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Article

Synthesis and Evaluation of the Plant Growth Regulatory Activity of 8-oxabicyclo[3.2.1]oct-6-en-3-one Derivatives

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A síntese de vários análogos do 8-oxabiciclo[3.2.1]oct-6-en-3-ona é relatada. O efeito desses compostos e do ácido 4-oxoexanóico sobre a germinação e crescimento radicular do *Sorghum bicolor* foi avaliado. Na concentração de 100 ppm os compostos 3-(metoxicarbonilmetil)-8-oxabiciclo[5.3.0]dec-4-eno-2,9-diona (**13**) e ácido 4-oxoexanóico (**17**) apresentaram efeito estimulador do crescimento radicular de 33-35% e a 1000 ppm um efeito inibitório foi observado em ambos os casos (29% (**13**) e 80,2% (**17**). Todos os outros compostos inibiram o crescimento radicular a 100 e 1000 ppm. Nenhum efeito significativo foi observado sobre a taxa de germinação.

The synthesis of several analogues of 8-oxabicyclo[3.2.1]oct-6-en-3-one is reported. The effect of these compounds and 4-oxohexanoic acid on the germination and radicle growth of *Sorghum bicolor* was evaluated. At 100 ppm compounds 3-(methoxycarbonylmethyl)-8-oxabicyclo[5.3.0]dec-4-ene-2,9-dione (**13**) and 4-oxohexanoic acid (**17**) showed 33-35% stimulatory radicle growth, and at 1000 ppm a 29% (**13**) and 80.2% (**17**) inhibition was observed. All the other compounds showed an inhibitory effect on the radicle growth at 100 and 1000 ppm. None of the compound had a clear effect on the germination rate.

Keywords: *germination, growth inhibition, lactones, [3+4] cycloaddition*

Introduction

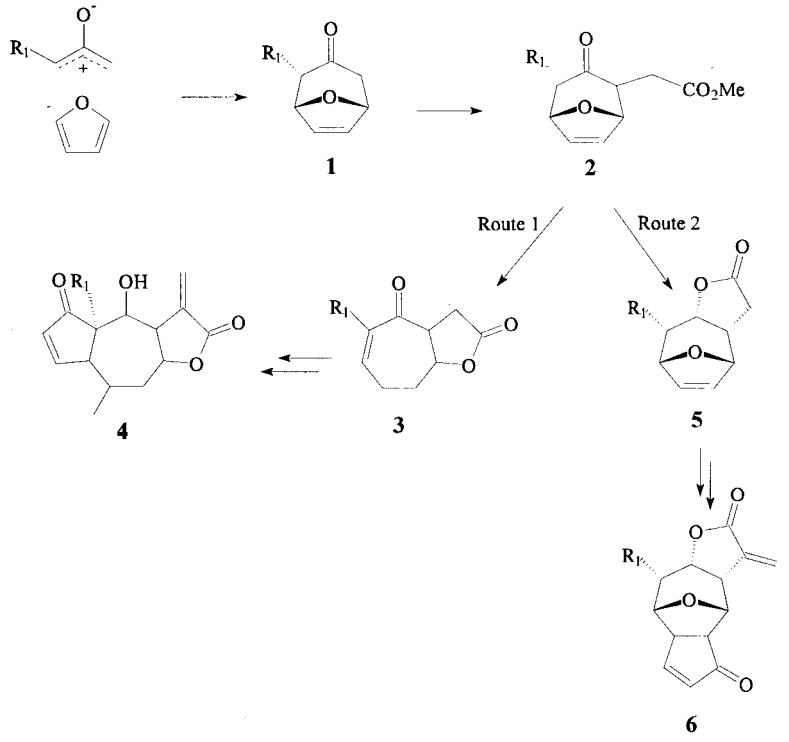
A number of sesquiterpene lactones affect plant growth, although the nature and extent of the effects produced depend on a number of factors, including the lactone tested, its concentration, and the species on which it acts[1]. Some sesquiterpene lactones have been reported to be responsible for the allelopathic properties of certain plants by affecting the germination and growth of other species[2]. The potential allelopathic activity of several natural and synthetic sesquiterpene lactones has been investigated and the presence of an α-methylene-β-butyrolactone has been shown be important for the biological activity[3]. The presence of other reactive centres such as α,β-unsaturated ketone, chlorohydrins, epoxide, hemiacetal, and also the molecules spatial arrangement is normaly important for the biological activity presented by those lactones[4-6].

As part of our research on the synthesis of new compounds with herbicidal and/or plant growth regulatory activity, derived from the easily available 8-oxabicyclo [3.2.1]oct-6-en-3-ones **1**[7], we devised a plan that would allow the preparation of several lactones **3-6** for biological evaluation[23] (Scheme 1).

Experimental

Synthesis

IR spectra were recorded on a Perkin-Elmer 881 double beam grating spectrophotometer. NMR spectra were re-



Scheme 1.

corded on a Perkin-Elmer R34 (220 MHz) instrument, a Bruker WH 400 spectrometer (400 MHz) or on a Varian T-60 (60 MHz) instrument, using tetramethylsilane as internal standard. Mass spectra were obtained on a VG ZAB-E high resolution mass spectrometer. Flash chromatography was performed using Crosfield Sorbsil C60 (40-60 μm). Solvents were purified according to Perrin and Armarego[26], and petroleum refers to the fraction with b.p. 40-60 °C, ether refers to diethyl ether.

8-Oxabicyclo[3.2.1]oct-6-en-3-one **(7)**

A two litre round bottomed flask was charged with freshly prepared Zn/Ag couple (48.83 g, 0.75 mol), furan (350 mL, 5 mol), and dry THF (150 mL). The flask was cooled down to -10 °C and a solution of 1,1,3,3-tetrabromoacetone (172 g, 460 mmol in 150 mL of THF) was added dropwise during 2 h under nitrogen atmosphere. The resulting solution was stirred at room temperature for 17 h. After this period of time the insoluble material was removed by filtration and the solution concentrated to a brown oily residue. This residue (62.3 g) was dissolved in a saturated methanolic solution of NH_4Cl (1000 mL) and freshly prepared Zn/Cu couple (200.5 g, 3.1 mol) was added. This mixture was stirred at room temperature for 2 h, and then the solid was removed by filtration. The filtrate was divided in three portions and each one was diluted with a saturated solution of Na_2EDTA (300 mL), followed by extraction with dichloromethane (4 x 300 mL). The combined extracts were dried ($MgSO_4$) and concentrated to a brown oil, which was purified by flash chromatography (1:2 petrol:ether) to afford 46.5% (26.50 g, 213.7 mmol) of the required oxabicyclo-octane **7** as a pale yellow oil. This oil crystallized on standing, m.p.37-39 °C. IR ($CHCl_3$) $\bar{\nu}_{max}$: 3080, 2960, 2905, 1710, 1340, 1180, 945 and 710 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.30 (d, 2H, J = 17 Hz, H-2α and H-4α), 2.80 (dd, 2H, J = 17 and J = 5 Hz, H-2β and H-4β), 5.10 (d, 2H, J = 5 Hz, H-1 and H-5) 6.30 (s, 2H, H-6 and H-7); MS m/z(%): 124(M^+, 80), 95(10), 82(90), 81(100), 68(10), 54(10).

8-Oxabicyclo[3.2.1]octan-3-one **(8)**

8-oxabicyclo[3.2.1]oct-6-en-3-one **7** (26 g, 209 mmol) was dissolved in ethyl acetate (150 mL), in a Parr hydrogenation bottle and 10% Pd-C (1.5 g) was added as a catalyst. The reaction was carried out under 3.0 x 10^5 Pa of hydrogen pressure, for 5 h. When the hydrogen uptake ceased, the catalyst was filtered off through a Celite pad and the solvent evaporated under reduced pressure. The reduced product **8** was obtained as a yellow oil, in quantitative yield (26.33 g, 209 mmol). IR (thin film) $\bar{\nu}_{max}$: 2940, 2840, 1720, 1470, 1410 and 1205 cm^{-1}; ^{1}H-NMR (220 MHz, $CDCl_3$) δ: 1.72-1.84 (bd, 2H, J = 5 Hz, H-6_{endo} and H-7_{endo}), 2.00-2.18 (m, 2H, H-6_{exo} and H-7_{exo}), 2.29 (dm, 2H, J = 16 Hz, H-2α and H-4α), 2.72 (dd, 2H, J_1 = 16 and J_2 = 5 Hz, H-2β and H-4β), 4.75 (m, 2H, H-1 and H-5); MS m/z: 126.0672 (M^+, $C_7H_{10}O_2$ requires 126.0678).

3-Trimethylsilyloxy-8-oxabicyclo[3.2.1]oct-2-ene **(9)**

Trimethylsilylchloride (1.02 mL, 0.87 g, 8.06 mmol) was added via syringe to a stirred solution of ketone **8** (604.8 mg, 4.8 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.24 g, 8.16 mmol) in DCM (15 mL), under nitrogen atmosphere. The stirred reaction mixture was refluxed at 55-60 °C for 1.5 h. After that period of time, the solution was cooled down to 0 °C, taken up in petroleum (100 mL), and washed with sat. aq. $NaHCO_3$ (3 x 30 mL), and with water (30 mL). The organic phase was dried ($MgSO_4$) and concentrated to give **9** as a pale yellow oil (896 mg, 4.52 mmol, 94% yield). This compound was used without any further purification. IR (thin film) $\bar{\nu}_{max}$: 3060, 2960, 2840, and 1660 cm^{-1};; ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.05 (s, 9H, $OSiMe_3$), 1.80-2.30 (m, 5H, 6-CH_2, 7-CH_2 and H-4α), 2.70 (bdd, 1H, J_1 = 16.5, J_2 = 5.0 Hz, H-4β), 4.40-4.70 (m, 2H, H-1 and H-5), 5.10 (d, 1H, J = 5.0 Hz, H-2).

2-(Methoxycarbonylmethyl)-8-oxabicyclo[3.2.1]octan-3-one **(10a)**

1.4 M MeLi in ether (3.4 mL, 4.76 mmol) was added to a stirred solution of **9** (895 mg, 4.52 mmol) in DME (20 mL), at -40 °C for 1.5 h, and then a solution of methyl bromoacetate (2.1 g, 13.73 mmol) in DME (10 mL) was added slowly. The resultant solution was allowed to warm up to room temperature, and stirred for further 8 h. Water (100 mL) was added and the mixture was extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to a brown oil. This oil was chromatographed (1:1 ethyl acetate: petrol) to afford 45% (403 mg, 2.03 mmol) of **10a** as an inseparable mixture of two isomers (α and β) and 25% of the parent ketone **8**. IR (thin film) $\bar{\nu}_{max}$: 2956, 2886, 1738, 1715, 1438, 1259, 1208, 1173, and 1033 cm^{-1}; ^{1}H-NMR (220 MHz, $CDCl_3$) δ: 1.60-2.30 (m, 4H, 6-CH_2, and 7-CH_2), 2.40-3.00 (m, 5H, H-2, 4-CH_2, and CH_2 from the alkyl chain), 3.72 and 3.80 (two singlets ratio 5:1, 3H, methoxy from β and α isomers), 4.48-4.70 (m, 2H, H-1 and H-5); MS m/z(%): 198 (M^+), 167 ([M-OMe]$^+$), 139, 126, 55.

3-(Methoxycarbonylmethyl)-8-oxabicyclo[5.3.0]dec-4-ene-2,9-dione **(13)**

Trimethylsilyltrifluoromethanesulfonate (TMSOTf, 2.32 mL, 12 mmol) was added to a stirred ice-cooled solution of keto esters **10a/10b** (800 mg) and TEA (1.95 mL, 14 mmol) in CCl_4 (3 mL). The resultant solution was stirred at room temperature for 2 h, and then poured into an ice-cooled sat. aq. $NaHCO_3$ solution (25 mL) and the product extracted into DCM (4 x 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to an orange oil. This oil was purified by chromatography (1:1 ethyl acetate: petrol) to afford the bicyclic lactone **13** in very low yield (70 mg, 0.35 mmol), m.p. 149-151°C; IR ($CHCl_3$) $\bar{\nu}_{max}$: 3020, 2971, 1781(lactone), 1717 (ester + ketone), 1516, 1459, 1370, 1290, 1151, 1046, 1016 and 788 cm^{-1}; ^{1}H-NMR (220 MHz, $CDCl_3$) δ: 2.20-2.30 (m, 1H, H-6), 2.40 (dd. 1H, $J_{10',10}$ = 16.5, $J_{10',1}$ = 5.0 Hz, H-10'), 2.50-2.70 (m, 1H, H-6'), 2.60 (dd, 1H, $J_{11,11'}$ = 17.5, $J_{11,3}$ = 9.0 Hz, H-11), 3.00 (dd, 1H, $J_{10,10'}$ = 16.5, $J_{10,1}$ = 8.5 Hz, H-10), 3.15 (dd, 1H, $J_{11',11}$ = 17.5, $J_{11',3}$ = 4.0 Hz, H-11'), 3.70-3.80 (m, 1H, H-1), 3.72 (s, 3H, OMe), 3.85 (ddd, 1H, $J_{3,11}$ = 9.0, $J_{3,4}$ = 7.0, $J_{3,11'}$ = 4.0 Hz, H-3), 4.95 (ddd, 1H, $J_{7,6}$ = 9.0, $J_{7,1}$ = 7.0, $J_{7,6'}$ = 4.0 Hz, H-7), 5.80-5.90 (m, 2H, H-4 and H-5); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 29.0, 29.8, 34.0 (C-11, C-6 and C-10), 49.0 (C-1), 50.0 (C-3), 52.0 (OMe), 80.0 (C-7), 125.0 and 130.5 (C-4 and C-5), 172.0 and 175.0 (C-12 and C-9), 205.0 (C-2); MS m/z(%): 238.0827 (M^+, $C_{12}H_{14}O_5$ requires 238.0837, 4), 207(7), 206(100), 188(15), 179(23), 160(18), 126(20), 94(18), 84(80), 55(69).

4-Oxohexanoic acid **(17)**

To a stirred solution of succinic anhydride (3.56 g; 35.6 mmol) in dry DCM (30 mL), kept under nitrogen atmosphere and at room temperature, was added $Et_3Al_2Cl_3$ (8.9 g; 8.15 mmol). The resultant mixture was refluxed at 60 °C for 3 h, and then poured into an ice-cooled solution of 15% H_2SO_4 (200 mL). After 30 min the two phases were separated and aqueous layer was extracted with DCM (5 x 60 mL). The combined organic extract was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to leave a pale yellow oil. This oil was purified by distillation under reduced pressure to afford the required acid **17** in 69% yield (3.19 g; 24.6 mmol; 90 °C/16 mmHg) and a small amount (5% 0.2 g 1.78 mmol; 65 °C/16 mmHg) of compound **16**. Data for **17**: IR (thin film) $\bar{\nu}_{max}$: 3500-2500, 1710, 1420, 1370, 1220, 1170, 1120, 960 and 840 cm^{-1}; ^{1}H-NMR (220 MHz, $CDCl_3$) δ: 1.20 (t, 3H, J = 7.0 Hz, CH_3), 2.50 (q, 2H, J = 7.0 Hz, CH_2), 2.60-2.80 (m, 4H, CH_2CH_2), 11.30 (bs, 1H, COOH); MS m/z(%): 131 ([M + 1]$^+$, 12), 113(100), 108(45), 73(22), 57(95), 45(30).

Methyl 4-oxohexanoate **(18)**

To a solution of the acid **17** (2.56 g; 1.97 mmol) in dry methanol (50 mL), was added conc. H_2SO_4 (0.5 mL). The resultant solution stirred at room temperature for 18 h, before addition of an aqueous solution of $NaHCO_3$ (sat. 10 mL). The aqueous layer was extracted with DCM (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to leave the required ester **18** in 88% yield (2.50 g; 17.4 mmol). No further purification was carried out. IR (thin film) $\bar{\nu}_{max}$: 2960, 2920, 1740, 1715, 1440, 1420, 1360, 1210, 1170, 1110 and 840 cm^{-1}; ^{1}H-NMR (220 MHz, $CDCl_3$) δ: 1.20 (t,

3H, J = 7 Hz, CH_3), 2.50 (q, 2H, J = 7 Hz, CH_2), 2.65 (bt, 2H, J = 7 Hz, CH_2), 2.75 (bt, 2H, J = 7 Hz, CH_2), 3.68 (s, 3H, OCH_3).

Methyl 3,5-dibromo-4-oxohexanoate **(19)**

Bromine (2.0 g; 12.5 mmol) was added dropwise to a stirred ice-cooled solution of ketoester **18** (0.9 g; 6.25 mmol) in ether (10 mL) and HBr aq. (48%; 5 mL). After 72 h stirring at room temperature, diethyl ether (80 mL) and an aqueous solution of $Na_2S_2O_5$ (10%, 30 mL) were added. The two phases were separated and the organic layer was washed with brine (2 x 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to leave a crude product as an yellow oil. This oil was purified by column chromatography (petroleum/ether, 2:1) to produce the dibromoketoester **19**, 42% yield (800 mg; 2.65 mmol) as a pale yellow oil. IR (thin film) $\bar{\nu}_{max}$: 3010, 2980, 2960, 2880, 1740, 1440, 1370, 1210, 920 and 860 cm^{-1}; ^{1}H-NMR (220 MHz, $CDCl_3$) δ: 1.85 (d, 3H, J = 6.5 Hz, CH_3), 3.00-3.20 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 5.05 (q, 1H, J = 6.5 Hz, CHBr), 5.20 (t, 1H, J = 6.5 Hz, CHBr).

2-(Methoxycarbonylmethyl)-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one **(20)**

A 100 mL round botton flask was fitted with a 10 mL dropping funnel and dry acetonitrile (20 mL). Dry NaI (1.99 g, 13.2 mmol) was added with vigorous stirring under a slow stream of nitrogen. Then powdered copper (0.61 g, 10.5 mmol) was added, followed by furan (1.89 mL, 26 mmol). A solution of dibromoketone **19** (800 mg, 2.64 mmol) in dry acetonitrile (5 mL) was added, via a dropping funnel, during 10 min, at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. After that time the flask was cooled to 0 °C and dichloromethane (30 mL) was added. The resultant mixture was then poured into a conical flask containing water (30 mL) and crushed ice (30 mL), and it was thoroughly stirred to allow the precipitation of copper salts. After filtration through a Celite pad, the mother liquor was washed with aqueous NH_3 solution (45% v/v, 3 x 20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated to a pale yellow oil. Further purification by flash chromatography (2:3 petrol:ether) gave 27% (150 mg, 0.7 mmol) overall yield of the required product **20** as an isomeric mixture, in a ratio of 4:1 (αα:ββ). Further purification by column chromatography afforded a pure sample of the major α,α-isomer. Data for **20a**: IR (thin film) $\bar{\nu}_{max}$: 3082, 2952, 1742, 1714, 1440, 1373, 1233, 1176, 1060, 924 and 819 cm^{-1}; ^{1}H-NMR (220 MHz, $CDCl_3$) δ: 0.96 (d, 3H, J = 6.5 Hz, CH_3), 2.02 (dd, 1H, J_1 = 16.8, J_2 = 7.0 Hz, H-8'), 2.70 (dd, 1H, J_1 = 16.8, J_2 = 7.0 Hz, H-8), 2.88 (dq, 1H, J_1 = 7.0, J_2 = 5.0 Hz, H-4), 3.30 (dt, 1H, J_1 = 7.0, J_2 = 4.0 Hz, H-2), 3.71 (s, 3H, OCH_3), 4.89 (dd, 1H, J_1 = 4.0, J_2 = 1.8 Hz, H-5), 4.98 (dd, 1H, J_1 = 4.0, J_2 = 1.8 Hz, H-1), 6.32 and 6.38 (2x dd, 2H, J_1 = 6.0, J_2 = 1.8 Hz, H-6 and H-7); MS m/z(%): 211.0970 ($[M+1]^+$, $C_{11}H_{15}O_4$ requires 211.0961, 12), 178(100), 151(15), 113(18), 94(13), 81(22), 67(5), 55(20).

2-(Methoxycarbonylmethyl)-4-methyl-8-oxabicyclo[3.2.1]octan-3-one **(21)**

The ketoester **20a** (504 mg, 2.4 mmol) was dissolved in ethyl acetate (25 mL), in a Parr hydrogenation bottle, and 10% Pd-C (70 mg) was added as a catalyst. The reaction was carried out under 3.0 x 10^5 Pa of hydrogen pressure for 22 h. The catalyst was filtered off through a Celite pad and the solvent removed under reduced pressure to leave the required product **21** as a pale yellow oil in quantitative yield. No further purification was necessary. IR (thin film) $\bar{\nu}_{max}$: 2953, 2840, 1738, 1711, 1440, 1360, 1270, 1200, 1180, 1160, 1050, 950 and 890 cm^{-1}; ^{1}H-NMR (220 MHz, $CDCl_3$) δ: 0.96 (d, 3H, J = 6.5 Hz, CH_3), 1.50-1.90 (m, 4H, CH_2CH_2), 2.03 (dd, 1H, J_1 = 16.8, J_2 = 7.0 Hz, H-8'), 2.78 (dd, 1H, J_1 = 16.8, J_2 = 7.0 Hz, H-8) 2.80-2.90 (m 1H, H-2), 3.25-3.35 (m, 1H, H-4), 3.70 (s, 3H, OCH_3), 4.45-4.60 (m, 2H, H-1 and H-5)

7-Methyl-5,11-dioxatricyclo[6.2.1.$0^{2,6}$]und-9-en-4-one **(22)** *and 7-Methyl-5,11-dioxatricyclo[6.2.1.$0^{2,6}$]undecan-4-one* **(23)**

To a stirred solution of ketone **20a** (210 mg, 1 mmol) in methanol (10 mL) was added $NaBH_4$ (80 mg, 2 mmol). After stirring at room temperature for 4 h, the reaction was quenched with water (20 mL), and the product extracted with DCM (3 x 30 mL). The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure to an yellow oil. This oil was purified by flash chromatography on silica gel (petrol:ether, 1:8) to afford the required lactone **22** in 59% yield as a white solid (210 mg, 1.2 mmol). This product was recrystallyzed from DCM:ether. A similar procedure was used to prepare lactone **23** from ketoester **21**. Data for **22**: m.p. 121-122 °C. white solid. IR ($CHCl_3$) $\bar{\nu}_{max}$: 3083, 2972, 2930, 2887, 1758, 1598, 1460, 1424, 1369, 1200, 1109, 1049, 989 and 816 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.05 (d, 3H, J = 7.0 Hz, CH_3), 2.05 (dd, 1H, J = 16.9, H-3), 2.20 (ddd, 1H, J_1 = 7.0, J_2 = 5.7, J_3 = 4.2 Hz, H-7), 2.57 (dd, 1H, J_1 = 16.9, J_2 = 9.1 Hz, H-3'), 2.80 (bdt, 1H, J_1 = 9.1, $J_2 \cong J_3 \cong$ 5.7 Hz, H-2), 4.45 (m, 1H, H-8), 4.53-4.60 (m, 2H, H-1 and H-6), 6.16 (dd, 1H, J_1 = 6.2, J_2 = 1.7 Hz, H-10), 6.38 (dd, 1H, J_1 = 6.2, J_2 = 1.8 Hz, H-9); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.45(CH_3), 32.02(C-3), 32.73/35.28(C-2/C-7) 79.04/80.75(C-1/C-8), 81.58(C-6), 130.74/136.18(C-9/C-10), 176.03(C-4); MS m/z(%): 180.0786 (M^+, $C_{10}H_{12}O_3$ requires 180.0786, (15), 121(3), 95(90), 91(8), 85(18), 81(100), 68(35), 67(45), 55(35); $C_{10}H_{12}O_3$ requires C 66.65 and H 6.71%; found C 66.64 and H 6.75%; Data for **23**: m.p. 78-79 °C; IR ($CHCl_3$) ν_{max}:

3005, 2980, 2880, 1765, 1480, 1220, 1180, 980 and 880 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.08 (d, 3H, J = 7.0 Hz, CH_3), 1.60-2.00 (m, 4H, CH_2CH_2), 2.09-2.20 (m, 1H, H-6), 2.18 (d, 1H, J = 17.0 Hz, H-3), 2.65 (dd, 1H, J_1 = 17.0, J_2 = 8.4 Hz, H-3'), 2.70-2.80 (m, 1H, H-2), 4.05-4.15 (m, 1H, H-8), 4.22 (bt, 1H, J_1 = 6.1 Hz, H-1), 4.41 (t, 1H, J = 4.7 Hz, H-6); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.77 (CH_3), 23.06/24.58 (C-9/C-10), 32.94 (C-3), 36.58/37.75 (C-2/C-7), 74.84/76.93 (C-1/C-8), 80.37 (C-6), 176.43 (C-4); MS m/z(%): 182.0943 (M^+, $C_{10}H_{14}O_3$ requires 182.0943, (33), 165(20), 124(20), 98(88), 80(75), 69(100), 55(65).; $C_{10}H_{14}O_3$ requires C 65.92 and H 7.74%; found C 65.89 and H 7.75%.

Bioassays

The bioassays were carried out according to the method of Einhelling *et al.*[23] with seeds of *Sorghum bicolor*. Dichloromethane solutions of compounds **7**, **13**, **17**, **20a**, **22** and **23** were prepared at concentrations of 100 and 1000 ppm.

Assays were conducted in a 100 x 15 mm glass Petri dishes lined with 1 sheet of Whatman No. 1 filter paper and sealed with parafilm. To each dish was added 2 mL of each solution and the solvent was evaporated before addition of 2 mL of water followed by 20 seeds of *Sorghum bicolor*. Assays were carried out at 25 °C under artificial fluorescent light (8 x 40W) in a incubator during three days, after which germination was scored and the radicle lenth was measured. Seeds were considered to be germinated if a radicle protuded at least 1 mm. A controling experiment was carried out under the same conditions described, using only water. Each bioassay was replicated 5 times in a complete randomized design.

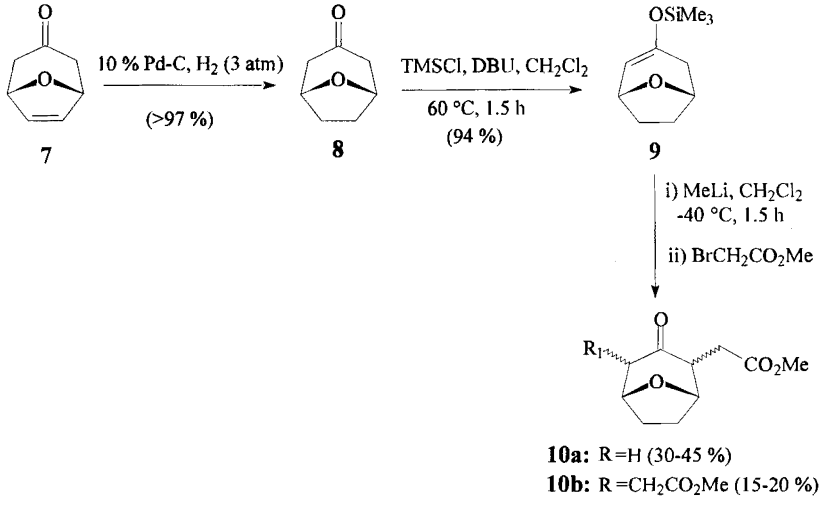
Results and Dicussion

Synthesis

The oxabicyclic ketone **7**, has already been transformed into a number of natural products and their analogues[8,9], and we thought to explore further its chemistry by using it as starting material for the synthesis of sesquiterpene lactone **4** (R_1 = H or CH_3), according to the strategy shown on Scheme 1.

The ketone **7** was prepared on a large scale using Sato and Noyori's methodology[10]. Catalytic hydrogenation of **7** using 10% Pd-C afforded the oxabicyclic ketone **8** in almost quantitative yield. The enol silyl ether **9** was prepared in about 95% yield using trimethylsilylchloride (TMSCl) in the presence 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The almost quantitative conversion of the parent ketone **8** into the required enol ether **9** was confirmed by the virtual disappearance of the carbonyl stretching at around 1715 cm^{-1} (in the infrared spectrum) with concomitant appearance of a very strong band at ~1640 cm^{-1} corresponding to the enol trimethylsilyl group.

The enol ether **9** was treated with methyl lithium and the enolate formed was trapped with methyl bromoacetate (Scheme 2). It was observed that when the enolate was generated at -78 °C/1.5 h, the reaction was incomplete resulting in 29% recovery of the starting enol ether. Raising the temperature to -40 °C resulted in complete transformation of **9** into the corresponding enolate. In general, typical overall yields for this alkylation was 30-45% for the monoalkylated compound **10a**, 15-20% for the corresponding dialkylated methyl ester **10b** and 20-30% recovery of the starting ketone **8**. It was found that separation of the monoalkylated **10a** from the dialkylated methyl ester **10b** was extremely difficult, and **10b** was not obtained in a pure form. Some reactions were carried out with **10a** contami-



7 8 9

10a: R=H (30-45 %)
10b: R=CH_2CO_2Me (15-20 %)

Scheme 2.

nated with 15-20% of **10b**, as estimated by 220 MHz ^{1}H-NMR.

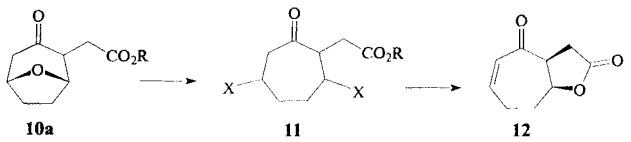
Although a high degree of *exo*-stereoselectivity for this alkylation has been claimed[11], the complexity of the signals for H-1 and H-5 between δ 4.50 and δ 4.70 associated with two signals for methoxy group at δ 3.72 and δ 3.80 (ratio 5:1) showed that a considerable amount (~20%) of the *endo*-alkylated product was formed (the sample analysed was not contaminated with **10b** as judged by the mass spectrum).

It was envisaged that the transformation of **10a** into lactone **12** could be achieved via an intermediate like **11**, formed by the cleavage of the ether bridge (Scheme 3).

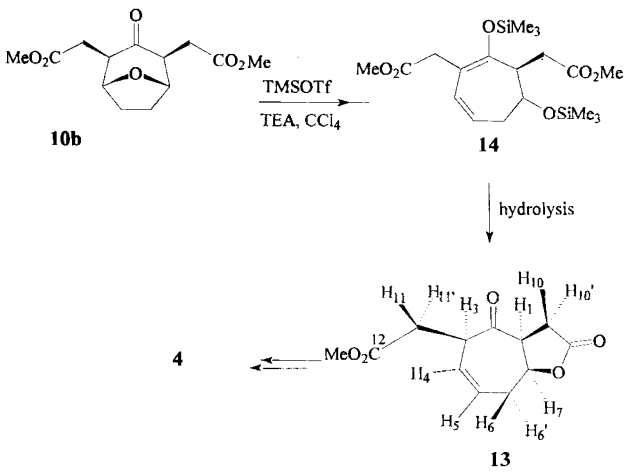
The ketoester **10a** was then submitted to a treatment with the following reagents in order to accomplish the ether cleavage: HBr (aq. 48%), hexadecyltributylphosphonium bromide, 48 h, 60 °C[12]; BF_3, KI, $CHCl_3$, 144 h, 55 °C[13,14]; Me_6Si_2, I_2, C_6H_6, 65 °C, 72 h, dark[15,16]; Me_3SiCl, NaI, CH_3CN, 70 °C 72 h, dark[17]; *t*-$BuMe_2SiCl$, NaI, CH_3CN, 65 °C 120 h, dark[18]; Me_2BBr, TEA, DCM, 0 °C, 4h[19]. In all these attempts no reaction or partial decomposition of the starting material, accompained by the formation of several compounds was observed as judged by TLC analysis.

Another attempt to produce lactone **12** was made by treating compound **10a** with trimethylsilyltrifluoromethanesulfonate (TMSOTf) and triethylamine (TEA)[20], for two hours at room temperature. In this case all the starting material was consumed and a very complex mixture was formed. However when a mixture of **10a+10b** was treated with TMSOTf/TEA, the only product isolated was the lactone **13** (Scheme 4).

The structure of the lactone **13** was deduced by spectroscopic means. In the high resolution mass spectrum, there was a peak at m/z 238.0827 corresponding to the proposed formula $C_{12}H_{14}O_5$. The infrared spectrum showed a very strong absorption at 1781 cm^{-1} due to the γ-butyrolactone, and another band at 1717 cm^{-1} for the ketone superimposed with the ester group. Special features in the ^{13}C-NMR spectrum are the absorptions at δ 172, 175 (lactone and ester), and δ 195 (ketone). Signals corresponding to three CH_2, one CH_3, and five CH were observed. The 220 MHz ^{1}H-NMR spectrum showed a singlet at δ 3.72 for the methoxy group, and a multiplet at δ 5.80-5.90 for alkene protons (Fig. 1).



Scheme 3.



Scheme 4.

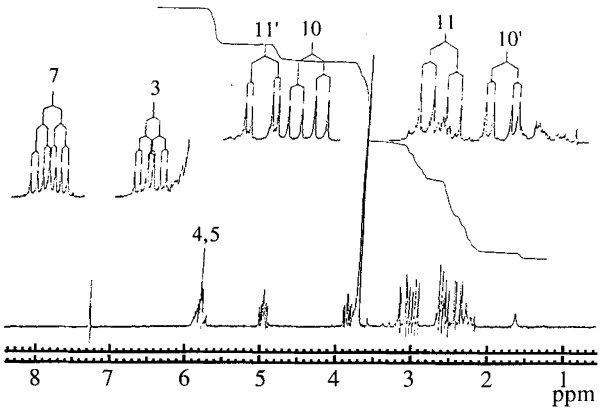


Figure 1. 220 MHz ^{1}H-NMR spectrum of the compound [13].

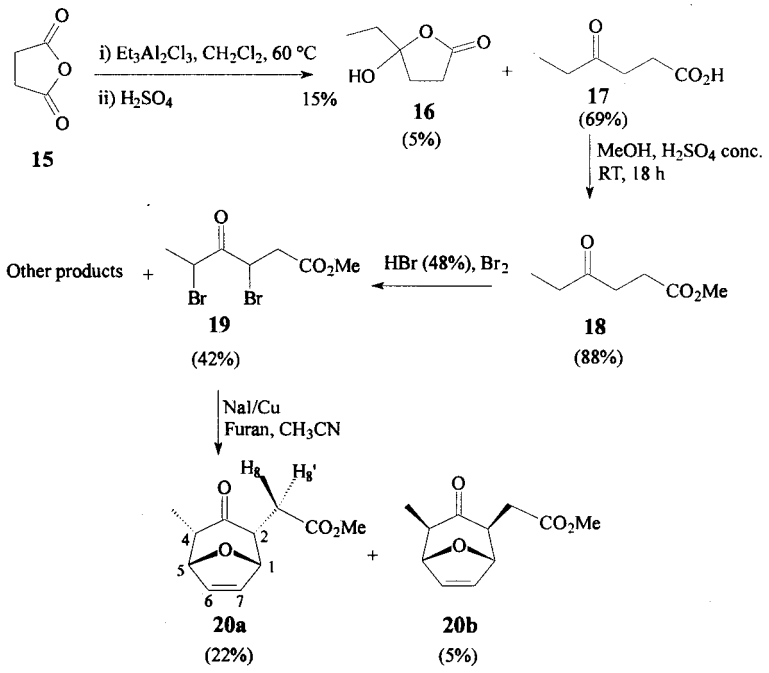
The formation of lactone **13** probably involves the intermediate **14**[18], and it shows the feasibility of our initial synthetic proposal (Scheme 1).

The formation of a complex mixture of products from this reaction is probably due to the fact that keto ester **10a** was a mixture of α and β-alkyl isomers and also because the cleavage of the ether bridge was not regioselective. A further investigation on the preparation of the **10b** and its reaction under the conditions described should be carried out, since one can envisage the transformation of lactone **13** into a pseudoguaianolide skeleton **4**.

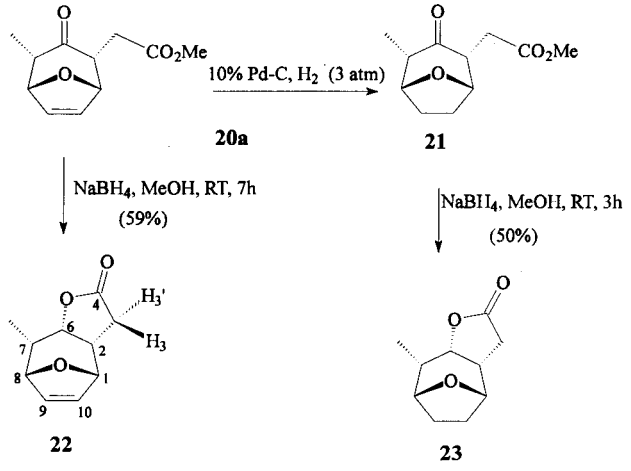
Due to the problems with the stereoselective monoalkylation of **8** and purification of **10a**, an alternative route leading to lactones **4** and **6** was investigated (Schemes 5 and 6).

Succinic anhydride was converted into the keto acid **17** in 69% yield[21]. After methylation with CH_3OH/H_2SO_4, the ester **18** formed was brominated with Br_2/HBr to afford the required dibromoketone **19** in 42% yield.

The cycloaddition between the dibromoketoester **19** and furan was carried out in the presence of Cu/NaI. The



Scheme 5.



Scheme 6.

required cycloadduct **20** was formed in 27% yield, and the ratio between αα- and ββ-isomers was around 4:1.

In order to accomplish the strategy presented on route 1, compound **20b** was required, and since this was the minor isomer formed, we used the major isomer **20a** to follow the synthesis according to route 2 (Scheme 1).

The bicyclic ketone **20a** was treated with $NaBH_4$/MeOH and the intermediate formed by the reduction of the keto group reacted in a intramolecular fashion with the carbomethoxy group resulting in the formation of lactone **22** in 59% yield (Scheme 6).

The hydrogenation of the oxabicyclo **20a** followed by similar treatment with $NaBH_4$/MeOH led to the isolation of the lactone **23** in 50% yield.

Work is know in progress to transform compounds **22** and **23** in to more complex and functionalized lactones.

Herbicidal Activity

The discovery of new herbicides usually involves the following approaches: i) the rational design of specific inhibitors of key metabolic processes; ii) analogue synthesis of compounds with known herbicidal activity and iii) the random screening of new chemicals.

Although in this work we planed to make use of strategy ii), by developing a synthetic route for the preparation of several sesquiterpene lactones, having an α,β-unsaturated carbonyl group, we decided to carry out a random screening on several synthetic intermediates (strategy iii).

For this screening the *in vivo* effect of compounds **7**, **13**, **17**, **20a**, **22** and **23** on the germination and radicle growth of *Sorghum bicolor* was evaluated according to the methodology proposed by Enhelling *et al.*[23]. Two concentrations (100 and 1000 ppm) of each compound were tested, since it has already been shown that some compounds exhibited both stimulatory and inhibitory effects on seedling growth, depending on the concentration[24].

Figure 2 shows the radicle lenth (mm) of *Sorghum* after 3 days incubation at 25 °C and the percentage of radicle growth (inhibition or stimulation) in relation to the control is presented in Table 1. At 100 ppm all compounds showed a condiderable inhibitory effect on the radicle growth, specially the ketoacid **17**, that caused a 80% inhibition. As compound **17** showed a remarkably different effect on plant development at lower and higher concentration[24], and since it can be easily prepared, it becames an interesting starting

Table 1. Germination and radicle growth inhibition of*Sorghum bicolor* by several synthetic compounds after 3 days, incubation at 25 °C.

	Inhibition (% control)[a]		Germination (% control)	
Compound	100 ppm	1000 ppm	100 ppm	1000 ppm
7	1.0 ± 9.5	34.0 ± 5.1	95	94
13	-33.0 ± 2.7	29.0 ± 5.3	95	93
17	-35.0 ± 7.2	80.2 ± 1.1	92	40
20a	26.2 ±2.8	45.4 ± 6.1	97	97
22	26.0 ± 4.8	40.6 ± 3.8	98	96
23	43.6 ± 5.4	7.6 ± 8.8	96	92

[a]Negative values correspond to radicle growth induction.

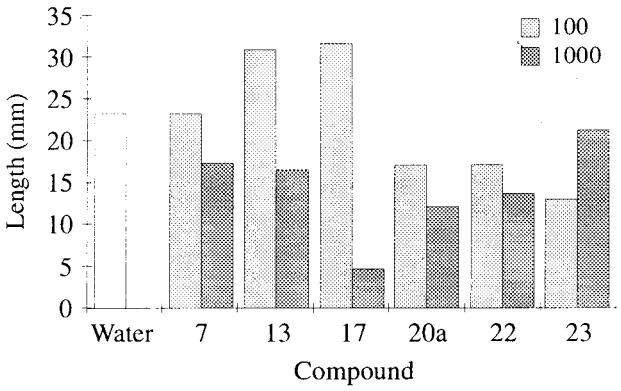


Figure 2. Root growth of *Sorghum bicolor* after exposure to various compounds (100 ppm and 1000 ppm) and water, after 3 days incubation at 25 °C.

material for the preparation of other products for biological evaluation. Although the lactone **13** showed a similar effect on radicle growth as **17**, its preparation is more laborious and this makes further biological evaluation less appealing. Compound **7** showed no clear effect at 100 ppm and 34% inhibition at a 1000 ppm.

Compound **20a** (at 100 ppm) was 26 times more active than its simple analogue **7**, and this effect can be attributed to the presence of the substituents at the 2 and 4 positions.

In view of these results and due to the versatility of the [3+4] cycloaddition methodology used[25] for the preparation of compounds **7** and **20a**, the synthesis of other oxabicyclic compounds like **7** having different substituents at various positions is now our next goal. Also an investigation of the herbicidal selectivity of the compounds already discussed towards a wide range of crops and weeds is underway and will be published elsewhere.

Acknowledgments

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