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Synthesis of β-aryl-γ-lactones and relationship: Structure – antifeedant and antifungal activity

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Abstract. Eighteen racemic β-aryl-γ-lactones derived from simple aromatic aldehydes have been obtained in the chemical synthesis. Iodolactones (**5c** and **6c**) were synthesized from (*E*)-4-(benzo[*d*][1′,3′]-dioxol-5′-yl)-but-3-en-2-one (**1**). Reductive dehalogenation of iodolactones **5a–c** and **6a–c** afforded γ-ethyl-γ-lactones (**7a–c**, **8a–c**) whereas the unsaturated lactones (**9a–c**, **10a–c**) were obtained by dehydrohalogenation of iodolactones. All synthesized lactones were fully characterized by spectroscopic data (NMR, IR, HRMS) and subjected to the tests on the antifeedant activity towards *Tribolium confusum*, *Trogoderma granarium* and *Sitophilus granaries* as well to the tests on the antifungal activity towards four *Fusarium* species. The biological tests allowed to find some relationships between the structure and biological activity of the compounds studied. γ-Ethyl-γ-lactones **7a–c**, **8a–c** and unsaturated lactones **9a–c**, **10a-c** were usually stronger antifeedants than their parent iodolactones **5a–c** and **6a–c**. *trans*-Iodolactones **6a–c** were more active than *cis* isomers **5a-c** both in antifeedant and antifungal assays. The structure of aromatic substituent was the key factor in antifungal activity. The lactones with benzo [*d*][1,3]dioxole ring (**5c**, **6c**, **7c**, **8c**, **9c**) were the most active whereas those with unsubstituted benzene ring exhibited almost no activity.

Keywords. Lactones; aromatic ring; feeding deterrents; storage pests; antifungal activity.

1. Introduction

One of the fundamental challenges in agriculture is reduction of losses in crops caused by insect pests and phytopathogenic fungi. Application of classical insecticides and fungicides is not effective because of increasing resistance of pests.[1] Moreover, some chemicals used as plant protection agents concentrate along the food chain causing the environmental pollution.[2] While searching for new alternative methods in plant protection, much attention has been paid to the compounds which inhibit feeding of insect pests by affecting their taste receptors and cause death by starvation despite food accessability. Feeding deterrents are specific in action, biodegradable and do not show any neurotoxic effect on mammals which makes them environment-friendly.[3,4] Natural feeding deterrents belonging to plant secondary metabolites are mainly sesquiterpene or diterpene lactones.[5–12] The lactone ring is also present in natural compounds possessing antifungal activity.[13,14] Three general modes of action for the antifungal agents have been described: inhibition of cell wall formation by blocking β-glucane synthesis, cell membrane disruption by binding to ergosterol or inhibition of its synthesis, and inhibition of cell division by targeting the microtubule assembly, DNA, RNA or protein synthesis.[15]

Nevertheless, the practical application of natural lactones is limited by their low concentration in plants and difficult isolation. Their synthesis is also complicated due to the complex structures. Therefore, an increasing interest in synthesis of their chemical analogues is observed. Up to the present day, many biologically active lactones, mostly with isoprenoid skeleton, have been synthesized by our research team. They exhibited antifeedant activity towards storage insect pests,[16–20] aphids,[21,22] lesser mealworm[23,24] or colorado potato beetle.[2,25] Some of the obtained lactones also inhibited the growth of pathogenic fungi.[26]

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In this paper, we report the synthesis of another series of lactones, namely, racemic β-aryl-γ-lactones derived from natural aromatic aldehydes. Their deterrent activity against common storage pests: *Tribolium confusum*, *Trogoderma granarium* and *Sitophilus granaries* was tested. We also evaluated the fungistatic activity of synthesized lactones towards four *Fusarium* strains. These fungi cause head blight *Fusarium* (FHB) of small grain cereals (barley, wheat, oats, rye, millet) and maize.[27] They also produce mycotoxins which exhibit cytotoxic, genotoxic, mutagenic or carcinogenic properties.[28,29] The high thermostability of mycotoxins makes them resistant to heating. Therefore, one of the effective methods of their removal from food is the limitation the growth of fungi producing those secondary metabolites.

2. Experimental

2.1 *Materials, methods and instruments*

(*E*)-4-(Benzo[*d*][1′,3′]-dioxol-5′-yl)-but-3-en-2-one (**1**) was obtained earlier from piperonal.[30] Iodolactones **5a**, **b** and **6a**, **b** were obtained earlier in five-step syntheses from benzaldehyde and 4-methylbenzaldehyde respectively.[31] Triethyl orthoacetate (purity 97%), tributyltin hydride (97%), dimethyl sulfoxide (DMSO, purity ≥ 99.9%) were purchased from Sigma-Aldrich® (USA). Sodium borhydride (98%) was purchased from ABCR GmbH & Co. KG (Germany). Propionic acid, sodium bicarbonate, potassium iodide, iodine and organic solvents, all of analytical grade, were purchased from Chempur (Poland). Anhydrous magnesium sulphate was purchased from POCH (Poland). Sodium hydroxide (analytical grade), sodium chloride (analytical grade) and hydrochloric acid (35–37%) were purchased from P.P.H. Stanlab (Poland). Silica gel (Kieselgel 60, 230–400 mesh), used as the stationary phase for the purification of the products by column chromatography, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, ≥98%) and didecyldimethylammonium chloride (DDAC, 50% solution in propan-2-ol/water 2:3), were purchased from Merck (Germany).

^{1}H NMR, ^{13}C NMR (including DEPT 135), HMBC and HMQC spectra were recorded in $CDCl_3$ solutions on Brüker Avance DRX 300 spectrometer. IR spectra were determined using Mattson IR 300 Thermo Nicolet spectrophotometer using KBr pellets or as neat. High resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) technique on a Brüker micrOTOF-Q II system or on a Waters ESI-Q-TOF Premier XE system. The melting points (uncorrected) were determined on Boetius apparatus. The indexes of refraction were measured on Carl Zeiss Jena refractometer. Thin layer chromatography (TLC) was performed on silica gel-coated aluminum plates (DC-Alufolien Kieselgel 60 F_{254}, Merck). Gas chromatography was performed on Agilent Technologies 6890N instrument using DB-5HT column (polyimide-coated fused silica tubing, 30m×0.25mm×0.10μm) with hydrogen as gas carrier and autosampler. The following temperature program was used: injector 220°C (split injection - 50:1), detector (FID) 330°C, column temperature 90–330°C (rate of 20°C/min), 330°C (hold 2 min).

2.2 *Synthesis*

2.2a *Preparation of (E)-4-(benzo[d][1′,3′]dioxol-5′-ylo)-but-3-en-2-ol (**2**)*: The solution of ketone **1** (6.84 g, 36 mmol) in methanol (100 mL) was placed in an ice bath and solution 1.77 g (47 mmol) of $NaBH_4$ in water (10 mL) was added dropwise to the stirring mixture. When the reaction was over (3 h), 30 mL of hot water was added and the product was extracted with methylene chloride (3×40 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and filtered. The organic solvent was evaporated on a vacuum evaporator.

Yield 92% (6.36 g); yellow crystals; M.p. 36−38°C (lit[32] 35−37°C); IR (KBr) ν_{max}3259, 1611, 1502, 1254, 1041, 926, 801 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, d, J = 6.6 Hz, CH_3-1), 1.62 (1H, s, OH), 4.45 (1H, m, H-2), 5.95 (2H, s, CH_2-2′), 6.09 (1H, dd, J = 15.6, 6.6 Hz, H-3), 6.47 (1H, d, J = 15.6 Hz, H-4), 6.75 (1H, d, J = 8.1 Hz, H-7′), 6.80 (1H, dd, J = 8.1, 1.8 Hz, H-6′), 6.92 (1H, d, J = 1.8 Hz, H-4′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4 (C-1), 68.9 (C-2), 101.0 (C-2′), 105.7 (C-4′), 108.3 (C-7′), 121.1 (C-6′), 129.1 (C-4), 131.1 (C-5′), 131.8 (C-3), 147.2 (C-3′a), 148.0 (C-7′a); ESI-HRMS for $C_{11}H_{12}O_3$ $[M+Na]^+$: calculated 215.0684, found 215.0688.

2.2b *Preparation of (E)-3-(benzo[d][1′,3′]-dioxol-5′-yl)hex-4-enoic acid ethyl ester (**3**)*: Alcohol **2** (6.34 g, 33 mmol) was dissolved in 60 mL of triethyl orthoacetate (330 mmol) and drop of propionic acid was added. The reaction mixture was heated for 24 h at 138–140°C under reflux with simultaneous distilling off the resulting ethanol. The product was purified by column chromatography (silica gel, hexane/acetone, 10:1).

Yield 77% (6.66 g); light yellow liquid; n_D^{20} = 1.4933; (lit[32] 1.4930); IR (film) ν_{max}1732, 1481, 1247, 1039, 934, 811 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, t, J = 7.2 Hz, CH_3-8), 1.65 (3H, d, J =

6.6 Hz, CH_3-6), 2.60 (1H, dd, J = 15.0, 7.2 Hz, one of CH_2-2), 2.64 (1H, dd, J = 15.0, 8.4 Hz, one of CH_2-2), 3.72 (1H, m, H-3), 4.06 and 4.08 (2H, two dqd, J = 10.8, 7.2 Hz, CH_2-7), 5.48 (1H, dqd, J = 15.6, 6.6 Hz, H-5), 5.54 (1H, dd, J = 15.6, 7.2 Hz, H-4), 6.66 (1H, dd, J = 7.8, 1.8 Hz, H-6′), 6.69 (1H, d, J = 1.8 Hz, H-4′), 6.73 (1H, d, J = 7.8 Hz, H-7′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (C-8), 17.9 (C-6), 41.1 (C-2), 44.6 (C-3), 60.3 (C-7), 100.8 (C-2′), 107.9 (C-4′), 108.2 (C-7′), 120.3 (C-6′), 125.5 (C-5), 133.2 (C-4), 137.3 (C-5′), 146.0 (C-3′a), 147.6 (C-7′a), 171.9 (C-1); ESI-HRMS for $C_{15}H_{18}O_4$ $[M+H]^+$: calculated 263.1283, found 263.1275.

2.2c *Preparation of (E)-3-(benzo[d][1′,3′]-dioxol-5′-yl)hex-4-enoic acid (**4**)*: Ester **3** (6.29 g, 24 mmol) was dissolved in 15 mL of ethanol and 50 mL of 2.5% aqueous solution of NaOH was added. The mixture was heated under reflux for 6 h. When the substrate reacted completely, ethanol was evaporated and the crude reaction mixture was acidified with 1M HCl and extracted with methylene chloride (3×40 mL). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$ and filtered. The organic solvent was evaporated on a vacuum evaporator and acid **4** was obtained with physical and spectral data given below.

Yield 89% (4.98 g); dense brown liquid; IR (film) ν_{max} 2500–3500, 1708, 1486, 1246, 934, 811 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (3H, d, J = 6.0 Hz, CH_3-6), 2.66 and 2.70 (2H, two dd, J = 15.6, 7.8 Hz, CH_2-2), 3.72 (1H, m, H-3), 5.49 (1H, dqd, J = 15.6, 6.0 Hz, H-5), 5.55 (1H, dd, J = 15.6, 6.6 Hz, H-4), 5.92 (2H, s, CH_2-2′), 6.66 (1H, dd, J = 7.8, 1.8 Hz, H-6′), 6.69 (1H, d, J = 1.8 Hz, H-4′), 6.73 (1H, d, J = 7.8 Hz, H-7′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9 (C-6), 40.7 (C-2), 44.1 (C-3), 100.9 (C-2′), 107.8 (C-4′), 108.3 (C-7′), 120.3 (C-6′), 125.7 (C-5), 132.9 (C-4), 137.0 (C-5′), 146.1 (C-3′a), 147.7 (C-7′a), 177.6 (C-1); ESI-HRMS for $C_{13}H_{14}O_4$ $[M+H]^+$: calculated 235.0970, found 235.0976.

2.2d *Preparation of δ-iodo-γ-lactones **5c**, **6c***: Aqueous solution of 0.5M $NaHCO_3$ (20 mL) was added to the solution of acid **4** (4.68 g, 20 mmol) in diethyl ethyl (20 mL) and the mixture was stirred on magnetic stirrer for 1 h. Then 40 mL of aqueous solution of I_2 (15 g, 59 mmol) and KI (30 g) was added dropwise. The reaction mixture was stirred for 24 h and washed with a saturated aqueous solution of $Na_2S_2O_3$ until the mixture became colourless and then the products were extracted with diethyl ether (3×30 mL). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$ and filtered. The organic solvent was evaporated on a vacuum evaporator. Separation of the reaction mixture on column chromatography (silica gel, hexane/acetone 10:1) afforded two pure products **5c** and **6c** with physical and spectral data shown below.

cis-5-(1-Iodoethyl)-4-(benzo[d][1′,3′]dioxol-5′-yl) dihydrofuran-2-one (***5c***). Yield 37% (2.66 g); white crystals; M.p. 58−62°C; IR (KBr) ν_{max} 1784, 1488, 1505, 1247, 1038, 933, 813, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (3H, d, J = 7.2 Hz, CH_3-7), 2.66 (1H, d, J = 17.4 Hz, one of CH_2-3), 3.10 (1H, dd, J = 17.4, 8.4 Hz, one of CH_2-3), 3.55 (1H, dqd, J = 10.8, 7.2 Hz, H-6), 3.83 (1H, dd, J = 8.4, 5.4 Hz, 1H, H-4), 4.77 (1H, dd, J = 10.8, 5.4 Hz, H-5), 5.97 (2H, s, CH_2-2′), 6.72 (1H, dd, J = 7.8, 1.8 Hz, H-6′), 6.73 (1H, d, J = 1.8 Hz, H-4′), 6.75 (1H, d, J = 7.8 Hz, H-7′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (C-6), 25.5 (C-7), 39.0 (C-3), 44.8 (C-4), 87.8 (C-5), 101.2 (C-2′), 108.4 (C-4′), 108.6 (C-7′), 122.1 (C-6′), 130.8 (C-5′), 147.2 (C-3′a), 147.9 (C-7′a), 176.4 (C-2);. ESI-HRMS for $C_{13}H_{13}IO_4$ $[M+Na]^-$: calculated 380.9600, found 380.9613.

*trans-5-(1-Iodoethyl)-4-(benzo[d][1′,3′]dioxol-5′-yl) dihydrofuran-2-one (**6c**)* Yield 27% (1.96 g); dense brown liquid; IR (film) ν_{max} 1781, 1488, 1504, 1249, 1039, 931, 810, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (3H, d, J = 7.2 Hz, CH_3-7), 2.65 (1H, dd, J = 18.3, 6.9 Hz, one of CH_2-3), 3.11 (1H, dd, J = 18.3, 10.2 Hz, one of CH_2-3), 3.54 (1H, ddd, J = 10.2, 6.9, 5.4 Hz, H-4), 4.19 (1H, t, J = 5.4 Hz, H-5), 4.35 (1H, qdd, J = 7.2, 5.4 Hz, H-6), 5.97 (2H, s, CH_2-2′), 6.70 (1H, dd, J = 7.8, 1.8 Hz, H-6′), 6.73 (1H, d, J = 1.8 Hz, H-4′), 6.78 (1H, d, J = 7.8 Hz, H-7′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4 (C-7), 28.3 (C-6), 37.7 (C-3), 45.2 (C-4), 89.5 (C-5), 101.3 (C-2′), 107.1 (C-4′), 108.7 (C-7′), 120.3 (C-6′), 134.9 (C-5′), 147.1 (C-3′a), 148.4 (C-7′a), 174.7 (C-2); ESI-HRMS for $C_{13}H_{13}IO_4$ $[M+H]^+$: calculated 382.9937, found 382.9932.

2.2e *General procedure for preparation of γ-ethyl-γ-lactones **7a–c** and **8a–c***: The solution δ-iodo-γ-lactone **5a–c** or **6a–c** (1.1 mmol) and tri-*n*-butyltin hydride (0.5 mL, 3.3 mmol) in anhydrous benzene (20 mL) was heated under reflux for 6 h. When the substrate reacted completely, benzene was evaporated under *vacuo* and the crude product was purified twice by column chromatography (silica gel, hexane/acetone 4:1 followed by hexane/acetone 10:1). The physical and spectral data of the products **7a–c** and **8a–c** are shown below.

*cis-5-Ethyl-4-phenyldihydrofuran-2-one (**7a**)*. Yield 76% (0.16 g); colourless liquid; n_D^{20} = 1.5275 ((4*R*, 5*S*)-

enantiomer known previously[33]); IR (film) ν_{max}1776, 1455, 1188, 1138, 962, 765, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.8 Hz, CH_3-7), 1.21 (1H, dqdd, J = 14.4, 7.8, 4.8 Hz, one of CH_2-6), 1.32 (1H, ddqd, J = 14.4, 9.0, 7.8 Hz, one of CH_2-6), 2.76 (1H, dd, J = 17.4, 4.8 Hz, one of CH_2-3), 2.97 (1H, dd, J = 17.4, 8.4 Hz, one of CH_2-3), 3.73 (1H, ddd, J = 8.4, 6.6, 4.8 Hz, H-4), 4.63 (1H, ddd, J = 9.0, 6.6, 4.8 Hz, H-5), 7.13-7.34 (5H, m, H-2′, H-3′, H-4′, H-5′, H-6′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3 (C-7), 24.4 (C-6), 35.8 (C-3), 44.4 (C-4), 85.6 (C-5), 127.5 (C-4′), 127.7 (C-2′ and C-6′), 128.7 (C-3′ and C-5′), 138.0 (C-1′), 176.8 (C-2); ESI-HRMS for $C_{12}H_{14}O_2$ $[M+H]^+$: calculated 191.1072, found 191.1066.

cis-5-Ethyl-4-(4′-methylphenyl)dihydrofuran-2-one ***(7b)***. Yield 77% (0.17 g); colourless liquid, n_D^{20} = 1.5268; IR (film) ν_{max} 1780, 1517, 1186, 1137, 962, 828 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.2 Hz, CH_3-7), 1.21 (1H, dqdd, J = 14.4, 7.2, 4.8 Hz, one of CH_2-6), 1.33 (1H, ddqd, J = 14.4, 9.6, 7.2 Hz, one of CH_2-6), 2.33 (3H, s, CH_3-8), 2.74 (1H, dd, J = 17.4, 4.8 Hz, one of CH_2-3), 2.95 (1H, dd, J = 17.4, 8.4 Hz, one of CH_2-3), 3.70 (1H, ddd, J = 8.4, 6.6, 4.8 Hz, H-4), 4.61 (1H, ddd, J = 9.6, 6.6, 4.8 Hz, H-5), 7.01−7.03 (2H, m, H-2′ and H-6′), 7.13−7.15 (2H, m, H-3′ and H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3 (C-7), 21.0 (C-8), 24.4 (C-6), 35.9 (C-3), 44.1 (C-4), 85.8 (C-5), 127.7 (C-2′ and C-6′), 129.4 (C-3′ and C-5′), 134.9 (C-1′), 137.3 (C-4′), 176.9 (C-2); ESI-HRMS for $C_{13}H_{16}O_2$ $[M+Na]^+$: calculated 227.1047, found 227.1053.

cis-4-(Benzo[d][1′,3′]dioxol-5′-yl)-5-ethyldihydrofuran-2-one ***(7c)***. Yield 74% (0.19 g); yellow liquid; n_D^{20} = 1.5283; IR (film) ν_{max} 1771, 1505, 1490, 1265, 1040, 935, 739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.2 Hz, CH_3-7), 1.26 (1H, dqdd, J = 14.4, 7.2, 4.8 Hz, one of CH_2-6), 1.35 (1H, ddqd, J = 14.4, 9.0, 7.2 Hz, one of CH_2-6), 2.69 (1H, dd, J = 17.4, 4.8 Hz, one of CH_2-3), 2.94 (1H, dd, J = 17.4, 8.7 Hz, one of CH_2-3), 3.65 (1H, ddd, J = 8.7, 6.3, 4.8 Hz, H-4), 4.57 (1H, ddd, J = 9.0, 6.3, 4.8 Hz, H-5), 5.96 (2H, s, CH_2-2′), 6.58 (1H, dd, J = 7.8, 1.8 Hz, H-6′), 6.61 (1H, d, J = 1.8 Hz, H-4′), 6.76 (1H, d, J = 7.8 Hz, H-7′);^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3 (C-7), 24.3 (C-6), 36.0 (C-3), 44.1 (C-4), 85.7 (C-5), 101.2 (C-2′), 108.0 (C-4′), 108.3 (C-7′), 120.9 (C-6′), 131.7 (C-5′), 146.9 (C-3′a), 148.0 (C-7′a), 176.7 (C-2); ESI-HRMS for $C_{13}H_{14}O_4$ $[M+H]^+$: calculated 235.0970, found 235.0969.

trans-5-Ethyl-4-phenyldihydrofuran-2-one ***(8a)***. Yield 73% (0.15 g); colourless liquid; n_D^{20} = 1.5261 ((4*R*, 5*R*)-enantiomer known previously[33,34]); IR (film) ν_{max} 1781, 1456, 1201, 1170, 969, 760, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, t, J = 7.8 Hz, CH_3-7), 1.73 (1H, m, one of CH_2-6), 1.79 (1H, dqdd, J = 14.4, 7.8, 4.2 Hz, one of CH_2-6), 2.78 (1H, dd, J = 17.4, 10.2 Hz, one of CH_2-3), 2.98 (1H, dd, J = 17.4, 8.4 Hz, one of CH_2-3), 3.34 (1H, dt, J = 10.2, 8.4 Hz, H-4), 4.43 (td, J = 8.4, 4.2 Hz, H-5), 7.27−7.41 (5H, m, H-2′, H-3′, H-4′, H-5′, H-6′); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.9 (C-7), 27.0 (C-6), 37.5 (C-3), 47.2 (C-4), 88.2 (C-5), 127.2 (C-2′ and C-6′), 127.7 (C-4′), 129.1 (C-3′ and C-5′), 139.1 (C-1′), 175.7 (C-2); ESI-HRMS for $C_{12}H_{14}O_2$ $[M+K]^+$: calculated 229.0630, found 22.0619.

trans-5-Ethyl-4-(4′-methylphenyl)dihydrofuran-2-one ***(8b)***. Yield 72% (0.16 g); dense liquid; IR (film) ν_{max} 1780, 1517, 1199, 1169, 980, 816 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.2 Hz, CH_3-7), 1.68 (1H, m, one of CH_2-6), 1.76 (1H, dqdd, J = 14.4, 7.2, 4.2 Hz, one of CH_2-6), 2.35 (3H, s, CH_3-8), 2.73 (1H, dd, J = 17.4, 10.2 Hz, one of CH_2-3), 2.92 (1H, dd, J = 17.4, 8.4 Hz, one of CH_2-3), 3.28 (1H, dt, J = 10.2, 8.4 Hz, H-4), 4.37 (1H, td, J = 8.4, 4.2 Hz, H-5), 7.12−7.14 (2H, m, H-2′ and H-6′), 7.17−7.18 (2H, m, H-3′ and H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.9 (C-7), 21.0 (C-8), 26.9 (C-6), 37.6 (C-3), 46.8 (C-4), 88.3 (C-5), 127.1 (C-2′ and C-6′), 129.7 (C-3′ and C-5′), 136.0 (C-1′), 137.4 (C-4′), 175.8 (C-2); ESI-HRMS for $C_{13}H_{16}O_2$ $[M+H]^+$: calculated 205.1228, found 205.1237.

trans-4-(Benzo[d][1′,3′]dioxol-5′-yl)-5-ethyldihydrofuran-2-one ***(8c)***. Yield 71% (0.18 g); colourless liquid; n_D^{20} = 1.5475; IR (film) ν_{max} 1777, 1515, 1253, 1034, 969, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.5 Hz, CH_3-7), 1.68 (1H, m, one of CH_2-6), 1.75 (1H, dqdd, J = 14.4, 7.5, 4.2 Hz, one of CH_2-6), 2.67 (1H, dd, J = 17.7, 10.5 Hz, one of CH_2-3), 2.91 (1H, dd, J = 17.7, 8.7 Hz, one of CH_2-3), 3.23 (1H, dt, J = 10.5, 8.7 Hz, H-4), 4.32 (1H, td, J = 8.7, 4.2 Hz, H-5), 5.96 (2H, s, CH_2-2′), 6.68 (1H, dd, J = 7.8, 1.8 Hz, H-6′), 6.72 (1H, d, J = 1.8 Hz, H-4′), 6.78 (1H, d, J = 7.8 Hz, H-7′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.9 (C-7), 26.9 (C-6), 37.6 (C-3), 47.0 (C-4), 88.2 (C-5), 101.2 (C-2′), 107.2 (C-4′), 108.6 (C-7′), 120.6 (C-6′), 132.7 (C-5′), 147.0 (C-3′a), 148.2 (C-7′a), 175.6 (C-2); ESI-HRMS for $C_{13}H_{14}O_4$ $[M+H]^+$: calculated 235.0970, found 235.0979.

2.2f *General procedure for preparation of unsaturated lactones* ***9a–c*** *and* ***10a–c***: δ-Iodo-γ-lactone **5a–c** (3.2 mmol) was dissolved in 20 mL of anhydrous benzene and 2 mL of 1.8-diazabicyclo[5.4.0]undec-7-ene (DBU) (13 mmol) was added. The reaction mixture was heated under reflux for 6 h, then benzene was evaporated in *vacuo* and the crude reaction mixture was

acidified with 1M HCl. The products were extracted with diethyl ether (3×30 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and filtered. The organic solvent was evaporated and the products were separated on column chromatography (silica gel, hexane/acetone 10:1). Physical and spectral data of the products **9a–c** and **10a–c** are shown below.

(E)-5-Ethylidene-4-phenyldihydrofuran-2-one ***(9a)***. Yield 55% (0.33 g); white crystals; M.p. 46−49°C; IR (KBr) ν_{max}1799, 1696, 1452, 1124, 1084, 829, 751, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (3H, dd, J = 7.2, 1.2 Hz, CH_3-7), 2.64 (1H, dd, J = 18.0, 3.6 Hz, one of CH_2-3), 3.22 (1H, dd, J = 18.0, 10.2 Hz, one of CH_2-3), 4.36 (1H, m, H-4), 5.42 (1H, qdd, J = 7.2, 1.8 Hz, H-6), 7.25−7.38 (5H, m, H-2′, H-3′, H-4′, H-5′, H-6′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.6 (C-7), 38.3 (C-3), 41.3 (C-4), 101.3 (C-6), 126.6 (C-2′ and C-6′), 127.4 (C-4′), 129.2 (C-3′ and C-5′), 141.0 (C-1′), 151.9 (C-5), 173.8 (C-2); ESI-HRMS for $C_{12}H_{12}O_2$ $[M+H]^+$: calculated 189.0916, found 189.0907.

(E)-5-Ethylidene-4-(4′-methylphenyl)dihydrofuran-2-one ***(9b)***. Yield 50% (0.32 g); white crystals; M.p. 37−40°C; IR (KBr) ν_{max}1788, 1697, 1514, 1180, 1135, 1088, 908, 813 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (3H, dd, J = 7.2, 1.2 Hz, CH_3-7), 2.33 (3H, s, CH_3-8), 2.59 (1H, dd, J = 18.3, 3.6 Hz, one of CH_2-3), 3.17 (1H, dd, J = 18.3, 10.5 Hz, one of CH_2-3), 4.30 (1H, m, H-4), 5.37 (1H, qdd, J = 7.2, 1.8 Hz, H-6), 7.09−7.12 (2H, m, H-2′ and H-6′), 7.14−7.16 (2H, m, H-3′ and H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.6 (C-7), 21.0 (C-8), 38.3 (C-3), 41.0 (C-4), 101.1 (C-6), 126.5 (C-2′ and C-6′), 129.8 (C-3′ and C-5′), 137.0 (C-4′), 138.0 (C-1′), 152.1 (C-5), 174.0 (C-2); ESI-HRMS for $C_{13}H_{14}O_2$ $[M+H]^+$: calculated 203.1072, found 203.1076.

(E)-4-(Benzo[d][1′,3′]dioxol-5′-yl)-5-ethylidenedihydrofuran-2-one ***(9c)***. Yield 38% (0.28 g); yellow liquid; n_D^{20} = 1.5433; IR (film) ν_{max} 1800, 1699, 1489, 1504, 1248, 1137, 1038, 933, 812 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (3H, dd, J = 7.2, 1.2 Hz, CH_3-7), 2.57 (1H, dd, J = 18.3, 3.6 Hz, one of CH_2-3), 3.16 (1H, dd, J = 18.3, 10.5 Hz, one of CH_2-3), 4.26 (1H, m, H-4), 5.38 (1H, qdd, J = 7.2, 1.8 Hz, H-6), 5.96 (2H, s, CH_2-2′), 6.68 (1H, dd, J = 8.4, 2.1 Hz, H-6′), 6.69 (1H, d, J = 2.1 Hz, H-4′), 6.77 (1H, d, J = 8.4 Hz, H-7′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.6 (C-7), 38.4 (C-3), 41.1 (C-4), 101.2 (C-2′), 101.3 (C-6), 106.9 (C-4′), 108.6 (C-7′), 119.8 (C-6′), 134.8 (C-5′), 146.8 (C-3′a), 148.3 (C-7′a), 151.9 (C-5), 173.7 (C-2); ESI-HRMS for $C_{13}H_{12}O_4$ $[M+H]^+$: calculated 233.0814, found 233.0818.

cis-4-Phenyl-5-vinyldihydrofuran-2-one ***(10a)***. Yield 8% (0.032 g); yellow liquid; n_D^{20} = 1.5426 (lit[35] n_D^{20} no reported); IR (film) ν_{max} 1763, 1496, 1168, 1132, 988, 738, 701 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 2.83 (1H, dd, J = 17.4, 7.8 Hz, one of CH_2-3), 2.90 (1H, dd, J = 17.4, 8.4 Hz, one of CH_2-3), 3.89 (1H, m, H-4), 5.14 (1H, m, one of CH_2-7), 5.21 (1H, m, H-5), 5.29 (1H, m, one of CH_2-7), 5.36 (1H, ddd, J = 17.4, 10.2, 5.4 Hz, H-6), 7.12−7.35 (5H, m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.9 (C-3), 45.1 (C-4), 83.3 (C-5), 118.6 (C-7), 127.7 (C-4′), 127.8 (C-2′ and C-6′), 128.7 (C-3′ and C-5′), 132.4 (C-6), 136.8 (C-1′), 176.2 (C-2); ESI-HRMS for $C_{12}H_{12}O_2$ $[M+H]^+$: calculated 189.0916, found 189.0911.

cis-4-(4′-Methylphenyl)-5-vinyldihydrofuran-2-one ***(10b)***. Yield 8% (0.05 g); yellow liquid; n_D^{20} = 1.5392; IR (film) ν_{max} 1785, 1518, 1192, 1165, 988, 819 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (3H, s, CH_3-8), 2.80 (1H, dd, J = 17.1, 7.8 Hz, one of CH_2-3), 2.89 (1H, dd, J = 17.1, 8.1 Hz, one of CH_2-3), 3.85 (1H, m, H-4), 5.14 (1H, m, one of CH_2-7), 5.19 (1H, m, H-5), 5.30 (1H, m, one of CH_2-7), 5.38 (1H, ddd, J = 17.1, 9.6, 5.4 Hz, H-6), 7.00−7.03 (2H, m, H-2′ and H-6′), 7.13−7.16 (2H, m, H-3′ and H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (C-8), 34.0 (C-3), 44.7 (C-4), 83.4 (C-5), 118.4 (C-7), 127.7 (C-2′ and C-6′), 129.4 (C-3′ and C-5′), 132.5 (C-6), 133.7 (C-1′), 137.3 (C-4′), 176.4 (C-2); ESI-HRMS for $C_{13}H_{14}O_2$ $[M+H]^+$: calculated 203.1072, found 203.1078.

cis-4-(Benzo[d][1′,3′]dioxol-5′-yl)-5-vinyldihydrofuran-2-one ***(10c)***. Yield 53% (0.39 g); yellow liquid; n_D^{20} = 1.5483; IR (film) ν_{max} 1782, 1506, 1494, 1254, 1039, 935, 737 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 2.74 (1H, dd, J = 17.4, 7.8 Hz, one of CH_2-3), 2.86 (1H, dd, J = 17.4, 8.1 Hz, one of CH_2-3), 3.79 (1H, m, H-4), 5.14 (1H, m, one of CH_2-7), 5.18 (1H, m, H-5), 5.30 (1H, m, one of CH_2-7), 5.42 (1H, ddd, J = 17.1, 9.9, 5.7 Hz, H-6), 5.95 (2H, s, CH_2-2′), 6.58 (1H, dd, J = 7.8, 1.8 Hz, H-6′), 6.61 (1H, d, J = 1.8 Hz, H-4′), 6.75 (1H, d, J = 7.8 Hz, H-7′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.1 (C-3), 44.8 (C-4), 83.6 (C-5), 101.2 (C-2′), 108.0 (C-4′), 108.3 (C-7′), 118.5 (C-7), 121.0 (C-6′). 130.5 (C-5′), 132.4 (C-6), 147.0 (C-3′a), 148.0 (C-7′a), 176.0 (C-2); ESI-HRMS for $C_{13}H_{12}O_4$ $[M+H]^+$: calculated 233.0814, found 233.0813.

2.3 *Antifeedant activity assays*

Lactones **5a–c**,**6a–c**, **7a–c**,**8a–c**,**9a–c** and **10a–c** were tested for feeding deterrent activity against storage pests: larvae and adults of confused flour beetle (*Tribolium confusum*), larvae of khapra beetle (*Trogoderma granarium*) and adults of granary weevil (*Sitophilus*

granarius). Tests were carried out according to the procedure described earlier.[18] Tested insects were reared on wheat grain (*Sitophilus granarius*) or whole wheat meal diet (*Tribolium confusum* and *Trogoderma granarium*) at 26°C and 70% of relative humidity. There were used 7–10 days old adults and their 5–30 days larvae. The compounds were tested as 1% ethanol solutions applied to wheat wafer discs (1 cm diameter, 1 mm thick). In the choice test, insects had a possibility of choice between control discs (dipped in 96% ethanol) or treated discs (dipped in 1% ethanol solutions of the tested compounds). In the no-choice test, the insects were offered only treated discs or control discs. The number of test insects depended on the degree of consumption of wheat wafer discs (3 adults of *S. granaries*, 20 adults of *T. confusum*, 10 larvae of *T. confusum* and 10 larvae of *T. granarium*). The wafer discs were weighed after drying in air for 30 min before the experiments and again after 5 days of feeding. Each experiment was repeated five times.

Three coefficients of deterrence were calculated: 1) Relative, R=[(C-E/C+E)] ×100 (in the choice test) 2) Absolute, A=[(CC-EE/CC+EE)] × 100 (in the no-choice test) 3) Total, T= A+R, where C and CC is the amount of food consumed from control discs; E and EE is the amount of consumed food from discs treated with tested compound.

The value of the total coefficient of deterrence (T) ranges from − 200 to + 200. The negative value indicates that a compound is a feeding attractant. The positive value indicates feeding deterrent activity, within the range 0–50 described as week, 50–100 – medium, 100–150 – good, and 150–200 – very good.

2.4 *Antifungal activity assays*

The phytopathogenic fungal strains, *Fusarium culmorum* AM 9, *Fusarium avenaceum* AM 11, *Fusarium oxysporum* AM 13 and *Fusarium solani* AM 203, were obtained from the collection of Department of Chemistry of Wrocław University of Environmental and Life Sciences. Antifungal activity was tested according to the procedure described earlier by Olejniczak *et al.*[26] Lactones **5a-c**, **6a-c**, **7a-c**, **8a-c**, **9a-c** and **10a-c** were dissolved in DMSO and mixed with sterilized potato dextrose agar (PDA) in 6 cm Petri dishes to give a series of final concentrations: 50, 100, 150, 200 and 250 μg/mL. Fungal cakes of *Fusarium* strains (*F. culmorum* AM 9, *F. avenaceum* AM 11, *F. oxysporum* AM 13 or *F. solani* AM 203) were placed in the hole (10 mm diameter) cut at the centre of a dish. As control dishes there were used PDA with DMSO only. Petri dishes were incubated at 28°C and 70% of relative humidity. Afterwards, diameters of growth zone in control samples and experimental dishes were measured. Each experiment was repeated three times. Didecyldimethylammonium chloride (DDAC) was used as reference compound.

The results showing percentages of inhibition of mycelium growth of fungi at the concentration of compounds 200 μg/mL are shown in table 2. For the most active compounds, IC_{50} (the half maximal inhibitory concentration) values were calculated (table 3) according to the following formula: $IC_{50} = (1\text{-}D_a/D_b) \times 100\%$, where D_a is diameter of growth zone in a experimental dish (cm), D_b is diameter of growth zone in a control dish (cm).

2.5 *Statistical analysis*

The results of tests presented in tables 1 and 3 were analyzed by means of one-way ANOVA. The least significant differences (LSD) at the 5% level were calculated and the Tukey's test was performed. Values in a single column accompanied by the same letter do not differ significantly ($p>0.05$).

3. Results and Discussion

3.1 *Synthesis of lactones*

Our synthetic goal was to obtain three groups of compounds with lactone moiety possessing aromatic substituent: β-aryl-δ-iodo-γ-lactones, products of their reductive dehalogenations and products of elimination of HI from iodolactones - unsaturated lactones. Among δ-iodo-γ-lactones compounds **5a**, **b** and **6a**, **b** were obtained earlier in a five-step synthesis from benzaldehyde and 4-methylbenzaldehyde.[31] Substrate in the synthesis of iodolactones **5c** and **6c** was (*E*)-4-(benzo[*d*][1′,3′]-dioxol-5′-yl)-but-3-en-2-one (**1**), obtained earlier by Claisen-Schmidt condensation of piperonal with acetone under alkali conditions (NaOH).[30]

Ketone **1** was reduced using $NaBH_4$. In the IR spectrum of the product **2** the strong band at 3259 cm^{-1} indicated the presence of O-H group, whereas the value of coupling constant between olefinic protons H-3 and H-4 (J = 15.6 Hz) in ^{1}H NMR spectrum confirmed unchanged *E* configuration of double bond. Allylic alcohol **2** was subjected to Claisen rearrangement[36] in the reaction with triethyl orthoacetate followed by alkaline hydrolysis of γ, δ-unsaturated ester **3** to afford acid **4**. The presence of ester moiety in the ester **3** was confirmed by strong bands at 1732 cm^{-1} and 1247 cm^{-1} in

Table 1. Values of deterrent coefficients for tested lactones 5a-c, 6a-c, 7a-c, 8a-c, 9a-c and 10a-c[a].

compound	granary weevil (*Sitophilus granarius*) adults						confused flour beetle (*Tribolium confusum*) adults						confused flour beetle (*Tribolium confusum*) larvae						khapra beetle (*Trogoderma granarium*) larvae					
	R[b]		A[c]		T[d]		R		A		T		R		A		T		R		A		T	
5a	79.1	a	−8.5	a	70.6	ab	96.7	c	18.6	abc	115.3	bcd	78.2	a	38.9	abcd	117.1	abcd	32.5	a	20.1	a	52.6	a
6a	99.2	a	−10.7	a	88.5	ab	96.2	bc	30.1	bc	126.3	d	94.5	a	55.1	cd	149.6	cd	66.3	a	42.6	a	108.9	abc
5b	96.1	a	5.7	a	101.8	ab	27.2	a	22.0	abc	49.1	a	54.8	a	22.8	abc	77.5	abc	78.2	a	13.9	a	92.1	abc
6b	100.0	a	5.0	a	105.0	ab	96.7	c	24.6	abc	121.3	cd	92.5	a	28.6	abcd	121.1	abcd	92.0	a	59.1	a	151.1	bc
5c	68.7	a	13.3	a	82.0	ab	84.1	bc	−16.1	a	68.0	abc	44.4	a	3.2	a	47.6	a	45.7	a	32.8	a	78.5	abc
6c	10.0	a	15.5	a	115.5	ab	100.0	c	13.5	abc	113.5	bcd	87.1	a	36.4	abcd	123.6	abcd	69.4	a	42.7	a	112.1	abc
7a	93.1	a	0.7	a	93.9	ab	85.1	bc	19.2	abc	104.3	abcd	63.3	a	40.4	abcd	103.7	abcd	87.8	a	−0.1	a	87.6	abc
8a	100	a	19.1	a	119.1	B	99.1	c	29.7	bc	128.9	d	94.8	a	67.6	d	162.4	d	95.4	a	48.7	a	144.1	bc
7b	65.4	a	13.4	a	78.8	ab	95.2	bc	−8.3	ab	86.9	abcd	63.9	a	34.4	abcd	98.3	abcd	72.0	a	51.8	a	123.8	abc
8b	96.1	a	−0.6	a	95.6	ab	100.0	c	22.0	abc	122.0	cd	87.0	a	21.6	abc	108.6	abcd	100.0	a	67.9	a	167.9	c
7c	95.8	a	18.4	a	114.2	ab	89.0	bc	33.8	c	122.8	cd	84.9	a	33.8	abcd	118.7	abcd	40.0	a	24.1	a	64.1	ab
8c	100.0	a	−8.1	a	91.9	ab	99.1	c	2.9	abc	102.0	abcd	94.4	a	16.1	abc	110.5	abcd	96.1	a	42.6	a	138.6	abc
9a	68.9	a	−4.1	a	64.9	A	59.8	ab	0.5	abc	60.3	ab	38.8	a	18.6	abc	57.3	ab	45.3	a	22.6	a	67.9	ab
9b	91.3	a	−9.5	a	81.8	ab	81.1	bc	13.2	abc	94.3	abcd	90.1	a	51.4	bcd	141.6	cd	100.0	a	23.4	a	123.4	abc
9c	98.0	a	10.1	a	108.1	ab	93.9	bc	−13.6	a	80.3	abcd	51.9	a	7.7	ab	59.6	ab	95.5	a	6.9	a	102.4	abc
10a	93.3	a	6.6	a	99.9	ab	95.5	bc	32.5	bc	128.0	d	94.2	a	38.9	abcd	133.1	bcd	69.7	a	33.7	a	103.4	abc
10b	98.9	a	3.3	a	102.2	ab	94.0	bc	14.3	abc	108.3	bcd	91.8	a	23.2	abcd	115.1	abcd	95.1	a	39.9	a	135.0	abc
10c	98.6	a	−8.9	a	89.8	B	81.2	bc	21.2	abc	102.4	abcd	80.2	a	9.8	ab	90.0	abcd	76.8	a	1.4	a	78.2	abc
azadirachtin	100.0		74.3		174.3		100.0		88.4		188.4		100.0		85.0		185.0		100.0		94.2		194.2	
$LSD_{0.05}$	38.1		37.6		52.2		36.9		41.6		55.7		65.1		45.0		80.7		68.2		68.8		91.4	

[a]Values in a single column accompanied by the same letter do not differ significantly ($p>0.05$). [b]Relative deterrent coefficient. [c]Absolute deterrent coefficient. [d]Total deterrent coefficient

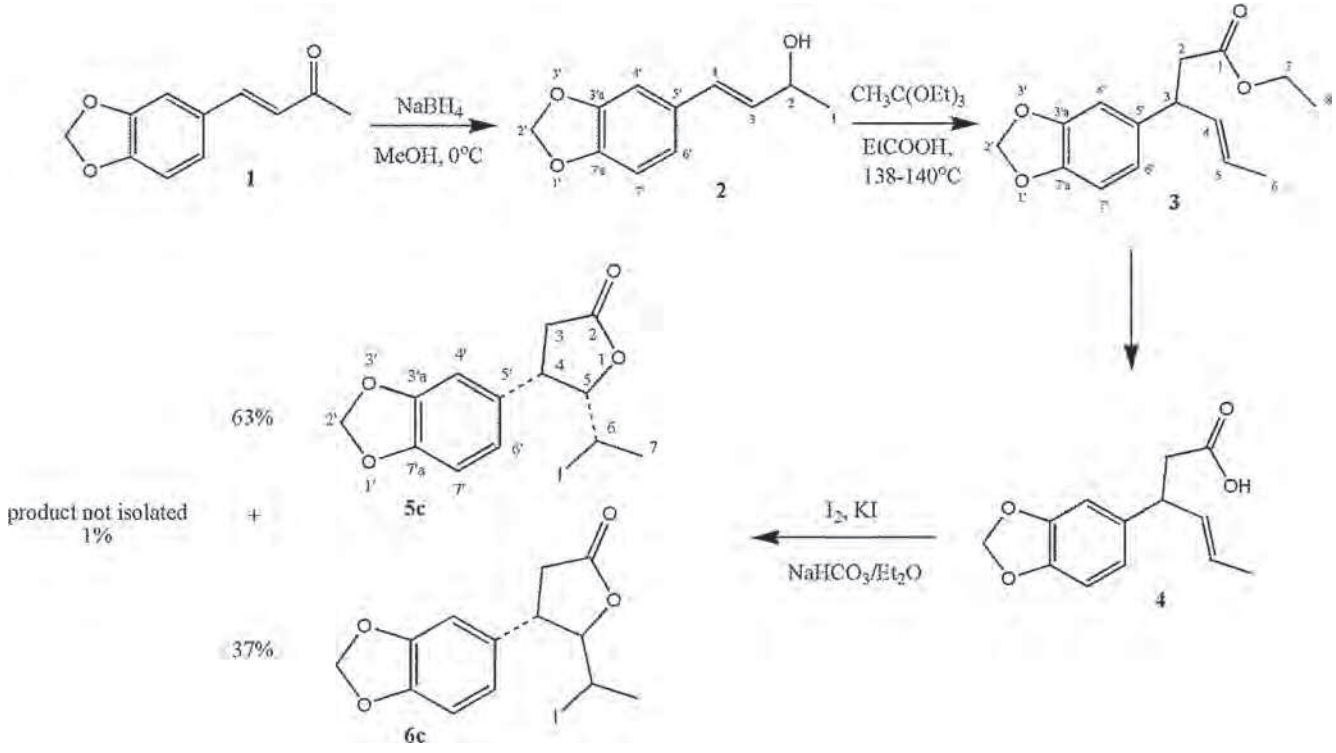
the IR spectrum as well as by triplet from protons of CH_3-8 group ($\delta = 1.18$ ppm) and two doublets of quartets from diastereotopic protons of CH_2-7 group in the ^{1}H NMR spectrum ($\delta = 4.06$ and 4.08 ppm). A broad band at the range 2500–3500 cm^{-1} and strong band at 1708 cm^{-1} undoubtedly indicated the presence of carboxylic group of the compound **4**. The value of coupling constant between H-4 and H-5 protons found in the spectra of both compounds ($J = 15.6$ Hz) proved the *E* configuration of C-4-C-5 double bond.

Iodolactonization of acid **4** (scheme 1) resulted in the formation of two major products, not described previously, formed by 5-*exo* cyclization: *cis*-δ-iodo-γ-lactone **5c** (63%) and *trans*-δ-iodo-γ-lactone **6c** (36%) and the third one which constituted about 1% of the reaction mixture. Two major products were separated by column chromatography and their structures were established by comparative analysis of their spectral data with those obtained earlier for iodolactones **5a**, **b** and **6a**, **b**.[31] IR spectrum showed characteristic bands for γ-lactone ring at 1784 cm^{-1} for **5c** and 1781 cm^{-1} for **6c**. In the case of *cis*-δ-iodo-γ-lactone **5c**, signal of H-5 proton was doublet of doublets ($J = 10.8$ and 5.4 Hz), whereas in case of *trans*-δ-iodo-γ-lactone **6c** proton H-5 gave triplet ($J = 5.4$ Hz). The location of signals from H-6 in the spectra of **5c** and **6c** was significantly different. Unexpected shift towards the upper field (3.55 ppm) in the spectrum of **5c** is due to location of H-6 in the shielding cone of the aromatic ring which is possible in *cis* isomer. In case of **6c** proton H-6 is outside the shielding cone of the aromatic ring due to *trans* orientation of substituents at carbons C-4 and C-5 and the corresponding multiplet appears at lower field ($\delta =$ 4.35 ppm).

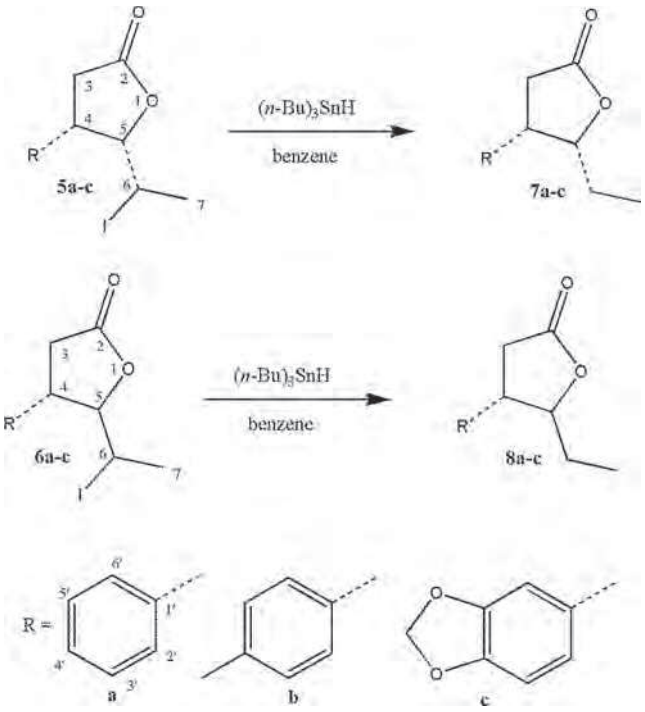
The third, minor product was not isolated due to its very low quantity in the products mixture (about 1%). Comparing with the results obtained during the synthesis of iodolactones with phenyl (**5a** and **6a**) and 4-methylphenyl ring (**5b** and **6b**)[31] it could be presumed that this minor product is *trans*, *cis* γ-iodo-δ-lactone which in those cases constituted 24 and 22%, respectively. The clear predomination of products of 5-*exo* cyclization over the products of 6-*endo* cyclization as well as *cis* γ-lactones over their *trans* isomers were also observed in the course of iodolactonization of γ, δ-unsaturated acid with 4-methoxyphenyl ring.[37]

Iodolactones **5a-c** and **6a-c** were reduced with tributyltin hydride to afford γ-ethyl-γ-lactones **7a-c** and **8a-c** respectively (scheme 2). Iodolactones **5a-c** were also subjected to dehydrohalogenation with DBU to give unsaturated lactones **9a-c** and **10a-c** (scheme 3). Both reactions were carried out in refluxing benzene according to known procedures.[38]

The presence of γ-lactone ring in the products of dehalogenation (**7a-c** and **8a-c**) was confirmed by corresponding bands of C=O stretching vibrations in the



Scheme 1. Synthesis of δ-iodo-γ-lactones **5c** and **6c**.

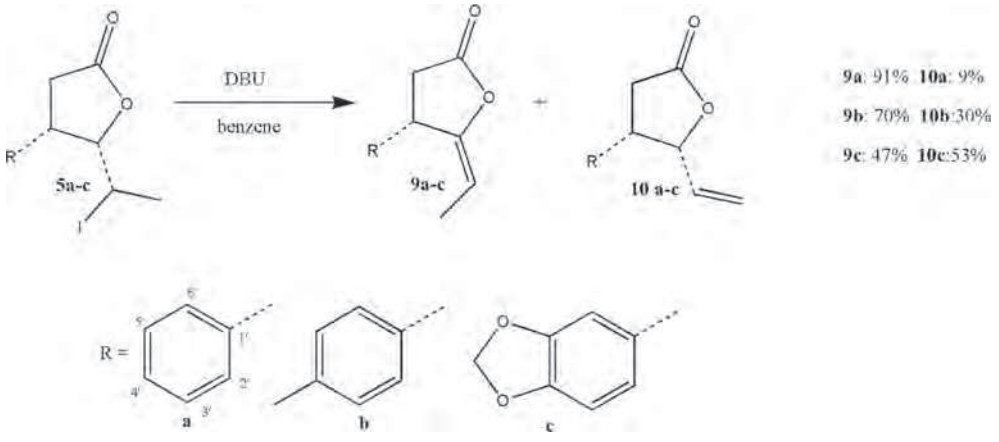


Scheme 2. Reductive dehalogenation of δ-iodo-γ-lactones **5a-c** and **6a-c**.

IR spectrum (e.g. 1771 cm^{-1} for **7c**, 1777 cm^{-1} for **8c**) and the signal from H-5 present above 4 ppm in the ^1H NMR spectra (e.g. 4.57 ppm for **7c**, 4.32 ppm for **8c**). The presence of ethyl group at C-4 was confirmed by triplet of CH_3-7 group (e.g. 0.91 ppm for **7c**) and two separate multiplets from diastereomeric protons of CH_2-6 group (e.g. for **7c** doublet of quadruplets of doublets at 1.26 ppm and doublet of doublets of quadruplets at 1.35 ppm). Those signals were apparently shifted downfield in *trans* isomers **8a-c** comparing to *cis* isomers **7a-c**. Lactones **7b**, **c** and **8b**, **c** were not described previously in the literature. Lactones **7a** and **8a** were obtained earlier as pure enantiomers, $4R, 5S$ and $4R, 5R$ respectively, by the hydrolysis of corresponding hydroxynitriles.[33] $4R, 5R-$Enantiomer of lactone **8a** was also synthesized by Brown *et al.*[34] in the reaction of corresponding iodomethylactone with 5 molar equivalents of Me_2CuLi in THF at 0°C.

Dehydrohalogenation of iodolactones **5a-c** with DBU in all cases afforded mixture of two products that were separated by column chromatography. The location of double bond in these compounds was proved by different number and shape of signals from olefinic protons. In the case of lactones **9a-c** only one-proton multiplet in the range characteristic for olefinic protons appeared as quadruplet of doublets (e.g. 5.42 ppm for **9a**). In the case of lactones **10a-c** signal from H-6 was described as doublet of doublets of doublets and additionally, two signals from diastereomeric vinyl protons of CH_2-7 group were found (e.g. 5.14 and 5.29 ppm for **10a**). These data indicated that lactones **9a-c** possess the exocyclic double bond whereas in lactones **10a-c** the vinyl group at C-5 is present.

The composition of the reaction mixtures (according to GC, scheme 3) indicates that the course of the reaction with DBU strongly depended on the structure of aromatic substituent. The highest content of product with exocyclic double bond (91%) was observed in the case of dehydrohalogenation of iodolactone possessing unsubstituted benzene ring (**5a**), this regioisomer was also the major one (70%) in the mixture of products of dehydrohalogenation of iodolactone with 4-methylphenyl ring (**5b**). On the contrary, in the case of iodolactone containing benzodioxol ring (**5c**) the major product of dehydrohalogenation was γ-vinyl-γ-lactone **10c**. This type of elimination proceeds according to E2 mechanism and requires anti-periplanar conformation of iodine and proton eliminated by the base. Generally formation of thermodynamically more stable exocyclic bond is favoured. Considering the crystal structure



Scheme 3. Dehydrohalogenation of δ-iodo-γ-lactones **5a-c**.

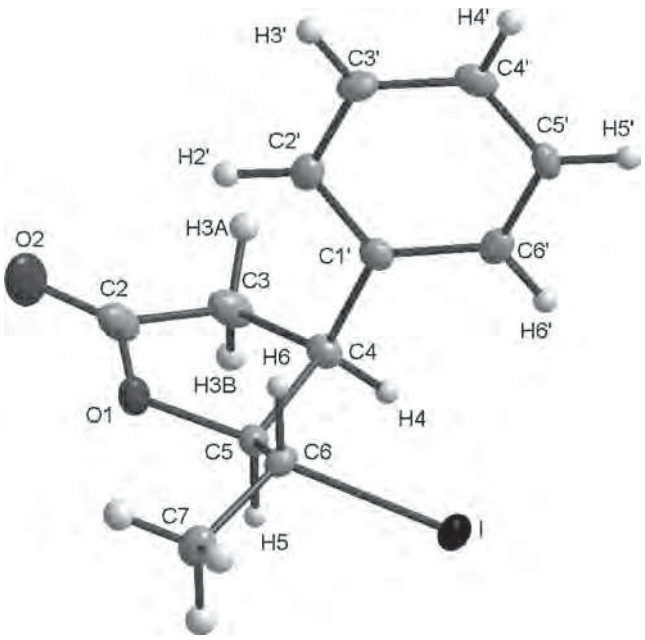


Figure 1. Crystal structure of the iodolactone **5a** (published by Gładkowski et al.[31]) with the numbering consistent with NMR description.

of iodolactone **5a** (figure 1) one can see that in *cis* isomers the anti-periplanar conformation of iodine and proton H-5 is obtained by the rotation around C-5-C-6 bond. This conformational change causes the close approach of iodine atom to the aromatic substituent at C-4 and their electronic repulsions. These repulsions are increased when the phenyl ring has electron donating substituents, as in **5c**, therefore the stronger electron donating substituent is attached to phenyl ring the less contribution of ethylidene lactone in the products mixture is observed. The requirements of type E2 elimination resulted in the *E* configuration of the double bond in ethylidene lactones which is consistent with the results obtained by Obara *et al.*[39] Among the unsaturated lactones, only lactone **10a** was described previously. It was obtained earlier by Hon *et al.*[35] as one of the products of ozonolysis of double bond of 3-phenylpent-4-enoic ethyl ester followed by treatment with triethylamine and vinylmagnesiumbromide.

3.2 *Antifeedant and antifungal activity*

Feeding deterrent activity towards selected storage insect pests is presented in table 1. In 42 tests the compounds turned out to be at least good deterrents (with total deterrent coefficient >100) which makes up 58% of all tests. Among eighteen synthesized lactones, the most active was compound **8a** which exhibited very good activity against larvae of *T. confusum* (T = 162.4) and good activity against adults of *S. granarius* (T = 119.1), adults of *T. confusum* (T = 128.9) and larvae of *T. granarium* (T = 144.1). Good activity towards all tested insects was also found for lactones **6b**, **6c** and **10b**. Lactones **6a**, **8c** and **10a** had a good activity against adults (T = 126.3, 102 and 128, respectively) and larvae (149.6, 110.5 and 133.1, respectively) of *T. confusum* as well as larvae of *T. granarium* (T = 108.9, 138.6 and 103.4, respectively) and lower activity for adults of *S. granarius* (T = 88.5, 91.9 and 89.8, respectively). The similar dependence was observed for lactone **8b** but in this case very high activity towards larvae of *T. granarium* was determined (T = 167.9). This value of T coefficient was the highest one among all determined in these tests. On the other hand, lactone **7c** was a good deterrent against the tested insects except for larvae of *T. granarium* (T = 64.1). Lactone **9b** exhibited good activity against larvae of *T. confusum* (T = 141.6) and larvae of *T. granarium* (T = 123.4), lactones **5a** and **7a** were good deterrents towards both adults (T = 115.3 and 104.3, respectively) and larvae of *T. confusum* (T = 117.1 and 103.7, respectively) whereas lactone **9c** had good activity against adults of *S. granarius* (T = 108.1) and larvae of *T. granarium* (T = 102.4). The lowest activity was determined for lactone **5b** against adults of *T. confusum* (T = 49.1) and lactone **5c** for larvae of *T. confusum* (T = 47.6). In all other cases the activity of the tested lactones was medium.

The results of antifungal tests are presented in table 2 as the percentages of inhibition of mycelium growth of *Fusarium* strains. At least 50% inhibition growth of *Fusarium* was determined in 13 cases which makes 18% of all tests. Eight lactones were active against all strains tested. The highest inhibition was observed for lactone **8c** which inhibited the growth of *F. oxysporum* AM 13 in 70%, *F. avenaceum* AM 11 and *F. solani* AM 203 in 66% and *F. culmorum* AM 9 in 55%. Lactone **7c** was highly active only towards *F. oxysporum* AM 13 (62% of inhibition). Considerably high activity (50%) was found for lactone **5c** in the case of *F. avenaceum* AM 11 and *F. oxysporum* AM 13 and lactone **9c** against *F. culmorum* AM 9 (55%), *F. avenaceum* AM 11 and *F. solani* AM 203 (both 50%). Lactones **6b**, **10a** and **8b** inhibited the growth of *F. avenaceum* AM 11 in 50% and lactone **8b** was also relatively active towards *F. culmorum* AM 9 (44%), *F. oxysporum* AM 13 (38%) and *F. solani* AM 203 (33%). No activity towards tested fungi was found for lactones **5a**, **7a** and **9a**. For the most active lactones **8b**, **5c**, **8c** and **9c** the half maximal inhibitory concentrations (IC_{50}) were determined (table 3). Among them the most active turned out to be *trans* γ-ethyl-γ-lactone with benzodioxole ring (**8c**).

Table 2. Percentages of inhibition of mycelium growth of selected *Fusarium* strains by tested lactones 5a-c, 6a-c, 7a-c, 8a-c, 9a-c and 10a-c at the concentration of 200μg/mL.

compound	*F. culmorum* AM 9	*F.avenaceum* AM 11	*F. oxysporum* AM 13	*F. solani* AM 203
5a	0	0	0	0
6a	0	17	0	0
5b	17	33	18	19
6b	15	50	25	13
5c	44	50	50	30
6c	40	43	10	19
7a	0	0	0	0
8a	0	0	25	0
7b	44	13	0	0
8b	44	50	38	33
7c	14	13	62	33
8c	55	66	70	66
9a	0	0	0	0
9b	30	16	0	0
9c	55	50	37	50
10a	12	50	12	0
10b	11	0	25	14
10c	14	16	10	16

3.3 *Relationship: Structure-activity*

Studying the structure of synthesized lactones we could draw some conclusions about the influence of aromatic substituents, *cis-trans* isomerism or the substituent at C-5 on their biological activity. While analyzing the results of feeding deterrence tests, it should be noticed that γ-ethyl-γ-lactones (**7a-c** and **8a-c**) and unsaturated lactones (**9a-c** and **10a-c**) were generally more active than their parent iodolactones (**5a-c** and **6a-c**). In the case of four ethyllactones and three unsaturated lactones, the total coefficients of deterrence exceeded 130, whereas among iodolactones, such results were obtained in only two cases. In almost all tests *trans* δ-iodo-γ-lactones were more active than their *cis* isomers. This regularity is particularly clear in the case of activity of lactones **5b** and **6b** towards adults of *T. confusum* (T = 49.1 and 121.3, respectively) and activity of lactones **5c** and **6c** towards larvae of *T. confusum* (T = 47.6 and 123.6, respectively). The higher activity of *trans* isomers was also confirmed in the group of γ-ethyl-γ-lactones with phenyl and 4-methylphenyl ring (**7a**, **b** and **8a**, **b**) but in the case of lactones with benzodioxol ring (**7c** and **8c**) slightly higher activity for the *cis* isomers was generally observed. The lactones with exocyclic double bond (**9a-c**) exhibited generally higher activity than their regioisomers possessing vinyl group (**10a-c**). The effect of aromatic substituents was most complex and different in various groups of compounds. Among iodolactones (**5a-c** and **6a-c**) and unsaturated lactones (**9a-c** and **10a-c**) compounds with phenyl (**5a**, **6a**, **9a** and **10a**) and 4-methylphenyl ring (**5b**, **6b**, **9b** and **10b**) were more active. In the group of *cis* γ-ethyl-γ-lactones **7a-c**

Table 3. The half maximal inhibitory concentration (IC_{50}) [μg/mL] for the most active lactones against selected fungal strains[a].

compound	*F. culmorum* AM 99	*F. avenaceum* AM 11	*F. oxysporum* AM 13	*F. solani* AM 203
8b	271.4 b	221.4 b	276.0 b	325.0 b
5c	230.5 b	242.8 b	217.8 b	350.0 b
8c	175.0 a	185.7 a	175.0 a	215.6 a
9c	183.3 ab	225.0 ab	271.4 ab	217.8 ab
DDAC	10.0	35.0	24.0	40.0
$LSD_{0.05}$	13.2	35.9	36.6	49.1

[a] Values in a single column accompanied by the same letter do not differ significantly ($p>0.05$)

higher activity was usually found for lactone with benzodioxol ring (**7c**), whereas in the group of *trans* γ-ethyl-γ-lactones (**8a-c**) the compounds with unsubstituted benzene ring (**8a**) were the most active. The studies showed also the different susceptibility of the insects to the lactones tested. The most resistant turned out to be adults of *S. granarius* - in this case none of the T coefficients was higher than 120. The most susceptible were larvae of *T. granarium*, in this case five T coefficients exceeded 130. Stage of *T. confusum* had also the influence on their susceptibility to the tested lactones with the larvae being more sensitive than adults.

Taking into account the relationship of structure-antifungal activity, the key factor is the kind of aromatic substituent. The least active, in some cases completely deprived of activity, were lactones with unsubstituted benzene ring (*e.g.* **5a**, **6a**, **7a**, **8a**, **9a**), higher activity was observed for those with 4′-methylphenyl substituent (*e.g.* **5b**, **6b**, **8b)** and the most active were lactones possessing benzodioxol ring (particularly **5c**, **8c**, **9c**). In the latter two groups, the presence of iodine atom increased the activity in the case of *cis* isomers but for *trans* isomers the reverse dependence was observed. The influence of location of double bond was diverse: among lactones with benzodioxol ring compound with ethylidene group (**9c**) was more active whereas among those with unsubstituted benzene ring only the activity of lactone with vinyl group (**10a**) was observed. In the group of compounds with 4′-methylphenyl ring lactone with ethylidene group (**9b**) was more active towards *F. culmorum* AM 9 and *F. culmorum* AM 11 whereas that with vinyl group (**10b**) showed activity towards *F. oxysporum* AM 13 and *F. solani* AM 203. Similarly to deterrent properties, the antifungal activity of *trans* isomers were generally higher than *cis* isomers, except for iodolactones **5c** and **6c**. *F. culmorum* AM 9 and *F. solani* AM 203 turned out to be the most resistant to the tested lactones - for each strain only in two cases the growth inhibition was at least 50%. On the other hand, the most susceptible strain was *F. avenaceum* AM 11, in this case at least 50% of inhibition was exhibited by six lactones.

Considering all the results, one can see that a crucial structural element in the context of antifungal activity of the studied γ-butyrolactones is the presence of benzodioxol ring at β-position. Three of four most active compounds (**5c**, **8c**, **9c**) contained this fragment in their structures. This aromatic system is widely present in many natural compounds with different biological activities, including antifungal (homoisoflavonoids)[40] or antitumor (*i.a.* isochaihulactone, parabenzlactone, phodophyllotoxin, etoposide).[41] On the other hand, some lignans with a piperonyl moiety, especially yatein, exhibit strong antifeedant properties against *Tribolium confusum*, *Trogoderma granarium* and *Sitophilus granaries*.[9,42] In our studies, in 13 cases of lactones with benzodioxol ring turned out to be good antifeedants. But synthesis of aromatic lactones with different electron withdrawing or donating groups at the phenyl ring will allow one to draw important conclusions about the relationship structure-antifeedant activity in this group of compounds.

4. Conclusions

In summary, eighteen β-aryl-γ-lactones with aromatic ring were synthesized, eleven of them were not reported previously in the literature. Highest activities were found in the group of *trans* γ-ethyl-γ-lactones (**8a-c**): lactone **8a** and **8b** were strong antifeedants whereas the lactone **8c** exhibited the highest antifungal activity. The investigations carried out allowed us to find some relationship between the structure and biological activity of the compounds studied. These findings are likely basis for future research over design and synthesis of more active lactone derivatives with aromatic substituents. Further structural modifications are needed to find additional important structural factors influencing the biological activity, including length of aliphatic chain or the type of substituent in aromatic ring (electron withdrawing or donating group).

Supplementary Information

The spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS) of synthesized compounds are presented in the Supplementary Information available at www.ias.ac.in/chemsci. Crystal data for lactone **5a** were reported earlier by Gładkowski *et al.*[31] and have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number 944820. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union road, Cambridge CB12 1EZ, UK (fax +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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