Struct Chem (2012) 23:61–69
DOI 10.1007/s11224-011-9848-2

ORIGINAL RESEARCH

Synthesis and stereochemistry of new spiro[5.5]undecane derivatives with 1,3-dioxane, 1,3-dithiane, or 1,3-oxathiane rings

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Received: 26 May 2011 / Accepted: 19 July 2011 / Published online: 3 August 2011

Abstract The synthesis and the structural investigations of spiro[5.5]undecane derivatives with S and O containing heterocycles, exhibiting similar [bis(1,3-oxathiane) spiranes] or different (1,3-dioxane-1,3-dithiane spiranes) heterocycles, in the spirane units are reported.

Keywords Spiranes · 1,3-Diheteracyclohexanes · Heterocycles isomerisation · Chirality · Molecular modeling

Introduction

Spiro compounds with saturated six-membered rings revealed intriguing conformational and configurational aspects, and their stereochemistry was extensively investigated [1–10]. These polyspiranes exhibit helical disposition of the six-membered rings, and the helix can turn identical with itself after each fourth six-membered ring.

Spiro[5.5]undecane, considered as the parent compound of the series, is chiral (Scheme 1) and its chirality is due to the helicity of the spirane skeleton (the helix begins to be built). The flipping of the six-membered rings transforms the M enantiomer into the P one and vice versa (I ⇆ II), this conformational equilibrium being an enantiomeric inversion. The barrier of the process is not high enough for the discrimination and separation of the enantiomers of this compound.

The 3,9-disubstituted-spiro[5.5]undecane derivatives (and the similar compounds with 1,3-dioxane or 1,3-dithiane rings) show anancomeric structures (Scheme 2), and the conformational equilibria are shifted toward the conformers with the larger groups in equatorial orientation. In these cases, the enantiomers (III and IV), generated by the helix of the spirane skeleton, can be discriminated and isolated, the racemization of the compounds being not possible anymore [1].

On the other hand, the 1,3-oxathiane derivatives exhibit some peculiar stereochemistry aspects. The heterocycle is chiral and its flipping is an enantiomeric inversion (V ⇆ VI) [11–13]. The chirality of the heterocycle can be attributed to a virtual tricoordinated chiral center (C*, Scheme 3, structures V and VI).

Many derivatives with 2,4,8,10-tetraheteroatom-spiro[5.5]undecane skeleton (bearing either oxygen or sulfur atoms in the rings, Chart 1, structures VII and VIII) were already investigated [5–8, 14, 15], but very few data about spiranes showing both heteroatoms in the spirane unit such as 1,3-dioxane-1,3-dithiane spiranes (IX) or bis(1,3-oxathiane) spiranes (X) were reported [16–20].

The most important reported results deal with the synthesis of a series of non-symmetrically substituted derivatives having the 1,3-dithiane-1,3-dioxane skeleton (type IX) using acetalization (**1** → **2**; **3** → **4**) and transthioacetalization (**2** → **3**) processes (Scheme 4) [16]. Further substitutions of the 1,3-dithiane ring were carried out on these compounds by deprotonation (BuLi) in position 3

Electronic supplementary material The online version of this article (doi:10.1007/s11224-011-9848-2) contains supplementary material, which is available to authorized users.

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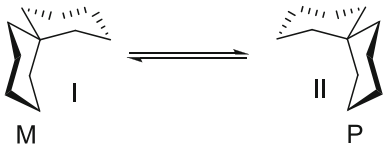
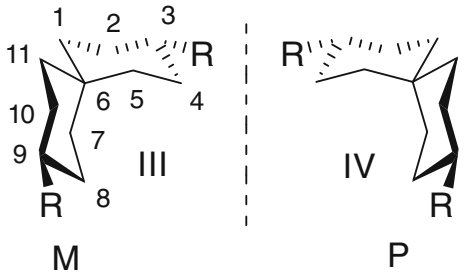
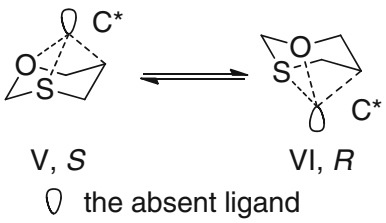


Scheme 1 Conformational equilibrium for spiro[5.5]undecane



Scheme 2 Enantiomers of 3,9-disubstituted-spiro[5.5]undecane derivatives



Scheme 3 Virtual tricoordinated chiral centers of 1,3-oxathiane

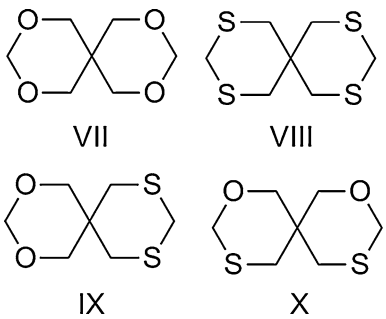
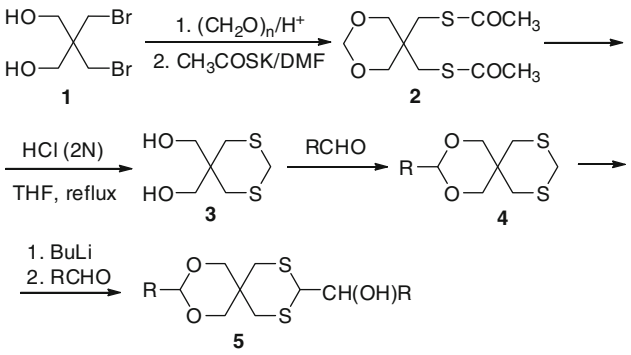


Chart 1 Spirane skeletons with 1,3-dioxane (VII, IX), 1,3-dithiane (VIII, IX), and 1,3-oxathiane (X) rings

(**4** → **5**), followed by the reaction with different electrophiles (e.g., RCHO, Scheme 4) [16, 18].

We considered of interest to study the stereochemistry of new spiro compounds showing skeletons of types IX and X. In view of the complexity of configurational and conformational aspects of such compounds, we were interested in obtaining symmetrically substituted derivatives (XI and XII, Chart 2) and in investigations concerning their structure carried out by NMR spectroscopy, mass spectrometry, and molecular modeling.



Scheme 4 Synthesis of compound **5**

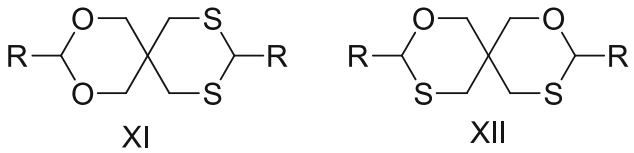


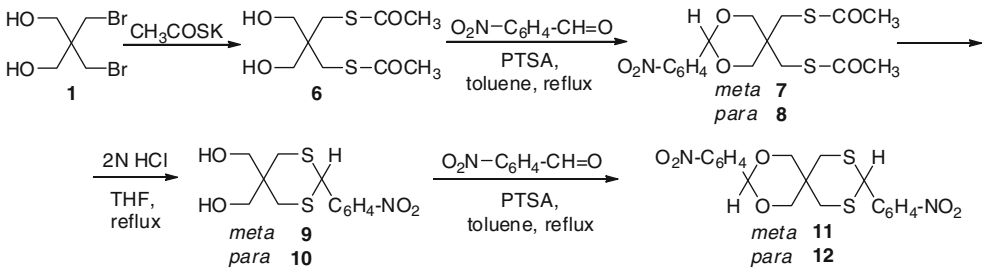
Chart 2 Target symmetrically substituted 1,3-dioxane-1,3-dithiane (XI) and bis(1,3-oxathiane) (XII) compounds

Results and discussions

Two synthetic strategies were employed to access spiranes with S and O atoms in the rings. The first option (named Method A) was to carry out the synthesis of derivatives of type XI by the methodology that was used for obtaining non-symmetrically substituted compound **5**. The next considered possibility (Method B) was to carry out the (thio)acetalization reaction of 2,2-bis(mercaptomethyl)-1,3-propanediol with different aldehydes and to separate compounds of types XI and XII which theoretically can be formed during this reaction.

Method A (acetalization and transacetalization starting from 2,2-dibromomethyl-1,3-propanediol **1**)

This synthetic strategy was developed after the procedure used for the preparation of 1,3-dioxane-1,3-dithianes **5** (Scheme 4) [16]. This procedure based on acetalization and transthioacetalization processes was slightly modified as the original reaction-path gave poor yields for the first steps; hence thioacetylation was performed before acetalization. The protected dimercaptodiol **6** (obtained from the dibromo derivative **1** by a typical procedure) [21] was subjected to acetalization reaction to afford the 1,3-dioxane compounds **7** and **8** (Scheme 5). Reflux of 1,3-dioxane derivative with HCl in THF leads to deprotection of the mercapto group followed by transthioacetalization (procedure similar to the synthesis of **3**, Scheme 4) and the obtaining of dithianes **9** and **10**, respectively. In the next step, the 1,3-dithiane compounds (**9** and **10**) were



Scheme 5 Synthesis of compounds **11** and **12** by method A

submitted to the acetalization reaction with the formation of 1,3-dioxane-1,3-dithiane compounds (**11**, **12**), respectively. Formation of the corresponding bis(1,3-oxathiane) derivatives (XII) was not observed in this reaction; compounds **11** and **12** were purified by column chromatography.

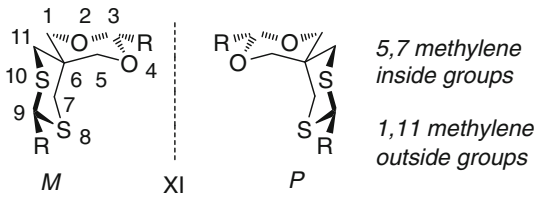
Method B [(thio)acetalization of 2,2-bis(mercaptomethyl)-1,3-propanediol **13**)]

The (thio)acetalization (Scheme 6) of *m*- or *p*-nitrobenzaldehyde with 2,2-bis(mercaptomethyl)propane-1,3-diol **13** (obtained by the reduction of **6** with $LiAlH_4$) [19] resulted into the mixture of 1,3-dioxane-1,3-dithiane spiranes (**11** and **12**) and the corresponding bis(1,3-oxathiane) derivatives (**14** and **15**). The composition of the crude products in 1,3-dioxane-1,3-dithiane spiranes and bis(1,3-oxathiane) derivatives could be correlated with the reaction time (Table 1). The diminishing of the reaction time lead to smaller overall yields but increased the ratio in bis(1,3-oxathiane) spiranes (Table 1). Separation of the crude mixtures by column chromatography (pentane/ethylacetate = 2/1) allowed the isolation of 1,3-dioxane-1,3-dithiane compounds (**11** and **12**) along with fractions containing mixtures of isomers of bis(1,3-oxathiane) derivatives (**14** and **15**).

Compounds **11** and **12** (type XI, Chart 2) are anancomeric and exhibit stable enantiomers (P or M configuration of the helix, theoretically separable) (Scheme 7). The bis(1,3-oxathiane) spiro compounds **14** and **15** (type XII) are also anancomeric, but they have a more complex

Table 1 Results of the synthesis of compounds **11**, **12**, **14**, and **15** using different methods

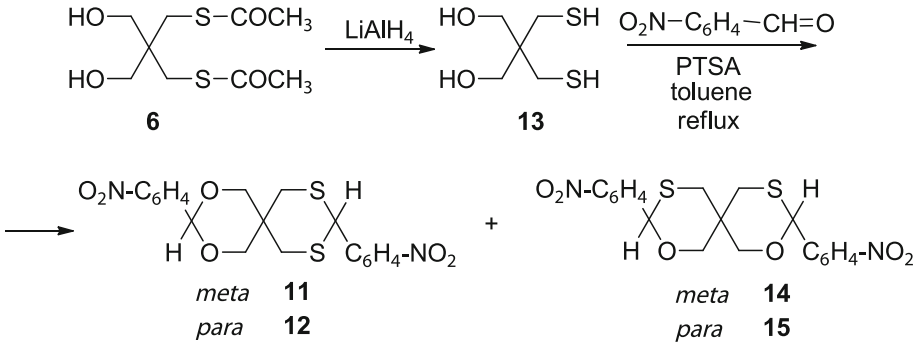
Method	Yields %			
	11	**14**	**12**	**15**
A	42	–	34	–
B1 (10 h)	45	<3	38	<3
B2 (2 h)	27	8	21	11

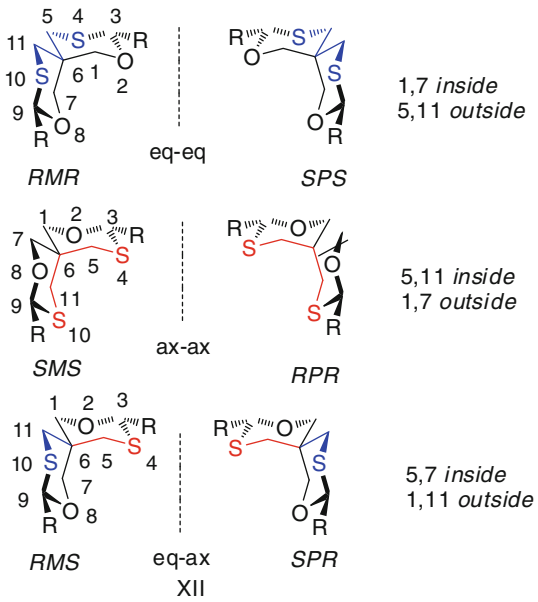


Scheme 7 Enantiomers of **11** and **12**

stereochemistry. In agreement with the fact that type X structures (Chart 1) exhibit three chiral elements (besides the helicity of the spirane unit, there are two tricoordinated virtual chiral centers belonging to the 1,3-oxathiane rings), the bis(1,3-oxathianes) XII exhibit three diastereoisomers all with the substituents at positions 3 and 9 in equatorial orientations (Scheme 8). The $–CH_2S–$ unit (with highest precedence) incorporated in one cycle can be considered as a substituent of the other cycle and it can exhibit either axial or equatorial positions. The three diastereoisomers are

Scheme 6 Synthesis of **11**, **12**, **14** and **15** by method B





Scheme 8 Stereoisomers of **14** and **15**

denoted as equatorial–equatorial (eq–eq), axial–equatorial (ax–eq), or axial–axial (ax–ax) (Scheme 8).

Two of the three isomers of **15** could be isolated by a second column chromatography separation (pentane/dichloromethane = 1/2) of the isomeric mixture and they were identified by the NMR spectra as being the equatorial–equatorial (eq–eq) and equatorial–axial (eq–ax) isomers. All column chromatography attempts to separate the isomers of **14** were unsuccessful.

In order to determine the ratios at equilibrium between compounds with 1,3-dioxane-1,3-dithiane (**11** or **12**) and bis(1,3-oxathiane) (**14** or **15**) structures, compound **11** (or **12**) was refluxed for 2 days in toluene (PTSA was used as acidic catalyst). Investigation of the crude (TLC and NMR) showed the recovery of spirane **11** (**12**, respectively) and no formation of **14** (**15**) could be observed. However, when a mixture of isomers of **14** (or **15**) was submitted to the same equilibration procedure, the total transformation of **14** (**15**) into compound **11** (**12**, respectively) was noticed (Scheme 9). Transformation of **14** or **15** into the more stable **11** or **12** was observed even for samples stored in the refrigerator.

It is to suppose that the two types of compounds [1,3-dioxane-1,3-dithiane and bis(1,3-oxathiane) spiranes] are both formed during the direct thioacetalization reaction (Method B). The fact that compounds **11** and **12** are obtained as major products by Method B (Table 1) could be explained by considerably higher stability of these compounds (see the molecular modeling results described below). Meanwhile, the less stable bis(1,3-oxathiane) spiranes **14** and **15** are transformed (isomerized) into the more stable derivatives **11** and **12**.

When Method B was used, the reaction was stopped before the entire amount of **14** or **15** was isomerized into **11** or **12**.

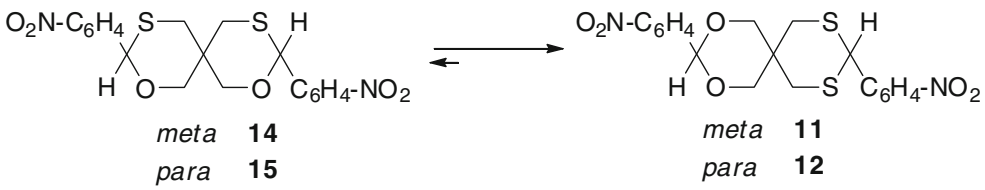
Structural investigations

The optimized geometries of the 1,3-dioxane-1,3-dithiane **12** and of the isomers of the bis(1,3-oxathiane) **15** were obtained using DFT methods. Details regarding the software packages, the functionals, the basis sets, the number of imaginary frequencies, as well as the Cartesian coordinates of equilibrium arrangements are included in the Supporting Information. The representations of the equilibrium structures obtained by calculations at the BP86/TZ2P level of theory are shown in Fig. 1.

The results of theoretical calculations on **12** and **15** are consistent with the experimental data. In the gas phase, **12** with ca. 3 kcal/mol is more stable than the isomers of **15** (Table 2). The values of the energy differences between the isomers of the bis(1,3-oxathiane) **15** are small and dependent on the chosen functional and basis sets, respectively. Still, a higher stability induced by the equatorial orientation of the CH_2S groups can be suggested. Considering the experimental data, the proposed order of stability for structures XI and XII is XI $\gg$ XII(eq–eq) > XII(eq–ax) > XII(ax–ax).

The structure of compounds **11** and **12** in solution was investigated by NMR spectroscopy. ^{1}H NMR spectra exhibit different signals for the protons at positions 3 and 9 and for the protons of the two aromatic units. The CH_2 groups of the 1,3-dioxane ring (positions 1 and 5) as well as those of the 1,3-dithiane ring (7 and 11) are diastereotopic (Scheme 7). Positions 5 and 7 represent *methylene inside* groups being oriented toward the other heterocycle of the spirane, while positions 1 and 11 are considered *methylene outside* groups (Scheme 7). The equatorial protons of the *methylene inside* positions are strongly deshielded by the influence (through space) of the two heteroatoms of the

Scheme 9 1,3-Dioxane-1,3-dithiane and bis(1,3-oxathiane) derivatives equilibrium



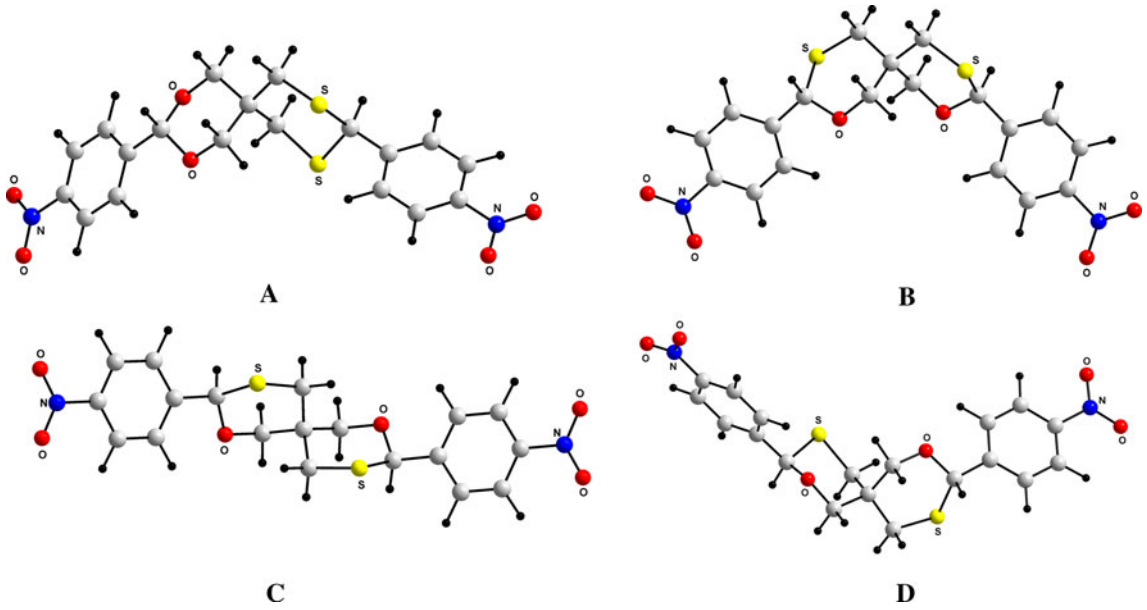


Fig. 1 Equilibrium structures for **12** (**a**) and **15** (eq–eq) (**b**), **15** (ax–ax) (**c**), and **15** (eq–ax) (**d**)

Table 2 Calculated relative energies between **12** and the isomers of **15** at different levels of theory

Compd.	E^{a}_{rel} [kcal/mol]	E^{b}_{rel} [kcal/mol]	E^{c}_{rel} [kcal/mol]
15 (ax–ax)	3.07	3.35	3.45
15 (ax–eq)	3.06	3.02	3.18
15 (eq–eq)	3.57	3.13	3.06
12	0	0	0

[a] ADF BP86/TZ2P; [b] GAMESS B3LYP/6-31G(d); [c] ORCA B3LYP/6-31G(d,p)

other heterocycle (Table 3). The relevant fragment of the ^{1}H NMR spectrum of **12** is presented in Fig. 2a.

As expected, the NMR spectra of isomeric **15** (eq–eq) and **15** (eq–ax) are quite different. In the spectrum of the eq–eq isomer, the two –CH_2O– groups (positions 1 and 7) and the two –CH_2S– groups (positions 5 and 7) have similar pattern in NMR. The methylene groups connected to the oxygen atoms (–CH_2O–) are both *methylene inside*, while those of the –CH_2S– moieties are both *methylene outside* groups. The equatorial protons of the *methylene inside* –CH_2O– groups are very deshielded (δ_e = 5.19 ppm, Fig. 2b) in agreement with the data obtained for the similar protons in **12** (δ_e = 5.29 ppm, methylene inside –CH_2O– group) and with the previously reported NMR investigations carried out with 2,4,8,10-tetraoxa-spiro[5.5]undecane derivatives [1, 2, 4, 22, 23]. The protons of positions 3 and 9 in **15** (eq–eq) are equivalent and they give a unique signal (δ = 5.86 ppm, Fig. 2b). The assignment of this spectrum (Fig. 2b) to the eq–eq isomer and not to the ax–ax isomer (which should exhibit a similar ^{1}H NMR pattern) was based on the chemical shifts (deshielding) of the signals. In the ax–ax isomer of **15**, both –CH_2–O– groups are *methylene outside*, while the –CH_2S– groups are both *methylene inside*. The signals for the *methylene outside* –CH_2–O– group in **12** appear at δe = 3.99 and δa = 3.87 ppm), while the signals pertaining to the *methylene inside* –CH_2S– in **12** give the signals δe = 3.59 and δa = 3.04 ppm (for NMR data on 2,4,8,10-tetrathia-spiro[5.5]undecane derivatives see [8]).

Table 3 ^{1}H NMR data (selected, δ, ppm) for compounds **11**, **12**, and **15**

Compound	3-H	9-H	–O–CH_2– (inside)		–S–CH_2– (inside)		–O–CH_2– (outside)		–S–CH_2– (outside)	
			Heq	Hax	Heq	Hax	Heq	Hax	Heq	Hax
11	5.55	5.19	5.30 (5)	3.71 (5)	3.59 (7)	3.05 (7)	3.99 (1)	3.88 (1)	2.54 (11)	2.90 (11)
12	5.54	5.18	5.29 (5)	3.70 (5)	3.59 (7)	3.04 (7)	3.99 (1)	3.87 (1)	2.53 (11)	2.90 (11)
15 (eq–eq)	5.86		5.19 (1,7)	3.53 (1,7)	–	–	–	–	2.56 (5, 11)	3.18 (5, 11)
15 (eq-ax)	5.81; 5.85		5.28 (7)	3.03 (7)	3.58–3.61 (5)	3.91–3.93 (5)	3.91–3.93 (1)	3.58–3.61 (1)	2.41 (11)	3.16 (11)

The numbering of the inside and outside positions in different structures is shown inside the brackets

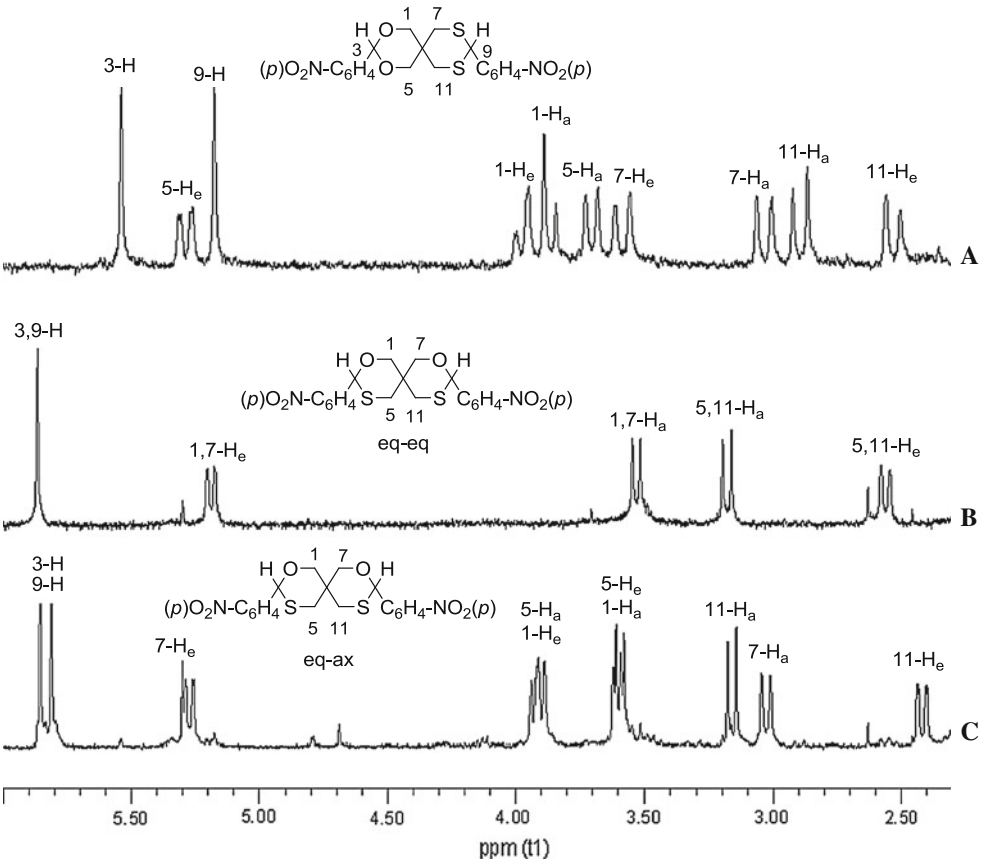


Fig. 2 ^{1}H NMR spectra (fragments) of compounds **12** (**a**), **15** (eq–eq) (**b**), and **15** (eq–ax) (**c**)

The spectrum in Fig. 2b was assigned to the eq–eq isomer on the basis of the very deshielded signal (δe = 5.19 ppm) which belongs to equatorial protons of *methylene inside* –CH_2O– groups and such groups exist only in the eq–eq isomer.

The ^{1}H NMR spectrum of the eq–ax isomer of **15** is more complicated, for either –CH_2O– or –CH_2S– fragments there are *methylene inside* and *methylene outside* groups. The protons at positions 3 and 9 give different signals (δ = 5.81 and 5.85 ppm, Fig. 2c) as one of them is connected to the ring having *methylene inside* group of –CH_2O– moiety and the other one is attached to the ring in which the *methylene inside* group belongs to the –CH_2S– fragment. The protons at positions 1 and 7 as well as those at positions 5 and 11 give different signals. The more deshielded signal belongs to the equatorial proton of the –CH_2O– *methylene inside* fragment (δ_e = 5.28 ppm), while the equatorial proton of the *methylene outside* –CH_2S– moiety is the most shielded one (Fig. 2c; Table 3).

Conclusions

Spiro[5.5]undecane derivatives with O and S atoms in the rings exhibit different stabilities in correlation with the nature of the constituent heterocycles. The molecular modelling and the equilibration experiments showed that bis(1,3-oxathiane) spiranes are less stable than the isomeric spiranes bearing both 1,3-dioxane and 1,3-dithiane rings. The synthesis based on the (thio)acetalization reaction of 2,2-bis(mercaptomethyl)-1,3-propanediol **6** leads to the initial formation of both bis(1,3-oxathiane) (XII) and 1,3-dioxane-1,3-dithiane (XI) spiranes, but during the process the bis(1,3-oxathiane) derivative (XII) can be totally isomerized into the more stable spirane with different heterocycles (XI). The structures of the compounds were deduced based on important differences between the NMR spectra of spiranes XI and the isomers belonging to spiranes XII.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 300 or 400 spectrometers operating at 300 (400) MHz for proton and 75 (100) MHz for carbon atoms; δ are given in ppm (relative to TMS) and coupling constants (J) in Hz. Mass spectra were recorded under ESI ion trap mass spectrometer (Agilent 6320) in positive mode and/or under EI mode (70 eV) on a VG-Autospec mass spectrometer. Melting points were measured with a Kleinfeld melting point apparatus and are uncorrected. Elemental

analyses were determined at Babes-Bolyai University, Cluj-Napoca. Thin-layer chromatography was performed on Merck silica gel 60 F 254 sheets. Silica gel Merck (40–63 μm) was used for flash chromatography.

Procedure for the synthesis of 2,2-bis(acetylthiomethyl)-1,3-propandiol **6**

To a stirred solution of 2,2-bis(bromomethyl)-1,3-propandiol **1** (6.5 g, 25 mmol) in anhydrous DMF (190 mL) under argon, potassium thioacetate (13.11 g, 115 mmol) was added at room temperature (RT). The stirring was continued for 6 days (TLC control), then the mixture was concentrated to 20 mL volume. CH_2Cl_2 (150 mL) is added and the organic solution was washed with brine (4 × 90 mL). The separated organic phase was dried over sodium sulfate and concentrated. The crude product was subjected to column chromatography (*n*-hexane/ethylacetate = 2/1). Compound **6** was obtained as white solid in 38% yield (2.4 g) [21].

Procedure for the synthesis of 5,5-bis(mercaptomethyl)-2-(*m*- or *p*-)nitrophenyl-1,3-dioxanes **7** and **8**

A solution of 2,2-bis(acetylthiomethyl)-1,3-propandiol **6** (0.22 g, 0.872 mmol), *m*- or *p*-nitrobenzaldehyde (0.16 g, 1.05 mmol), and PTSA (0.05 g, 0.3 mmol) in toluene (30 mL) was refluxed for 12 h using a Dean-Stark trap. The mixture was cooled to RT and neutralized with sodium acetate (0.2 g). The mixture was washed with water (2 × 50 mL), the organic layer was separated and dried over sodium sulfate and concentrated. The solid residue was purified by column chromatography (hexane/dichloromethane = 1/1).

*5,5-Bis(mercaptomethyl)-2-m-nitrophenyl-1,3-dioxane **7***

White crystals, m.p. = 117–118 C. $R_f = 0.14$ (hexane/CH_2Cl_2 = 1/1). Yields 70%. Found: C, 50.07; H, 4.80; N, 3.78; S, 16.38, $C_{16}H_{19}N_2O_6S_2$ requires C, 49.86; H, 4.97; N, 3.63; S, 16.64. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.09$ (3H, s, CH_{3e}), 2.11 (3H, s, CH_{3a}), 2.85 (2H, d, J = 14.5 Hz, 4-H_a, 6-H_a), 3.04 (2H, d, $J = 14.5$ Hz, 4-H_e, 6-H_e), 4.05 [2H, s, 5(5′)-CH_{2e}–], 4.64 [2H, s, 5(5′)-CH_{2a}–], 5.17 (1H, s, 2-H_a), 7.55 (1H, t, $J \approx J' \approx 8.0$ Hz, 5′-H), 7.87 (1H, d, $J = 7.8$ Hz, 6′-H), 8.18 (1H, d, $J = 8.3$ Hz, 4′-H), 8.36 (1H, s, 2′-H), ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 20.73$ (5-CH_{3e}), 20.80 (5-CH_{3a}), 32.03 (C^5), 35.08 ($C^{4,6}$), 50.19 (C^2), 62.72 (5-CH_{2e}–), 67.52, (5-CH_{2a}–), 123.04; 123.64, 129.85, 133.95 (tertiary aromatic carbon atoms), 140.02, 148.35 (quaternary aromatic carbon atoms), 170.52, 170.54 (–S–CO–).

*5,5-Bis(mercaptomethyl)-2-p-nitrophenyl-1,3-dioxane **8***

White crystals, m.p. = 134–135 °C. $R_f = 0.21$ (hexane/CH_2Cl_2 = 1/1). Yields 32%. Found: C, 49.64; H, 4.77; N, 3.79; S, 16.74, $C_{16}H_{19}N_2O_6S_2$ requires C, 49.86; H, 4.97; N, 3.63; S, 16.64. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.08$ (3H, s, CH_{3e}), 2.10 (3H, s, CH_{3a}), 2.84 (2H, d, $J = 14.4$ Hz, 4-H_a, 6-H_a), 3.03 (2H, d, $J = 14.4$ Hz, 4-H_e, 6-H_e), 4.04 [2H, s, 5(5′)-CH_{2e}-], 4.64 [2H, s, 5(5′)-CH_{2a}-], 5.15 (1H, s, 2-H_a), 7.67 (2H, d, $J = 8.7$ Hz, 2′-H, 6′-H), 8.20 (1H, d, $J = 8.7$ Hz, 3′-H, 5′-H), ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 20.75$ (5-CH_{3e}), 20.83 (5-CH_{3a}), 31.99 (C^5), 35.09 ($C^{4,6}$), 50.39 (C^2), 62.63 (5-CH_{2e}–), 67.56, (5-CH_{2a}–), 124.02; 128.94 (tertiary aromatic carbon atoms), 144.95, 147.85 (quaternary aromatic carbon atoms), 170.54, 170.59 (–S–CO–).

Procedure for the synthesis of 5,5-bis(hydroxymethyl)-2-(*m*- or *p*-)nitrophenyl-1,3-dithianes **9** and **10**

A solution of 1,3-dioxanes **7** or **8** (0.20 g, 0.519 mmol) in THF (40 mL) and 2 N HCl (10 mL) was refluxed for 24 h. The mixture was cooled to RT, neutralized with 5% Na_2CO_3 to pH = 8–9 with stirring (1 h). The solution was extracted with dichloromethane (3 × 50 mL), the separated organic phase was dried over sodium sulfate and concentrated. The solid residue was purified by column chromatography (pentane/dichloromethane = 1/4).

*5,5-Bis(hydroxymethyl)-2-m-nitrophenyl-1,3-dithiane **9***

White crystals, m.p. = 143–144 °C. $R_f = 0.18$ (pentane/CH_2Cl_2 = 1/4). Yields 48%. Found: C, 47.54; H, 4.92; N, 4.79; S, 21.04, $C_{12}H_{15}NO_4S_2$ requires C, 47.82; H, 5.02; N, 4.65; S, 21.28. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 2.91$ (4H, s, 4-H, 6-H), 3.67 (2H, s, 5-CH_{2e}–) 4.29 (2H, s, 5-CH_{2a}–), 5.16 (1H, s, 2-H_a), 7.53 (1H, t, $J \approx J' \approx 8.0$ Hz, 5′-H), 7.84 (1H, d, $J = 8.0$ Hz, 6′-H), 8.18 (1H, d, $J = 7.8$ Hz, 4′-H) 8.39 (1H, s, 2′-H), ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 33.41$ (C^5), 34.31 ($C^{4,6}$), 49.49 (C^2), 60.42 (5-CH_{2e}–), 66.61 (5-CH_{2a}–), 122.32; 122.83, 129.65, 133.87 (tertiary aromatic carbon atoms), 139.22, 147.65 (quaternary aromatic carbon atoms).

*5,5-Bis(hydroxymethyl)-2-p-nitrophenyl-1,3-dithiane **10***

White crystals, m.p. = 203–204 °C. $R_f = 0.17$ (pentane/CH_2Cl_2 = 1/4). Yields 60%. Found: C, 47.61; H, 5.15; N, 4.37; S, 21.11, $C_{12}H_{15}NO_4S_2$ requires C, 47.82; H, 5.02; N, 4.65; S, 21.28. ^{1}H NMR (400 MHz, CD_3OD) $\delta = 2.79$ (2H, d, J = 14.3 Hz, 4-H_a, 6-H_a), 3.07 (2H, d, J = 14.3 Hz, 4-H_e, 6-H_e), 3.52 (2H, s, 5-CH_{2e}–) 4.09 (2H, s, 5-CH_{2a}–), 5.34 (1H, s, 2-H_a), 7.75 (2H, d, J = 8.7 Hz, 2′-H, 6′-H), 8.23 (2H, d, J = 8.7 Hz, 3′-H, 5′-H), ^{13}C NMR (100 MHz, CD_3OD) $\delta = 33.48$ (C^5), 34.31 ($C^{4,6}$), 49.82

(C^2), 60.42 (5-CH_{2e}–), 66.61 (5-CH_{2a}–), 123.42, 128.79 (tertiary aromatic carbon atoms), 144.73, 146.21 (quaternary aromatic carbon atoms).

Procedure for the synthesis of 2,2-bis(mercaptomethyl)-1,3-propandiol **13**

To a stirred solution of 2,2-bis(acetylthiomethyl)-1,3-propandiol **6** (0.22 g, 0.872 mmol) in anhydrous THF (22 mL) under argon, $LiAlH_4$ (0.165 g, 4.348 mmol) was added at RT. The stirring was continued for 16 h, then the mixture was cooled on an ice bath and a solution of HCl 18% was added to pH = 1.5–2. The solution was extracted with diethylether (5 × 50 mL), and then the combined organic phase was washed with brine (2 × 15 mL). The separated organic phase was dried over sodium sulfate and concentrated. Compound **13** was obtained as strong-smelling white crystals in 52% yield. The synthesis of this compound by other procedures has already been reported [19, 20].

Procedures for the synthesis of spiro-1,3-dioxane-1,3-dithiane **11** and **12** and of bis(1,3-oxathiane)spiranes **14** and **15**

Method A

A solution of 2-(*m*- or *p*-)-nitrophenyl-5,5-bis(hydroxymethyl)-1,3-dithiane (**9** or **10**; 0.100 g, 0.33 mmol), *m*- or *p*-nitrobenzaldehyde (0.060 g, 0.4 mmol), and PTSA (0.010 g, 0.06 mmol) in toluene (10 mL) was refluxed for 10 h using a Dean-Stark trap. After the mixture was cooled to RT, the unreacted mercapto derivative was neutralized with KOH 0.1 M (1.5 mL). The mixture was washed with water (2 × 10 mL), the organic layer was separated and dried over sodium sulfate and concentrated. The crude product was crystallized from methanol to afford 1,3-dioxane-1,3-dithiane spiranes **11** or **12**.

Method B

A solution of 2,2-bis(mercaptomethyl)-1,3-propanediol **13** (0.100 g, 0.59 mmol), *m*- or *p*-nitrobenzaldehyde (0.218 g, 1.44 mmol), and PTSA (0.015 g, 0.09 mmol) in toluene (20 mL) was refluxed for 10 h (A1) or 2 h (A2) using a Dean-Stark trap. After the mixture was cooled to RT, the unreacted mercapto derivative was neutralized with KOH 0.1 M (3 mL). The mixture was washed with water (2 × 10 mL), the organic layer was separated and dried over sodium sulfate and concentrated. The crude product was subjected to column chromatography (pentane/ethylacetate = 1/2). Pure samples of 1,3-dioxane-1,3-dithiane (**11** or **12**) were thus obtained along with a diastereomeric mixture of bis(1,3-oxathiane)spiranes (**14** or **15**). The (eq–eq) and (eq–ax) isomers of **15** were separated from this mixture by a subsequent column chromatography (pentane/dichloromethane = 1/2).

Procedure for the isomerization of bis(1,3-oxathiane)spiranes **9b** and **10b** into spiro-1,3-dioxane-1,3-dithiane **9a** and **10a**

The solution of the mixture of isomers of **14** or **15** (0.020 g) and PTSA (0.001 g, catalytic amounts) in toluene (10 mL) was refluxed for 2 days. After cooling at RT, 1 mL KOH 0.1 M was added and the toluene solution was stirred for 1 h. The toluene solution was washed with water (2 × 5 mL) then the organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed by vacuum distillation, and the crude product was investigated by chromatographical methods and by NMR spectra and the entire transformation of **14** or **15** into **11** or **12** was observed.

*3,9-Bis(m-nitrophenyl)-2,4-dioxa-8,10-dithia-spiro[5.5] undecane (**11**)*

White crystals, m.p. = 171–172 °C, R_f = 0.19 (pentane/ethylacetate = 1/2). Yields 45% (A1). Found: C, 52.31; H, 4.31; N, 6.63; S, 14.92, $C_{19}H_{18}N_2O_6S_2$ requires C, 52.52; H, 4.18; N, 6.45; S, 14.76. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.54 (1H, dd, J = 14.3, 1.8 Hz, 11-H_e), 2.90 (1H, d, J = 14.3 Hz, 11-H_a), 3.05 (1H, d, J = 14.2, 7-H_a), 3.59 (1H, dd, J = 14.2, 1.8 Hz, 7-H_e), 3.71 (1H, d, J = 11.6, Hz, 5-H_a), 3.88 (1H, d, J = 11.5 Hz, 1-H_a), 3.99 (1H, dd, J = 11.5, 2.7 Hz, 1-H_e), 5.19 (1H, s, 9-H_a), 5.30 (1H, dd, J = 11.6, 2.7 Hz, 5-H_e), 5.55 (1H, s, 3-H_a), 7.56–7.58 (2H, overlapped peaks, 5′-H, 5″-H), 7.85–7.87 (2H, overlapped peaks, 6′-H, 6″-H), 8.20–8.23 (2H, overlapped peaks, 4′-H, 4″-H), 8.39–8.41 ppm (2H, overlapped peaks, 2′-H, 2″-H). ^{13}C NMR (100 MHz, $CDCl_3$), 27.21 ($C^{7,11}$), 36.08 (C^6), 50.79 (C^9), 71.14, 76.13 ($C^{1,5}$), 100.54 (C^3), 121.49, 123.11, 123.91, 124.07, 128.96, 129.33, 129.87, 133.98 (tertiary aromatic carbon atoms), 139.64, 140.12, 148.18, 148.42 (quaternary aromatic carbon atoms), MS (APCI); m/z = 435.1.

*3,9-Bis(p-nitrophenyl)-2,4-dioxa-8,10-dithia-spiro[5.5] undecane (**12**)*

White crystals, m.p. = 250–251 °C, R_f = 0.80 (pentane/ethylacetate = 1/2). Yields 38% (A1). Found: C, 52.43; H, 4.51; N, 6.62; S, 14.58, $C_{19}H_{18}N_2O_6S_2$ requires C, 52.52; H, 4.18; N, 6.45; S, 14.76. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.53 (1H, d, J = 14.2, 11-H_e), 2.90 (1H, d, J = 14.2 Hz, 11-H_a), 3.04 (1H, d, J = 15.0 Hz, 7-H_a), 3.59 (1H, d, J = 15.0 Hz, 7-H_e), 3.70 (1H, d, J = 11.9 Hz, 5-H_a), 3.87 (1H, d, J = 11.6 Hz, 1-H_a), 3.99 (1H, dd,

$J = 11.6$, 1.6 Hz, 1-H_e), 5.18 (1H, s, 9-H_a), 5.29 (1H, dd, $J = 11.9$, 1.6 Hz, 5-H_e), 5.54 (1H, s, 3-H_a), 7.65–7.72 [4H, overlapped peaks, 2′(2″)-H, 6′(6″)-H], 8.20–8.24 [4H, overlapped peaks, 3′-H, 3″-H, 5′-H, 5″-H], ^{13}C NMR (100 MHz, $CDCl_3$) 27.27, 29.74 ($C^{7,11}$), 36.15 (C^6), 50.79 (C^9), 71.15, 76.17 ($C^{1,5}$), 100.70 (C^3), 123.55, 124.13, 127.24, 128.99 (tertiary aromatic carbon atoms), 117.28, 131.07, 144.07, 145.08 (quaternary aromatic carbon atoms), MS (APCI); m/z = 435.1.

*3,9-Bis(m-nitrophenyl)-2,8-dioxa-4,10-dithia-spiro[5.5] undecane (**14**, mixture of isomers)*

White crystals, $R_f = 0.25$ (pentane/ethylacetate = 1/2). Yields 8% (A2). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.52–2.58 (1H, overlapped peaks, 11-H_e), 3.13–3.19 (2H, overlapped peaks, 7-H_a, 11-H_a), 3.52–3.89 (4H, overlapped peaks, 1-H_a, 5-H_e, 1-H_e, 5-H_a), 5.19–5.21 (1H, overlapped peaks, 7-H_e), 5.49, 5.86 (2H, s, 3-H, 9-H), 7.55–7.57 (2H, overlapped peaks, 5′-H, 5″-H), 7.82–7.84 (2H, overlapped peaks, 6′-H, 6″-H), 8.21–8.24 (2H, overlapped peaks, 4′-H, 4″-H), 8.36–8.39 (2H, overlapped peaks, 2′-H, 2″-H), MS (APCI); m/z = 435.1

*3,9-Bis(p-nitrophenyl)-2,8-dioxa-4,10-dithia-spiro[5.5]undecane (**15**, eq–eq isomer)*

White crystals, m.p. = 244–245 °C, $R_f = 0.36$ (pentane/CH_2Cl_2 = 1/2). Yields 7% (A2). Found: C, 52.67; H, 4.29; N, 6.28; S, 14.92, $C_{19}H_{18}N_2O_6S_2$ requires C, 52.52; H, 4.18; N, 6.45; S, 14.76. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.56 (2H, dd, $J = 14.2$, 1.0 Hz 5-H_e, 11-H_e), 3.18 (2H, d, $J = 14.2$ Hz, 5-H_a, 11-H_a), 3.53 (2H, d, $J = 15.0$ Hz, 1-H_a, 7-H_a), 5.19 (2H, dd, $J = 15.0$ Hz, 1.0 Hz, 1-H_e, 7-H_e), 5.86 (2H, s, 3-H, 9-H), 7.68 (4H, d, $J = 8.5$ Hz, 2′-H, 2″-H, 6′-H, 6″-H), 8.24 (4H, d, $J = 8.5$ Hz, 3′-H, 3″-H, 5′-H, 5″-H), ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 26.53 ($C^{5,11}$), 37.67 (C^6), 69.81 ($C^{1,7}$), 88.82 ($C^{3,9}$), 123.68, 127.00 (tertiary aromatic carbon atoms), 144.34, 147.37 (quaternary aromatic carbon atoms). MS (APCI); m/z = 435.1.

*3,9-Bis(p-nitrophenyl)-2,8-dioxa-4,10-dithia-spiro[5.5]unde cane (**15**, eq–ax isomer)*

White crystals, m.p. = 233–234 °C, $R_f = 0.25$ (pentane/CH_2Cl_2 = 1/2). Yields 4% (A2). Found: C, 52.30; H, 4.03; N, 6.67; S, 14.59, $C_{19}H_{18}N_2O_6S_2$ requires C, 52.52; H, 4.18; N, 6.45; S, 14.76. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.41 (1H, dd, $J = 13.7$, 2.0 Hz, 11-H_e), 3.03 (1H, d, $J = 14.0$ Hz, 7-H_a), 3.16 (1H, d, $J = 13.7$ Hz, 11-H_a), 3.58–3.61 (2H, overlapped peaks, 1-H_a, 5-H_e), 3.91–3.93 (2H, overlapped peaks, 1-H_e, 5-H_a), 5.28 (1H, dd, $J = 12.2$, 2.0 Hz, 7-H_e), 5.81 (1H, s, 3-H), 5.85 (1H, s, 9-H), 7.62–7.65 (4H, overlapped peaks, 2′-H, 2″-H, 6′-H, 6″-H), 8.21–8.24 (4H, overlapped peaks, 3′-H, 3″-H, 5′-H, 5″-H), ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 34.28, 36.89 ($C^{5,11}$), 43.76 (C^6), 68.85, 72.78 ($C^{1,7}$), 83.62, 83.82 ($C^{3,9}$), 123.66, 123.71 126.89, 126,99 (tertiary aromatic carbon atoms), 140.93, 141.10, 144.19, 145.52 (quaternary aromatic carbon atoms). MS (APCI); m/z = 435.1.

Acknowledgments This work was supported by CNCSIS-UEFISCSU, projects number PNII-IDEI 570/2007 and 2278/2008. We are grateful to the Sectoral Operational Programme for Human Resources Development 2007–2013 (co-financed by the European Social Fund, project number POSDRU/107/1.5/S/77946) for the fellowship given to MLG.

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