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# NEW [2.2]PARACYCLOPHANE DERIVATIVES

Ph.D. DISSERTATION ABSTRACT

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IAŞI
2014

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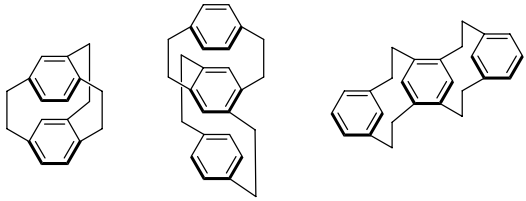
## INTRODUCTION

According to literature, cyclophane chemistry represents an important chapter in organic chemistry. The first studies on [*m.n*]paracyclophanes were performed by Cram at the beginning of the 1950s. Cram was also the first one to use the name ”paracyclophanes” for this class of bridged aromatic compounds, thus indicating their cyclic nature, as well as their two main components: the aromatic rings and the aliphatic bridges. Starting with his research, no other class or aromatic compounds has received so much attention as the cyclophanes have in the past few decades.

As far as their design goes, the versatile structure of paracyclophanes offers numerous possibilities. Thus, any aromatic system can act as an aromatic component and the aliphatic bridge can be a saturated or unsaturated polymethilenic chain. Moreover, there are even multibridged paracyclophanes as well as multi stratified paracyclophanes:



Cyclophane chemistry presents a wide interest, mainly due to their structural characteristics, like the nonplanarity of the aromatic rings and abnormal angles and bond lenghts, as well as their geometrical and sterical properties, transannular properties and ring strain. Moreover, special attention is being paid to the electronic interactions between the sandwitch-positioned aromatic rings, the influence that these interactions have on electrophilic aromatic substitution, as well as their role in charge transfer complex formation.

Amongst the binuclear cyclophanes, [2.2]paracyclophane is the most studied molecule and it is also the molecule around which this thesis has been built. Although the number of publications in this field is impressive, this paper comes to offer more arguments in favour of continuing the research based on paracyclophane chemistry. A particular interest has been devoted to the functionalization of the aliphatic bridges, as well as the formation of new bridges, as a result of transannular interactions.

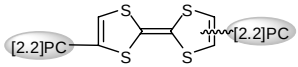
## II. PERSONAL RESEARCH

### Objectives

The Ph.D. Dissertation named ”New [2.2]paracyclophane derivatives” aims to develop new [2.2]paracyclophane hybrid derivatives which also incorporate tetrathiafulvalene or indolizine moieties, as well as to synthesize [2.2]paracyclophanes analogous to natural endiynes.

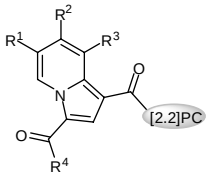
The propossed objectives are the following:

1. The synthesis of new [2.2]paracyclophane-tetrathiafulvalene hybrids.




2. Reacting the newly obtained hybrids with tetracianoquinodimethane, with the aim of obtaining complexes that display metallic properties, such as electrical conductivity.

3. The synthesis of new [2.2]paracyclophane-indolizine hybrids that are analogous to phenstatin, where the **A** ring is replaced by a [2.2]paracyclophane moiety.




4. The synthesis of new *pseudo*-geminally substituted [2.2]paracyclophanes, analogous to natural endiynes.

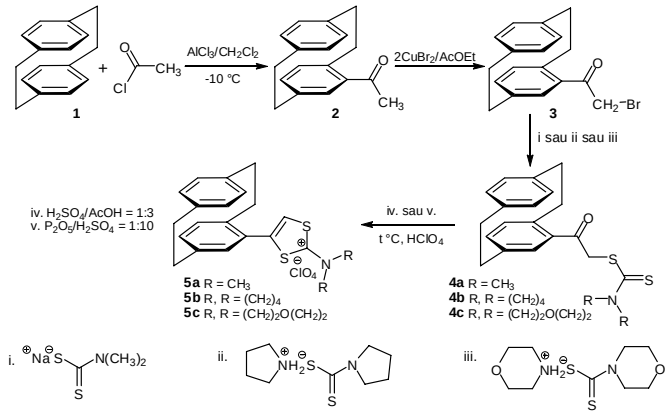
5. Studying the reactions between *pseudo*-geminally substituted [2.2]paracyclophanes and Selenium-based electrophiles.

6. Studying the Birch reduction of some *pseudo*-geminally substituted [2.2]paracyclophanes.

7. The structural characterization of the newly synthesized derivatives, using elemental analysis and various spectral methods (IR, $^{1}$H-NMR, $^{13}$C-NMR, MS and X-ray diffraction).

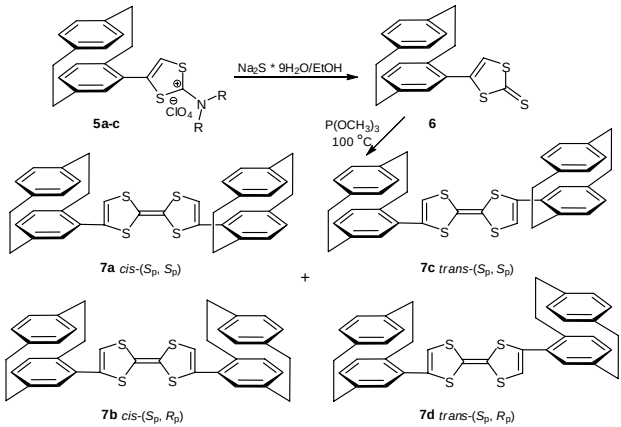
## II.1. [2.2]PARACYCLOPHANE SUBSTITUTED TETRATHIAFULVALENE DERIVATIVES

Because of their distinct chemical and physical properties, tetrathiafulvalene (TTF) derivatives are the subject of many studies. Considering this fact, we decided to synthesize and investigate some new [2.2]paracyclophane-TTF hybrids. In order to do this, we first obtained the 1,3-dithiolium perchlorates **5a-c**, by using [2.2]paracyclophane **1** as starting material, as presented in Scheme II.1.




**Scheme II.1.** The synthesis of perchlorates **5a-c**

Perchlorates **5a-c** were then converted to 1,3-dithiol-2-thione **6** using sodium sulfide, at room temperature. By heating 1,3-dithiol-2-thione **6** with trimethylphosphite, a mixture of four TTF isomers was obtained, namely compounds **7a-d**, as shown in Scheme II.2.




**Scheme II.2.** The synthesis of TTF derivatives **7a-d**

The structures of the newly obtained compounds were established using IR, $^{1}$H-NMR, $^{13}$C-NMR and mass spectrometry. The structures of compounds **4a** and **6** were also confirmed using X-ray diffraction.

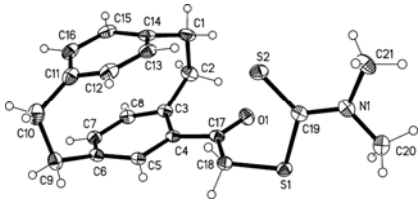



**Figure II.1.3.** The structure of compound **4a**

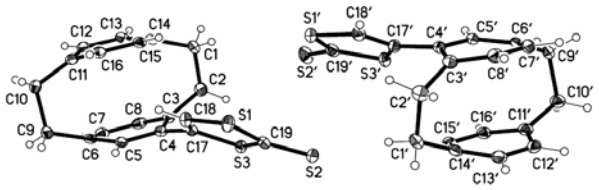


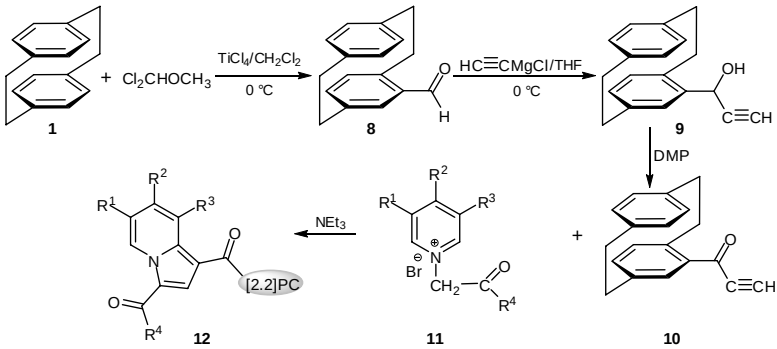

**Figure II.1.7.** The structure of compound **6**

The following stage was the reaction between the mixture of isomers and tetracyanoquinodimethane (TCNQ), which resulted in the formation of complexes that displayed metal-like properties, such as electrical conductivity. The reaction between donors **7a-d** and TCNQ took place in refluxing acetonitrile and yielded four complexes, namely *cis*-($S_p$, $S_p$)-TTF-TCNQ, *cis*-($S_p$, $R_p$)-TTF-TCNQ, *trans*-($S_p$, $S_p$)-TTF-TCNQ, *trans*-($S_p$, $R_p$)-TTF-TCNQ, as a dark-green polycrystalline solid.

## II.2. [2.2]PARACYCLOPHANE SUBSTITUTED INDOLIZINE DERIVATIVES

Another objective of this dissertation was the synthesis of new indolizine derivatives, analogous to phenstatin, which is known for its anti-cancer properties.[195]

The first stage requires the synthesis of 4-formyl[2.2]paracyclophane **8**, using [2.2]paracyclophane.[202, 203] The next step requires the addition of ethynilmagnesium chloride to the carbony group, when the corresponding propargylic alcohol **9** is formed. Next, the alcohol is oxidized to ketone **10** using Dess-Martin periodane (DMP).[204, 205] The final stage is a [3+2]cycloaddition between ketone **10** and various *N*-ylides generated *in situ* using pyridinium salts **11a-d** and triethylamine. This yields the desired [2.2]paracyclophane sustituted indolizines **12a-d**.[206]

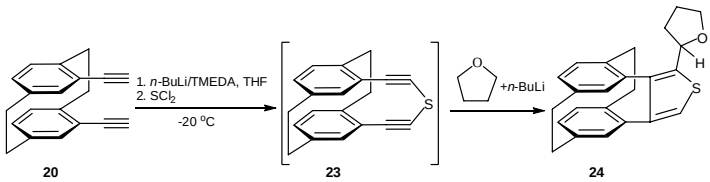



**Scheme II.3.** The synthesis of indolizines **12a-d**

## II.3. *PSEUDO-GEMINALLY* SUSTITUTED PARACYCLOPHANES, ANALOGOUS TO NATURAL ENDIYNES

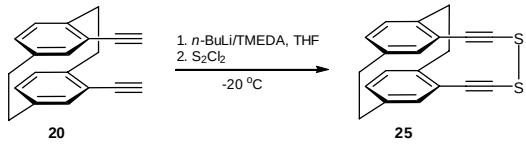
The aim of this chapter was to study the intramolecular electronic interactions and their influence on aromatic substitution reactions, as well as the design and synthesis of new compounds analogous to natural endiynes.

Representative to this chapter is 4,15-bisethynil[2.2]paracyclophane **20**, which is synthesized according to a seven step procedure.[208] The first reaction that was studied involved treating it with *n*-BuLi in anhydrous THF and then with sulfur dichloride, $SCl_2$. This leads to the formation of paracyclophane derivative **24**, which contains a thiophenic ring, most likely formed through cycloaromatization, induced by the nucleophilic attack of a tetrahydrofurane anion on an acetylenic carbon atom in compound **23** (Scheme II.9.).[210]



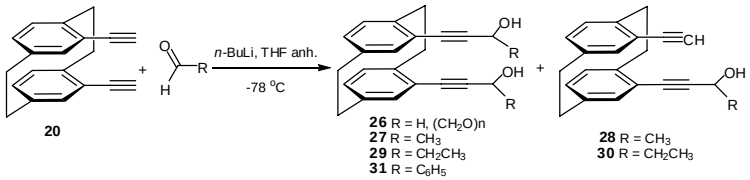

**Scheme II.9.** The reaction between paracyclophane **20** and $SCl_2$

Under the same reaction conditions, paracyclophane **20** reacts with sulfur monochloride, yielding the corresponding disulfide **25** (Scheme II.10.).



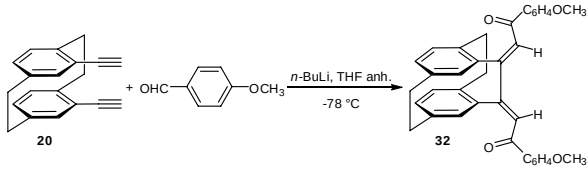

**Scheme II.10.** The reaction between paracyclophane **20** and $S_2Cl_2$

Another type of studied reactions is the one involving paracyclophane **20** and a series of aliphatic and aromatic aldehydes, as shown is Scheme II.11.



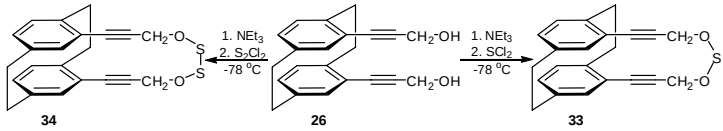

**Scheme II.11.** The reaction between derivative **20** and some aliphatic and aromatic aldehydes

The reaction takes place differently when *p*-methoxybenzaldehyde is used. The major product is bisketone **32**, most likely a product of intramolecular anionic interactions that lead to the formation of a new bridge (Scheme II.12.).




**Scheme II.12.** The reaction between paracyclophane **20** and *p*-methoxybenzaldehyde

Another stage in our studies involved the reaction between bis propargylic alcohol **26** and sulfur halides. To this end, paracyclophane **26** was treated with triethylamine and sulfur monochoride or sulfure dichloride, yielding the three-bridged compounds **33** and **34** (Scheme II.13.).



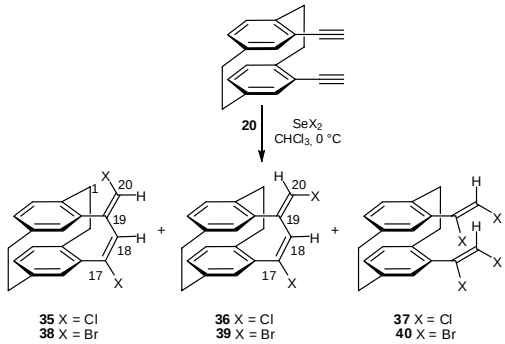

**Scheme II.13.** The reaction between paracyclophane **26** and $SCl_2/S_2Cl_2$

## II.4. REACTIONS BETWEEN *PSEUDO-GEMINALLY* SUBSTITUTED [2.2]PARACYCLOPHANE AND SELENIUM-BASED ELECTROPHILES

Our investigations concerning *pseudo-geminally* substituted [2.2]paracyclophanes eventually led us to a series of reactions between bis acetylene **20** and some selenium electrophiles.

In order to introduce another bridge in the [2.2]paracyclophane molecule, we attempted a double addition reaction between paracyclophane **20** and one equivalent of selenium dichloride. Thus, by treating paracyclophane **20** with *in situ*

generated[217] selenium dichloride, in chloroform, we obtained an additon mixture of and not the expected selenium-bridged derivative (Scheme II.14.).

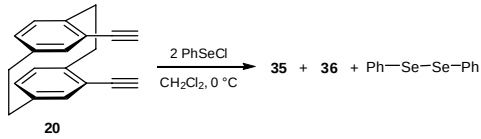



**Scheme II.14.** The reaction between paracyclophane **20** and $SeCl_2$/$SeBr_2$

Upon sepparation, by using spectral analysis and mass spectrometry, we were able to determine the structures of isomeric cyclic dienes **35** and **36**, as well as that of the tetrachloro derivative **37**. The configurations for compounds **35** (17*E*, 19*Z*) and **36** (17*E*, 19*E*) were determined using NOESY, by irradiating protons H-18 and H-20.

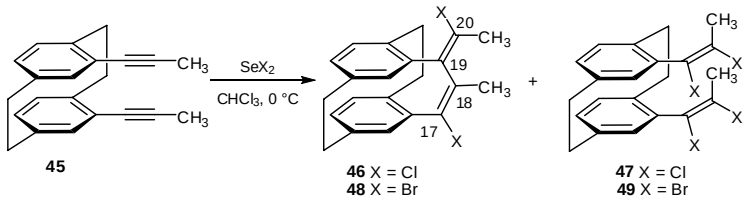
The reaction with selenium dibromide generated *in situ*[217] takes palce in a similar manner, leading to two isomeric cyclic dienes, **38** and **39** and the tetrabromo derivative **40** (Schema II.14.).

Both reaction lead to the formation of elemental selenium as a byproduct. Under the same reaction conditions, but by using two equivalents of selenium dihalide, only the cyclic dienes **35**, **36** and **38**, **39** were formed. These results determined us to investigate the reaction between paracyclophane **20** and phenylselenyl chloride. Surprisingly, by using two equivalents of phenylselenyl chloride, only cyclic dienes **35** and **36** were formed, along with diphenyl diselenide (Scheme II.15.).




**Scheme II.15.** The reaction between paracyclophane **20** and PhSeCl

We decided to extend these studies, by replacing 4,15-bisethynil[2.2]paracyclophane **20** with 4,15-bis(propin-1-yl)[2.2]paracyclophane **45**. Thus, by reacting paracyclophane **45** with one equivalent of selenium dichloride, (17*E*, 19*E*)-diene **46** and tetrachloro derivative **47** were obtained (Scheme II.17.).

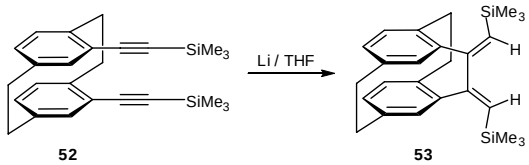



**Scheme II.17.** The reaction between paracyclophane **45** and $SeCl_2$/ $SeBr_2$

Similarly, by using selenium dibromide instead of selenium dichloride, (17*E*, 19*E*)-diene **48** and tetrabromo derivative **49** are obtained (Scheme II.17.).

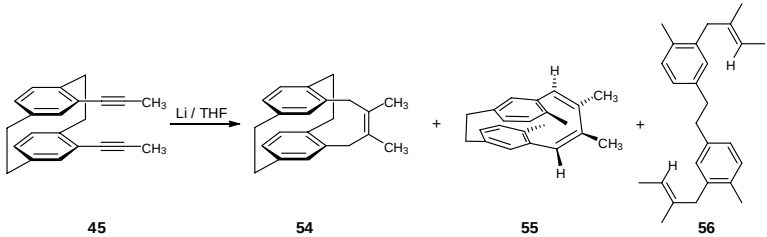
## II.5. THE BIRCH REDUCTION OF *PSEUDO–GEMINALLY* SUBSTITUTED [2.2]PARACYCLOPHANES

Considering the latest progress in pentalene chemistry, another direction investigated by us comprised of the reactions between some bisethynil *pseudo-geminally* substituted [2.2]paracyclophanes and lithium. One first such reaction is that between paracyclophane **52** and ten equivalents of lithium powder in anhydrous THF, when compound **53** is formed (Scheme II.19.).




**Scheme II.19.** The reaction between paracyclophane **52** and lithium

The studies were then extended to paracyclophane **45** which, under the same conditions, led to the formation of a reaction mixture, some of which could not be identified (Scheme II.20.). Upon sepparation using preparative TLC and analysing the different fractions obtained (spectral analysis, mass spectrometry), the structures of compounds **54**, **55** and **56** were determined.




**Scheme II.20.** The reaction between paracyclophane **45** and lithium

## CONCLUSIONS

Given the conducted research and the results obtained and presented in this paper, the following conclusions can be drawn:

1. New [2.2]paracyclophane derivatives have been synthesized and characterized by varying the substituent in position 4, with the purpose of obtaining [2.2]paracyclophane-TTF hybrids.

2. 3 New dithiocarbamates (**4a-c**) and 3 new 1,3-dithiolium perchlorates (**5a-c**) containing a [2.2]paracyclophane moiety have been obtained and their structure has been confirmed by spectral analysis and mass spectrometry. 1,3-Dithiol-2-thione **6** has been synthesized, which was then used to obtain the diastereomers **7a-d**.

3. The reaction between diastereomers **7a-d** and tetracyanoquinodimethane led to a mixture of four compounds. The IR spectra of this mixture displays four absorption bands that have been assigned to the CN group, at 2222 $cm^{-1}$, 2204 $cm^{-1}$, 2183 $cm^{-1}$ and 2150 $cm^{-1}$, each corresponding to a different complex.

4. Four new indolizine-[2.2]paracyclophane hybrids have been synthesized by reacting 4-(1-oxopropin-1-yl)[2.2]paracyclophane **10** with various *N*-ylides, generated from their corresponding piridinium salts.

5. New [2.2]paracyclophane derivatives analogous to natural endiynes have been synthesized, using 4,15-bisethynyl[2.2]paracyclophane **20** as a starting point.

6. The reactions of [2.2]paracyclophane **20** with sulfur halides have been studied. Depending on the used halide, either tiophen derivative **24** or disulfide **25** is obtained.

7. Reactions between [2.2]paracyclophane **20** and various aldehides were also studied. The reaction with *p*-methoxybenzaldehide provided unexpected results, when bisketone **32** was obtained as a major product. Its formation is likely the product of intramolecular anionic interactions and a mechanism has been proposed to explain the process.

8. The reactivity of [2.2]paracyclophane **26** was studied by treating it with sulfur chlorides ($SCl_2$, $S_2Cl_2$) and the corresponding multi-bridged derivatives **33** and **34** were obtained.

9. In the case of [2.2]paracyclophane **20** and **45**, interactions between the *pseudo-geminally* positioned groups were studied, by treatment with various selenium and selenyl halides. The reaction between [2.2]paracyclophane **20**

and one equivalent of selenium halide $SeX_2$ (X = Cl, Br) leads to the formation of cyclic isomeric dienes **35**, **36** (X = Cl) and **38**, **39** (X = Br) and the tetrahalogeno derivatives **37** (X = Cl) and **40** (X = Br). Under the same conditions, but using two equivalents of selenium halide $SeX_2$, only cyclic dienes **35**, **36** (X = Cl) and **38**, **39** (X = Br) were obtained.

10. By reacting [2.2]paracyclophane **45** with one equivalent of selenium halide $SeX_2$ (X = Cl, Br), cyclic dienes **46** (X = Cl) and **48** (X = Br) and tetrahalogeno derivatives **47** (X = Cl) and **49** (X = Br) were isolated. When two equivalents of selenium halide were used, only cyclic dienes **46** (X = Cl) and **48** (X = Br) were obtained.

11. The reactions between [2.2]paracyclophane **52** and [2.2]paracyclophane **45** with lithium were studied. The Birch reduction of *pseudo-geminally* substituted [2.2]paracyclophanes is dependent on the substituents bound to the [2.2]paracyclophane moiety. Thus, the trimethylsilyl groups lead to the formation of a new bridge with two *exo*-cyclic double bonds, whereas the less bulky methyl groups determined the formation of a new bridge with two *endo*-cyclic double bonds.

12. This Ph.D. Dissertation reports 41 new compounds.

13. Part of the results described are the subject of two scientifical papers published in ISI recognized journals and two manuscripts submitted for publication. Morover, some of the results obtained were presented at national and international conferences.

- Published papers:

1. **Sarbu, L. G.**; Bicu, E.; Hopf, H.; Birsa, M. L., [2.2]Paracyclophane Substituted Indolizines, *Revista de Chimie*, **2014**, *65 (4)*, 398-400.

2. **Sarbu, L. G.**; Birsa, A.; Hopf, H.; Birsa, L. M, New Bridges in [2.2]Paracyclophanes: The Interaction of Chalcogenide Halides with *pseudo-geminal* Triple Bonds, *Phosphorus, Sulfur and Silicon*, **2011**, *186 (5)*, 1246-1250.

3. **Sarbu, L. G.**; Hopf, H.; Jones, P. G.; Birsa, M. L., Selenium halide induced bridge formation in [2.2]paracyclophanes, *Manuscript Submitted to Beilstein Journal of Organic Chemistry*, **2014**.

4. **Sarbu, L. G.**; Hopf, H.; Grunenberg, J.; Birsa, M. L., Birch Reduction of *pseudo-geminally* [2.2]Paracyclophanes, *Manuscript Submitted to Synlett*, **2014**.

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210. **Sarbu, L. G.**; Birsa, A.; Hopf, H.; Birsa, L. M, *Phosphorus, Sulfur and Silicon*, **2011**, *186 (5)*, 1246.

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218. **Sarbu, L. G.**; Hopf, H.; Jones, P. G.; Birsa, M. L., *Beilstein J. Org. Chem.*, manuscris trimis spre publicare, **2014**.

228. **Sarbu, L. G.**; Hopf, H.; Grunenberg, J.; Birsa, *Synlett*, manuscris trimis spre publicare, **2014**.