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Synthesis, characterization and antiproliferative activity of β-aryl-δ-iodo-γ-lactones

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ABSTRACT

A convenient pathway for the synthesis of new of β-aryl-δ-iodo-γ-lactones is described. The synthetic route led to both *cis* and *trans* isomers which were separated by column chromatography or crystallization. The structures of synthesized compounds were confirmed by spectroscopic methods: IR, NMR and HR-MS. For lactones with naphthyl ring (**6e** and **7e**) the crystal structures were also obtained. The lactones were screened for biological evaluation against cancer line HL-60 (human promyelocytic leukemia). The tests showed that the presence of substituent at the benzene ring does not significantly affect the antiproliferative activity of the compound.

1. Introduction

Compounds with a lactone ring are widespread in nature [1]. Their diversity is related to numerous functions in both animal and vegetable kingdoms. For instance, they are responsible for aromas and tastes of flowers and fruits [2] and also function as insects antifeedants [3,4]. In the world of animals lactones are the components of insect pheromones [5]. Furthermore, a great deal of compounds containing lactone moiety with characteristic flavor and fragrance can be found in food products [6] as well as in alcoholic beverages [7].

Naturally occurring lactones display a wide range of biological activities [8,9]. For instance, the lactones isolated from plant *Goniothalamus* show cytotoxic activity against human liver cancer cell lines (HepG2, HepG2-R) [10].

Taking into consideration the fact that synthetic lactones have also interesting biological properties as antifeedant [11], antimicrobial [12] or anticancer [13], the subject of our research was the synthesis of new lactone compounds and evaluation of their antiproliferative activities.

2. Results and discussion

2.1. Synthesis

Several methods can be applied in the synthesis of lactones with aromatic substituents [14]. Aromatic aldehydes are relatively cheap substrates in these syntheses and they can easily be transformed to lactones starting from aldol condensation with acetone [15].

In this work, we present another synthetic pathway using commercially available aromatic aldehydes **1a**–**e** as the starting materials. The synthetic route for the synthesis of β-aryl-δ-iodo-γ-lactones is outlined in Scheme 1. In the first step aldehydes **1a**–**e** were converted into known α,β-unsaturated methyl esters **2a**–**e** by Doebner condensation with monomethyl malonate [16]. Spectroscopic data of the compounds obtained were in full agreement with literature data [17]. The coupling constant between olefinic protons (J = 15.9 Hz) confirmed the E configuration of double bond. The yields of the products ranged from 42% to 94%. Selective reduction of the ester group in compounds **2a**–**e** using lithium borohydride ($LiBH_4$) in diethyl ether afforded known [18] allylic alcohols **3a**–**e** with the retention of E configuration of double bond. The alcohols were obtained in yields 74–90%.

The Johnson–Claisen rearrangement of allylic alcohols **3a**–**e** led to four new (**4a**,**b**,**d**,**e**) and one known (**4c**) γ,δ-unsaturated ethyl esters [19]. The strong IR absorption band (1719 cm^{-1} for **4a**,

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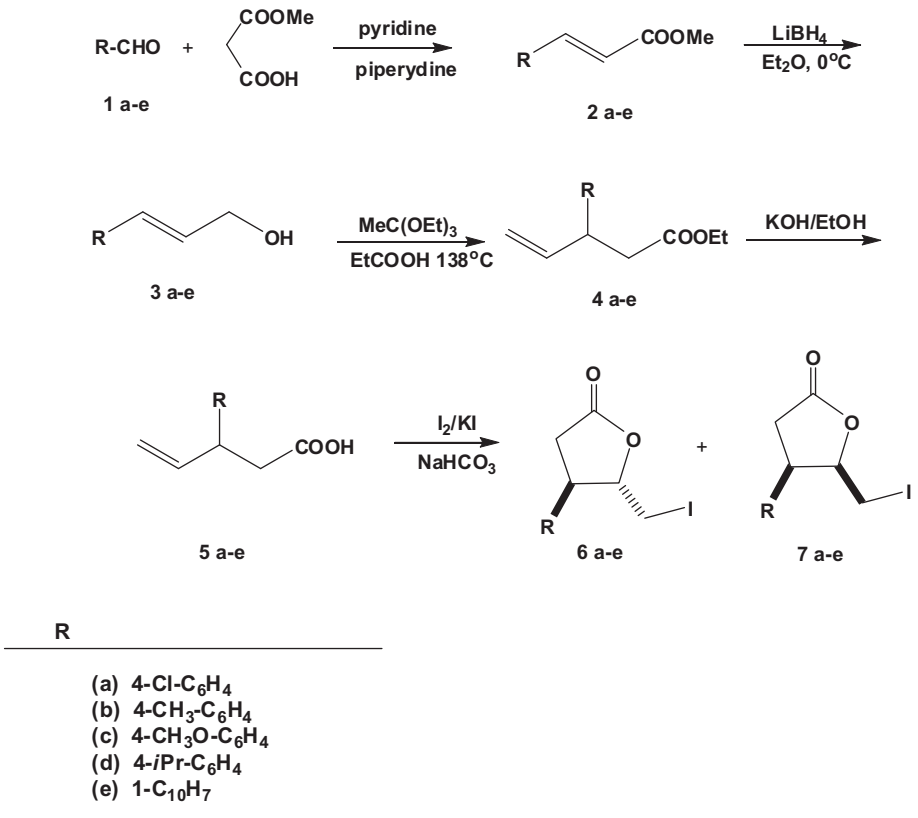

Scheme 1. Five-step synthesis of diastereoisomeric β-aryl-δ-iodo-γ-lactones **6a**–**e** and **7a**–**e**.

1718 cm^{-1} for **4b**, 1736 for **4d** and 1732 cm^{-1} for **4e**) typical for the stretching vibrations of the C=O bond in ester group, as well as characteristic signals from the ethyl group (triplet at 1.18 ppm and quartet at the range 4.08–4.11 ppm) confirmed the structure of the products. Subsequent *hydrolysis of the esters with* ethanolic KOH solution gave high yields pure carboxylic acids **5a**–**e**. While acids **5a**–**c** were previously described in the literature [20], compounds **5d**–**e** were new ones. The confirmation of the presence of free carboxyl group were two bands: one broad band in the range of 2830–3036 cm^{-1} from stretching vibrations of O—H bond and the stretching vibrations band of C=O bond at 1712 cm^{-1}. No signals from the ethyl group were present in the ^1H NMR spectra.

The final step of the synthesis was the iodolactonization of γ,δ-unsaturated acids **5a**–**e** carried out in the presence of I_2 in KI in a two-phase system: *ethyl ether/NaHCO$_3$ solution*. In these alkaline conditions, the mixtures of diastereoisomeric γ-iodolactones: *trans* (**6a**–**e**) and *cis* (**7a**–**e**) were formed.

In all cases, the *cis* isomers were the major ones making up 63–72% of the product mixtures (Table 1). They were characterized by lower value of R_f and lower solubility in solvents compared to the *trans* isomers. After iodolactonization of acids **5a** and **5d**, the mixtures of lactones were separated by column chromatography in the hexane–ethyl acetate as an eluent. In case of the reaction of acid **5e** having naphthyl ring, the lactones precipitated directly from the reaction mixture during heating, therefore, ethyl acetate was used for the extraction of the products as a replacement for diethyl ether and the separation was conducted using methylene chloride. The diastereoisomers of iodolactones obtained from acids containing *p*-methylphenyl and *p*-methoxyphenyl ring (**6b**–**c** and **7b**–**c**) had the same value of retention factors in all solvents tested. We were able to separate these mixtures by applying the difference in solubility of both isomers. The pure *cis* isomers of lactones (**7b** and **7c**) precipitated from hexane–ethyl acetate (5:1) mixture after 24 h cooling. After filtration of the *cis* isomer of lactone with *p*-methyl substituted phenyl ring (**7b**), the filtrate contained pure *trans* isomer (**6b**). In the case of mixture of lactones with *p*-methoxyphenyl ring our attempts to isolate pure *trans* isomer failed. The filtrate contained the mixture of both *cis* and *trans* isomers in ratio 53:47 on the basis of ^1H NMR analysis.

Iodolactones **6**–**7a** with chlorine substituent were previously described in literature [21]. The structures of the new lactones **6**–**7b**–**e** were elucidated by detailed spectroscopic analysis and additionally for both isomers of 4-(α-naphthyl)-5-iodomethyltetrahydrofuran-2-one (**6**–**7e**) by X-ray diffraction studies. Crystal data and other parameters related to data collection are summarized in Table 2.

The following crystal structures have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 849589 and 849590.

Both isomers of lactone bearing naphthyl ring crystallize in the monoclinic *Pn* and *P2$_1$/c* space groups, respectively, with one molecule in the asymmetric unit. The setting of hydrogen atoms H-3 and H-4 with respect to the lactone ring is the main difference between both isomers. In the case of bond lengths in lactone ring, the difference is only for C4—C5 bond, which is 1.556(3) Å for the *trans*

Table 1
The composition (%) of product mixtures after iodolactonisation of acids **5a**–**e** (according to GC analysis).

Substrate	Products	
	trans δ-Iodo-γ-lactones **6a**–**e**	*cis*-δ-Iodo-γ-lactones **7a**–**e**
5a	33.3	66.7
5b	27.5	72.5
5c	28.3	71.7
5d	36.5	63.5
5e	30.0	70.0

Table 2
Experimental details of the crystallographic analysis for lactones **6e** and **7e**.

Parameter	*trans*-4-(α-Naphthyl)-5-iodomethyltetrahydrofuran-2-one (**6e**)	*cis*-4-(α-Naphthyl)-5-iodomethyltetrahydrofuran-2-one (**7e**)
Crystal data		
Empirical formula	$C_{15}H_{13}IO_2$	$C_{15}H_{13}IO_2$
M_r	352.15	352.15
Crystal system, space group	Monoclinic, *Pn*	Monoclinic, $P2_1/c$
Temperature (K)	100	100
a, *b*, *c* (Å)	4.7978(3), 10.4518(7), 12.5179(9)	10.278(1), 10.957(1), 11.369(1)
β (°)	97.690(4)	100.897(2)
V (Å^3)	622.07(7)	1257.3(2)
Z	2	4
Radiation type	MoKα	MoKα
μ (mm^{-1})	2.56	2.54
Crystal size (mm)	0.20 × 0.20 × 0.02	0.20 × 0.10 × 0.10
Data collection		
Diffractometer	Kappa ApexII Ultra CCD diffractometer	Kappa ApexII Ultra CCD diffractometer
Absorption correction	Multi-scan *SADABS2008*/1 – Bruker Nonius area detector scaling and absorption correction	Multi-scan *SADABS2008*/1 – Bruker Nonius area detector scaling and absorption correction
T_{min}, T_{max}	0.628, 0.951	0.631, 0.786
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	12,530, 2861, 2803	17,677, 2388, 2242
R_{int}	0.023	0.042
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.014, 0.034, 1.10	0.020, 0.050, 1.07
No. of reflections	2861	2388
No. of parameters	163	163
No. of restraints	2	0
H-atom treatment	H-atom parameters constrained	H-atom parameters constrained
Δ⟩max, Δ⟩min (eÅ^{-3})	0.50, −0.21	0.46, −0.32

Computer programs: Bruker *SMART*, Bruker *SAINT*, *SHELXS97* (Sheldrick, 1990), *SHELXL97* (Sheldrick, 1997), *WinGX*, Mercury, Bruker *SHELXTL*.

isomer **6e** and 1.564(3) for the *cis* isomer (**7e**). The bend of the lactone ring is bigger for the *cis* isomer **7e**, for which the O1—C2—C3—C4 torsion angle is 22.9(3)°. For the *trans* isomer **6e** the equivalent torsion angle is −14.4(3)°. In the crystal lattice of the *trans* isomer **6e** molecules interact by weak interactions e.g. weak C—H···O hydrogen bonds, C—H···π and I···π interactions (Fig. 1). The lengths of weak C8′—H8′···O2#2 and C6—H6···O2#2 hydrogen bonds is 3.384(4) Å and 3.266(3) Å respectively (for symmetry codes see the caption of Fig. 1). The C—H···O interactions occur also between the lacton ring O1 oxygen atom and the H4 #3 hydrogen atom from the neighboring molecule [3.401(3) Å]. Molecules connected by the above interactions form molecular layers connected by short I···π interactions. The distance between I1 and the C5′#1 atom in the phenyl ring is 3.508(2) Å. A search of Cambridge Structural Database (CSD) for such interactions returns 15 hits defined by the following condition: $R < 5\%$, only organic (CSD version 5.32, November 2010). The I···π contact distances obtained for these hits are between 3.492 Å and 3.673 Å with the average value 3.564 Å.

Molecules of the *cis* isomer **7e** form dimers which are connected by two hydrogen atoms forming the 12-atom rings with the inversion center at its center (Fig. 2; for the definition of symmetry operators see the caption). The length of the C—H···O interaction between O2···C6#3 is 3.506(3) Å. Another interaction of this kind also occurs between O2 and C4′#2 with the length 3.465(3) Å. The molecules also forms layers connected by weak hydrogen and halogen bonds (I1···I1#1). The contact distance between the iodine atoms is 3.5657(4) Å. Interactions within the layer are more

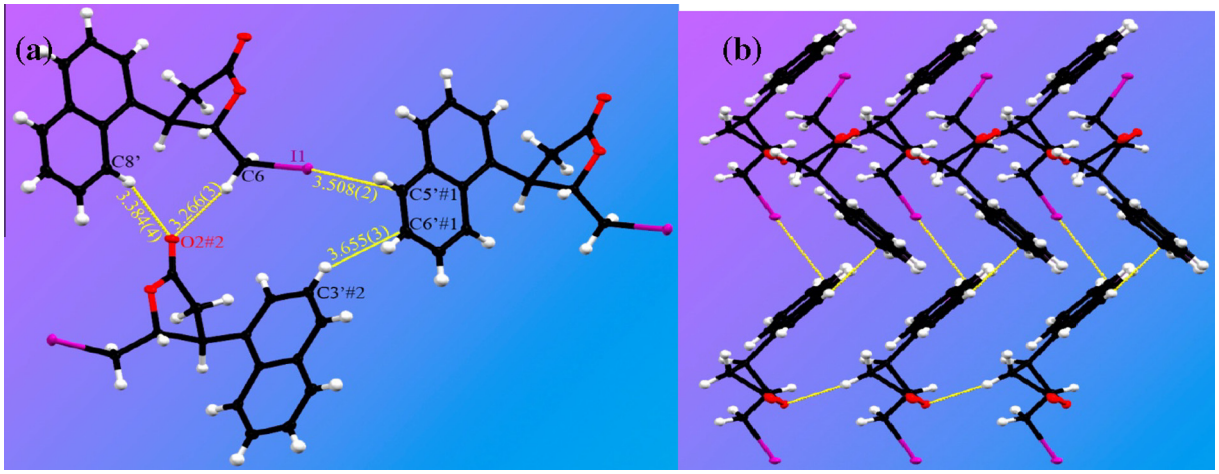

Fig. 1. (a) Visualization of interactions in the crystal lattice of the *trans* isomer **6e** with labeled atoms and symmetry codes; #1 = (*x*, *y* − 1, *z*); #2 = (*x* − ½, 1 − *y*, ½ + *z*); #3 = (1 + *x*, *y*, *z*); #4 = (½ + *x*, 2 − *y*, *z* − ½) and (b) packing of the *trans* isomer **6e** structure along the *Z*-axis.

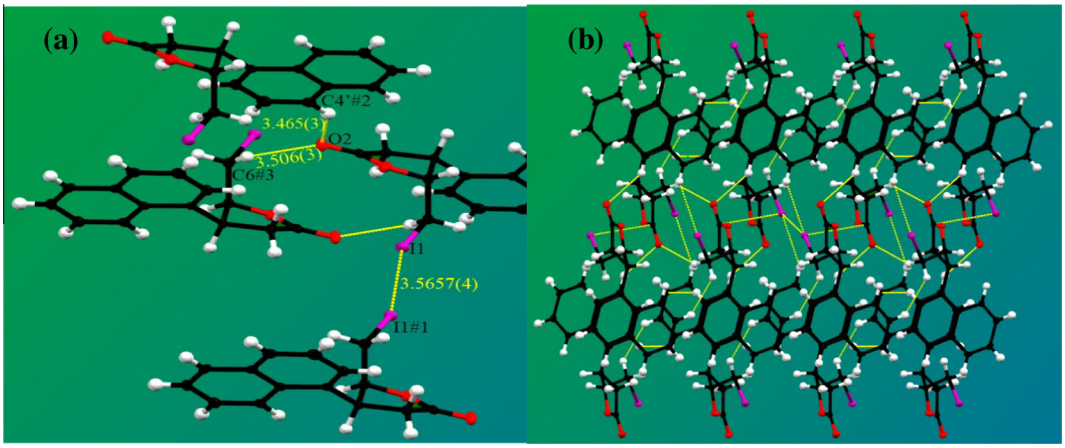

Fig. 2. (a) Molecular structure and interaction in the crystal lattice in the *cis* isomer **7e** structure with labeled atoms forming interactions and their symmetry codes; #1 = (1 − *x*, −*y*, −*z*); #2 = (−1 − *x*, −*y*, −*z*); #3 = (1 − *x*, 1 − *y*, −*z*); #4 = (2 − *x*, 1 − *y*, 1 − *z*) and (b) packing of the *cis* isomer **7e** structure along the *Y*-axis.

hydrophobic with the predominant role of the π···π stacking. The shortest distance between the phenyl rings is 3.577(3) Å (C10′···C8′#4).

The analysis of the ^{1}H NMR spectra of both iodolactonization products shows the differences in chemical shifts of the protons in the methylene group CH_2—I. In both NMR spectra, the diastereotopic protons CH_2—I give ABX system in which two doublets of doublets at 3.39 ppm and 3.55 ppm for the isomer *trans* **6e** and at 2.75 ppm and 2.79 ppm for the isomer *cis* **7e** are observed. The signals of these protons observed in the spectrum of the *trans* isomer **6e** are shifted downfield by $\Delta\delta$ = 0.64 ppm and $\Delta\delta$ = 0.79 ppm, respectively.

The characteristic differences have been also noted in the chemical shifts and multiplicities of H-3 and H-4 protons. The signal of the H-3 proton in the case of *trans* isomer **6e** appeared at 4.35 ppm as triplets of doublets whereas for the *cis* isomer **7e** this signal was shifted downfield by 0.43 ppm and its shape was close to quartet. Proton H-4 gave doublet of triplets at 4.67 ppm in case of *trans* isomer **6e**, while the signal from this proton in the spectrum of the *cis* isomer **7e** appeared as triplet of doublets at 5.25 ppm.

The reason for various multiplicity of the signals discussed are the values of dihedral angles between the corresponding bonds which results in different coupling of the corresponding protons. The chemical shift differences between the protons described above are caused by different location of the naphthalene ring relative to the substituent linked to C-5 in both diastereoisomers. In the case of lactone **7e**, opposite to its *trans* isomer **6e**, the protons of the CH_2—I group are located in the region of shielding cone of the aromatic ring and their signals are shifted upfield. In turn, in case of the *trans* isomer **6e**, the H-3 and H-4 protons experience a significant shielding effect due to the ring current of the aromatic π electrons. As a result, the absorption of these protons *occurs in the higher field* compared to the spectrum of the *cis* isomer. The

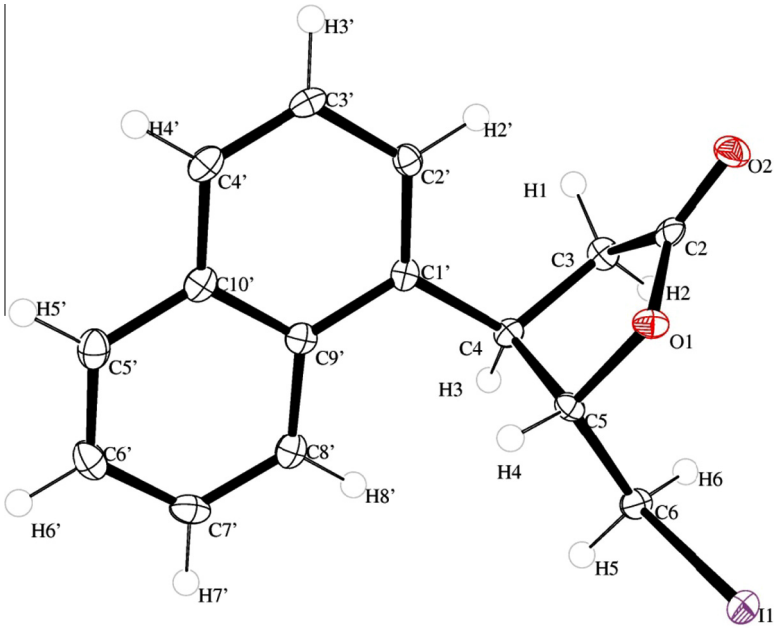

Fig. 3. The crystal structure of the *trans*-4-(α-naphthyl)-5-iodomethyltetrahydrofuran-2-one (**6e**) with the atom numbering scheme.

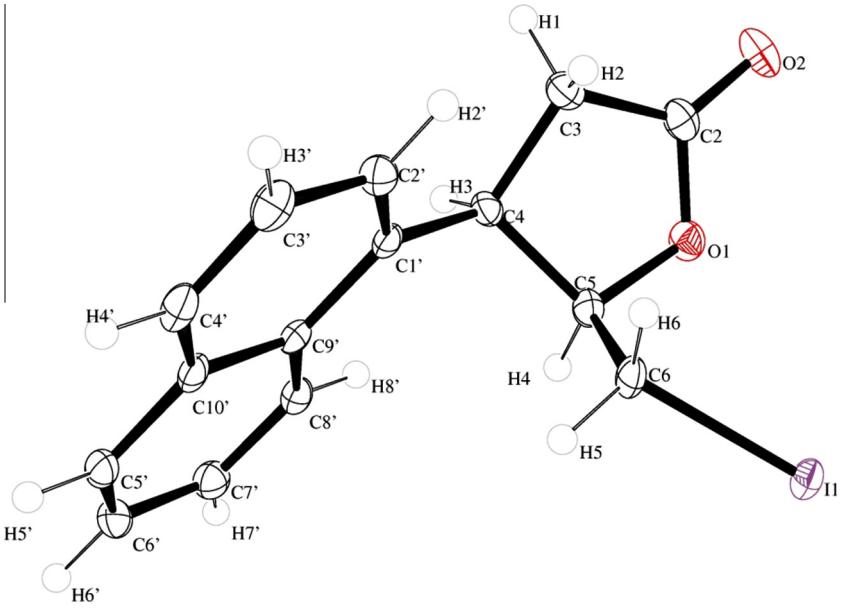

Fig. 4. The crystal structure of *cis*-4-(α-naphthyl)-5-iodomethyltetrahydrofuran-2-one (**7e**) with the atom numbering scheme.

location of aromatic ring in both diastereoisomers is illustrated by crystal structures obtained for lactones **6e** and **7e** (Figs. 3 and 4).

The comparative analysis of the spectra **6e** and **7e** with the spectra of other isolated products let us to identify the lactones **6a**–**d** and **7a**–**d** as *trans* or *cis* isomers, respectively.

2.2. Antiproliferative activity

The synthesized β-aryl-δ-iodo-γ-lactones were subjected to antiproliferative activity bioassays towards human promyelocytic leukemia cells (HL-60) with carboplatin as the reference compound. In order to evaluate influence of substituents in phenyl group on compounds activity, both geometric isomers: **6f** and **7f** with unsubstituted phenyl ring were synthesized according to the procedure described in literature [22]. The isomers were successfully separated by taking advantage of their differing solubilities in acetone/hexane (4/1).

The results are shown in Table 3.

The cytotoxicities of the lactones were about 10–20 times lower than those observed for carboplatin. No significant differences in activity between the compounds with different substituents at the phenyl ring were observed. Synthesis of new series of the compounds with other substituents is needed to search for more active compounds.

Table 3
Activity of β-aryl-δ-iodo-γ-lactones **6**, **7a-f** towards HL-60 cells.

Compound	Substituent *R*	IC_{50} (μg/mL)
6a	4-Cl—C_6H_4	27.31 ± 5.66
7a		30.24 ± 3.01
6b	4-CH_3—C_6H_4	36.98 ± 6.49
7b		30.11 ± 3.05
6c	4-CH_3O—C_6H_4	Not determined
7c		58.30 ± 7.10
6d	4-*i*Pr—C_6H_4	29.69 ± 3.98
7d		28.71 ± 4.93
6e	1-$C_{10}H_7$	46.78 ± 5.56
7e		69.74 ± 4.24
6f	C_6H_5	31.36 ± 4.67
7f		38.43 ± 6.31
Carboplatin	–	2.9 ± 0.1

3. Conclusion

The efficient and convenient method for the synthesis of new β-aryl-δ-iodo-γ-lactones was described starting from commercially available aromatic aldehydes. Detailed spectroscopic analysis (IR, NMR, HR-MS) for all lactones was performed. For lactones **6e** and **7e**, X-ray crystal analysis was also carried out which showed numerous weak interactions in their crystal lattices including C—H···O hydrogen bonds, C—H···π and I···π interactions in **6e** and C—H···O and I(1)···I(1) interactions in **7e**. All the lactones were screened for cytotoxic activity towards HL-60 cells. Synthesis of next series of lactones with different electron-withdrawing or electron-donating substituents at the aromatic ring in the search of more sophisticated structure–activity correlation is in progress.

4. Experimental

4.1. General methods

All reagents used in this work were purchased from Fluka. NMR spectra were recorded in solutions ($CDCl_3$) on Bruker Avance DRX 300 spectrometer. Mass spectra were recorded on QTOF-II Bruker with the electrospray (ESI) technique at the Structural Research Laboratory of the UJK University. Melting points (uncorrected) were recorded on a Boetius melting point instrument. IR spectra were recorded on a Specord M-80 Carl Zeiss Jena Spectrometer. Refractive indexes were determined on Carl Zeiss Jena refractometer.

Gas chromatography (GC) was performed on a Hewlett-Packard 5890 A II apparatus using DB-5 HT capillary column. The temperatures during GC analysis were as follows: injector 160 °C, detector (FID) 300 °C, column temperature: 90 °C, 90–200 °C (rate 20 °C/min), 200–320 °C (rate 30 °C/min), 300 °C (hold 1 min). Analytical thin layer chromatography (TLC) was carried out on silica gel G (Merck), various developing systems were applied. Compounds were detected in the iodide chamber. Column chromatography was performed on silica gel (Kieselgel 60, 230–400 mesh, Merck).

The crystallographic data were collected using the BRUKER KAPPA APEXII ULTRA controlled by APEXII software [23], equipped with MoKα rotating anode X-ray source (λ = 0.71073 Å, 50.0 kV, 22.0 mA) monochromatized by multi-layer optics and APEX-II

CCD detector. The experiments were carried out at 100 K using the Oxford Cryostream cooling device. The crystal was mounted on Mounted CryoLoop with a droplet of Pantone–N oil and immediately cooled. Indexing, integration and initial scaling were performed with *SAINT* [24] and *SADABS* [25] software (Bruker, 2008). The data collection and processing statistics are reported in tables for according structures.

In each data collection, the crystal was positioned at 50 mm from the CCD camera. 600 frames were measured at 2° intervals with a counting time of 2 s.

The structures were solved by direct methods approach using the SHELXS-97 [26] program and refined with the SHELXL-97 [27]. Multi-scan absorption correction have been applied in the scaling procedure.

The refinement was based on F^2 for all reflections except those with negative intensities. Weighted *R* factors *wR* and all goodness-of-fit *S* values were based on F^2, whereas conventional R factors were based on the amplitudes, with *F* set to zero for negative F^2. The $F_0^2 > 2\sigma(F_0^2)$ criterion was applied only for *R* factors calculation was not relevant to the choice of reflections for the refinement. The *R* factors based on F^2 are for all structures about twice as large as those based on *F*. The hydrogen atoms were located in idealized geometrical positions, except hydrogen in solvent molecule. Scattering factors were taken from Tables 4.2.6.8 and 6.1.1.4 from the International Crystallographic Tables, vol. C [28].

4.2. Doebner condensation [17]

General procedure: A mixture of aldehyde **1a**–**e** (0.02 mol), monomethyl malonate (0.04 mol, 4.72 g) in pyridine as a solvent (10 mL), in the presence of catalytic amount of piperidine (0.25 mL) was refluxed for 6 h. Then, the solvent was removed *in vacuo* and the oily residue was purified by column chromatography on silica gel with hexane–acetone (9:1) as eluent. According to this procedure, pure esters **2a**–**e** with good yields were obtained as a colorless oils. Their physical and spectral data were in accordance with those reported in the literature [16].

4.2.1. (E)-Methyl 3-(p-chlorophenyl)prop-2-enoate (**2a**)

Yield = 42%; **^{1}H NMR** ($CDCl_3$) δ: 3.81 (s, 3H, —CO_2CH_3), 6,54 (d, *J* = 15.9 Hz, 1H, =C**H**CO_2CH_3), 7.36 (d, *J* = 15.9 Hz, 1H, Ar**CH**=), 7.41–7.47 (m, 2H, *p*-C_6H_4), 7.58–7.66 (m, 2H, *p*-C_6H_4).

4.2.2. (E)-Methyl 3-(p-methylphenyl)prop-2-enoate (**2b**)

Yield = 94%; **^{1}H NMR** ($CDCl_3$), δ: 1.27 (s, 3H, —CH_3), 3.81(s, 3H, —OCH_3), 6.41 (d, *J* = 15.9 Hz, 1H, =C**H**CO_2CH_3), 7.69 (d, *J* = 15.9 Hz, 1H, ArC**H**=), 7.24–7.27 (m, 2H, *p*-C_6H_4), 7.46–7.48 (m, 2H, *p*-C_6H_4).

4.2.3. (E)-Methyl 3-(p-methoxyphenyl)prop-2-enoate (**2c**)

Yield = 76%, **^{1}H NMR** ($CDCl_3$) δ: 3.71 (s, 3H, —CO_2CH_3), 3.83 (s, 3H, —OCH_3), 6.31 (d, *J* = 15.9 Hz, 1H, =C**H**CO_2CH_3), 7.65 (d, *J* = 15.9 Hz, 1H, ArC**H**=), 6.88–6.91 (m, 2H, *p*-C_6H_4), 7.46–7.49 (m, 2H, *p*-C_6H_4).

4.2.4. (E)-Methyl 3-(p-isopropylphenyl)prop-2-enoate (**2d**)

Yield = 89%, **^{1}H NMR** ($CDCl_3$) δ: 1.26 (d, *J* = 6.9 Hz, 6H, —$CH(CH_3)_2$), 2.88 (septet, *J* = 6.9 Hz, 1H, C**H**$(CH_3)_2$), 3.81 (s, 3H, —CO_2CH_3), 6.41 (d, *J* = 15.9 Hz, 1H, =C**H**CO_2CH_3), 7.23–7.28 (m, 2H, *p*-C_6H_4), 7.44–7.48 (m, 2H, *p*-C_6H_4), 7.67 (d, *J* = 15.9 Hz, 1H, ArC**H**=).

4.2.5. (E)-Methyl 3-(α-naphthyl)prop-2-enoate (**2e**)

Yield = 87%, **^{1}H NMR** ($CDCl_3$) δ: 3.86 (s, 3H, —OCH_3), 6.54 (d, *J* = 15.9 Hz, 1H, =C**H**CO_2CH_3), 7.46–8.21 (m, 7H, Ar**H**), 8.54 (d, *J* = 15.9 Hz, 1H, ArC**H**=).

4.3. Reduction of esters **2a**–**e**

General procedure: A 2 M solution of $LiBH_4$ in THF (16.5 mL) was added dropwise to a solution of ester **2a**–**e** (0.0165 mol) in anhydrous diethyl ether (50 mL) at 0 °C. The mixture was stirred at room temperature for 16 h, poured onto ice and diluted *HCl was added carefully* to quench the excess of hydride reagent. The aqueous and *ethereal layers were separated*. The aqueous *layer* was extracted three times with diethyl ether (15 mL). The combined etheral solutions were washed with saturated brine, H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give crude alcohols **3a**–**e**. After purification by column chromatography with hexane–ethyl acetate (3:1) as eluent, pure alcohols **3a**–**e** were obtained as colorless oils. Their physical and spectral data were the same as reported in literature [18].

4.3.1. (E)-3-(p-chlorophenyl)prop-2-en-1-ol (**3a**)

Yield = 74%, **^{1}H NMR** ($CDCl_3$) δ: 1.77 (s, 1H, —O**H**), 4.32 (dd, *J* = 5.4 Hz, 1.5 Hz, 2H, —C**H**$_2$OH), 6.35 (dt, *J* = 15.9 Hz, 5.7 Hz, 1H, =C**H**—CH_2—), 6.57 (dt, *J* = 15.9 Hz, 1.5 Hz, 1H, ArC**H**=), 7.28–7.29 (m, 4H, *p*-C_6H_4).

4.3.2. (E)-3-(p-methylphenyl)prop-2-en-1-ol (**3b**)

Yield = 90%, **^{1}H NMR** ($CDCl_3$) δ: 1.68 (s, 1H, —O**H**), 2.35 (s, 3H, —C**H**$_3$), 4.31 (dd, *J* = 5.7 Hz, 1.2 Hz, 2H, —C**H**$_2$OH), 6.32 (dt, *J* = 15.9 Hz, 5.7 Hz, 1H, =C**H**—CH_2—), 6.59 (d, *J* = 15.9 Hz, 1H, ArC**H**=), 7.12–7.15 (m, 2H, *p*-C_6H_4), 7.23–7.30 (m, 2H, *p*-C_6H_4).

4.3.3. (E)-3-(p-methoxyphenyl)prop-2-en-1-ol (**3c**)

Yield = 85%, **^{1}H NMR** ($CDCl_3$) δ: 1.61 (s, 1H, —O**H**), 3.81 (s, 3H, —O**CH**$_3$), 4.29 (dd, *J* = 6.0 Hz, 1.2 Hz, 2H, —C**H**$_2$OH), 6.23 (dt, *J* = 15.9 Hz, 6.0 Hz, 1H, =C**H**—CH_2—), 6.84–6.87 (m, 2H, *p*-C_6H_4), 7.11 (d, *J* = 15.9 Hz, 1H, ArC**H**=), 7.31–7.34 (m, 2H, *p*-C_6H_4).

4.3.4. (E)-3-(p-isopropylphenyl)prop-2-en-1-ol (**3d**)

Yield = 81%, **^{1}H NMR** ($CDCl_3$) δ: 1.25 (d, *J* = 6.9 Hz, 6H, —$CH(CH_3)_2$), 1.59 (broad s, 1H, —O**H**), 2.91 (septet, *J* = 6.9 Hz, 1H, C**H**$(CH_3)_2$), 4.31 (dd, *J* = 6.0 Hz, 1.2 Hz, 2H, —C**H**$_2$OH), 6.33 (dt, *J* = 5.9 Hz, 6.0 Hz, 1H, =C**H**—CH_2—), 6.60 (d, *J* = 15.9 Hz, 1H, ArC**H**), 7.18–7.20 (m, 2H, *p*-C_6H_4), 7.31–7.34 (m, 2H, *p*-C_6H_4).

4.3.5. (E)-3-(α-naphtyl)prop-2-en-1-ol (**3e**)

Yield = 84%, **^{1}H NMR** ($CDCl_3$) δ: 1.63 (s, 1H, —O**H**), 4.45 (dd, *J* = 5.7 Hz, 1.5 Hz, 2H, —C**H**$_2$OH), 6.41 (dt, *J* = 15.6 Hz, 5.7 Hz, 1H, =C**H**—CH_2—), 7.36–7.88 (m, 7H, Ar**H**), 8.10 (dd, *J* = 15.6 Hz, 1H, ArC**H**=).

4.4. Claisen rearrangement

General procedure: A mixture of alcohol **3a**–**e** (0.013 mol), ethyl orthoacetate (24 mL, 0.13 mol) and propionic acid (0.1 mL, 0.001 mol) was heated (138 °C) for 5 h with simultaneous distilling off the ethanol formed. Then orthoacetate was distilled off and the crude products were purified by column chromatography (hexane–ethyl acetate, 80:1) to afford pure esters **4a**–**e**.

4.4.1. Ethyl 3-(p-chlorophenyl)pent-4-enoate (**4a**)

Yield = 65%, n_D^{20} = 1,5723; **IR** (KBr, ν cm^{-1}): 1719, 1645, 1526, 1494, 1411, 1353, 1237, 1155, 971, 814; **^{1}H NMR** ($CDCl_3$) δ: 1.18 (t, *J* = 7.2 Hz, 3H, —OCH_2CH_3), 2.65 (dd, *J* = 15.3 Hz, 7.8 Hz, 1H, one of —C**H**$_2$$CO_2$Et), 2.74 (dd, *J* = 15.3 Hz, 7.8 Hz, 1H, one of —C**H**$_2$-CO_2Et), 3.86 (m, 1H, —ArC**H**—), 4.07 (q, *J* = 7.2 Hz, 2H, —OC**H**$_2$$CH_3$), 5.06 (dt, *J* = 17.1 Hz, 1.2 Hz, 1H, one of C**H**$_2$=), 5.09 (dt, *J* = 10.5 Hz, 1.2 Hz, 1H, one of C**H**$_2$=), 5.94 (ddd, *J* = 17.1 Hz, 10.5 Hz, 6.6 Hz; 1H, —C**H**=), 7.15 (m, 2H, *p*-C_6H_4), 7.27 (m, 2H, *p*-C_6H_4); **^{13}C NMR** ($CDCl_3$) δ: 14.131 (—OCH_2**C**H_3), 40.12 (C2), 44.90 (C3), 60.48

(—O***C***H_2CH_3), 115.14 (C5), 6 C_{Ar}: 128.65, 128.96, 129.14, 129.17, 140.87, 143.11; 139.79 (C4), 171.57 (C1). **HRMS** $[M+Na]^+$: 261.0655 (calculated for $[M+Na]^+$: 261.0658).

*4.4.2. Ethyl 3-(p-methylphenyl)pent-4-enoate (**4b**)*

Yield = 84%, n_D^{20} = 1,4893; IR (KBr, ν cm^{-1}): 1718, 1631, 1542, 1472, 1409, 1372, 1243, 1164, 968, 851; **^{1}H NMR** ($CDCl_3$) δ: 1.19 (t, *J* = 7.2 Hz, 3H, —OCH_2***CH_3***), 2.32 (s, 1H, —CH_3), 2.67 (dd, *J* = 15.0 Hz, 7.5 Hz, 1H, one of —***CH_2***CO_2Et), 2.76 (dd, *J* = 15.0 Hz, 8.1 Hz, 1H, one of —***CH_2***CO_2Et), 3.84 (m, 1H, ArC***H***—), 4.08 (q, *J* = 7.2 Hz, 2H, —O***CH_2***CH_3), 5.04 (dt, *J* = 17.7 Hz, 1.2 Hz, 2H, 1H, one of C***H_2***=), 5.09 (dt, *J* = 11.4 Hz, 1.2 Hz, 1H, one of C***H_2***=), 5.97 (ddd, *J* = 17.7 Hz, 11.4 Hz, 6.9 Hz, 1H, —***CH***=), 7.09–7.14 (m, 4H, *p*-C_6H_4). **^{13}C NMR** ($CDCl_3$) δ: 14.14 (—OCH_2***C***H_3), 20.97 (***C***H_3), 40.33 (C2), 45.21 (C3), 60.31 (—O***C***H_2CH_3), 114.51 (C5), 6 C_{Ar}: 127.34, 129.20, 136.15, 140.44; 139.42 (C4), 171.89 (C1); **HRMS** $[M+Na]^+$: 241.1205 (calculated for $[M+Na]^+$: 241.1204).

*4.4.3. Ethyl 3-(p-methoxyphenyl)pent-4-enoate (**4c**)*

Its physical and spectral data coincided with that of literature [19].

Yield = 35%, **^{1}H NMR** ($CDCl_3$) δ: 1.18 (t, *J* = 6.9 Hz, 3H, —OCH_2-***CH_3***), 2.65 (dd, *J* = 15.0 Hz, 7.8 Hz, 1H, one of —***CH_2***CO_2Et), 2.73 (dd, *J* = 15.0 Hz, 7.8 Hz, 1H, one of C***H_2***CO_2Et), 3.78 (s, 1H, —O***CH_3***), 3.82 (m, 1H, ArC***H***—), 4.07 (q, *J* = 7.2 Hz, 2H, —O***CH_2***CH_3), 5.05 (dt, *J* = 17.4 Hz, 1.2 Hz, 2H, 1H, one of C***H_2***=), 5.09 (dt, *J* = 11.1 Hz, 1.2 Hz, 1H, one of C***H_2***=), 5.96 (ddd, *J* = 17.4 Hz, 11.1 Hz, 6.9 Hz, 1H, —***CH***=), 6.84 (m, 2H, *p*-C_6H_4), 7.13 (m, 2H, *p*-C_6H_4).

*4.4.4. Ethyl 3-(p-isopropylphenyl)pent-4-enoate (**4d**)*

Yield = 82%, n_D^{20} = 1,5004; IR (KBr, ν cm^{-1}): 1736, 1640, 1512, 1488, 1400, 1368, 1256, 1164, 976, 832; **^{1}H NMR** ($CDCl_3$) δ: 1.18 (t, *J* = 6.9 Hz, 3H, —OCH_2C***H_3***), 1.23 (d, *J* = 6.9 Hz, 6H, —$CH(C$***H_3***$)_2$), 2.67 (dd, *J* = 15.0 Hz, 5.5 Hz, 1H, one of —***CH_2***CO_2Et), 2.74 (dd, *J* = 15.0 Hz, 8.7 Hz, 1H, one of —***CH_2***CO_2Et), 2.88 (septet, *J* = 6.9 Hz, 1H, C***H***$(CH_3)_2$), 3.84 (m, 1H, ArC***H***—), 4.08 (q, *J* = 6.9 Hz, 2H, —O***CH_2***-CH_3), 5.08 (ddd, *J* = 17.1 Hz, 2.4 Hz, 1.2 Hz, 1H, one of C***H_2***=), 5.09 (dd, *J* = 10.5 Hz, 1.5 Hz, 1H, one of C***H_2***=), 5.98 (ddd, *J* = 17.1 Hz, 10.5 Hz, 7.2 Hz, 1H, —***CH***=), 7.12–7.18 (m, 4H, *p*-C_6H_4); **^{13}C NMR** ($CDCl_3$) δ: 14.12 (—OCH_2***C***H_3), 23.95 (***C***H_3), 33.65 (***C***H), 40.38 (C2), 45.28 (C3), 60.30 (—O***C***H_2CH_3), 114.53 (C5), 6 C_{Ar}: 126.41, 127.33, 128.26, 147.14; 140.40 (C4), 171.94 (C1); **HRMS** $[M+Na]^+$: 269.1495 (calculated for $[M+Na]^+$: 269.1517).

*4.4.5. Ethyl 3-(α-naphtyl)pent-4-enoate (**4e**)*

Yield = 77%; n_D^{20} = 1.5680; **IR** (KBr, ν cm^{-1}):, 1732, 1512, 1368, 1256, 1172, 1032, 920, 776 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 1.18 (t, *J* = 7.2 Hz, 3H, —OCH_2C***H_3***), 2.89 (d, *J* = 7.5 Hz, 2H, —***CH_2***CO_2Et), 4.11 (q, *J* = 7.2 Hz, 2H, —O***CH_2***CH_3), 4.76 (m, 1H, ArC***H***—), 5.15 (dd, *J* = 17.8 Hz, 1.2 Hz, 1H, one of C***H_2***=), 5.16 (dd, *J* = 9.6 Hz, 1.2 Hz, 1H, one of C***H_2***=), 6.12 (ddd, *J* = 17.8 Hz, 9.6 Hz, 6.5 Hz, 1H, —***CH***=), 7.36–7.58, (four m, 4H, Ar***H***), 7.75, 7.86 and 8.19 (three m, 3H, Ar***H***); **^{13}C NMR** ($CDCl_3$) δ: 14.13 (—OCH_2C***H_3***), 39.91 (C2), 40.32 (C3), 60.46 (—O***C***H_2CH_3), 115.33 (C5), 10 C_{Ar}: 123.30, 124.09, 125.39, 125.53, 126.05, 127.31, 128.95, 131.25, 133.99, 138.47; 139.81 (C4), 171.99 (C1); **HRMS** $[M+K]^+$: 293.0927 (calculated for $[M+K]^+$: 293.0944).

*4.5. Hydrolysis of esters **4a–e***

General procedure: A solution of KOH (0.05 mol) in ethanol (25 mL) was added to ester **4a–e** (0.01 mol). The reaction mixture was refluxed for 6 h. The progress of the reaction was monitored by TLC. Then ethanol was distilled off and the crude product was solved in water (20 mL) and washed with diethyl ether (100 mL). Next the aqueous layer was acidified with 0.1 M HCl (pH ≈ 1) and the crude product was extracted with ether (7 × 50 mL). The etheral solution was dried over $MgSO_4$. The ether was distilled off and pure acids **5a–e** were obtained as yellow solids.

The physical and spectral data of **5a–c** were the same with those reported in literature [20].

*4.5.1. 3-(p-Chlorophenyl)pent-4-enoic acid (**5a**)*

Yield = 72%, **^{1}H NMR** ($CDCl_3$) δ: 2.70 (dd, *J* = 15.9 Hz, 7.5 Hz, 1H, one of —***CH_2***CO_2Et), 2.79 (dd, *J* = 15.9 Hz, 7.5 Hz, 1H, one of —***CH_2***-CO_2Et), 3.83 (m, 1H, ArC***H***—), 5.07 (dt, *J* = 17.1 Hz, 1.2 Hz, one of C***H_2***=), 5.11 (dt, *J* = 10.2 Hz, 1.2 Hz, one of C***H_2***=), 5.94 (ddd, *J* = 17.1 Hz, 10.2 Hz, 6.6 Hz, 1H, —***CH***=), 7.13–7.16 (m, 2H, *p*-C_6H_4), 7.27–7.30 (m, 2H, *p*-C_6H_4).

*4.5.2. 3-(p-Methylphenyl)pent-4-enoic acid (**5b**)*

Yield = 88%, **^{1}H NMR** ($CDCl_3$) δ: 2.33 (s, 1H, CH_3), 2.72 (dd, *J* = 15.6 Hz, 7.2 Hz, 1H, one of —***CH_2***CO_2Et), 2.79 (dd, *J* = 15.6 Hz, 7.8 Hz, 1H, one of —***CH_2***CO_2Et), 3.83 (m, 1H, ArC***H***—), 5.04 (dt, *J* = 17.7 Hz, 1.2 Hz, 1H, one of C***H_2***=), 5.09 (dt, *J* = 10.2 Hz, 1.2 Hz, 1H, one of C***H_2***=), 5.97 (ddd, *J* = 17.7 Hz, 10.2 Hz, 6.9 Hz, 1H, —***CH***=), 7.12–7.16 (m, 4H, *p*-C_6H_4).

*4.5.3. 3-(p-Methoxyphenyl)pent-4-enoic acid (**5c**)*

Yield = 75%, **^{1}H NMR** ($CDCl_3$) δ: 2.70 (dd, *J* = 15.6 Hz, 7.5 Hz, 1H, one of C***H_2***CO_2Et), 2.78 (dd, *J* = 15.6 Hz, 8.1 Hz, 1H, one of C***H_2***CO_2-Et), 3.79 (s, 3H, —O***CH_3***), 3.85 (m, 1H, —CH_2—C***H***—), 5.05 (dt, *J* = 17.4 Hz, 1.2 Hz, 2H, 1H, one of C***H_2***=), 5.09 (dt, *J* = 11.1 Hz, 1.2 Hz, 1H, one of C***H_2***=), 5.96 (ddd, *J* = 17.4 Hz, 11.1 Hz, 6.6 Hz, 1H, —***CH***=), 6.84–6.87 (m, 2H, *p*-C_6H_4), 7.12–7.15 (m, 2H, *p*-C_6H_4).

*4.5.4. 3-(p-Isopropylphenyl)pent-4-enoic acid (**5d**)*

Yield = 87%, m.p. = 35–35.5 °C, **IR** (KBr, ν cm^{-1}): 2830–3036, 1712, 1640, 1512, 1416, 1284, 1112, 1056, 920, 832; **^{1}H NMR** ($CDCl_3$) δ: 1.23 (d, *J* = 6.9 Hz, 6H, —$CH(C$***H_3***$)_2$), 2.77 (dd, *J* = 8.1 Hz, 3.9 Hz, 2H, —***CH_2***—), 2.90 (septet, *J* = 6.9 Hz, 1H, C***H***$(CH_3)_2$), 3.85 (q, *J* = 7.2 Hz, 1H, —CH_2—C***H***—), 5.09 (dd, *J* = 11.1 Hz, 1.5 Hz, 1H, one of C***H_2***=), 5.11 (dt, *J* = 17.1 Hz, 1.5 Hz, 1H, one of C***H_2***=), 5.99 (ddd, *J* = 17.1 Hz, 11.1 Hz, 7.1 Hz, 1H, —***CH***=), 7.13–7.20 (m, 4H, *p*-C_6H_4); **^{13}C NMR** ($CDCl_3$): 23.95 (***C***H_3), 33.67 (***C***H), 39.93 (C2), 44.81 (C3), 114.81 (C5), 6 C_{Ar}: 126.41, 126.66, 127.31, 139.47; 140.11 (C4), 171.72 (C1); **HRMS** $[M+Na]^+$: 241.1227 (calculated for $[M+Na]^+$: 241.1204).

*4.5.5. 3-(α-Naphtyl)pent-4-enoic acid (**5e**)*

Yield = 71%, m.p. = 89–90.5 °C; **IR** (KBr, ν cm^{-1}): 2833–3032, 1712, 1432, 1304, 1264, 1016, 928, 784 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 2.89–2.98 (m, 2H, —***CH_2***C(O)—), 4.75 (m, 1H, —CH_2—C***H***—), 5.17 (dd, *J* = 17.0 Hz, 1.5 Hz, 1H, one of C***H_2***=), 5.18 (dd, *J* = 10.6 Hz, 1.5 Hz, 1H, one of C***H_2***=), 6.13 (ddd, *J* = 17.0 Hz, 10.6 Hz, 6.4 Hz, 1H, —***CH***=), 7.36–7.56 (four m, 4H, Ar***H***), 7.76, 7.87 and 8.16 (three m, 3H, Ar***H***); **^{13}C NMR** ($CDCl_3$) δ: 39.48 (C2), 39.95 (C3), 115.67 (C5), 10 C_{Ar}: 123.18, 124.04, 125.43, 125.61, 126.19, 127.47, 128.95, 131.15, 134.03, 138.09; 139.40 (C4), 178.19 (C1); **HRMS** $[M+K]^+$: 265.0631 (calculated for $[M+K]^+$: 265.0684).

*4.6. Iodolactonization of acids **5a–e***

General procedure: A 0.5 M solution of $NaHCO_3$ (20 mL) was added to a solution of carboxylic acid **5** (0.006 mol) in diethyl ether (25 mL). The reaction mixture was stirred at room temperature for 30 min. Then the mixture of iodine (0.01 mol) and KI (0.03 mol) dissolved in water (30 mL) was added dropwise and the reaction mixture was refluxed for 5 h. Then the mixture was cooled to room temperature, diluted with ethyl acetate (50 mL) and washed with aqueous saturated solution of sodium thiosulfate. The water layer was extracted by ethyl ether (or with ethyl acetate in case of

products of iodolactonization of acid **5e**). The combined organic solution was washed with aqueous saturated $NaHCO_3$ solution, brine and dried over $MgSO_4$. After evaporation of the solvent the crude products mixture was separated by column chromatography with hexane–ethyl acetate 5:1 (in case of pairs of isomers **6a** and **7a**, **6d** and **7d**) or methylene chloride (in case of isomers **6e** and **7e**) as eluent or by crystallization from hexane:ethyl acetate 5:1 in case of pairs of isomers **6b** and **7b**, **6c** and **7c**.

4.6.1. 4-(p-Chlorophenyl)-5-iodomethyltetrahydrofuran-2-one

The physical and spectral data of **6–7a** were the same with those reported in literature [21].

*Isomer trans (**6a**)*: Yield = 17%, ^{1}H NMR ($CDCl_3$) δ: 2.78 (dd, *J* = 18.0 Hz, 9.3 Hz, 1H, one of C(O)—C***H₂***—), 3.07 (dd, *J* = 18.0 Hz, 9.3 Hz, 1H, one of C(O)—C***H₂***—), 3.33 (dd, *J* = 11.1 Hz, 4.8 Hz, 1H, one of —C***H₂***I), 3.47 (dd, *J* = 11.1 Hz, 4.8 Hz, 1H, one of —C***H₂***I), 3.52 (td, *J* = 9.3 Hz, 7.2 Hz, >C***H***—Ar), 4.29 (dt, *J* = 7.2 Hz, 4.8 Hz, >C***H***—CH_2I), 7.19–7.22 (m, 2H, *p*-C_6H_4), 7.35–7.38 (m, 2H, *p*-C_6H_4).

*Isomer cis (**7a**)*: Yield = 38%, **^{1}H NMR** ($CDCl_3$) δ: 2.66 (dd, *J* = 10.2 Hz, 8.1 Hz, 1H, one of —C***H₂***I), 2.78 (dd, *J* = 17.7 Hz, 3.0 Hz, 1H, one of C(O)—C***H₂***—), 3.10 (dd, *J* = 17.7 Hz, 8.4 Hz, 1H, one of C(O)—C***H₂***—), 3.15 (dd, *J* = 10.2 Hz, 6.0 Hz, 1H, one of —C***H₂***I), 3.87 (ddd, *J* = 8.4 Hz, 6.0 Hz, 3.0 Hz, >C***H***—Ar), 4.94 (dt, *J* = 8.1 Hz, 6.0 Hz, >C***H***—CH_2I), 7.15–7.18 (m, 2H, *p*-C_6H_4), 7.32–7.35 (m, 2H, *p*-C_6H_4).

4.6.2. 4-(p-Methylphenyl)-5-iodomethyltetrahydrofuran-2-one

*Isomer trans (**6b**)*: Yield = 15%, n_D^{20} = 1.5771, **IR** (KBr, ν cm^{-1}): 1765, 1691, 1548, 1247, 1112, 839, 667, 558; **^{1}H NMR** ($CDCl_3$) δ: 2.35 (s, 3H, —CH_3), 2.81 (dd, *J* = 18.0 Hz, 9.3 Hz, 1H, one of C(O)—C***H₂***—), 3.05 (dd, *J* = 18.0 Hz, 9.3 Hz, 1H, one of C(O)—C***H₂***—), 3.32 (dd, *J* = 11.4 Hz, 4.5 Hz, 1H, one of —C***H₂***I), 3.48 (dd, *J* = 11.1 Hz, 4.5 Hz, 1H, one of —C***H₂***I), 3.49 (td, *J* = 9.3 Hz, 7.5 Hz, >C***H***—Ar), 4.28 (dt, *J* = 7.5 Hz, 4.5 Hz, >C***H***—CH_2I), 7.13–7.21 (m, 4H, *p*-C_6H_4), **^{13}C NMR** ($CDCl_3$) δ: 6.22 (C6), 21.03 (***C***H_3), 37.02 (C3), 46.95 (C4), 84.26 (C5), C_{Ar}: 127.01,129.95, 135.22, 137.94; 174.42 (C2); **HRMS** $[M+Na]^+$: 338.9903 (calculated for $[M+Na]^+$: 338.9858).

*Isomer cis (**7b**)*: Yield = 42%, m.p. = 104–105 °C; **IR** (KBr, ν cm^{-1}): 1769, 1587, 1285, 1246, 974, 836, 724, 543; **^{1}H NMR** ($CDCl_3$) δ: 2.34 (s, 3H, —CH_3), 2.72 (dd, *J* = 10.5 Hz, 7.5 Hz, 1H, one of —C***H₂***I), 2.80 (dd, *J* = 17.7 Hz, 3.3 Hz, 1H, one of C(O)—C***H₂***—), 3.06 (dd, *J* = 17.7 Hz, 8.7 Hz, 1H, one of C(O)—C***H₂***—), 3.07 (dd, *J* = 10.5 Hz, 6.3 Hz, 1H, one of —C***H₂***I), 3.84 (ddd, *J* = 8.7 Hz, 6.0 Hz, 3.3 Hz, >C***H***—Ar), 4.93 (m, >C***H***—CH_2I), 7.08–7.16 (m, 4H, *p*-C_6H_4).

^{13}C NMR ($CDCl_3$) δ: 1.58 (C6), 21.04 (***C***H_3), 36.94 (C3), 43.73 (C4), 83.08 (C5), C_{Ar}: 127.89,129.63, 133.28, 137.93; 175.80 (C2); **HRMS** $[M+Na]^+$: 338.9915 (calculated for $[M+Na]^+$: 338.9858).

4.6.3. 4-(p-Methoxyphenyl)-5-iodomethyltetrahydrofuran-2-one

*Isomer trans (**6c**)*: (in mixture with *cis* isomer **7c**), **^{1}H NMR** ($CDCl_3$) δ: 2.79 (dd, *J* = 17.4 Hz, 9.9 Hz, 1H, one of C(O)—C***H₂***—), 3.02 (dd, *J* = 17.7 Hz, 9.9 Hz, 1H, one of C(O)—C***H₂***—), 3.32 (dd, *J* = 11.1 Hz, 4.5 Hz, 1H, one of —C***H₂***I), 3.46 (dd, *J* = 11.1 Hz, 4.5 Hz, 1H, one of —C***H₂***I), 3.48 (td, *J* = 9.9 Hz, 7.5 Hz, >C***H***—Ar), 3.80 (s, 3H. —OCH_3), 4.25 (dt, *J* = 7.5 Hz, 4.5 Hz, >C***H***—CH_2I), 6.88–6.92 (m, 2H, *p*-C_6H_4), 7.14–7.19 (m, 2H, *p*-C_6H_4).

*Isomer cis (**7c**)*: Yield = 35%, m.p. = 95.0–95.5 °C; **IR** (KBr, ν cm^{-1}): 1975, 1772, 1615, 1548, 1286, 1198, 912, 681, 573; **^{1}H NMR** ($CDCl_3$) δ: 2.70 (dd, *J* = 10.2 Hz, 7.5 Hz, 1H, one of —C***H₂***I), 2.79 (dd, *J* = 17.4 Hz, 3.0 Hz, 1H, one of C(O)—C***H₂***—), 3.06 (dd, *J* = 17.4 Hz, 8.7 Hz, 1H, one of C(O)C***H₂***—), 3.10 (dd, *J* = 10.2 Hz, 6.3 Hz, 1H, one of —C***H₂***I), 3.81 (s, 3H, —OCH_3), 3.84 (ddd, *J* = 8.7 Hz, 6.3 Hz, 3.0 Hz, >C***H***—Ar), 4.92 (dt, *J* = 7.5 Hz, 6.3 Hz, >C***H***—CH_2I), 6.85–6.90 (m, 2H, *p*-C_6H_4), 7.11–7.16 (m, 2H, *p*-C_6H_4).**^{13}C NMR** ($CDCl_3$) δ: 1.56 (C6), 37.06 (C3), 43.33 (C4), 55.27 (O***C***H_3), 83.16 (C5), C_{Ar}: 114.30, 129.10, 159.29; 175.830 (C2); **HRMS** $[M+Na]^+$: 354.9863 (calculated for $[M+Na]^+$: 354.9807).

4.6.4. 4-(p-Isopropylphenyl)-5-iodomethyltetrahydrofuran-2-one

*Isomer trans (**6d**)*: Yield = 22%, m.p. = 94.5–95.5 °C; **IR** (KBr, ν cm^{-1}): 1776, 1512, 1460, 1429, 1392, 1280, 1144, 116, 981, 860, 572; **^{1}H NMR** ($CDCl_3$) δ: 1.25 (d, *J* = 6.9 Hz, 6H, —CH(C***H₃***)₂), 2.83 (dd, *J* = 18.0 Hz, 9.0 Hz, 1H, one of C(O)—C***H₂***—), 2.91 (septet, *J* = 6.9 Hz, 1H, C***H***$(CH_3)_2$), 3.05 (dd, *J* = 18.0 Hz, 9.0 Hz, 1H, one of C(O)—C***H₂***—), 3.33 (dd, *J* = 11.1 Hz, 4.5 Hz, 1H, one of —C***H₂***I), 3.49 (dd, *J* = 11.1 Hz, 4.5 Hz, 1H, one of —C***H₂***I), 3.50 (td, *J* = 9.0 Hz, 7.5 Hz, 1H, >C***H***—Ar), 4.29 (dt, *J* = 7.5 Hz, 4.5 Hz, >C***H***—CH_2I), 7.16–7.23 (m, 4H, *p*-C_6H_4). **^{13}C NMR** ($CDCl_3$) δ: 6.35 (C6), 23.89 (***C***H_3), 33.75 (***C***H), 37.00 (C3), 46.96 (C4), 84.24 (C5), C_{Ar}: 127.09, 127.34, 135.48, 148.91; 174.47 (C2); **HRMS** $[M+Na]^+$: 367.0225 (calculated for $[M+Na]^+$: 367.0171).

*Isomer cis (**7d**)*: Yield = 48%, m.p. = 88–89 °C; **IR** (KBr, ν cm^{-1}): 1784, 1617, 1512, 1467, 1418, 1369, 1272, 1182, 1076, 976, 919, 821, 568; **^{1}H NMR** ($CDCl_3$) δ: 1.24 (d, *J* = 6.9 Hz, 6H, —CH(C***H₃***)₂), 2.74 (dd, *J* = 10.5 Hz, 7.2 Hz, 1H, one of —C***H₂***I), 2.83 (dd, *J* = 17.7 Hz, 3.3 Hz, 1H, one of C(O)—C***H₂***—), 2.90 (septet, *J* = 6.9 Hz, 1H, C***H***$(CH_3)_2$), 3.04 (dd, *J* = 17.7 Hz, 8.7 Hz, 1H, one of C(O)C***H₂***—), 3.07 (dd, *J* = 10.5 Hz, 6.3 Hz, 1H, one of —C***H₂***J), 3.85 (ddd, *J* = 8.7 Hz, 6.0 Hz, 3.3 Hz, 1H, >C***H***—Ar), 4.94 (m, 1H, >C***H***—CH_2I), 7.11–7.14 (m, 2H, *p*-C_6H_4), 7.19–7.22 (m, 2H, *p*-C_6H_4). **^{13}C NMR** ($CDCl_3$) δ: 1.79 (C6), 23.84 (***C***H_3), 23.87 ***C***H_3), 33.70 (***C***H), 36.83 (C3), 43.77 (C4), 83.19 (C5), C_{Ar}: 127.00, 127.93, 133.55, 148.85; 175.80 (C2); **HRMS** $[M+Na]^+$: 367.0277 (calculated for $[M+Na]^+$: 367.0171).

4.6.5. 4-(α-Naphthyl)-5-iodomethyltetrahydrofuran-2-one

*Isomer trans (**6e**)*: Yield = 14%, m.p. = 159–160 °C, **IR** (KBr, ν cm^{-1}): 1786, 1424, 1296, 1176, 1160, 1140, 964, 924, 800, 784, 672, 584, 544; **^{1}H NMR** ($CDCl_3$) δ: 2.88 (dd, *J* = 18.0 Hz, 8.4 Hz, 1H, one of C(O)—C***H₂***—), 3.27 (dd, *J* = 18.0 Hz, 8.4 Hz, 1H, one of C(O)—C***H₂***—), 3.39 (dd, *J* = 11.4 Hz, 4.5 Hz, 1H, one of —C***H₂***I), 3.55 (dd, *J* = 11.4 Hz, 4.5 Hz, 1H, one of —C***H₂***I), 4.35 (td, *J* = 8.4 Hz, 6.6 Hz, >C***H***—Ar), 4.67 (dt, *J* = 6.6 Hz, 4.5 Hz, >C***H***—CH_2I), 7.44–7.64 (four m, 4H, Ar***H***), 7.83, 7.92 and 8.06 (three m, 3H, Ar***H***); ^{13}C **NMR** ($CDCl_3$) δ: 7.12 (**C**-6), 37.44 (**C**-3), 41.96 (**C**-4), 83.63 (**C**-5), 7 **C**$_{Ar}$: 122.34, 123.73, 125.58, 126.21, 126.94, 128.59, 129.38; 174.51 (**C**-2); **HRMS** $[M+K]^+$: 391.2527 (calculated for $[M+K]^+$: 391.2653).

*Isomer cis (**7e**)*: Yield = 28%, m.p. = 189.5–192 °C, **IR** (KBr, ν cm^{-1}): 1772, 1408, 1320, 1164, 1048, 1000, 992, 776, 688; **^{1}H NMR** ($CDCl_3$) δ: 2.75 (dd, *J* = 11.1 Hz, 5.5 Hz, 1H, one of —C***H₂***I), 2.79 (dd, *J* = 11.1 Hz, 7.4 Hz, 1H, one of C***H***$_2$I) 3.04 (dd, *J* = 17.5 Hz, 8.6 Hz, 1H, one of C(O)—C***H₂***—), 3.22 (dd, *J* = 17.5 Hz, 8.0 Hz, 1H, one of C(O)—C***H₂***—), 4.78 (m, 1H, >C***H***—Ar), 5.25 (td, *J* = 7.4 Hz, 5.5 Hz, >C***H***—CH_2I), 7.39 and 7.49 (two m, 2H, Ar***H***), 7.53–7.64 (two m, 2H, Ar***H***), 7.86, 7.92 and 8.00 (three m, 3H, Ar***H***); **^{13}C NMR** (DMSO-d_6) δ: 4.68 (**C**-6), 31.97 (**C**-3), 39.59 (**C**-4), 81.14 (**C**-5), 7 **C**$_{Ar}$: 123.33, 124.33, 125.33, 125.97, 126.70, 128.06, 128.72; 175.25 (**C**-2); **HRMS** $[M+K]^+$: 391.2516 (calculated for $[M+K]^+$: 391.2653).

4.7. Antiproliferative assay in vitro

4.7.1. Cell line

The established *in vitro* cancer line HL-60 (human promyelocytic leukemia) was applied. This line was obtained from American Type Culture Collection (Rockville, Maryland, USA) and is being maintained in the Institute of Immunology and Experimental Therapy, Wrocław, Poland.

HL-60 cells were cultured in RPMI1640 medium (Gibco, Scotland, UK) with 10% fetal bovine serum (FBS), 1 mM sodium

pyruvate, 4.5 g/L glucose and 4 mM L-glutamine (all from Sigma–Aldrich Chemie GmbH, Steinheim, Germany). The culture medium was also supplemented with 100 μg/mL streptomycin and 100 U/mL penicillin (both from Polfa Tarchomin S.A., Warsaw, Poland). Cell line was grown at 37 °C, 5% CO_2 in humidified atmosphere.

4.7.2. Cytotoxic tests

Prior to usage, the compounds were dissolved in the mixture of DMSO and culture medium (1:9) to the concentration of 1 mg/mL, and subsequently diluted in culture medium to reach the required concentrations. 24 h before addition of the tested compounds, the cells were plated in 96-well plates (Sarstedt, Germany) at a density of 1×10^4 cells per well. Antiproliferative acivity of tested compounds was determined by MTT assay which was performed after 72 h of *in vitro* exposure of the cells to varying concentrations of the tested agents (0.1; 1; 10 and 100 μg/mL).

In MTT assay the following procedure was applied: 20 μL of MTT solution (MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (Sigma–Aldrich Chemie GmbH, Steinheim, Germany); stock solution: 5 mg/mL) was added to each well and incubated at 37 °C for 4 h. After the incubation time was complete, 80 μL of the lysing mixture was added to each well (lysing mixture: 225 mL dimethylformamide, 67.5 g sodium dodecyl sulfate (Sigma–Aldrich Chemie GmbH, Steinheim, Germany) and 275 mL of distilled water). The optical densities of the samples were read after 24 h on a Multiskan RC photometer (Labsystems, Helsinki, Finland) at 570 nm.

The results were calculated as the ID_{50} – the dose of tested agent which inhibits 50% of the proliferation of the cancer cell population. Each compound at each concentration was tested in triplicate in a single experiment which was repeated 3–5 times. The results (mean values ± SD) are presented in Table 3.

References

[1] (a) B.M. Fraga, Nat. Prod. Rep. 23 (2006) 943;
(b) Y. Asakawa, M. Toyota, F. Nagashima, et al., Heterocycles 54 (2001) 1057;
(c) T.K. Devon, A.J. Scott, Naturally Occurring Compounds: Terpenes, vol. II, Academic Press, New York and London, pp. 1072.

[2] (a) G. Ohloff, Scent and Fragrances, Springer-Verlag, Berlin, 1992;
(b) H. D Berlitz, W. Grosch, Food Chemistry, Springer-Verlag, London, Berlin, 1987;
(c) A. Mosandl, C. Gunther, J. Agric. Food Chem. 37 (1983) 413.

[3] E. Paruch, Wiadomości Chem. 55 (1–2) (2001) 93.

[4] (a) C.C Chang, K. Nakanishi, J. Chem. Soc. Chem. Commun. (1983) 605;
(b) A.G. Stephenson, J. Chem. Ecol. 8 (1982) 1025;
(c) I. Kubo, I. Miura, K. Nakanishi, J. Am. Chem. Soc. 98 (1976) 6704;
(d) K.H. Overton, H.H. Appel, R.P. Bond, Tetrahedron 19 (1963) 635;
(e) I. Y Kubo, E. Lee, M. Pettei, F. Pilkiewicz, K. Nakanishi, J. Chem. Soc. Chem. Commun. (1976) 1013.

[5] (a) K. Mori, S. Scenda, Tetrahedron 41 (1985) 541;
(b) T. Ebata, K. Matsumoto, H. Yoshikosi, K. Kosecki, H.K. Okano, H. Matsushita, Heterocycles 36 (1993) 1017;
(c) T. Honda, S. Yamane, K. Naito, Y. Suzuki, Heterocycles 37 (1994) 515;
(d) Y. Suzuki, W. Mori, H. Ishizone, K. Naito, T. Honda, Tetrahedron Lett. 33 (1992) 4931;
(e) H.C. Brown, S.V. Kulkarni, U.S. Racherla, J. Org. Chem. 59 (1994) 365;
(f) H. Kotsuki, I. Kadota, M. Ochi, J. Org. Chem. 55 (1990) 4417.

[6] (a) D.G. Peterson, G.A. Reineccius, Flavor Fragr. J. 18 (2003) 320;
(b) D.S. Mottram, R.A. Edwards, H.A. Macfie, J. Sci. Food Agric. 33 (1982) 934;
(c) G. Macleod, Flavour of Meat, Meat Products and Seafoods, Blackie, Academic & Professional, London, UK, 1998. pp. 62.

[7] (a) K.L. Wilkinson, G.M. Elsey, R.H. Prager, et al., J. Agric. Food Chem. 48 (2000) 1186;
(b) J.A. Moreno, L. Zea, L. Moyano, et al., Food Control 16 (2005) 333;
(c) H. Guth, Helv. Chim. Acta 79 (1996) 1559;
(d) H. Guth, J. Agric. Food Chem. 45 (1997) 3022.

[8] (a) F. Kurosaki, A. Nishi, Phytochemistry 22 (1983) 669;
(b) G.P. Mc Glacken, I.J.S. Fairlamb, Nat. Prod. Rep. 22 (2005) 369.

[9] (a) K.-H. Lee, B.-R. Huang, Eur. J. Med. Chem. 37 (2002) 333;
(b) A.M.S. Mayer, K.R. Gustafson, Eur. J. Cancer 40 (2004) 2676;
(c) Â. Fátima, L.K. Kohn, J.E. Carvalho, R.A. Pilli, Bioorg. Med. Chem. 14 (2006) 622.

[10] Z. Tian, S. Chen, Y. Zhang, M. Huang, L. Shi, F. Huang, C. Fong, M. Yang, P. Xiao, Phytomedicine 13 (2006) 181.

[11] (a) M. Szczepanik, M. Grabarczyk, A. Szumny, C. Wawrzeńczyk, J. Plant Protect. Res. 43 (2003) 87;
(b) C. Wawrzeńczyk, I. Dams, A. Szumny, M. Szczepanik, J. Nawrot, A. Prądzyńska, B. Gabryś, K. Dancewicz, E. Magnucka, B. Gawdzik, R. Obara, A. Wzorek, Pol. J. Environ. Stud. 14 (2005) 69.

[12] H.-U. Blaser, F. Spindler, Top Catal. 4 (1997) 275.

[13] T. Janecki, E. Błaszczyk, K. Studzian, A. Janecka, U. Krajewska, M. Różalski, J. Med. Chem. 48 (2005) 3516.

[14] (a) S. GowriSankar, C.G. Lee, I.N. Kim, Tetrahedron Lett. 45 (2004) 6949;
(b) T. Ohno, Y. Ishino, Y. Tsumagari, I. Nishiguchi, J. Org. Chem. 60 (1995) 458.

[15] M. Mazur, W. Gładkowski, C. Wawrzeńczyk, Przem. Chem. 90 (5) (2011) 918.

[16] A. Galat, J. Am. Chem. Soc. 68 (1946) 376.

[17] (a) G.P. Newsoroff, S. Styernhell, Aust. J. Chem. 21 (1968) 747;
(b) L.H. Klemm, D.R. Olson, J. Org. Chem. 38 (1973) 3390;
(c) G.R. Ramage, J. Chem. Soc. 397 (1938);
(d) B.M. Choudary, M.R. Sarma, K.K. Rao, Tetrahedron Lett. 31 (1990) 5781;
(e) K. Mani Bushan, G. Venugopal Rao, T. Soujanya, V. Jayathirtha Rao, S. Saha, A. Samanta, J. Org. Chem. 66 (2001) 681.

[18] (a) A.B. Charette, C. Molinaro, C. Brochu, J. Am. Chem. Soc. 123 (2001) 12168;
(b) R. Takeuchi, N. Ue, K. Tanabe, K. Yamashita, N. Shiga, J. Am. Chem. Soc. 123 (2001) 9525;
(c) O. Shigenori, A. Yasuyoshi, K. Kouki, O. Masahiro, S. Masaki, Takeda Pharmaceutical Company Limited, Patent US 2002/160996A1, 2002.;
(d) A.M. Echavarren, J.K. Stille, J. Am. Chem. Soc. 109 (1987) 5478.

[19] A. Srikrishna, S. Nagaraju, P. Kondaiah, Tetrahedron 51 (1995) 1809.

[20] M. Gao, D. Wang, Q. Zheng, M. Wang, J. Org. Chem. 71 (2006) 9532.

[21] E. Brown, C. Deroye, J. Touet, Tetrahedron Assymet. 9 (1998) 1605.

[22] (a) B. Pisarski, C. Wawrzeńczyk, Ann. Pol. Chem. Soc. 1 (2005) 133;
(b) B. Pisarski, C. Wawrzeńczyk, Tetrahedron Lett. 47 (2006) 6875.

[23] APEXII-2008v1.0, Bruker Nonius, 2007.

[24] SAINT V7.34A, Bruker Nonius, 2007.

[25] SADABS-2008/1, Bruker Nonius Area Detector Scaling and Absorption Correction, 2008.

[26] G.M. Sheldrick, Acta Crystallogr. A46 (1990) 467.

[27] G.M. Sheldrick, SHELXL93, Program for the Refinement of Crystal Structures, Univ. of Göttingen, Germany.

[28] A.J.C. Wilson (Ed.), International Tables for Crystallography, vol. C, Kluwer, Dordrecht, 1992.