chlorophenoxy fragments (2,4-dichlorophenoxy, 2-methyl-4-chlorophenoxy, 2,4,5-trichlorophenoxy), eugenol, thymol, carvacrol, vanillin, ferulic acid [6, 7], gallic acid [8] and piperidine derivatives [9] have been proposed.

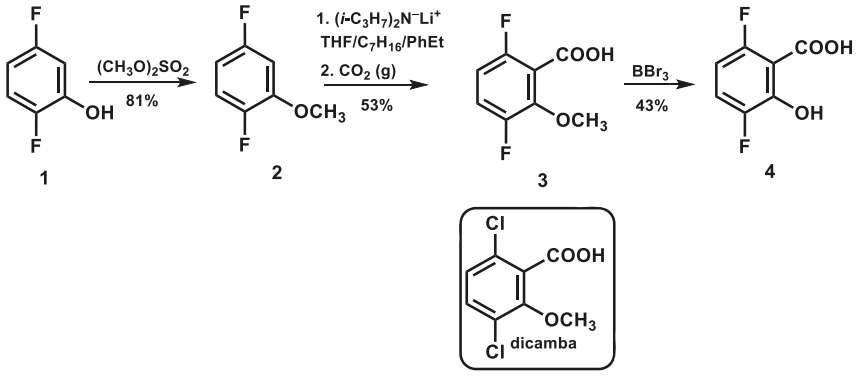
The purpose of this study is to exchange the chlorine atoms in the chlorinated herbicides dicamba (Scheme 1) and tricamba (Scheme 2) with fluorine, in order to examine the herbicidal and fungistatic activity of the fluorine analogs and to compare it with the activity of the parent herbicides.

2 Results and discussion

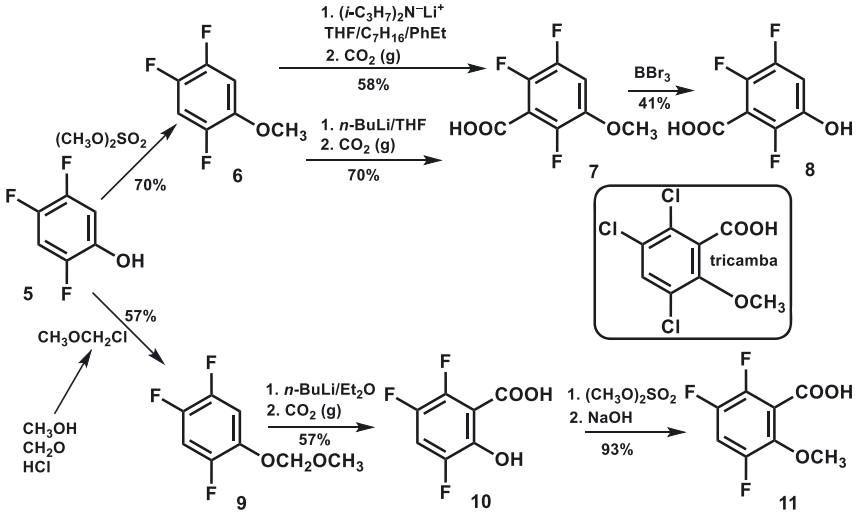
The syntheses of the fluorine analog of the herbicide dicamba (2-methoxy-3,6-difluorobenzoic acid (**3**)) and the fluorine analog of the herbicide tricamba (2,3,5-trifluoro-6-methoxybenzoic acid (**11**)) are presented in Schemes 1 and 2, respectively.

The fluorine analog of the herbicide dicamba (2-methoxy-3,6-difluorobenzoic acid (**3**)) was synthesized by the lithiation of 1,4-difluoro-2-methoxybenzene (2,5-difluoroanisole (**2**)) with lithium diisopropylamide (LDA), followed by the carboxylation with the gaseous carbon dioxide [10] (Scheme 1).

A fluorine analog of the herbicide tricamba (2,3,5-trifluoro-6-methoxybenzoic acid (**11**)) was synthesized by the lithiation of 1,2,4-trifluoro-5-(methoxymethoxy)benzene (**9**) with *n*-buthyllithium followed by carboxylation with gaseous carbon dioxide. The salicylic acid derivative 2-hydroxy-3,5,6-trifluorobenzoic acid (3,5,6-trifluorosalicylic acid (**10**)) thus obtained was then methylated with dimethyl sulfate to the target 2,3,5-trifluoro-6-methoxybenzoic acid (**11**) (Scheme 2).



Scheme 1: Synthesis of fluorine analog **3** of dicamba.



Scheme 2: Synthesis of fluorine analog **11** of tricamba.

The lithiation of 1,2,4-trifluoro-5-methoxybenzene (2.4.5-trifluoroanisole (**6**)) with either LDA or *n*-buthyllithium followed by the carboxylation with the gaseous carbon dioxide lead to the regioisomeric (in relation to the tricamba scaffold) compound 3-methoxy-2,5,6-trifluorobenzoic acid (**7**) (Scheme 2).

The observed difference between the regiodirected lithiation of **6** ($ArOCH_3$) and **9** ($ArOCH_2OCH_3$, ArOMOM) is a result consistent with the work of Schlosser [11], and in accordance with the known *ortho*-directing ability of the OMOM substituent during lithiation processes [12–18].

The methylation with dimethyl sulfate of the compound bearing both carboxyl and hydroxyl groups (**10** → **11**) yielded a mixture of the desired ether and the methyl ester of the carboxylic acid. To avoid the unnecessary separation of both ether and ester, dimethyl sulfate was used in excess. The crude product was routinely treated with sodium hydroxide solution to hydrolyze the undesired ester.

It is noteworthy to mention, that the synthesis of the compounds **10** and **11** has been reported using a different starting material. The elimination of one fluorine atom from the benzene ring containing four fluorine atoms was proposed. The reaction of 2,3,5,6-tetrafluorobenzoic acid with magnesium methoxide gave **11** (no experimental data due to the co-presence of dimethoxide side-product). Further demethylation and hydrolysis using HBr of the corresponding acid chloride yielded well characterized **10** [19].

For additional confirmation of the structure of the obtained anizole derivatives **3** and **7**, they were demethylated using boron tribromide yielding the corresponding hydroxyl derivatives **4** and **8**.

The structures of the synthesized compounds were confirmed by spectroscopic methods. The structures of the starting phenolic ethers (**2**, **6**, **9**) were confirmed and characterized using MS and IR spectra. The structures of the carboxylated derivatives, compounds **3**, **4**, **7**, **8**, **10**, and **11**, were confirmed as characterized by MS, ^{1}H, ^{13}C, ^{19}F NMR and IR spectra. The new compounds **7** and **11** were additionally characterized by HRMS measurements. The mass spectra of the synthesized compounds show the parent signals with great intensity (100% for **7** and **8**).

The regioselectivity of the compounds **7**, **8**, **10**, **11** was confirmed by the analysis of the coupling pattern and

coupling constants of the hydrogen atom with the fluorine ones.

The ^{1}H NMR of the hydrogen atom signal in the benzene ring are presented in Figure 1a (the fluorine analog of tricamba **11** and the corresponding salicylic acid **10**) and in Figure 1b (the isomeric compounds **7** and **8**.).

Comparison of the coupling constants of the hydrogen atom with the fluorine atoms for the pairs **11** and **10**, as well as for **7** and **8** confirms the position of the hydrogen atom in the ring. For the compounds **7** and **8**, the hydrogen atom is coupled with one fluorine atom in the *ortho* position (d, $J \sim 11$ Hz) and two fluorine atoms in the *meta* position (t, $J \sim 7.5$ Hz) This leads to a doublet of triplets – the pattern presented in Figure 1b.

For the compounds **10**, **11** the situation is opposite. A hydrogen atom in the ring is coupled with two fluorine atoms in the *ortho* postion (t, $J \sim 11$ Hz) and one fluorine atom in the *meta* position (d, $J \sim 7.5$ Hz). This leads to a triplet of doublets – the pattern presented in Figure 1a.

The herbicidal activity of the obtained compounds was tested against the following species of weeds: cleavers (*Galium aparine*), pale smartweed (*Polygonum lapathifolium*), common poppy (*Papaver rhoeas*), barnyard grass (*Echinochloa crusgali*), gallant soldier (*Galinsoga parviflora*), fathen (*Chenopodium album*), ribwort (*Plantago lanceolata*), black mustard (*Brassica nigra*), red-root amaranth (*Amaranthus retroflexus*), common chickweed (*Stellaria media*). The results are presented in Table 1.

The fluorine analog of dicamba (2-methoxy-3,6-difluorobenzoic acid (**3**)) showed herbicidal activity slightly weaker than dicamba itself (2-methoxy-3,6-dichlorobenzoic acid). Dicamba itself destroyed eight weed species respectively with >90% efficiency. Compound **3** did not reveal pre-emergent activity.

The fluorine analog of tricamba (2,3,5-trifluoro-6-methoxybenzoic acid (**11**)) showed no herbicidal activity as opposed to the tricamba itself (2,3,5-trichloro-6 methoxybenzoic acid), which destroyed four weed species with >90% efficiency.

None of the tested salicylic acids 3,6-difluoro-2-hydroxybenzoic acid (3,6-difluorosalicylic acid (**4**)), 3,6-dichloro-2-hydroxybenzoic acid (3,6-dichlorosalicylic acid), 2,3,5-trifluoro-6-hydroxybenzoic acid (3,5,6-trifluorosalicylic acid (**10**)), as well as 2,3,5-trichloro-6-hydroxybenzoic acid (3,5,6-trichlorosalicylic acid) showed herbicidal activity.

Fungistatic activity of the obtained compounds was tested against the following phytopathogenic strains: *Alternaria alternata*, *Botrrytis cinerea*, *Fusarium culmorum*, *Phytophtora cactorum*, *Rhizoctonia solani*, *Phytophtora infestans*. The results are presented in Table 2.

The fluorine analog of dicamba (3,6-difluoro-2-methoxybenzoic acid (**3**)) as well as dicamba itself showed

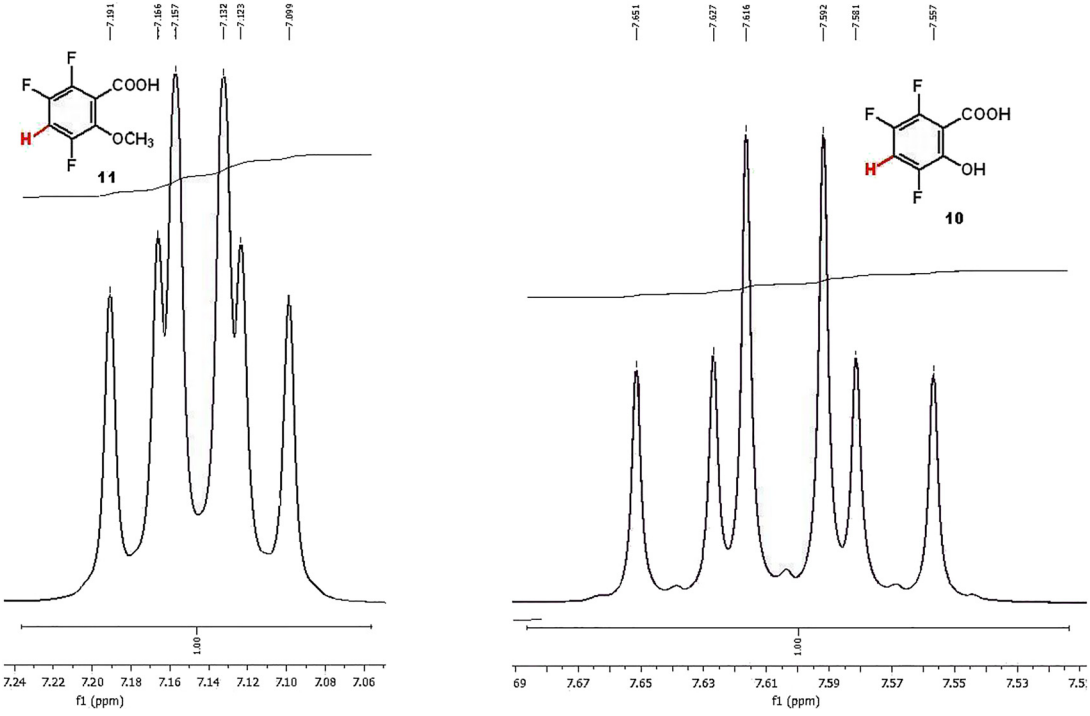


Figure 1a: ^{1}H NMR: the hydrogen atom signal in the benzene ring for the fluorine analog of tricamba **11** (td, J = 10.2, 7.5 Hz), and the corresponding salicylic acid **10** (td, J = 10.5, 7.2 Hz).

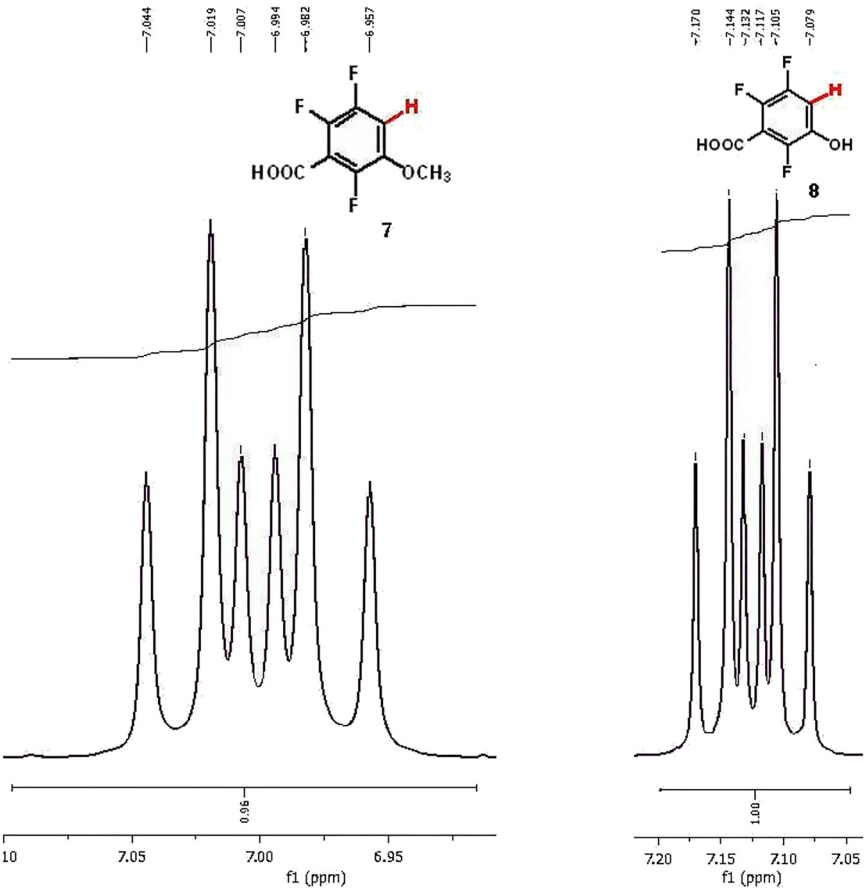


Figure 1b: ^{1}H NMR: the hydrogen atom signal in the benzene ring for the isomeric compounds **7** (dt, J = 11.1, 7.5 Hz) and **8** (dt, J = 11.7, 7.95 Hz).

no fungicidal activity. The fluorine analog of tricamba (2,3,5-trifluoro-6-methoxybenzoic acid (**11**)), tricamba itself (2,3,5-trichloro-6-methoxybenzoic acid) and all tested salicylic acids 3,6-difluoro-2-hydroxybenzoic acid (3,6-difluorosalicylic acid (**4**)), 3,6-dichloro-2-hydroxybenzoic acid (3,6-dichlorosalicylic acid), 2,3,5-trifluoro-6-hydroxybenzoic acid (3,5,6-trifluorosalicylic acid (**10**)) as well as 2,3,5-trichloro-6-hydroxybenzoic acid (3,5,6-trichlorosalicylic acid) showed weak fungicidal activity against individual tested strains of phytopathogenic fungi.

The isomeric compounds 2,3,6-trifluoro-5-methoxy benzoic acid (**7**) and 2,3,6-trifluoro-5-hydroxybenzoic acid (**8**) showed but weak fungistatic activity.

3 Conclusions

The chlorine atoms in two herbicides 2,5-dichloro-6-methoxybenzoic acid (dicamba) and 2,3,5-trichloro-6-methoxybenzoic acid (tricamba) were replaced with fluorine atoms. The fluorine analogs of dicamba and tricamba 2,5-difluoro-6-methoxybenzoic acid (**3**) and 2,3,5-trifluoro-6-methoxybenzoic acid (**11**), respectively, were characterized by spectroscopic methods (MS, HRMS, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR), which fully confirmed their structures. The fluorine analogs **3** and **11** were evaluated for their herbicidal and fungistatic activities which revealed a weaker herbicidal and fungistatic activity than the parent herbicides dicamba and tricamba.

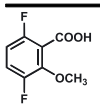
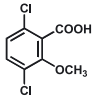
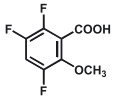
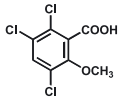
4 Experimental part

4.1 General

2,5-Difluorophenol, 2,4,5-trifluorophenol, dimethyl sulfate, boron tribromide, as well as *n*-butyllithium and LDA solutions were commercially available and used as received.

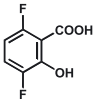
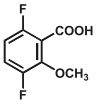
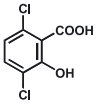
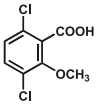
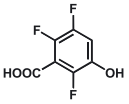
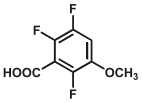
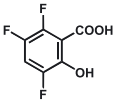
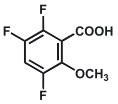
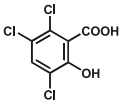
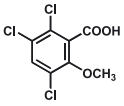
Chloromethylmethyl ether (MOMCl) was synthesized according to ref. [20]. Gaseous HCl was passed through a mixture of methanol (44 g, 1.375 mol, 55.6 mL) and 37.5% aqueous solution of formaldehyde (90 g, 1.125 mol) for 6 h in accord with the literature procedure. MOMCl (49.13 g, 54.25%, b.p. 55–60 °C/760 mmHg) (lit. 55–60 °C/760 mmHg [20]) was obtained.

Table 1: Herbicidal activity of the fluorine analog of dicamba **3** and the fluorine analog of tricamba **11** against weeds (pre-emergent/post-emergent activities).[a]

Compound	Dose (g ha^{-1})	Cleavers (*Galium aparine*)	Pale smartweed (*Polygonum lapathifolium*)	Common poppy (*Papaver rhoeas*)	Barnyard grass (*Echinochloa crusgali*)	Gallant soldier (*Galinsoga parviflora*)	Fathen (*Chenopodium album*)	Ribwort (*Plantago lanceolata*)	Black mustard (*Brassica nigra*)	Red-root amaranth (*Amaranthus retroflexus*)	Common chickweed (*Stellaria media*)
 **3**	2000	20	100	90	0	100	100	40	55	40	40
		55	100	100	0	100	100	55	70	100	70
	300	0	0	0	0	0	0	0	0	0	0
		20	70	70	0	100	100	40	70	100	40
	150	0	0	0	0	0	0	0	0	0	0
		10	40	40	0	70	70	20	40	100	20
 Dicamba	2000	100	100	100	100	100	100	100	100	100	100
		100	100	100	95	100	100	100	100	100	100
	300	60	40	100	0	40	100	0	70	60	65
		100	100	100	0	100	100	70	100	100	100
	150	40	20	70	0	20	70	0	40	20	0
		90	100	100	0	100	100	40	70	100	70
 **11**	2000	40	20	70	0	40	70	0	60	20	40
		40	40	40	0	40	40	20	40	40	40
	300	0	0	0	0	0	0	0	0	0	0
		0	0	0	0	0	0	0	0	0	0
 Tricamba	2000	100	100	70	0	70	100	20	90	100	70
		95	100	100	20	100	100	90	100	100	100
	300	0	0	0	0	0	0	0	0	0	0
		60	100	55	0	100	100	40	65	100	55

[a]Results (degree [in %] of a visual observation of a phytotoxicity weed damage for a weed species used against control, dose 2 kg ha^{-1}) are expressed as a fraction: a numerator means a result (in %) of a pre-emergence (via soil) treatment, a denominator means a result (in %) of a post-emergence (on leaves) treatment.

Table 2: Fungistatic activity of fluorine analogs of dicamba **3** and **4**, fluorine analogs of tricamba **10** and **11**, as well as isomeric derivatives **7** and **8**; against phytopathogenic fungi; concentration: 200 mg L^{-1}; solvent: acetone.[a]

Compound	Formula	*Alternaria alternata*	*Botrytis cinerea*	*Fusarium culmorum*	*Phytophtora cactorum*	*Rhizoctonia solani*	*Phytophtora infestans*
4		0	6.3	27.1	0	0	4.2
3		0	0	0	0	0	2.1
3,6-Dichloro-2-hydroxybenzoic acid (3,6-dichloro-salicylic acid)		11.9	6.3	16.7	0	0	0
Dicamba		0	0	0	0	0	0
8		0	8.2	26.2	7.2	25.5	0
7		0	0	28.6	0	0	12.5
10		0	6.3	22.9	0	0	0
11		4.8	0	6.3	0	0	6.2
2,3,5-trichloro-6-hydroxybenzoic acid (3,5,6-trichloro-salicylic acid)		16.7	41.7	22.9	21.2	0	12.5
Tricamba		0	0	16.7	0	0	4.2

[a]The results are expressed as a percentage of linear growth reduction of a fungus colony; percentage of linear growth reduction = ([colony diameter of a control plate − colony diameter of a tested plate]/[colony diameter of a control plate]) × 100.

TLC was carried out on silica gel Merck Alurolle 5562 or Alufolien 5554; typical mobile phases: hexane-ethyl acetate (9:1); benzene-ethyl acetate (9:1); benzene-methanol (9:1). TLC visualization was achieved using UV 254 nm light and/or I_2 vapor. Column chromatography was performed on silica gel 0.040–0.063 mm, 230–400 mesh: Merck 1.09385.1000 or Zeochem 60 hyd. mobile phases: benzene, benzene-ethyl acetate (95:5, 9:1, 4:1). EI MS data (70 eV) were recorded on an AMD 604 and Agilent Technologies 5975 B mass spectrometers. EI HR MS data were recorded by using an AMD 604 mass spectrometer. IR spectra were recorded on an FT/IR Jasco 420 spectrophotometer. ^{1}H, ^{13}C and ^{19}F NMR data were collected using a Varian UNITYplus 300 or 500 spectrophotometers (at 200 or 500 MHz for ^{1}H, respectively).

4.2 1,4-Difluoro-2-methoxybenzene (2,5-difluoroanisole) (2)

A mixture of 2,5-difluorophenol (**1**, 11.96 g, 0.092 mol), triturated anhydrous potassium carbonate (15.25 g, 0.11 mol), dimethyl sulfate (13.92 g, 10.45 mL, 0.11 mol) and acetone (240 mL) was stirred at reflux for 2 h. After cooling, the precipitate was filtered off and washed with acetone (10 mL). The filtrate was evaporated. Water (150 mL) was added to the residue (16.5 g) and the mixture was extracted with diethyl ether. The ether layer was washed with water, ammonium hydroxide (15%, 150 mL, stirring for 1.5 h), and with water to pH 7–8 again. The ether layer was dried over anhydrous magnesium sulfate. Filtration of the drying agent and evaporation of the solvent gave the crude product (14.4 g) which was distilled under reduced pressure to give 2.5-difluoroanisole (**2**, 10.7 g, 81.4%, colorless oil, b.p. 59–60 °C/15 mm Hg (lit. 72–73 °C/25 mm Hg [21]). – MS (EI, 70 eV): *m/z* (%) = 144 (96) $[M]^+$, 129 (47), 115 (12), 114 (15), 113 (11), 101 (100), 96 (4), 95 (6), 81 (10), 75 (15), 63 (19), 57 (11), 51 (10), 50 (6). – IR (cm^{-1}, film): ν = 3100, 3010, 2980, 2946, 2920, 2890, 2850, 1626, 1514, 1453, 1420, 1325, 1290, 1250, 1210, 1192, 1150, 1101, 1101, 1031, 950, 836, 786, 715, 608.

4.3 3,6-Difluoro-2-methoxybenzoic acid (3)

1,4-Difluoro-2-methoxybenzene (2,5-difluoroanisole, **2**, 5.56 g, 0.039 mol) in anhydrous THF (15 mL) was cooled to –60 °C. A solution of LDA 1.5 m (30.5 mL, 0.045 mol) was added with a syringe via septum in portions (9, 4, 4, 6, 7.5 mL). Because the temperature of the reaction mixture rose rapidly, adding of LDA was carried out at such a rate that the temperature of the reaction mixture did not increase above –50 °C. After adding LDA, the reaction mixture was stirred for 30 min at –70 °C. Gaseous carbon dioxide was bubbled through the reaction mixture for 1 h. The temperature was maintained at –78 to –50 °C. The reaction mixture was allowed to slowly warm to 0 °C and then was carefully acidified with 30% H_2SO_4 to pH 3–4. The aqueous layer was extracted with ether (2 × 50 mL). The organic layer was concentrated. The residue was dissolved in 2 m NaOH (50 mL) and washed with hexane to remove unreacted 2,5-difluoroanisole (**2**). The aqueous layer was acidified with 30% H_2SO_4 to pH 3–4 and left for 12 h in a refrigerator. The precipitate (7.14 g) was dissolved in ethyl acetate. The solution was dried over anhydrous magnesium sulfate, and after removing the drying agent, concentrated. Crude 3,6-difluoro-2-methoxybenzoic acid (**3**, 5.43 g) was purified by a double column chromatography (eluent: hexane-ethyl acetate 4:1). 3,6-Difluoro-2-methoxybenzoic acid (**3**) was obtained as a colorless solid, 3.87 g, 53.3%, m.p. 81–82 °C (lit. 82–83 °C [10]). – MS (EI, 70 eV): *m/z* (%) = 188 (56) $[M]^+$, 171 (22), 170 (18), 169 (8), 159 (32), 156 (34), 141 (100), 128 (29), 115 (13), 114 (7), 113 (15), 112 (14), 101 (21), 100 (20), 99 (12). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.27 (1 H, s, COOH), 7.20 (1H, td, *J* = 10.0, 5.1 Hz, Ph), 6.84 (1H, td, *J* = 8.85, 3.6 Hz, Ph), 4.06 (3H, s, OMe). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 62.30 (d, *J* = 6.3 Hz, OCH3), 110.83 (dd, *J* = 24.1, 7.4 Hz), 116.02 (d, *J* = 17.5 Hz), 119.71 (dd, *J* = 21.8, 10.3 Hz), 146.38 (dd, *J* = 13.7, 5.6 Hz), 151.55 (dd, *J* = 244.8, 3.5 Hz), 155.81 (dd, *J* = 251.8, 2.4 Hz), 168.28 (s, COOH). – ^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.96 (m), –133.94 (tm, *J* = 13.8 Hz). – IR (cm^{-1}, KBr): ν = 430, 2962, 2680, 2580, 1705, 1622, 1489, 1429, 1320, 1291, 1239, 1059, 969, 913, 819, 764.

4.4 3,6-Difluoro-2-hydroxybenzoic acid (3,6-difluoro-salicylic acid) (4)

To a solution of 3,6-difluoro-2-methoxybenzoic acid (**3**, 0.5 g, 0.0027 mol) in anhydrous dichloromethane (20 mL), 1.0 m solution of boron tribromide (5.4 mL, 2 eq.) in dichloromethane was added with magnetic stirring, using a syringe, at 0 °C, under argon atmosphere. The reaction mixture was stirred for 2 h at 0 °C, then was allowed to slowly warm to room temperature and the stirring was continued for 12 h. In order to quench the reaction, methanol (approx. 5 mL) was added dropwise at 0 °C. During the methanol addition, the temperature rose to 17 °C. Water was added to the reaction mixture. The layers were separated. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration of the drying agent and concentration gave the crude product (0.5 g), which was purified by column chromatography with hexane-ethyl acetate 20:1, 9:1, 4:1 as eluents. The fractions containing the product were combined and concentrated. The residue was washed with hexane to give 3,6-difluoro-2-hydroxybenzoic acid (**4**, 0.2 g, 42.6%, HPLC: 99.95%, m.p.: 154–155 °C (lit. 154–155 °C [11])). – MS (EI, 70 eV): *m/z* (%) = 174 (38) $[M]^+$, 156 (100), 128 (54), 100 (44), 81 (12). – ^{1}H NMR (300 MHz, acetone-d_6): δ = 11.58 (bs), 7.41 (1H, ddd, *J* = 10.35, 9.2, 4.8 Hz), 6.70 (1H, ddd, *J* = 10.35, 9.2, 3.6 Hz). – ^{13}C NMR (75.5 MHz, acetone-d_6): δ = 170.99 (t, *J* = 3.28 Hz, COOH), 158.90 (dd, *J* = 256.2, 2.76 Hz), 152.15 (dd, 1*J* = 4.65, 4.38 Hz), 148.63 (dd, *J* = 240.28, 3.66 Hz), 122.04 (dd, *J* = 19.78, 11.55 Hz), 106.45 (dd, *J* = 25.82, 6.72 Hz), 105.23 (dd, *J* = 15.44, 3.05 Hz). – ^{19}F NMR (282.5 MHz, acetone-d_6): δ = –111 (ddd, *J* = 17.37, 10.45, 4.7 Hz), –142.12 (ddd, *J* = 17.44 Hz, 10.38, 3.53 Hz). – IR (cm^{-1}, KBr): ν = 3427, 3100, 1715, 1662, 1640, 1495, 1445, 1249, 1181, 1035, 810, 760.

4.5 1,2,4-Trifluoro-5-methoxybenzene (2.4.5-trifluoroanisole) (6)

A mixture of 2,4,5-trifluorophenol (**5**, 5.03 g, 0.034 mol), triturated anhydrous potassium carbonate (8.28 g, 0.06 mol), dimethyl sulfate (5.68 mL, 0.06 mol, 7.56 g), and acetone (90 mL) was stirred at reflux for 2 h. After cooling, the precipitate was filtered and washed with acetone (10 mL). The filtrate was evaporated. Water (55 mL) was added to the residue (7.6 g) and the mixture was extracted with diethyl ether. The ether layer was washed with water, ammonium hydroxide (15%, 55 mL, stirring for 1.5 h) and with water to pH 7–8 again. The ether layer was dried over anhydrous magnesium sulfate. Filtration of the drying agent and evaporation of the solvent afforded the crude 1,2,4-trifluoro-5-methoxybenzene (**6**, 3.84 g, 69.7%, GC: 97.8%, colorless solid, m.p. 37–38 °C (lit. m.p. 35–37 °C [22], 36–37 °C [23])) which was used without purification for the next step. – GC/MS: GC: t.r. = 6.164 min. – MS (EI, 70 eV): *m/z* (%) = 163(8), 162 (94) $[M]^+$,148 (5), 147 (71), 131 (6), 120 (6), 119 (100), 81 (16), 69 (9). – IR (cm^{-1}, KBr): ν = , 2962, 1640, 1529, 1261, 1096, 1020, 802.

4.6 2,3,6-Trifluoro-5-methoxybenzoic acid (7)

4.6.1 Lithiation with *n*-butyllithium

2,4,5-Trifluoroanisole (**6**, 2.9 g, 0.018 mol) was placed in anhydrous THF (36 mL) under argon. The solution was cooled to –65 °C. 2.5 m *n*-butyllithium solution (8 mL, 0.02 mol) was added in portions with a syringe through a septum. The temperature of the reaction mixture rose to –60 °C. *n*-Butyllithium solution were added dropwise in two portions (2 × 4 mL). After completion of the addition, the reaction mixture was stirred for 0.5 h at –65 °C. Gaseous carbon dioxide was passed through the reaction mixture for 1 h at approx. –64 °C. A copious amount of white precipitate was observed. The reaction mixture was allowed to warm to 0 °C, and hydrolyzed with 30% H_2SO_4 (5 mL) to pH about two. Layers were separated. The aqueous layer was washed with diethyl ether (2 × 20 mL). The combined organic layers were washed with water (2 × 20 mL) and dried over anhydrous sodium sulfate (TLC control of **7** benzene-acetone 1:1). After evaporation the crude **7** was obtained (6.6 g). The crude 2,3,5-trifluoro-6-methoxybenzoic acid **7** was purified by column chromatography. The crude product was dissolved in ethyl acetate, silica gel (20 g) was added and the mixture was evaporated to dryness. The product applied on the gel was placed on the top of a chromatography column. Elution with hexane-ethyl acetate 9:1 (100 mL), 4:1 (200 mL), 1:1 (100 mL), acetone gave the purified 2,3,5-trifluoro-6-methoxybenzoic acid (**7**, 2.61 g, 70.4%, colorless solid, m.p. 130–133 °C).

4.6.2 Lithiation with lithium diisopropyl amide (LDA)

2,4,5-Trifluoroanisole (**6**, 4.05 g, 0.025 mol) was placed in anhydrous THF (20 mL) under argon. The solution was cooled to –70 °C. A 1.5 m LDA solution (approx. 20 mL, 0.029 mol) was added in portions with a syringe through a septum. The temperature of the reaction mixture rose to –66 °C. LDA solution was added dropwise in five portions (5 × 4 mL). After completion of the addition, the reaction mixture was stirred for 0.5 h at –72 °C. Gaseous carbon dioxide was passed through the reaction mixture for 1 h. Initially, the temperature of the reaction mixture rapidly increased to –45 °C, then it maintained at approx. –70 °C. A copious amount of white precipitate was observed. The reaction mixture was allowed to warm to 0 °C, and hydrolyzed with 30% H_2SO_4 to pH 3–4 (10 mL). After the addition of the first 2 mL of H_2SO_4, the reaction mixture thickened and a copious amount of CO_2 was evolved. Diethyl ether was added (approx. 15 mL). The presence of **7** was controlled with TLC benzene-acetone 1:1). The organic layer was extracted with water (30 mL). The aqueous layer was additionally acidified (30% H_2SO_4, 1 mL) and extracted with ether (20 mL). The combined ether extracts were dried over anhydrous sodium sulfate. After evaporation the crude product **7** was obtained (4.23 g). The crude **7** was purified by double column chromatography. The crude product was dissolved in ethyl acetate, silica gel (20 g) was added and the mixture evaporated to dryness. The product applied on the gel, was placed on the top of a chromatography column. Elution with hexane (150 mL), hexane-ethyl acetate 9:1 (100 mL), 4:1 (200 mL), 1:1 (100 mL), gave pre-purified product (3.52 g) which was subjected to a second chromatography. The second chromatography gave finally 2,3,5-trifluoro-6-methoxybenzoic acid (**7**, 3.0 g, light-creamy solid, 58.3%, GC: 99.73%, HPLC: 99.5%, m.p. 130–135 °C, dec.). – MS (EI, 70 eV): *m/z* (%) = 207 (12), 206 (100) $[M]^+$, 191 (16), 189 (14), 171 (33), 161 (11), 147 (22), 146 (11), 143 (36), 119 (32), 118 (15), 115 (9), 99 (27), 81 (9), 80 (9), 68 (9). – HRMS (EI, 70 eV): *m/z* = 206.0190 (calcd. 206.0191 for $C_8H_5F_3O_3$, $[M]^+$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.738 (1H, bs, COOH), 7.00 (1H, dt, J = 11.1, 7.5 Hz, Har), 3.90 (1H, s, OCH_3). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.66 (s, COOH), 146.40 (ddd, J = 253.831, 7.32, 4.15 Hz), 146.22 (dd, J = 246.55, 4.33 Hz),

144.31 (ddd, J = 11.91, 7.87, 3.83 Hz), 141.98 (ddd, J = 253.79, 15.41, 4.49 Hz), 111.47 (t, J = 15.18 Hz), 105.79 (dd, J = 22.42, 2.72 Hz), 57.14 (s, OCH_3). – ^{19}F NMR (282.5 MHz, $CDCl_3$): δ = –135.43 (ddd, J = 13.56, 7.49, 6.215), –139.20 (ddd, J = 21.89, 13.42, 11.3 Hz), –145.35 (dt, J = 22.32, 6.50 Hz). – IR (cm^{-1}, KBr): ν = 3111, 2690, 1711, 1610, 1499, 1453, 1412, 1378, 1299, 1209, 1038, 954, 906, 849, 694.

4.7 2,3,6-Trifluoro-5-hydroxybenzoic acid (8)

To a solution of 2,3,6-trifluoro-5-methoxybenzoic acid (**7**, 1.0 g, 0.0049 mol) in anhydrous dichloromethane (20 mL), 1.0 m solution of boron tribromide (9.7 mL, 2 eq.) in dichloromethane was added with magnetic stirring using a syringe, at 0 °C under argon atmosphere. The reaction mixture was stirred for 2 h at 0 °C, then was allowed to slowly warm to room temperature and the stirring was continued for 12 h. In order to quench the reaction, methanol (approx. 5 mL) was added dropwise at 0 °C. During the methanol addition, the temperature rose to 17 °C. Water was added to the reaction mixture. The layers were separated. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration of the drying agent and concentration gave the crude product (0.36 g, m.p. 97–98 °C). The aqueous layer was extracted with ethyl acetate. After evaporation of the ethyl acetate, an additional 0.82 g of the product was obtained (0.42 g after washing with hexane and drying). The combined crude products were purified by column chromatography with hexane-ethyl acetate 95:5, 9:1, 4:1. The fractions containing the product were combined and concentrated. The residue was washed with hexane to give 2,3,6-trifluoro-5-hydroxybenzoic acid (0.26 g, m.p. 134–137 °C and 0.13 g, m.p. 138–142 °C (lit. 136–137 °C [11]). Yield of **8** in total 0.39 g, 41.4%. – MS (EI, 70 eV): m/z (%) = 193 (8), 192 (100) $[M]^+$, 175 (39), 149 (8), 148 (20), 147 (25), 128 (8), 119 (23), 100 (42), 99 (30), 75 (9), 69 (12). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.02 (2H, bs, COOH, OH), 7.00 (1H, dt, J = 11.7, 7.95 Hz, Har). – ^{13}C NMR (75.5 MHz, acetone-d_6): δ = 161.73 (d, J = 13.25 Hz, COOH), 147.25 (ddd, J = 243.19, 13.55, 3.78 Hz, C–F), 145.39 (ddd, J = 246.92, 4.57, 3.25 Hz, C–F), 142.68 (ddd, J = 14.80, 9.74, 3.47 Hz), 141.43 (ddd, J = 246.53, 15.50, 5.51 Hz, C–F), 114.21 (t, J = 17.86 Hz), 108.76 (dd, J = 21.71, 3.59 Hz). – ^{19}F NMR (282.5 MHz, acetone-d_6): δ = –141.08 (ddd, J = 13.56, 7.91, 5.79 Hz), –142.58 (ddd, J = 22.11, 13.28, 11.51 Hz), –150.45 (ddd, J = 22.18, 7.77, 5.93 Hz). – IR (cm^{-1}, KBr): ν = 3228, 1700, 1650, 1620, 1499, 1416, 1271, 1170, 946, 707.

4.8 1,2,4-Trifluoro-5-(methoxymethoxy) benzene (9)

2,4,5-Trifluorophenol (5 g, 0.031 mol), and *N*-ethyl-diisopropylamine (5.1 mL, 0.034 mol) in methylene chloride (23 mL) were placed in a reaction flask. The reaction mixture was cooled to 0 °C and MOMCl (2.6 mL, 0.034 mol) was added dropwise at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was poured into 3 M sodium hydroxide (60 mL) and extracted with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate, and concentrated. The oily residue was obtained (5.68 g) and distilled under reduced pressure. 1,2,4-Trifluoro-5-(methoxymethoxy) benzene was obtained (3.67 g, 56.6%, GC/MS 97.5%, b.p. 70–72 °C/10 mm Hg (lit. 61–62 °C/8 mmHg, [11])). – n_D^{20} = 1.4475 (lit. n_D^{20} = 1.4407 [11]). – MS (EI, 70 eV): m/z (%) = 192 (17) $[M]^+$, 162 (4), 161 (12), 148 (5), 147 (8),133 (4), 131 (11), 119 (20), 99 (4), 81 (13), 45 (100). – IR (cm^{-1}, film): ν = 3800, 2963, 2840, 1523, 1431, 1218, 1157, 1076, 981, 853, 688.

4.9 2,3,5-trifluoro-6-hydroxybenzoic acid (3,5,6-trifluorosalicylic acid) (10)

1,2,4-Trifluoro-5-(methoxymethoxy)benzene (**9**, 1.8 g, 0.0094 mol) was placed in anhydrous diethyl ether (30 mL). under argon. The solution was cooled to –64 °C. 2.5 m *n*-butyllithium solution (0.0104 mol, 4.5 mL) was added in portions with a syringe through septum. The temperature of the reaction mixture rose to –61 °C. *n*-Butyllithium solution were added dropwise in five portions (4 × 1, 1 × 0.5 mL). After completion of the addition, the reaction mixture was stirred for 4 h at –65 °C. Gaseous carbon dioxide was passed through the reaction mixture for 1 h. The reaction mixture initially rose to –45 °C, then it maintained at approx. –65 °C. A copious amount of white precipitate was observed. The reaction mixture was allowed to warm to 0 °C, Water (10 mL) was added carefully. Aqueous layer was extracted with ether (after evaporation of the ether layer, residue was approx. 0.135 g). The aqueous layer was acidified with concentrated HCl to pH 1, stirred for 5 min. and extracted with ether. The combined ether layers were dried over anhydrous sodium sulfate. After evaporation of the solvent, a solid residue (1.49 g) was obtained. In order to remove the OMOM protection, the residue was dissolved in 6 mL of diethyl ether. A 2 n HCl (6 mL) was added and stirred at room temperature for 7 h (TLC control: benzene-acetone, 1:1). Diethyl ether layer was

evaporated. Concentrated HCl (0.2 mL) was added to the residue and the mixture was stirred at room temperature for 12 h. The mixture was extracted with methylene chloride. Drying of the organic layer over anhydrous sodium sulfate and evaporation gave 2,3,5-trifluoro-6-hydroxybenzoic acid (**10**, 1.03 g, 57.2%, colorless solid, m.p. 170–178 °C, which was subjected without further purification to the methylation to **11**. For analytical purposes, a sample of about 0.25 g was subjected to purification by column chromatography. The crude acid **10** was dissolved in ethyl acetate, silica gel (1 g) was added and evaporated to dryness. The sample applied on the gel was placed on the top of a chromatography column. Elution with hexane, hexane-ethyl acetate 9:1, 4:1, 1:1, ethyl acetate, methanol gave the product **10** (0.17 g) which was stirred with hexane at room temperature. The solid was filtered off. The filtrate was concentrated. 2,3,5-Trifluoro-6-hydroxybenzoic acid was obtained (**10**, 0.13 g, colorless solid, m.p. 173–174 °C. An analytical sample purified by column chromatography had an m.p. of 178–180 °C (lit. 173 °C [24]; 166–168 °C [11]; 165–167 °C [19]). – MS (EI, 70 eV): *m/z* (%) = 192 (39) $[M]^+$, 175 (20), 174 (100), 147 (8), 146 (50), 119 (21), 118 (65), 99 (27), 75 (8), 69 (8), 68 (8), 45 (8). – ^{1}H NMR (300 MHz, acetone-d_6): δ = 11.39 (1H, bs, COOH), 7.61 (1H, td, J = 10.5, 7.2 Hz, Har). – ^{13}C NMR (75.5 MHz, acetone-d_6): δ = 170.03 (dd, J = 6.64, 3.32 Hz, COOH), 147.81 (dt, J = 14.345, 2.53 Hz), 147.26 (ddd, J = 243.808, 9.7, 3.7 Hz), 146.91 (ddd, J = 256.9, 14.25, 4.1 Hz), 143.10 (ddd, J = 239.66, 14.9, 10.7 Hz), 111.69 (td, J = 23.2, 1.58 Hz), 106.13 (dd, J = 11.627, 3.775 Hz). – ^{19}F NMR (282.5 MHz, acetone-d_6): δ = –138.50 (ddd, J = 22.18, 15.11, 7.2 Hz), –139.49 (ddd, J = 15.1, 10.6, 2.0 Hz), –148.89 (ddd, J = 22.0, 10.5, 2.26 Hz). – IR (cm^{-1}, KBr): ν = 3440, 3100, 1682, 1644, 1496, 1445, 1269, 1178, 956, 714.

4.10 2,3,5-Trifluoro-6-methoxybenzoic acid (11)

To 2,3,5-trifluoro-6-hydroxybenzoic acid (**10**, 0.7 g, 0.0036 mol), acetone (12 mL), triturated anhydrous potassium carbonate (1.24 g, 0.009 mol), dimethyl sulfate (0.85 mL, 1.134 g, 0.009 mol) was added and refluxed for 7.5 and stirred 12 h at room temperature. The precipitate was then filtered off, the filtrate was concentrated and the crude methyl 2,3,5-trifluoro-2-methoxybenzoate (0.9 g) was obtained and subjected to basic hydrolysis with 40% potassium hydroxide (0.51 mL) in methanol (1 mL). The reaction mixture was stirred under reflux for 3 h. TLC analysis showed only partial hydrolysis (pH approx.7). Additional amount of 40% potassium hydroxide (0.3 mL) and methanol (1 mL) were added and the hydrolysis was continued for 1 h. TLC analysis showed complete hydrolysis of the ester. Methanol was evaporated, the residue was acidified with concentrated HCl. The product was extracted with ethyl acetate (3 × 15 mL) and methylene chloride (3 × 15 mL). Drying over anhydrous magnesium sulfate and concentration afforded 2,3,5-trifluoro-6-methoxybenzoic acid (**11**, 0.7 g, colorless solid, 93.2%, m.p. 86–89 °C). For analytical purposes a sample of approx. 0.25 g was subjected to purify by column chromatography. The crude 2,3,5-trifluoro-6-methoxybenzoic acid (**11**) was dissolved in warm benzene and applied to the top of the chromatography column. Elution with benzene, benzene-ethyl acetate 4:1, hexane-ethyl acetate 1:1 gave 2,3,5-trifluoro-6-methoxybenzoic acid (**11**, colorless solid, 0.22 g, m.p. 87–89 °C). – MS (EI, 70 eV): *m/z* (%) = 207 (6), 206 (62) $[M]^+$, 189 (16), 188 (12), 177 (28), 175 (12), 174 (37), 160 (28), 159 (100), 149 (8), 147 (18), 146 (33), 143 (14), 135 (10), 133 (16), 131 (18), 130 (17), 119 (54), 118 (33), 113 (13), 99 (34), 81 (26), 80 (12), 75 (15), 69 (11), 68 (13), 45 (9). – HRMS (EI, 70 eV): *m/z* = 206.0193 (calcd 206.0191 for $C_8H_5F_3O_3$, $[M]^+$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.84 (1H, s, COOH), 7.14 (1H, td, J = 10.2, 7.5 Hz, Har), 4.02 (3H, d, J = 1.5 Hz, OCH_3). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.91 (t, J = 3.29 Hz, COOH), 150.71 (ddd, J = 248.72, 9.11, 3.6 Hz), 145.70 (ddd, J = 248.94, 14.13, 10.5 Hz), 144.41 (ddd, J = 254.93, 14.8, 4.0 Hz), 142.15 (dt, J = 13.44, 3.7 Hz), 117.22 (dd, J = 13.70, 2.68 Hz), 108.71 (ddd, J = 24.59, 21.86, 1.27 Hz), 62.78 (dd, J = 5.51, 0.53 Hz, OCH_3). – ^{19}F NMR (282.5 MHz, $CDCl_3$): δ = –130.1 (t, J = 12 Hz), –138.42 (dd, J = 22.18, 9.8 Hz), –140.54 (ddd, J = 21.89, 14.13, 7.49 Hz). IR (cm^{-1}, KBr): ν = 3430, 3073, 1713, 1498, 1410, 1304, 1006, 868, 725.

4.11 2,3,5-Trichloro-6-methoxybenzoic acid (tricamba)

To 2,3,5-trichloro-6-hydroxybenzoic acid (4.8 g, 0.02 mol), acetone (67 mL), triturated anhydrous potassium carbonate (6.9 g, 0.05 mol), dimethyl sulfate (4.7 mL, 6.3 g, 0.05 mol) was added and refluxed for 7.5 h. The precipitate was filtered off, the filtrate was concentrated and the crude methyl 2,3,5-trichloro-2 methoxybenzoate (6.03 g) was obtained and subjected to basic hydrolysis. with 40% sodium hydroxide (3.1 mL) in methanol (5.6 mL). The reaction mixture was stirred under reflux. After about 1 h the reaction mixture solidified. Water (about 5 mL) was added and heating was continued for 5 h under reflux. Methanol was evaporated, the residue was acidified with concentrated HCl. The product was extracted with ethyl acetate. After drying over anhydrous magnesium sulfate and

concentration, the residue (8.13 g) was purified by column chromatography. Elution with hexane, hexane-ethyl acetate 4:1, 1:1, acetone gave 4.1 g of a colorless solid, which was washed with hexane and dried. 2,3,5-Trichloro-6-methoxybenzoic acid was obtained (3.0 g, 58.8%, GC 99.5%, HPLC 98.3%, m.p. 135–138 °C (lit. 137–139 °C [25])) – GC-MS (EI, 70 eV): *m/z* (%) = 258 (29), 256 (92), 254 (95) $[M]^+$, 241 (19), 239 (43), 23 (15), 237 (39), 236 (12), 227 (29), 226 (18), 225 (37), 224 (39), 222 (33), 213 (18), 212 (15), 211 (51), 210 (40), 209 (100), 208 (410, 207 (92), 196 (25), 194 (26), 185 (22), 183 (39), 181 (29), 176 (19), 175 (31), 169 (30), 167 (30), 149 (17), 147 (31), 146 (17), 145 (25), 143 (17), 133 (35), 131 (47), 111 (150, 109 (27), 108 (27), 107 (17), 97 (24), 96 (37), 74 (180), 73 (22), 61 (34). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.19 (1H, bs, COOH), 7.60 (1H, s, Ph), 3.98 (s, 3H, OCH_3). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.94 (s, COOH), 152.34 (s), 132.33 (s), 130.54 (s), 129.22 (s), 128.07 (s), 127.40 (s), 62.62 (s, OCH3). – IR (cm^{-1}, KBr): ν = 2949, 1713, 1649, 1461, 1421, 1243, 1136, 1014, 875, 685.

4.12 Herbicidal bioassay, pre- and post-emergence experiments

Herbicidal activity was evaluated using different weed species in pot experiments under controlled conditions. Polyethylene pots, 3.5 L capacity, were filled with 0.75 kg of soil (physicochemical characteristic: sandy clay, pH/KCl/6.7; organic matter 2.8%) and were wetted with water. Seeds of the weed species were planted in soil (0.5 cm depth). Plants were grown to the two-leaf stage under normal glasshouse propagation conditions (temperature, 20 ± 5 °C; lighting, 14 h photoperiod of daylight supplemented by lamps, 400 W). The pots were watered overhead. The test compounds were dissolved in an appropriate volume of acetone-water solution (1:3) with the addition of Tween 20 (0.05% *v*/*v*) to give the required dose of the tested substance. All treatments were applied as a pre-emergence or post-emergence spray at a volume rate of 300 L ha^{-1} using track laboratory sprayer (nozzle TeeJet60, pressure 0.2 MPa). There were three replicate pots per treatment arranged in a randomized block design. Pots after spraying were transferred to the growth chamber (temperature, day/night 20/15 °C; lighting, 16 h photoperiod, white fluorescent tubes giving 200 μmol m^{-2} s^{-2} PAR [photosynthetic active radiation]). A visual assessment of phytotoxicity separately for each species was made (18 or 25 days after treatment for pre- and post-emergence experiments) as a percentage compared to the untreated plants. Results (degree [%] of a visual observation of a phytotoxicity weed damage for a weed species used against control in doses: 2000, 300, 150 g ha^{-1}) are expressed as a fraction: a numerator means a result (in %) of a pre-emergence (via soil) treatment, a denominator means a result (in %) of a post-emergence (on leaves) treatment.

4.13 Fungistatic bioassay *in vitro*

Fungitoxicity of the tested compounds against phytopathogenic fungi was assessed *in vitro* using agar growth medium poison technique. PDA media in 100 mm Petri plates containing the acetone solutions of the tested compounds in the defined concentrations were infected with agar disks with thin mycelium of fungi cultures, and allowed the solvent to evaporate. Linear growth of each colony was determined after 3–5 days. The effect of each compound on mycelial growth was assessed by calculating the percentage of growth reduction of a fungus colony; percentage of linear growth reduction = ([colony diameter of a control plate – colony diameter of a tested plat]/[colony diameter of a control plate]) × 100.

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5 Supporting information

MS, ^{1}H, ^{13}C, ^{19}F NMR, and IR spectra are given as supplementary material available online (https://doi.org/10.1515/znb-2020-0179).

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