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Synthesis and Phytotoxic Activity of Ozonides

LUIZ C. A. BARBOSA,*,† ULISSES A. PEREIRA,† RÓBSON R. TEIXEIRA,† CÉLIA R. A. MALTHA,† SERGIO A. FERNANDES,† AND GIUSEPPE FORLANI‡

Department of Chemistry, Federal University of Viçosa, Avenida P.H. Rolfs, CEP 36570-000, Viçosa, MG, Brazil, and Department of Biology and Evolution, University of Ferrara, via L. Borsari 46, I-44100 Ferrara, Italy

The [4 + 3] cycloaddition of the proper furans with the oxyallyl cation, generated *in situ* from 2,4-dibromopentan-3-one, produced a series of 8-oxabicyclo [3.2.1]oct-6-en-3-ones. Exposure of the oxabicycles to ozone afforded the corresponding 8,9,10,11-tetraoxatricyclo[5.2.1.$1^{2,6}$]undecan-4-ones in variable yields (7−100%). The phytotoxic properties of these ozonides (or 1,2,4-trioxolanes) and their oxabicycle precursors were evaluated as the ability to interfere with the growth of *Sorghum bicolor* and *Cucumis sativus* seedlings. Among oxabicycles, the highest inhibitory activity was shown by compounds possessing a α,β-unsaturated carbonyl moiety. A differential sensitivity of the two crops was evident with ozonides. The most active compounds were also tested against the weed species *Ipomoea grandifolia* and *Brachiaria decumbens*. To the best of our knowledge, this is the first article describing ozonides as potential herbicides.

KEYWORDS: [4 + 3] Cycloaddition; herbicides; oxabicycles; oxallyl cation; ozonides; plant growth regulators

INTRODUCTION

Artemisinin **1** (Qinghaosu, **Figure 1**) is a secondary metabolite isolated from the shoots of sweet wormwood (*Artemisia annua* L.) (*1*), a shrub long used in traditional Chinese medicine. This unique sesquiterpene lactone displays antimalarial activity (*2, 3*), which has been hypothesized to rely upon the presence of an endoperoxide bridge in its structure. As a consequence, artemisinin has been considered a lead structure toward the development of new substances to fight malaria, such as the water-soluble artesunate **2** and the lipid-soluble artemether **3**, already available as commercial drugs in China and other countries, and the clinical candidate **8**, named 0Z277 (**Figure 1**) (*4, 5*).

In addition to its antimalarial activity, artemisinin **1** has a powerful inhibitory effect on plant growth (*6, 7*). The phytotoxic activity also seems to be related to the generation of reactive oxygen species since deoxyartemisinin **11** (**Figure 1**) is inactive (*8*). To understand the structural requirements for such a capability, several analogues were synthesized and found to inhibit seed germination of some monocotyledonous and root growth of some dicotyledonous species (*9*). The synthetic derivatives **4**−**7** showed higher effectiveness than the lead compound, and all phytotoxic analogues exerted similar effects *in vivo*; thus, a common mode of action was suggested (*9*). However, the molecular target of artemisinin **1** in plants is still unknown. Other compounds containing an endoperoxide bridge have been recently described as natural, potent phytotoxins. For instance, the steroids **9** and **10** (**Figure 1**) exhibited higher biological activity against *Echinochloa crus-galli* than the commercial herbicide Logran (*10*).

Several years ago, compound **13** (**Figure 2**) was unexpectedly synthesized from the alkene precursor 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one **12** (*11*). This ozonide was unusually stable, being inert to Jones oxidation, and survived complete

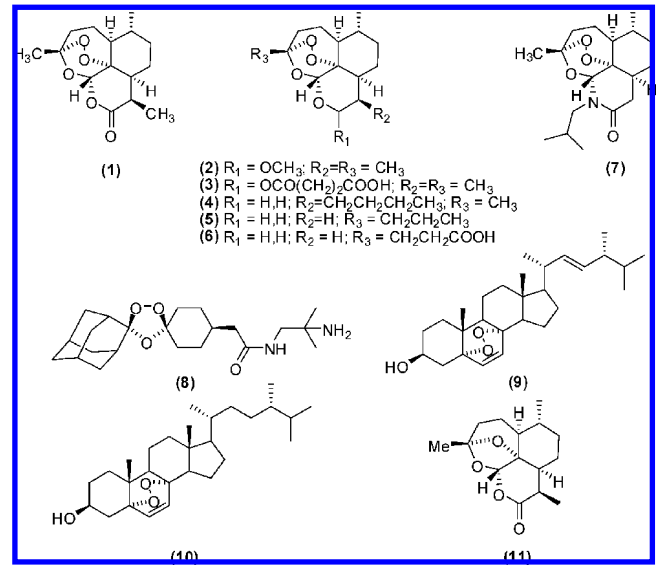

Figure 1. Structures of compounds **1**−**11**.

* To whom correspondence should be addressed. Fax: (55) 31 3899 3065. E-mail: lcab@ufv.br.
† Federal University of Viçosa.
‡ University of Ferrara.

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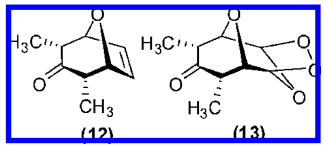


Figure 2. Structures of oxabicycle **12** and ozonide **13**.

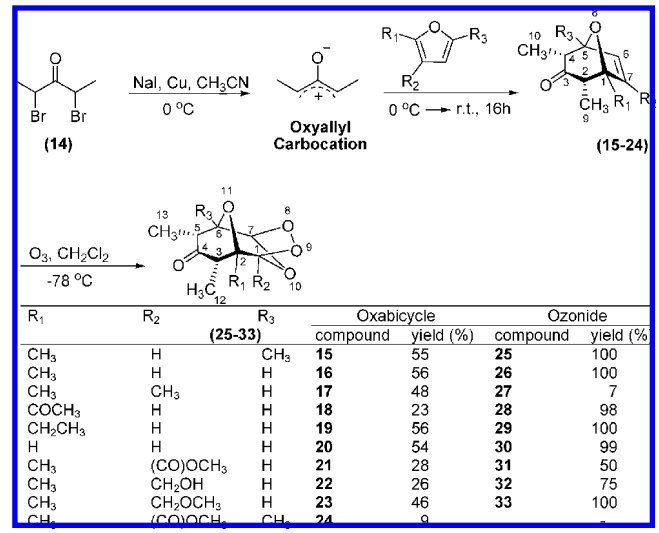
structure elucidation including X-ray structure determination. In view of the relationship between the presence of an endoperoxide moiety in artemisinin and its antimalarial activity, various analogues of compound **13** were synthesized and found to exhibit activity against a chloroquine-resistant strain of the malaria parasite *Plasmodium falciparum* (*12, 13*).

Within the frame of long-established research of new active principles to control weeds (*14*−*21*), we decided to evaluate the phytotoxicity of ozonides similar to compound **13**. Herein, we describe the preparation of a series of (8,9,10,11-tetraoxatricyclo[5.2.1.1^{2,6}]undecan-4-ones) from the corresponding alkene precursors. The evaluation of their inhibitory potential against either crop (*Sorghum bicolor* and *Cucumis sativus*) or weed (*Ipomoea grandifolia* and *Brachiaria decumbens*) species is also presented. To the best of our knowledge, this is the first article on phytotoxic activity of ozonides.

MATERIALS AND METHODS

General Experimental Procedures. Reagents and solvents were purified, when necessary, according to Perrin and Armarego (*22*). 2,4-dibromopentan-3-one **14** was obtained from the bromination of the commercially available pentan-3-one (Aldrich, Milwaukee, WI) according to a procedure described in the literature (*20*). The preparation of 3-hydroxymethyl-2-methylfuran was carried out as previously reported (*21*). The compound 3-(methoxymethyl)-2-methylfuran was prepared via a modified previously published procedure (*23*). All reactions were carried out under a protective atmosphere of dry nitrogen. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 instrument (300 and 75 MHz, respectively), using deuterated chloroform as a solvent and tetramethylsilane (TMS) as internal standard ($\delta = 0$). IR spectra were recorded from a Perkin-Elmer Paragon 1000 FTIR spectrophotometer, using thin film on cesium iodide (for the oxabicycles) or potassium bromide (for the ozonides) plates, scanning from 500 to 4000 cm^{-1}. Mass spectra were recorded on a Shimadzu GCMS-QP5050A instrument under electron impact (70 eV) conditions. Melting points are uncorrected and were obtained from an MQAPF-301 melting point apparatus (Microquimica, Brazil). Analytical thin layer chromatography analysis was conducted on aluminum packed precoated silica gel plates. Column chromatography was performed over silica gel (60−230 mesh).

Syntheses. *1-Acetyl-2α,4α-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**18**).* To a two neck round-bottomed flask (100 mL), fitted with a 10 mL dropping funnel, dry acetonitrile (40 mL) and sodium iodide (4.92 g, 32.8 mmol) were added during vigorous stirring under a slow stream of nitrogen. The mixture was cooled to 0 °C. Then, powdered copper (1.56 g, 24.6 mmol) was added, followed by 2-acetylfuran (1.17 g, 10.66 mmol). A solution of 2,4-dibromopentan-3-one **14** (2.0 g, 8.20 mmol) dissolved in dry acetonitrile (24 mL) was added, via a dropping funnel, during 30 min at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. After this time, the mixture was cooled down to 0 °C, and dichloromethane (50 mL) and water (50 mL) were added. The mixture was extracted with dichloromethane (2 × 40 mL) and filtered through a Celite pad. The mother liquor was washed with NH_4OH 35% (v/v) aqueous solution (50 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting material was purified by column chromatography on silica gel eluted with hexane/diethyl ether (10:1 v/v). This procedure afforded compound **18** as a yellow oil in 23% yield (372 mg; 1.92 mmol). IR (CsI, cm^{-1}),$\bar{\nu}_{max}$ 3091, 2977, 2938, 2877, 1715, 1679, 1570, 1458, 1379, 1360, 1161, 1059, 933, 811, 743; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (d, 3H, $J = 7.1$ Hz, H9), 0.99 (d, 3H, $J = 6.9$ Hz, H10), 2.32 (s, 3H, C$\underline{H}_3$CO-), 2.75 (dq, 1H, $J = 0.3$ Hz and $J = 7.1$ Hz, H2), 2.85 (ddq, 1H, $J = 0.3$ Hz, $J = 4.8$ Hz, and $J = 6.9$ Hz, H4), 4.94 (dd, 1H, $J = 1.8$ Hz and $J = 4.8$ Hz, H5), 6.36 (dd, 1H, $J = 1.8$ Hz and $J = 6.0$ Hz, H6), 6.43 (d, 1H, $J = 6.0$ Hz, H7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.78 (C9), 10.61 (C10), 25.73 (C$\underline{H}_3$CO-), 50.16 (C4), 52.00 (C2), 83.27 (C5), 94.87 (C1), 132.59 (C7), 134.40 (C6), 205.02 (CH$_3$C$\underline{O}$-)*, 207.53 (C3)*; MS, *m*/*z* (%): 194 (M$^+$, 1), 138 (96), 137 (6), 134 (5), 96 (20), 95 (76), 81 (13), 67 (32), 65 (10), 55 (12), 43 (100), 41 (39), 39 (30). *These assignments could be reversed.



R$_1$	R$_2$	R$_3$ (25-33)	Oxabicycle compound	Oxabicycle yield (%)	Ozonide compound	Ozonide yield (%
CH$_3$	H	CH$_3$	**15**	55	**25**	100
CH$_3$	H	H	**16**	56	**26**	100
CH$_3$	CH$_3$	H	**17**	48	**27**	7
COCH$_3$	H	H	**18**	23	**28**	98
CH$_2$CH$_3$	H	H	**19**	56	**29**	100
H	H	H	**20**	54	**30**	99
CH$_3$	(CO)OCH$_3$	H	**21**	28	**31**	50
CH$_3$	CH$_2$OH	H	**22**	26	**32**	75
CH$_3$	CH$_2$OCH$_3$	H	**23**	46	**33**	100
CH$_3$	(CO)OCH$_3$	CH$_3$	**24**	9		

Figure 3. Preparation of oxabicycles and ozonides.

The other oxabicycles (**15**−**17** and **19**−**24**) were prepared employing a procedure similar to that described for compound **18**, and yields are presented in **Figure 3**. The synthesized compounds were fully characterized by IR, NMR (^{1}H and ^{13}C) and mass spectrometry. Structural characterization of compounds **15**, **16**, **19**, and **20** has already been described (*12, 13, 20, 24*). Structures for the remaining compounds are supported by the following spectroscopic data.

*Data for 1,2α,4α,7-Tetramethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**17**).* Yellow oil; purified by column chromatography, eluent hexane/dichloromethane (1:1.5 v/v); IR (CsI, cm^{-1}), $\bar{\nu}_{max}$ 2977, 2937, 2874, 1710, 1643, 1449, 1375, 1168, 1023, 903, 864; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, 3H, $J = 6.9$ Hz, H10), 1.04 (d, 3H, $J = 7.2$ Hz, H9), 1.46 (s, 3H, 1-C$\underline{H}_3$), 1.76 (dd, 3H, $J = 1.7$ Hz and $J = 1.1$ Hz, 7-C$\underline{H}_3$), 2.64 (q, 1H, $J = 7.2$ Hz, H2), 2.74 (dq, 1H, $J = 6.9$ Hz and $J = 4.8$ Hz, H4), 4.64−4.68 (m, 1H, H5), 5.80−5.83 (m, 1H, H6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.88 (C9), 10.57 (C10), 14.54 (7-C$\underline{H}_3$), 20.60 (1-C$\underline{H}_3$), 49.64 (C4), 56.52 (C2), 81.00 (C5), 88.67 (C1), 126.37 (C6), 146.40 (C7), 210.03 (C3); MS, *m*/*z* (%): 180 (M$^+$, 23), 165 (20), 137 (6), 124 (17), 123 (52), 109 (100), 96 (13), 95 (26), 81 (16), 79 (12), 67 (10), 55 (16), 53 (14), 43 (61), 40 (30), 39 (25).

*Data for 7-(Methoxycarbonyl)-1,2α,4α-trimethyl-8-oxabicyclo[3.2.1]-oct-6-en-3-one (**21**).* Yellow oil; purified by column chromatography, eluent hexane/diethyl ether (7:1 v/v); IR (CsI, cm^{-1}), $\bar{\nu}_{max}$ 3089, 2980, 2940, 2875, 1713, 1613, 1438, 1379, 1265, 1227, 1165, 1090, 1025, 916, 861, 762; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, 3H, $J = 7.2$ Hz, H10), 1.05 (d, 3H, $J = 7.2$ Hz, H9), 1.69 (s, 3H, 1-C$\underline{H}_3$), 2.67 (q, 1H, $J = 7.2$ Hz, H2), 2.85 (dq, 1H, $J = 5.1$ Hz and $J = 7.2$ Hz, H4), 3.72 (s, 3H, C$\underline{H}_3$OCO-), 4.87 (dd, 1H, $J = 5.1$ Hz and $J = 2.1$ Hz, H5), 7.12 (d, 1H, $J = 2.1$ Hz, H6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.78 (C9), 10.39 (C10), 21.34 (1-C$\underline{H}_3$), 49.49 (C4), 52.04 (C$\underline{H}_3$OCO-), 56.82 (C2), 80.94 (C5), 88.52 (C1), 141.20 (C7), 144.83 (C6), 163.24 (CH$_3$O$\underline{C}$O-), 208.59 (C3); MS, *m*/*z* (%): 224 (M$^+$, 15), 209 (8), 192 (7), 177 (22), 168 (40), 167 (34), 165 (7), 153 (91), 149 (12), 136 (7), 135 (23), 121 (16), 109 (75), 107 (11), 93 (10), 79 (15), 65 (15), 56 (14), 55 (29), 53 (20), 43 (100), 41 (30), 39 (35).

*Data for 7-Hydroxymethyl-1,2α,4α-trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**22**).* White solid; mp 68.0−68.9 °C; purified by column chromatography, eluent hexane/diethyl ether (2:1 v/v); IR (CsI, cm^{-1}), $\bar{\nu}_{max}$ 3600−3100 (broadband), 2977, 2937, 2875, 1708, 1449, 1377, 1325, 1168, 1037, 977, 940, 907, 864, 801; ^{1}H NMR (300 MHz,

Table 1. Effect of Oxabicyclic Compounds on Germination and Radicle Growth of *S. bicolor* and *C. sativus* Seedlings

	Sorghum bicolor						*Cucumis sativus*					
	7.5×10^{-5} mol L^{-1}			7.5×10^{-4} mol L^{-1}			7.5×10^{-5} mol L^{-1}			7.5×10^{-4} mol L^{-1}		
compound	radicle length (cm)[a]	inhibition (%)	germination (%)	radicle length (cm)[a]	inhibition (%)	germination (%)	radicle length (cm)[a]	inhibition (%)	germination (%)	radicle length (cm)[a]	inhibition (%)	germination (%)
15	3.16a	−0.3	94	3.59 a	3.5	96	5.63a	−0.7	99	5.14 ab	8.1	99
16	3.35a	−6.3	93	3.81 a	−2.4	97	5.20a	7.0	98	5.62 a	−0.5	96
17	3.15a	0.0	95	3.39ab	8.9	96	4.82a	13.8	99	4.01 bc	28.3	98
18	3.24a	−2.9	93	3.48ab	6.5	93	5.24a	6.3	99	4.84abc	13.4	100
19	3.40a	−7.9	91	3.63 a	2.4	96	5.18a	7.3	96	4.91abc	12.2	100
20	2.96a	6.0	97	3.69 a	0.8	91	6.11a	−9.3	98	5.45 a	2.5	97
21	3.51a	−11.4	89	1.75 c	53.0	95	5.89a	−5.4	96	3.67 c	34.3	97
22	3.05a	3.2	89	3.47ab	6.7	96	5.34a	4.5	98	5.31 ab	5.0	98
23	2.96a	6.0	91	3.23ab	13.2	93	5.48a	2.0	98	4.79abc	14.3	98
24	3.49a	−10.8	93	2.62bc	29.6	91	5.88a	−5.2	97	4.73abc	15.4	100
control	3.15a	0.0	95	3.72 a	0.0	93	5.59a	0.0	100	5.59 a	0.0	100

[a] Mean values in the same column with the same letter are not significantly different at $P = 0.05\%$ by Tukey's test.

Table 2. Effect of Ozonides and Artemisinin on Germination and Radicle Growth of *S. bicolor* and *C. sativus* Seedlings

	Sorghum bicolor						*Cucumis sativus*					
	7.5×10^{-5} mol L^{-1}			7.5×10^{-4} mol L^{-1}			7.5×10^{-5} mol L^{-1}			7.5×10^{-4} mol L^{-1}		
compound	radicle length (cm)[a]	inhibition (%)	germination (%)	radicle length (cm)[a]	inhibition (%)	germination (%)	radicle length (cm)[a]	inhibition (%)	germination (%)	radicle length (cm)[a]	inhibition (%)	germination (%)
25	3.17 b	13.6	96	2.25 d	48.3	94	5.78 a	−3.4	99	3.67 bc	34.3	95
26	4.20 a	−14.4	95	3.59 bc	17.5	98	5.87 a	−5.0	98	5.37 ab	3.9	99
28	3.70 ab	−0.8	97	3.86 ab	11.3	87	6.13 a	−9.7	97	5.60 a	−0.2	100
29	3.68 ab	−0.3	96	2.98 cd	31.5	93	5.55 a	0.7	99	7.00 a	−25.2	100
30	4.17 a	−13.6	92	3.76 ab	13.6	88	5.25 ab	6.1	96	5.49 a	1.8	98
31	3.66 ab	0.3	90	3.79 ab	12.9	96	5.82 a	−4.1	97	5.82 a	−4.1	100
32	3.88 ab	−5.7	94	4.38 a	−0.7	89	5.45 a	2.5	97	6.18 a	−10.6	100
33	3.55 ab	3.3	95	3.77 ab	13.3	95	5.97 a	−6.8	96	6.62 a	−18.4	100
control	3.67 ab	0.0	92	4.35 ab	0.0	96	5.59 a	0.0	100	5.59 a	0.0	100
artemisinin	0.81 c	77.9	90	0.61 e	86.0	93	3.82 b	31.7	99	3.54 c	36.7	99

[a] Means in the same column with the same letter are not significantly different at $P = 0.05\%$ by Tukey's test. Compound **27** was not evaluated because of the low amounts obtained.

Table 3. Effect of Compounds **21**, **24**, **25**, and **29** (0.1 μmol a.i./g Substrate) on Radicle Growth of *Ipomoea grandifolia* and *Brachiaria decumbens*

	Ipomoea grandifolia				*Brachiaria decumbens*			
	24 h		48 h		24 h		48 h	
compound	radicle length[a] (cm)	inhibition (%)	radicle length[a](cm)	inhibition (%)	radicle length[a] (cm)	inhibition (%)	radicle length[a] (cm)	inhibition (%)
21	1.11 d	33	1.22 de	63	1.76 bc	42	2.66 bc	49
24	1.09 d	34	1.68 cd	49	2.60 ab	14	4.29 ab	18
25	1.35 c	18	2.12 bc	36	1.71 c	43	2.60 c	50
29	1.93 a	−17	2.60 ab	21	2.43 abc	20	3.82 abc	27
artemisinin	0.70 e	58	0.76 e	77	0.45 d	85	0.45 d	91
control	1.65 b		3.29 a		3.02 a		5.23 a	

[a] Means, in the same column, with the same letter are not significantly different at $P = 0.05\%$ by Tukey's test.

$CDCl_3$): δ 0.95 (d, 3H, $J = 6.9$ Hz, H10), 1.03 (d, 3H, $J = 7.2$ Hz, H9), 1.48 (s, 3H, 1-CH_3), 1.88 (s, 1H, -CH_2OH), 2.66 (q, 1H, $J = 7.2$ Hz, H2), 2.79 (dq, 1H, $J = 4.5$ Hz and $J = 6.9$ Hz, H4), 4.22−4.21 (m, 2H, -CH_2OH), 4.75−4.78 (m, 1H, H5), 6.11−6.13 (m, 1H, H6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.71 (C9), 10.49 (C10), 20.82 (1-CH_3), 49.65 (C4), 56.54 (C2), 59.96 (-CH_2OH), 81.43 (C5), 88.22 (C1), 127.02 (C6), 150.72 (C7), 209.64 (C3); MS, *m/z* (%): 196 (M^+, 7), 139 (21), 125 (27), 122 (20), 120 (16), 111 (14), 109 (56), 95 (11), 79 (15), 77 (12), 57 (11), 55 (30), 53 (13), 43 (100), 41 (35), 39 (30), 31 (10).

*Data for 1,2α,4α-Trimethyl-7-(methoxymethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one (**23**).* Colorless oil; purified by column chromatography, eluent hexane/diethyl ether (2:1 v/v); IR (CsI, cm^{-1}), $\bar{\nu}_{max}$ 2978, 2935, 2875, 2827, 1710, 1449, 1377, 1197, 1168, 1115, 1097, 1023, 907, 865, 803; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, 3H, $J = 6.9$ Hz, H10), 1.03 (d, 3H, $J = 7.2$ Hz, H9), 1.47 (s, 3H, 1-CH_3), 2.64 (q, 1H, $J = 7.2$ Hz, H2), 2.78 (dq, 1H, $J = 4.5$ and $J = 6.9$ Hz, H4), 3.30 (s, 3H, -CH_2OCH_3), 3.90−4.04 (m, 2H, -CH_2OCH_3), 4.75−4.77 (m, 1H, H5), 6.09−6.11 (m, 1H, H6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.69 (C9), 10.53 (C10), 20.87 (1-CH_3), 49.56 (C4), 56.57 (C2), 58.53 (-CH_2OCH_3), 69.17 (-CH_2OCH_3), 81.43 (C5), 88.23 (C1), 128.87 (C6), 147.07 (C7), 209.44 (C3); MS, *m/z* (%): 210 (M^+; 4), 178 (17), 163 (12), 153 (15), 139 (14), 125 (30), 123 (10), 122 (60), 121 (29), 109 (49), 107 (13), 95 (16), 81 (10), 79 (27), 77 (17), 55 (20), 53 (13), 45 (42), 43 (100), 39 (23).

*Data for 1,2α,4α,5-Tetramethyl-7-(methoxycarbonyl)-8-oxabicyclo-[3.2.1]oct-6-en-3-one (**24**).* Yellow oil; purified by column chromatography, eluent hexane/diethyl ether (5:1 v/v); IR (CsI, cm^{-1}), $\bar{\nu}_{max}$ 3086, 2979, 2939, 2875, 1722, 1712, 1619, 1438, 1378, 1339, 1273, 1166, 1042, 975, 891, 768; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (d, 3H, $J = 7.2$ Hz, H10), 1.05 (d, 3H, $J = 6.9$ Hz, H9), 1.51 (s, 3H, 5-CH_3), 1.68 (s, 3H, 1-CH_3), 2.59 (q, 1H, $J = 6.9$ Hz, H2), 2.63 (q, 1H, $J = 7.2$ Hz, H4), 3.70 (s, 3H, CH_3OCO-), 6.92 (s, 1H, H6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.04 (C9), 10.33 (C10), 21.66 (1-CH_3),

Table 4. Effect of Compounds **21**, **24**, **25**, and **29** (0.1 μmol a.i./g Substrate) on the Growth of *Ipomoea grandifolia* and *Brachiaria decumbens* under Greenhouse Conditions after 21 Days

	Ipomoea grandifolia				*Brachiaria decumbens*			
compound	aerial part[a] (mg)	inhibition (%)	roots[a] (mg)	inhibition (%)	aerial part[a] (mg)	inhibition (%)	roots[a] (mg)	inhibition (%)
21	16.0 bc	69	3.8 bc	76	22.1 bc	−21	8.9 ab	−7
24	12.5 c	76	1.8 c	88	25.7 b	−40	8.8 ab	−6
25	30.4 bc	41	9.1 b	42	21.8 bc	−19	7.8 b	6
29	34.9 ab	33	8.0 b	49	34.1 a	−86	11.9 a	−43
control	51.8 a		15.6 a		18.3 c		8.3 b	

[a] Means, in the same column, with the same letter are not significantly different at $P = 0.05\%$ by Tukey's test. *I. grandifolia* and *B. decumbens* seedlings did not develop in the presence of artemisinin, applied at the same concentration.

21.82 (5-$\underline{C}H_3$), 51.94 ($\underline{C}H_3OCO$-), 54.89 (C2), 55.98 (C4), 85.84 (C5), 88.04 (C1), 140.67 (C7), 147.64 (C6), 163.32 ($CH_3O\underline{C}O$-), 208.82 (C3); MS, *m/z* (%): 238 (M^+, 4), 206 (26), 179 (20), 167 (48), 163 (22), 151 (13), 137 (12), 135 (18), 123 (27), 122 (11), 79 (14), 77 (11), 55 (14), 53 (11), 43 (100), 41 (12), 39 (12).

*2-Acetyl-3-exo,5-exodimethyl-8,9,10,11-tetraoxatricyclo[5.2.1.1^{2,6}]-undecan-4-one (**28**).* Ozone was passed through a solution of the oxabicycle **18** (100 mg, 0.51 mmol) in anhydrous dichloromethane (120 mL) at −78 °C. After 5 min, the reaction was judged to be complete by TLC analysis. The excess of ozone was removed by bubbling nitrogen through the solution for about 10 min. After that, the solvent was removed under reduced pressure to afford the ozonide **28** as a white solid (122 mg; 0.50 mmol) in 98% yield. No further purification was carried out. Mp 128.7−129.6 °C; IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 2983, 2943, 1716, 1418, 1382, 1363, 1239, 1188, 1163, 1093, 1071, 1038, 940, 879, 797; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (d, 3H, $J = 7.2$ Hz, H12), 1.18 (d, 3H, $J = 6.9$ Hz, H13), 2.31 (s, 3H, $C\underline{H}_3CO$-), 2.61 (dq, 1H, $J = 1.2$ Hz and $J = 7.2$ Hz, H3), 2.95−3.04 (m, 1H, H5), 4.22 (dd, 1H, $J = 6.9$ Hz and $J = 0.9$ Hz, H6), 5.73 (brs, 1H, H7), 6.08 (brs, 1H, H1); ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.79 (C12), 9.86 (C13), 25.11 ($\underline{C}H_3CO$-), 45.74 (C5), 47.52 (C3), 77.26 (C6), 84.95 (C2), 99.45 (C7), 100.28 (C1), 204.79 (C4)*, 205.10 ($CH_3\underline{C}O$-)*. *These assignments could be reversed. This reaction was carried out on a 10 mmol scale with the same results.

Compounds **25**−**27** and **29**−**33** were prepared employing a procedure similar to that described for compound **28**, and yields are presented in **Figure 3**. Structures of the ozonides were confirmed by IR and NMR. The molecular formulas were confirmed on the basis of elemental analyses. Structural characterization of compounds **29** and **30** has been already described (*13*). Structures for the remaining compounds are supported by the following spectroscopic data.

*Data for 2,3-exo,5-exo-6-Tetramethyl-8,9,10,11-tetraoxatricyclo-[5.2.1.1^{2,6}]undecan-4-one (**25**).* White solid; mp 109.5−110.7 °C; IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 2987, 2944, 1711, 1453, 1376, 1320, 1299, 1247, 1183, 1061, 939, 865, 798; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (d, 6H, $J = 7.2$ Hz, H12 and H13), 1.32 (s, 6H, 2-$\underline{C}H_3$ and 6-$\underline{C}H_3$), 2.51 (q, 2H, $J = 7.2$ Hz, H3 and H5), 5.45 (s, 2H, H1 and H7); ^{13}C NMR ($CDCl_3$): δ 9.75 (C12 and C13), 21.32 (2-$\underline{C}H_3$ and 6-$\underline{C}H_3$), 51.18 (C3 and C5), 78.45 (C2 and C6), 101.30 (C1 and C7), 206.88 (C4). Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07; found, C, 57.71; H, 6.99.

*Datafor2,3-exo,5-exoTrimethyl-8,9,10,11-tetraoxatricyclo[5.2.1.1^{2,6}]-undecan-4-one (**26**).* White solid; mp 102.5−103.4 °C; IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 2982, 2941, 2878, 1713, 1383, 1187, 1077, 941, 881, 853, 789; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (d, 3H, $J = 7.2$, H13), 1.18 (d, 3H, $J = 6.9$, H12), 1.32 (s, 3H, 2-CH_3), 2.54 (dq, 1H, J =1.2, $J = 6.9$, H3), 2.88 (dquint, 1H, J =1,2, $J = 7.2$, H5), 4.06 (dd, 1H, $J = 7.2$, $J = 1.2$, H6), 5.46 (s, 1H, H1), 5.69−5.70 (m, 1H, H7), ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.52 (C12), 9.96 (C13), 21.34 (2-CH_3), 45.29 (C5), 51.81 (C3), 76.42 (C6), 79.57 (C2), 99.31 (C1), 102.14 (C7), 207.14 (C4). Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59; found, C, 56.10; H, 6.52.

*Data for 1,2,3-exo,5-exoTetramethyl-8,9,10,11-tetraoxatricyclo[5.2.1.1^{2,6}]undecan-4-one (**27**).* Colorless oil; IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 2983, 2943, 2878, 1715, 1624, 1462, 1388, 1287, 1197, 1166, 1078, 959, 934, 885, 843; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (d, 3H, $J = 6.9$ Hz, H13), 1.22 (d, 3H, $J = 7.2$ Hz, H12), 1.37 (s, 3H, 2-$\underline{C}H_3$), 1.50 (s, 3H, 1-$\underline{C}H_3$), 2.70 (dq, 1H, $J = 1.2$ Hz and $J = 7.2$ Hz, H3), 2.84−2.93 (m, 1H, H5), 4.13 (dd, 1H, $J = 6.9$ Hz and $J = 1.5$, H6), 5.68 (d, 1H, $J = 1.5$ Hz, H7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.85 (C13), 11.14 (C12), 18.23 (2-$\underline{C}H_3$), 21.70 (1-$\underline{C}H_3$), 45.20 (C5), 52.90 (C3), 77.10 (C6), 83.47 (C2), 101.30 (C7), 109.94 (C1), 207.26 (C4). Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07; found, C, 57.81; H, 7.11.

*Data for 2,3-exo,5-exoTrimethyl-1-(methoxycarbonyl)-8,9,10,11-tetraoxatricyclo [5.2.1.1^{2,6}]undecan-4-one (**31**).* White solid; mp 104.2−105.8 °C; IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 2994, 2943, 2889, 1755, 1700, 1446, 1383, 1323, 1185, 1120, 1097, 1053, 992, 865, 885; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, 3H, $J = 7.3$ Hz, H12), 1.15 (d, 3H, $J =$ 6.9 Hz, H13), 1.54 (s, 3H, 2-$\underline{C}H_3$), 2.62 (q, 1H, $J = 7.3$ Hz, H3), 2.90 (m, 1H, H5), 3.83 (s, 3H, $\underline{C}H_3OCO$-), 4.16 (dd, 1H, $J = 6.5$ Hz and J = 1.2 Hz, H6), 5.90 (d, 1H, $J = 1.2$ Hz, H7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.20 (C12), 9.80 (C13), 22.17 (2-$\underline{C}H_3$), 45.01 (C5), 52.26 (C3), 53.83 ($\underline{C}H_3OCO$-), 76.39 (C6), 83.05 (C2), 102.47 (C7), 105.00 (C1), 162.72 ($CH_3O\underline{C}O$-), 205.97 (C4). Anal. Calcd. for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92; found, C, 53.00; H, 5.88.

*Data for 1-Hydroxymethyl-2,3-exo,5-exotrimethyl-8,9,10,11-tetraoxatricyclo[5.2.1.1^{2,6}] undecan-4-one (**32**).* White solid; mp 108.4−109.8 °C; IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3640−3280 (broadband), 2996, 2980, 2949, 2883, 1719, 1382, 1296, 1185, 1159, 1078, 1015, 949, 936, 874; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (d, 3H, $J = 7.0$ Hz, H13), 1.19 (d, 3H, $J = 7.2$ Hz, H12), 1.33 (s, 3H, 2-$\underline{C}H_3$), 1.90 (s, 1H, -$CH_2\underline{O}H$), 2.70 (m, 1H, H3), 2.91 (m, 1H, H5), 3.74 (d, 1H, $J = 13.2$ Hz, -$C\underline{H}_2OH$), 3.92 (d, 1H, $J = 13.2$, -$C\underline{H}_2OH$), 4.18 (dd, 1H, $J = 7.0$ Hz and $J = 1.2$ Hz, H6), 5.77 (brs, 1H, H7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.85 (C13), 10.69 (C12), 21.34 (2-$\underline{C}H_3$), 45.20 (C5), 52.64 (C3), 58.32 (-$\underline{C}H_2OH$), 77.03 (C6), 82.70 (C2), 101.53 (C7), 110.07 (C1), 206.61 (C4). Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60; found, C, 53.89; H, 6.64.

*Data for 2,3-exo,5-exoTrimethyl-1-(methoxymethyl)-8,9,10,11-tetraoxatricyclo[5.2.1.1^{2,6}] undecan-4-one (**33**).* Amorphous white solid; IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 2993, 2947, 2883, 2819, 1705, 1472, 1455, 1381, 1206, 1167, 1118, 1093, 1054, 977, 950, 931, 894, 885, 842; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, 3H, $J = 6.8$ Hz, H13), 1.21 (d, 3H, $J =$ 7.5 Hz, H12), 1.36 (s, 3H, 2-$\underline{C}H_3$), 2.70 (dq, 1H, $J = 1.2$ Hz and $J =$ 7.5 Hz, H3), 2.89 (m, 1H, H5), 3.40 (s, 3H, -$CH_2O\underline{C}H_3$), 3.66 (d, 2H, $J = 3.0$ Hz, -$C\underline{H}_2OCH_3$), 4.15 (dd, 1H, $J = 6.8$ Hz and $J = 1.2$ Hz, H6), 5.74 (d, 1H, $J = 1.2$ Hz, H7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.83 (C13), 10.49 (C12), 21.55 (2-$\underline{C}H_3$), 45.16 (C3), 52.73 (C5), 60.58 (-$CH_2\underline{C}H_3$), 69.38 (-$\underline{C}H_2OCH_3$), 76.87 (C6), 83.03 (C2), 100.92 (C7), 109.54 (C1), 206.73 (C4). Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02; found, C, 55.92; H, 6.99.

Plant Growth Inhibition Assays. In order to evaluate the growth regulatory potential of the synthesized oxabicycles and ozonides, three different bioassays were carried out.

Radicle Elongation Assay on Filter Paper (25). Three-milliliter aliquots of 1×10^{-3} mol L^{-1} or 1×10^{-4} mol L^{-1} solutions of cycloadducts **15**−**24**, ozonides **25**−**33**, and artemisinin **1** in dichloromethane were used to imbibe two sheets of filter paper (Whatman number 1) placed in 100 × 15 mm glass Petri dishes. The solvent was evaporated, then 4 mL of water was added before seeds of *Sorghum bicolor* (L.) Moench (Geneze Company, Paracatu, Minas Gerais State, Brazil) and *Cucumis sativus* L. (purchased from a local market) were sown, 20 seeds for each dish. Plates were incubated at 25 °C under

fluorescent light (8 × 40 W) for 3 days. Radicle length was then measured and total germination recorded. Treatments were carried out in a completely randomized design with five replications. The data, expressed as percentage of radical growth inhibition with respect to untreated controls, were analyzed using Tukey's test at 0.05 probability level (*26*).

Radicle Elongation Assay on Sand. Stock solutions of the most active compounds **21**, **24**, **25**, and **29** were prepared by dissolving a proper amount in xylene (84 μL) and pentan-3-one (42 μL) (*21*). After the addition of the surfactant Tween 80 (127 μL), the resulting suspension was transferred to a volumetric flask and water-diluted to 88 mL, so as to obtain a final concentration of 7.5×10^{-4} mol L^{-1}. These suspensions were sonicated for 5 min, then 22 mL aliquots were used to imbibe acid-washed sand (165 g) in 90-mm Petri dishes. Seven pregerminated seeds of *Ipomoea grandifolia* or *Brachiaria decumbens* (from the collection of the Weed Science Laboratory at the Federal University of Viçosa) were transferred into each plate, and dishes were sealed with Parafilm and incubated at room temperature, in darkness and inclined at 75°. After 24 and 48 h, the radicle length was measured to the nearest millimeter. Treatments were carried out in a completely randomized design with four replications. The data were expressed and analyzed as described above.

Greenhouse Trials (20). Plastic pots (0.35 L) were filled with acid-washed sand, which was saturated with the solution of the test compound (60 mL/450 g of sand, corresponding to 0.1 μmol of the test compound -a.i.- per gram of substrate). Six seeds of *I. grandifolia* or *B. decumbens* were placed in each pot. Seedlings were grown in a greenhouse and watered as required with tap water or, twice a week, with half-strength Hoagland solution, to maintain the humidity at 13.3% w/w. Twenty-one days after sowing, plants were harvested, and the roots and aerial parts were separated and weighted. Tissues were then dried at 60 °C until constant weight, and the corresponding dry mass was determined. The percentage of root and aerial part growth inhibition was calculated in relation to the mass of the respective control. Data were expressed and analyzed as previously indicated.

Inhibition of the Photosynthetic Electron Transport. The ability of some of the synthesized ozonides to interfere at 100 μmol L^{-1} with the photosynthetic electron transport chain from water to $K_3Fe(CN)_6$ was evaluated *in vitro* on functionally intact spinach chloroplasts, as previously described (*18, 19*).

RESULTS AND DISCUSSION

Synthesis of Oxabicycles and Ozonides. The starting materials for the ozonolysis were prepared using a [4 + 3] cycloaddition reaction, a very useful synthetic transformation to obtain seven-membered ring compounds (*27*). Thus, the oxyallyl cation, generated *in situ* from 2,4-dibromopentan-3-one **14**, was captured with various furans. This procedure afforded the 8-oxabicyclo[3.2.1]oct-6-en-3-ones **15**−**24** in variable yields (**Figure 3**). In general, lower yields were obtained with furan containing electron withdrawing groups (compounds **18**, **21**, **24**), in agreement with the literature (*30*). Also, the low yield obtained for alcohol **22** (26%) could be explained considering that the free OH present in the precursor furyl alcohol may react in different ways with the intermediate oxyallyl cation, resulting in side products that were not isolated. Detailed IR, NMR, and MS analyses confirmed the structures of all synthesized oxabicycles. Bidimensional NMR experiments were also used to assist in the complete assignment of hydrogen and carbon signals. The major isolated cycloadducts were obtained as the endo-isomers in which the 2-methyl and the 4-methyl groups are pointing toward the double bond. Although the [4 + 3] cycloaddition reactions can also produce exo-cycloadducts in small amounts (*27*), they were not isolated in the present study. As previously reported, in the endo-isomer, the coupling constant (*J*) values between hydrogen-4 and hydrogen-5 (see **Figure 3** for numbering) range from 4.5 to 5 Hz (*28*). Similar values were found for the $J_{4,5}$ of the synthesized cycloadducts, as described in the Materials and Methods section. With oxabicycles **15**−**24** in hand, we turned our attention to the ozonolysis reaction. Exposure of compounds **15**−**23** to ozone gave the corresponding ozonides with the yields presented in **Figure 3**. IR and NMR analyses confirmed their identity. ^{1}H NMR spectra exhibited signals for H7 ranging from δ 5.68 to 5.90, together with other expected hydrogen signals. Also, the number of signals observed in ^{13}C NMR spectra was in agreement with the expected structures. It should be noted that in some cases the ozonides were obtained in quantitative yields, as previously reported for other oxabicycles (*12, 13*). Although the ozonolysis can be successfully carried out with substrates containing different functionalities (*31*), in the case of oxabicycle **17** a low yield was found, and for compound **24**, a complex mixture was obtained from which no ozonide could be isolated. At this point, we have no clear explanation for these results. The yields reported in **Figure 3** are the average of two independent preparations, in which very similar values were obtained. We have prepared the ozonides **26** and **28** on a 10 mmol scale, and the yields were almost quantitative. Therefore, the reaction can in principle be scaled up for the preparation of larger quantities of at least some of the compounds for detailed biological evaluation.

Biological Activity. The effects of compounds **15**−**24** on germination and radicle growth of *S. bicolor* and *C. sativus* are summarized in **Table 1**.

Considering that the compounds are lipophilic, their solubility in water is very low (not measured), and the real concentration in the water phase is lower than the one reported. In such circumstances, the results obtained could be affected by a formulation that could increase the substance's solubility. However, as this type of test is a preliminary one and commonly used (*25*) for a general screening of phytotoxic substances, no special formulation was prepared at this point. As observed in **Table 1**, none of the compounds exerted a significant effect on the germination rate. At the lower concentration tested, only minor variations were evident also with respect to radicle length. On the contrary, various degrees of inhibition were found at 7.5×10^{-4} mol L^{-1}. Compounds **21** and **24**, which share the presence of a carbonyl group of esters conjugated with a double bond, displayed the highest effectiveness against *S. bicolor*, causing 53.0% and 29.6%-inhibition, respectively. The latter has an extra methyl group attached to carbon-5 that therefore seems not beneficial for activity. Similar patterns were found with *C. sativus*, as in this case also maximal inhibition was achieved with compound **21**. According to Macías and co-workers (*29*), an α,β-unsaturated carbonyl moiety could act as a Michael acceptor with some nucleophilic residue of a biomolecule. However, some difference was also evident. Compound **17**, which was scarcely effective against sorghum, was almost equipotent to compound **21** against cucumber and retained an inhibitory effect, even though not statistically significant, at the lower dose tested. Although more data are required to strengthen the occurrence of a true differential effect, variability in plant susceptibility is a promising feature toward the development of new herbicides.

Similarly to cycloadducts, the ozonides were also evaluated against *S. bicolor* and *C. sativus*. Results, shown in **Table 2**, pointed out quite a different pattern since a poor relationship was evident between the effectiveness of a compound and that

of the oxabicycle counterpart. The most phytotoxic compound was ozonide **25**, which at the higher dose caused on *C. sativus* an inhibition similar to that of artemisinin, used as a comparison term. Differential effects were scored between the two crops. *S. bicolor*, a monocotyledonous species, showed an overall higher sensitivity. Interestingly, contrasting effects were found with compounds **28** and **32**, which were inhibitory against sorghum but exerted a stimulatory effect on radicle growth in cucumber. The low activity of the ozonides in this test cannot be associated with their water solubility once such compounds are very polar and hydrophilic.

The phytotoxic activity of the most active oxabicycles (**21**, **24**) and ozonides (**25**, **29**) was further investigated on two weed species, namely, *Ipomoea grandifolia* and *Brachiaria decumbens*. For these experiments, the compounds were formulated as previously described (*21*), using a mixture of xylene, pentan-3-one, and Tween in order to increase their water solubility and improve the biological activity. The results presented in **Table 3** show that all compounds significantly inhibited radicle growth in both species. Consistent with previous findings, the presence of a methyl attached to carbon-5 in compound **24** led to a decrease of the inhibitory activity compared to that of compound **21**, which was the most effective against *I. grandifolia*. In the case of *B. decumbens*, ozonide **25** was equipotent to oxabicycle **21**. However, if the effect was evaluated over a longer time period, a completely different result was obtained (**Table 4**). While an inhibitory effect was still evident in *I. grandifolia* at both the root and the shoot level, in the case of *B. decumbens* it was completely relieved, and on the contrary, certain stimulation was found. No information is available to date about the molecular basis of such a behavior, which could be suggestive of the occurrence of detoxifying pathways. To investigate the basis of the phytotoxic activity of the synthesized ozonides, their ability to interfere with ferricyanide reduction by isolated spinach chloroplasts was also assessed. None of them was found to significantly reduce the rate of the photosynthetic electron flow (data not shown). Further trials are currently in progress to shed some light on their mechanism(s) of action.

In summary, several stable ozonides were prepared from the corresponding oxabicycles. Although some oxabicycles were more active than the ozonides, the latter displayed phytotoxic effects on both monocotyledonous and dicotyledonous species, with various patterns of action. These compounds seem thus worthy of further investigation, and could be exploited for the design of new substances endowed with herbicidal activity.

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