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ABSTRACT

Ph.D. THESIS

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Synthesis and structural analysis of new heterocyclic compounds: cyclopenta[*c*]pyrans, polydentate aza-heteroaromatic ligands and spiro-1,3-dioxane macrocycles

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Diastereoisomers

Aza-hetarene ligands

Pyridines

Chirality

Spiro-1,3-dioxane macrocycles

2,4,8,10-Tetraoxaspiro[5.5]undecane

LIST OF ABBREVIATIONS

AIBN	2,2′-Azobis(2-methylpropionitrile)
$AlMe_3$	Trimethylaluminium
AP	Alpha-pyrone
APCI	Atmosphere Pressure Chemical Ionisation
APT	Attached Proton Test
bipy	Bipyridine
n-BuLi	*n*-butyllithium
t-BuLi	*t*-butyllithium
$CDCl_3$	Chloroform-*d*
CH_2Cl_2 (DCM)	Dichloromethane
COSY	Correlated Spectroscopy
CPD	Cyclopentadiene
δ	Chemical shift (NMR)
DEPT	Distortionless Enhancement by Polarization Transfer
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Dimethyl sulfoxide-d_6
DIBAL-H	Diisobutylaluminium hydride
EE	Diethyl ether
eq.	Equivalent
EL	Enol-lactone
EI	Electron impact
ESI	Electronic Spray Ionization
HMBC	Heteronuclear multiple bond correlation experiment
HTMP	2,2,6,6-tetramethylpiperidine
m.p.	Melting point
m/z	Mass-to-charge ratio
Me	methyl
MS	Mass Spectrometry
MTBE	Methyl-*tert*-Butyl Ether
NBS	N-bromosuccinimide

NEt_3	Triethyl amine
NMR	Nuclear Magnetic Resonance
OLED	Organic Light Emitting Diodes
PE	Petroleum ether
Ph	Phenyl
py	Pyridine
pym	Pyrimidine
R_f.	Retention factor
rt	Room temperature
TFAA	Trifluoroacetic anhydride
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TOF	Time of flight
Ts	Tosyl
TsCl	Tosyl chloride
UV/Vis	Ultraviolet/Visible
Φ	Quantum yields

Designation of NMR signals

s	singlet
d	doublet
t	triplet
m	multiplet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
dt	doublet of triplets
ddt	doublet of doublet of triplets
dq	doublet of quartets

TABEL OF CONTENTS

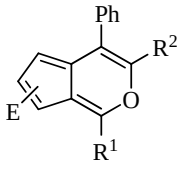
PART 2. Synthesis and analysis of new aza-hetarene ligands

PART 3. Synthesis and analysis of new spiro-1,3-dioxane macrocycles

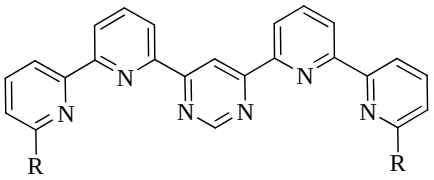
GENERAL INTRODUCTION

The research work presented in this thesis is conducted in three main fields with reference to synthesis of new heterocyclic derivatives like cyclopenta[c]pyrans (I), aza-hetarene ligands (II) and spiro-1,3-dioxane macrocycles (III). All three subjects were developed at Babes-Bolyai University in the research group of Prof. Univ. Dr. Ion Grosu.

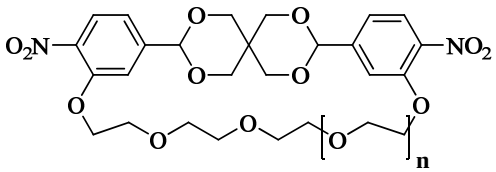
The first subject represents a study of pseudoazulenic derivatives possessing cyclopenta[*c*]pyran skeleton (I). The study comprises synthesis, analysis and reactivity of such derivatives and their intermediates. Biological properties of cyclopenta[*c*]pyrans, with natural occurrence, are of great interest being used in traditional medicine, and investigated for phytotherapeutic, cytotoxic, sedative, antifungal, antiviral, antimicrobial or antitumor activities, making a challenge to synthesise and investigates new cyclopenta[*c*]pyran derivatives.



I



II



III

n=1,2,3

The second subject concerns the synthesis of aza-hetarenes II and functionalisation at the extremities of the molecules in alpha position of the terminal pyridinic unit. Molecules possessing sequences of bipyridine-pyrimidine-bipyridine exhibit helicoidal chirality due to the spatial arrangement of the pyridine units. The number of nitrogen atoms ensures a high coordination degree especially for transitional metal ions, forcing the entire molecule to adopt a linear configuration. The chemistry of such molecular items is the main feature used in construction of supramolecular architectures with specific movements, emerged from their coordinative properties and intelligent design, bringing the necessity to improve the synthesis of components and to chose the proper functional groups in order to put together the whole assembly.

The third subject manages the synthesis, analysis and structural investigation of new macrocyclic derivatives containing spiro-1,3-dioxane unit. The structural characteristic aspects of spiro-1,3-dioxane compounds, for instance the helical chirality, the anancomeric

behaviour and spatial rearrangement makes these compounds versatile substrates for macrocycles with high potential for chemioselective coordination of cation or small neutral molecules. The steric similarities of target macrocycles III with analogous macrocycles obtained from sugars and heterobicycloalkenes which exhibit interesting coordination properties motivate the interest for investigating this type of macrocycles.

PART 1. SYNTHESIS AND ANALYSIS OF NEW CYCLOPENTA[*C*]PYRANS

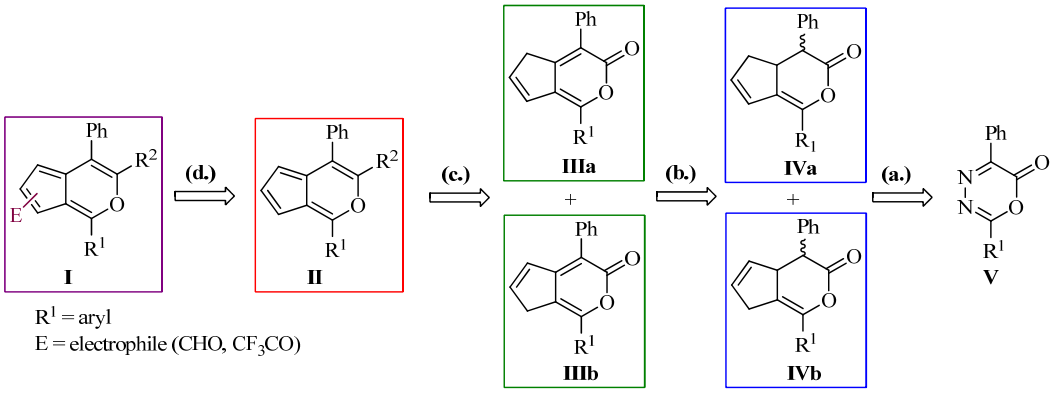
1.1. INTRODUCTION

Cyclopenta[*c*]pyrans belong to a large class of heterocycles, namely pseudoazulenes,[1] which are π-isoelectronic analogues of the non-benzenoid aromatic hydrocarbon azulene. Similar to azulene, dipolar resonance structures contributes to the electron distribution of the ground state of cyclopenta[*c*]pyran, showing an enhanced electron density in the five-membered ring and an electron deficiency in the six-membered one. This similarity suggests an analogy of the properties with those of azulene, foreshadowing the chemical behavior of the cyclopenta[*c*]pyran entity.

1.3. RESULTS AND DISCUSSIONS

1.3.1. Synthesis of cyclopenta[*c*]pyran derivatives

The objective of the first part of the thesis is to synthesise and analyse some new cyclopenta[*c*]pyran derivatives and to investigate their behaviour in aromatic electrophilic substitution reactions. Following a multi-step procedure developed by Christl,[2] a series of new aromatic cyclopenta[*c*]pyran derivatives have been synthesised (scheme 25). Employing this method was possible to synthesise cyclopenta[*c*]pyran derivatives bearing different substituents, which increases the stability of the heterocycle.

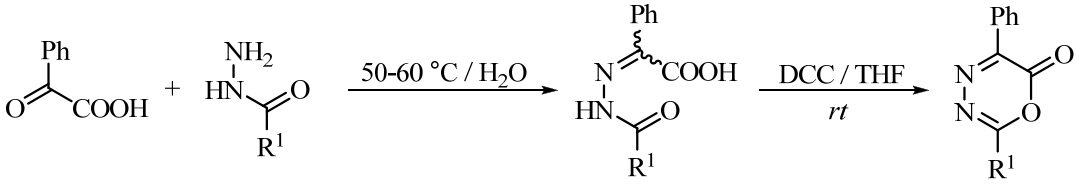


Scheme 25

[1] H.-J. Timpe, A. V. El'tsov, *Adv. Heterocycl. Chem.* **1983**, *33*, 185.
[2] M. Christl, N. Bien, G. Bodenschatz, E. Feineis, J. Hegmann, C. Hofmann, S. Mertelmeyer, J. Ostheimer, F. Sammtleben, S. Wehner, E.-M. Peters, K. Peters, M. Pfeiffer, D. Stalke, *Chem. Commun.* **1998**, 2387.

1.3.1.1. Synthesis of 6-oxo-6*H*-1,3,4-oxadiazine derivatives

Oxadiazinone derivatives **4** were prepared in two steps as described in scheme 26.[3,4] In the first step, phenylglyoxilic acid (**1**) was reacted with aroylhydrazines **2a-k** to form the condensation products **3a-k** (scheme 26).[5,6] In the second step, the hydrazones **3a-k** undergo cyclisation in presence of DCC in anhydrous THF with formation of the desired [3,4]-diazalactones **4** (scheme 26).[7,8] By this method new oxadiazinone derivatives (**4f-i** and **4k)** were synthesised.



1 **2** **3** **4**

a R^1 = Ph	**86%**
b R^1 = C_6H_4-*p*-OCH_3	**82%**
c R^1 = C_6H_4-*p*-CH_3	**89%**
d R^1 = C_6H_4-*p*-Cl	**94%**
e R^1 = C_6H_4-*p*-Br	**88%**
f R^1 = C_6H_4-*p*-*t*Bu	**88%**
g R^1 = C_6H_4-*m*-OCH_3	**92%**
h R^1 = C_6H_4-*m*-Cl	**99%**
i R^1 = C_6H_4-*m*-Br	**75%**
j R^1 = COOMe	**52%**
k R^1 = 3-pyryl	**71%**

Scheme 26

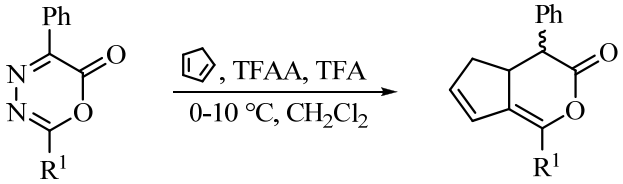
1.3.1.2. Synthesis of 3,4,4a,5-tetrahydrocyclopenta[*c*]pyran-3-one derivatives

Acid-catalysed inverse-electron-demand Diels-Alder is the key-step of the proposed strategy, when the cyclopenta[*c*]pyran skeleton is formed.[9] Addition of cyclopentadiene monomer to oxadiazinones **4a-h** in presence of TFA and TFAA led to formation of the enol-lactones, 3,4,4a,5-tetrahydrocyclopenta[*c*]pyran-3-ones derivatives **5** (scheme 27). The enol-lactone derivatives are obtained in fair to very good yields; except the case of oxadiazinone **4k** (R^1=3-pyryl), when the corresponding dihydro-α-pyrone was not obtained in these reaction conditions, probably because TFA interacts with

[3] [3] W. Steglich, *Synthesis*, **1977**, 252.
[4] A. Padwa, P. Eisenbarth, *J. Heterocyclic Chem.* **1985**, 61.
[5] M. Christl, U. Lanzendoerfer, M.M. Groetsch, E. Ditterich, J. Hegmann, *Chem.Ber.* **1990**, *123*, 2031.
[6] M. Christl, U. Lanzendorfer, K. Peters, E.-M. Peters, H.G. von Schnering, *Tetrahedron Lett.* **1983**, *24*, 353.
[7] M. Christl, U. Lanzendorfer, J. Hegmann, K. Peters, E.-M. Peters, H.G. von Schnering, *Chem. Ber.* **1985**, *118*, 2940.
[8] A. Padwa, P. Eisenbarth, *Tetrahedron Lett.* **1984**, *25*, 5489.
[9] E. Feineis, H. Schwarz, J. Hegmann, M. Christl, E.-M. Peters, *Chem. Ber.* **1993**, *126*, 1743.

pyridine substituent. Increasing the amount of TFA added did not led to formation of the enol-lactone **5k**. By acid-catalysed inverse-electron-demand Diels-Alder new enol-lactone derivatives (**5c**, **5d**, **5e**, **5f**, **5g** and **5h**) were synthesised.

Cycloaddition of the cyclopentadiene to oxadiazinones does not occur stereoselective or regioselective. Theoretically, two regioisomers can be formed as result of the five-membered ring double bond positioning: regioisomer **5** exhibiting the double bond in C-6–C-7 position and regioisomer **6** which has the double bond in C-5–C-6. Also, each regioisomer can be expressed as a set of diastereoisomers due to the asymmetric centers found in positions 4 and 4a. In theory four possible isomers can be formed in the reaction (**5'**, **5"** and **6'**, **6"**).



a R^1 = Ph	**69%**
b R^1 = C_6H_4-*p*-OCH_3	**80%**
c R^1 = C_6H_4-*p*-CH_3	**45%**
d R^1 = C_6H_4-*p*-Cl	**35%**
e R^1 = C_6H_4-*p*-Br	**42%**
f R^1 = C_6H_4-*p*-*t*Bu	**15%**
g R^1 = C_6H_4-*m*-OCH_3	**22%**
h R^1 = C_6H_4-*m*-Cl	**40%**
k R^1 = 3-pyryl	–

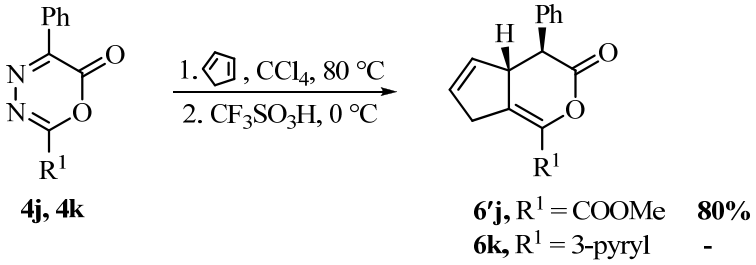
Scheme 27

Table 1. Ratios of diastereoisomers **5** in conditions TFAA 1eq.; TFA 0.3 eq.; CPD 5eq.;0-10 °C

	Ratio	
	5′	**5″**
a R^1 = Ph	1	1.2
b R^1 = C_6H_4-*p*-OCH_3	1	1
c R^1 = C_6H_4-*p*-CH_3	1.6	1
d R^1 = C_6H_4-*p*-Cl	1	4
e R^1 = C_6H_4-*p*-Br	1	5.8
f R^1 = C_6H_4-*p*-*t*Bu	1	-
g R^1 = C_6H_4-*m*-OCH_3	1.8	1
h R^1 = C_6H_4-*m*-Cl	1	-

In most cases regioisomer **5** is preponderantly formed, while in some cases formation of **6** is not observed. When 0.3 eq. of TFAA were used, only the formation of regioisomers **5** was observed. The ratio between the diastereoisomers **5** depends on the substituent′s nature (table 1). During the reaction, the temperature of mass reaction was maintained low by using an ice-bath, which does not ensure constant temperature; this fact may influence the isomers ratios.

In case of diazalactone **4j** another preparation strategy was followed[2] (scheme 28) due to the fact that the previous mentioned conditions reactions did not led to the expected product. Attempt to obtain the enol-lactone **6k** under this reaction conditions did not succeed. Mass reaction analysis showed the presence of many unindentifieble products.



4j, 4k

6′j, R^1 = COOMe **80%**
6k, R^1 = 3-pyryl -

Scheme 28

In most cases the diastereoisomers *R*/*S* were not separable by conventional chromatography because the diastereoisomers exhibit very close R_f even in less polar eluent. Enol-lactone **5′e** and **5″e**, (R^1=4-bromophenylene) were separated as individuals due to a larger ΔR_f. In all cases, the isomeric mixture can be precipitated from the reaction mass by trituration with diethyl ether and pentane.

Precipitated with diethyl ether from the crud mixture, in case of derivative with R^1=3-chlorophenylene only one product was obtained. The ^{1}H NMR spectrum (figure 5) notified the formation of *trans* diastereoisomer **5′h** ($^3J_{4,4a}$ = 14.5 Hz). The isomer exhibits characteristic signals for the expected structure.

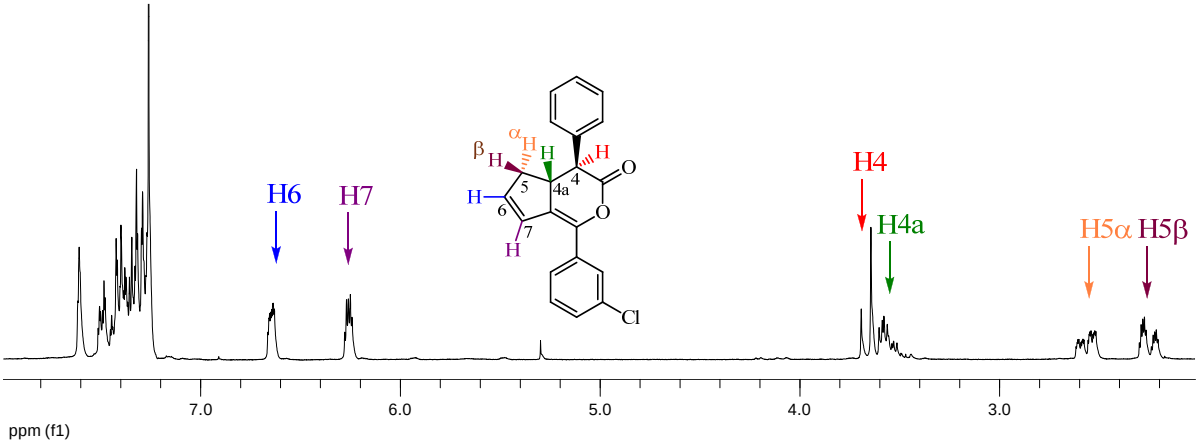


Figure 5. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the isomer **5′h.**

The electronic spectra of the enol-lactone derivatives display blue shifted absorption maxima. Some examples of UV/Vis spectra of enol-lactones **5′e** (R^1 = 4-bromophenylene), **5′d** (R^1 = 4-chlorophenylene), **5′f** (R^1 = 4-*tert*butylphenylene) and **6′j** (R^1 = COOMe) exhibit the maximum of absorption at 306, 303, 295, and 252 nm repectively.

X-ray diffraction analysis of the enol-lactone **5′c** reveals a triclinic spatial disposition with two molecules per unit in a parallel head-to-tail orientation as seen in the lattice view (figure 11), situation which requires that each molecule has a C_s symmetry, and to be located on a crystallographic mirror plane. Very weak interactions were observed between carbonyl oxygen of one molecule and the proton linked on C-7 of another molecule, from the same row, with a distance d = 2.513 Å which is 0.207 Å shorter than the sum of van der Waals radii. The X-ray diagram shows a *trans* orientation of the hydrogen atoms H-4–C-4–C-4a–H-4a confirming the diastereoisomer revealed by the ^{1}H NMR spectrum, with a specific *trans* coupling constant ($^3J_{4,4a}$ = 14.5 Hz).

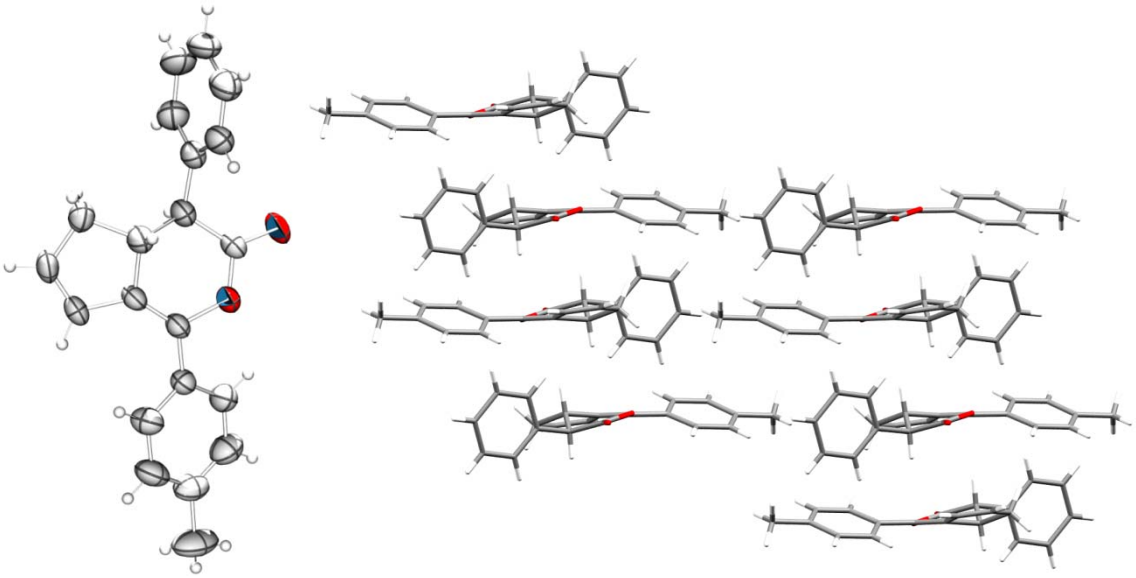
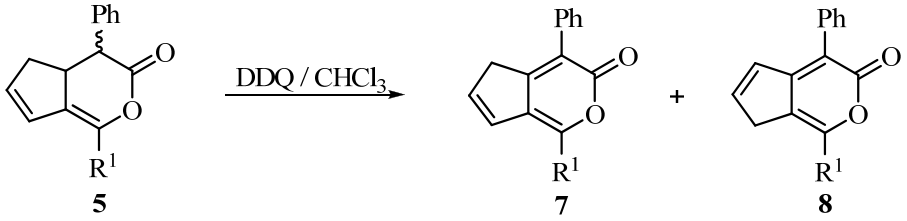


Figure 11. ORTEP diagram (left) and view in the lattice (MERCURY representation) along *b* axis of enol-lactone **5′c**.

1.3.1.3. Synthesis of 1,4-diaryl-dihydrocyclopenta[*c*]pyran derivatives

In the next step, by dehydrogenation of the enol-lactone isomeric mixture, in presence of DDQ in chloroform at 0 °C, room temperature or under reflux, *α*-pyrones are obtained in good yields as mixture of two isomers **7** and **8** (scheme 29).[2] The ratios between isomers depend on a series of factors: the ratio of enol-lactones subjected to dehydrogenation, the basic or acidic media used (solvent, silica gel, aluminium oxide).



a R^1 = Ph **69%**
b R^1 = C_6H_4-*p*-OCH_3 **74%**
c R^1 = C_6H_4-*p*-CH_3 **62%**
d R^1 = C_6H_4-*p*-Cl **22%**
e R^1 = C_6H_4-*p*-Br **70%**
f R^1 = C_6H_4-*p*-*t*Bu **13%**
g R^1 = C_6H_4-*m*-OCH_3 **22%**
h R^1 = C_6H_4-*m*-Cl **25%**

Scheme 29

By DDQ-mediated oxidation ten new *α*-pyrone derivatives were synthesised (**7c**, **7d**, **7e**, **7f**, **7g**, **7h**, **8b**, **8d**, **8e**, **8f**). The *α*-pyrone structures were analysed and characterised by NMR, UV spectroscopy and MS spectrometry. Specific signals in ^{1}H NMR spectrum for *α*-pyrones **7** are the signals given by protons form position 5 (triplet), 6 (doublet of triplets) and 7 (doublet of triplets).

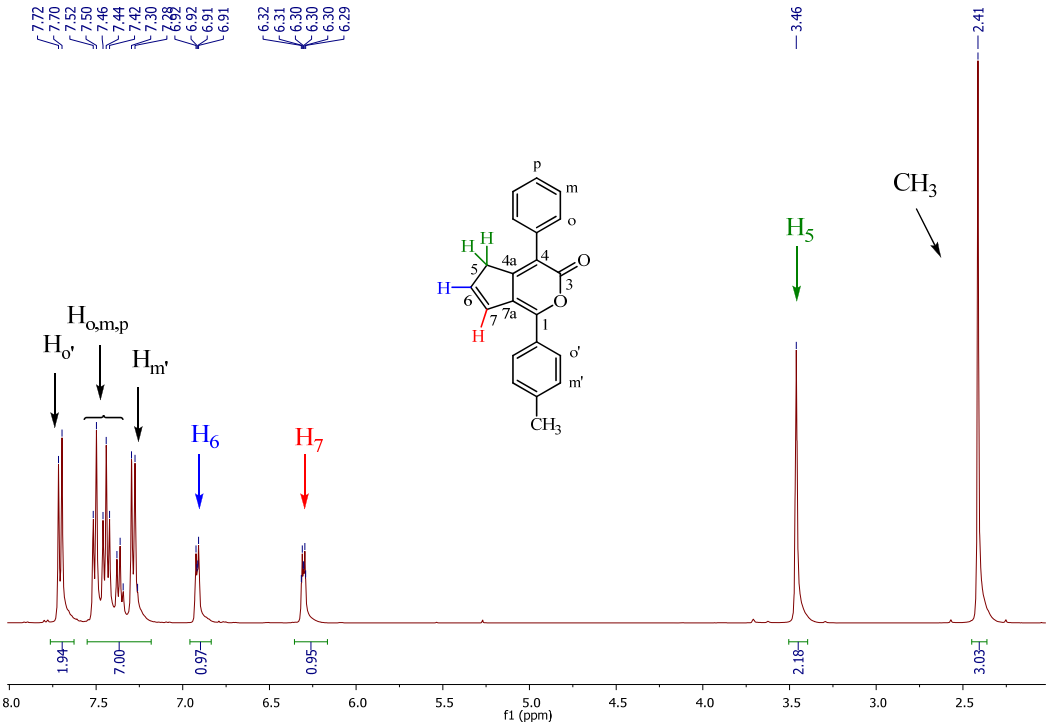
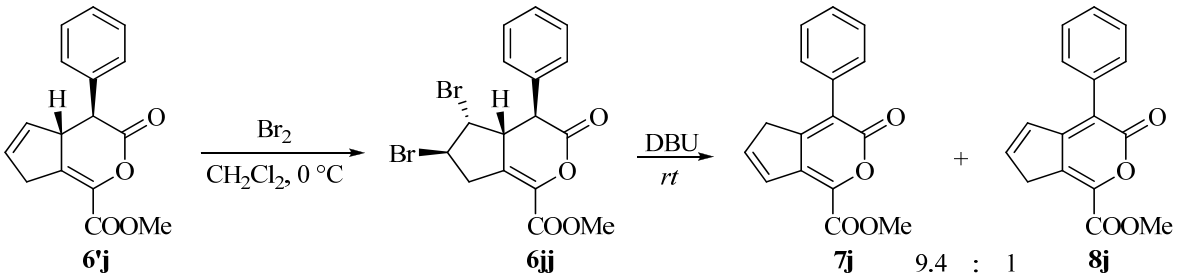


Figure 12. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of derivative **7c**

For example, compound **7c** exhibit a triplet at 3.46 ppm corresponding to H-5, a pair of doublet of triplets at 6.30 ppm and 6.92 ppm (J = 3.8, 2.0 Hz) assigned to H-7 and H-6, respectively and a singlet for the methyl group at 2.41 ppm (figure 12). The two phenyl groups give signals well resolved in the

aromatic area, as an AA′BB′ system at 7.29 and 7.71 ppm, corresponding to the *para*-disubstituted ring, and two triplets and a doublet at 7.37, 7.44, 7.51 ppm for the phenyl group.

Synthesis of the α-pyrones **7/8j**, as in case of corresponding enol-lactone, requires different reaction conditions (scheme 30). In the first step, the enol-lactone[2] was treated with bromine resulting the dibrominated derivative **6jj**, which in presence of diaza(1,3)bicyclo[5.4.0]undecane (DBU) led to formation of derivatives **7j** and **8j** in 1:9.4 ratio, after purification on silica gel.



Scheme 30

Purification by chromatography on neutral aluminium oxide, revealed that isomer **7** of the α-pyrones is transformed to isomer **8**. The isomerisation occurs with partial degradation of the product, which is a possible explanation of the very low yields. Purification of the α-pyrones on silica gel led to a mixture of isomers with very low yields.

After purification of isomer **7d** on neutral alumina, using a mixture of diethyl ether and pentane (1:4) as eluent, the isomer **8d** was obtained in 22% yield. Derivative **8d** presents similar pattern of ^{1}H NMR spectrum with the one of isomer **7d**, differences are observed to the upfield chemical shifts of the signals corresponding to the protons of the five-membered ring. Protons in position 5 and 6 give two signals as doublet of triplets at 6.89 and 6.81 ppm respectively and a triplet at 3.75 ppm corresponding to protons in position 7 (figure 14).

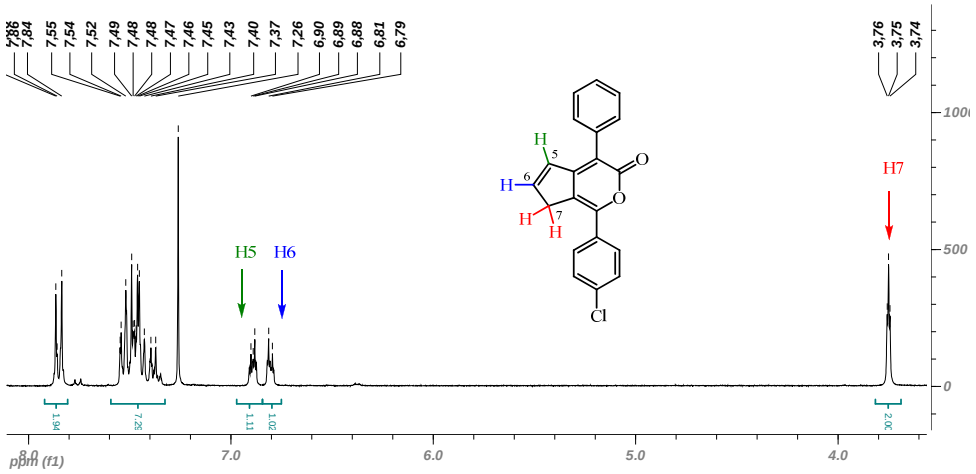


Figure 14. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of derivative **8d**

The absorption maxima in the electronic spectra for the dihydrocyclopenta[*c*]pyrans are situated around 337-371 nm (table 2). *α*-Pyrones show good emission, except for **7f** which has a weaker emission, probably due to the shorter conjugation length. All the investigated *α*-pyrone derivatives are blue emitters (443-476 nm). Emission of the *α*-pyrone derivatives show better than the emission of the corresponding enol-lactones, but the quantum yields calculated relative to coumarine 1 were extremely low (<1%). Remarkably, the fluorescence quantum yields of compound **8j** is significantly different (Φ = 57%) as listed in table 2, showing a substantial effect of the COOMe substituent through resonance electronic interaction over the entire heterocycle.

Table 2. Absorbtion and emission data for alpha-pyrone derivatives

Compound	Absorption λ_{max} [nm][a]	Emission λ_{max} [nm][a]	*Stokes* shift [cm^{-1}]/(nm)	Φ^b
7c	249, 265, **369**	470	5800/(101)	< 1%
7f	247, 266, **369**	462	5500/(93)	< 1%
7g	246, 267, **365**	444	4900/(79)	< 1%
8b	278, **382**	476	5200/(94)	< 1%
8d	248, 265, **367**	467	5800/(100)	< 1%
8e	266, **371**	467	5500/(96)	< 1%
8j	248, **337**	443	7100/(106)	**57%**

[a] Recorded in CH_2Cl_2.[b] Determined in CH_2Cl_2 with Coumarin 1 as reference (Φ = 73%)[10]

Monocrystal of isomer **8a** was obtained by slow evaporation at room temperature from solution of a mixture of **7a** and **8a** dissolved in chloroform and hexane (1:1). X-ray analysis of **8a** (figure 16) show a spatial arrangement in the crystal by a monoclinic system with $P2_1/c$ space group containing four molecules per cell. Unexpectedly, dihydrocyclopenta[*c*]pyran unit is nearly planar and the bond lengths (five-membered ring C5-C6 1.474, C6-C7 1.354, C7-C8 1.457, C8-C9 1.511 Å; six-membered ribg C1-C9 1.340, C3-C4 1.444, C4-C5 1.378, C5-C9 1.444 Å) indicates variation in agreement with structure **8a** (distinctive single and double bonds).

[10] G. Jones, W.R. Jackson, C. Choi, W.R. Bergmark, *J. Phys. Chem.* **1985**, 89, 294.

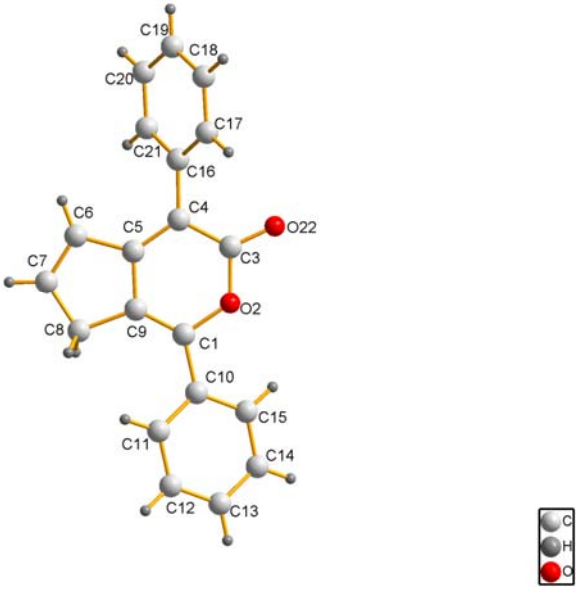


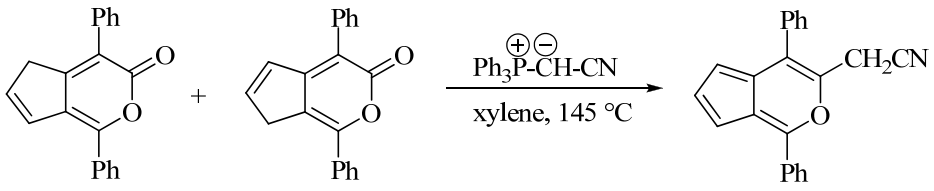
Figure 16. DIAMOND diagrame of **8a**

1.3.1.4. Sinteza derivatilor de ciclopenta[*c*]piran

In order to obtain compounds with cyclopenta[*c*]pyran skeleton from *α*-pyrones the following steps were taken into consideration: 1) Wittig reactions at the carbonyl group with formation of 1,3,4-trisubstituted cyclopenta[*c*]pyran derivatives; 2) Selective reduction in the presence of DIBAL-H in order to obtain 1,4-disubstituted cyclopenta[*c*]pyran derivatives; 3) Reaction with trimethyllaluminium with formation of 1,3,4-trisubstituted cyclopenta[*c*]pyran derivatives, having a methyl group in position 3.

1.3.1.4.1. Synthesis of cyclopenta[*c*]pyrans *via* Wittig reactions

A series of Wittig reactions were carried out using as substrate a mixture of *α*-pyrones **7a** and **8a** (scheme 33) and (triphenylphosphoranylidene)acetonitrile, varying reaction conditions: temperature, solvent (xylene or toluene), amount of phosphorylide.



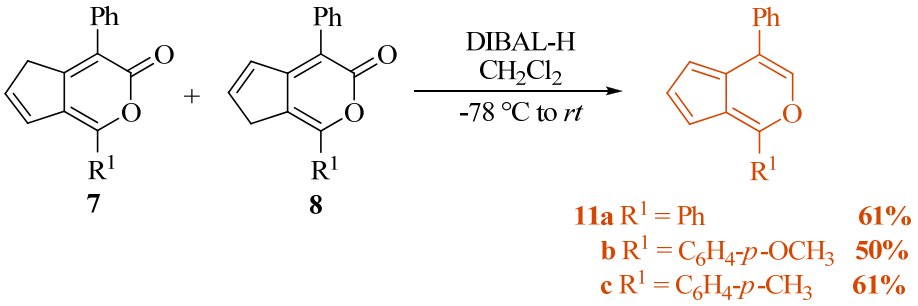
7 **8** **10**

Scheme 33

When xylene was used as solvent, and 21 eq. of phosphorylide were added in several steps derivative cyclopenta[*c*]pyran **10** was obtained only in traces,. The strategy to obtain 1,3,4-trisubstituted-cyclopenta[*c*]pyrans derivatives by Wittig reaction has not registered the same success as in the case of 3-substituted cyclopenta[*c*]pyrans.[11] A possible explanation of the low yields may be the presence of the phenyl at C-4, impeding the nucleophilic attack that takes place at C-3, so that the four-membered cycle of typical Wittig reactions mechanism cannot be form.

1.3.1.4.2. Synthesis of cyclopenta[*c*]pyrans *via* reduction reaction with DIBAL-H

Selective reduction of the *α*-pyrones **7a-c** and **8a-c** with DIBAL-H (scheme 34) led to the formation of 1,4-disubstituted-cyclopenta[*c*]pyrans **11a-c** in good yields (50-61%). The products are deep-red powders, which easily decompose at room temperature in few hours, but they can be store in the freezer for a longer period of time.



Scheme 34

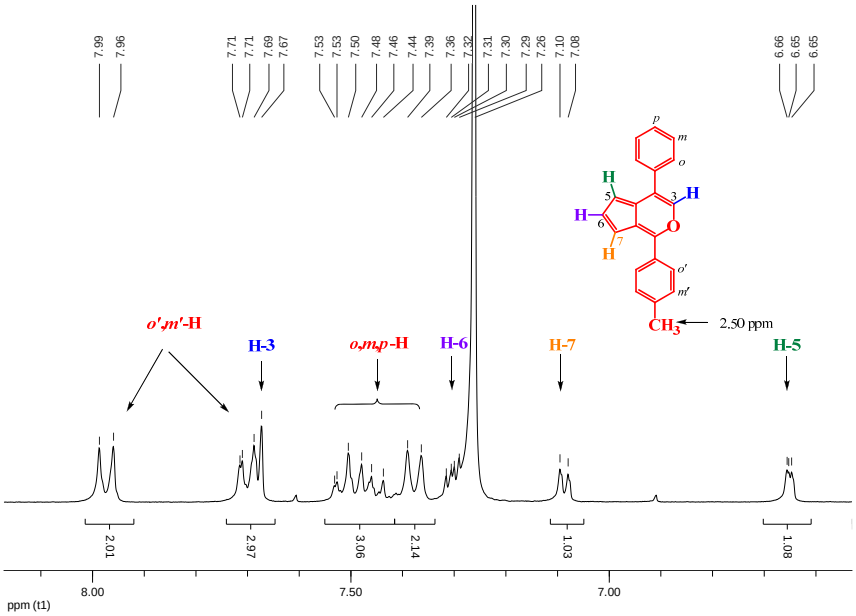


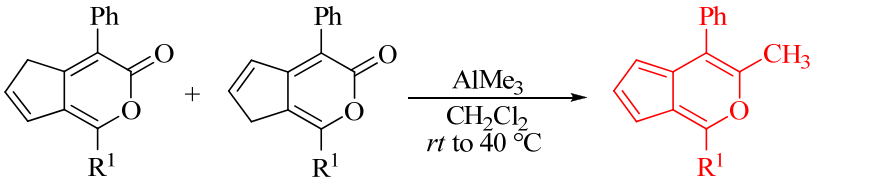
Figure 19. Fragment of ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **11c**

[11] E. Güllük, E. Bogdan, M. Christl, *Eur. J. Org. Chem.* **2006**, 531.

The cyclopenta[*c*]pyran **11c** was obtained in 61% and its ^{1}H NMR spectrum is in agreement with the predicted structure (figure 19). The protons H-5, H-6 and H-7 give three doublets of doublets signals at 7.09, 7.30 and 6.65 ppm with the coupling constant $J_{5,6}$ = 2.6, $J_{6,7}$ = 4.7, $J_{5,7}$ = 0.9 Hz.

1.3.1.4.3. Synthesis of cyclopenta[*c*]pyrans *via* reaction with $AlMe_3$

According to literature,[2] by reacting α-pyrones **7a** and **8a** with a solution of $AlMe_3$ in anhydrous dichloromethane at room temperature, then heating to 40 °C for 2 hours lead to the formation of derivative **12a** in 40% yield (scheme 35), as deep red amorphous solid. Recrystallisation from petroleum ether at low temperature led to the formation of deep red crystals.



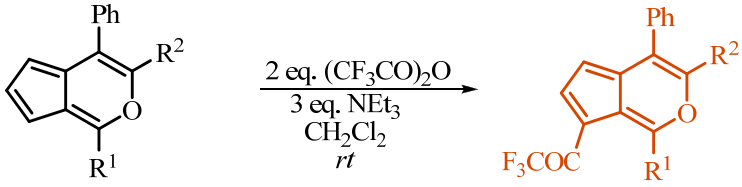
Scheme 35

Attempts to obtain **12b** and **12c** by reacting the corresponding α-pyrones with trimethylaluminium did not led to the expected products, instead the reactants were recuperated.

1.3.2. Chemical behaviour of cyclopenta[*c*]pyrans in electrophilic substitution reactions

1.3.2.1. Acetylation reaction

Cyclopenta[*c*]pyrans **11** (R^3 = H), **12** (R^3 = Me) and **13** (R^3 = Ph) are reacted at room temperature with trifluroacetic anhydride in presence of triethylamine when a single monosubstituted product was formed (scheme 37). As shown, in case of pseudoazulene-[*c*]-series[1] the position susceptible to the electrophilic attack are in order 7 and 5. Contrary to expectation, monosubstituted derivative in position 5 was not formed. Formation of disubstituted derivative or the 5-monosubstituted derivative were not observed if temperature was raised up to 40 °C and maintained for 2h.



11, 12, 13

14 a R^1 = Ph, R^2 = H, **74%**
b R^1 = C_6H_4-*p*-OCH_3, R^2 = H, **77%**
c R^1 = Ph, R^2 = CH_3, **60%**
d R^1, R^2 = Ph, **64%**

Scheme 37

Derivatives **14** are orange solids which presents strong orange fluorescence by irradiation at 365 nm at the UV lamp. These compounds (**14**) have higher stability compared with the corresponding cylopenta[*c*]pyran derivatives (**11-13**), and are easier to handle at room temperature.

Owing a series of three cyclopenta[*c*]pyran derivatives possessing the same chromophore, a trifluoroacetyl group in position 7, and a different group in position 3 (H, Me or Ph) we have next investigated their photophysical properties. Concerning the absorption behaviour comparing to reference compound **14a**, the maximum absorption band are around 449-465 nm, which are slightly bathochromic shifted (ca. 8-16 nm) due to the presence of the Me or Ph group in position 3 of the cyclopenta[*c*]pyran derivative for compounds **14c** and **14d** respectively. The absorption bands are extended into the visible region of the spectrum indicating that these compounds are orange coloured.

Emission data of **14a**, **14c** and **4d** also show bathochromic shifted emission spectra. Photoluminescence wavelengths of the compounds were not influenced by the nature of the substituents. They are yellow-orange emitters, the maximum emission band of compounds **14a**, **14c** and **14d** is around 582-584 nm and Stokes shifts of 119-133 nm.

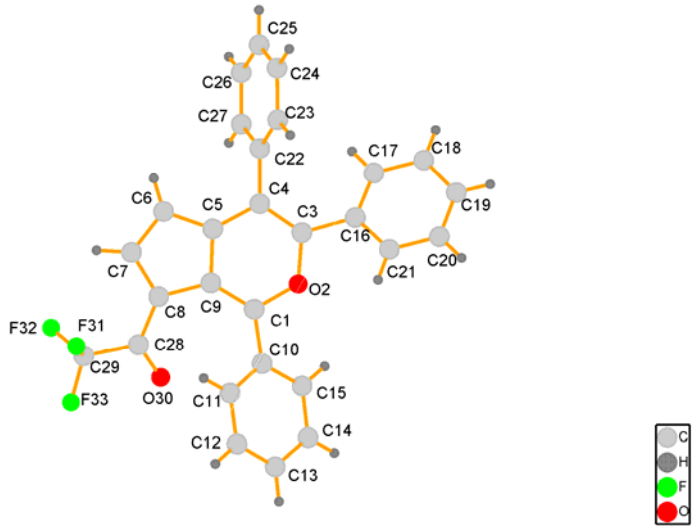
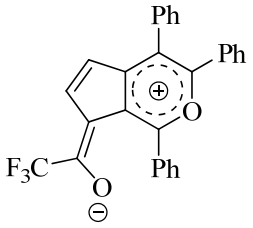


Figure 22. DIAMOND diagram of compound **14d** and its crystallographic numbering

Single crystal X-ray analysis of cyclopenta[*c*]pyran **14d** (figure 22) revealed a monoclinic spatial disposition with P21/c space group with four molecules per unit. The cyclopenta[*c*]pyran skeleton is nearly planar. The carbon-carbon length in the five-membered ring [C8-C9 1.443(6), C6-C7 1.390(6), C7-C8 1.385(6), C5-C6 1.368 Å] and in the six-membered ring [C5-C9 1.445(6), C4-C5 1.421(6), C3-C4 1.361 Å] and C8-C28 1.446(6) and C28-O30 1.207 Å indicate that the real structure is not in full agreement with the drowned structure of **14d**, suggesting that the cannonic form **14d′** has an important contribution to the ground state resonance hybrid (figure 23). Also, were observed, peculiar distances in the carbon-oxygen bond lengths in the six-membered ring [C3-O2 1.375(5), C1-O2 1.351(5) Å] and also shorter and unequal carbon-fluorine length [C28-F33 1.304(5), C28-F32 1.320(6), C28-F31 1,327(6) Å].



14d'

Figure 23.

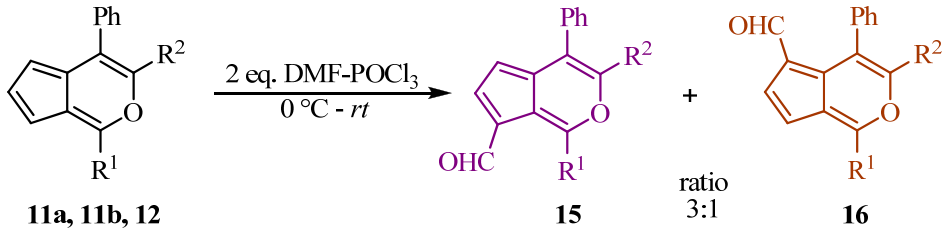
Different C-F length in the $COCF_3$ group may indicate different interactions in the lattice of the three fluorine atoms. An interesting feature is the C-5–C-9 distance of 1.445, which is shorther than the transannular distances in other azulene-like compounds (1.47-1.50 Å).[12] The lattice view of the derivative presents a *zig-zag* disposition of the layers with a distance between of 3.35 Å, while two consecutive layers have the molecules in opposite orientation. Each fluorine atom of the $COCF_3$ group establish interaction with two fluorine atoms of two other molecules with 2.905 Å length, which is 0.035 Å shorter than the sum of the van der Waals radii. There was also observed a C-H···F interaction of 2.546 Å, with 0.124 Å shorter than the sum of the van der Waals radii, in an angle of 146.16°.

1.3.2.2. Formylation reaction

When subjected to formylation, cyclopenta[*c*]pyrans behave differently by comparation with trifluoroacetylation reaction. The reactions were performed in DMF, which has both the role of solvent and reagent.

[12] A.W. Hanson, *Acta Cryst. B* **1965**, *19*, 135; H.L. Ammon, M. Sundaralingam, *J. Am. Chem. Soc.* **1966**, *88,* 4794; G. Bastiansen, J.L. Derrisen, *Acta Chem. Scand.* **1966**, *29*, 1319; H.L. Ammon, P.H. Watts, A.G. Anderson, D.M. Forkey, L.D. Grina, Q. Johnson, *Tetrahedron* **1970**, *26*, 5707.

Cyclopenta[*c*]pyrans **11a**, **11b**, and **12** were treated with 2 eq. of $POCl_3$ in DMF at 0 °C to form mixture of monosubstiuted products at position 5 and 7, in 1:3 ratio, in very good yields (65-85%, scheme 38). The mixture was purified by chromatography on basic aluminium oxide, but the separation of isomers was not possible due the same R_f.



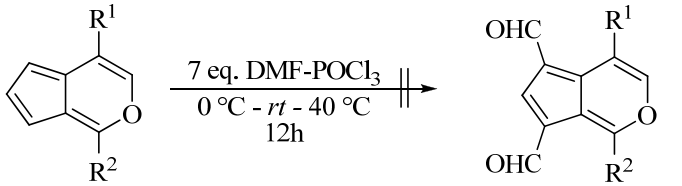
11a, 11b, 12 **15** **16**

a $R^1 = Ph$, $R^2 = H$ **65%**
b $R^1 = C_6H_4$-*p*-CH_3, $R^2 = H$ **75%**
c R^1, $R^2 = Ph$, $R^3 = CH_3$ **85%**

Scheme 38

Formylation of cyclopenta[*c*]pyran **12** with 2 eq. of $POCl_3$ and heated to 40 °C for 2h, showed the formation in low yield (5%) of the disubstituted product along with the monosubstituted products (85%). In expectancy to obtain disubstituted products, 7 eq. of $POCl_3$ are added to the reaction mixture, the temperature was raised to 40 °C and reaction time increased to 4 hours, then 12 hours.

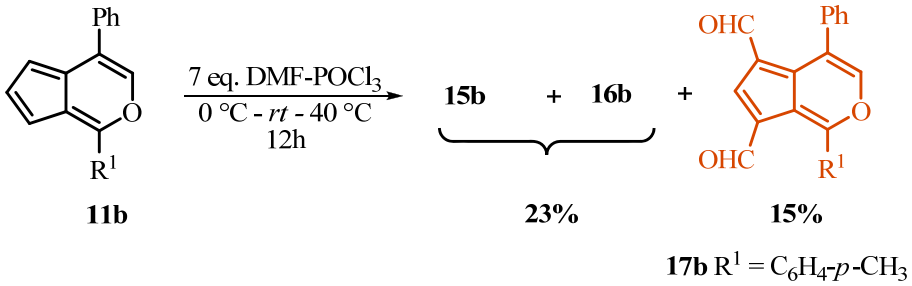
Nature of the substituents has a strong influence on the results. For cyclopenta[*c*]pyran **11a,** no formation of the disubstituted product **17a** was recorded (scheme 39), while the monosubstituted products started to decompose under these conditions. Recovery of the monosubstituted products is up to 30%.



11a **17a** R^1, $R^2 = Ph$

Scheme 39

In the case of cyclopenta[*c*]pyran **11b** the same formylation conditions led to different results (scheme 40). In the reaction mixture, three products were identified: **15b**, **16b** and **17b** in 1:3:2 molar ratios. Attempt to separate the mixture by chromatography column on basic aluminium oxide led to two fractions in the best case. The first fraction contains a mixture of the two monosubstituted isomers (23%) and the second contains the pure disubstitution product (15%).



11b **23%** **15%**

17b $R^1 = C_6H_4$-*p*-CH_3

Scheme 40

The structure of **17b** was confirmed by X-ray diffraction (figure 27) of a monocrystal obtained from $CDCl_3$ and hexane, by slow evaporation at room temperature. The cyclopenta[*c*]pyran unit is not planar, the observed bond distances show substantial deviations from those values expected for the formally written structure (i.e. **17b**), with alternating single and double bonds. As in case of compound **14d,** the transannular C-2–C-6 distance is 1.444, being shorter than the distances in other azulene-like compounds (1.47-1.50 Å).[12] The formyl groups have the oxygens atoms in an outward orientation, almost coplanar with the plane formed by C5–C6–C7.

a) **b)**

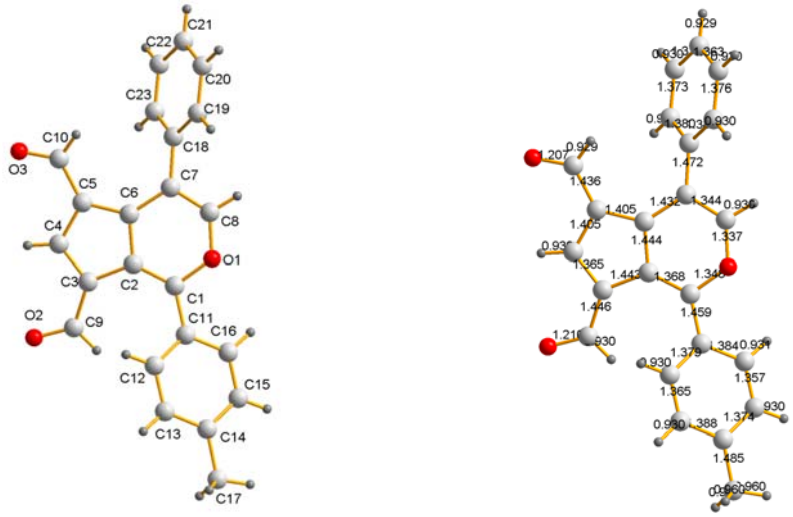
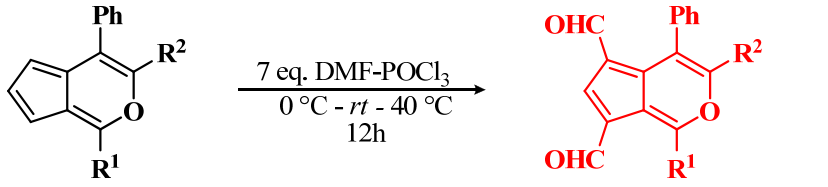


Figure 27. X-ray Diamond diagram of **17b**: a) crystallographic numbering, b) bond lengths

H-bond is observed between two neighbouring molecules found in an orientation head-to-tail, involving a hydrogen atom of the cyclopenta[*c*]pyran ring of one molecule and the oxygen from the formyl group of the other molecule. Thus, C-8–H-8···O-2 has a 2.345 Å length, shorter with 0.375 Å than the sum of the van der Waals radii, in an angle of 150.95°. The other formyl group of the same molecule, also forms a H-bond with a hydrogen of the *para*-substituted phenyl ring, C-12–H-12···O-3 having the length 2.472 Å, shorter with 0.248 Å than the sum of the van der Waals radii, in an angle of 166.27°. In the network can be also observed the existence of C-H···π interactions of 2.828 Å between a hydrogen of

the phenyl group of one molecule and the core of *para*-methyl-phenyl unit belonging to the vicinal molecule.

In case of cyclopenta[*c*]pyrans **12** and **13** the formylation reaction with an excess of electrophile, led to formation of the disubstituted products **18c**, **18d** (scheme 41) in very good yields.



12, 13 **18**

c R^1 = Ph, R^2 = CH_3, **75%**
d R^1, R^2 = Ph, **63%**

Scheme 41

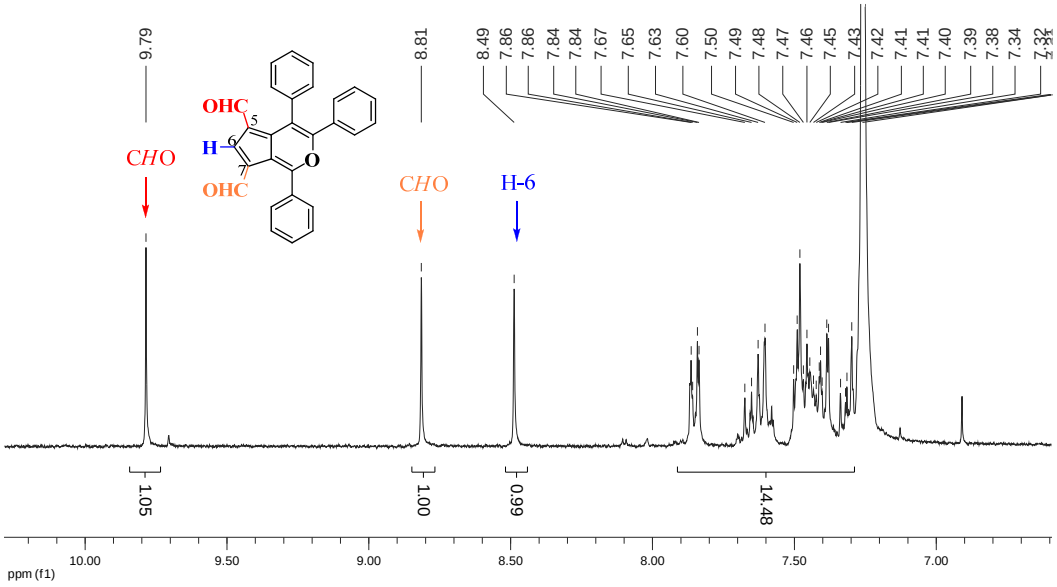


Figure 30. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **18d**

The ^{1}H NMR of diformylated cyclopenta[*c*]pyran **18d** (figure 30) exhibit two signals corresponding to the two formyl groups at 9.79 ppm and 8.81 ppm respectively, and a signal corresponding to the proton on position 6 at 8.49 ppm. The rest of the signals in the range 7.27-7.86 ppm belong to the three phenyl groups.

1.4. CONCLUSIONS

In this first part of the thesis was presented a literature overview with respect to pseudoazulenic heterocyclic system made of cyclopenta[*c*]pyran possessing aromatic skeleton and the original results with reference to synthesis of new cyclopenta[*c*]pyran derivatives.

The literature overview comprises all the work up to day concerning isolation, biological properties and synthesis of the titled heterocyclic system and makes the subject of a review accepted for publication.[13]

The original part contains our results obtained in the synthesis and analysis of some new cyclopenta[*c*]pyran derivatives and their precursors. Following a multi-step strategy for synthesis of new cyclopenta[*c*]pyrans, were obtained five new 6-oxo-6*H*-1,3,4-oxadiazine derivatives, six new 3,4,4a,5-tetrahydrocyclopenta[*c*]pyran derivatives (four of them as mixture of two diastereoisomers), ten new 3,5-dihydrocyclopenta[*c*]pyran derivatives and twelve new cyclopenta[*c*]pyran variously substituted derivatives.

The analysis of the new compounds was based on 1D, 2D NMR and UV/Vis/fluorescence spectroscopy, EI, ESI or APCI mass spectrometry and X-ray diffractometry.

The *3,4,4a,5-tetrahydrocyclopenta[c]pyran* derivatives were obtained as mixture of diastereoisomers. In the case of two compounds was obtained only a single diastereoisomer, and in one case was possible to isolate the two diastereoisomers. These compounds present blue fluorescence at the UV lamp (365 nm) but in solution they presents very weak signal. One of these compounds was investigated by X-ray diffraction. In the lattice are observed C-H···O and C-H···π interactions.

The *3,5-dihydrocyclopenta[c]pyran* derivatives are yellow coloured compounds which present blue fluorescence in solution but very small quantum yields. They are obtained usually as one isomer (the other isomer is formed in very small amount) with the double bond in position C-6–C-7 in the five-membered ring which isomerise on neutral alumina to its isomer with the double bond in position C-5–C-6. One of these compounds was investigated by X-ray diffraction. Important features observed in the lattice are C-H···O and C-H···π interactions.

One new *1,4-disubstituted-cyclopenta[c]pyran* is obtained by reduction with hydride of the corresponding 3,5-dihydrocyclopenta[*c*]pyran (*α*-pyrone) derivative.

Electrophilic substitution of a series of *cyclopenta[c]pyran* derivatives led to different results determined by different substituents attached to the heterocycle and the electrophile. When subjected to

[13] **M. Țînțaș**, E. Bogdan, I. Grosu, *J. Heterocycl. Chem.* **2010**, in print.

electrophilic substitution with trifluoroacetic anhydride only one product substituted in position 7 is exclusively obtained. Using excess of trifluoroacetic anhydride did not led to formation of other substituted products. X-ray diffraction of a 7-trifluoroacetyl-cyclopenta[*c*]pyran derivative show special items in the lattice, like C-H···π, C-F···F and C-H···F interactions.

Vilsmeier-Haack formylation led to mixture of products substituted in position 7 and 5 in ratio 3:1. When excess of electrophile was used, in some cases, the disubstituted product was obtained.

X-ray diffraction of 5,7-diformyl-cyclopenta[*c*]pyran derivative showed intermolecular interactions like C-H···π and strong hydrogen bonding C-H···O.

PART 2. SYNTHESIS AND ANALYSIS OF NEW AZA-HETARENE LIGANDS

2.1. INTRODUCTION

Supramolecular chemistry was defined as being the chemistry beyond molecules and which focuses on the chemical systems made up of a discrete number of assembled molecular subunits or components. The forces responsible for the spatial organisation of such systems may vary from weak (e.g. intermolecular forces, electrostatic or hydrogen bonding) to strong (e.g. covalent bonding).[1,2] These forces include hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, pi-pi interactions and electrostatic effects.

Important concepts that have been demonstrated by supramolecular chemistry include molecular self-assembly, folding, molecular recognition, host-guest chemistry, mechanically-interlocked molecular architectures, and dynamic covalent chemistry. The study of non-covalent interactions is vital to understanding many biological processes from cell structure to vision that rely on these forces for structure and function. Biological systems are often the inspiration for supramolecular research.

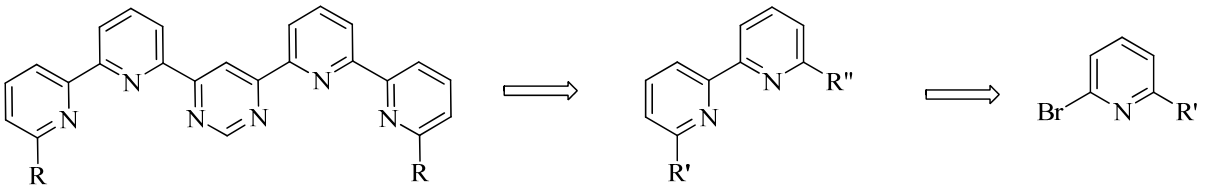
2.3. RESULTS AND DISCUSSIONS

Molecules possessing the sequence bipy-pym-bipy exhibit helicoidal chirality due to the spatial arrangement of the pyridine units. The nitrogen atoms ensure a high coordination degree, two N atoms from bipy and one from pym forms one site in which transitional metal ions will bind, forcing the entire molecule to adopt a linear configuration. By complexation with metal ions the distance between the extremities of the ligand molecule will increase, making them interesting to be investigate in order to determine the effect of complexation and decomplexation; for example, if used as pedals incorporated in a molecular scissors. The components of the molecular scissors may contain a tetrasubstituted ferrocene unit which will act as a pivot, aryl, biaryl, teraryl or alkines units as rods and/or bladders, and the pedal formed by a polydentate aza-heteroaromatic ligand, attached like a strap. At the end of bladders a bis-1,3-dioxane will be attached as a second strap, able to change its conformation as a mechanic response of the chemical pedal.

The objective of this part of the thesis is to synthesise new functionalised ligands containing successive units of bipyridine (bipy) and pyrimidine (pym) following a series of steps as described in

[1] J.-M. Lehn, *Science* **1993**, *260,* 1762–1763.
[2] J.-M. Lehn, Supramolecular Chemistry, **1995**, Wiley-VCH.

scheme 8. Starting from bromo-pyridine derivatives **III** by Stille coupling reaction with other pyridine units forms the synthon **II**, which further by a second coupling reaction led to formation of the ligand **I**.



I **II** **III**

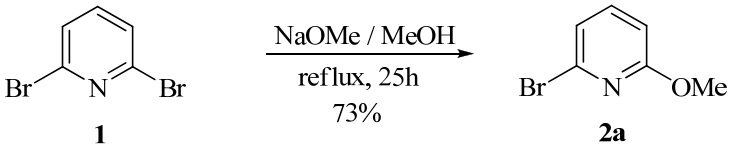
Scheme 8

2.3.1. Synthesis of new aza-hetarene ligands

In order to compile this type of molecules containing bipy–pym-bipy units and functionalised at the extremities (with CH_2Br or Br), at first, a literature strategy was employed to synthesise the nitrogen heterocycles intermediates,[3] then, in order to improve the yield, another multi-step strategy, described in literature for similar ligand, was employed.

2.3.1.1. Synthesis *via* bipyridine intermediates

The strategy is a multi-step reaction, starting with the synthesis of marginal 2,6-disubstituted pyridine units of the target molecule. Synthesis of the bipy units was started from 2-bromo-6-methyl-pyridine and 2-bromo-6-methoxy-pyridine derivatives. The first pyridine is commercially available, while 2-bromo-6-methoxy-pyridine **2a** was synthesised (scheme 9).

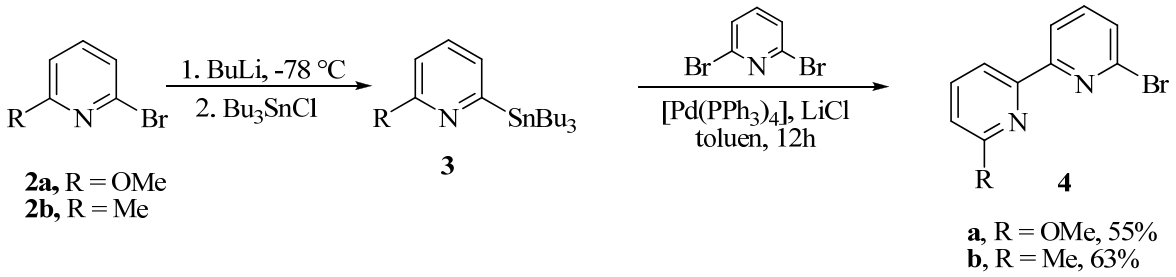


1 **2a**

Scheme 9

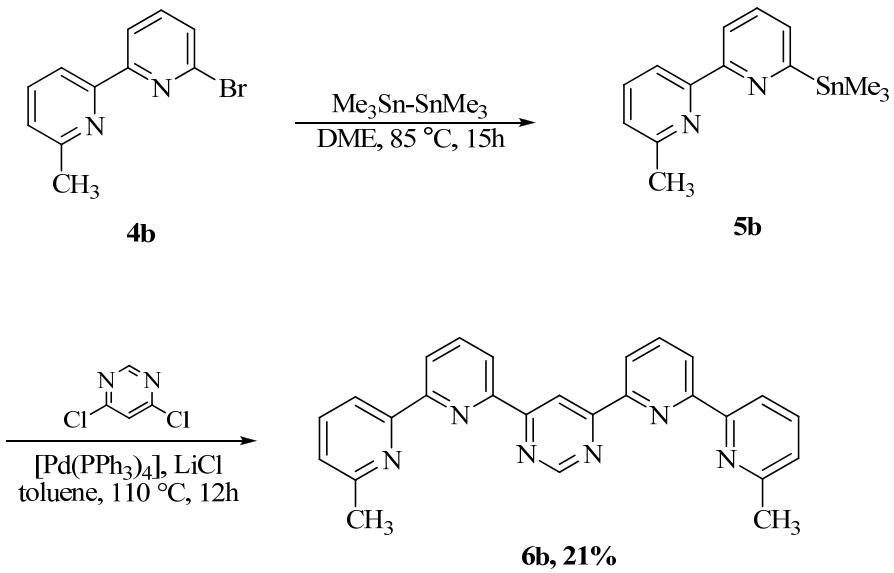
[3] V. Patroniak, M. Kubicki, A.R. Stefankiewicz, A.M. Grochowska, *Tetrahedron* **2005**, *61*, 5475.

Bipyridines **4** were obtained in good yields (55-63%) following a two-step synthesis (scheme 10). First, 6-methyl-2-bromo-pyridine **2a** (or 6-methoxy-2-bromo pyridine **2b**) was transformed into tributylstannyl derivative **3a** (respectively **3b**),[4] which was further reacted with 2,6-dibromopyridine by Pd^0 catalysed heterocoupling reaction, which led to formation of the expected bipyridine **4a** (respectively **4b**).



Scheme 10

Next, a two-step reaction was employed to synthesise the ligand **6b**. Therefore, the reaction mixture of **4b**, hexamethylditin and 3–5% of $[Pd(PPh_3)_4]$ was degassed, then dry DME was added and heated at 80 °C for 15 h.[5] The solvent was evaporated and the residue was left under vacuum overnight. Without purification, 6-methoxy-6′-(trimethylstannyl)-2,2′-bipyridine (**5b**) obtained *in situ* was treated with 4,6-dichloropirymidine in the two-fold Stille coupling reaction that led to formation of 4,6-bis(6′-methyl-2,2′-bipyridin-6-yl)pyrimidine (**6b**) in 21% yield (scheme 11).



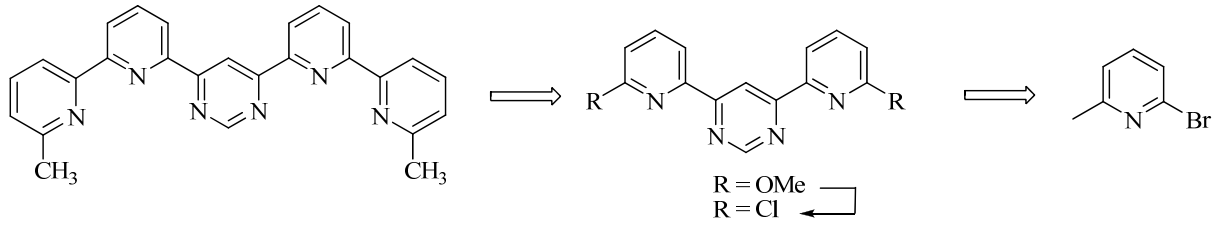
Scheme 11

[4] L. Testaferri, M. Tiecco, M. Tingoli, D. Bartoli, **A.** Massoli, *Tetrahedron* **1985**, *41,* 1373.
[5] M. Benaglia, S. Toyota, , C. R. Woods, J. S. Siegel, *Tetrahedron Lett.* **1997**, *38*, 4737; T. R. Kelly, Y.-J. Lee, R. J. Mears, *J. Org. Chem.* **1997**, *62*, 2774.

In the reaction mixture other coupling products were obtained, which explains the low yield of the two-folded Stille coupling reaction. The stannyl derivative **5b** is obtained *in situ*, therefore if **4b** was not completely transformed it will interfere later to the coupling reaction giving birth to different non-desired coupling products.

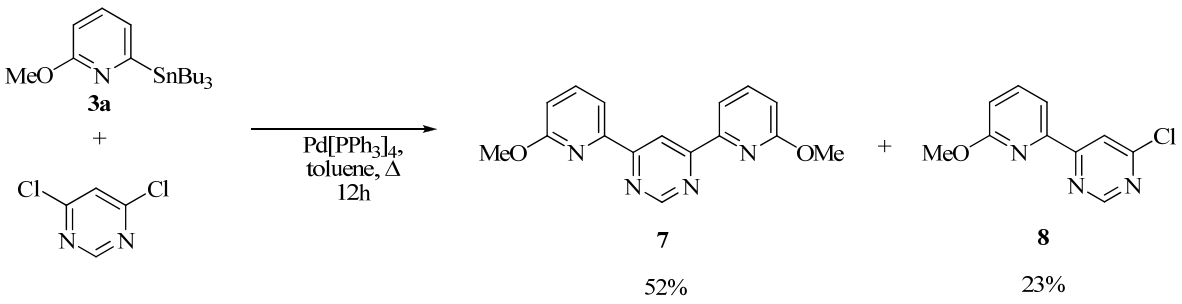
2.3.1.2. Synthesis *via* mixed pyridine-pyrimidine intermediates

In order to improve the yield of **6b**, a second strategy was followed as shown in scheme 12. Therefore, to pyrimidine core, pyridine units are attach to form the py-pym-py synthon, to which, other two pyridine units are later attached on each side, leading to formation of the desired structure.[6]



Scheme 12

The stannane **3a** was subjected to a two-folded Stille cross-coupling in presence of Pd^0 with 4,6-dichloropyrimidine to form 4,6-bis(6-methoxypyridin-2-yl)pyrimidinedine (**7**) in 52% yield, along with the monocoupling product 4-chloro-6-(6-methoxypyridin-2-yl)pyrimidine (**8**) (23%) (scheme 13). Discrimination between the two products was based on the slightly different NMR and MS spectra.



Scheme 13

^{1}H NMR spectrum of **7** (figure 7) is in agreement with the proposed structure. Pyrimidine protons H-2 and H-5 give two set of doublets at 9.29 and 9.34 ppm (^5J = 0.45 Hz) being the most deshielded protons. The pyridine protons H-3′, H-5′ and H-4′ appear as two doublets and a triplet at 6.90 (J = 8.2 Hz), 8.13 (J = 7.4 Hz), and 7.76 (J = 8.2 Hz) ppm respectively.

[6] D.P. Funeriu, J.M. Lehn, K. Fromm, D. Fenske, *Chem. Eur. J.* **2000**, *6*, 2103.

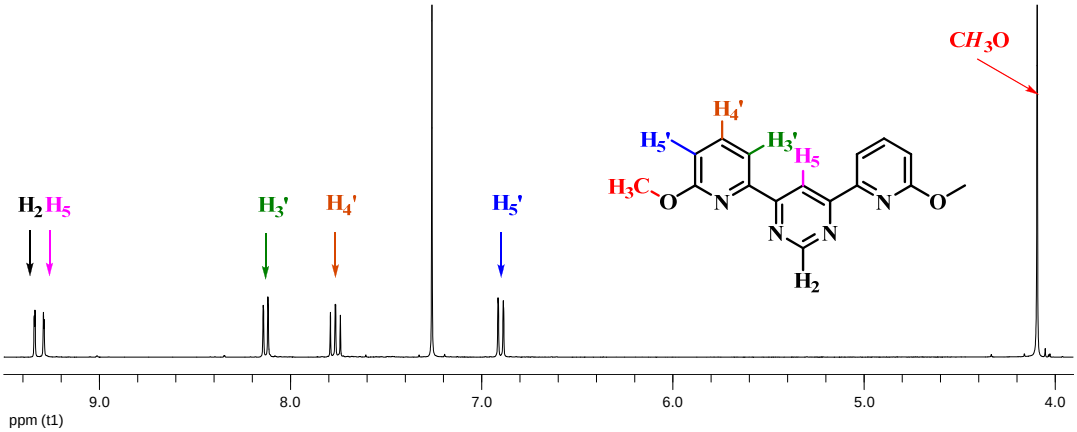
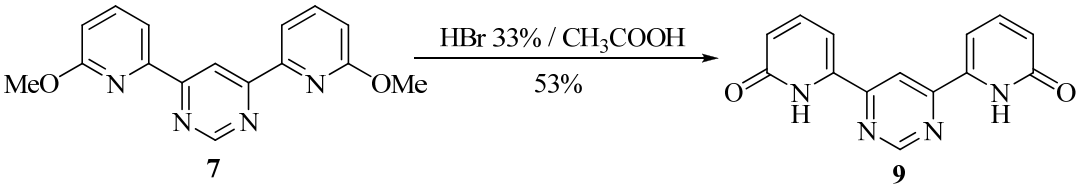


Figure 7. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **7**

In the next step, refluxing compound **7** in hydrogen bromide 33% (w/w) solution in acetic acid led to the deprotection of the methyl ether forming the dipyridone **9** in 53% yield (scheme 14) as a yellow solid with poor solubility in most common organic solvents.



7 **9**

Scheme 14

^{1}H NMR spectrum of **9** in DMSO-d_6 presents the specific signal of the proposed structure (figure 13). Pyrimidine protons H-2 and H-5 appear as singlets at 9.02 ppm and 9.33 ppm, while pyridone protons H-3′ and H-4′ appears as overlapped signals at 7.76-7.81 ppm and H-5′ give a doublet at 6.78 ppm.

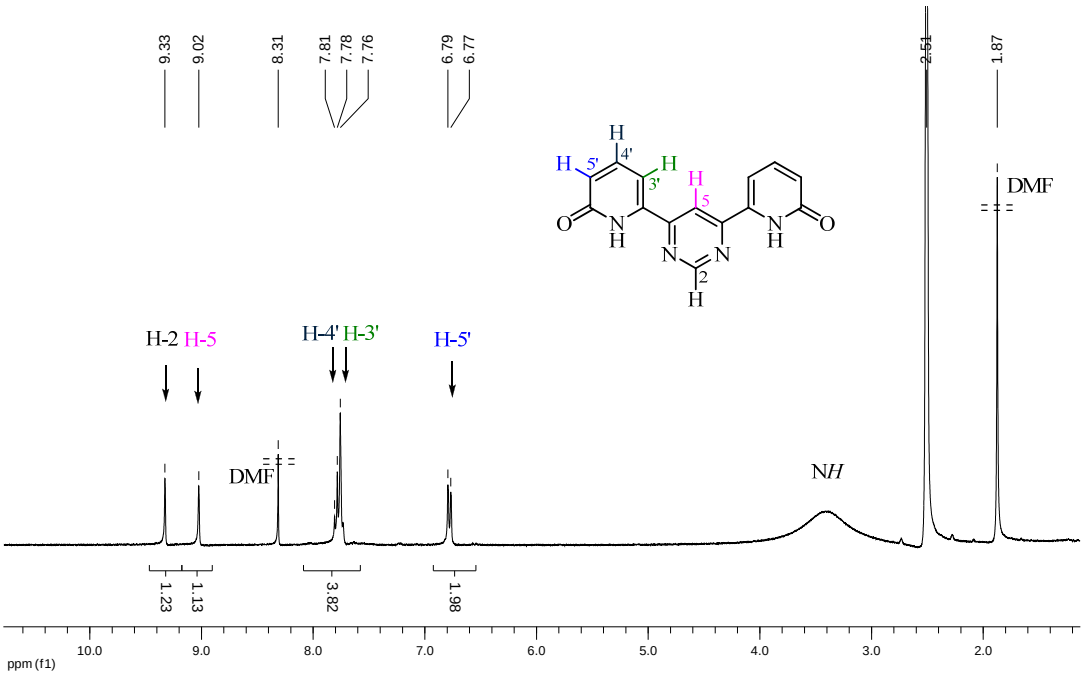
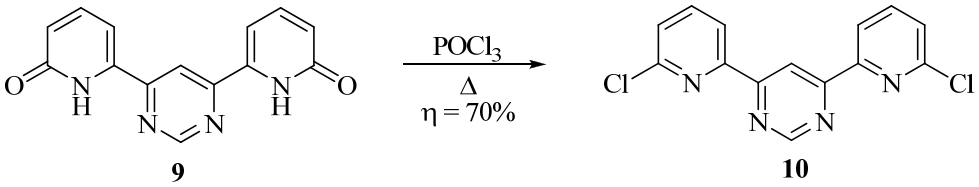


Figure 13. ^{1}H NMR (300 MHz, DMSO-*d6*) spectrum of the derivative **9**

Bispyridone **9** was heated overnight with $POCl_3$ excess, yielding 4,6-bis(6-chloropyridin-2-yl)pyrimidine **10** (scheme 15). After removal of the $POCl_3$ under vacuum, ice was added over the residuum, then a solution of $NaHCO_3$ for neutralisation. The mixture was extracted with dichloromethane followed by filtration on alumina to afford the dichlorinated derivative **10**, which presents low solubility in usual organic solvents.



9 **10**

Scheme 15

The structure of the compound **10** was confirmed by the ^{1}H NMR spectrum (figure 15) which presents well-resolved signals for all the protons in the molecule. The pyrimidine protons H-2 and H-5 appears as doublets at 9.42 and 9.15 ppm respectively, while the pyridine protons give two doublets for H-3′ and H-5′ at 7.42 and 8.32 ppm respectively and a triplet at 8.15 for H-4′.

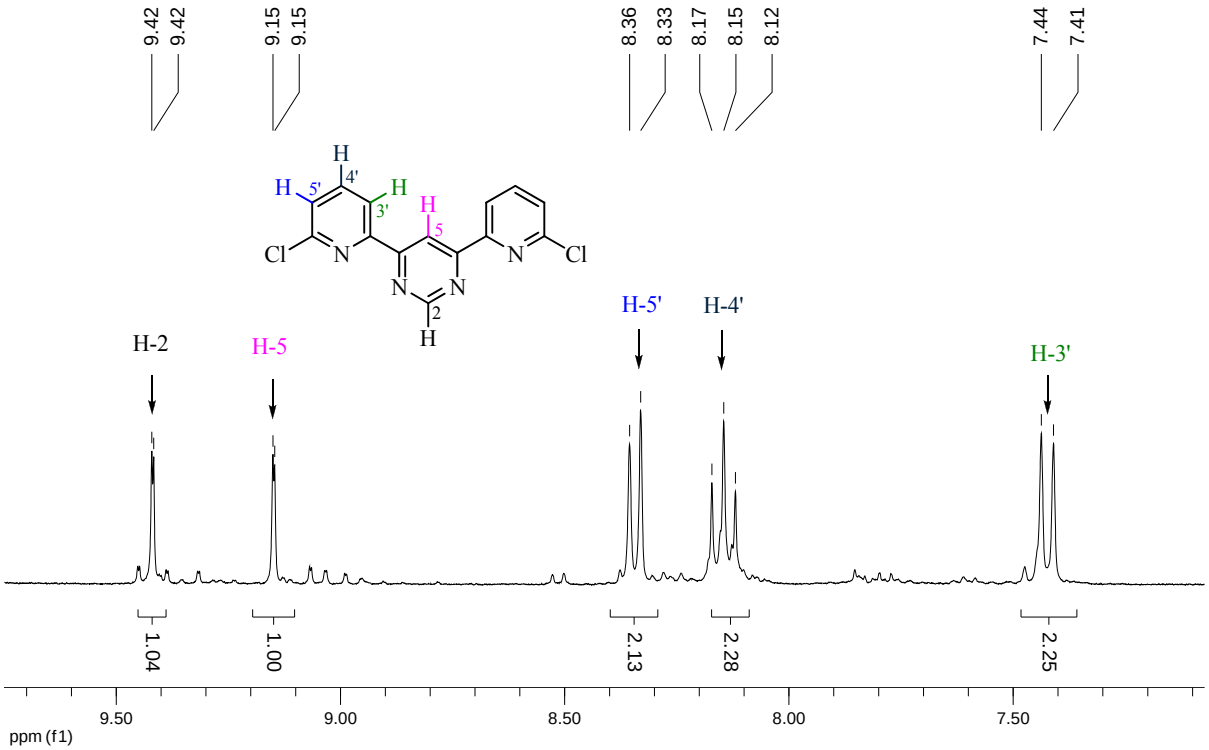
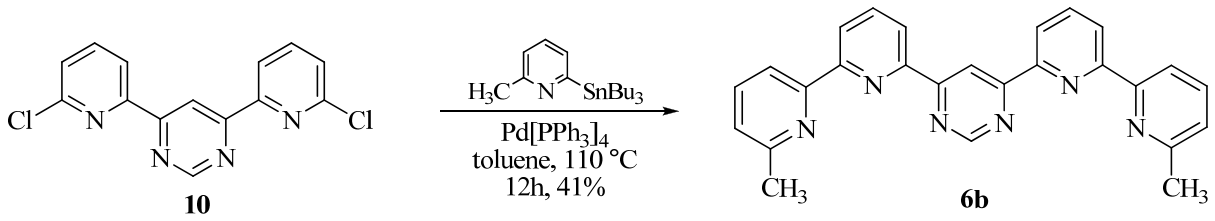


Figure 15. ^{1}H NMR (300 MHz, DMSO-*d6*) spectrum of the compound **10**

Next, ligand **6b** was synthesised by Stille reaction between derivative **10** and the stannyl compound **3a** (synthesised as shown in Scheme 10) in presence of palladium(0)-catalyst (scheme 16). Following the second route for obtaining the ligand **6b**, we succeeded improving the yield with 20%.



Scheme 16

^{1}H NMR and ^{13}C NMR spectroscopy together with mass spectrometry confirmed the anticipated structure. Proton spectroscopic data of compound **6b** show well defined signals for each type of proton in accordance with the symmetrical structure of the molecule.

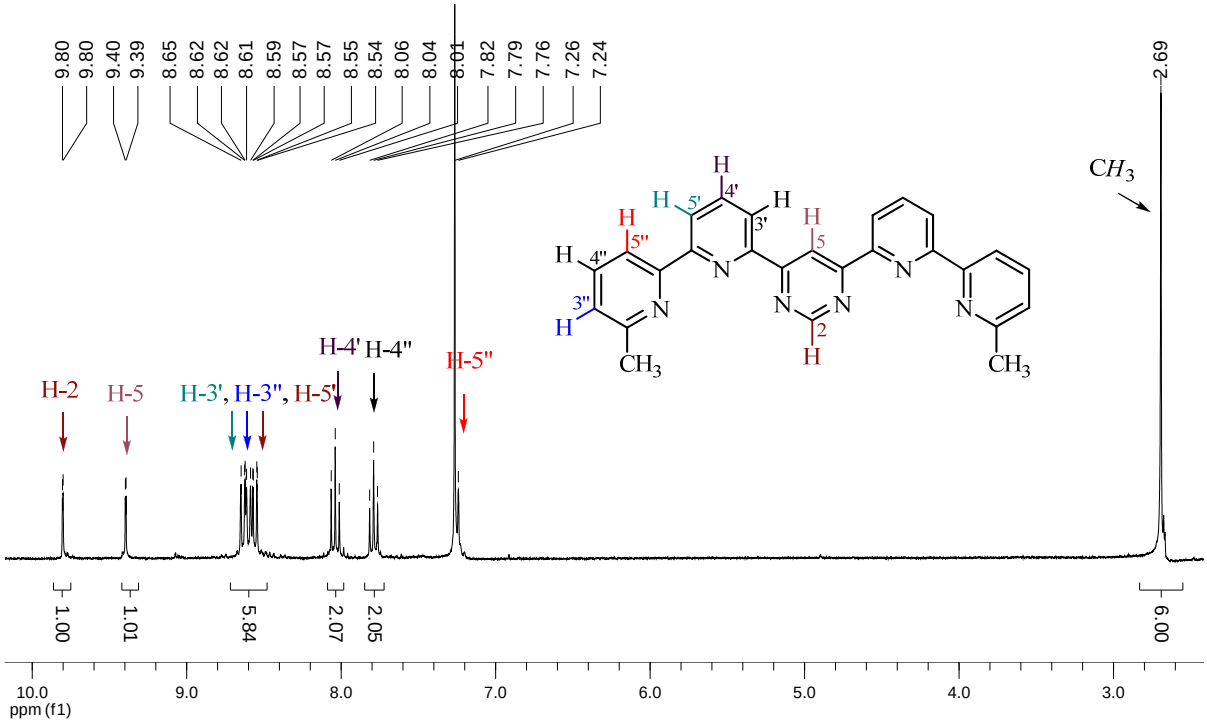


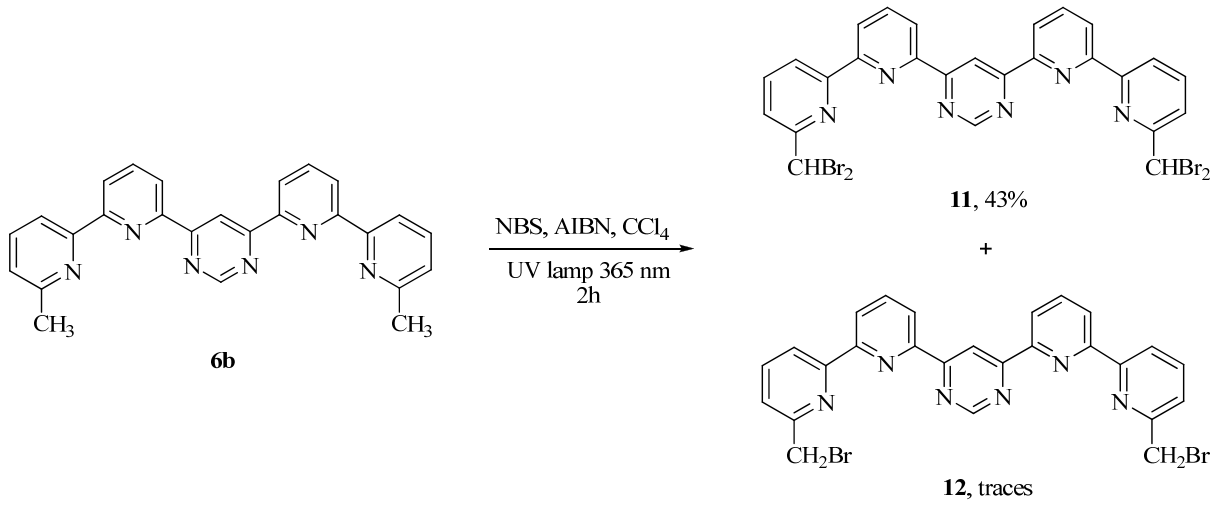
Figure 16. ^{1}H NMR spectrum of compound **6b**

Pyrimidine protons H-2 and H-5 are the most deshielded signals appearing as doublets at 9.80 and 9.40 ppm. H-3′, H-3″ and H-5′ give overlapped signals at 8.54-8.65 ppm, and H-5″ gives a doublet at 7.25 ppm. Protons H-4′ and H-4″ appear as triplets at 7.79 and 8.04 ppm. The picoline aliphatic protons give a singlet at 2.69 ppm (figure 16).

2.3.1.3. Functionalisation by bromination reaction

Further, to functionalise the bipy-pym ligand **6b**, a fotochemical reaction with excess of NBS (10 eq.) in presence of AIBN (5% wt) in anhydrous tetrachloromethane was performed.[7] The reaction mixture was irradiated for one hour at 150 W, and then heated for other twelve hours. After work-up results a cream solid, very insoluble and impossible to analyse. Repeating the reaction, but with irradiation at 365 nm provided from the UV-lamp and reflux for two hours, compound **6b** led to formation of a mixture of brominated products **11** and **12** (scheme 18). The target compound **12** was obtained only in traces, in the ^{1}H NMR spectrum of the crud reaction the peak corresponding to the bromomethylene group appears at 4.64 ppm. NMR and MS spectra (figure 17 and 18) revealed that the major component of the reaction mass is the tetrabrominated product **11** obtained in 43% yield.

[7] S.C. Rawle, P. Moore, N.W. Alcock *Chem.Commun.* **1992**, *9*, 684; J. Polin, E. Schmohel. V. Balzani, *Synthesis* **1998**, *3*, 321; R. Custelcean, J. Bosano, V. Kertesz, B.P. Hay, P.V. Bonnesen, *Angew. Chem.* **2009**, *48*, 4025.



Scheme 18

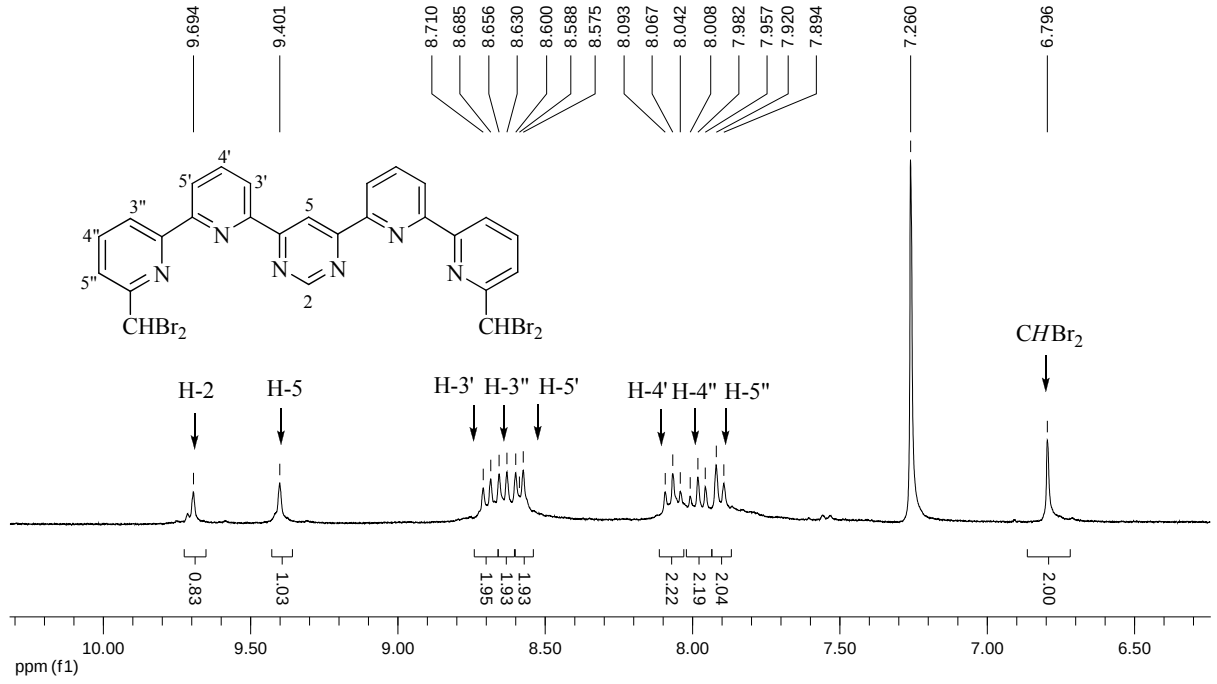


Figure 17. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **11**

^{1}H NMR spectrum of compound **11** exhibit the expected pattern presenting a very deshielded signal for dibromomethyl group at 6.80 ppm, two triplets for H-4″ and H-4′at 7.98 ppm and 8.07 ppm respectively, four doublets for H-5″, H-5′, H-3″ and H-3′ at 7.91, 8.59, 8.65 and 8.70 ppm respectively. The pyrimidine protons appear as singlets at 9.40 and 9.70 ppm.

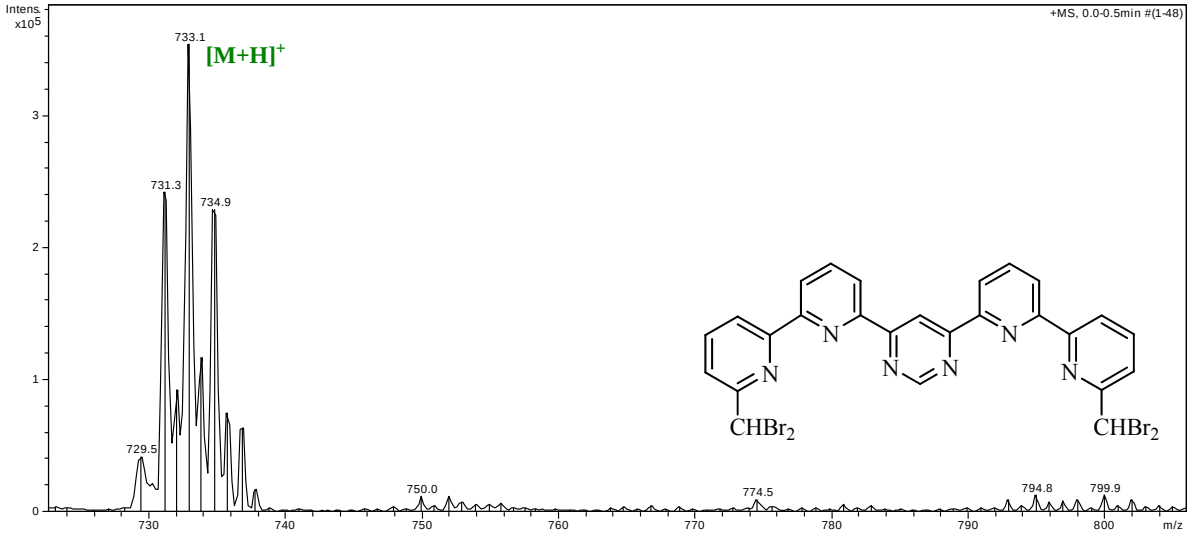


Figure 18. APCI-MS of compound **11**

In perspective we intend to optimise the method in order to obtain the bis(bromomethyl) product **11** in better yields, and also to synthesise the dibromo-bipy-pym ligand by conversion of the corresponding dimethoxyligand.

2.4. CONCLUSIONS

In the second part of the thesis I have presented the results obtained in the synthesis of some new functionalised aza-hetarene ligands possessing bipy-pym-bipy skeleton.

The ligand with two methyl groups in alpha position of the marginal pyridine units was synthesised by two methods. The first method performed, required to synthesise in the first step the bipyryl units, followed by a two folded Stille hetero-coupling reaction with the central pyrimidine unit in low yield. In order to obtain the dimethylated ligand in higher yield a second method was employed. By Stille heterocoupling reactions pyridine units were attached to the pyrimidine core to form py-pym-py intermediate, to which were subsequently attached marginal methyl-pyridine units. Following the second method was succeeded to increasing the yield of up to 20%. Five new intermediates containing pyridine and/or pyrimidine units were obtained in fair yield.

In order to obtain functionalised ligands, the dimethylated ligand was subjected to radicalic bromination with NBS in presence of AIBN. The reaction performed with excess of NBS led to formation of the bis(dibromomethyl) product in good yield, while the bis(bromomethyl) derivative was obtained only in traces. The structure of the compounds were analysed and confirmed by 1D and 2D NMR spectroscopy and MS spectrometry.

PART 3. SYNTHESIS AND ANALYSIS OF NEW SPIRO-1,3-DIOXANE MACROCYCLES

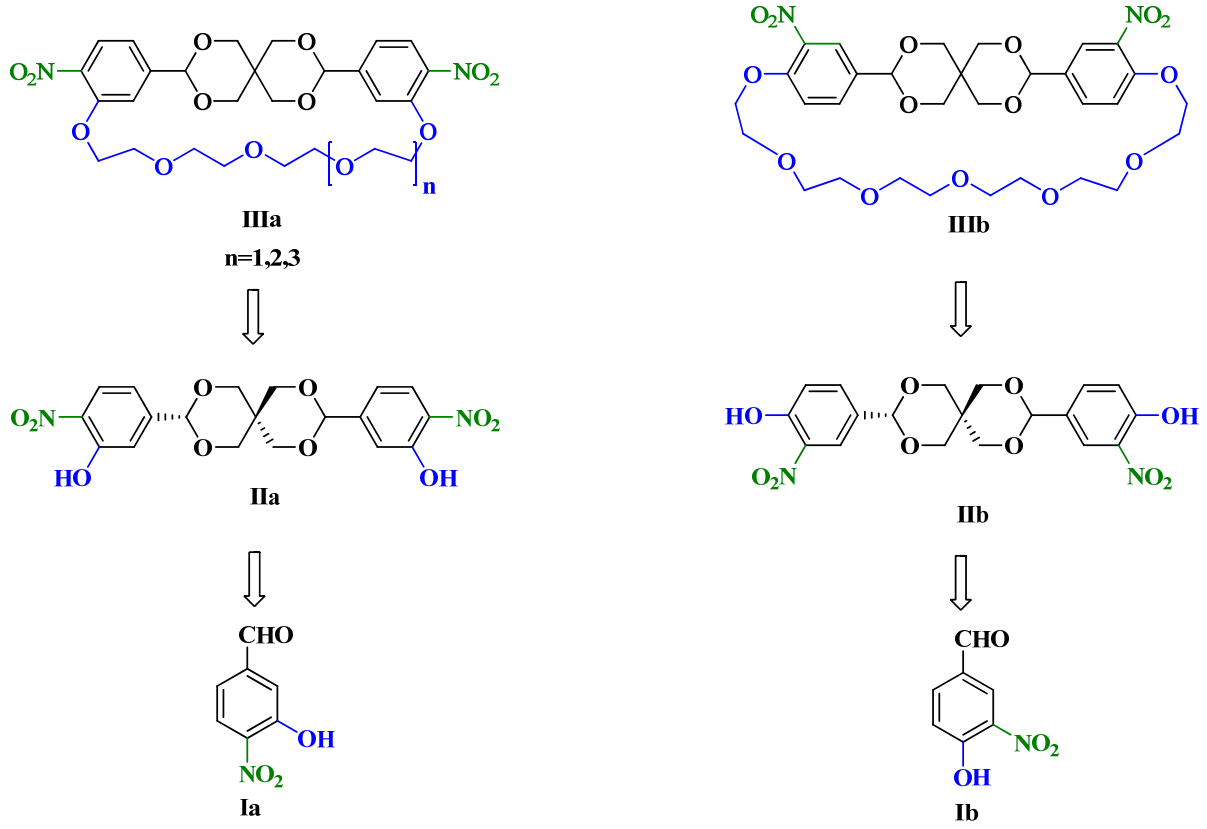
3.1. INTRODUCTION

Macrocycles are very useful ingredients in supramolecular chemistry, as they provide whole cavities having different sizes which are able to completely surround *guest* molecules; and may be chemically modified in order to improve their properties. Crown ethers form stable inclusion complexes with protonated primary amines. Pioneering studies have demonstrated that chiral crown ethers can be used in conjunction with extraction,[1,2] NMR spectroscopy, chromatographic separations,[3] and phase transfer systems[4] to differentiate the enantiomers of protonated chiral amines, amino alcohols, and amino acids. Further uses of chiral crown ethers for enantioselection purposes have been described.[5]

3.3. RESULTS AND DISCUSSIONS

In this chapter are presented the syntheses of some new macrocycles containing 2,4,8,10-tetraoxa-spiro[5.5]undecane skeleton following a strategy described in the retrosynthetic scheme 9. Starting from bezaldehydes **Ia** or **Ib** the macrocycles precursors **IIa** and **IIb** are obtained by a double acetalysation reaction**,** and which in appropriate conditions led to formation of the target macrocycles **IIIa** or **IIIb**.

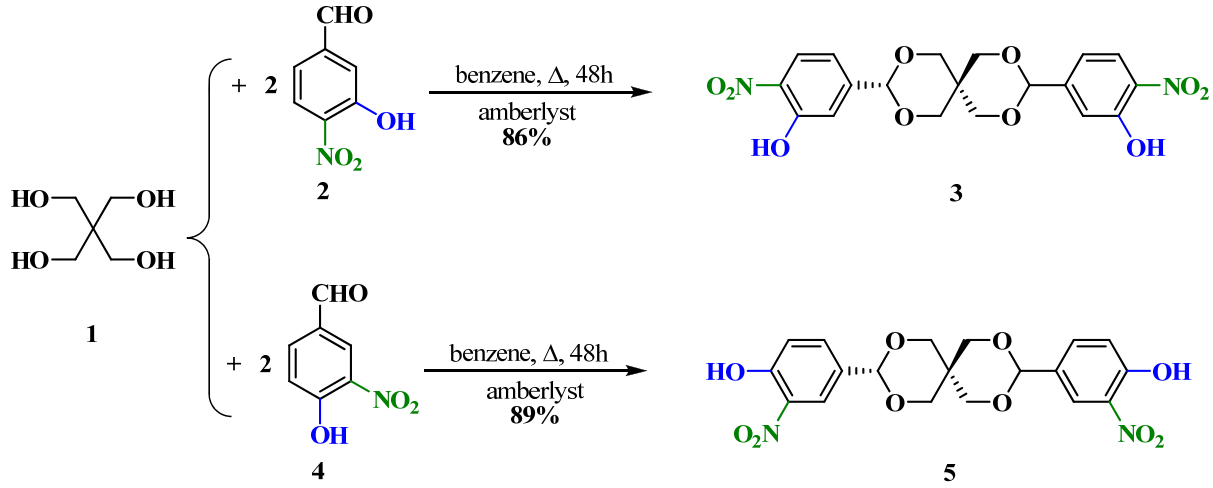
[1] R.C. Helgeson, J.M. Timko, P. Moreau, S.C. Peacock, J.M. Mayer, D.J. Cram, *J. Am. Chem. Soc.* **1974**, *96*, 6762.
[2] W.D. Curtis, D.A Laidler, J.F. Stoddart, G.H. Jones, *J. Chem. Soc., Chem. Commun.* **1975**, 835.
[3] L.R. Sousa, G.D.I. Sogah, D.H. Hoffman, D.J. Cram, *J. Am. Chem. Soc.* **1978**, *100*, 4569.
[4] M. Newcomb, J.L. Toner, R.C. Helgeson, D.J. Cram, *J. Am. Chem. Soc.* **1979**, *101*, 4941.
[5] X.X. Zhang, J. S. Bradshaw, R.M. Izatt, *Chem. Rev.***1997**, *97*, 3313.



Scheme 9

3.3.1. Synthesis of spiro-1,3-dioxane derivatives

By a two-folded acetalysation reaction, between pentaerythritol and the appropriate benzaldehyde (**2** or **4,** scheme 10), at reflux in benzene in the presence of amberlyst as catalyst, two new spiro-1,3-dioxanes, **3** and **5**, were obtained as precursors for the synthesis of new macrocycles.



Scheme 10

As already reported in literature, this type of compounds display three chiral elements: a helix with M or P configuration, characteristic to polyspiraneic skeleton with six-membered rings, and two chiral axes C(3)-C(6) with the substituents Ar and H at C-3, and C(6)-C(9) with the substituents Ar and H at C-9 (figure 9). The 1,3-dioxanes ring are anacomeric, the high A-value of aryl groups located at the acetal part determines a strong shifting of the conformational equilibria, involving the flipping of the 1,3-dioxane rings towards only two conformers with both aryl groups in equatorial orientation (figure 9). Considering the chirality exhibited by spiro skeleton, these compounds are obtained under the usual conditions of the acetalysation reaction, as racemic mixture (M and P configuration of the helix).

The structure of the new synthesised spiranes was investigated by 1D and 2D NMR spectrometry and ESI-MS, which present specific features in accordance with their stereochemistry. The chirality presented by these compounds determines the diastereotopicity of position 1 (identical with 11) and 5 (identical with 7). The anancomeric nature of the dioxane units leads to differentiation of the equatorial and axial protons (figure 9). The protons in positions 1 and 11 are oriented towards oxygen atoms of the other ring becoming CH_2-*inside* groups, and the protons in positions 5 and 7 are oriented on the exterior being considered CH_2-*outside* groups (figure 9).

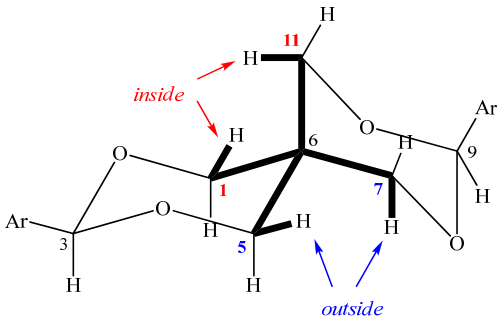


Figure 9. Spatial arrangement of the anancomer 3,9-disubstituted spiro-1,3-dioxane skeleton

Analysis of the ^{1}H NMR spectra of derivatives **3** and **5** are in agreement with the predicted structure (figure 10). Therefore, for compound **3**, the phenol groups give a very deshielded singlet at 10.58 ppm, and another singlet appears at 5.44 ppm assigned to the acetal protons H-3 and H-9. 1,3-Dioxane protons exhibit different signals: two doublets of doublets at 4.78 and 3.86 ppm for the equatorial protons in positions 1 and 11 (J = 11.7, 2.5 Hz) and the equatorial protons in position 5 and 7 respectively; and two doublets at 3.84 and 3.52 ppm for the axial protons in positions 1 and 11 (J = 11.7 Hz) and the axial protons in position 5 and 7 respectively. Equatorial protons present a supplementary split due to the W planar arrangement of the bonds H_{eq}–$C_{1(11)}$–C_6–$C_{5(7)}$–H_{eq}.

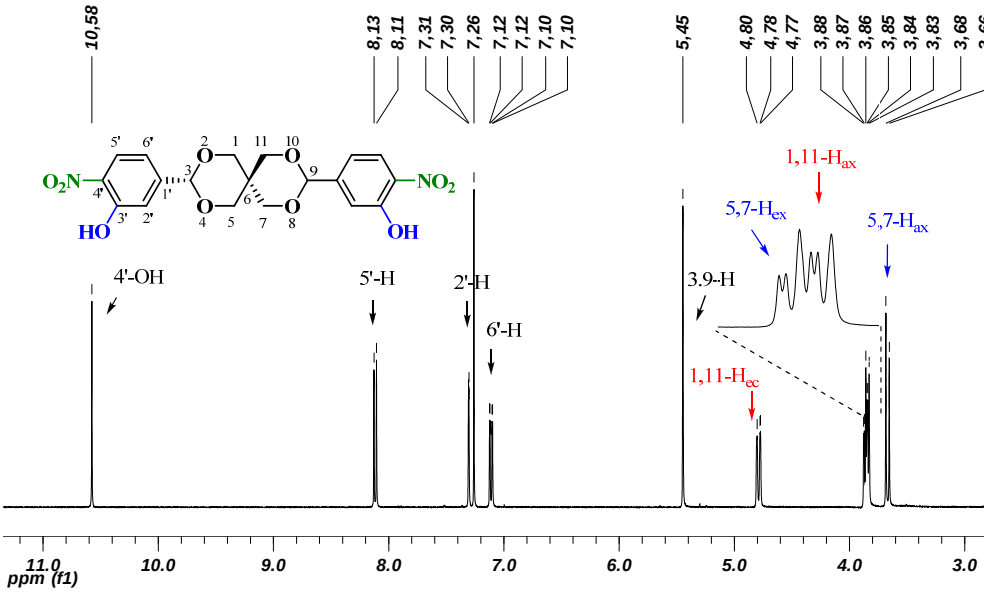


Figure 10. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of spirane **3**

Diastereotopicity of the dioxane protons is better shown in ^{1}H NMR performed in deuterated benzene for the compound **5**. In figure 15 are presented the aliphatic zones of the two NMR spectra recorded in $CDCl_3$ and C_6D_6 respectively. Four signals corresponding to the four types of dioxane protons can be observed in deuterated benzene, with a visible migration of the chemical shifts to more upfield values by comparison to the spectrum recorded in $CDCl_3$.

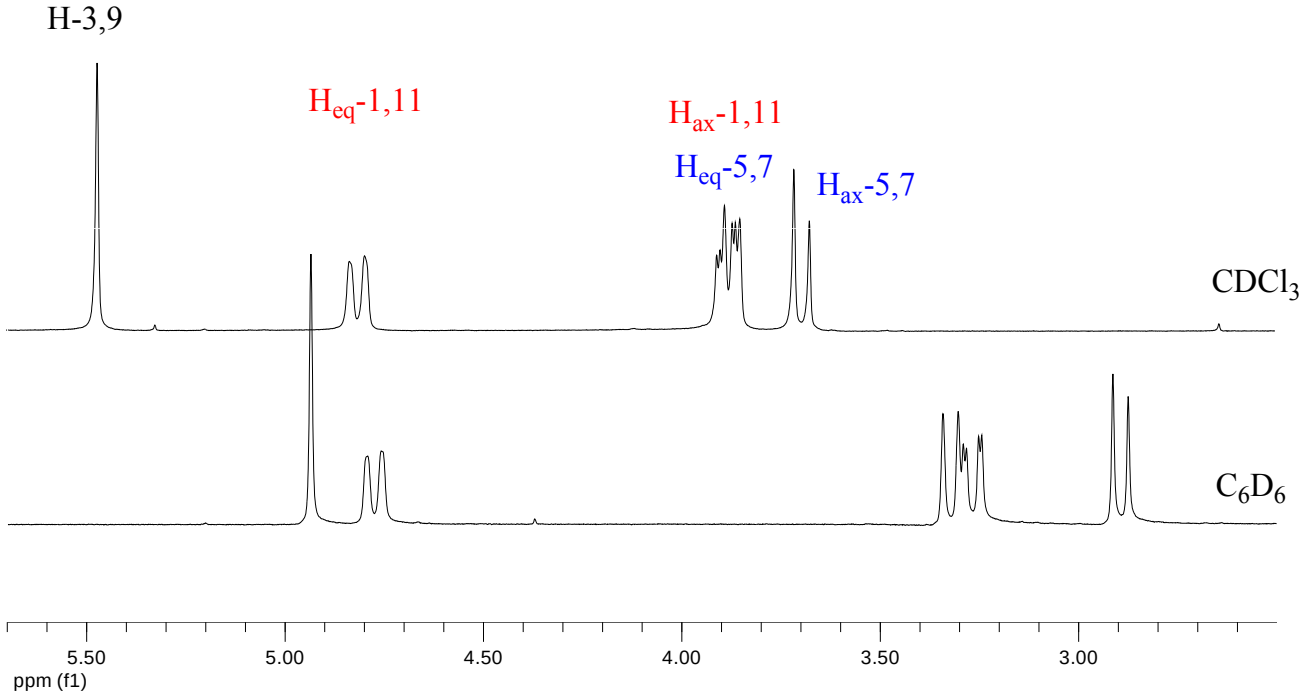


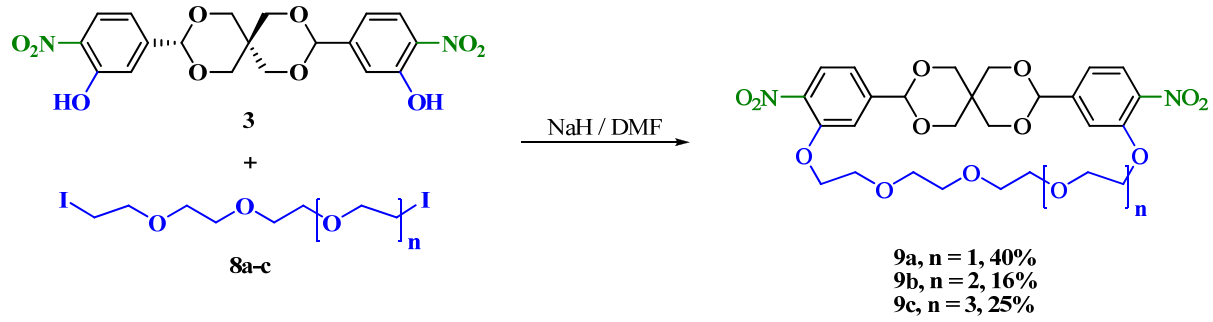
Figure 15. Fragments of the ^{1}H-NMR spectra of spirane **5** in $CDCl_3$ and C_6D_6

3.3.2. Synthesis of spiro-1,3-dioxane macrocycles

The synthesis of the new macrocycles **9a-c** consists in two steps: first the synthesis of the spirane unit, and second, the ring closure using polyethyleneoxid chains in specific condition reactions. The acetalysation reaction is based on a nucleophilic substitution reaction of the iodine of the polyethyleneoxide chain.

In the next step the synthesis of macrocyclic compounds was performed by using the classical reaction conditions as described in literature. *Template* method with Cs or K salts in *ultradilution* conditions did not led to the desired compounds most possible because of the insolubility of spirane salt in the solvent used. Changing the acetonitrile with THF, acetone or DMF did not led to formation of the expected product. Other reaction conditions were tried in order to promote the salt solubility and the nucleophilic attack.

In order to avoid solubility issues less bulky metal ions were used. Therefore, using NaH, as base, and dry DMF, as solvent, led to formation of the diphenoxide sodium salts, to which diiodinated chains **8a-c** are added slowly. Following this new procedure the desired macrocycles **9a-c** are obtained in good yields (16-40%) as mixture of enantiomers M and P (scheme 13). The structure of the new products was determined by NMR analysis and confirmed by ESI-MS spectrometry. After purification by conventional chromatography only monomers were isolated. We assume that the higher terms like dimers, trimers, or even tetramers might have been formed in very small amounts.



Scheme 13

The NMR spectra of the macrocycles **9a-c** confirm the structure of the molecules. The ^{1}H-NMR spectrum in deuterated DMSO of compound **9a** (figure 16) exhibit two doublets and one singlet, as the most deshielded signals corresponding to the aromatic protons H-17, H-29 at 7.83 ppm, H-30, H-36 at 7.68, and H-18, H-28 at 7.13 ppm respectively. The acetalic protons H-20, H-26 give a singlet at 5.60 ppm, while the 1,3-dioxane rings exhibit four signals at 4.61 ppm for H_{eq}-22, H_{eq}-24, at 3.95 ppm for H_{ax}-

33, H_{ax}-34, at 3.85 ppm for H_{eq}-22, H_{eq}-24 and at 3.75 ppm for H_{ax}-22, H_{ax}-24 (overlapped with the signals of the polyethyloxy chain H-4, H-12). The protons in position H-2, H-13 appears as a overlapped doublet of doublet at 4.41 ppm as the most deshielded protons of the chain. The rest of the protons of the polyethyloxy chain, H-6, H-7, H-9, H-10 appears as a broad singlet at 3.54 ppm.

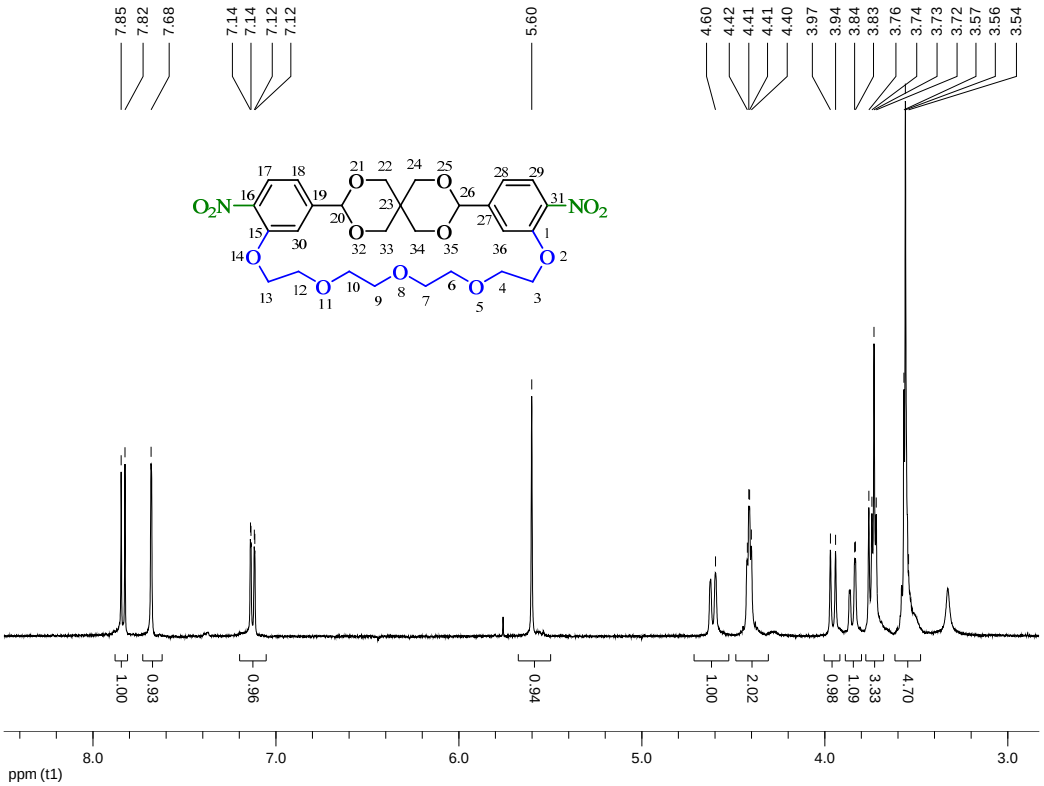


Figure 16. ^{1}H-NMR spectrum (300 MHz, DMSO-*d6*) of derivative **9a**

ESI-MS spectrum of compound **9c** shows three peaks corresponding to different complexes macrocycle:cation = 1:1 formed in solution: $[M+H]^+$ (13%), $[M+H_2O]^+$ (46%) and $[M+Na]^+$ (100%) (figure 24).

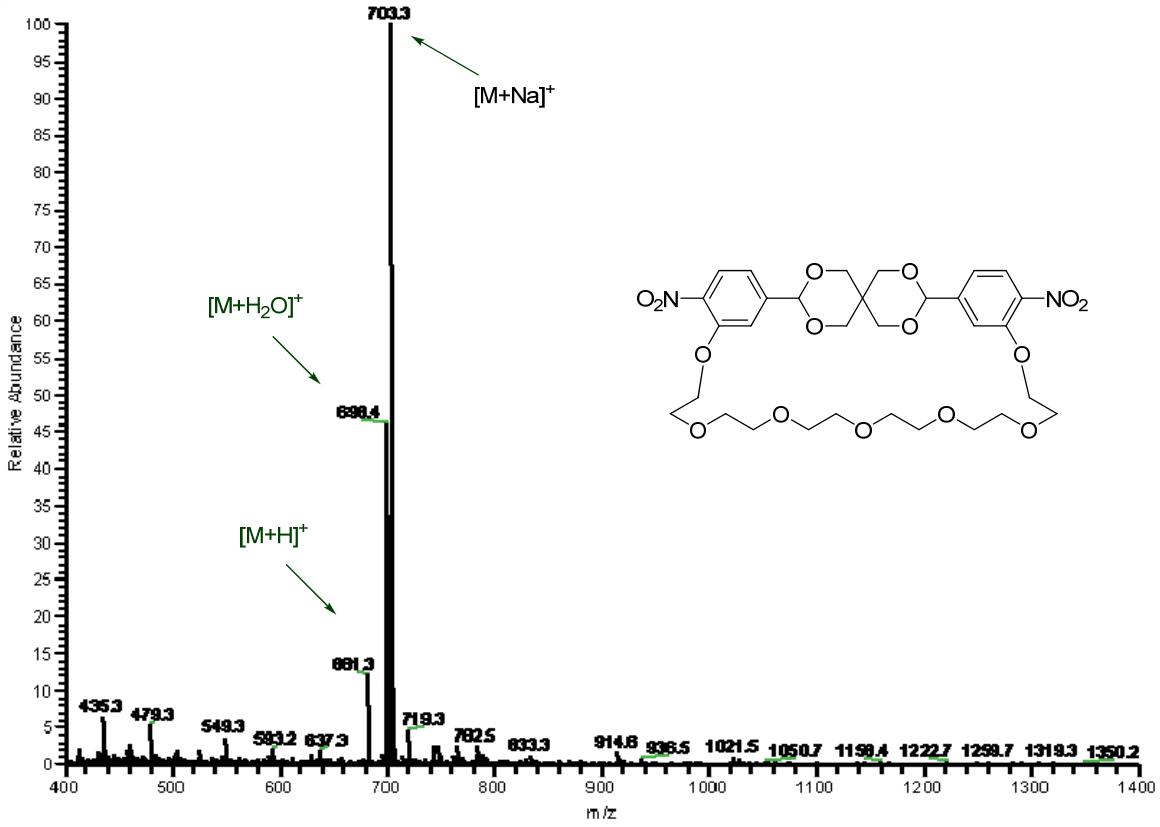
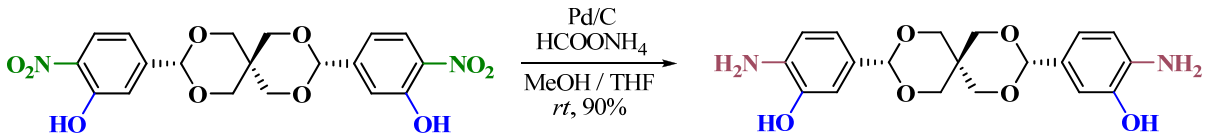


Figure 24. ESI-MS spectrum of macrocycle **9c**

In order to separate the two macrocyclic enantiomers, M and P, the derivatisation with a chiral agent was taken into consideration. First, the nitro group was reduced to amine, which, if reacted with a chiral acid will lead to the formation of two separable diastereoisomers. Initially was tried reduction of the nitro groups to amine of dioxane **3**, following a procedure developed by Fuchs,[6] catalised by Pd/C in the presence of ammonium formate (scheme 14). The spiro-1,3-dioxane **11** was formed in very good yield. The diamino-spirane precipitated from the reaction solution by addition of petroleum ether. The diamine **11** is relatively stable compound with low solubility in chloroform.

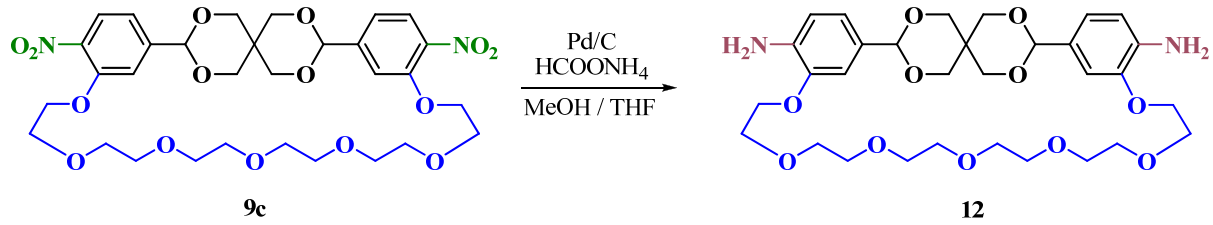


3 **11**

Scheme 14

[6] H. Jatzke, K. Frische, M.e Greenwald, L. Golender, B. Fuchs, *Tetrahedron* **1997**, *53*, 4821-4834.

New spiro-1,3-dioxane macrocycle derivative **12** (scheme 15) was obtained by reduction of the dinitromacrocycle derivative **9c** with Pd/C catalyst and ammonium formate as source of hydrogen, in a methanol/tetrahydrofuran 1/1 solvent mixture.



9c **12**

Scheme 15

Thin layer chromatography shows the formation of the diamine **12**, which was visualised with ninhydrine, and ^{1}H NMR spectrum of the crude reaction, shows the presence of three compounds: monoamino-, diamino-product and nitro-spirane. Purification attempts lead to decomposition of the amine products after solvent evaporation.

As perspective, the derivatisation of the enantiomers should include the synthesis *in situ* of the intermediate **12**.

3.4. CONCLUSIONS

The work presented in this chapter deals with the synthesis and structural analysis of two new 2,4,8,10-tetraoxa[5.5]undecane derivatives as precursors for the synthesis of macrocycles, and one new amine derivative by hydrogenation of its nitro relative. A new method was applied in order to obtain three new macrocycles containing spiro-1,3-dioxane units and bearing aromatic units at the margins, which are connected through a polyethylene glycol chain.

The structural analysis of the compounds is based on 1D and 2D NMR spectroscopy and mass spectrometry. The structure of the two new 2,4,8,10-tetraoxa[5.5]undecane derivatives present specific stereochemistry, possessing an anancomeric structure, and exhibits helicoidal and axial chirality. Both 1,3-dioxane units have a equatorial disposition of the aromatic unit, which is a favourable angle to promote the macrocyclisation.

The macrocyclisation reaction led to formation of monomers, the presence of dimers or higher terms was not detected.

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