Synthesis and Evaluation of Phytotoxicity of Disugran Analogues

Silvana M. Basso, Juan P. Montañez and Ana N. Santiago*

INFIQC, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Haya de la Torre esq. Medina Allende, Ciudad Universitaria, 5000 Córdoba, Argentina

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Abstract: We report the synthesis and phytotoxicity of the compounds involved in the $S_{RN}1$-Stille reactions such as methyl 2,5-diphenylbenzoate (**6**), methyl 5-chloro-2-phenylbenzoate (**7**) and methyl 2-methoxy-3,6-diphenylbenzoate (**8**) as well as the phytotoxicity of intermediates. **8** has a good herbicide activity compared to Disugran and it isn't a chlorinated compound.

Keywords: Herbicide, chloroarene, bioassay, $S_{RN}1$ Reactions, Stille Reactions.

INTRODUCTION

Halogenated organic compounds (HOCs) have been heavily used as pesticides. Some of these compounds are very toxic and cause severe problems to human health and to the environment. These compounds are recalcitrant to degradation in the environment, and great efforts are being made to prevent further pollution and to decontaminate environmental media that are already polluted from their previous use [1, 2]. 3,6-Dichloro-2-methoxy benzoic acid (known as Dicamba) is among the most widely used chlorinated herbicides in many countries. These compounds are relatively stable under natural conditions and have become prominent contaminants in soil and hydrologic systems [3, 4].

Thus, the synthesis and testing of new derivatives, presenting advantages over the known herbicides, is one challenge for organic chemists.

The scope of radical nucleophilic substitution ($S_{RN}1$ reaction) has been considerably increased. Nowadays, this reaction is used to achieve substitution of different substrates [5-7], being an important synthetic pathway. The reaction of aryl halides with triorganostannyl ions as nucleophiles [8, 9] affords good yields of aryltrimethylstannanes by this mechanism. We have proved the $S_{RN}1$ reaction provides an interesting alternative route for the synthesis of stannanes [9, 10] which could have biological activity like azocyclotin (1-(tricyclohexyl stannyl)-1H-1,2,4-triazole) or cyhexatin (tricycle hexylhydroxy stannane) tested as acaricide [11]. Furthermore, organostannanes are well known fungicides [12-15].

On the other hand, tetraorganostannyl products are of particular relevance, mainly because they can be used as intermediates in further synthetic paths, such as the Stille reaction increasing the scope of probable bioactive compounds that can be synthesized by sequential reactions. The Stille cross-coupling reaction of tetraorganostannanes with organic electrophiles is one of the most reliable methods for the selective formation of carbon–carbon bonds [16, 17], in particular C_{sp2}–C_{sp2} bonds [18-20] affording a coupling product. Thus, a new C-C bond is formed with Pd^0 species as catalysts.

To this point, the tandem reactions of $S_{RN}1$ followed by Stille [9, 21] appear as an interesting synthetic pathway to obtain new derivatives of known chlorinated herbicides, providing a convenient way to explore the production of new agrochemicals, which could have better properties or less ecotoxicity than their precursors.

The main goal of the present work was to investigate both synthesis and biological activity of novel and potential chlorinated herbicides with $^-SnMe_3$ ions and the stannyl derivatives thus formed were replaced with phenyl group, generating a new C-C bond. The phytotoxicity of new derivatives was evaluated by bioassays using their precursor herbicides as reference.

RESULTS AND DISCUSSION

We have demonstrated [10] that the photostimulated reaction of either methyl 2,5-dichlorobenzoate (**1**) or methyl 3,6-dichloro-2-methoxybenzoate (**2**) (known as Disugran, is the methyl ester of Dicamba) with $^-SnMe_3$ ions affords good yields of disubstitution products (**3** or **4** respectively) by the $S_{RN}1$ mechanism in liquid ammonia (eqs. **1** and **3**). However, in the dark, only the mono-substitution product methyl chloro (trimethylstannyl)benzoate is obtained in 81% yield when methyl 2,5-dichlorobenzoate was the substrate (eq. **2**) [10]. In this reaction, two isomers (methyl 5-chloro-2-(trimethylstannyl)benzoate or methyl 2-chloro-5-(trimethylstannyl)benzoate) might be formed [10] however only one was observed. The isomer formed was determined through cleavage of trimethylstannyl group carried out in methyl chloro(trimethylstannyl)benzoate which was stirred in concentrate nitric acid at room temperature for 24 hours [22]. The product obtained was compared with an authentic sample by NMR yielding methyl *m*-chlorobenzoate. This confirms the position of chloro in methyl 5-chloro-2-(trimethylstannyl)benzoate (**5**).

*Address correspondence to this author at the Department of Organic Chemistry, Facultad Ciencias Químicas, Universidad Nacional de Córdoba. Haya de la Torre esq. Medina Allende, Ciudad Universitaria. (5000) - Córdoba – Argentina; Tel: +54 351 4333030; Fax: Extension 151;
E-mail: santiago@mail.fcq.unc.edu.ar

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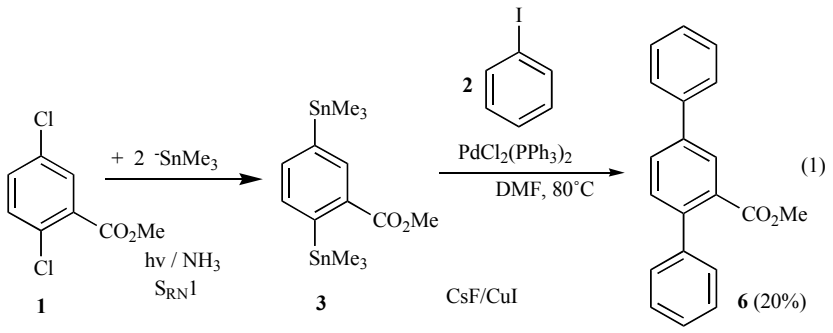


Equation 1.

Table 1. Reaction of methyl 5-chloro-2-(trimethylstannyl) benzoate (5) or methyl 2,5-bis(trimethylstannyl) benzoate (3) or methyl 2-methoxy-3,6-bis(trimethylstannyl) benzoate (4) with PhI under Stille conditions

Exp.	substrate:PhI ratio (10^{-2})	DMF mL	Conditions [a]	Products (%)[b]
1	**3**, 5: 10	4	PPh_3[c]	**6** (0)
2	**3**, 5: 10	4	CsF,[d] CuI	**6** (20)
3[e]	**5**, 2.5: 2.5	12	PPh_3[c]	**7** (0)
4	**5**, 2.5: 2.5	12	CsF,[f] PPh_3[c]	**7** (30)
5	**5**, 2.5: 2.5	12	CuI,[g] PPh_3[c]	**7** (28)
6	**4**, 2.5 : 5	8	CsF,[h] PPh_3[c]	**8**(27), **9** (54)[i]
7	**4**, 5: 10	8	CsF,[j] CuI	**8**(70), **9** (2)

[a]The catalyst was $PdCl_2(PPh_3)_2$ (6 mol % from substrate) in DMF at 80 °C for 24 h. [b]Isolated yields. [c]Reaction was carried out with $PdCl_2(PPh_3)_2$ and PPh_3 as a ligand in a ratio 1:10. [d]The ratio of **3**:CsF:CuI was 1:2:0.1. [e]This reaction was carried out in one pot from **1**. [f]The ratio **5**:CsF was 1:3. [g]The ratio of **5**:CuI was 1:10. [h]The ratio of **4**:CsF was 1:3. [i]GC relative yields. [j]The ratio of **6**:CsF:CuI was 1:2:0.1.

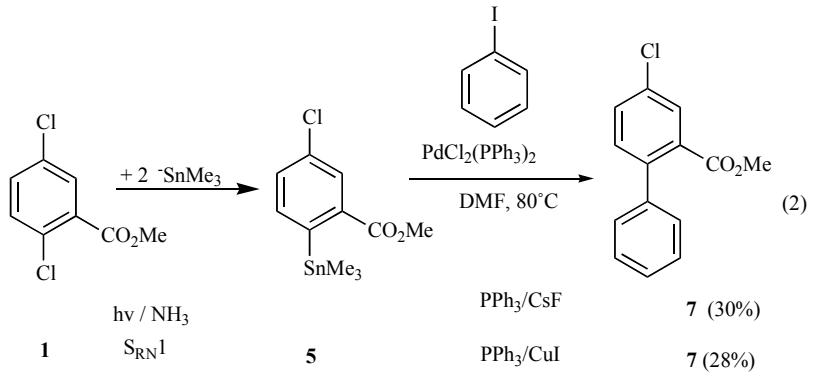
Reactions of Methyl 2,5-bis(trimethylstannyl) Benzoate (3) with PhI Under Stille Conditions

The reaction of **3** with 2 mol of PhI and $PdCl_2(PPh_3)_2$ as catalyst and PPh_3 as ligand in DMF did not occur (Table **1**, expt. 1). Nevertheless, the use of fluoride anion or Cu^+ to enhance the reactivity of the stannane in this type of reactions is widely known. Mee *et al*. have observed a synergic effect of fluoride anion and Cu^+ ions allowing the coupling of aryl halides by the Stille reaction [23-25]. In order to find best conditions of reaction we decided to test this effect. The reaction of **3** with 2 mol of PhI and $PdCl_2(PPh_3)_2$ as catalyst and CsF, CuI in DMF afforded methyl 2,5-diphenyl benzoate (**6**) in 20% isolated yield (eq. **1**) (Table **1**, expt. 2) [26], generating two new C-C bonds by Stille reaction.

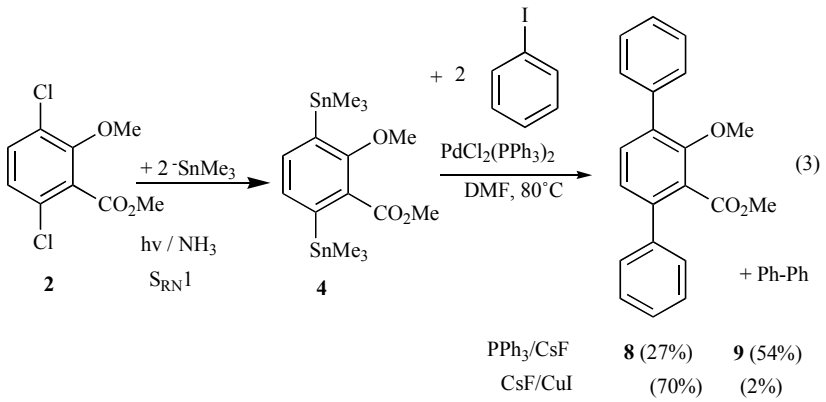
Reactions of Methyl 5-chloro-2-(trimethyl stannyl) Benzoate (5) with PhI Under Stille Conditions

The reaction of **5** with PhI and $PdCl_2(PPh_3)_2$ as catalyst and PPh_3 as ligand in DMF did not occur. However, when CsF or CuI were added, it afforded the coupling product methyl 5-chloro-2-phenylbenzoate (**7**) in 30-28% isolated yields (eq. **2**) (Table **1**, expts. 3-5) [26].

The use of fluoride anion or Cu+ enhances the reactivity of **5**. Fluoride ion probably gives rise to pentacoordinated



Equation 2.



Equation 3.

species with enhanced reactivity in the transmetalation step, as demonstrated by García Martínez *et al*. [27, 28].

Reactions of Methyl 2-methoxy-3,6-bis(trimethyl stannyl)benzoate (4) with PhI Under Stille Conditions

Generally iodides undergo coupling reactions fairly well, but when one or both of the coupling partners are sterically hindered or deactivated, they can be reluctant to couple efficiently. This is probably the case because the reaction of **4** with PhI and $PdCl_2(PPh_3)_2$ as catalyst and CsF in DMF afforded the coupling product methyl 2-methoxy-3,6-diphenylbenzoate (**8**) in only 27% relative yield together with 54% of biphenyl (**9**) (eq. **3**) (Table **1**, expt. 6) [26]. However the conditions of this reaction were optimized and when CsF and CuI were added without ligand (PPh_3) the product **8** was isolated in 70% yield (Table **1**, expt. 7). The formation of biphenyl is due to a homocoupling reaction which is a well-known competition reaction with Stille reactions [29].

Thus, a new C-C bond is formed with Pd^0 species as catalyst and the phytotoxicity of these new coupling products **6**, **7** and **8** were evaluated by bioassays.

BIOSSAY

Material Seed Test

The vegetal materials used for bioassays was one dicotyledon species, lettuce seeds (*Lactuca sativa* L.), and one monocotyledon species, oat seeds (*Avena sativa* L.) [30, 31].

Toxicity Test of Solvents on *Lactuca sativa* L.

Solvents used to dissolve tested compounds need to be non phytotoxic. Results show that a solution of DMSO 1% in distilled water did not exhibit significant suppression on germination or growth of lettuce seeds (number of germinated seeds (G) G=26, shoot length (L_S) L_S= 1.40 and root length (L_R) L_R=1.47) compared to control of water. Also DMSO 2% did not show important toxicity and can be used

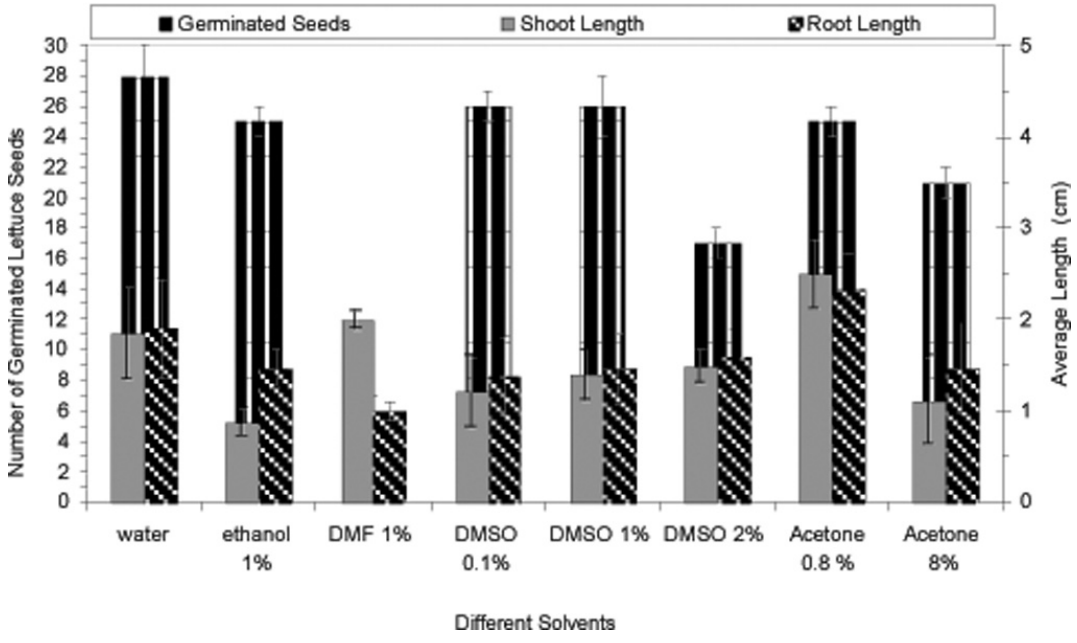


Fig. (1). Shoot Length, root length (average length in cm) and the number of germinated lettuce seeds in different solvents. Vertical bar indicates the standard error of the mean of three replicates.

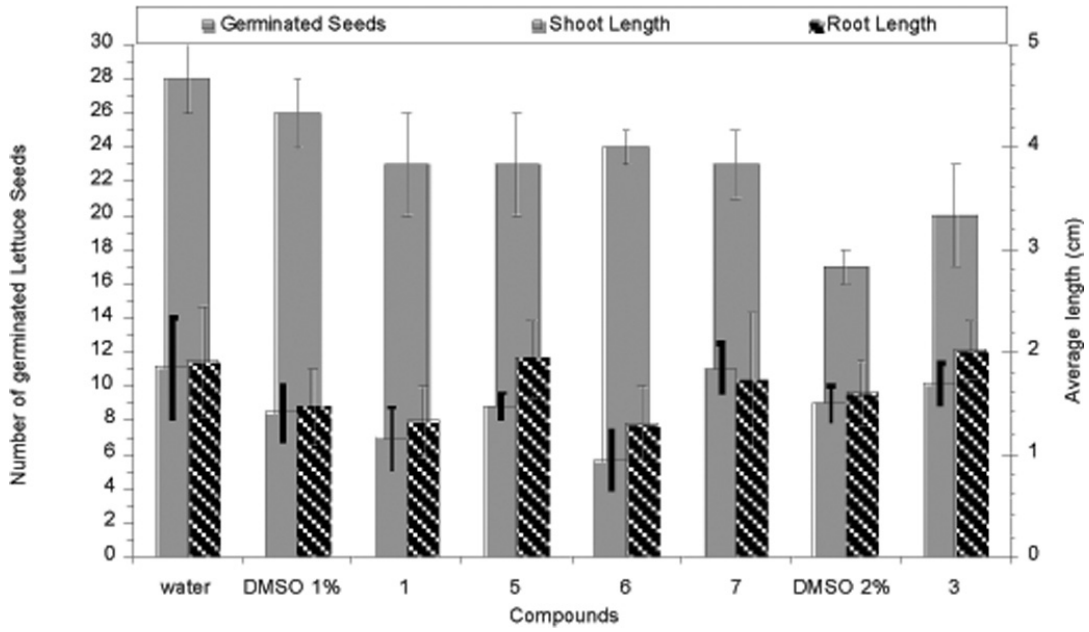


Fig. (2). Effects of the methyl 2,5-dichlorobenzoate family on germination or growth against *Lactuca sativa* L. Vertical bar indicates the standard error of the mean of three replicates. The solutions were in 1% DMSO at 100 ppm unless otherwise indicated. The solution of **3** was in 2% DMSO at 100 ppm. Its derivatives did not present significant differences at this concentration.

as solvent during toxicity tests. However, DMF 1% shows important suppression on germination and cannot be used as solvent during toxicity tests (Fig. **1**).

Toxicity Test of Solvents on *Avena sativa* L.

The solutions of DMSO 1% or 2% in distilled water did not show significant suppression on germination of oat seeds (G= 30, G= 30 and G= 28 respectively) although DMSO shows slight suppression on growth. However DMSO can be used as solvent during toxicity tests.

Evaluations of the Inhibition Percentage

The inhibition percentage [32] was calculated considering the number of germinated seeds in the treatment (Gt) and the number of germinated seeds in the control of the solvent (Gc) as follows:

Inhibition percentage (%I)= [1 – (Gt/ Gc)] 100.

Phytotoxicity of Methyl 2,5-dichlorobenzoate and its Derivatives on *Lactuca sativa* L.

Results in Fig. (**2**) show that **1**, **5**, **6**, **7** (DMSO 1 %) and **3** (DMSO 2%) did not exhibit important suppression on germination when tested at 100 ppm (G=20-24) in comparison with the control (G=26 or G=17) [30].

The Inhibition Percentage (%I) of Germination of Methyl 2,5-dichlorobenzoate and its Derivatives on Different Seeds

Results in Table **2** show the inhibition percentage of germination on different seeds when treated with the methyl 2,5-dichlorobenzoate derivatives (**1**, **3**, **5**, **6** and **7**) at 100 ppm. The methyl 2,5-dichlorobenzoate and its derivatives did not present important herbicidal activity on lettuce seeds or oat seeds at this concentration.

Phytotoxicity of Disugran and its Derivatives on *Lactuca sativa* L.

Results in Fig. (**3**) show that **2** (G=9) and **4** (G=8) exhibited important suppression on germination of *Lactuca sativa* L. when used at 100 ppm in comparison with the control (G=26). Furthermore, the compound **2** demonstrated suppression on the shoot growth (Fig. **3**) [30]. Also, **8** exhibited suppression on germination of *Lactuca sativa* L (G=15).

The Inhibition Percentage (%I) of Germination of Disugran and its Derivatives on Different Seeds

Results in Table **2** show the inhibition of germination in different seeds treated with the Disugran derivatives at 100 ppm. In *Lactuca sativa* L., **2** and **4** present important herbi-

Table 2. Inhibition Percentage on Germination Treated with Methyl 2,5-dichlorobenzoate Derivatives or with Disugran Derivatives at 100 ppm.

Compounds	1	3	5	6	7	2	4	8
%I *Lactuca sativa* L.	12	0	12	8	12	65	69	46
%I *Avena sativa* L.	0	0	0	0	0	6	0	0

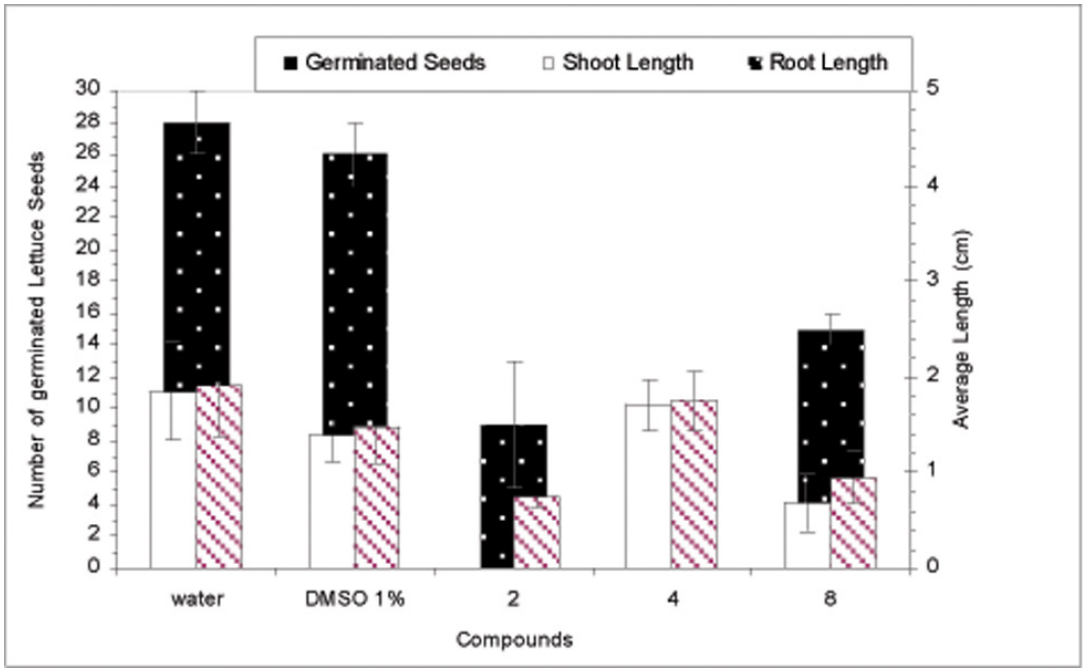


Fig. (3). Effects of Disugran derivatives on germination and growth of *Lactuca sativa* L. at 100 ppm. The solutions were in 1% DMSO at 100 ppm. Vertical bar indicates the standard error of the mean of three replicates. In **2**, shoot length shorter than 40% of control was not considered. **2** (A), **4** (A) and **8** (B) different letters indicate significant differences ($p <= 0.05$).

cidal activity at this concentration whereas **8** shows less, but also quite important, herbicidal activity. In *Avena sativa* L., none of them present herbicidal activity at this concentration. The fact that **8** has herbicidal activity at this concentrations is a very important result because it shows that it is possible to have good herbicidal activity if we change chlorinated compounds for phenylated ones.

Otherwise, as evident from Table **2**, Disugran (**2**, 65%) show his recognized herbicide properties against *Lactuca sativa* L. at 100 ppm. It is noticeable that methyl 2,5-dichlorobenzoate (**1**, 12%), which differs from Disugran by only one –OMe group, does not show inhibitory activity, thus demonstrating that the functional group has significant influence on the bioactivity of Disugran. None of its derivatives (**3**, **5**, **6**, **7**) has activity against *Lactuca sativa* L. (%I=0-12).

Calculation of IC_{50}

Owing to the results obtained during the inhibition tests with **4** and **8** (Table **2**), we decided to test the effects of **4** or **8** on the germination of *Lactuca sativa* L. in comparison with a commercial herbicide like Disugran (**2**). Thus, we calculated the concentration that inhibits the germination *of Lactuca sativa* L. by 50%, considering the negative logarithm of the molar concentration of the tested compound (IC_{50}) [33]. Therefore, the IC_{50} of **8** was approximately -log[3 x 10^{-4} M] (100 ppm), using data on lettuce seeds from Table **2**.

The molar concentration of Disugran necessary for the suppression on 50% of the germination of lettuce seeds was obtained by linear regression of percentage of inhibition on germination *vs*. the used herbicide molar concentration (-

Table 3. Inhibition Percentage on Germination Treated with Disugran (2) Against *Lactuca sativa* L.[a]

Comp	Concentration		Seeds		% I
	ppm	-log[M]	G	NG	
2	100	3.37	9 ± 3	21	65
4		3.69	8 ± 2	22	69
2	10	4.37	28 ± 1	2	2
4		4.69	29 ± 1	1	1
2	1	5.38	27 ± 3	3	1
4		5.69	27 ± 3	3	0
2	0.5	5.68	28 ± 2	2	1
4		5.99	28 ± 1	2	0

[a]G= Germinated seeds, NG= non germinated seeds. Values represent the mean ± SD (n =3).

log[M]) using data from Table **3**. The IC_{50} of **2** was -log[3.6 10^{-4} M] (R^2= 0.728).

Then, the results show that **8** is as active as **2** but probably the first is a less toxic and persistent compound. Therefore, **8** could be a good regulator of germination, raising questions on its probable use as a selective herbicide.

Otherwise, the IC_{50} of **4** necessary for the suppression on 50% of the germination of lettuce seeds was -log[1.3 10^{-4} M] (R^2= 0.728) using data from Table **3**. These concentrations suggest that **4** was almost three times more active as herbicide than Disugran (**2**).

CONCLUSIONS

Concerning stannyl derivatives, **4** is the most active compound, and **3** is one of the least phytotoxic compounds. Compound **3** was one of the least phytotoxic compounds tested against *Lactuca sativa* L. or against *Avena sativa* L. at 100 ppm.

Moreover, Disugran and its derivatives have activity against *Lactuca sativa* L. In this case, if we compare **2** with **8** we can see that by changing chloro for phenyl group, we obtain a compound with appropriate phytotoxic activity.

In conclusion, we describe the synthesis of **6** and **7** showing the poor results obtained on inhibition of either germination or growth against *Lactuca sativa* L. or *Avena sativa* L. at 100 ppm. However, **8** shows a good inhibition of germination against *Lactuca sativa* L. but not against *Avena sativa* L. at 100 ppm. This could be a great advantage as selective herbicide.

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[25] Mee S.P.H.; Lee V.; Baldwin J.E. *Chem. Eur. J.,* **2005**, *11*, 3294.

[26] **Typical procedure by Stille reactions.** The following procedure is representative of palladium catalyzed cross coupling reactions of **3**, **4** and **5** with PhI. In a Schlenk tube with nitrogen and magnetic stirrer, $PdCl_2(PPh_3)_2$, PPh_3, CuI, CsF were added respectively. The tube was deoxygenated and refilled with a nitrogen atmosphere three times. Next, DMF, PhI and the corresponding organotin compound were added. The solution was warmed at 80ºC for 24 hours. After that, the reaction was cooled and water was added before being extracted with diethyl ether. The products were isolated by column chromatography.

Methyl 2,5-diphenylbenzoate (**6**): Isolated as oil after column chromatography on silica gel, eluted with pentane-diethyl ether (98:2). ^{1}H-NMR (200.13 MHz, $CDCl_3$) δ: 3.60-3.70 (3H,s); 7.30-7.54 (9H, m); 7.60-7.70 (2H, m); 7.71-7.80 (1H, m) 8.0-8.08 (1H, d). ^{13}C-NMR (50.0 MHz, $CDCl_3$) δ: 51.99; 127.08; 127.29; 127.78; 128.08; 128.34; 128.42; 128.91; 129.72; 131.23; 131.34; 139.74; 140.20; 140.96; 141.28; 169.12. EM (EI+) m/z (%): 290 (3), 289 (22), 288 (M^+, 90), 257 (100), 244 (2), 228 (44), 202 (13), 152 (8), 129 (12), 101 (12), 88 (7), 54 (4).

Methyl 5-chloro-2-phenylbenzoate (**7**): Isolated as an oil after column chromatography on silica gel, eluted with pentane-diethyl ether (98:2): ^{1}H-NMR (200.13 MHz, $CDCl_3$) δ: 3.64 (3H, s); 7.27-7.41 (5H, m); 7.47-7.48 (1H, d); 7.51-7.52 (1H, d); 7.80-7.82 (1H, d). ^{13}C-NMR (50.0 MHz, $CDCl_3$). δ: 52.15; 127,54; 128.13; 128.24; 129.75; 130.50; 131.23; 131.77; 132.04; 133.20; 140.96; 167.75. EM (EI+) m/z (%): 248 (20), 246 (M^+, 59), 245 (11), 217 (34), 215 (100), 179 (6), 152 (87), 126 (6), 99 (3), 76 (35), 50 (4).

Methyl 2-methoxy-3,6-diphenylbenzoate (**8**): Isolated as white solid after column chromatography on silica gel, eluted with pentane-diethyl ether (98:2). ^{1}H-NMR (200.13 MHz, $CDCl_3$) δ: 3.40-3.48 (3H, s); 3.65-3.72 (3H, s); 7.18-7.25 (1H, d) 7.29-7.52 (9H, m); 7.59-7.68 (2H, m). ^{13}C-NMR (50.0 MHz, $CDCl_3$) δ: 52.18; 61.67; 125.49; 127.62; 127.73; 128.27; 128.46; 128.53; 128.91; 132.12; 133.76; 137.51; 139.64; 140.21; 154.63; 168.53. EM (EI+) m/z (%): 320 (3), 319 (20), 318 (M^+, 100), 287 (84), 286 (18), 271 (12), 269 (13), 241 (28), 215 (39), 106 (13).

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[30] **Solution of compounds tested:** 10 mg of the tested compound was dissolved in organic solvent (1-2 mL of DMSO or 8 mL of acetone according to indicate) and then diluted with distilled water in a 100 mL volumetric flask (100 ppm). These stock solutions allow the preparation of different dilutions: 10 ppm, 1 ppm and 0.5 ppm. In

some cases, sonication for 10 minutes was necessary to get the complete dissolution of the compound.

Biological Test. For each compound, four different concentrations were prepared and assayed in comparison to its respective control. Lettuce and oat seeds (30 units) were placed in a Petri dish over a piece of wet filter paper with 2 mL solution (5 mL for oat seeds). Petri dishes were protected with polystyrene bags and in the dark incubated at 22 ± 2ºC for 4 days (7 days for oat seeds). Bioassays of control solutions were performed in the same way using distilled water or solvent instead of a solution of a tested compound. In germinated seeds, shoot and root lengths were determined and recorded after 4 and 7 days. Two separate sets of seeds were treated in triplicate at each of the tested concentrations (n=6 for each seed set at a particular concentration).

[31] Palacios, S. M.; Vaccarini, C. E.; Alonso, R.; Novo, R. *QSAR and Molecular Modeling: Concepts. Computational Tools and Biological Applications*. eds. Sanz, F.; Giraldo, J.; Manaunt, F. Prous Science Publishers, **1995**, 180; and references cited there.

[32] Hong, N. H.; Xuan, T. D.; Eiji, T.; Hiroyuki, T.; Mitsuhiro, M.; Khanh, T. D. *Crop Protection*, **2003**, *22*, 829.

[33] IC_{50}= - log [molar concentration of the herbicide for the suppression on 50% of the germination].