JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY
ARTICLE

J. Agric. Food Chem. 2009, 57, 10107–10115 10107
DOI:10.1021/jf902540z

Synthesis and Biological Evaluation of New Ozonides with Improved Plant Growth Regulatory Activity

Luiz C. A. Barbosa,*,† Célia R. A. Maltha,† Raphael C. Cusati,† Róbson R. Teixeira,† Filipe F. Rodrigues,† Antônio A. Silva,‡ Michael G. B. Drew,§ and Fyaz M. D. Ismail∥

†Department of Chemistry and ‡Department of Plant Science, Federal University of Viçosa, Avenida P.H. Rolfs, CEP 36570-000, Viçosa, MG, Brazil, §School of Chemistry, The University of Reading, P.O. Box 224, Whiteknights, Reading RG6 6AD, U.K., and ∥Medicinal Chemistry Research Group, School of Pharmacy & Biomolecular Sciences, Institute for Health Research, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, U.K.

The iron oxyallyl carbocation generated from 2,7-dibromocycloheptanone was induced to undergo [4 + 3] cycloaddition reactions with various furans, affording a series of 12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one adducts. Similar methodology was used to prepare two additional cycloadducts using menthofuran and two homologous aliphatic dibromoketones. Dipolar cycloaddition of ozone to the adducts afforded the corresponding secondary ozonides (i.e., 1,2,4-trioxolanes) in variable yields. Ozonides were investigated by quantum mechanics at the B3LYP/6-31+G* level to study structural features including close contacts which may be responsible for enhancing ozonide stability. The effect of these ozonides and their corresponding precursor cycloadducts upon radicle growth of both *Sorghum bicolor* and *Cucumis sativus* was evaluated at 5.0 × 10^{-4} mol L^{-1}. The most active cycloadducts and ozonides were also evaluated against the weed species *Ipomoea grandifolia* and *Brachiaria decumbens*, and the results are discussed. Compared to ozonides previously synthesized in our laboratory, the new ozonides described herein present improved plant growth regulatory activity.

KEYWORDS: Herbicides; plant growth regulators; 1,2,4-trioxolanes; stable ozonides; [4 + 3] cycloaddition; density functional theory

INTRODUCTION

The Chinese medicinal herb sweet wormwood (*Artemisia annua* L.) produces a variety of secondary metabolite terpenes including artemisinin **1** (qinghaosu) (*1*). A series of investigations (*2*−*4*) demonstrated that artemisinin **1** (**Figure 1**) and its semisynthetic analogues have a powerful inhibitory effect on plant growth. Some of the analogues, such as the *aza*-compound **2**, were more potent than artemisinin **1**. Phytotoxic activity is dependent upon the presence of the peroxide moiety since deoxyartemisinin **3** is inactive (*5*). However, the exact mode of action of artemisinin **1** as a phytotoxin is still unknown.

In addition to its phytotoxic activity, artemisinin **1** and its more potent semisynthetic analogues, such as artesunate **4** and artemether **5**, have been successfully used against malaria parasites that have become resistant to chloroquine (*6*, *7*). In view of its clinically useful antimalarial activity, artemisinin **1** has been considered as a lead or prototype structure toward the development of new substances to fight malaria (*8*−*10*), resulting in the discovery of designed antimalarial drugs *in vitro* (*11*) and more recently *in vivo* such as compound **6** encoded 0Z277 (**Figure 1**) (*12*−*14*). Several investigations suggest that artemisinin antimalarial activity is also attributed to an intact peroxide bridge (*15*−*17*).

*Author to whom correspondence should be addressed (fax, (55) 31 3899 3065; e-mail lcab@ufv.br).

In view of the phytotoxic activity displayed by artemisinin **1**, and other compounds possessing peroxide bridges (*18*), we pursued an investigation involving putative phytotoxicity of various ozonides possessing the general structure **7** depicted in **Figure 1**. Several stable 8,9,10,11-tetraoxatricyclo[5.2.1.1^{2,6}]undecan-4-ones were prepared from the corresponding oxabicycle precursors using a methodology previously reported (*11*). These ozonides displayed phytotoxic effects on both crops and weeds (*19*). Following our ongoing studies to develop new herbicides and plant growth regulators (*20*−*30*), this report details the preparation of several new stable ozonides with improved phytotoxic activity. Notably, in some cases, the observed plant growth inhibition is comparable to artemisinin **1**.

MATERIALS AND METHODS

General Experimental Procedures. Reagents and solvents were purified, when necessary, according to procedures described by Perrin and Armarego (*31*). The 2,7-dibromocycloheptanone **8**, 2,4-dibromopentan-3-one **21** and 3,5-dibromoheptan-4-one **22** were prepared, respectively, from the bromination of the commercially available cycloheptanone, pentan-3-one and heptan-4-one (The Sigma-Aldrich Chemical Co., Milwaukee, WI) according to known procedures (*32*). Furans, (±)-menthofuran and diiron nonacarbonyl were also purchased from Sigma-Aldrich. 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

Published on Web 10/15/2009

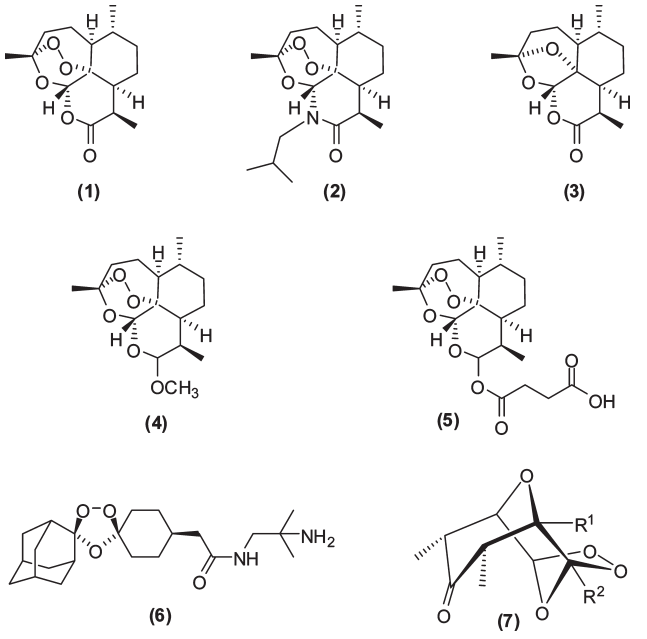


Figure 1. Structures of compounds **1**−**7**.

Mercury 300 instrument (300 and 75 MHz respectively), using deuterated chloroform as the solvent and tetramethylsilane (TMS) as internal standard ($\delta = 0$). IR spectra were recorded using a Perkin-Elmer Paragon 1000 FTIR spectrophotometer, as thin films on cesium iodide or potassium bromide plates, scanning from 400 to 4000 cm^{-1}. Accurate mass (HRMS) data were recorded under conditions of positive ion ESI on a Bruker MicroToF spectrometer (resolution = 10000 fwhm) using a lock-spray source. The lock-mass used for calibration was tetraoctylammonium bromide in positive ion mode. Electron impact mass spectra were recorded on a Shimadzu GCMS-QP5050A instrument (70 eV) under conditions of positive ion mode. Melting points are uncorrected and were obtained using a MQAPF-301 melting point apparatus (Microquimica, Brazil). Analytical thin layer chromatography analyses were conducted on precoated silica gel plastic sheets (Macherey-Nagel GmbH & Company, Düren, Germany). Column chromatography was performed using silica gel (60−230 mesh).

Syntheses. *2-Ethyl-(1α,6α,2β,5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one* (***11***). To a two neck round-bottomed flask (50 mL) were added 2,7-dibromocycloheptanone **8** (1.00 g, 3.71 mmol) and diiron nonacarbonyl (2.50 g, 6.76 mmol). After the system was flushed with dry nitrogen, anhydrous toluene (20.0 mL) and 2-ethylfuran (3.57 g, 37.1 mmol) were charged into the flask over a 10 min period using a syringe. The resulting mixture was then stirred at 50 °C for 72 h. Subsequently, the reaction mixture was cooled to room temperature and filtered through a Celite pad (i.d. = 8 cm; height = 1.5 cm). The mother liquor was washed several times with diethyl ether (4 × 100 mL) until the red coloration was discharged, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane−diethyl ether (5:1 v/v). The aforementioned procedure thereby afforded compound **11** as a pale yellow oil in 31% yield (177 mg; 0.86 mmol) IR (CsI, cm^{-1}) $\bar{\nu}_{max}$ 3078, 2968, 2933, 2856, 1708, 1453, 1327, 1216, 1165, 1089, 909, 729; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 3H, 2-CH_2CH_3), 1.20−1.30 (m, 1H, H7a), 1.50−1.74 (m, 5H, H8a, H9a, H10a and 2-CH_2CH_3), 1.80−2.00 (m, 4H, H7b, H8b, H9b and H10b), 2.41−2.46 (m, 1H, H1), 2.50−2.55 (m, 1H, H6), 4.68 (t, 1H, J = 1.8 Hz, H5), 6.10 (d, 1H, J = 6.0 Hz, H3), 6.22 (dd, 1H, J = 6.0 Hz and J = 1.8 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.5 (2-CH_2CH_3), 25.6 (2-CH_2CH_3), 26.3 and 26.7 (C8 and C9), 27.3 (C7), 28.5 (C10), 53.1 (C6), 56.6 (C1), 83.6 (C5), 88.9 (C2), 134.1 (C4), 136.7 (C3), 211.2 (C11); MS m/z (%) 206 ($M^{+\bullet}$, 5), 191 (11), 149 (16), 135 (22), 121 (15), 110 (100), 109 (78), 107 (20), 96 (25), 95 (44), 93 (12), 91 (19), 82 (11), 81 (81), 79 (36), 77 (27), 69 (21), 68 (8), 67 (29), 66 (20), 65 (20), 57 (50), 55 (81), 53 (38), 51 (15), 43 (23), 41 (65), 39 (59). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.73; H, 8.74; O, 15.53; found, C, 75.39; H, 8.60.

The cycloadducts **9**, **10**, **12**−**14** were prepared employing a procedure similar to that described for compound **11**, and yields are presented in **Figure 2**. The synthesized compounds were fully characterized by IR, NMR (^{1}H and ^{13}C) and mass spectrometry. Structural characterization of compound **9**, (1α,6α,2β,5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one, has already been fully described (*33*). Structures for the remaining compounds are supported by the following spectroscopic data.

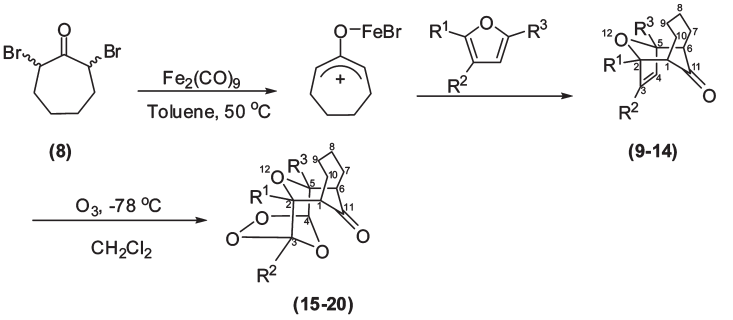
Data for 2-Methyl-(1α,6α,2β,5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one (***10***). Pale yellow oil; purified by column chromatography, eluent hexane/diethyl ether (12:1 v/v): IR (CsI, cm^{-1}) $\bar{\nu}_{max}$ 3072, 2933, 2856, 1711, 1441, 1378, 1327, 1218, 1168, 1088, 883, 727; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22−1.34 (m, 1H, H8a or H9a), 1.41 (s, 3H, 2-CH_3), 1.50−1.66 (m, 3H, H7a, H8a or H9a and H10a), 1.88−2.00 (m, 4H, H7b, H8b, H9b and H10b), 2.37−2.41 (m, H, H1), 2.48−2.54 (m, 1H, H6), 4.67 (t, 1H, J = 1.6 Hz, H5), 6.06 (dd, 1H, J = 5.7 Hz and J = 0.3 Hz, H3), 6.20 (ddd, 1H, J = 5.7 Hz, J = 1.6 Hz and J = 0.3 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8 (2-CH_3), 26.3 and 28.5 (C7 and C10), 26.9 and 27.2 (C8 and C9), 52.7 (C6), 57.9 (C1), 83.8 (C5), 85.4 (C2), 133.8 (C4), 138.7 (C3), 211.2 (C11); MS m/z (%) 192 ($M^{+\bullet}$, 5), 149 (8), 135 (5), 121 (32), 110 (73), 108 (11), 107 (11), 95 (100), 93 (9), 91 (12), 82 (39), 81 (27), 79 (24), 77 (17), 69 (16), 68 (7), 67 (20), 66 (10), 65 (13), 55 (50), 54 (11), 53 (26), 51 (11), 43 (78), 41 (43), 39 (48). Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33; O, 16.67; found, C, 74.88; H, 8.17.

Data for 2,3-Dimethyl-(1α,6α,2β,5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one (***12***). Pale yellow oil; purified by column chromatography, eluent hexane/diethyl ether (6:1 v/v): IR (CsI, cm^{-1}) $\bar{\nu}_{max}$ 3066, 2970, 2928, 2855, 1711, 1650, 1574, 1439, 1376, 1316, 1219, 1195, 1162, 1071, 1024, 883; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23−1.25 (m, 1H, H9a), 1.33 (s, 3H, 2-CH_3), 1.52−1.60 (m, 3H, H7a, H8a and H10a), 1.69 (m, 3H, 3-CH_3), 1.85−1.97 (m, 4H, H7b, H8b, H9b and H10b), 2.37−2.41 (m, 1H, H1), 2.42−2.47 (m, 1H, H6), 4.51−4.54 (m, 1H, H5); 5.77−5.79 (m, 1H, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1 (3-CH_3), 18.5 (2-CH_3), 26.3 (C7), 26.9 (C10), 27.3 (C9), 28.2 (C8), 51.7 (C6), 56.6 (C1), 82.0 (C5), 86.4 (C2), 127.5 (C4), 147.2 (C3), 211.51 (C11); MS m/z (%) 206 ($M^{+\bullet}$, 11), 163 (15), 135 (31), 121 (10), 110 (91), 109 (100), 97 (11), 96 (55), 95 (80), 93 (11), 91 (18), 81 (29), 79 (33), 77 (22), 69 (13), 67 (25), 65 (15), 55 (56), 53 (29), 51 (12), 43 (96), 41 (59), 39 (43). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.73; H, 8.74; O, 15.53; found, C, 75.18; H, 8.13.

Data for 2,5-Dimethyl-(1α,6α,2β,5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one (***13***). Pale yellow oil; purified by column chromatography, eluent hexane/diethyl ether (10:1 v/v): IR (CsI, cm^{-1}) $\bar{\nu}_{max}$ 3071, 2983, 2952, 2911, 2862, 1711, 1598, 1455, 1380, 1219, 1155, 873, 867, 754; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38−1.41 (m, 2H, H8a and H9a), 1.40 (s, 6H, 2-CH_3 and 5-CH_3), 1.60−1.70 (m, 2H, H7a and H10a), 1.75−1.90 (m, 4H, H7b, H8b, H9b and H10b), 2.35−2.40 (m, 2H, H1 and H6), 5.97 (s, 2H, H3 and H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1 (C13 and C14), 25.8 (C7 and C10), 26.6 (C8 and C9), 56.4 (C1 and C6), 85.9 (C2 and C5), 138.1 (2-CH_3 and 5-CH_3), 212.0 (C11); MS m/z (%) 206 ($M^{+\bullet}$, 6), 163 (13), 149 (6), 135 (14), 121 (11), 110 (10), 109 (73), 107 (8), 96 (23), 95 (27), 93 (11), 91 (10), 81 (15), 79 (19), 77 (13), 67 (13), 66 (20), 55 (34), 53 (18), 51 (8), 43 (100), 41 (33), 39 (30). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.73; H, 8.74; O, 15.53; found, C, 75.62; H, 8.83.

Data for 2-Acetyl-(1α,6α,2β,5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one (***14***). Pale yellow oil; purified by column chromatography, eluent hexane/diethyl ether (3:1 v/v): IR (CsI, cm^{-1}), $\bar{\nu}_{max}$ 3423, 3098, 2924, 2855, 1722, 1598, 1447, 1354, 1155, 1061, 909, 742; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20−1.40 (m, 3H, H8a and H9), 1.60−1.80 (m, 2H, H7a and H10a), 1.80−2.00 (m, 2H, H8b and H10b), 2.10−2.30 (m, 1H, H7b), 2.43 (s, 3H, 2-$COCH_3$), 2.50−2.58 (m, 1H, H1), 2.94−3.00 (m, 1H, H6), 4.76 (t, 1H, J = 1.5 Hz, H5), 6.42 (dd, 1H, J = 6.0 Hz and J = 1.5 Hz, H4), 6.56 (d, 1H, J = 6.0, H3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4 (C8), 27.5 (C10), 28.3 (C7), 28.8 (2-$COCH_3$), 29.9 (C9), 41.2 (C1), 54.8 (C6), 75.2 (C2), 84.5 (C5), 135.2 (C3), 136.1 (C4), 200.3 (2-$COCH_3$), 202.4 (C11); MS m/z (%) 220 ($M^{+\bullet}$, 1), 219 (6), 191 (43), 175 (7), 149 (6), 137 (5), 123 (9), 107 (6), 95 (6), 93 (5), 91 (15), 81 (13), 79 (11), 77 (12), 67 (7), 65 (13), 55 (19), 53 (13), 51 (10), 43 (100), 41 (14), 39 (25), 32 (15). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.91; H, 7.27; O, 21.82; found, C, 71.18; H, 7.50.

2,6,9α,11α-Tetramethyl-12-oxatricyclo[6.3.1.0^{3,8}]dodec-2-en-10-one (***23***). To a two neck round-bottomed flask (100 mL), fitted with a 10 mL dropping funnel, were added dry acetonitrile (60 mL) and sodium



Substituents			Cycloadduct		Ozonide	
R_1	R_2	R_3	Compound	Yield (%)	Compound	Yield (%)
H	H	H	**9**	48	**15**	50
CH_3	H	H	**10**	37	**16**	37
C_2H_5	H	H	**11**	31	**17**	42
CH_3	CH_3	H	**12**	37	**18**	28
CH_3	H	CH_3	**13**	27	**19**	55
CH_3CO	H	H	**14**	6	**20**	24

Figure 2. Preparation of cycloadducts **9**−**14** and ozonides **15**−**20**.

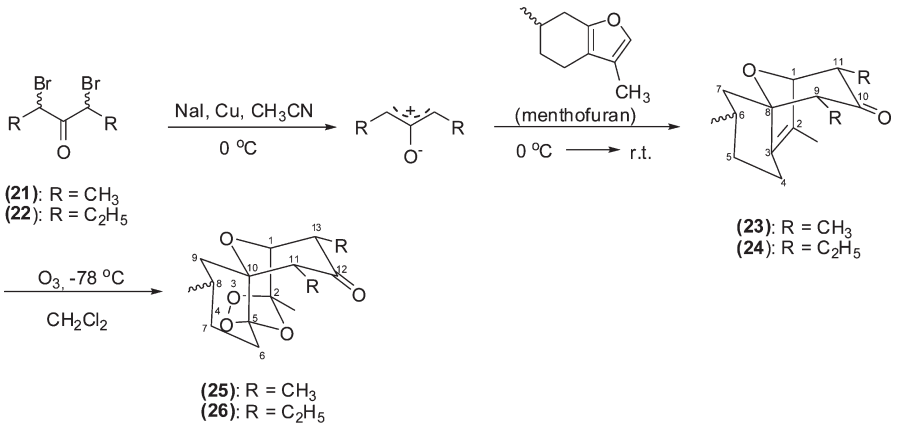
iodide (7.38 g, 49.2 mmol) during vigorous stirring under a slow stream of dry nitrogen. The mixture was cooled to 0 °C. Subsequently, powdered copper (2.34 g, 36.9 mmol) was added, followed by racemic menthofuran (2.40 g, 16.00 mmol). A solution of 2,4-dibromopentan-3-one **21** (3.0 g, 12.30 mmol) dissolved in dry acetonitrile (36 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 18 h. After this time, the mixture was cooled down to 0 °C and dichloromethane (50 mL), water (50 mL) and ice were added. The mixture was extracted with dichloromethane (2 × 40 mL) and filtered through a Celite pad (i.d. = 8 cm; height = 1.5 cm). The mother liquor was washed with NH_4OH 35% (2 × 50 mL), 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 (3:1 v/v). This procedure afforded compound **23** as pale yellow oil in 94% yield (2.0 g, 8.55 mmol): IR (CsI, cm^{-1}), $\bar{\nu}_{max}$ 2926, 2870, 2732, 1708, 1456, 1374, 1342, 1226, 1179, 1152, 1108, 1024, 894, 843; ^1H NMR (300 MHz, $CDCl_3$) δ (signals related to the minor isomer are presented within brackets) [0.89 (d, 1H, J = 6.0 Hz, 6-CH_3')], 0.90−0.95 (m, 1H, H5b), 0.92 (d, 2H, J = 6.3 Hz, 6-CH_3), 0.97 (d, 2H, J = 7.2 Hz, 11-CH_3), [0.98 (d, 1H, J = 6.9 Hz, 11-CH_3')], [1.02 (d, 1H, J = 7.2 Hz, 9-CH_3')], 1.07 (d, 2H, J = 6.9 Hz, 9-CH_3), 1.35−1.40 (m, 1H, H4b), [1.67 (s, 1H, 2-CH_3')], 1.68 (s, 2H, 2-CH_3), 1.70−1.73 (m, 1H, H5a), 1.75−1.78 (m, 1H, H6), 1.81−1.83 (m, 1H, H7b), 2.07−2.14 (m, 1H, H4a), 2.38−2.41 (m, 1H, H7a), [2.59 (q, 1/3H, J = 7.2 Hz, H9′)], 2.72 (q, 2/3H, J = 6.9 Hz, H9), 2.76−2.87 (m, 1H, H11), [4.44 (d, 1/3H, J = 4.5 Hz, H1′)], 4.49 (d, 2/3H, J = 4.8 Hz, H11); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major isomer) 10.3 (9-*C*H_3), 10.8 (11-*C*H_3), 12.6 (2-*C*H_3), 22.9 (6-*C*H_3), 25.3 (C7), 30.3 (C6), 34.0 (C5), 44.9 (C4), 50.0 (C11), 57.2 (C9), 85.7 (C1), 88.1 (C8), 132.0 (C2), 133.3 (C3), 210.2 (C10); δ (minor isomer) 10.1 (9-*C*H_3), 10.6 (11-*C*H_3), 12.8 (2-*C*H_3), 21.6 (6-*C*H_3), 22.8 (C7), 28.5 (C6), 34.1 (C5), 41.4 (C4), 50.1 (C11), 54.8 (C9), 85.3 (C1), 89.9 (C8), 132.7 (C2), 135.0 (C3), 210.6 (C10); MS m/z (%) 234 ($M^{+\bullet}$, 16), 219 (16), 191 (6), 178 (19), 177 (100), 163 (30), 150 (12), 149 (17), 135 (13), 121 (10), 108 (13), 93 (10), 91 (17), 84 (12), 79 (17), 77 (18), 65 (9), 55 (27), 53 (11), 51 (12). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40; O, 13.68; found, C, 77.07; H, 9.43.

The cycloadduct **24**, prepared utilizing a procedure similar to that described for compound **23** (**Figure 3**), was obtained in 74% yield. The target compound was fully characterized by IR, NMR (^1H and ^{13}C) and mass spectrometry and its structure is supported by the following spectroscopic data.

Data for 9α,11α-Diethyl-2,6-dimethyl-12-oxatricyclo-[6.3.1.0^{3,8}]dodec-2-en-10-one (***24***). Pale yellow oil; purified by column chromatography, eluent hexane/diethyl ether (10:1 v/v): IR (CsI, cm^{-1}) $\bar{\nu}_{max}$ 2953, 2928, 2872, 1707, 1456, 1435, 1376, 1356, 1324, 1279, 1236, 1152, 1040, 999, 934, 857; ^1H NMR (300 MHz, $CDCl_3$) δ (signals related to the minor isomer are presented within brackets) 0.90−1.03 (m, 9H, 6-CH_3, 9-CH_2CH_3 and 11-CH_2CH_3), 1.09−1.22 (m, 2H, 11-CH_2CH_3 b and 9-CH_2CH_3 b), 1.32−1.44 (m, 3H, H5a, H5b and H4b), [1.63 (d, 1/3 H, 2-CH_3')], 1.65 (d, 2/3H, 2-CH_3), 1.71−1.83 (m, 3H, H6, 11-CH_2CH_3 a and 9-CH_2CH_3 a), 1.98 (dd, 1H, J = 6.9 Hz and J = 2.1 Hz, H7b), 2.14 (ddd, 1H, J = 13.5 Hz, J = 4.2 Hz and J = 1.5 Hz, H4a), [2.32 (dd, 1/3H, J = 9.6 Hz and J = 1.5 Hz, H9′)], 2.36−2.42 (m, 1H, H7), 2.55 (dd, 2/3H, J = 10.2 Hz and J = 3.0 Hz, H9), 2.60−2.67 (m, 1H, H11), [4.56 (d, 1/3H, J = 4.2 Hz, H1′)], 4.60 (d, 2/3H, J = 4.5 Hz, H1); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major isomer) 12.1 (11-CH_2CH_3), 12.6 (9-CH_2CH_3), 14.8 (2-*C*H_3), 18.4 (11-CH_2CH_3), 18.4 (9-CH_2CH_3), 22.9 (6-*C*H_3), 24.7 (C7), 30.9 (C6), 34.0 (C5), 44.6 (C4), 58.3 (C11), 65.2 (C9), 84.3 (C1), 88.6 (C8), 132.6 (C2), 138.8 (C3), 208.7 (C10); δ (minor isomer) 12.3 (11-CH_2CH_3), 12.6 (9-CH_2CH_3), 15.2 (2-*C*H_3), 18.3 (11-CH_2CH_3), 18.7 (9-CH_2CH_3), 20.1 (C7), 21.6 (6-*C*H_3), 27.1 (C5), 30.9 (C6), 41.1 (C4), 57.8 (C11), 62.6 (C9), 83.7 (C1), 90.1 (C8), 134.2 (C2), 138.8 (C3), 209.5 (C10); MS m/z (%) 262 ($M^{+\bullet}$, 10), 234 (15), 233 (89), 192 (15), 191 (100), 177 (9), 163 (39), 150 (31), 149 (19), 121 (15), 108 (20), 107 (12), 105 (12), 93 (17), 91 (30), 81 (13), 79 (29), 77 (28), 69 (43), 67 (11), 65 (11), 55 (51), 53 (15), 43 (37), 41 (56), 39 (18). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.86; H, 9.92; O, 12.22; found, C, 77.66; H, 9.43.

Ozonide of 2-Ethyl-(1α,6α,2β,5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one (***17***). Ozone was passed through a solution of the cycloadduct **11** (250 mg, 1.21 mmol) in anhydrous dichloromethane (125 mL) at −78 °C. After 5 min, the reaction was judged to be complete by TLC analysis. Excess ozone was removed by bubbling nitrogen through the solution for approximately 10 min. Subsequently, the solvent was removed under reduced pressure to afford a pale yellow oil. Recrystallization from diethyl ether afforded ozonide **17** as a white solid (128 mg, 0.50 mmol) in 42% yield: mp 107.5−108.9 °C; IR (KBr, cm^{-1}) $\bar{\nu}_{max}$ 3396, 2971, 2941, 2863, 1706, 1449, 1239, 1183, 1154, 1108, 928, 869; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, 3H, 2-CH_2CH_3), 1.28−1.37 (m, 1H, H8a), 1.50−1.70 (m, 7H, H7a, H9, H10 and 2-CH_2CH_3), 1.74−1.90 (m, 1H, H8b), 2.00−2.20 (m, 1H, H7b), 2.62−2.67 (m, 1H, H1), 2.74−2.80 (m, 1H, H6), 3.81−3.84 (m, 1H, H5), 5.45−5.47 (m, 1H, H3), 5.58 (dd, 1H, J = 1.5 Hz and J = 0.6 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.8 (2-CH_2CH_3), 25.0 (2-CH_2CH_3), 25.8 (C10), 26.0 (C9), 26.5 (C8), 28.6 (C7), 48.1 (C6), 50.3 (C1), 78.8 (C5), 79.7 (C2), 100.4 (C4), 102.0 (C3), 207.4 (C11). HRMS m/z ($M + Na^+$): Calcd for $C_{12}H_{16}NaO_5$, 263.0890; found, 263.0889.

Compounds **15**, **16**, **18**−**20**, **25** and **26** were prepared employing a procedure similar to that described for compound **17** and yields are presented in **Figures 2** and **3**. Structures of the ozonides were confirmed based on IR and NMR spectral analyses. The molecular formulas were validated using positive ion electron spray mass spectrometry analyses. Structures for the remaining compounds are supported by the following spectroscopic and spectrometric data.



Substituents	Cycloadduct		Ozonide	
R	Compound	Yield (%)	Compound	Yield (%)
CH_3	**23**	94	**25**	92
C_2H_5	**24**	74	**26**	76

Figure 3. Synthesis of cycloadducts **23**, **24** and ozonides **25**, **26**.

Data for Ozonide of (1α,6α,2β,5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one (***15***). White solid: mp 111.4−112.6 °C; IR (KBr, cm^{-1}) $\bar{\nu}_{max}$ 2983, 2937, 2859, 1705, 1445, 1351, 1236, 1173, 1134, 935, 842, 798, 687, 663, 540; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40−1.55 (m, 2H, H8a and H9a), 1.60−1.70 (m, 2H, H7a and H10a), 1.80−2.00 (m, 4H, H7b, H8b, H9b and H10b), 2.73−2.80 (m, 2H, H1 and H6), 3.85−3.90 (m, 2H, H2 and H5), 5.59−5.61 (m, 2H, H3 and H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2 (C8 and C9), 29.6 (C7 and C10), 49.0 (C1 and C6), 78.9 (C2 and C5), 101.3 (C3 and C4), 206.5 (C11). HRMS *m*/*z* (M + Na^+): Calcd for $C_{11}H_{14}NaO_5$, 249.0733; found, 249.0737.

Data for Ozonide of 2-Methyl-(1α,6α,2β,5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one (***16***). White solid: mp 106.0−106.3 °C; IR (KBr, cm^{-1}) $\bar{\nu}_{max}$ 2984, 2937, 2858, 1711, 1443, 1378, 1239, 1197, 1155, 1108, 1055, 966, 941, 892, 863, 689; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 3H, 2-CH_3), 1.26−1.32 (m, 1H, H8a), 1.44−1.56 (m, 2H, H7a and H10a), 1.66−1.74 (m, 2H, H9), 1.80−1.96 (m, 2H, H8b and H10b), 2.06−2.18 (m, 1H, H7b), 2.50−2.55 (m, 1H, H1), 2.75−2.81 (m, 1H, H6), 3.78−3.84 (m, 1H, H5), 5.23−5.24 (m, 1H, *J* = 0.9 Hz, H3), 5.58−5.60 (dd, 1H, *J* = 0.9 Hz and *J* = 1.5 Hz, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (2-*C*H_3), 25.7 (C9), 26.6 (C8), 26.7 (C10), 28.2 (C7), 47.7 (C6), 52.9 (C1), 77.9 (C2), 78.7 (C5), 100.1 (C4), 104.1 (C3), 207.6 (C11). HRMS *m*/*z* (M + Na^+): Calcd for $C_{13}H_{18}NaO_5$, 277.1046; found, 277.1049.

Data for Ozonide of 2,3-Dimethyl-(1α,6α,2β,5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one (***18***). White solid: mp 112.8−113.8 °C; IR (KBr, cm^{-1}) $\bar{\nu}_{max}$ 2988, 2932, 2858, 1710, 1445, 1385, 1243, 1199, 1180, 1121, 1056, 954, 886, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20−1.25 (m, 1H, H9a), 1.24 (s, 3H, 2-CH_3), 1.43 (s, 3H, 3-CH_3), 1.50−1.55 (m, 2H, H7a and H10a), 1.60−1.65 (m, 2H, H8), 1.80−1.90 (m, 2H, H9b and H10b), 2.04−2.14 (m, 1H, H7b), 2.65 (dd, 1H, *J* = 3.0 Hz and *J* = 6.6 Hz, H1), 2.72−2.78 (m, 1H, H6), 3.84−3.90 (m, 1H, H5), 5.55−5.57 (m, 1H, H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5 (3-*C*H_3), 19.7 (2-*C*H_3), 25.7 (C8), 26.6 (C9), 27.0 (C10), 28.4 (C7), 47.2 (C6), 53.0 (C1), 79.2 (C5), 80.8 (C2), 102.0 (C4), 110.6 (C3) 208.2 (C11). HRMS *m*/*z* (M + Na^+): Calcd for $C_{13}H_{18}NaO_5$, 277.1046; found, 277.1050.

Data for Ozonide of 2,5-Dimethyl-(1α,6α,2β,5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one (***19***). White solid: mp 111.3−112.4 °C; IR (KBr, cm^{-1}) $\bar{\nu}_{max}$ 2985, 2935, 2866, 1703, 1433, 1373, 1245, 1184, 1067, 1049, 941, 874, 687; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 6H, 2-CH_3 and 5-CH_3), 1.40−1.50 (m, 2H, H8a), 1.44−1.56 (m, 2H, H8a and H9a), 1.60−1.80 (m, 6H, H7, H8b, H9b and H10), 2.51−2.54 (dd, 2H, H1 and H6), 5.24 (s, 2H, H3 and H4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4 (2-CH_3 and 5-*C*H_3), 24.8 (C7 and C10), 26.0 (C8 and C9), 51.7 (C1 and C6), 77.4 (C2 and C5), 103.1 (C3 and C4), 208.4 (C11). HRMS *m*/*z* (M + Na^+): Calcd for $C_{13}H_{18}NaO_5$, 277.1046; found, 277.1046.

Data for Ozonide of 2-Acetyl-(1α, 6α, 2β, 5β)-12-oxatricyclo-[4.4.1.1^{2,5}]-dodec-3-en-11-one (***20***). White solid: mp 121.7−122.4 °C; IR (KBr, cm^{-1}) $\bar{\nu}_{max}$ 2929, 2862, 1783, 1721, 1449, 1353, 1228, 1164, 949, 902, 873, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28−1.34 (m, 1H, H8a), 1.60−1.67 (m, 2H, H10), 1.80−1.90 (m, 2H, H9), 1.92−2.00 (m, 1H, H8b), 2.20−2.27 (m, 2H, H7), 2.30−2.40 (m, 2H, H1), 2.43 (s, 3H, 2-COCH_3), 3.11−3.16 (m, 1H, H6), 3.99−4.01 (m, 1H, H5), 5.64 (dd, 1H, *J* = 0.9 Hz and *J* = 1.5 Hz, H4), 6.46 (t, 1H, *J* = 0.9 Hz, H3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6 (C8), 27.1 (C9), 28.6 (2-CO*C*H_3), 28.8 (C7 and C10), 40.8 (C1), 48.7 (C6), 70.2 (C2), 79.1 (C5), 99.9 (C4), 102.8 (C3), 197.9 (2-*C*OCH$_3$), 203.5 (C11). HRMS *m*/*z* (M + Na^+): Calcd for $C_{13}H_{16}NaO_6$, 291.0839; found, 291.0843.

Data for Ozonide of 2,6,9α,11α-Tetramethyl-12-oxatricyclo-[6.3.1.0^{3,8}]dodec-2-en-10-one (***25***). White solid: mp 102.3−104.8 °C; IR (KBr, cm^{-1}) $\bar{\nu}_{max}$ 2952, 2870, 1715, 1457, 1385, 1174, 1160, 1059, 1037, 981, 956, 908; ^{1}H NMR (300 MHz, $CDCl_3$) δ (signals related to the minor isomer are presented within brackets) [0.90 (d, 1/3H, *J* = 6.6 Hz, 8-CH_3')], 0.93 (d, 2/3H, *J* = 6.6 Hz, 8-CH_3), 1.08−1.17 (m, 1H, H7b), 1.16 (d, 3H, *J* = 7.2 Hz, 13-CH_3), 1.25 (d, 2H, *J* = 7.2 Hz, 11-CH_3), [1.34 (d, 1H, *J* = 7.5 Hz, 11-CH_3')], 1.36−1.42 (m, 1H, H6b), 1.49 (d, 3H, *J* = 2.6 Hz, 2-CH_3), 1.65−1.77 (m, 2H, H9b and H7a), 1.85−2.15 (m, 3H, H9a, H8 and H6a), [2.53 (q, 1/3H, *J* = 7.5 Hz, H11′)], 2.80 (q, 2/3H, *J* = 7.2 Hz, H11), 3.05−3.15 (m, 1H, H13), 4.10 (dd, 1H, *J* = 5.7 Hz, *J* = 2.6 Hz, H1); ^{13}C NMR (75 MHz, $CDCl_3$) (major isomer) δ 9.5 (11-*C*H_3), 11.4 (13-*C*H_3), 18.2 (2-*C*H_3), 22.5 (8-*C*H_3), 27.5 (C9), 29.1 (C8), 30.6 (C7), 43.9 (C6), 46.5 (C13), 54.3 (C11), 81.4 (C10), 82.0 (C1), 108.8 (C2), 111.5 (C5), 207.8 (C12); (minor isomer) δ 11.2 (13-*C*H_3), 12.8 (11-*C*H_3), 17.3 (2-*C*H_3), 21.9 (8-*C*H_3), 25.4 (C9), 28.8 (C8), 29.7 (C7), 44.4 (C6), 45.0 (C11), 46.5 (C13), 81.5 (C10), 81.8 (C1), 109.8 (C2), 110.6 (C5), 207.5 (C12). HRMS *m*/*z* (M + Na^+): Calcd for $C_{15}H_{22}NaO_5$, 305.1359; found, 305.1354.

Data for Ozonide of 9α,11α-Diethyl-2,6-dimethyl-12-oxatricyclo[6.3.1.0^{3,8}]dodec-2-en-10-one (***26***). Pale yellow oil; purified by column chromatography, eluent hexane/ethyl acetate (3:1 v/v): IR (KBr, cm^{-1}) $\bar{\nu}_{max}$ 2957, 2934, 2873, 1718, 1457, 1436, 1380, 1366, 1174, 1156, 1066; ^{1}H NMR (300 MHz, $CDCl_3$) δ (signals related to the minor isomer are presented within brackets) 0.87−1.01 (m, 9H, 13-CH_2CH_3, 11-CH_2CH_3 and 8-CH_3), 1.18−1.36 (m, 3H, H7b, H6b and 11-CH_2CH$_3$ b), [1.45 (s, 1/3H, 2-CH_3')], 1.46 (s, 2/3H, 2-CH_3), 1.66−1.80 (m, 3H, H9b, H7a and 13-CH_2CH$_3$ b), 1.88−2.06 (m, 5H, H9a, H8, H6a, 13-CH_2CH$_3$ a and 11-CH_2CH$_3$ a), [2.29−2.34 (m, 1/3H, H11′)], 2.50−2.53 (m, 2/3H, H11), 2.79−2,87 (m, 1H, H13), 4.13 (d, 1H, *J* = 5.4 Hz, H1); ^{13}C NMR (75 MHz, $CDCl_3$) (major isomer) δ 13.6 (13-CH_2CH_3), 15.6 (11-CH_2CH_3), 18.1 (2-*C*H_3), 19.3 (11-*C*H_2CH$_3$), 19.8 (13-*C*H_2CH$_3$), 22.7 (8-*C*H_3), 29.0 (C9), 29.3 (C8), 30.5 (C7), 44.2 (C6), 55.0 (C13), 62.8 (C11), 80.7 (C1), 82.1 (C10),

109.8 (C2), 110.3 (C5), 206.1 (C12); (minor isomer) δ 13.7 (C21), 15.5 (C19), 17.4 (C18), 17.7 (C16), 19.2 (C20), 21.9 (C17), 26.2 (C8), 26.3 (C9), 27.5 (C7), 43.7 (C6), 55.0 (C13), 61.9 (C11), 81.4 (C1), 82.3 (C10), 108.8 (C2), 111.7 (C5), 205.8 (C12). HRMS m/z (M + Na^+): Calcd for $C_{17}H_{26}NaO_5$, 333.1672; found, 333.1669.

Biological Assays. *Plant Growth Regulatory Activity*. Two different bioassays were carried out to evaluate the plant growth regulatory activity of the [4 + 3] cycloadducts and ozonides using seeds of *Sorghum bicolor* and *Cucumis sativus*. The most active compounds from this preliminary test (**14**, **15**, **17**, **19** and **24**) were subsequently evaluated against two weed species *Ipomoea grandifolia* and *Brachiaria decumbens*. For the biological assays, stock solutions at 5.0×10^{-4} mol L^{-1} of each tested compound were prepared as follows. Each compound was dissolved in a mixture of xylene (168 μL), the surfactant Tween 80 (254 μL) and pentan-3-one (84 μL). The resulting suspension was shaken for 1 min, transferred to a volumetric flask, made up to the mark with water to 175 mL, and sonicated for 5 min. A solution with the same composition described above, but without the compound under evaluation, was used as control in the biological assays.

Radicle Elongation Assay on Sand with Seeds of S. bicolor and C. sativus. Twenty-two milliliter aliquots of the stock solutions (5.0×10^{-4} mol L^{-1}) were used to adsorb acid-washed sand (165 g) in Petri dishes (i.d. = 9 cm; height = 3 cm). This corresponds to a final concentration of 5.9×10^{-8} mol a.i./g of substrate. Groups of eight pregerminated *S. bicolor* seeds were placed onto each plate. The Petri dishes were sealed with Parafilm and incubated at 28 ± 1 °C, in darkness while inclined at 75°. After 24 and 48 h, the root length was measured to the nearest millimeter. All treatments were replicated four times in a completely randomized design. The percentage of radicle growth inhibition or stimulation was calculated in relation to the radicle length of the control. Seeds were considered to have germinated if a radicle protruded at least 1 mm beyond the seed body. The data were analyzed using Tukey's test at the 0.05 probability level (*34*). This biological assay was repeated with *C. sativus*.

Greenhouse Trials with S. bicolor, C. sativus, Ipomoea grandifolia and Brachiaria decumbens. Plastic pots (0.12 L) were filled with acid washed sand (165 g), which was saturated with 22 mL of stock solution (5.0×10^{-4} mol L^{-1}) of the test compound. This corresponds to a final concentration of 5.9×10^{-8} mol a.i./g of substrate. Four seeds of each test plant 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. Fifteen days (for *S. bicolor* and *C. sativus*) or twenty days (for *I. grandifolia* and *B. decumbens*) after sowing, plants were harvested, and the roots and aerial parts were separated and weighed. They were then dried at 70 °C, until constant weight, and the mass of the dried matter was determined. The percentage of root and aerial part growth inhibition was calculated with respect to the mass of the control, respectively. The data were analyzed using Tukey's test at the 0.05 probability level (*34*).

Molecular Modeling. Structures were built using Gauss View and geometry optimized at the B3LYP/6-31+G* level using the Gaussian03 program (*35*). Log *P* values were calculated using CS ChemDraw Ultra (Version 10.0).

RESULTS AND DISCUSSION

Synthesis of Cycloadducts and Ozonides. The [4 + 3] cycloaddition between oxyallyl cations and dienes is a versatile and synthetically useful reaction to prepare seven-membered rings (*36*−*40*). By employing this reaction, two different sets of cycloadducts, i.e. precursors for the ozonolysis reactions, were prepared. The first set was synthesized via reaction of iron oxyallyl cation, generated *in situ* from 2,7-dibromocycloheptanone **8** in the presence of $Fe_2(CO)_9$ with various furans (*33*). This procedure afforded the cycloadducts **9**−**14** with the yields shown in **Figure 2**.

Analyses indicated that the ketone **8** was not fully consumed in all of the cycloadduct forming reactions. Thus, yields shown in **Figure 2** are based on conversion of the reactants. The lowest yield was observed with compound **14**, prepared from a furan containing an electron-withdrawing group, in agreement with a previous literature report (*41*).

Table 1. Calculated Lipophilicity of Cycloadducts and Ozonides

cycloadducts		ozonides	
compd	Log *P*	compd	Log *P*
9	1.72	**15**	1.89
10	1.94	**16**	2.11
11	2.43	**17**	2.59
12	2.12	**18**	2.46
13	2.16	**19**	2.32
14	1.07	**20**	1.23
23	2.69	**25**	3.37
24	3.53	**26**	4.36
artemisinin	3.17		

Table 2. Effect of Cycloadducts on Germination and Radicle Growth of *S. bicolor* and *C. sativus* Seedlings after 48 h

	Sorghum bicolor[a]			*Cucumis sativus*[a]		
compd	radicle length (cm)[b]	inhibn (%)	germination (%)	radicle length (cm)[b]	inhibn (%)	germination (%)
9	1.9 bcd	62.0	93	0.9 cd	82.2	90
10	2.1 bcd	58.9	99	1.2 cd	74.7	95
11	1.8 bcd	64.2	100	1.3 cd	73.2	100
12	0.9 cd	82.5	79	0.9 cd	82.1	96
13	0.9 cd	83.4	100	1.4 cd	70.7	82
14	0.6 d	88.5	96	0.9 cd	82.1	86
23	1.5 bcd	71.4	96	1.3 cd	72.4	96
24	1.7 bcd	68.0	93	1.8 bcd	62.9	96
control	5.1 a	0.0	100	4.8 a	0.0	100

[a] 5.0×10^{-4} mol L^{-1}. [b] Mean values in the same column with the same letter are not significantly different at $P = 0.05\%$ by Tukey's test.

The IR spectrum of the cycloadducts exhibited strong diagnostic IR absorptions in a 1708−1722 cm^{-1} range concordant with carbonyl stretching. The vinylic hydrogens in these cycloadducts were observed at δ_H 5.8−6.6 while resonance signals for the methyl groups were observed at δ_H 0.9−2.4. Two-dimensional NMR experiments were used to adduce assignment of hydrogen and carbon signals. The molecular formulas of the cycloadducts were confirmed by positive molecular ion peak in the mass spectrum and elemental analyses.

The second set of cycloadducts was synthesized reacting commercially available racemic menthofuran, with two homologous aliphatic α,α'-dibromo ketones (**Figure 3**). In this case, the oxyallyl cations were generated by the Hoffmann−Cookson methodology by exposing the ketones to a NaI/Cu couple (*19*, *21*, *30*, *32*).

Lipophilicity, i.e. Log *P*, is one of several important factors involved in selecting compounds for research and the development of new agrochemicals (*42*, *43*). For instance, it can help to determine the bioavailability of a given organic compound facilitating uptake into a plant (*44*). The rationale underling our approach was based on calculations which demonstrated that ozonides containing the menthofuran moiety possessed Log *P* values similar to artemisinin (**Table 1**). For instance, artemisinin has a Log *P* value of 3.17, and the ozonide **25** is very similar (Log *P* = 3.37) whereas compound **26** is somewhat higher (Log *P* = 4.36) suggesting superior bioavailability for both compounds into plants. Notably, all of the cycloadducts, except **14**, have lipophilicity values that will permit rapid absorption into plants (**Table 1**). However, a simple unimodal correlation between lipophilicty and plant growth inhibition alone could not be found. It is apparent that absorption into the plant, a necessary condition for conferring bioactivity, is insufficient in explaining the biological activity reported in **Tables 2**−**6**. Consequently, a

Table 3. Effect of Ozonides on Germination and Radicle Growth of *S. bicolor* and *C. sativus* Seedlings after 48 h

	Sorghum bicolor[a]			*Cucumis sativus*[a]		
compd	radicle length (cm)[b]	inhibn (%)	germination (%)	radicle length (cm)[b]	inhibn (%)	germination (%)
15	2.1 bc	59.7	96	1.5 bcd	68.5	100
16	1.5 cd	71.5	96	2.3 bc	52.0	70
17	2.4 bc	52.5	100	2.1 bcd	57.2	96
18	1.0 d	80.2	100	0.8 d	84.2	100
19	2.7 b	47.1	100	1.5 bcd	69.1	100
25	1.4 cd	72.1	96	2.9 b	39.9	93
26	2.3 bc	55.1	100	2.1 bcd	55.6	96
control	5.1 a	0.0	100	4.8 a	0.0	100

[a] 5.0×10^{-4} mol L^{-1}. [b] Mean values in the same column with the same letter are not significantly different at $P = 0.05\%$ by Tukey's test. Compound **20** was not evaluated because of the low amount obtained.

Table 4. Effect of Cycloadducts on the Development of *S. bicolor* and *C. sativus* under Greenhouse Conditions after 15 Days

	Sorghum bicolor[a]				*Cucumis sativus*[a]			
compd	aerial part[b] (mg)	inhibn (%)	roots[b] (mg)	inhibn (%)	aerial part[b] (mg)	inhibn (%)	roots[b] (mg)	inhibn (%)
9	18.1 ab	4.5	13.1 a	6.2	32.7 abcd	30.4	16.5 cde	47.3
10	10.9 cd	42.6	9.7 bcd	30.7	26.0 cde	44.6	17.6 cd	43.1
11	9.7 cd	48.8	7.7 cd	49.0	14.5 f	69.2	15.8 cde	49.2
12	10.0 cd	47.4	7.1 d	49.6	16.3 ef	65.4	11.7 de	62.1
13	12.7 bcd	32.9	11.9 ab	14.8	39.7 abc	15.6	10.5 de	66.2
14	17.8 ab	6.0	10.7 bc	23.2	20.0 de	57.4	4.9 f	84.1
23	14.0 abc	26.3	13.1 a	6.2	44.2 ab	5.9	20.3 bc	34.4
24	13.7 abc	28.1	12.7 ab	9.3	30.7 bcd	34.6	6.3 ef	79.7
control	19.0 a	0.0	14.0 a	0.0	47.0 a	0.0	31.0 a	0.0

[a] 5.0×10^{-4} mol L^{-1}. [b] Mean values in the same column with the same letter are not significantly different at $P = 0.05\%$ by Tukey's test.

more detailed QSAR study, which is beyond the scope of the current investigation, is underway in which lipophilic, steric and electronic parameters are being correlated with phytotoxicity of compounds reported herein (as well as those reported by us previously) (*19*), and will be reported on at a future date.

The cycloadducts **23** and **24** (**Figure 3**) were obtained as a mixture of *endo* diastereomers in which the alkyl groups near the carbonyl functionality are pointing toward the double bond.

As previously reported, in the *endo* isomer the coupling constant (J) values between hydrogen-1 and hydrogen-11 (vide **Figure 3** for numbering) range from 4.5 to 5 Hz (*41*). Similar values were found for the $J_{1,11}$ of the cycloadducts **23** and **24** as described in the Materials and Methods section. The diastereoisomers were obtained in a 2:1 ratio accurately determined by NMR spectroscopy. Elemental analyses and mass spectrometric analyses confirmed the molecular formulas of the new synthesized cycloadducts.

Having synthesized the cycloadducts, we turned our attention to the ozonolysis reactions. Exposure of the compounds **9**−**14**, **23** and **24** to ozone gave the corresponding ozonides with yields presented in **Figures 2** and **3**. The yields observed for ozonides **15**−**20** are lower compared to ozonides synthesized in our previous work (*19*). This can be ascribed to the formation of various nonisolated/characterized byproduct as revealed by TLC analyses. IR, NMR analyses confirmed the identity of the ozonides. The expected molecular formulas were confirmed by high resolution mass spectrometric analyses as sodiated species.

Modeling. The possible structures of compounds **15**−**20** were investigated by quantum mechanics at the B3LYP/6-31+G* level using the Gaussian03 program (*35*). For all six compounds, two structures were considered which can be called *endo* and *exo*

Table 5. Effect of Ozonides on the Development of *S. bicolor* and *C. sativus* under Greenhouse Conditions after 15 Days

	Sorghum bicolor[a]				*Cucumis sativus*[a]			
compd	aerial part[b] (mg)	inhibn (%)	roots[b] (mg)	inhibn (%)	aerial part[b] (mg)	inhibn (%)	roots[b] (mg)	inhibn (%)
15	10.4 cd	45.1	10.3 cd	26.4	34.1 abc	27.5	6.9 ef	77.8
16	15.4 ab	20.0	12.7 ab	11.8	17.0 ef	63.9	10.6 cde	65.9
17	10.3 cd	45.4	10.2 cd	27.1	24.4 cde	48.0	7.7 def	75.2
18	11.1 cd	41.8	9.2 cd	34.6	32.9 abc	29.9	13.2 cd	57.4
19	8.8 d	53.9	11.5 ab	18.2	26.4 cd	43.8	6.3 ef	79.7
25	17.7 ab	6.8	12.7 ab	9.1	29.7 bc	36.9	15.3 cd	50.8
26	11.5 cd	39.6	13.1 ab	6.5	30.1 bc	36.0	29.0 ab	6.5
control	19.0 a	0.0	14.0 a	0.0	47.0 a	0.0	31.0 a	0.0

[a] 5.0×10^{-4} mol L^{-1}. [b] Mean values in the same column with the same letter are not significantly different at $P = 0.05\%$ by Tukey's test. Compound **20** was not evaluated because of the low amounts obtained.

Table 6. Effect of Compounds **14**, **15**, **17**, **19**, **24** and Artemisinin **1** on the Development of *I. grandifolia* and *B. decumbens* under Greenhouse Conditions after 21 Days

	I. grandifolia[b]				*B. decumbens*[b]			
compd	aerial part[a] (mg)	inhibn (%)	roots[a] (mg)	inhibn (%)	aerial part[a] (mg)	inhibn (%)	roots[a] (mg)	inhibn (%)
14	10.9 b	39.4	8.6 b	46.2	7.4 b	66.5	4.5 c	78.4
15	9.6 b	46.5	7.4 b	53.6	12.3 b	44.1	8.3 b	60.2
17	9.4 b	47.7	9.1 b	43.0	5.7 c	74.4	4.6 c	77.9
19	6.2 c	65.4	5.7 b	64.6	4.4 c	79.7	3.6 c	83.0
24	6.9 c	61.8	2.4 c	85.3	5.4 c	75.3	3.4 c	85.5
artemisinin	1.2 d	93.6	0.7 d	95.0	2.9 d	93.6	3.1 c	95.0
control	17.8 a	0.0	18.4 a	0.0	22.0 a	0.0	21.2 a	0.0

[a] Mean values in the same column with the same letter are not significantly different at $P = 0.05\%$ by Tukey's test. [b] 5.0×10^{-4} mol L^{-1}.

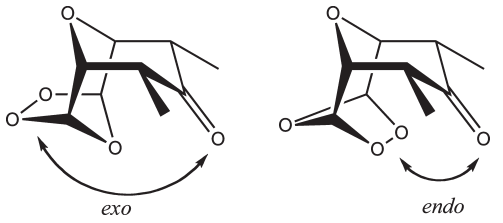


Figure 4. The *exo* and *endo* isomers of **27**.

distinguished by the position of the peroxide bond relative to the carbonyl group. A related compound 1α,2β,3β,5β,6β,7α-3,5-dimethyl-8,9,10,11-tetraoxatricyclo[5.2.1^{2,4}]undecan-4-one **27** has previously been studied (*45*), and its *exo* and *endo* structures are drawn in **Figure 4**.

In that case, a crystal structure of this unexpectedly stable ozonide was previously determined (*45*) and found to be *exo*, as shown in **Figure 5**.

For **15**−**20**, both *endo* and *exo* structures were geometry optimized. In all cases, the *exo* isomer had an energy ca. 5 kcal mol^{-1} less than that of the *endo* isomer and, therefore, this is likely to be the correct structure. Although all structures **15**−**20** show similar results, the two possible structures of **16** are taken as typical and shown in **Figure 6** after geometry optimization.

In this case, the structure of the *exo* isomer has an energy 5.02 kcal mol^{-1} less than that of the *endo* isomer. The relative positions of the carbonyl bond with respect to the ozonide bond are very similar to that in **27**. Taking the midpoints of the two bonds, a distance of 4.687 Å is found in **16**-*exo* compared to 4.639 Å in **27**, showing that the presence of the nine-membered ring has made very little difference. A notable feature of the

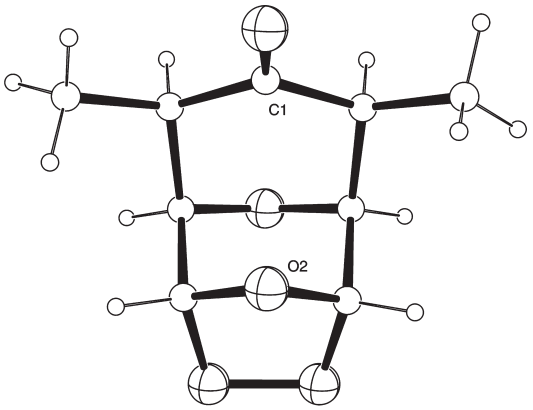


Figure 5. The *exo* structure of 1α,2β,3β,5β,6β,7α-3,5-dimethyl-8,9,10,11-tetraoxatricyclo[5.2.1^{2,4}]undecan-4-one **27**.

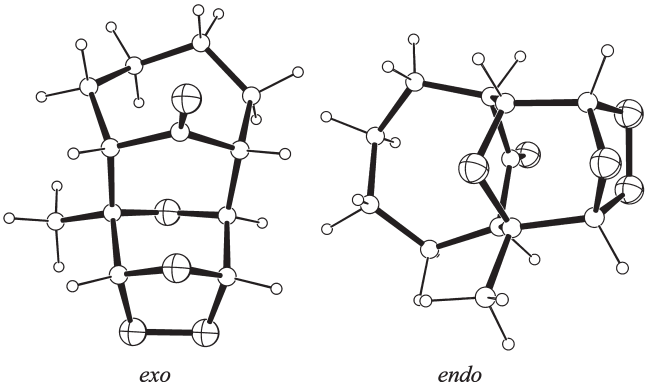


Figure 6. The structures of **16**-*exo* and **16**-*endo* after geometry optimization with quantum mechanics.

structure of **27** was a close contact between C1 and O2 of 2.67 Å (*45*), a short distance which is maintained in **16**-*exo* as 2.66 Å.

In the **16**-*endo* isomer the equivalent distance is a very different 2.955 Å. A comparison with artemisinin shows significant differences, as in that structure, the distance is 4.007 Å, so while there is some geometry similarity with artemisinin, there are also some significant structural differences which may explain the observed differences in activity between the two classes of compound. In **16** the O−O bond length, after optimization is 1.482 Å. This is slightly greater than the mean value found in crystal structures for O−O bonds in the Cambridge Crystallographic Database which suggest that may be more reactive and consequently slightly less stable than compounds we have previously reported (*46*−*48*). A sample restricted to O−O bonds in C−O−O−C environments showed 772 hits, and analysis of their bond lengths gave a mean of 1.472 Å and a median of 1.474 Å.

Biological Activity. In a preliminary screening carried out on Petri dishes, the effects of cycloadducts **9**−**14**, **23** and **24** (**Table 2**) and the ozonides **15**−**19**, **25** and **26** (**Table 3**) on the radicle growth of *S. bicolor* and *C. sativus* at 5.0×10^{-4} mol L^{-1} were evaluated. This type of test is commonly used as a general screening for identifying phytotoxic substances (*49*). Although our primary interest in this work was to evaluate the phytotoxicity of ozonides, the cycloadducts were also evaluated based on phytotoxic effects associated with other cycloadducts previously reported (*19*, *21*, *30*, *32*). All the compounds significantly inhibited the radicle growth of both crops. As a general trend, the cycloadducts **9**−**14**, **23** and **24** exhibited higher phytotoxic activity than the ozonides **15**−**19**, **25** and **26**. However, the new ozonides evaluated in this work displayed improved plant growth regulatory activity compared to structurally similar ozonides previously synthesized in our laboratory. In our previous work (*19*), after 48 h and at 7.5×10^{-4} mol L^{-1}, the highest observed inhibitory activity was approximately 34% against *C. sativus*; and against *S. bicolor*, the highest observed value was about 14%. As can be seen in **Table 3** and **Figure 7**, at a concentration value 1.5 times lower (5.0×10^{-4} mol L^{-1}), the most active ozonide (compound **18**) inhibited the radicle growth of *C. sativus* and *S. bicolor* by 80.2% and 84.2%, respectively. Although the menthofuran derivatives **23**, **24**, **25** and **26** revealed significant inhibitory activities, they are comparable to other synthesized compounds in this study.

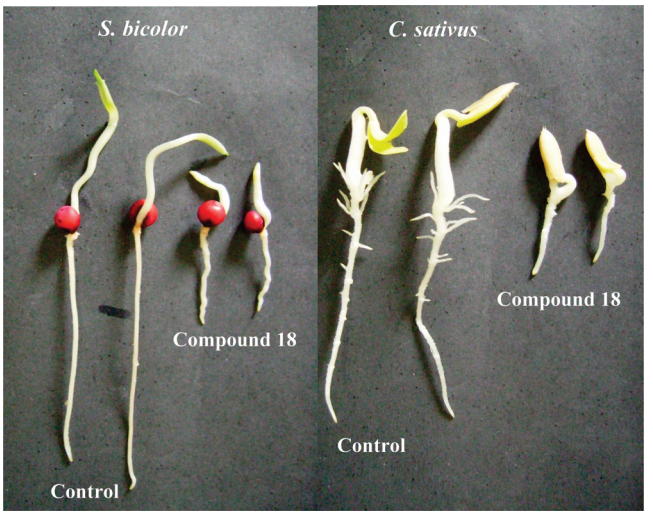


Figure 7. Effect of compound **18** on the development of *S. bicolor* and *C. sativus* in relation to control.

The cycloadducts and the ozonides were subsequently submitted to an experiment in a greenhouse employing plastic flower pots and sand. Although it was not possible to establish a comprehensive structure−biological activity relationship with the small number of compounds evaluated, **Table 4** suggests that a certain substitution pattern within cycloadducts modulates phytotoxic activity. When differential effects were scored between the two crops, the test plant *C. sativus*, a dicotyledonous species was, in general, more sensitive.

Comparing the results shown in **Tables 4** and **5** it is apparent, with few exceptions, that the inhibitory effects displayed by the ozonides under greenhouse conditions are comparable and in some cases superior to the cycloadduct precursors.

The phytotoxic activities of the most active cycloadducts **14** and **24** and ozonides **15**, **17** and **19** were further evaluated on two weed species, namely, *Ipomoea grandifolia* and *Brachiaria decumbens*, and the results are presented in **Table 6**. Artemisinin was used as a reference compound.

The results in **Table 6** show that all compounds significantly inhibit the development of weed species. It can be seen that *B. decumbens* presented higher sensitivity to the test compounds. In addition, some substances display activities comparable to artemisinin **1**. Two further aspects deserve comment. First, the inhibitory activity profile displayed by the most active ozonides tested (compounds **15**, **17** and **19**) is superior to our most active ozonides previously evaluated against the same weed species (*19*). Second, cycloadduct **24**, possessing a menthofuran moiety, was the most active compound against both weed species. Considering the superior inhibitory activity associated with substance **24**, investigations of substances incorporating this structural feature in the development of potential new plant growth regulators may prove worthwhile.

In summary, we have demonstrated that a new set of cycloadducts, prepared from [4 + 3] cycloaddition reactions, as well as their ozonide derivatives reveal useful phyto-growth regulatory activity. Some of the ozonides demonstrate improved biological activity when compared to similar structural compounds synthesized in our laboratory (*19*). Preliminary experiments involving menthofuran skeleta suggest that this type of structural motif can be further exploited for the design of novel substances endowed with plant growth regulator activity.

Supporting Information Available: Data for calculated structures of *endo* and *exo* **16** after geometry optimization with quantum mechanics. This material is available free of charge via the Internet at http://pubs.acs.org.

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Received July 22, 2009. Revised manuscript received September 23, 2009. Accepted September 24, 2009. We are grateful to the following Brazilian agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for research fellowship (L.C.A.B.) and financial support; Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG) and FINEP for financial support; CAPES for a postdoctoral fellowship to R.R.T.