SYNTHESIS AND ANTIFUNGAL ACTIVITY EVALUATION OF 3-HETARYL-2,5-DIHYDROFURAN-2-ONES. AN UNUSUAL FRAGMENTATION OF THE OXAZOLE RING *via* 2,3-SELENOXIDE SHIFT

Jiří Kuneš[a1], Vojtěch Balšánek[a2], Milan Pour[a3,*] and Vladimír Buchta[b]

[a] *Department of Inorganic and Organic Chemistry, Faculty of Pharmacy, Charles University, Heyrovského 1203, CZ-500 05 Hradec Králové, Czech Republic; e-mail: [1] kunes@faf.cuni.cz, [2] balsanek@faf.cuni.cz, [3] pour@faf.cuni.cz*

[b] *Department of Biological and Medicinal Sciences, Faculty of Pharmacy, Charles University, Heyrovského 1203, CZ-500 05 Hradec Králové, Czech Republic; e-mail: buchta@faf.cuni.cz*

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Dedicated to the memory of late Dr Václav Černý.

In continuing the studies on the synthesis and evaluation of antifungal activity of the analogues of (–)incrustoporine, the replacement of the phenyl moiety at C3 of the furanone ring with a hetaryl substituent was considered. Thus, a series of 5-alkyl-3-hetaryl-2,5-dihydrofuran-2-ones with the thienyl, furyl and thiazolyl moieties attached to C3 was synthesized, and the compounds subjected to antifungal activity screening. In the preparation of compounds containing the oxazolyl fragment, the [2,3]-sigmatropic rearrangement led to the fragmentation of the oxazole ring, resulting in the formation of 3-(1-benzamido-2-oxoethylidene)-5-methyltetrahydrofuran-2-one. Somewhat surprisingly, the antifungal efficiency of the derivatives was lower in comparison with analogues containing a substituted phenyl at C3.

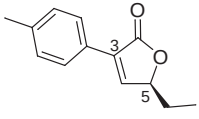
Keywords: (–)Incrustoporine; 2,5-Dihydrofuran-2-ones; Oxazoles; Thiophenes; Thiazoles; [2,3]-Sigmatropic rearrangement; Allylic selenoxide; Antifungal activity.

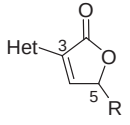
In 1995, Zapf *et al.* isolated a secondary metabolite from the Basidiomycete *Incrustoporia carneola*[1], which displayed certain antifungal activity against plant pathogenic fungi. The structure of this compound, named (–)incrustoporine, was corroborated by a total synthesis in 1996 (ref.[2]). In conjunction with our long-term projects, focused on exploring small, biologically active natural compounds as prototypes of potential drugs, we used this substance as a lead structure in the design and synthesis of novel antifungals. So far, we have synthesized[3,4] structures with different substitu-

ents on the benzene ring attached to C3 of the lactone moiety and methyl/hydroxymethyl/acyloxymethyl groups at C5. Biological evaluation of the analogues revealed that antifungal activity is supported by substitution of the benzene ring with halogens and by introducing an (acyloxy)methyl moiety to C5 of the furanone. Most notably, 5-[(acyloxy)methyl]-3-(halophenyl)-2,5-dihydrofuran-2-ones possessed *in vitro* antifungal activity comparable to that of amphotericin B, one of the most potent systemic antifungals currently on the market. Since most chemical drugs contain heterocyclic rings, some of which are also isosteric to phenyl, we were naturally interested in replacing the phenyl moiety at C3 with a heteroaryl one (Fig. 1). Herein we describe the syntheses and biological evaluation of a series of compounds with thienyl, bromothienyl, furyl and thiazolyl substituents, as well as attempts to prepare substances bearing the oxazole ring at C3 of the furanone system.

Chemistry

In order to prepare 2- and 3-thienyl derivatives (Schemes 1 and 2), we used (2- or 3-thienyl)acetic acids as the starting materials and prepared the target compounds as described previously by us[3]. Thus, the thienylacetic acids were converted into the corresponding methyl esters, which were enolized with LDA. The quenching of the enolates with allyl bromide furnished 2-(2-thienyl)- (**1**) and 2-(3-thienyl)pent-4-enoic acid (**2**). As the thiophene ring is extremely prone to sulfonation, the acids could not be treated directly[3] with H_2SO_4, and the desired cyclization to saturated lactones **3** and **4** was effected through the addition of HBr across the double bond, followed by nucleophilic substitution of bromine with the carboxylate anion. Finally, the endocyclic double bond was introduced into lactones **3** and **4** *via* enolization, subsequent treatment of the enolates with PhSeCl and oxi-

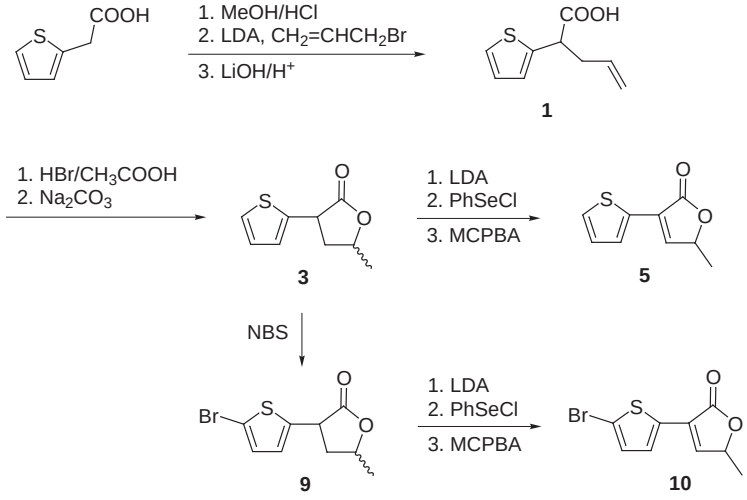




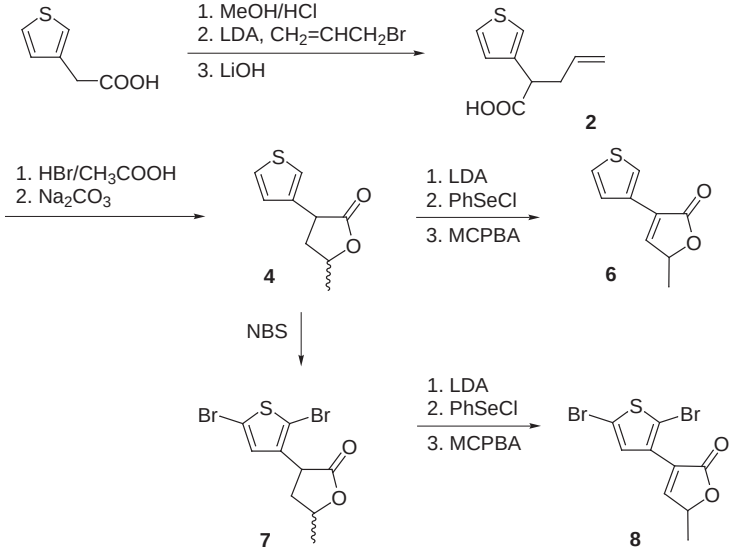
Het: 2-, 3-thienyl, 4-thiazolyl, 4-oxazolyl, 2- furyl
R: CH_3, C_2H_5

FIG. 1
Structure of (–)incrustoporine and its hetaryl-analogues

dative *syn*-elimination of the phenylselanyl moiety. This uneventful sequence of reactions smoothly afforded furanones **5** and **6**.

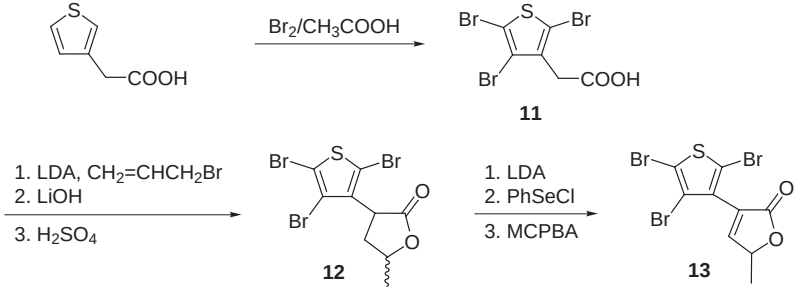


SCHEME 1



SCHEME 2

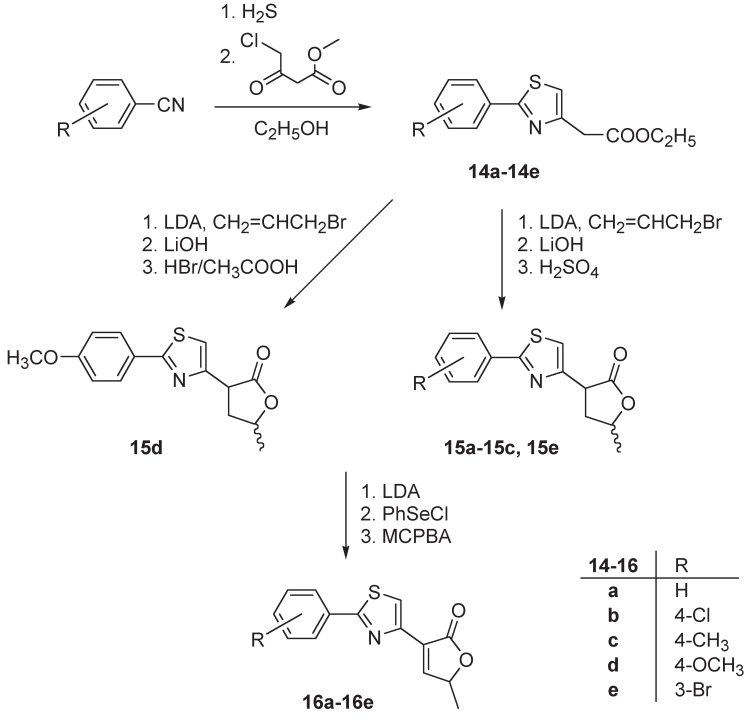
Given our previous results, we also intended to prepare bromothienyl analogues of compounds **5** and **6**, since we supposed that the introduction of the bromine would be likely to increase antifungal activity. From the synthetic point of view, it appeared advantageous to introduce bromine at the stage of the saturated lactone (**3** and **4**). Since bromine itself is too reactive, we used a milder brominating agent, NBS (refs[5,6]). However, the reaction of lactone **4** with this agent in AcOH–MeOH gave an inseparable mixture of 3-(2-bromo-3-thienyl)-5-methyltetrahydrofuran-2-one, 3-(2,5-dibromo-3-thienyl)-5-methyltetrahydrofuran-2-one (**7**) and the starting material. The compounds were identified by the comparison of the ^{1}H NMR spectrum of the mixture with the spectra of lactones **4** and **7** (*vide infra*). In the hope that the compounds would become separable upon the introduction of the double bond, the mixture was subjected to the above described enolization/PhSeCl/ *syn*-elimination sequence. To our disappointment, only furanone **6** could be separated from the brominated analogues, which had identical R_F values in a number of mobile phases. Given these results, lactone **4** was treated with a large excess of NBS to yield 3-(2,5-dibromo-3-thienyl)-5-methyltetrahydrofuran-2-one **7** in 92% yield and this substance was converted into the target furanone **8** as described above. On the other hand, lactone **3** was selectively brominated (86%) in position 5, which enabled us to prepare 3-(5-bromo-2-thienyl)-5-methyl-2,5-dihydrofuran-2-one **10**. With the partially brominated analogues **8** and **10** in hand, we also attempted the preparation of fully brominated compounds. While NBS was too mild to achieve bromination of all positions in the thiophene ring, the reaction of saturated lactones **3** and **4** with Br_2/AcOH generally led to intractable mixtures of compounds. Fortunately, the same reaction carried out on the methyl ester of 3-thienylacetic acid (Scheme 3) yielded the methyl 2,4,5-tribromo-3-thienylacetate (**11**) in 95% yield and this compound was further con-



SCHEME 3

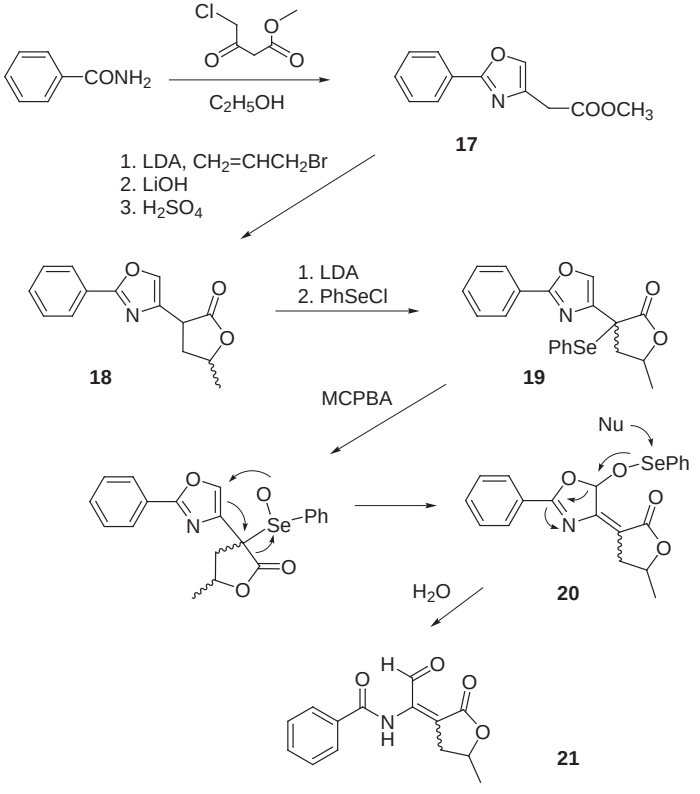
verted into 3-(2,4,5-tribromo-3-thienyl)-5-methyl-2,5-dihydrofuran-2-one (**13**) (Scheme 3). It was interesting to observe that the methyl ester of the isomeric 2-thienylacetic acid gave a mixture of compounds upon treatment with bromine in acetic acid.

Another group of derivatives included those with a 2-(substituted phenyl)-4-thiazolyl moiety, where the substituents on the benezene ring were selected according to the approach of Toppliss[7]. The starting materials, methyl esters of 2-(substituted phenyl)-4-thiazolylacetic acids, were prepared from substituted benzonitriles, which were converted into the corresponding thioamides by the addition of H_2S. The thioamides were then subjected to a condensation with the methyl 4-chloro-3-oxobutanoate[8], giving rise to methyl esters **14a**–**14e**, which were further elaborated towards the target compounds **16a**–**16e** (Scheme 4) *via* the sequence depicted in Scheme 4. In a similar fashion, we strove to prepare another subset of analogues bearing a 2-(substituted phenyl)-4-oxazolyl moiety. The feasibility of the sequence was first evaluated on benzamide as the starting compound[9].



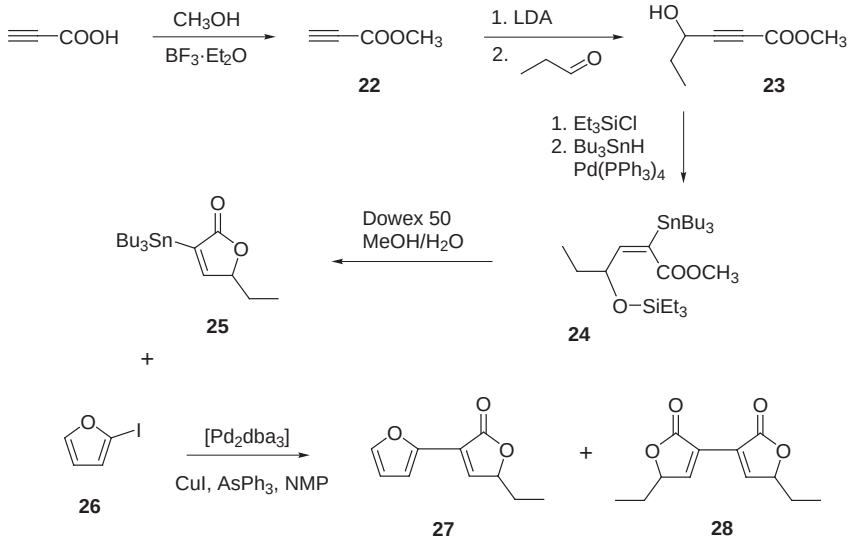
SCHEME 4

As shown in Scheme 5, the reactions proceeded as planned until the stage of introducing the double bond, which led to 3-(1-benzamido-2-oxoethylidene)-5-methyltetrahydrofuran-2-one **21** arising from the fragmentation of the oxazole ring as the only isolable product. The structure of amide **21** was corroborated by 2D NMR spectroscopy using gHSQC and gHMBC experiments. Since we observed the formation of phenylselanyl compound **19**, the fragmentation must have occurred upon oxidation into the corresponding selenoxide with MCPBA in $CHCl_3$. Interestingly, instead of *syn*-elimination with the α-hydrogen, the selenoxide probably preferred [2,3]-sigmatropic rearrangement[10] to furnish intermediate **20**, which underwent hydrolysis leading to the fragmentation of the oxazole moiety (Scheme 5). Unfortunately, the only observable NOE was between the NH group and the aldehydic proton, and numerous attempts to crystallize aldehyde **21** failed. Consequently, the configuration of compound **21** remains unresolved and will be the subject of further investigation.



SCHEME 5

The last analogue, the synthesis of which we executed, was the 3-(2-furyl) derivative **27** (Scheme 6). Instead of the pathway depicted in Scheme 1, we tested a synthesis based on a Stille reaction between 2-iodofuran **26** and the stannyl compound **25** as the key step. 2-Iodofuran was prepared by the direct iodination of furan[11] and compound **25** was synthesized from propiolic acid. Acid was esterified[12], and the resultant methyl ester was sequentially



SCHEME 6

treated with LDA and acetaldehyde to give the methyl 4-hydroxy-2-hexynoate[13] (**23**). Following the protection of the hydroxy group with triethylsilyl chloride, the addition of Bu_3SnH (ref.[14]) across the triple bond in compound **23** catalyzed by $Pd(PPh_3)_3$ afforded (tributylstannyl)alkene **24** as the major product. Upon deprotection of the triethylsilyl group, the liberated hydroxy function immediately cyclized onto the ester group to furnish the second desired component for the Pd coupling, the α-(tributylstannyl)lactone **25**. The coupling[15] step between **25** and **26** was not an easy task due to a somewhat limited stability of both compounds. Not surprisingly, the reaction failed under a number of different conditions, including catalyst systems ($Pd(Ph_3)_4$, $Pd(dba)_2$, "$Pd(Ph_3)_2$", "$Pd[P(2\text{-furyl})_3]_2$"[16], solvents (THF, DMF). Fortunately, upon using *N*-methylpyrrolidone as the solvent and a catalytic system composed of triphenylarsine as the ligand, $Pd_2(dba)_3$ as the source of palladium and Cu_2I_2 as the cocatalyst[17,18], the required transformation was effected, albeit in a rather low yield (38%) with the product of self-coupling **28** being the major isolated compound (56%).

Biological Activity

The target compounds were evaluated for their *in vitro* antifungal activity against a set of human pathogenic fungi including the representatives of both yeast and filamentous strains using the microdilution format of the NCCLS M27-A guidelines[19]. Ketoconazole and the racemic form of (–)incrustoporine[2] were used as the standards for comparison. The activities, expressed as minimum inhibitory concentrations (MICs), are summarized in Table I. Surprisingly, the introduction of a five-membered hetaryl (furyl, thienyl, 2-phenylthiazolyl) moiety into position 3 of the lactone ring does not increase the antifungal effect, as derivatives **5**, **6**, **10**, **16c**–**16e**, and **27** are virtually inactive. The unwanted self-coupling product, bislactone **28**, possesses higher activity than unsubstituted and monosubstituted heterocyclic derivatives. As expected, the antifungal activity of the thienyl derivatives increases with a higher degree of bromination, probably due to a change in lipophilicity. As compared to the racemic form of the natural product, the lactones bearing a bromothienyl moiety at C3 display substantially higher biological activity, because the increased lipophilicity of the compounds gives rise to a higher capability to penetrate the fungal cell wall.

In summary, we have synthesized a series of analogues of (–)incrustoporine with different five-membered hetaryl substituents attached to C3 of the lactone ring. Some of the compounds, however, could not be obtained due to the properties of the heterocyclic rings.

EXPERIMENTAL

Chemistry

The other commercially available reagents were used directly, unless otherwise indicated. THF was freshly distilled from sodium benzophenone ketyl. DMF was dried over 3 Å molecular sieves. Melting points were determined on a Kofler block and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions at ambient temperature on a Varian Mercury-Vx BB 300 spectrometer operating at 300 MHz for ^{1}H. Chemical shifts were recorded as δ values in ppm and were indirectly referenced to tetramethylsilane (TMS) *via* the solvent signal (7.26 for ^{1}H, 77.0 for ^{13}C in $CDCl_3$). Coupling constants (*J*) are given in Hz. Where NMR spectra of mixtures were recorded, only those data which could be determined unequivocally were given. Infrared spectra (wavenumbers in cm^{-1}) were recorded in $CDCl_3$ on a Nicolet Impact 400 spectrophotometer. Low resolution mass spectra were measured on a Magnum Finnigan Mat apparatus. Elemental analysis was carried out on a CHNS-OCE FISONS EA 1110 instrument. Analytical thin-layer chromatography (TLC) was conducted on Merck TLC plates (silica gel 60 F_{254}, aluminium back), and the plates were visualized under

TABLE I
Antifungal activity of the incrustosporin analogues

Strain (code)		MIC, μmol l^{-1}												
		5	**6**	**8**	**10**	**12**	**15a**	**15b**	**15c**	**15d**	**15e**	**27**	**28**	**R**	**KET**
TM	72 h	250	500	31.25	125	31.25	62.5	62.5	>250	>250	>250	>250	125	125	0.98
	120 h	250	500	31.25	250	62.5	125	125	>250	>250	>250	>250	250	250	1.95
CA	24 h	500	500	125	125	125	>500	>250	>250	>250	>250	>250	62.5	250	0.12
	48 h	>1 000	>1 000	250	500	>500	>500	>250	>250	>250	>250	>250	125	250	0.12
CT	24 h	>1 000	1 000	250	500	>500	>500	>250	>250	>250	>250	>250	>500	500	31.25
	48 h	>1 000	>1 000	>500	1 000	>500	>500	>250	>250	>250	>250	>250	>500	>500	62.5
CK	24 h	>1 000	>1 000	250	500	>500	>500	>250	>250	>250	>250	>250	>500	500	3.91
	48 h	>1 000	>1 000	>500	1 000	>500	>500	>250	>250	>250	>250	>250	>500	>500	3.91
CG	24 h	>1 000	>1 000	>500	>1 000	>500	>500	>250	>250	>250	>250	>250	>500	500	0.24
	48 h	>1 000	>1 000	>500	>1 000	>500	>500	>250	>250	>250	>250	>250	>500	>500	0.98
TB	24 h	>1 000	>1 000	125	250	>500	>500	>250	>250	>250	>250	>250	>500	500	0.12
	48 h	>1 000	>1 000	500	1 000	>500	>500	>250	>250	>250	>250	>250	>500	500	0.24
AF	24 h	1 000	1 000	125	125	62.5	>500	>250	>250	>250	>250	>250	62.5	250	15.63
	48 h	>1 000	>1 000	250	>1 000	62.5	>500	>250	>250	>250	>250	>250	>500	500	15.63
AC	24 h	1 000	1 000	31.25	250	62.5	125	125	>250	>250	>250	>250	125	250	32.25
	48 h	>1 000	>1 000	125	125	62.5	125	125	>250	>250	>250	>250	250	250	32.25

TM, *Trichophyton mentagrophytes* 445; CA, *Candida albicans* ATCC 44859; CT, *Candida tropicalis* 1561; CK, *Candida krusei* E28; CG, *Candida glabrata* 20/I; TB, *Trichosporon beigelii* 1188; AF, *Aspergillus fumigatus* 231; AC, *Absidia corymbifera* 272; KET, ketoconazole; R, natural incrustoporine in racemic form.

UV light and in iodine vapours. Silica gel 60 (230–400 mesh) for column chromatography was purchased from Merck.

Preparation of Methyl Esters of Thienylacetic Acids. General Procedure

A solution of a thienylacetic acid (1.70 g, 12 mmol) in methanol saturated with hydrogen chloride (100 ml) was heated under reflux for 3 h. The solvent was removed *in vacuo* and the residue redissolved in ethyl acetate. The solution was washed with 5% aqueous Na_2CO_3, dried over anhydrous Na_2SO_4, and the solvent evaporated to give the corresponding methyl ester in quantitative yield. The compounds were used in the next step without purification and characterization.

Methyl (2,4,5-Tribromo-3-thienyl)acetate (**11**)

Bromine (3.0 ml) in acetic acid (8.0 ml) was added dropwise to a solution of the methyl (3-thienyl)acetate (2.13 g, 13.66 mmol) in chloroform (8.0 ml). After stirring at room temperature for 2 h, the mixture was diluted with ethyl acetate, washed with 5% aqueous NaOH, brine, saturated aqueous $Na_2S_2O_3$, and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue purified by column chromatography (petroleum ether–ethyl acetate 95 : 5). Yield 5.108 g (95%), m.p. 31–33 °C. ^{1}H NMR ($CDCl_3$): 3.73 s, 3 H (CH_3); 3.72 s, 2 H (CH_2). ^{13}C NMR ($CDCl_3$): 169.10, 134.00, 115.87, 111.20, 110.01, 52.42, 35.83. MS, *m/z* (%): 394 ($M^{+\bullet}$ + H, 100), 335 (79), 313 (42), 285 (3), 254 (9), 173 (10), 125 (6), 94 (33), 81 (4), 69 (11), 50 (12). IR ($CDCl_3$), ν_{max}: 2 955, 1 740, 1 534, 1 437, 1 406, 1 351, 1 328, 1 267.

Methyl (2-Phenyloxazol-4-yl)acetate (**17**)

A mixture of benzamide (4.83 g, 39.87 mmol) and methyl 3-chloroacetoacetate (5.00 g, 33.21 mmol) was heated at 120 °C for 2.5 h. After cooling to room temperature, ethyl acetate (60 ml) was added, and the resulting solution washed with brine and dried over anhydrous Na_2SO_4. Column chromatography (petroleum ether–ethyl acetate 9 : 1) afforded 3.187 g (44%) of the product. All physical data and spectral characteristics were consistent with those reported in the literature[20].

Preparation of Methyl and Ethyl (2-Phenylthiazol-4-yl)acetates (**14a**–**14e**). General Procedure

Substituted benzonitriles were dissolved in pyridine and dry sulfane was passed through the solution until TLC indicated that the reactions were complete. All physical data were consistent with those reported in literature[21,22]. A mixture of a substituted thiobenzamide (19.16 mmol), methyl 3-chloroacetoacetate (2.00 ml, 17.42 mmol) and pyridine (1.54 ml, 19.16 mmol) in ethanol (10 ml) was heated under reflux for 6 h. The solvent was removed *in vacuo*, the residue redissolved in ethyl acetate and dried over anhydrous Na_2SO_4. The products were purified by column chromatography (petroleum ether–ethyl acetate 95 : 5).

Methyl (2-phenylthiazol-4-yl)acetate (**14a**). Yield 3.55 g (83%). All physical data and spectral characteristics were consistent with those reported in the literature[20].

Ethyl [2-(4-chlorophenyl)thiazol-4-yl]acetate (**14b**). Yield 3.40 g (69%). All physical data and spectral characteristics were consistent with those reported in the literature[23].

Ethyl [2-(4-methylphenyl)thiazol-4-yl]acetate (**14c**). Yield 3.98 g (87%). ^{1}H NMR ($CDCl_3$): 7.84–7.78 m, 2 H (AA′BB′); 7.25–7.19 m, 2 H (AA′BB′); 7.15 t, 1 H, *J* = 0.8 (thiazole); 4.21 q, 2 H, *J* = 7.1 (CH_2); 3.88 d, 2 H, *J* = 0.8 (H2); 2.38 s, 3 H (Ar-CH_3); 1.29 t, 3 H, *J* = 7.1 (CH_3). ^{13}C NMR ($CDCl_3$): 170.43, 168.00, 149.60, 140.16, 130.89, 129.52, 126.43, 115.45, 61.00, 37.17, 21.38, 14.17. MS, *m/z* (%): 261 ($M^{+\bullet}$, 100), 247 (2), 216 (3), 188 (36), 161 (2), 147 (2), 135 (3), 118 (17), 91 (5), 71 (11), 51 (3). IR ($CDCl_3$), ν_{max}: 2 984, 2 926, 1 732, 1 513, 1 456, 1 371.

Ethyl [2-(4-methoxyphenyl)thiazol-4-yl]acetate (**14d**). Yield 3.45 g (72%). ^{1}H NMR ($CDCl_3$): 7.88–7.83 m, 2 H (AA′BB′); 7.11 t, 1 H, *J* = 0.8 (thiazole); 6.96–6.90 m, 2 H (AA′BB′); 4.21 q, 2 H, *J* = 7.1 (CH_2); 3.86 d, 2 H, *J* = 0.8 (H2); 3.84 s, 3 H (OCH_3); 1.29 t, 3 H, *J* = 7.1 (CH_3). ^{13}C NMR ($CDCl_3$): 170.45, 167.70, 161.03, 149.47, 127.99, 126.51, 114.99, 114.15, 61.00, 55.35, 37.17, 14.17. MS, *m/z* (%): 277 ($M^{+\bullet}$, 100), 267 (2), 231 (4), 204 (32), 190 (2), 177 (2), 134 (15), 103 (4), 91 (4), 71 (21), 55 (3). IR ($CDCl_3$), ν_{max}: 2 984, 2 938, 1 732, 1 610, 1 514, 1 458, 1 305.

Ethyl [2-(3-bromomethyl)thiazol-4-yl]acetate (**14e**). Yield 4.60 g (81%). All physical data and spectral characteristics were consistent with those reported in the literature[23].

Preparation of Methyl and Ethyl 2-Hetarylpent-4-enoates. General Procedure

A solution of 1.6 M butyllithium in hexanes (8.27 ml, 13.2 mmol) was added to a solution of diisopropylamine (1.77 ml, 12.6 mmol) in dry THF (60 ml) at 0 °C under argon. After 10 min at 0 °C, the LDA solution was cooled to –60 °C and a solution of methyl or ethyl hetarylacetate (12 mmol) was added. After maintaining the mixture at –60 °C for 30 min, allyl bromide (1.09 ml, 12.6 mmol) was added dropwise. The reaction mixture was slowly allowed to warm to room temperature (2 h) in order to drive the reaction to completion. The solution was then diluted with ethyl acetate (100 ml), washed with saturated aqueous NH_4Cl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to yield the crude ester of the corresponding 2-hetarylpent-4-enoic acid. The products were purified by column chromatography (petroleum ether–ether 95 : 5) and directly used in further steps.

Methyl 2-(2-thienyl)pent-4-enoate. Yield 2.22 g (95%). ^{1}H NMR ($CDCl_3$): 7.23–7.19 m, 1 H (Ar5); 6.98–6.93 m, 2 H (Ar3,4); 5.82–5.67 m, 1 H (H4) ;5.16–5.02 m, 2 H (H5); 3.96 dd, 1 H, J_1 = 8.3, J_2 = 7.2 (H2); 3.70 s, 3 H (CH_3); 2.89–2.75 m, 1 H (H3A); 2.66–2.54 m, 1 H (H3B). ^{13}C NMR ($CDCl_3$): 172.76, 140.61, 134.44, 126.54, 125.31, 124.53, 117.43, 52.24, 46.70, 38.68. MS, *m/z* (%): 196 ($M^{+\bullet}$ + H, 6), 155 (100), 137 (64), 127 (60), 97 (12), 77 (3), 65 (9), 59 (7). IR ($CDCl_3$), ν_{max}: 3 082, 2 954, 1 735, 1 642, 1 437, 1 338, 1 280.

Methyl 2-(3-thienyl)pent-4-enoate. Yield 2.05 g (87%). ^{1}H NMR ($CDCl_3$): 7.28 dd, 1 H, J_1 = 5.0, J_2 = 3.0 (Ar5); 7.15 dd, 1 H, J_1 = 3.0, J_2 = 1.4 (Ar2); 7.06 dd, 1 H, J_1 = 5.0, J_2 = 1.4 (Ar4); 5.81–5.65 m, 1 H (H4); 5.14–4.98 m, 2 H (H5); 3.80 dd, 1 H, J_1 = 8.6, J_2 = 6.8 (H2); 3.68 s, 3 H (CH_3); 2.84–2.72 m, 1 H (H3A); 2.59–2.47 m, 1 H (H3B). ^{13}C NMR ($CDCl_3$): 173.52, 138.63, 135.02, 127.10, 125.74, 121.89, 117.10, 51.99, 46.76, 37.45. MS, *m/z* (%): 196 ($M^{+\bullet}$ + H, 4), 155 (40), 137 (100), 127 (68), 97 (13), 91 (7), 77 (4), 65 (12), 51 (6). IR ($CDCl_3$), ν_{max}: 3 082, 2 953, 1 733, 1 642, 1 437, 1 342, 1 280.

Methyl 2-(2,4,5-tribromo-3-thienyl)pent-4-enoate. Yield 3.81 g (73%), m.p. 53–54 °C. ^{1}H NMR ($CDCl_3$): 5.77–5.61 m, 1 H (H4); 5.06–4.94 m, 2 H (H5); 4.04 dd, 1 H, J_1 = 9.9, J_2 = 5.8 (H2); 3.70 s, 3 H (CH_3); 3.00–2.87 m, 1 H (H3A); 2.73–2.59 m, 1 H (H3B). ^{13}C NMR ($CDCl_3$): 171.25, 137.23, 134.37, 117.63, 114.94, 110.71, 110.62, 52.45, 46.38, 33.97. MS, *m/z* (%): 433 ($M^{+\bullet}$, 5), 391 (5), 353 (62), 333 (7), 312 (4), 293 (100), 273 (12), 254 (7), 212 (83), 186

(6), 161 (6), 148 (10), 134 (53), 107 (10), 89 (26), 59 (19). IR ($CDCl_3$), ν_{max}: 3 082, 2 953, 1 736, 1 643, 1 521, 1 436, 1 263.

Methyl 2-(2-phenyloxazol-4-yl)pent-4-enoate. Yield 1.10 g (36%). ^{1}H NMR ($CDCl_3$): 8.05–7.98 m, 2 H (Ar); 7.63 d, J = 0.8 (oxazole); 7.46–7.40 m, 3 H (Ar); 5.86–5.71 m, 1 H (H4); 5.15–5.02 m, 2 H (H5); 3.84–3.78 m, 1 H (H2); 3.73 s, 3 H (CH_3); 2.83–2.66 m, 2 H (H3). ^{13}C NMR ($CDCl_3$): 172.68, 161.45, 139.29, 135.39, 134.50, 130.31, 128.66, 127.35, 126.39, 117.48, 52.13, 43.84, 35.91. MS, *m/z* (%): 257 ($M^{+\bullet}$, 71), 242 (5), 225 (97), 198 (100), 188 (32), 168 (9), 156 (50), 145 (6), 128 (23), 113 (18), 105 (80), 91 (14), 77 (63), 67 (45), 51 (31). IR ($CDCl_3$), ν_{max}: 3 082, 2 954, 1 736, 1 588, 1 555, 1 437, 1 340.

Methyl 2-(2-phenylthiazol-4-yl)pent-4-enoate. Yield 2.62 g (80%). ^{1}H NMR ($CDCl_3$): 7.96–7.91 m, 2 H (Ar); 7.47–7.39 m, 3 H (Ar); 7.14 s, 1 H (thiazole); 5.88–5.73 m, 1 H (H4); 5.16–5.01 m, 2 H (H5); 4.06 dd, 1 H, J_1 = 8.1, J_2 = 7.0 (H2); 3.72 s, 3 H (CH_3); 2.92–2.71 m, 2 H (H3). ^{13}C NMR ($CDCl_3$): 171.36, 168.31, 149.68, 145.84, 133.09, 130.43, 129.00, 126.66, 126.48, 118.90, 77.67, 19.07. MS, *m/z* (%): 272 ($M^{+\bullet}$ – H, 100), 259 (3), 214 (14), 204 (10), 180 (3), 149 (3), 129 (5), 121 (13), 104 (7), 91 (3), 77 (14), 69 (8), 51 (7). IR ($CDCl_3$), ν_{max}: 3 067, 2 953, 1 735, 1 642, 1 512, 1 436, 1 267.

Ethyl 2-[2-(4-methylphenyl)thiazol-4-yl]pent-4-enoate. Yield 3.20 g (89%). ^{1}H NMR ($CDCl_3$): 7.85–7.79 m, 2 H (AA′BB′); 7.25–7.19 m, 2 H (AA′BB′); 7.11 d, 1 H, J = 0.6 (thiazole); 5.89–5.74 m, 1 H (H4); 5.17–5.01 m, 2 H (H5); 4.25–4.13 m, 2 H (CH_2); 4.03 dd, 1 H, J_1 = 8.2, J_2 = 6.7 (H2); 2.90–2.70 m, 2 H (H3); 2.38 s, 3 H (Ar-CH_3); 1.26 t, 3 H, J = 7.1 (CH_3). ^{13}C NMR ($CDCl_3$): 172.44, 167.76, 154.24, 140.12, 135.02, 130.97, 129.49, 126.44, 117.11, 114.23, 60.89, 47.99, 36.65, 21.39, 14.20. MS, *m/z* (%): 301 ($M^{+\bullet}$, 100), 282 (23), 272 (67), 254 (14), 228 (63), 207 (18), 188 (12), 149 (17), 135 (55), 118 (32), 111 (24), 91 (31), 73 (54), 67 (30), 55 (23). IR ($CDCl_3$), ν_{max}: 2 983, 2 925, 1 728, 1 642, 1 504, 1 457, 1 371, 1 262.

Ethyl 2-[2-(4-chlorophenyl)thiazol-4-yl]pent-4-enoate. Yield 2.97 g (77%), m.p. 41–43 °C. ^{1}H NMR ($CDCl_3$): 7.89–7.85 m, 2 H (AA′BB′); 7.41–7.37 m, 2 H (AA′BB′); 7.16 d, 1 H, J = 0.6 (thiazole); 5.88–5.73 m, 1 H (H4); 5.16–5.01 m, 2 H (H5); 4.25–4.13 m, 2 H (CH_2); 4.02 dd, 1 H, J_1 = 8.1, J_2 = 6.8 (H2); 2.90–2.69 m, 2 H (H3); 1.25 t, 3 H, J = 7.1 (CH_3). ^{13}C NMR ($CDCl_3$): 172.30, 166.23, 154.62, 135.83, 134.87, 132.08, 129.05, 127.72, 117.25, 115.12, 60.97, 47.94, 36.59, 14.20. MS, *m/z* (%): 322 ($M^{+\bullet}$, 100), 306 (2), 292 (28), 276 (4), 248 (36), 224 (6), 208 (5), 155 (24), 138 (8), 111 (22), 85 (4), 77 (20), 69 (13), 51 (9). IR ($CDCl_3$), ν_{max}: 3 082, 2 983, 1 729, 1 642, 1 597, 1 495, 1 447, 1 263.

Ethyl 2-[2-(3-bromophenyl)thiazol-4-yl]pent-4-enoate. Yield 3.44 g (78%). ^{1}H NMR ($CDCl_3$): 8.11 t, 1 H, J = 1.8 (Ar2); 7.84 ddd, 1 H, J_1 = 8.0, J_2 = 1.7, J_3 = 1.1 (Ar4); 7.53 ddd, 1 H, J_1 = 8.0, J_2 = 1.9, J_3 = 1.1 (Ar6); 7.29 t, 1 H, J = 8.0 (Ar5); 7.19 d, 1 H, J = 0.6 (thiazole); 5.88–5.73 m, 1 H (H4); 5.16–5.01 m, 2 H (H5); 4.25–4.14 m, 2 H (CH_2); 4.04 dd, 1 H, J_1 = 8.0, J_2 = 6.9 (H2); 2.90–2.70 m, 2 H (H3); 1.26 t, 3 H, J = 7.1 (CH_3). ^{13}C NMR ($CDCl_3$): 172.23, 165.73, 154.62, 135.29, 134.79, 132.79, 130.34, 129.30, 125.13, 122.98, 117.29, 115.52, 60.99, 47.87, 36.60, 14.18. MS, *m/z* (%): 366 ($M^{+\bullet}$, 100), 338 (15), 292 (24), 258 (5), 210 (4), 199 (10), 111 (8), 103 (3), 77 (5), 65 (6), 51 (4). IR ($CDCl_3$), ν_{max}: 3 082, 2 983, 1 730, 1 593, 1 565, 1 508, 1 273.

Ethyl 2-[2-(4-methoxyphenyl)thiazol-4-yl]pent-4-enoate. Yield 3.13 g (82%). ^{1}H NMR ($CDCl_3$): 7.89–7.85 m, 2 H (AA′BB′); 7.07 d, 1 H, J = 0.6 (thiazole); 6.95–6.91 m, 2 H (AA′BB′); 5.89–5.72 m, 1 H (H4); 5.17–4.99 m, 2 H (H5); 4.25–4.14 m, 2 H (CH_2); 4.02 dd, 1 H, J_1 = 8.2, J_2 = 6.9 (H2); 3.85 s, 3 H (OCH_3); 2.89–2.68 m, 2 H (H3); 1.26 t, 3 H, J = 7.0 (CH_3). ^{13}C NMR ($CDCl_3$): 172.43, 167.50, 161.06, 154.03, 135.02, 128.03, 126.50, 117.11, 114.15, 113.79, 60.89, 55.37, 47.92, 36.64, 14.20. MS, *m/z* (%): 317 ($M^{+\bullet}$, 100), 302 (6), 288 (48), 273

(5), 244 (55), 220 (15), 204 (13), 177 (4), 151 (41), 134 (23), 111 (20), 77 (30), 67 (16), 51 (10). IR ($CDCl_3$), ν_{max}: 2 983, 2 840, 1 728, 1 609, 1 505, 1 459, 1 305, 1 254.

Preparation of 2-Hetarylpent-4-enoic Acids. General Procedure

The methyl/ethyl 2-hetarylpent-4-enoate (8 mmol) was dissolved in a mixture of MeOH–H_2O 3 : 1 (40 ml) and aqueous solution of LiOH (57 wt.%; 0.44 g, 10.4 mmol) was added to the solution. After 20 h at ambient temperature, the reaction mixture was concentrated *in vacuo*, diluted with water and acidified with concentrated HCl to pH 4. The mixture was extracted with ethyl acetate (3×), the combined extracts dried over anhydrous Na_2SO_4, and solvent evaporated. The resulting acids were directly used in further steps.

2-(2-Thienyl)pent-4-enoic acid (**1**). Yield 1.45 g (100%). ^{1}H NMR ($CDCl_3$): 7.23 dd, 1 H, J_1 = 5.0, J_2 = 1.4 (Ar5); 7.00 dd, 1 H, J_1 = 5.0, J_2 = 3.3 (Ar4); 6.96 dd, 1 H, J_1 = 3.3, J_2 = 1.4 (Ar3); 5.84–5.68 m, 1 H (H4); 5.18–5.03 m, 2 H (H5); 3.97 t, 1 H, J = 7.7 (H2); 2.90–2.77 m, 1 H (H3A); 2.69–2.56 m, 1 H (H3B).

2-(3-Thienyl)pent-4-enoic acid (**2**). Yield 1.46 g (100%). ^{1}H NMR ($CDCl_3$): 7.30 dd, 1 H, J_1 = 5.0, J_2 = 3.0 (Ar5); 7.19 dd, 1 H, J_1 = 3.0, J_2 = 1.4 (Ar2); 7.09 dd, 1 H, J_1 = 5.0, J_2 = 1.4 (Ar4); 5.83–5.68 m, 1 H (H4); 5.16–5.02 m, 2 H (H5); 3.81 t, 1 H, J = 7.8 (H2); 2.87–2.74 m, 1 H (H3A); 2.62–2.51 m, 1 H (H3B).

2-(2,4,5-Tribromo-3-thienyl)pent-4-enoic acid. Yield 3.27 g (98%), m.p. 74–77 °C. ^{1}H NMR ($CDCl_3$): 5.75–5.59 m, 1 H (H4); 5.08–4.93 m, 2 H (H5); 4.12 dd, 1 H, J_1 = 9.9, J_2 = 5.5 (H2); 2.97–2.86 m, 1 H (H3A); 2.78–2.65 m, 1 H (H3B).

2-(2-Phenyloxazol-4-yl)pent-4-enoic acid. Yield 1.93 g (99%), m.p. 70–73 °C. ^{1}H NMR ($CDCl_3$): 8.06–7.97 m, 2 H (Ar); 7.65 s, 1 H (oxazole); 7.48–7.40 m, 3 H (Ar); 5.88–5.72 m, 1 H (H4); 5.18–5.03 m, 2 H (H5); 3.85 t, 1 H, J = 7.0 (H2); 2.88–2.68 m, 2 H (H3).

2-(2-Phenylthiazol-4-yl)pent-4-enoic acid. Yield 2.01 g (97%), m.p. 69–72 °C. ^{1}H NMR ($CDCl_3$): 7.96–7.89 m, 2 H (Ar); 7.47–7.41 m, 3 H (Ar); 7.15 s, 1 H (thiazole); 5.87–5.72 m, 1 H (H4); 5.15–5.03 m, 2 H (H5); 4.02 t, 1 H, J = 7.3 (H2); 2.95–2.71 m, 2 H (H3).

2-[2-(4-Methylphenyl)thiazol-4-yl]pent-4-enoic acid. Yield 2.19 g (100%), m.p. 54–56 °C. ^{1}H NMR ($CDCl_3$): 7.83–7.77 m, 2 H (AA′BB′); 7.26–7.20 m, 2 H (AA′BB′); 7.11 s, 1 H (thiazole); 5.87–5.71 m, 1 H (H4); 5.15–5.02 m, 2 H (H5); 4.00 t, 1 H, J = 7.3 (H2); 2.92–2.70 m, 2 H (H3); 2.40 s, 3 H (Ar-CH_3).

2-[2-(4-Chlorophenyl)thiazol-4-yl]pent-4-enoic acid. Yield 2.35 g (100%), m.p. 78–79 °C. ^{1}H NMR ($CDCl_3$): 7.88–7.82 m, 2 H (AA′BB′); 7.42–7.37 m, 2 H (AA′BB′); 7.17 s, 1 H (thiazole); 5.86–5.71 m, 1 H (H4); 5.16–5.03 m, 2 H (H5); 4.02 t, 1 H, J = 7.3 (H2); 2.92–2.70 m, 2 H (H3).

2-[2-(3-Bromophenyl)thiazol-4-yl]pent-4-enoic acid. Yield 2.70 g (100%). ^{1}H NMR ($CDCl_3$): 8.08 t, 1 H, J = 1.8 (Ar2); 7.82 ddd, 1 H, J_1 = 8.0, J_2 = 1.7, J_3 = 1.1 (Ar4); 7.54 ddd, 1 H, J_1 = 8.0, J_2 = 1.9, J_3 = 1.1 (Ar6); 7.30 t, 1 H, J = 8.0 (Ar5); 7.20 s, 1 H (thiazole); 5.86–5.71 m, 1 H (H4); 5.16–5.03 m, 2 H (H5); 4.03 t, 1 H, J = 7.4 (H2); 2.93–2.71 m, 2 H (H3).

2-[2-(4-Methoxyphenyl)thiazol-4-yl]pent-4-enoic acid. Yield 2.24 g (97%). ^{1}H NMR ($CDCl_3$): 7.88–7.81 m, 2 H (AA′BB′); 7.06 s, 1 H (thiazole); 6.97–6.92 m, 2 H (AA′BB′); 5.87–5.70 m, 1 H (H4); 5.15–5.02 m, 2 H (H5); 3.98 t, 1 H, J = 7.3 (H2); 3.85 s, 3 H (OCH_3); 2.92–2.70 m, 2 H (H3).

Preparation of 3-Hetaryl-5-methyltetrahydrofuran-2-ones **12**, **15a**–**15c**, **15e** and **18**. General Procedure

A 2-hetarylpent-4-enoic acid (8 mmol) was treated with concentrated H_2SO_4 (5 ml) at 0 °C for 20 min and the solution was subsequently poured into brine. The mixture was neutralized with saturated aqueous Na_2CO_3 to pH 8 and extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated. The crude products were purified by column chromatography (petroleum ether–ethyl acetate 9 : 1) to afford the saturated diastereomeric lactones that were directly used in further steps.

5-Methyl-3-(2,4,5-tribromo-3-thienyl)tetrahydrofuran-2-one (**12**). Yield 2.33 g (69%), m.p. 119–122 °C. ^{1}H NMR ($CDCl_3$): diastereomer *A*: 5.01–4.98 m, 1 H (H5); 4.27 dd, 1 H, J_1 = 10.8, J_2 = 10.3 (H3); 2.72–2.49 m, 1 H (H4A); 2.33–2.09 m, 1 H (H4B); 1.48 d, 3 H, *J* = 6.6 (CH_3); diastereomer *B*: 4.76–4.63 m, 1 H (H5); 4.25 dd, 1 H, J_1 = 12.6, J_2 = 9.3 (H3); 2.72–2.49 m, 1 H (H4A); 2.33–2.09 m, 1 H (H4B); 1.55 d, 3 H, *J* = 6.0 (CH_3). ^{13}C NMR ($CDCl_3$): diastereomer *A*: 174.01, 134.63, 116.51, 112.77, 111.30, 75.54, 41.10, 33.92, 21.52; diastereomer *B*: 174.30, 135.23, 116.82, 113.07, 111.88, 75.15, 43.78, 35.55, 20.69. MS (mixture of diastereomers), *m/z* (%): 418 ($M^{+\bullet}$ – H, 34), 376 (21), 361 (6), 348 (11), 335 (5), 295 (62), 280 (45), 267 (12), 255 (8), 214 (100), 186 (9), 159 (5), 135 (60), 107 (11), 93 (20), 81 (10), 69 (19), 51 (9). IR ($CDCl_3$) (mixture of diastereomers), ν_{max}: 2 984, 2 933, 1 770, 1 524, 1 456, 1 387, 1 342.

5-Methyl-3-(2-phenyloxazol-4-yl)tetrahydrofuran-2-one (**18**). Yield 1.79 g (92%), m.p. 77–80 °C. ^{1}H NMR ($CDCl_3$): diastereomer *A*: 8.05–7.98 m, 2 H (Ar); 7.69 d, 1 H, *J* = 0.8 (oxazole); 7.48–7.41 m, 3 H (Ar); 4.99–4.88 m, 1 H (H5); 3.97 dd, 1 H, J_1 = 12.1, J_2 = 8.8 (H3); 2.79–2.69 m, 1 H (H4A); 2.39–2.30 m, 1 H (H4B); 1.48 d, 3 H, *J* = 6.3 (CH_3); diastereomer *B*: 8.05–7.98 m, 2 H (Ar); 7.78 d, 1 H, *J* = 1.1 (oxazole); 7.48–7.41 m, 3 H (Ar); 4.75–4.62 m, 1 H (H5); 3.97 dd, 1 H, J_1 = 12.1, J_2 = 8.8 (H3); 2.91–2.80 m, 1 H (H4A); 2.28–2.14 m, 1 H (H4B); 1.52 d, 3 H, *J* = 6.3 (CH_3). ^{13}C NMR ($CDCl_3$): diastereomer *A*: 175.81, 162.12, 137.54, 135.72, 130.54, 128.72, 127.18, 76.17, 38.59, 35.60, 20.90; diastereomer *B*: 175.39, 161.90, 137.12, 135.36, 130.48, 128.72, 126.41, 75.85, 40.19, 36.98, 20.76. MS (mixture of diastereomers), *m/z* (%): 243 ($M^{+\bullet}$, 26), 228 (2), 207 (2), 199 (16), 184 (4), 171 (5), 156 (4), 143 (5), 128 (4), 115 (5), 105 (100), 89 (4), 77 (13), 67 (6), 51 (9). IR ($CDCl_3$) (mixture of diastereomers), ν_{max}: 2 985, 1 769, 1 555, 1 488, 1 449, 1 342.

5-Methyl-3-(2-phenylthiazol-4-yl)tetrahydrofuran-2-one (**15a**). Yield 1.80 g (87%), m.p. 86–88 °C. ^{1}H NMR ($CDCl_3$): diastereomer *A*: 7.96–7.89 m, 2 H (Ar); 7.46–7.39 m, 3 H (Ar); 7.22 d, 1 H, *J* = 0.6 (thiazole); 5.08–4.94 m, 1 H (H5); 4.12 dd, 1 H, J_1 = 11.8, J_2 = 8.8 (H3); 2.95–2.79 m, 1 H (H4A); 2.44–2.28 m, 1 H (H4B); 1.49 d, 3 H, *J* = 6.3 (CH_3); diastereomer *B*: 7.96–7.89 m, 2 H (Ar); 7.46–7.39 m, 3 H (Ar); 7.33 d, 1 H, *J* = 0.8 (thiazole); 4.77–4.60 m, 1 H (H5); 4.12 dd, 1 H, J_1 = 11.8, J_2 = 8.8 (H3); 2.95–2.79 m, 1 H (H4A); 2.44–2.28 m, 1 H (H4B); 1.53 d, 3 H, *J* = 6.1 (CH_3). ^{13}C NMR ($CDCl_3$): diastereomer *A*: 176.14, 168.64, 152.20, 133.31, 130.15, 128.87, 126.48, 115.56, 76.35, 43.28, 36.61, 20.96; diastereomer *B*: 175.74, 168.24, 151.84, 133.41, 130.06, 128.87, 126.50, 115.94, 75.60, 44.20, 37.59, 20.87. MS (mixture of diastereomers), *m/z* (%): 259 ($M^{+\bullet}$, 100), 231 (60), 215 (80), 200 (26), 188 (17), 175 (6), 153 (2), 136 (3), 121 (97), 112 (43), 104 (40), 97 (35), 84 (11), 77 (30), 69 (18), 51 (22). IR ($CDCl_3$) (mixture of diastereomers), ν_{max}: 3 116, 2 984, 1 767, 1 515, 1 461, 1 387.

3-[2-(4-Chlorophenyl)thiazol-4-yl]-5-methyltetrahydrofuran-2-one (**15b**). Yield 1.74 g (74%), m.p. 131–132 °C. ^{1}H NMR ($CDCl_3$): diastereomer *A*: 7.89–7.82 m, 2 H (AA′BB′); 7.42–7.36 m, 2 H (AA′BB′); 7.24 d, 1 H, *J* = 0.6 (thiazole); 5.06–4.94 m, 1 H (H5); 4.11 dd, 1 H, J_1 = 11.8, J_2 =

8.8 (H3); 2.93–2.77 m, 1 H (H4A); 2.42–2.28 m, 1 H (H4B); 1.49 d, 3 H, *J* = 6.3 (CH_3); diastereomer *B*: 7.89–7.82 m, 2 H (AA′BB′); 7.42–7.36 m, 2 H (AA′BB′); 7.34 d, 1 H, *J* = 0.6 (thiazole); 4.76–4.62 m, 1 H (H5); 4.11 dd, 1 H, J_1 = 11.8, J_2 = 8.8 (H3); 2.93–2.77 m, 1 H (H4A); 2.42–2.28 m, 1 H (H4B); 1.53 d, 3 H, *J* = 6.3 (CH_3). ^{13}C NMR ($CDCl_3$): diastereomer *A*: 176.00, 167.27, 152.42, 136.07, 131.80, 129.08, 127.70, 115.91, 76.31, 43.18, 36.54, 20.98; diastereomer *B*: 175.63, 166.88, 152.05, 135.97, 131.91, 129.08, 127.70, 116.29, 75.61, 44.19, 37.58, 20.86. MS (mixture of diastereomers), *m/z* (%): 293 ($M^{+\bullet}$ – H, 100), 278 (4), 265 (17), 248 (61), 234 (24), 222 (27), 180 (4), 155 (83), 138 (24), 112 (66), 97 (52), 79 (25), 69 (25), 58 (34). IR ($CDCl_3$) (mixture of diastereomers), ν_{max}: 2 984, 1 767, 1 597, 1 498, 1 454, 1 388.

5-Methyl-3-[2-(4-methylphenyl)thiazol-4-yl]tetrahydrofuran-2-one (**15c**). Yield 1.87 g (85%), m.p. 108–111 °C. ^{1}H NMR ($CDCl_3$): diastereomer *A*: 7.84–7.78 m, 2 H (AA′BB′); 7.25–7.20 m, 2 H (AA′BB′); 7.18 d, 1 H, *J* = 0.8 (thiazole); 5.07–4.94 m, 1 H (H5); 4.11 dd, 1 H, J_1 = 11.7, J_2 = 8.8 (H3); 2.93–2.77 m, 1 H (H4A); 2.43–2.28 m, 1 H (H4B); 2.39 s, 3 H (Ar-CH_3); 1.49 d, 3 H, *J* = 6.3 (CH_3); diastereomer *B*: 7.84–7.78 m, 2 H (AA′BB′); 7.29 d, 1 H, *J* = 0.6 (thiazole); 7.25–7.20 m, 2 H (AA′BB′); 4.75–4.62 m, 1 H (H5); 4.11 dd, 1 H, J_1 = 11.7, J_2 = 8.8 (H3); 2.93–2.77 m, 1 H (H4A); 2.43–2.28 m, 1 H (H4B); 2.39 s, 3 H (Ar-CH_3); 1.53 d, 3 H, *J* = 6.0 (CH_3). ^{13}C NMR ($CDCl_3$): diastereomer *A*: 176.19, 168.82, 152.01, 140.41, 130.82, 129.54, 126.42, 115.03, 76.34, 43.31, 36.65, 21.40, 20.96; diastereomer *B*: 175.79, 168.42, 151.66, 140.30, 130.72, 129.54, 126.42, 115.42, 75.59, 44.21, 37.62, 21.40, 20.87. MS (mixture of diastereomers), *m/z* (%): 273 ($M^{+\bullet}$, 100), 258 (3), 245 (5), 229 (56), 214 (22), 202 (21), 189 (6), 147 (2), 135 (98), 118 (37), 112 (32), 97 (29), 91 (18), 79 (15), 69 (16), 58 (23). IR ($CDCl_3$) (mixture of diastereomers), ν_{max}: 2 984, 1 768, 1 511, 1 457, 1 388, 1 346.

3-[2-(3-Bromophenyl)thiazol-4-yl]-5-methyltetrahydrofuran-2-one (**15e**). Yield 2.66 g (98%), m.p. 109–110 °C. ^{1}H NMR ($CDCl_3$): diastereomer *A*: 8.09 t, 1 H, *J* = 1.8 (Ar2); 7.82 ddd, J_1 = 8.0, J_2 = 1.7, J_3 = 1.1 (Ar4); 7.53 ddd, J_1 = 8.0, J_2 = 1.9, J_3 = 1.1 (Ar6); 7.29 t, *J* = 8.0 (Ar5); 7.27 d overlapped, 1 H (thiazole); 5.06–4.94 m, 1 H (H5); 4.12 dd, 1 H, J_1 = 11.8, J_2 = 8.8 (H3); 2.94–2.79 m, 1 H (H4A); 2.43–2.29 m, 1 H (H4B); 1.50 d, 3 H, *J* = 6.3 (CH_3); diastereomer *B*: 8.10 t, 1 H, *J* = 1.8 (Ar2); 7.82 ddd, J_1 = 8.0, J_2 = 1.7, J_3 = 1.1 (Ar4); 7.53 ddd, J_1 = 8.0, J_2 = 1.9, J_3 = 1.1 (Ar6); 7.29 t, *J* = 8.0 (Ar5); 7.37 d, 1 H, *J* = 0.6 (thiazole); 4.76–4.63 m, 1 H (H5); 4.12 dd, 1 H, J_1 = 11.8, J_2 = 8.8 (H3); 2.94–2.79 m, 1 H (H4A); 2.43–2.29 m, 1 H (H4B); 1.54 d, 3 H, *J* = 6.3 (CH_3). ^{13}C NMR ($CDCl_3$): diastereomer *A*: 175.96, 166.73, 152.49, 135.21, 132.97, 130.38, 129.24, 125.11, 122.99, 116.29, 76.32, 43.14, 36.48, 20.99; diastereomer *B*: 175.58, 166.33, 152.11, 135.21, 132.87, 130.38, 129.20, 125.11, 122.99, 116.65, 75.63, 44.18, 37.58, 20.84. MS (mixture of diastereomers), *m/z* (%): 338 ($M^{+\bullet}$, 100), 311 (10), 295 (79), 280 (22), 266 (22), 212 (4), 199 (45), 182 (7), 154 (3), 112 (71), 97 (54), 79 (26), 69 (23), 58 (31). IR ($CDCl_3$) (mixture of diastereomers), ν_{max}: 2 985, 1 768, 1 565, 1 457, 1 388, 1 346.

Preparation of 3-Hetaryl-5-methyltetrahydrofuran-2-ones **3**, **4** and **15d**. General Procedure

A solution of HBr in AcOH (30 wt.%, 10 ml) was slowly added to a 2-hetarylpent-4-enoic acid (10 mmol) under argon. The solution was stirred for 6 h and the solvent removed *in vacuo*. The residue was redissolved in methanol (15 ml) and Na_2CO_3 (2.12 g, 20 mmol) was added to the solution. After stirring for 45 min, the solution was diluted with brine and the resulting mixture extracted with ethyl acetate. The organic phase was dried over anhydrous

Na_2SO_4 and the solvent evaporated. The products were purified by column chromatography (petroleum ether–ethyl acetate 9 : 1).

5-Methyl-3-(2-thienyl)tetrahydrofuran-2-one (**3**). Yield 1.35 g (74%). ^{1}H NMR ($CDCl_3$): diastereomer *A*: 7.28–7.23 m, 1 H (Ar5); 7.05–6.97 m, 2 H (Ar3,4); 4.89–4.77 m, 1 H (H5); 4.19–4.10 m, 1 H (H3); 2.67–2.57 m, 1 H (H4A); 2.17–2.04 m, 1 H (H4B); 1.47 d, 3 H, *J* = 6.3 (CH_3); diastereomer *B*: 7.28–7.23 m, 1 H (Ar5); 7.05–6.97 m, 2 H (Ar3,4); 4.70–4.58 m, 1 H (H5); 4.19–4.10 m, 1 H (H3); 2.93–2.83 m, 1 H (H4A); 2.45–2.34 m, 1 H (H4B); 1.50 d, 3 H, *J* = 6.3 (CH_3). ^{13}C NMR ($CDCl_3$): diastereomer *A*: 175.44, 138.44, 126.97, 125.60, 124.90, 75.41, 42.84, 39.62, 20.94; diastereomer *B*: 175.14, 138.02, 126.80, 125.39, 124.90, 75.08, 41.24, 38.17, 20.84. MS (mixture of diastereomers), *m/z* (%): 183 ($M^{+\bullet}$ + H, 21), 138 (71), 123 (100), 110 (13), 97 (11), 79 (7), 65 (7), 58 (5), 51 (6). IR ($CDCl_3$) (mixture of diastereomers), ν_{max}: 2 984, 1 772, 1 453, 1 388, 1 344.

5-Methyl-3-(3-thienyl)tetrahydrofuran-2-one (**4**). Yield 1.50 g (82%). ^{1}H NMR ($CDCl_3$): diastereomer *A*: 7.34 dd, 1 H, J_1 = 5.0, J_2 = 3.0 (Ar5); 7.21–7.19 m, 1 H (Ar2); 7.11–7.06 m (Ar4); 4.84–4.72 m, 1 H (H5); 4.04–3.93 m, 1 H (H3); 2.85–2.75 m, 1 H (H4A); 2.09–1.97 m, 1 H (H4B); 1.46 d, 3 H, *J* = 6.3 (CH_3); diastereomer *B*: 7.34 dd, 1 H, J_1 = 5.0, J_2 = 3.0 (Ar5); 7.21–7.19 m, 1 H (Ar2); 7.11–7.06 m (Ar4); 4.69–4.57 m, 1 H (H5); 4.04–3.93 m, 1 H (H3); 2.61–2.51 m, 1 H (H4A); 2.38–2.28 m, 1 H (H4B); 1.49 d, 3 H, *J* = 6.3 (CH_3). ^{13}C NMR ($CDCl_3$): diastereomer *A*: 176.31, 136.27, 126.76, 126.39, 121.97, 75.23, 41.13, 37.04, 20.86; diastereomer *B*: 175.98, 136.14, 126.62, 126.01, 121.59, 74.97, 42.67, 38.64, 20.76. MS (mixture of diastereomers), *m/z* (%): 183 ($M^{+\bullet}$ + H, 100), 137 (35), 123 (55), 110 (8), 97 (5), 65 (3), 53 (3). IR ($CDCl_3$) (mixture of diastereomers), ν_{max}: 2 983, 1 768, 1 456, 1 387, 1 344.

3-[2-(4-Methoxyphenyl)thiazol-4-yl]-5-methyltetrahydrofuran-2-one (**15d**). Yield 2.51 g (87%), m.p. 94–95 °C. ^{1}H NMR ($CDCl_3$): diastereomer *A*: 7.89–7.82 m, 2 H (AA′BB′); 7.14 d, 1 H, *J* = 0.6 (thiazole); 6.96–6.91 m, 2 H (AA′BB′); 5.06–4.94 m, 1 H (H5); 4.10 dd, 1 H, J_1 = 12.6, J_2 = 8.0 (H3); 3.85 s, 3 H (OCH_3); 2.92–2.76 m, 1 H (H4A); 2.42–2.26 m, 1 H (H4B); 1.48 d, 3 H, *J* = 6.3 (CH_3); diastereomer *B*: 7.89–7.82 m, 2 H (AA′BB′); 7.24 d, 1 H, *J* = 0.6 (thiazole); 6.96–6.91 m, 2 H (AA′BB′); 4.74–4.61 m, 1 H (H5); 4.10 dd, 1 H, J_1 = 12.6, J_2 = 8.0 (H3); 3.85 s, 3 H (OCH_3); 2.92–2.76 m, 1 H (H4A); 2.42–2.26 m, 1 H (H4B); 1.53 d, 3 H, *J* = 6.3 (CH_3). ^{13}C NMR ($CDCl_3$): diastereomer *A*: 176.21, 168.52, 161.17, 151.90, 127.99, 126.34, 114.55, 114.16, 76.34, 55.37, 43.31, 36.66, 20.96; diastereomer *B*: 175.80, 168.13, 161.11, 151.55, 127.98, 126.44, 114.95, 114.16, 75.57, 55.37, 44.21, 37.61, 20.88. MS (mixture of diastereomers), *m/z* (%): 289 ($M^{+\bullet}$, 100), 261 (5), 244 (26), 230 (9), 218 (10), 201 (2), 186 (2), 173 (3), 151 (57), 134 (8), 112 (7), 97 (10), 90 (3), 77 (5), 69 (5), 58 (8). IR ($CDCl_3$) (mixture of diastereomers), ν_{max}: 2 982, 2 937, 1 767, 1 609, 1 514, 1 460, 1 254.

3-(5-Bromo-2-thienyl)-5-methyltetrahydrofuran-2-one (**9**)

N-Bromosuccinimide (0.75 g, 4.20 mmol) was added to a solution of lactone **3** (0.73 g, 4.00 mmol) in a mixture of $CHCl_3$–AcOH 1 : 1 (20 ml). After 48 h at ambient temperature, the reaction mixture was diluted with ethyl acetate (50 ml), washed with 5% aqueous NaOH, brine, saturated aqueous $Na_2S_2O_3$, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (petroleum ether–ethyl acetate 95 : 5). Yield 0.90 g (86%), m.p. 65–68 °C. ^{1}H NMR ($CDCl_3$): diastereomer *A*: 6.93 d, 1 H, *J* = 3.6 (Ar); 6.76 d, 1 H, *J* = 3.6 (Ar); 4.87–4.75 m, 1 H (H5); 4.04 dd, 1 H, J_1 = 12.6, J_2 = 8.5 (H3); 2.64–2.52 m, 1 H (H4A); 2.43–2.33 m, 1 H (H4B); 1.46 d, 3 H, *J* = 6.3 (CH_3); diastereomer *B*: 6.94 d, 1 H, *J* = 3.8 (Ar); 6.77 d, 1 H, *J* = 3.8 (Ar);

4.70–4.57 m, 1 H (H5); 4.04 dd, 1 H, J_1 = 12.4, J_2 = 8.5 (H3); 2.91–2.79 m, 1 H (H4A); 2.12–1.97 m, 1 H (H4B); 1.49 d, 3 H, J = 6.3 (CH_3). ^{13}C NMR ($CDCl_3$): diastereomer *A*: 174.78, 139.78, 129.61, 125.74, 111.55, 75.22, 41.28, 37.45, 20.91; diastereomer *B*: 174.57, 139.40, 129.42, 125.89, 111.69, 75.40, 43.05, 38.99, 20.78. MS (mixture of diastereomers), *m/z* (%): 260 ($M^{+\bullet}$ – H, 46), 218 (52), 203 (37), 188 (11), 175 (5), 137 (68), 122 (100), 109 (23), 95 (11), 77 (4), 69 (15), 59 (7), 51 (7). IR ($CDCl_3$) (mixture of diastereomers), ν_{max}: 2 989, 2 877, 1 753, 1 466, 1 387, 1 356, 1 207.

3-(2,5-Dibromo-3-thienyl)-5-methyltetrahydrofuran-2-one (**7**)

N-Bromosuccinimide (1.78 g, 10.00 mmol) was added to a solution of **4** (0.73 g, 4.00 mmol) in a mixture of $CHCl_3$–AcOH 1 : 1 (20 ml). After 24 h at ambient temperature, the reaction mixture was diluted with ethyl acetate (50 ml), washed with 5% aqueous NaOH, brine, saturated aqueous $Na_2S_2O_3$, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (petroleum ether–ethyl acetate 95 : 5). Yield 1.25 g (92%). ^{1}H NMR ($CDCl_3$): diastereomer *A*: 6.82 s, 1 H (Ar); 4.87–4.76 m, 1 H (H5); 4.04 t, 1 H, J = 9.2 (H3); 2.41–2.32 m, 2 H (H4); 1.47 d, 3 H, J = 6.0 (CH_3); diastereomer *B*: 6.86 s, 1 H (Ar); 4.70–4.58 m, 1 H (H5); 4.02 dd, 1 H, J_1 = 12.6, J_2 = 8.5 (H3); 2.83–2.72 m, 1 H (H4A); 1.91–1.77 m, 1 H (H4B); 1.49 d, 3 H, J = 6.3 (CH_3). ^{13}C NMR ($CDCl_3$): diastereomer *A*: 175.29, 136.85, 128.97, 111.83, 110.97, 75.19, 40.48, 36.55, 20.80; diastereomer *B*: 174.96, 137.20, 129.19, 111.94, 111.14, 75.39, 42.94, 38.57, 21.07. MS (mixture of diastereomers), *m/z* (%): 340 ($M^{+\bullet}$, 71), 296 (19), 281 (6), 215 (20), 200 (21), 136 (100), 121 (18), 108 (9), 93 (6), 63 (5). IR ($CDCl_3$) (mixture of diastereomers), ν_{max}: 2 983, 2 932, 1 774, 1 388, 1 343, 1 268.

Preparation of 3-Hetaryl-5-methyl-2,5-dihydrofuran-2-ones. General Procedure

A solution of 1.6 M butyllithium in hexanes (2.07 ml, 3.3 mmol) was added to a solution of diisopropylamine (0.44 ml, 3.15 mmol) in dry THF (5 ml) at 0 °C under argon. After 10 min at 0 °C, the LDA solution was cooled to –60 °C and a solution of a saturated lactone (3 mmol) in THF (3 ml) was added. After maintaining the mixture at –60 °C for 30 min, a solution of phenylselanyl chloride (0.862 g, 4.5 mmol) in THF (2 ml) was added. The resulting mixture was slowly allowed to warm to room temperature (over 2 h), diluted with ethyl acetate (20 ml), washed with saturated aqueous NH_4Cl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude phenylselanyl derivative was rapidly purified by column chromatography (petroleum ether–ether 98 : 2), redissolved in $CHCl_3$ (10 ml), and MCPBA (57 wt.%, 1.36 g, 4.5 mmol) was added to the solution at 0 °C. After stirring at ambient temperature for 45 min, the mixture was diluted with ethyl acetate (50 ml), washed with 5% aqueous Na_2CO_3, dried over anhydrous Na_2SO_4, and the solvent evaporated. Products were purified by column chromatography (petroleum ether–ethyl acetate 9 : 1).

5-Methyl-3-(2-thienyl)-2,5-dihydrofuran-2-one (**5**). Yield 0.14 g (26%), m.p. 28–29 °C. ^{1}H NMR ($CDCl_3$): 7.55 dd, 1 H, J_1 = 3.6, J_2 = 1.1 (Ar4); 7.38 d, 1 H, J = 1.9 (H4); 7.36 dd overlapped, 1 H, J_2 = 1.1 (Ar2); 7.08 dd, 1 H, J_1 = 4.9, J_2 = 3.6 (Ar3); 5.17 qd, 1 H, J_1 = 6.9, J_2 = 1.9 (H5); 1.50 d, 3 H, J = 6.9 (CH_3). ^{13}C NMR ($CDCl_3$): 170.62, 145.03, 131.28, 127.64, 127.34, 127.06, 126.12, 77.37, 19.27. MS, *m/z* (%): 180 ($M^{+\bullet}$, 83), 165 (3), 152 (12), 137 (24), 123 (7), 109 (100), 91 (4), 77 (5), 65 (11), 51 (7). IR ($CDCl_3$), ν_{max}: 2 987, 2 935, 1 754, 1 640, 1 328, 1 318. For $C_9H_8O_2S$ calculated: 59.98% C, 4.47% H, 17.79% S; found: 59.98% C, 4.50% H, 17.91% S.

5-Methyl-3-(3-thienyl)-2,5-dihydrofuran-2-one (**6**). Yield 0.17 g (31%). ^{1}H NMR ($CDCl_3$): 8.19–8.16 m, 1 H (Ar); 7.39 d, 1 H, J = 1.9 (H4); 7.37–7.35 m, 2 H (Ar); 5.15 qd, 1 H, J_1 = 6.9, J_2 = 1.9 (H5); 1.50 d, 3 H, J = 6.9 (CH_3). ^{13}C NMR ($CDCl_3$): 171.53, 146.21, 130.04, 126.77, 126.05, 125.68, 125.20, 77.07, 19.29. MS, *m/z* (%): 180 ($M^{+\bullet}$, 89), 152 (8), 137 (27), 123 (6), 109 (100), 82 (4), 65 (13), 51 (7). IR ($CDCl_3$), ν_{max}: 2 986, 2 934, 1 757, 1 644, 1 319.

3-(2,5-Dibromo-3-thienyl)-5-methyl-2,5-dihydrofuran-2-one (**8**). Yield 0.35 g (34%), m.p. 74–76 °C. ^{1}H NMR ($CDCl_3$): 8.00 d, 1 H, J = 1.8 (H4); 7.66 s, 1 H (Ar); 5.19 qd, 1 H, J_1 = 6.9, J_2 = 1.8 (H5); 1.53 d, 3 H, J = 6.9 (CH_3). ^{13}C NMR ($CDCl_3$): 171.26, 151.68, 130.41, 130.15, 125.01, 111.71, 111.55, 77.37, 19.00. MS, *m/z* (%): 338 ($M^{+\bullet}$, 100), 295 (12), 267 (56), 228 (5), 186 (8), 134 (5), 121 (8), 106 (11), 93 (6), 63 (13), 50 (5). IR ($CDCl_3$), ν_{max}: 3 111, 2 987, 1 756, 1 532, 1 419, 1 324. For $C_9H_6Br_2O_2S$ calculated: 31.98% C, 1.79% H, 9.49% S; found: 32.16% C, 1.39% H, 9.32% S.

5-Methyl-3-(5-bromo-2-thienyl)-2,5-dihydrofuran-2-one (**10**). Yield 0.41 g (53%), m.p. 84–85 °C. ^{1}H NMR ($CDCl_3$): 7.45 d, 1 H, J = 4.1 (Ar); 7.33 d, 1 H, J = 1.9 (H4); 7.03 d, 1 H, J = 4.1 (Ar); 5.16 qd, 1 H, J_1 = 6.9, J_2 = 1.9 (H5); 1.50 d, 3 H, J = 6.9 (CH_3). ^{13}C NMR ($CDCl_3$): 170.52, 145.08, 132.83, 130.49, 127.66, 125.52, 114.98, 77.67, 19.05. MS, *m/z* (%): 260 ($M^{+\bullet}$ + H, 100), 232 (23), 217 (41), 201 (7), 189 (96), 151 (12), 134 (7), 122 (8), 108 (35), 91 (10), 82 (12), 69 (24), 63 (37), 50 (14). IR ($CDCl_3$), ν_{max}: 2 988, 2 935, 1 755, 1 637, 1 423, 1 321. For $C_9H_7BrO_2S$ calculated: 41.72% C, 2.72% H, 12.37% S; found: 41.96% C, 2.73% H, 12.12% S.

5-Methyl-3-(2,4,5-tribromo-3-thienyl)-2,5-dihydrofuran-2-one (**13**). Yield 0.37 g (30%), m.p. 138–140 °C. ^{1}H NMR ($CDCl_3$): 7.53 d, 1 H, J = 1.5 (H4); 5.28 qd, 1 H, J_1 = 6.9, J_2 = 1.5 (H5); 1.57 d, 3 H, J = 6.9 (CH_3). ^{13}C NMR ($CDCl_3$): 169.49, 157.23, 131.47, 127.51, 114.75, 112.61, 111.25, 78.01, 19.12. MS, *m/z* (%): 418 ($M^{+\bullet}$ + H, 100), 373 (16), 347 (56), 309 (10), 265 (18), 211 (13), 184 (12), 133 (11), 121 (14), 106 (16), 89 (17), 77 (13), 61 (17). IR ($CDCl_3$), ν_{max}: 2 985, 2 935, 1 762, 1 509, 1 376, 1 318. For $C_9H_5Br_3O_2S$ calculated: 25.93% C, 1.21% H, 9.49% S; found: 26.15% C, 1.15% H, 9.33% S.

5-Methyl-3-(2-phenylthiazol-4-yl)-2,5-dihydrofuran-2-one (**16a**). Yield 0.18 g (23%), m.p. 80–82 °C. ^{1}H NMR ($CDCl_3$): 8.24 s, 1 H (thiazole); 8.03–7.96 m, 3 H (2H Ar + H4), 7.50–7.43 m, 3 H (Ar); 5.24 qd, 1 H, J_1 = 6.9, J_2 = 1.4 (H5); 1.55 d, 3 H, J = 6.9 (CH_3). ^{13}C NMR ($CDCl_3$): 171.36, 168.31, 149.68, 145.84, 133.09, 130.43, 129.00, 126.66, 126.48, 118.90, 77.67, 19.07. MS, *m/z* (%): 257 ($M^{+\bullet}$, 100), 240 (1), 229 (7), 214 (17), 201 (5), 186 (83), 152 (1), 134 (1), 121 (2), 104 (6), 97 (5), 83 (21), 65 (7), 51 (11). IR ($CDCl_3$), ν_{max}: 3 125, 2 934, 1 755, 1 484, 1 359, 1 319. For $C_{14}H_{11}NO_2S$ calculated: 65.35% C, 4.31% H, 5.44% N, 12.46% S; found: 65.15% C, 4.37% H, 5.37% N, 12.17% S.

3-[2-(4-Chlorophenyl)thiazol-4-yl]-5-methyl-2,5-dihydrofuran-2-one (**16b**). Yield 0.25 g (29%), m.p. 183–185 °C. ^{1}H NMR ($CDCl_3$): 8.24 s, 1 H (thiazole); 7.94–7.89 m, 3 H (2H AA′BB′ + H4); 7.46–7.40 m, 2 H (AA′BB′); 5.24 qd, 1 H, J_1 = 6.9, J_2 = 1.7 (H5); 1.54 d, 3 H, J = 6.9 (CH_3). ^{13}C NMR ($CDCl_3$): 171.25, 166.90, 149.84, 145.99, 136.38, 131.56, 129.22, 127.83, 126.36, 119.08, 77.68, 19.04. MS, *m/z* (%): 291 ($M^{+\bullet}$ – H, 100), 263 (8), 248 (18), 235 (4), 220 (57), 185 (2), 137 (3), 111 (6), 97 (7), 83 (29), 75 (18), 65 (19), 51 (18). IR ($CDCl_3$), ν_{max}: 3 124, 2 986, 1 755, 1 483, 1 463, 1 359, 1 319. For $C_{14}H_{10}ClNO_2S$ calculated: 57.64% C, 3.45% H, 4.80% N, 10.99% S; found: 57.33% C, 3.69% H, 4.54% N, 10.70% S.

5-Methyl-3-[2-(4-methylphenyl)thiazol-4-yl]-2,5-dihydrofuran-2-one (**16c**). Yield 0.25 g (30%), m.p. 128–130 °C. ^{1}H NMR ($CDCl_3$): 8.20 s, 1 H (thiazole); 7.93 d, 1 H, J = 1.7 (H4); 7.90–7.84 m, 2 H (AA′BB′); 7.28–7.23 m, 2 H (AA′BB′); 5.23 qd, 1 H, J_1 = 6.9, J_2 = 1.7 (H5); 2.40 s, 3 H (CH_3-Ar); 1.54 d, 3 H, J = 6.9 (CH_3). ^{13}C NMR ($CDCl_3$): 171.37, 168.45, 149.55, 145.67, 140.74, 130.45, 129.65, 126.55, 126.49, 118.46, 77.64, 21.43, 19.07. MS, *m/z* (%):

271 ($M^{+\bullet}$, 97), 243 (6), 228 (14), 215 (6), 200 (100), 167 (1), 135 (2), 116 (6), 97 (5), 91 (10), 83 (19), 65 (10), 51 (6). IR ($CDCl_3$), ν_{max}: 3 125, 2 987, 1 755, 1 485, 1 360, 1 319. For $C_{15}H_{13}NO_2S$ calculated: 66.40% C, 4.83% H, 5.16% N, 11.82% S; found: 66.21% C, 4.92% H, 5.08% N, 11.55% S.

3-[2-(4-Methoxyphenyl)thiazol-4-yl]-5-methyl-2,5-dihydrofuran-2-one (**16d**). Yield 0.22 g (26%), m.p. 109–110 °C. ^{1}H NMR ($CDCl_3$): 8.16 s, 1 H (thiazole); 7.94–7.89 m, 3 H (2H AA′BB′ + H4); 6.99–6.93 m, 2 H (AA′BB′); 5.23 qd, 1 H, J_1 = 6.9, J_2 = 1.7 (H5); 3.86 s, 3 H (CH_3O); 1.54 d, 3 H, J = 6.9 (CH_3). ^{13}C NMR ($CDCl_3$): 171.38, 168.13, 161.39, 149.44, 145.56, 128.15, 126.49, 126.02, 118.07, 114.28, 77.62, 55.40, 19.07. MS, *m/z* (%): 287 ($M^{+\bullet}$, 100), 259 (10), 244 (10), 231 (5), 216 (70), 201 (5), 173 (4), 134 (5), 103 (4), 90 (4), 83 (13), 63 (6), 51 (5). IR ($CDCl_3$), ν_{max}: 3 125, 2 937, 1 755, 1 609, 1 523, 1 466, 1 360, 1 319. For $C_{15}H_{13}NO_3S$ calculated: 62.70% C, 4.56% H, 4.87% N, 11.16% S; found: 62.55% C, 4.75% H, 4.79% N, 10.92% S.

3-[2-(3-Bromophenyl)thiazol-4-yl]-5-methyl-2,5-dihydrofuran-2-one (**16e**). Yield 0.24 g (24%), m.p. 121–123 °C. ^{1}H NMR ($CDCl_3$): 8.26 s, 1 H (thiazole); 8.17 t, 1 H, J = 1.9 (Ar2); 7.96 d, 1 H, J = 1.9 (H4); 7.86 ddd, 1 H, J_1 = 8.0, J_2 = 1.8, J_3 = 1.1 (Ar4); 7.57 ddd, 1 H, J_1 = 8.0, J_2 = 1.8, J_3 = 1.1 (Ar6); 7.32 t, 1 H, J = 8.0 (Ar5); 5.25 qd, 1 H, J_1 = 6.9, J_2 = 1.9 (H5); 1.55 d, 3 H, J = 6.9 (CH_3). ^{13}C NMR ($CDCl_3$): 171.21, 166.33, 150.01, 146.02, 134.84, 133.19, 130.47, 129.35, 126.27, 125.24, 123.11, 119.32, 77.70, 19.01. MS, *m/z* (%): 337 ($M^{+\bullet}$ + H, 100), 307 (7), 294 (21), 279 (6), 266 (91), 185 (6), 102 (11), 83 (34), 65 (12), 51 (12). IR ($CDCl_3$), ν_{max}: 3 124, 2 987, 1 756, 1 565, 1 482, 1 359, 1 320. For $C_{14}H_{10}BrNO_2S$ calculated: 50.02% C, 3.00% H, 4.17% N, 9.54% S; found: 51.77% C, 3.49% H, 4.04% N, 9.20% S.

3-(1-Benzamido-2-oxoethylidene)-5-methyltetrahydrofuran-2-one (**21**). Yield 0.21 g (27%). ^{1}H NMR ($CDCl_3$): 10.80 s, 1 H (-COH); 8.55 s, 1 H (-NH-); 7.92–7.85 m, 2 H (Ar); 7.65–7.58 m, 1 H (Ar); 7.56–7.47 m, 2 H (Ar); 4.85–4.73 m, 1 H (H5); 3.22 dd, 1 H, J_1 = 19.5, J_2 = 6.9 (H4); 2.92 dd, 1 H, J_1 = 19.5, J_2 = 6.0 (H4); 1.50 d, 3 H, J = 6.3 (CH_3). ^{13}C NMR ($CDCl_3$): 186.66, 169.10, 164.11, 138.03, 133.06, 132.76, 128.99, 128.64, 127.76, 75.38, 39.00, 21.86. MS, *m/z* (%): 260 ($M^{+\bullet}$ + H, 7), 241 (16), 230 (5), 172 (2), 126 (7), 105 (100), 77 (26), 51 (12). IR ($CDCl_3$), ν_{max}: 3 362, 3 026, 2 931, 1 744, 1 698, 1 675, 1 501, 1 479, 1 281.

Methyl Propiolate

The compound was prepared and purified according to a literature procedure[12]. Yield 4.82 g (44%), b.p. 98–102 °C.

Methyl 4-Hydroxyhex-2-ynoate

The compound was prepared according to the procedure for the preparation of methyl 4-hydroxypent-2-ynoate[13]. Yield 3.55 g (96%). All spectra were consistent with those previously published[24].

Methyl 4-[(Triethylsilyl)oxy]hex-2-ynoate

Chloro(triethyl)silane (4.08 ml, 24.33 mmol) was added to a solution of methyl 4-hydroxyhex-2-ynoate (3.14 g, 22.12 mmol) and triethylamine (3.39 ml, 24.33 mmol) in CH_2Cl_2 (100 ml) at 0 °C. After 20 h at 0 °C, the solvent was removed *in vacuo*. The residue was diluted with petroleum ether and the crystals of triethylammonium chloride removed by filtration. Petroleum ether was evaporated and the crude product was purified by column

chromatography (petroleum ether). Yield 4.31 g (76%). ^{1}H NMR ($CDCl_3$): 4.40 t, 1 H, *J* = 6.3 (H4); 3.76 s, 3 H (OCH_3); 1.80–1.68 m, 2 H (H5); 0.99 t, 3 H, *J* = 7.4 (H6); 0.97 t, 9 H, *J* = 7.7 (CH_3); 0.69–0.60 m, 6 H (Si-CH_2). ^{13}C NMR ($CDCl_3$): 153.93, 88.89, 75.56, 63.52, 52.66, 31.03, 9.37, 6.66, 4.60. MS, *m/z* (%): 256 ($M^{+\bullet}$, 13), 227 (90), 219 (100), 197 (86), 169 (32), 143 (7), 125 (36), 115 (52), 93 (31), 82 (5), 65 (25), 53 (15). IR ($CDCl_3$), ν_{max}: 2 957, 2 938, 2 878, 1 713, 1 458, 1 436, 1 346, 1 258.

Methyl (*E*)-2-(Tributylstannyl)-4-[(triethylsilyl)oxy]hex-2-enoate (**24**)

The compound was obtained by the procedure of Rossi *et al.*[14]. Yield 6.61 g (81%). ^{1}H NMR ($CDCl_3$): 6.01 d, 1 H, *J* = 8.0 (H3); 4.75–4.64 m, 1 H (H4); 3.68 s, 3 H (OCH_3); 1.57–1.41 m, 8 H (CH_2 + H5); 1.36–1.23 m, 6 H (CH_2); 0.99–0.83 m, 27 H (Sn-CH_2 + CH_3 + H6); 0.64–0.53 m, 6 H (Si-CH_2). ^{13}C NMR ($CDCl_3$): 171.11, 156.61, 133.92, 72.19, 51.21, 30.66, 28.85, 27.24, 13.67, 10.26, 9.70, 6.79, 4.71. MS, *m/z* (%): 547 ($M^{+\bullet}$, 2), 519 (100), 486 (30), 464 (13), 396 (9), 338 (8), 273 (2), 250 (4), 228 (1), 176 (1), 96 (1). IR ($CDCl_3$), ν_{max}: 2 958, 2 932, 2 874, 2 854, 1 698, 1 458, 1 433.

5-Ethyl-3-(tributylstannyl)-2,5-dihydrofuran-2-one (**25**)

Dowex 50 (H^+ form) (5.0 g) was added to a solution of methyl (*E*)-2-(tributylstannyl)-4-[(triethylsilyl)oxy]hex-2-enoate (5.07 g, 9.25 mmol) in a mixture of MeOH–H_2O 5 : 1 (650 ml) and the mixture was stirred at 50 °C for 3 h. Dowex was then filtered off and the solvent removed *in vacuo*. The residue was purified by column chromatography (petroleum ether–ether 95 : 5). Yield 3.74 g (93%). ^{1}H NMR ($CDCl_3$): 7.43 d, 1 H, *J* = 1.4 (H4); 4.99–4.92 m, 1 H (H5); 1.87–1.59 m, 2 H (CH_2); 1.58–1.44 m, 6 H (CH_2); 1.39–1.23 m, 6 H (CH_2); 1.13–1.03 m, 6 H (Sn-CH_2); 0.97 t, 3 H (CH_3); 0.88 t, 9 H (CH_3). ^{13}C NMR ($CDCl_3$): 177.95, 165.13, 135.51, 85.99, 28.90, 27.14, 26.47, 13.64, 9.64, 8.97. MS, *m/z* (%): 400 ($M^{+\bullet}$ + H, 100), 371 (19), 333 (25), 249 (31), 214 (14), 192 (50), 96 (78), 68 (30), 53 (30). IR ($CDCl_3$), ν_{max}: 2 959, 2 926, 2 872, 2 853, 1 735, 1 580, 1 464, 1 331.

2-Iodofuran (**26**)

The compound was prepared according to a literature procedure[11]. Yield 0.91 g (63%).

Coupling of Compounds **25** and **26**

A solution of **26** (0.29 g, 1.5 mmol) in NMP (1 ml) was added to a suspension of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.02 g, 0.02 mmol), triphenylarsine (0.05 g, 0.16 mmol) and CuI (0.02 g, 0.08 mmol) in NMP (1 ml) under argon. The reaction mixture was warmed to 50 °C and a solution of **25** (0.40 g, 1 mmol) in NMP (1.5 ml) was added. The reaction temperature was maintained at 50 °C for 6 h and a saturated aqueous solution of KF was then added. After stirring for 30 min, the mixture was diluted with ethyl acetate (50 ml). The resulting suspension was filtered off, the filtrate washed with water, brine, and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue subjected to column chromatography (petroleum ether–ethyl acetate 95 : 5).

5-Ethyl-3-(2-furyl)-2,5-dihydrofuran-2-one (**27**). Yield 0.07 g (38%). ^{1}H NMR ($CDCl_3$): 7.48 d, 1 H, *J* = 1.8 (Ar5); 7.42 d, 1 H, *J* = 1.8 (H4); 7.13 dd, 1 H, J_1 = 3.3, J_2 = 0.6 (Ar3); 6.48 dd, 1 H, J_1 = 3.3, J_2 = 1.8 (Ar4); 5.08–5.01 m, 1 H (H5); 1.95–1.70 m, 2 H (CH_2); 1.04 t, 3 H, *J* = 7.5

(CH_3). ^{13}C NMR ($CDCl_3$): 170.12, 145.28, 143.52, 142.80, 123.37, 111.71, 111.02, 82.59, 26.75, 9.13. MS, *m/z* (%): 178 ($M^{+\bullet}$, 100), 161 (5), 150 (47), 133 (4), 121 (70), 105 (4), 93 (90), 77 (8), 65 (43), 57 (33), 51 (10). IR ($CDCl_3$), ν_{max}: 2 973, 2 936, 1 759, 1622, 1 462, 1 338.

5-Ethyl-3-(5-ethyl-2-oxo-2,5-dihydro-3-furyl)-2,5-dihydrofuran-2-one (**28**). Yield 0.06 g (56%), m.p. 86–88 °C. ^1H NMR ($CDCl_3$): 8.25 d, 2 H, *J* = 1.1 (H4); 5.10–5.01 m, 2 H (H5); 1.96–1.69 m, 4 H (CH_2); 1.04 t, 6 H, *J* = 7.4 (CH_3). ^{13}C NMR ($CDCl_3$): 171.38, 151.81, 121.89, 83.15, 26.37, 9.16. MS, *m/z* (%): 223 ($M^{+\bullet}$ + H, 100), 204 (88), 193 (9), 176 (21), 161 (12), 147 (12), 133 (11), 119 (18), 107 (10), 91 (32), 77 (17), 65 (13), 57 (86), 51 (21). IR ($CDCl_3$), ν_{max}: 2 974, 2 940, 1 758, 1 589, 1 462, 1 338. For $C_{12}H_{14}O_4$ calculated: 64.85% C, 6.35% H; found: 64.75% C, 6.42% H.

Biological Activity Evaluation

In vitro antifungal activities of the compounds, ketoconazole (Janssen–Cilag) and racemic incrustoporine, were evaluated on a panel of one ATCC (*Candida albicans* ATCC 44859) and seven clinical isolates of yeasts (*C. krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/I, *Trichosporon beigelii* 1188) and filamentous fungi (*Aspergillus fumigatus* 231, *Absidia corymbifera* 272, *Trichophyton mentagrophytes* 445) from the collection of fungal strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. All the isolates were maintained on Sabouraud dextrose agar prior to being tested.

Minimum inhibitory concentrations (MICs) were determined by the microdilution format of the NCCLS M27-A guidelines[10]. Dimethyl sulfoxide (100%) served as a diluent for all compounds; the final concentration did not exceed 2%. RPMI 1640 (Sevapharma, Prague) medium supplemented with L-glutamine and buffered with 0.165 M morpholinepropanesulfonic acid (Serva) to pH 7.0 by 10 M NaOH was used as the test medium. The wells of the microdilution tray contained 100 µl of the RPMI 1640 medium with two-fold serial dilutions of the compounds (1 000 to 0.24 µmol/l for the new compounds) and 100 µl of inoculum suspension. Fungal inoculum in RPMI 1640 was prepared to give a final concentration of $5 \cdot 10^3 \pm 0.2$ cfu ml^{-1}. The trays were incubated at 35 °C and MICs were read visually for filamentous fungi and photometrically for yeasts as an optical density (OD) at 540 nm after 24 and 48 h. The MIC values for the dermatophytic strain (*T. mentagrophytes*) were determined after 72 and 120 h. The MICs, defined as 80% inhibition of the growth of control, were determined twice and in duplicate. The deviations from the usually obtained values were no higher than the nearest concentration value up and down the dilution scale.

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REFERENCES

1. Zapf S., Anke T., Sterner O.: *Acta Chem. Scand.* **1995**, *49*, 233.
2. Yajima A., Mori K.: *Liebigs Ann.* **1996**, 1091.
3. Pour M., Špulák M., Balšánek V., Kuneš J., Buchta V., Waisser K.: *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1893.

4. Pour M., Špulák M., Buchta V., Kubanová P., Vopršalová M., Wsól V., Fáková H., Koudelka P., Pourová H., Schiller R.: *J. Med. Chem.* **2001**, *44*, 2701.
5. Jackson P. M., Moody Ch.: *J. Chem. Soc., Perkin Trans. 1* **1990**, *11*, 2909.
6. Corral C., Lissavetzky J.: *Synthesis* **1984**, *10*, 847 .
7. Waisser K., Čeladník M.: *Cesk. Farm.* **1982**, *31*, 129.
8. Brown D. J., Cook A. H., Heilbron I.: *J. Chem. Soc.* **1949**, S106.
9. Meguro K., Tawada H., Sugiyama Y., Fujita T., Kawamatsu Y.: *Chem. Pharm. Bull.* **1986**, *36*, 2840.
10. Koprowski M., Krawczyk E., Skowronska A., *et al.*: *Tetrahedron* **2001**, *57* 1105.
11. Carman C. S., Koser G. F.: *J. Org. Chem.* **1983**, *48*, 2534.
12. House H. O., Roelofs W. L., Trost B. M.: *J. Org. Chem.* **1966**, *31*, 646.
13. Lautens M., Fillion E.: *J. Org. Chem.* **1997**, *62*, 4418.
14. Rossi R., Carpita A., Cossi P.: *Tetrahedron* **1992**, *48*, 8801.
15. Hollingworth G. J., Perkins G., Sweeney J.: *J. Chem. Soc., Perkin Trans. 1* **1996**, *16*, 1913.
16. Pour M., Negishi E.: *Tetrahedron Lett.* **1997**, *38*, 525.
17. Liebeskind L. S., Riesinger S. W.: *J. Org. Chem.* **1993**, *58*, 408.
18. Farina V., Kapadia S., Kirshnan B., Wang C., Liebeskind L. S.: *J. Org. Chem.* **1994**, *59*, 5905.
19. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeasts: Approved standard; NCCLS Document M27-A. NCCLS, Villanova (PA) 1997.
20. Malamas M. S., Carlson R. P., Grimes D., Howell R., Glaser K.: *J. Med. Chem.* **1996**, *39*, 237.
21. Papadopoulos E.: *J. Org. Chem.* **1976**, *41*, 962.
22. Lee A. L., Mackay D., Manery E. L.: *Can. J. Chem.* **1970**, *48*, 3554.
23. Rooney C. S., Randall W. C., Streeter K. B., Ziegler C., Cragoe E. J.: *J. Med. Chem.* **1983**, *26*, 700 .
24. Hirao K., Yamashita A., Ando A., Hamada T., Yonemitsu O.: *J. Chem. Soc., Perkin Trans. 1* **1988**, 2913.