PhD Thesis

This PhD thesis is the result of colaboration between Babes-Bolyai University and University of Zaragoza having as directors Prof. Ion Grosu and Prof. Carlos Cativiela. Doctor Esteban Urriolabeitia was also directly involved in the Part 1 of the thesis while the Part 3 was accomplished after a Marie Curie reasearch stage of 6 months in Vienna under the supervision of Prof. Marko M. Mihovilovic from Vienna University of Technology.

Thesis is structured in three different parts, scientifically diverse but unitary in their goals. The first part is dedicated to the synthesis of new organometallic compounds of unsaturated 5(4*H*)-oxazolones. The second part deals with the *bottom up* Supramolecular Chemistry, more exactly with the synthesis of new rotaxanes intermediates. Finally the third part discuss the synsthesis of different *α*-keto-*β*-lactams as intermediates in Taxol synthesis.

Ion Grosu was born in 1955 in Cluj -Napoca, Romania. He obtained his PhD in Organic Chemistry at Babes-Bolyai University in Cluj-Napoca. Synthesis and conformational analysis of saturated heterocyclic compounds represented a research direction successfully aproached for 1,3-dioxanes and 1,3-oxathianes structures. A new research direction of the group refers to the domain of Supramolecular Chemistry: host-guest systems, coronands, cryptands, cyclophanes and molecular cages. He published 4 books and is the author of around 100 papers.

Carlos Cativiela is Full Professor of Organic Chemistry at the University of Zaragoza since 1996. His scientific activity started in the field of asymmetric synthesis oriented to the preparation of amino acids. He has developed different methodologies for the synthesis of a wide variety of nonnatural constrained amino acids in enantiomerically pure form either by enantio-/diastereoselective syntheses or by chromato-graphic resolution procedures. Current research interests also involve the incorporation of such non-natural amino acids into peptides of structural or biological interest. He is author of more than 320 papers and 10 reviews.

Esteban P. Urriolabeitia was born in San Sebastian, Spain in 1964 and he received his chemical education at the University of Basque Country and at the University of Zaragoza. He received his PhD in Inorganic Chemistry in 1991. After his postdoctoral period with M. Pfeffer at the University Louis Pasteur (Strasbourg) he returned to Zaragoza where he is Scientific Researcher of the CSIC at the ICMA (University of Zaragoza). His major current interests are the study of CH bond activation - functionalization processes using Pd and Pt complexes and the bonding properties of stabilized ylides toward transition metals.

Marko D. Mihovilovic received his PhD from VUT in 1996. In 1997 he moved to the University of New Brunswick, Canada, for a postdoctoral stay within the group of Prof. Margaret M. Kayser followed by a subsequent postdoctoral stay in the group of Prof. Jon D. Stewart at the University of Florida, in 1998. During this time he became strongly acquainted with research in the area of biocatalysis. After his return to VUT, he completed his Habilitation in 2003 in bioorganic chemistry and was appointed Associate Professor in 2004. His current research focuses on enzyme- and metalassisted methods in bioactive compound and natural product synthesis.

ROIBAN GHEORGHE-DORU

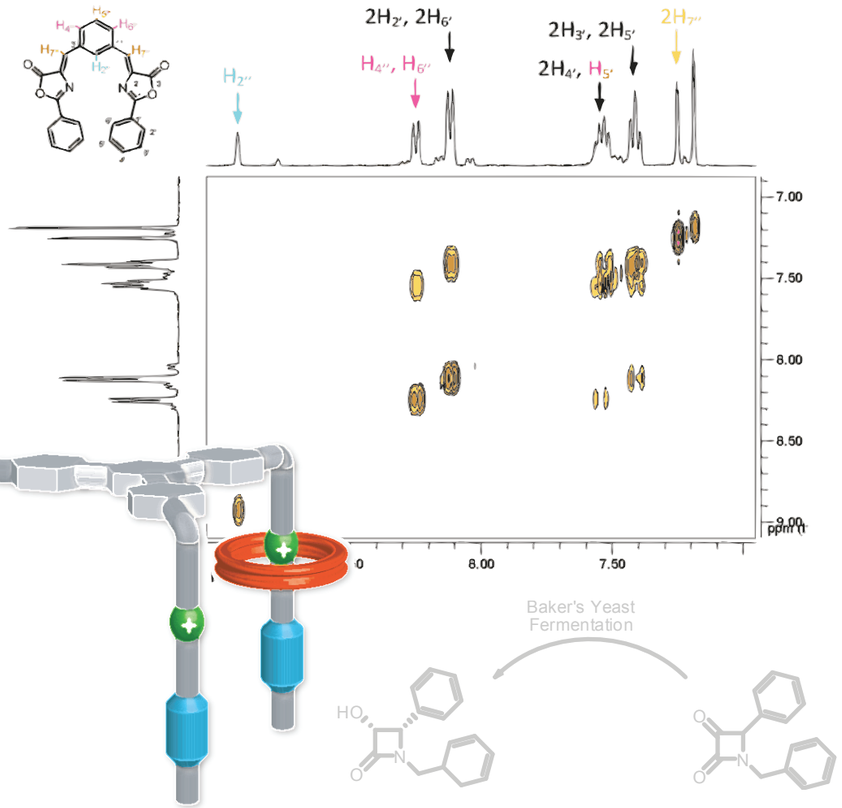
PhD Thesis

2009

PhD Thesis

Doru Roiban

Synthesis, Characterization, Structural Analysis and Reactivity of 5(4*H*)-Oxazolone Derivatives and Rotaxane Precursors



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Ph.D. Thesis

SYNTHESIS, CHARACTERIZATION, STRUCTURAL ANALYSIS AND REACTIVITY OF 5(4*H*)-OXAZOLONE DERIVATIVES AND ROTAXANE PRECURSORS

Ph.D. Thesis Abstract

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Cluj-Napoca
2009

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Cluj-Napoca
2009

Part 1

SYNTHESIS AND REACTIVITY OF NEW ORGANOMETALLIC COMPOUNDS CONTAINING 5(4*H*)-OXAZOLONES (1)

Part 2

SYNTHESIS AND STRUCTURAL ANALYSIS OF NEW ROTAXANE PRECURSORS (187)

Part 3

SYNTHESIS OF α-KETO-β-LACTAMS AS INTERMEDIATES IN TAXOL SYNTHESIS (269)

KEYWORDS

5(4*H*)-Oxazolone, Ortometalation, Palladium, Oxidative Addition, C-H Bond Activation, Pseudorotaxanes, Triaxle, Terpyridines, Macrocicles, Supramolecular Chemistry, Complexation, Lactams, Bioreduction

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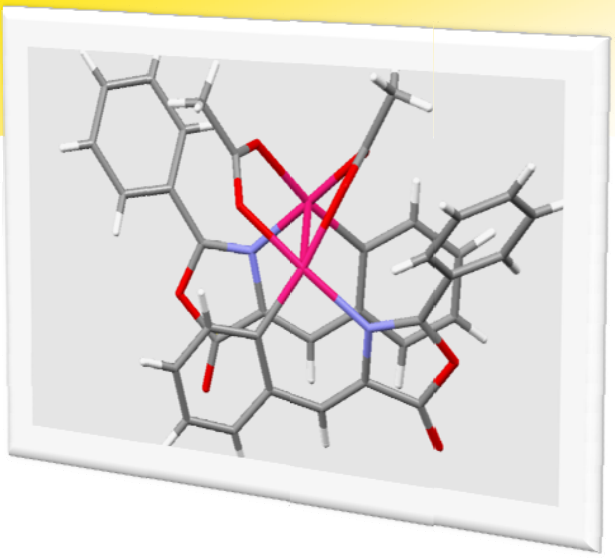
Part 1

SYNTHESIS AND REACTIVITY OF NEW ORGANOMETALLIC COMPOUNDS CONTAINING 5(4*H*)-OXAZOLONES



Contents

2. OBJECTIVES

The possibility of direct introduction of a new functionalities (or a new C–C bond) via direct C–H bond transformation or oxidative addition is a highly attractive strategy, owing to the ubiquitous nature of C–H bonds in organic substances.

Metallacycles represent a challenge to chemists not only in terms of their synthesis but also in terms of their structures, design, and types of ligands metallated. Of course the use of transition metal in metallacycle formation processes proved to be in generally a suave, clean and selective method.

There are several features which make reactions involving Pd catalysts and reagents particularly useful and versatile among many transition metals used for organic synthesis. No other transition metals can offer such versatile methods of the carbon–carbon bond formations as Pd.

As multifunctional compounds, 5(4*H*)-oxazolones can act as ligands and, as such, they can provide interesting organometallic transition metal complexes depending upon the coordination mode of the 5(4*H*)-oxazolone to the metal atom. The reaction of *saturated oxazolones* with organometallic complexes leads to a versatile chemistry. *Unsaturated 5(4H)-oxazolones have a great potential regarding the reactivity* and *their interaction with different transition metals has not been deeply investigated until now*.

That's why *the main purpose of this work was to find the reactive positions of the unsaturated 2-aryl-4-arylidene-5(4H)-oxazolones* (**Figure 1**), *through C-H bond activation* (X=H) and *oxidative addition* (X= Halogen) *using transition metals such as Hg, Pt and Pd*.

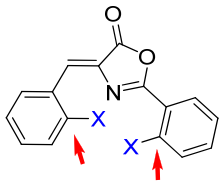


Figure 1. 2-phenyl-4-benzylidene-5-(4*H*)-oxazolone
possible activating substrate (X=H, Halogen)

C-H activation was chosen as derivatization method of oxazolones since is one of the most elegant forms to functionalize the substrate and has a big potential for producing functionalized hydrocarbons.

However, in some instances C−H bond activation can not be achieved, for whatever reason, and the corresponding metallacycle is not synthesized, fortunately there are synthetic alternatives such as oxidative addition.

Unsaturated aromatic oxazolones have two or more activated C-H bonds. In this case metallation of several C-H bonds can arise a regioselectivity problem. Another target was to *control the cyclometallation process in the favor of formation of five- and six-membered metallacycles*.

Thus, *we set out to address the considerable challenge of whether C-H functionalization could be realized in complex substrates and in a selective manner using different functional groups* (FG) (**Figure 2**).

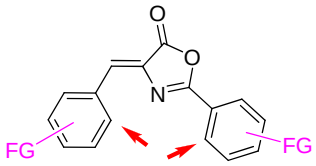


Figure 2. Regioselectivity in unsaturated oxazolones using different FG

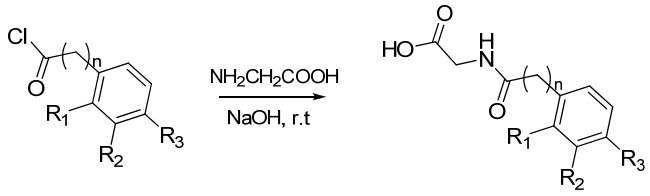
3. RESULTS AND DISCUSSIONS

In order to fulfill the objectives proposed different (*Z*)-2-aryl-4-arylidene-5(4*H*)-oxazolones were needed. Moreover, the prepared oxazolones should cover a wide range of electronic and steric requirements. We know that functional groups of the substrate affect the reactivity of metal. All of these issues must be considered and studied in a systematic fashion in order to develop a selective functionalization of different types of C-H bonds.

3.1. Synthesis of 2-aryl-4-(arylidene)-5(4*H*)-oxazolones

One of the most used procedures to prepare unsaturated 5(4*H*)-oxazolones is the Erlenmeyer synthesis. For the synthesis of 2-aryl-4-arylidene-5(4*H*)-oxazolones it must be employed an acylaminoacid and a carbonyl compound, in this case an amide, in the presence of a cyclodehydrating agent such as acetic anhydride. Aromatic aldehydes bearing various groups were commercially available, but excepting *N*-benzoylglycine, all other acylglycines had to be prepared.

In literature there are different methods to prepare amides the carbonyl component.[1] Amides **1**-**5** were prepared using the condensation method between an acylchloride and glycine (**Scheme 1**).



Scheme 1. *N*-acylglycine derivatives preparation

Derivatives **1**-**5** are listed in **TABLE 1** together with the IR characteristic frequency of absorption for NH group.

TABLE 1. IR Spectroscopic data for amides **1-5**.

Compound	n	R_1	R_2	R_3	v C=N (cm^{-1})	Yield (%)
1	0	Br	H	H	3256	74
2	0	I	H	H	3269	62

[1] *Compendium of Organic Synthetic Methods;* Wade, L. G. Jr., Ed.; Wiley, 2006, Vol. 4, pp 135-145 and references cited herein.

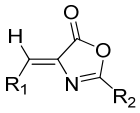
3	0	H	OCH_3	H	3318	72
4	0	H	OCH_3	OCH_3	3326	71
5	1	H	H	H	3371	68

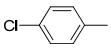
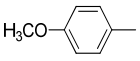
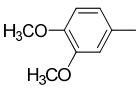
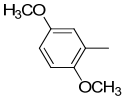
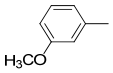
The ^{1}H NMR, ^{13}C NMR, mass and IR spectra of amides **1-5** fully agree with the expected structures.

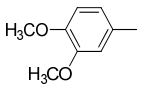
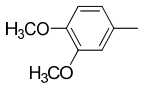
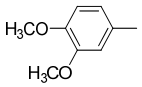
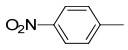
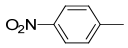
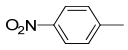
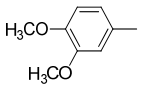
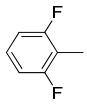
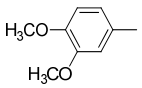
Having prepared amides **1**-**5**, the next step consisted in the synthesis of the (*Z*)-2-aryl-4-arylidene-5(4*H*)-oxazolones.

The procedure used was the Erlenmeyer synthesis that is still extensively used with some variations in the experimental conditions. Using this method (*Z*)-2-aryl-4-arylidene-5(4*H*)-oxazolones **6**-**21** (**TABLE 2**) were prepared in good yields.

TABLE 2. (*Z*)-2-aryl-4-arylidene-5(4*H*)-oxazolones



Entry	R_1	R_2	Yield (%)
6			80
7			72
8			81
9			76
10			72
11			78
12			67
13			75
14			77
15			78

16			37
17			84
18			48
19			87
20			74
21			74

Mass spectrometry, NMR and IR methods were employed to characterize the prepared oxazolones.

The ^{1}H NMR spectra of unsaturated 5(4*H*)-oxazolones show the deshielding influence of the *cis* N=C-C_6H_5 moiety on the olefinic hydrogen atom which shifts more downfield when the olefinic hydrogen is *cis* to the carbonyl group. A fragment of the ^{1}H NMR spectrum of (*Z*)-2-(2-iodophenyl)-4-benzylidene-5(4*H*)-oxazolone (**10**) is presented in **Figure 3**.

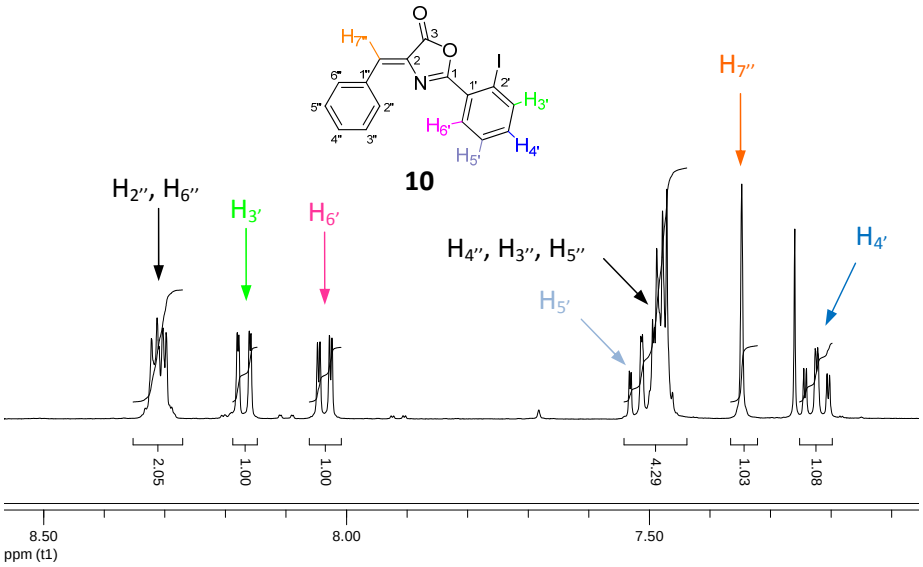
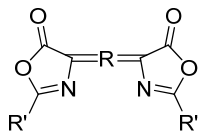


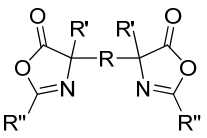
Figure 3. Fragment of the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **10**

3.2. Bisoxazolones cyclometallation (pincer YCY palladacycles)

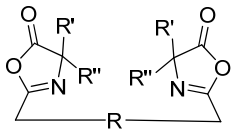
Little information is available in literature about compounds that incorporate two oxazolone rings, substrates called bisoxazolones. These compounds may be divided into four general classes which depend on the position of coupling (2 or 4) and the presence or absence of an exocyclic double bond at position 4 (**Figure 4**).[2]



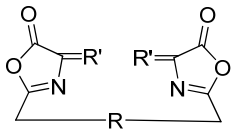
4,4'-bis-[5(4*H*)oxazolone]
(unsaturated)



4,4'-bis-[5(4*H*)oxazolone]
(saturated)



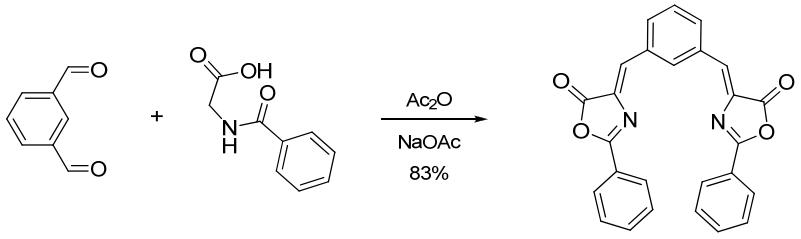
2,2'-bis-[5(4*H*)oxazolone]
(saturated)



2,2'-bis-[5(4*H*)oxazolone]
(unsaturated)

Figure 4. Different types of saturated and unsaturated bisoxazolones

Erlenmeyer method was preferred as preparation method having into account our previous experience in synthesizing oxazolones. Isoftalaldehyde was reacted with hippuric acid using Erlenmeyer conditions to obtain *Z,Z'*-2,2'-diphenyl-4,4'-*m*-phenylenedimethylene-bis-5[(4*H*,4'*H*)-oxazolone] **22** in 83% yield after recrystallization from EtOH. The reaction is stereoselective, only the *(Z,Z)* isomer being obtained, this isomer being thermodynamically more stable (**Scheme 2**).



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Scheme 2.

[2] Cleaver, C. S.; Pratt, B. C. *J. Am. Chem. Soc.* **1955**, *77*, 1544-1546.

The existence of a single diastereoisomer is proven by the symmetric molecular structure which leads to much decongested aromatic regions in the ^{1}H NMR spectra. From the H,H-COSY spectrum of compound **22** we can observe that there is only one singlet corresponding for the vinyl protons from position 7'' at 7.32 ppm. Also the protons $H_{4''}$ and $H_{6''}$ are chemically equivalent since they appear as doublet due to the vicinal coupling with $H_{5''}$. These observations together with all other spectroscopic data fully agree with the assigned *(Z,Z)* configuration (**Figure 5**).

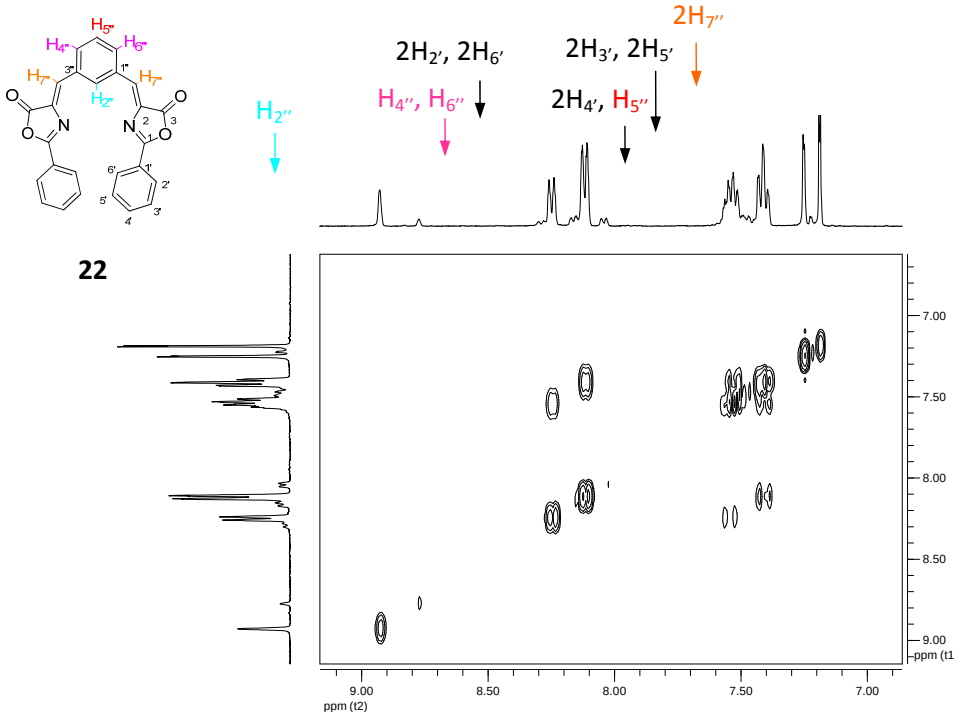
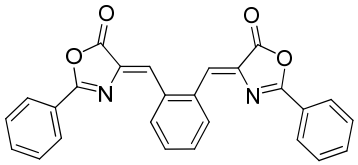


Figure 5. Fragment of the COSY spectrum for compound **22**

In the same manner oxazolones *Z,Z'*-2,2'-diphenyl-4,4'-*o*-phenylenedimethylene-bis-5[(4*H*,4'*H*)-oxazolone] **23** and *Z,Z'*-2,2'-diphenyl-4,4'-*p*-phenylene-dimethylene-bis-5[(4*H*,4'*H*)-oxazolone] **24**[3] have been prepared (**Figure 6**).

[3] Ahmed, M.; Abdel, H.; Elsayed, H.; Mohamed, K. *J. Am. Chem. Soc.* **1955**, *77*, 3860-3862.



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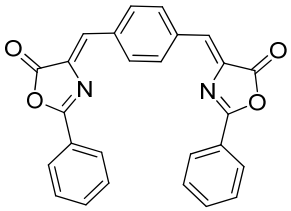

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Figure 6. Bisoxazolones **23** and **24**

3.3. Orthometallation through C-H bond activation

3.3.1. Cyclometallation of 2-aryl-4-arylidene-5(4*H*)-oxazolone (CY type)

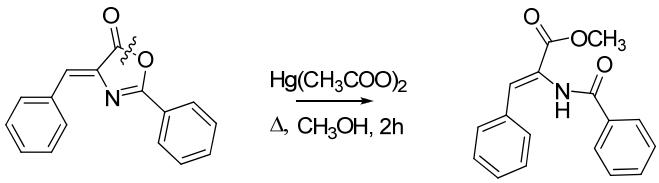
The cyclometallation is possible to occur with the formation of:

a) *five-membered rings* **A** (in this case the phenyl ring from the position 2 being involved in cyclometallation), theoretically more stable, it is the habitual activation form;
b) *six-membered* rings **B** (in this case benzylidene from the position 4 being involved in cyclometallation).

Our initial attempts to orthometallate the substrate consisted in reacting different oxazolones (**6**-**8**, **12**) (**TABLE 2**) with a variety of metal derivatives, mainly of mercury, palladium and platinum, in a wide variety of conditions.

3.3.1.1. Mercury derivatives

When oxazolone **6** was refluxed in methanol (**Scheme 3**), in the presence of $Hg(CH_3COO)_2$ the heterocyclic ring is opened and incorporates a molecule of methanol, affording 2-benzoylamino-3-phenylmethylacrylate **25**.



6 **25**

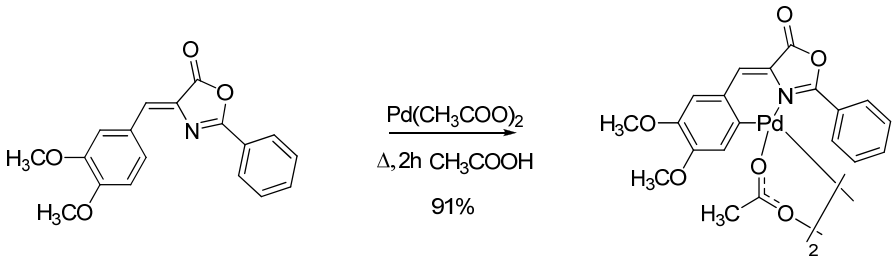
Scheme 3.

The same reaction occurs when oxazolones **7**, **8**, and **16** were treated with mercury acetate, ester derivatives **25-28** being obtained in high yields.

3.3.1.3. Use of palladium derivatives

3.3.1.3.1. Synthetic methods

The choice of the solvent was critical, and acetic acid proved to be the best option. When oxazolone **13** was reacted with $Pd(OAc)_2$ for 2 hours in refluxing acetic acid, cyclopalladated derivative was obtained (**Scheme 4**).



13 **29**

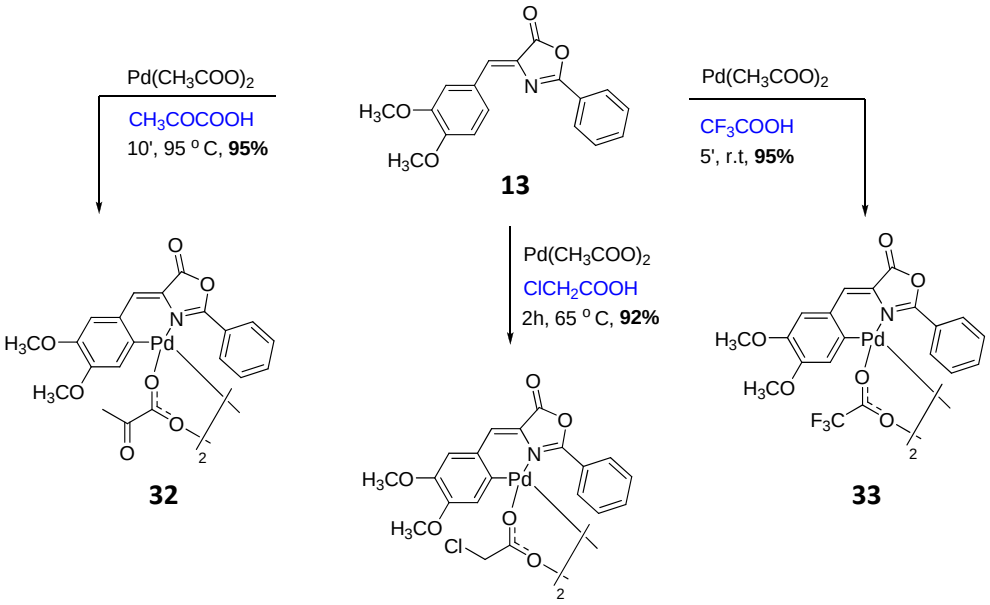
Scheme 4.

Note that a *six-membered* ring is formed instead of a *five-membered* ring, more stable in principle.

We have observed that *activated oxazolones with one methoxy did not give any orthometallated product in acetic acid* even we changed the reaction parameters.

In order to give a wider scope of this reaction, the influence of the solvent has been carefully checked. We have employed different organic acids as solvents: pyruvic acid, trimethylacetic acid, chloroacetic and trifluoroacetic acid. What we have noticed is that *acidity plays a very important role in the orthopalladation reaction*.

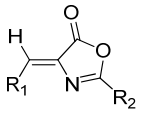
When oxazolone **13** was reacted with $Pd(CH_3COO)_2$ in pyruvic acid (pKa = 2.39) at room temperature overnight, or when it was heated for 10' to 95 ^{o}C (or 1 hour at 60 ^{o}C), orthopalladated compound **33** was obtained in a very good yield (**Scheme 5**). Note that larger reaction time or higher reaction temperature (more than 120 ^{o}C) produced the decomposition of palladium acetate and a decreasing of the yield until 60%, the reaction evolution being monitored by TLC.



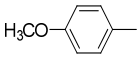
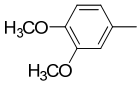
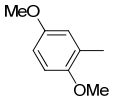
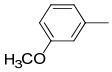
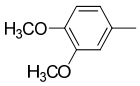
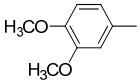
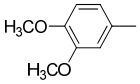
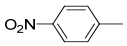
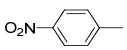
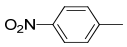
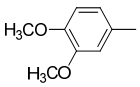
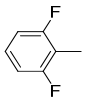
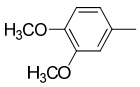
Scheme 5.

The reaction product from oxazolone **11** and palladium acetate in pyruvic acid was not separated for further characterization (**TABLE 3**). In contrast with this result, in acetic acid no reaction occurred. The very low reaction yield (31%) can be explained by the decomposition of palladium acetate in pyruvic acid with the increasing of time and the temperature. Also the reductive properties of pyruvic acid which undergoes decarbonylation can explain the reaction low yield.

TABLE 3. Reaction of 5(4*H*)-oxazolones with palladium acetate in different acids



Entry	R_1	R_2	Product (orthopalladation/solvent) / Yield (%)							
			AcOH		Pyruvic		Chloro-acetic		TFA	
			C	Y	C	Y	C	Y	C	Y
6			-		-		-		**34**	34%

11			-		*		-			
12			-		**35**	31%	-		**36**	87%
13			**29**	91%	**32**	93%	**31**	92%	**33**	95%
14			-		-		-		-	
15			-		-		-		**37**	91%
16			-		-		-		**38**	55%
17			**30**	82%	-		-		**39**	83%
18			-				-		-	
19			-		-		-		**40**	46%
20			-		-		-		**41**	57%
21										**

*the mixture of product and starting material was not totally separated;
- the reaction was not performed;
**the reaction did not give any identifiable product;
C- Compound; Y- Yield.

The structure of **38** was established by X-ray diffraction studies. The result is very interesting showing that a cycloaddition occurred with a formation of a cycloaddition product **38a** (**Figure 7**).

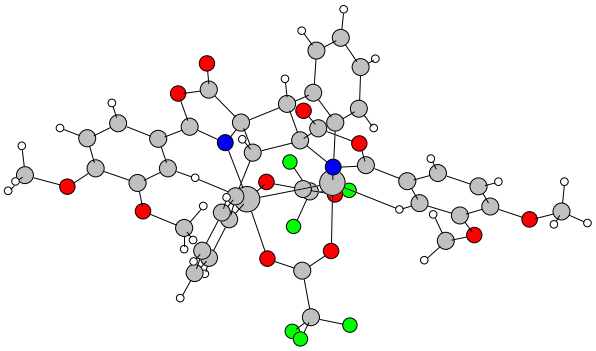
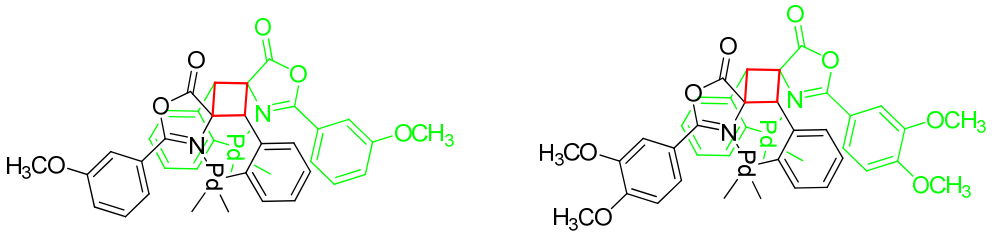


Figure 7. Diamond view of **38a** showing
the formation of the cycloaddition product

Based on the X-ray structure the proposed structures for **37a** and **38a** are drawn in **Figure 8**. The trifluoroacetate bridges were not drawn for simplicity reasons.



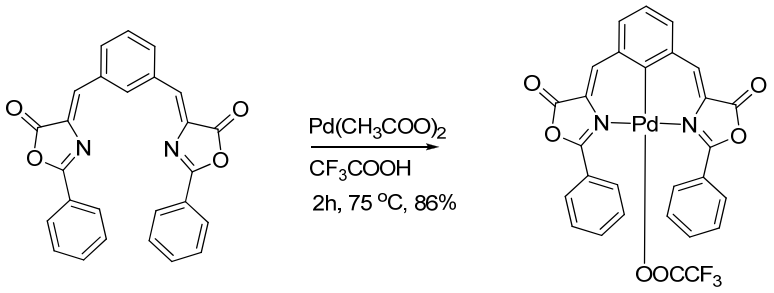
37a **38a**

Figure 8. Cycloaddition structures for **37a** and **38a**

3.3.2. Bisoxazolones cyclometallation (pincer YCY palladacycles)

When compound **22** was treated with palladium acetate in TFA, C-H bond activation occurred with the formation of compound, pincer compound which was easily isolated in analytically pure form by precipitation with water, further the solid obtained being solved in dichloromethane and precipitated with hexanes.

Further evidence for the palladation reaction pathway was provided by the spectroscopic data of the yellow precipitate**42**. As is can be seen in **42**, Pd(II) center removes a proton from the central benzene ring (**Scheme 6**).

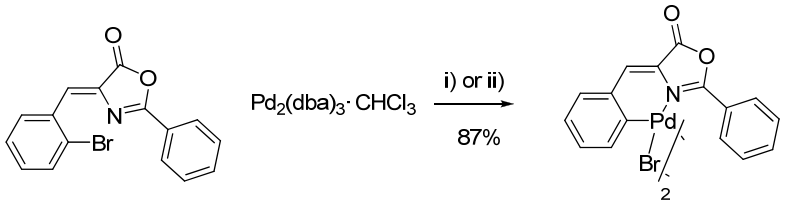


22 **42**

Scheme 6.

3.4. Orthometallation through oxidative addition and reactivity

The oxidative addition process is a very powerful synthetic tool for the preparation of cyclopalladated complexes, regardless of the organic group (aryl or alkyl), the donor atom [N, P, S, O, C (NHC), etc.] or the nature of the C-X bond to be activated. The reaction is regioselective, and only the functionalized position with the C-X bond is activated. Having completed the above requirements, oxazolone **8** was reacted with $Pd_2(dba)_3{\cdot}CHCl_3$[4] to give the dimer **43** in a good 87% yield (**Scheme 7**).



8 **43**

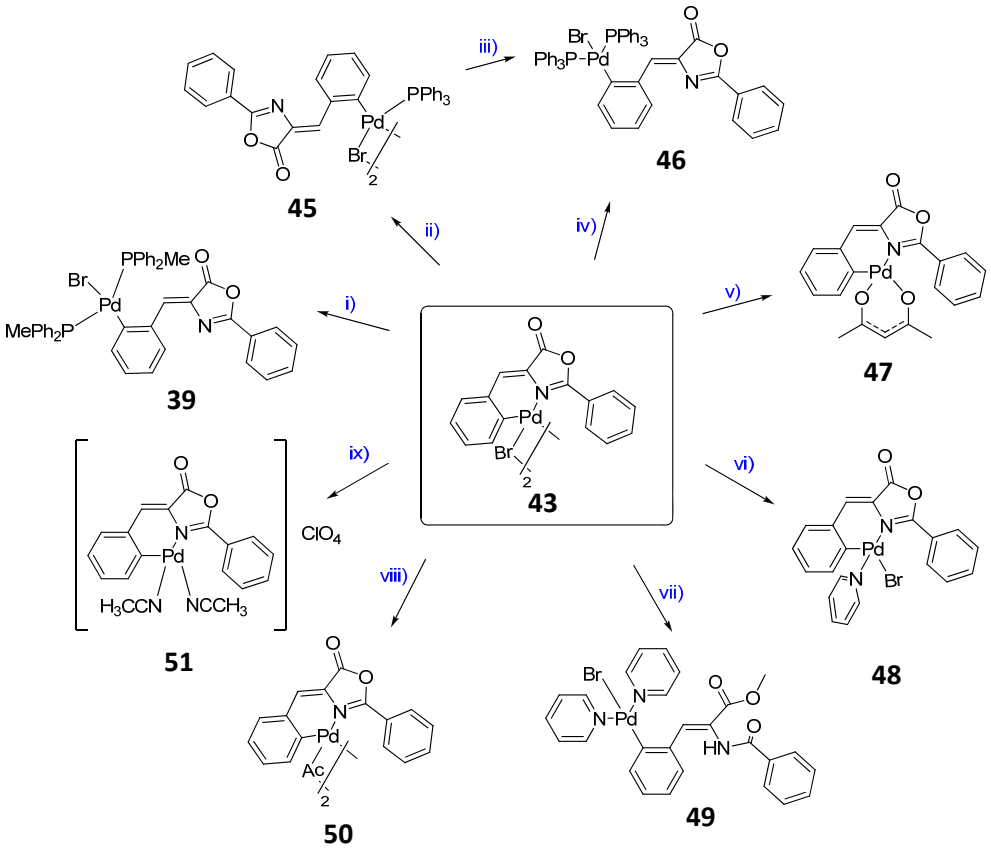
Scheme 7. *Reagents and conditions*: i) $Pd_2(dba)_3{\cdot}CHCl_3$, CH_2Cl_2, r.t, 24 h, argon; ii) $Pd_2(dba)_3{\cdot}CHCl_3$, toluene, r.t, 24 h, argon

The same product was obtained when toluene was employed instead of dichloromethane. Complex **43** was obtained as a greenish yellow solid (probably contaminated with residual Pd^o) insoluble in all usual organic solvents.

Due to the lack of solubility solution characterization was not possible, but structural evidences were obtained from its reactivity (**Scheme 8**). Moreover, the reactivity of **43** shown in **Scheme 8** gives valuable information about the stability of the palladacycle formed.

[4] Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem*. **1974**, *65*, 253-266.

Compound **43** was reacted with excess of PPh_2Me in chloroform as solvent to afford the yellow orthopalladated derivative **44** poorly soluble in common deuterated solvents (**Scheme 8**).



Scheme 8. *Reagents and conditions*: i) PPh_2Me, CH_2Cl_2, r.t, ii) PPh_3, $CHCl_3$, r.t; iii) PPh_3, MeOH, Δ; iv) PPh_3, MeOH, Δ; v) Tl(acac), $CHCl_3$, r.t. 2 h; vi) Py, CH_2Cl_2, r.t; vii) Py, MeOH, r.t; viii) CH_3COOAg, CH_2Cl_2, 12 h, r.t. argon; ix) $AgClO_4$, CH_3CN

3. CONCLUSIONS

A series of new orthometallated oxazolones were prepared through C-H bond activation and oxidative addition. Orthometallation through C-H bond activation proved to be strongly dependent of the metal employed while oxidative addition presented different behavior depending of the halogen.

⇨ *C-H bond activation*

Mercury acted as a catalyst and allowed the methanolysed opened oxazolones while platinum was totally inactive.

Palladium proved to be a successful alternative assisted with the presence of a protic solvent. In addition *orthometallation process took place regioselectively* at the benzylidene ring with the formation of *six-membered* rings. The change of the reaction solvent has allowed the optimization of the reaction conditions, in such a way that a more acidic solvent is able to metallate a less activated substrate at a lower temperature.

When investigations were directed to change the regioselectivity towards the phenyl ring the formation of *five-membered* palladacycles was not observed.

Cycloaddition products were formed when phenyl activated oxazolones were metallated in presence of TFA.

Also a new pincer palladated compound was prepared starting from bisoxazolones.

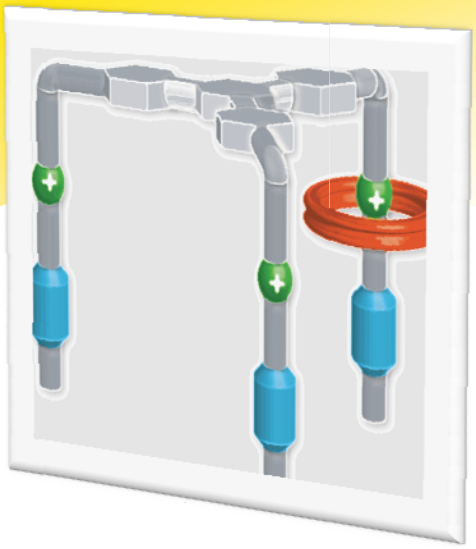
⇨ *Oxidative addition*

Different orthometallated *six-membered* ring derivatives were synthesized using oxidative addition. Some of the starting oxazolones who resisted to C-H bond activation were prepared using this method.

Oxidative addition proved to be also the only method in preparation of metallated palladacycles having palladium bounded at the phenyl from position 2. Even more, formation of metallated palladacycles at phenyl from position 2 was possible only using iodine as halogen.

Part 2

SYNTHESIS AND STRUCTURAL ANALYSIS OF NEW ROTAXANE PRECURSORS



Contents

2. OBJECTIVES

The main purpose of this work is *to obtain intermediates that can lead to compounds with special supramolecular properties*, which can be used to make pseudorotaxanes, rotaxanes, molecular machines and other molecular devices. Molecular aggregates which imitate, at molecular scale, the behavior encountered at macro scale of some machines or tools used in daily life, will represent in the future constitutive elements of molecular aggregates with complex functions.

Our initial objective *was to accomplish the synthesis of a C_3-symmetric aryl molecule and the obtaining of new terpyridine macrocycles which can thread a triaxle.* Also we had in plan to thread the triaxle with known crown ethers and study the interactions by the meaning of several methods as UV-Vis and NMR.

Our strategy for self-assembling [2]-, [3]-, [4]-pseudorotaxane dendrimers can be illustrated in **Figure 1**. A tritopic building block for the core designed to have three arms, each containing a guest moiety (represented by the green charged fragment) is capable of binding to the host moieties, represented by red circles or ellipses.

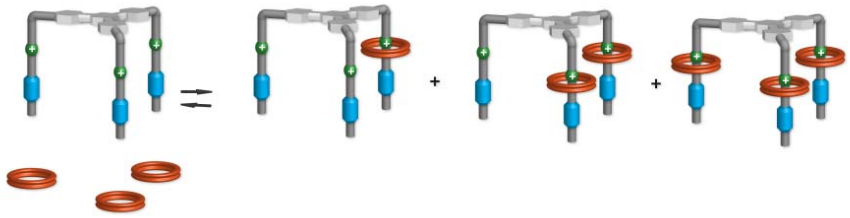


Figure 1. Cartoon representation of target compounds [2]-, [3]-, [4]-pseudorotaxanes

Due to the selectivity of the determined size and shape of the cavity, pseudorotaxanes are ideally suited to construct such nano-objects.

3. RESULTS AND DISCUSSIONS

Dendrimers with their controllable numbers of end groups, unique shapes, and physical properties provide an almost endless array of possibilities for design of materials with targeted end-use functionalities.[1]

We designed a tritopic core with three arms, capable of binding to the host moieties, represented by the red circle as it is outlined in **Figure 2**.

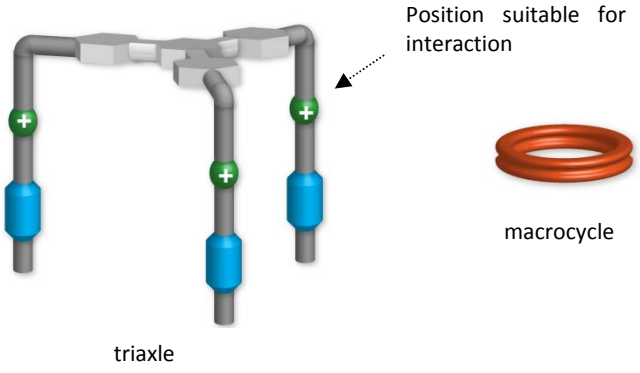


Figure 2. Cartoon representation of the pseudorotaxane components

The axle must be suitable for a connection with the macrocyclic ring by noncovalent bonding

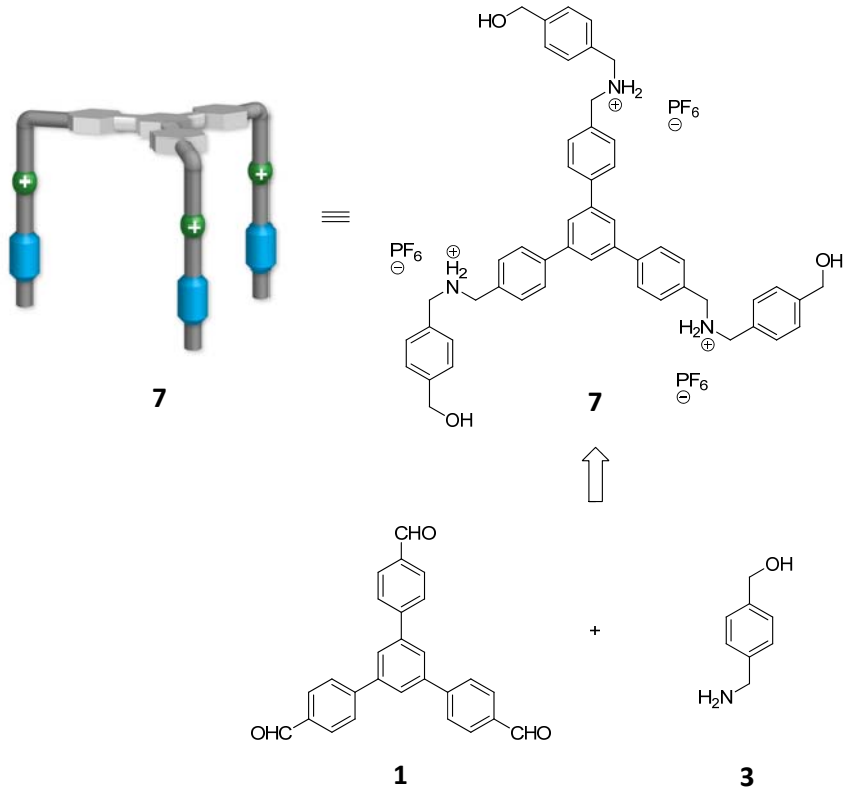
3.1. Synthesis of triaxle compound

The triaxle molecule consists in extended aromatic units which confer stronger electrodonating power. These structural features should direct and enhance the formation of [π-π] stacking

[1] (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules: Concepts, Synthesis, Perspectives*; VCH: Weinheim, 1996; (b) Matthews, O. A.; Shipway, A. N.; Stoddart, J. F. *Prog. Polym. Sci.* **1998**, *23*, 1-56; (c) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665-1688; (d) Newkome, G. R.; He, E.; Moorefield, C. N. *Chem. Rev.* **1999**, *99*, 1689-1746; (e) Tully, D. C.; Frechet, J. M. J. *Chem. Commun.* **2001**, 1229-1239; (f) Grayson, S. M.; Frechet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819-3868.

interactions with any macrocyclic ring.[2] Similar triaxle molecules have been reported in literature with variations of the central core and of the three arms.[2,3]

A general retrosynthetic pathway of the triaxle molecule is presented in **Scheme 1**.



Scheme 1.

The initial steps toward the formation of triaxle consisted in the trimerization of commercially 4-bromoacetophenone with triflic acid in toluene which furnished 1,3,5-tri(4-bromophenyl)benzene **2**[2b,4] in 74% yield (**Scheme 2**).

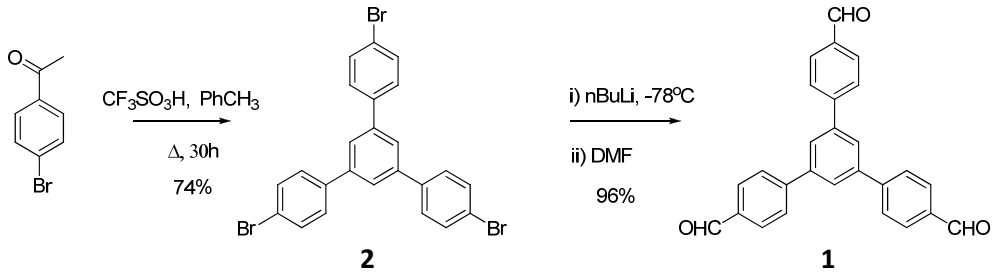
Further, 1,3,5-tri(4-bromophenyl)benzene **2** treated with *n*-BuLi and DMF afforded after workup 1,3,5-tri(4-formylphenyl)benzene **1**[2a,4d,e5] in a very good 95% yield as a white solid.

---

[2] Balzani, V.; Clemente-Leon, M.; Credi, A.; Lowe, J. N.; Badjic, J. D.; Stoddart, J. F.; Williams, D. J. *Chem. Eur. J.* **2003**, *9*, 5348-5360.

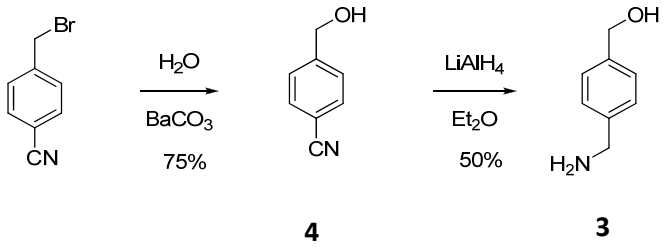
[3] Gibson, H. W.; Yamaguchi, N.; Hamilton, L.; Jones, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 4653-4665.

[4] (a) Plater, M. J.; McKay, M.; Jackson, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2695-2701; (b) Lyl, R. E.; DeWitt, E. J.; Nichols, N. M.; Cleland, W. *J. Am. Chem. Soc.* **1953**, *75*, 5959-5961; (c) Brunel, J.; Jutand, A.; Ledoux, I.; Zyss, J.; Blanchard-Desce, M. *Synth. Met.* **2001**, *124*, 195-199; (d) Berridge, R.; Skabara, P. J.; Andreu, R.; Garin, J.; Orduna, J.; Torra, M. *Tetrahedron Lett*. **2005**, *46*, 7871-7875.



Scheme 2.

Having prepared the aromatic core **1**, the next step for the synthesis of triaxle consisted in the preparation of the aminoalcohol **3** outlined in **Scheme 3**.



Scheme 3.

The commercially available bromotoluonitrile was boiled in distilled water in the presence of $BaCO_3$ to afford cyanoalcohol **4** in 75% yield.

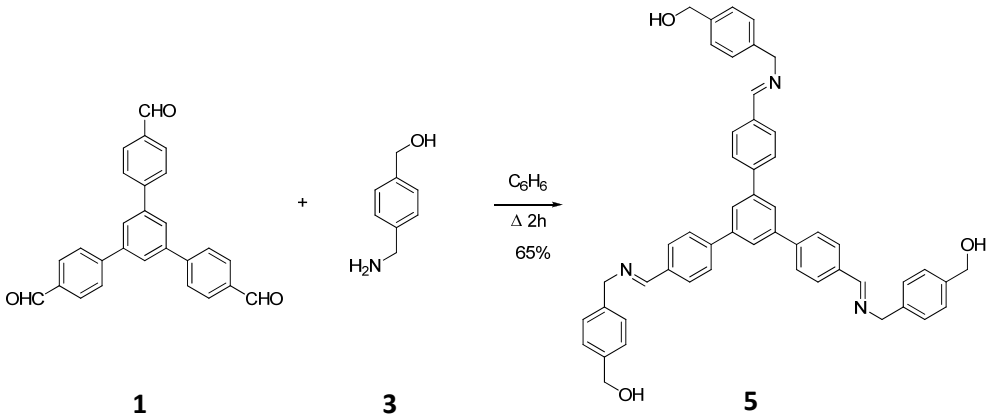
The alcohol **4** was then treated with an excess of $LiAlH_4$ in dry diethylether to afford the obtaining of the aminoalcohol **3**. NMR and spectrometric data fully agree with the proposed structure.

For the synthesis of trisimine **5**,[6] trialdehyde **1** was treated with aminoalcohol **3** in refluxing benzene. After the water was removed using a Dean-Stark trap, the solution was cooled down and the precipitate formed was filtered to give the imine **5** as a pale yellow solid in a good 65% yield

[5] (a) Weber, E.; Hecker, M.; Koepp, E.; Orlia, W.; Czugler, M.; Csoregh, I. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1251-1257; (b) Brunel, J.; Mongin, O.; Jutand, A.; Ledoux, I.; Zyss, J.; Blanchard-Desce, M. *Chem. Mater.* **2003**, *15,* 4139-4148; (c) Brunel, J.; Ledoux, I.; Zyss, J.; Blanchard-Desce, M. *Chem. Commun.* **2001**, 923-924; (d) Rajakumar, P.; Swaroop, M. G.; Jayavelu, S.; Murugesan, K. *Tetrahedron* **2006**, *62*, 12041-12050; (e) Mongin, O.; Brunel, J.; Porres, L.; Blanchard-Desce, M. *Tetrahedron Lett*. **2003**, *44*, 2813-2816; (f) Porres, L.; Mongin, O.; Blanchard-Desce, M. *Tetrahedron Lett.* **2006**, *47*, 1913-1917.

[6] Badjic, J. D.; Balzani, V.; Credi, A.; Lowe, J. N.; Silvi, S.; Stoddart, J. F. *Chem. Eur. J.* **2004**, *10*, 1926-1935.

(**Scheme 4**). This imine slowly decomposes upon standing on air this is why it must be employed in further steps immediately after its synthesis.

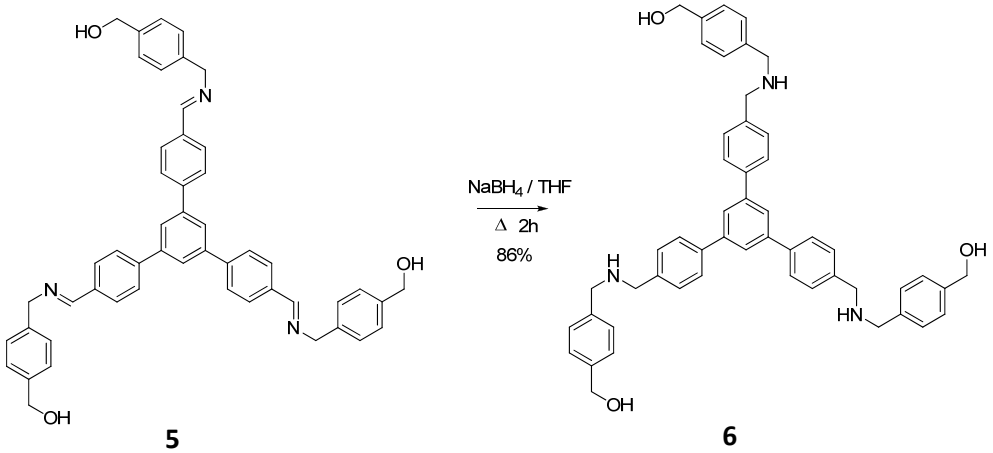


1 **3** **5**

Scheme 4.

The aromatic region of the ^{1}H NMR spectrum of **5** exhibits the expected number and pattern of resonances and their assignment was based on the COSY and HSQC experiments.

Further reduction of the imine **5** using $NaBH_4$ in THF gave 1,3,5-tris[*N*-(4-hydroxymethylbenzyl)benzylamine]benzene **6**[6] in 86% yield (**Scheme 5**).

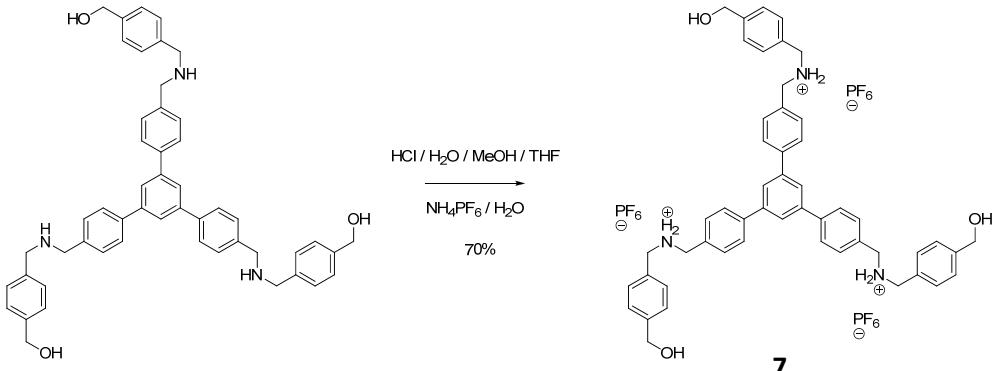


5 **6**

Scheme 5.

All the spectral data confirm the proposed reduced structure with C_3 symmetry. The characterization in solution (NMR) is also in good agreement with the assigned structure

The trisammonium ion $[\mathbf{6}\text{-}H_3]^{3+}$, named compound **7**, was further prepared as its hexafluorophosphate salt in good overall yield by reacting trifurcated trisamine 1,3,5-tris[*N*-(4-hydroxymethylbenzyl)benzylamine]benzene **6** with hydrochloric acid, followed by chlorine counterion exchange with hexafluorophosphate ion (**Scheme 6**).



6 **7**

Scheme 6.

With a diverse class of different compounds in hand, we next investigated their photophysical properties. The absorption bands were located in the UV-region (269-275 nm). The absorption in the UV-region was due to the predominantly aromatic structure.

The light-emitting properties of **2**, **1**, **6** and **7** have been also investigated.

3.2. Preparation of macrocycles containing terpyridine units

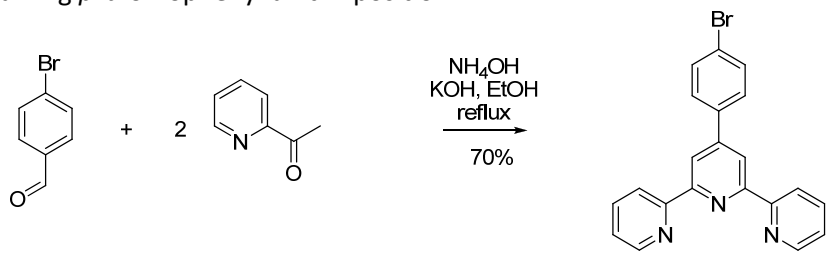
3.2.1. Synthesis

Having successfully developed a synthetic strategy for the new C_3-symmetric polyaromatic molecule **7**, we turned our attention to prepare the host moieties, represented by red circles or ellipses (**Figure 3**).

Figure 3. Cartoon representation of host moiety

The host moieties can be constituted from terpyridine units which can interact with the guest triaxle. In this purpose several macrocyclic terpyridines were needed.

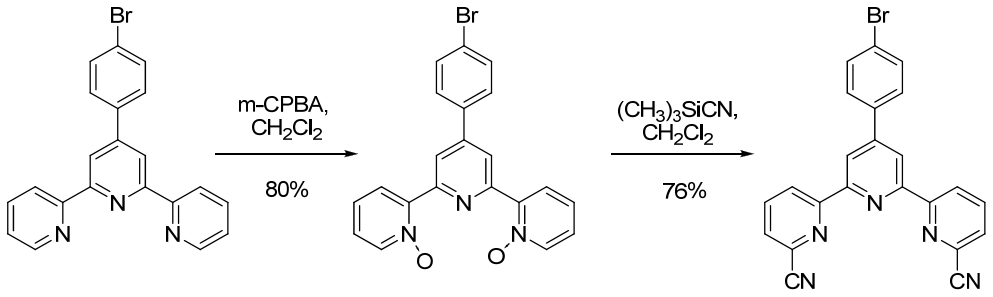
4'-(4-Bromophenyl)-2,2':6',2"-terpyridine **8** is a key compound in many studies concerned with metal complexes of rigid-rod type architectures[7] (**Scheme 7**). The bromine attached to the phenyl from position 4' can give a lot of pathways to follow. That's why our attention focused on preparation derivatives containing *p*-bromophenyl unit in position 4'.



8

Scheme 7.

The structure of compound **8** was inferred from spectroscopic (IR, NMR, MS spectrometry) data. For further functionalization, the terpyridine **8** was oxidized with *m*-CPBA to give *N,N*''-dioxidized compound **10**[7e,u] in excellent yield (**Scheme 8**).



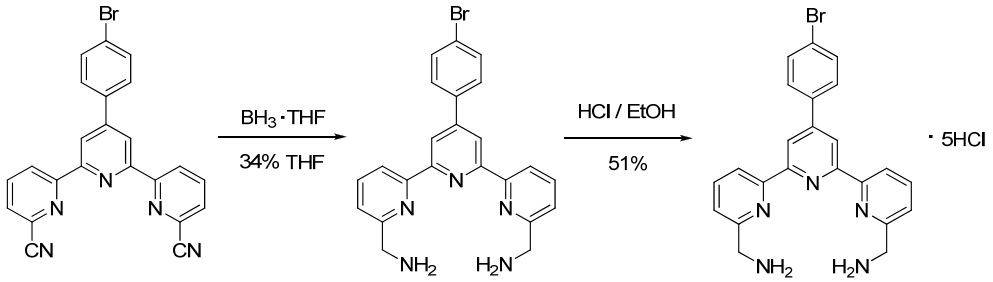
8 **10** **9**

Scheme 8.

The functional groups in pyridine rings, such as carbonitrile in **9** can be readily transformed into a number of other functional groups. The efficient synthesis makes this monoterpyridine attractive an precursor for the construction of diverse terpyridine derivatives.

[7] (a) Medlycott, E. A.; Hanan, G. S.; Abedin, T. S. M.; Thompson, L. K. *Polyhedron* **2008**, *27*, 493-501; (b) Han, F. S.; Higuchi, M.; Kurth, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 2073-2081; (c) Tu, S.; Jiang, B.; Yao, C.; Jiang, H.; Zhang, J.; Jia, R.; Zhang, Y. *Synthesis* **2007**, 1366-1372.

Reduction of the dinitrile **9** with diborane as its THF complex, afforded the bis(aminomethyl) derivative **12**, isolated as its hydrochloride salt **11**[7u] (**Scheme 9**). Initially our intents were to isolate the amine since for further macrocyclization it could be done easier in comparison with its salt.

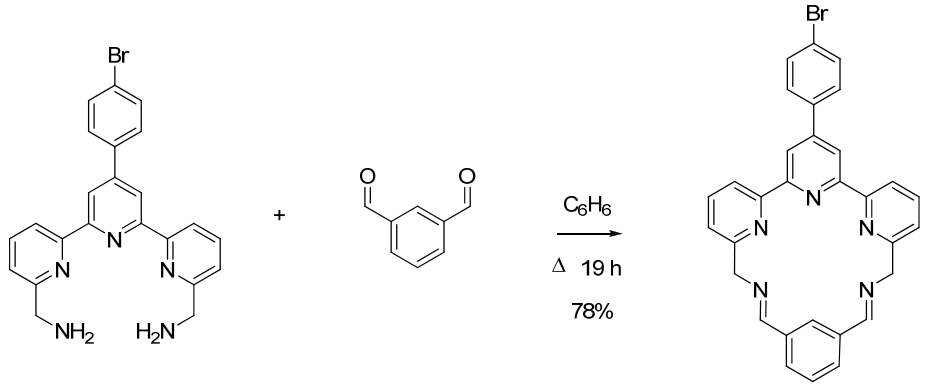


9 **12** **11**

Scheme 9.

With these useful monoterpyridine in hand, our attention shifted first to the construction of macrocyclic containing terpyridines.

To a slurried solution of amine **12** in benzene it was added isoftalaldehyde dropwise during 14 h followed by 5 hours of reflux (**Scheme 10**).



12 **13**

Scheme 10.

ESI MS spectrum of **13** recorded in positive mode, revealed the expected molecular peak. Indeed, the positive integration mode displayed peaks at *m*/*z* 566, *m*/*z* 567 and *m*/*z* 568 assignable to the $[MNa]^+$ specie for the expected isotopic pattern distribution of bromine derivatives.

3.2.2. Photochemical studies

3.2.2.1. UV-Vis absorption properties

With a diverse class of different terpyridines in hand, we next investigated their photophysical properties.

For the absorption behavior, a general observation is that, when compared to reference compound **8**, the maximum absorption band is around 280-282 nm, which is shifted slightly (ca. 2-7 nm) by appending either the CH_2NH_2 group or electron-withdrawing CN substituents at the peripheral pyridines (**Figure 4**).

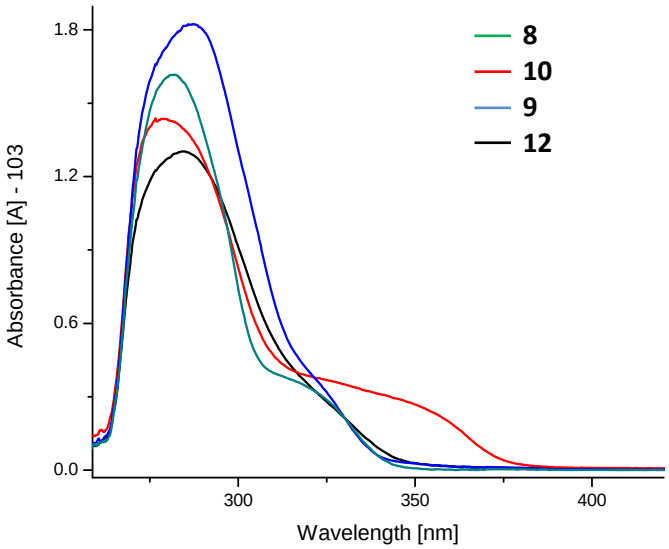


Figure 4. UV-Vis spectra of selected terpyridines **8**-**12** in DMSO (5 x 10^{-5} M, 298 K)

3.2.2.2. Solvent effect on the photophysical properties

To examine the solvent effect on the photophysical property, several selected compounds were investigated in two solvent systems: DMSO and EtOH since the solubility was limited. The results show that the photophysical behavior of the selected terpyridines **8**, **10**, **9** and **12** are similar in different solvent systems, indicating that the photophysical properties are less dependent on the solvent.

3.2.2.3. Emission properties

Emission colors of selected compounds **8**-**12** from left to right in DMSO excited with a 365 nm UV lamp are shown in **Figure 5**.

8 10 912

Figure 5. Emission colors of selected compounds **8**-**12**
(from left to right) in DMSO excited with a 365 nm UV lamp

3.3. Initial complexation investigation studies

3.3.1. Preparation methods

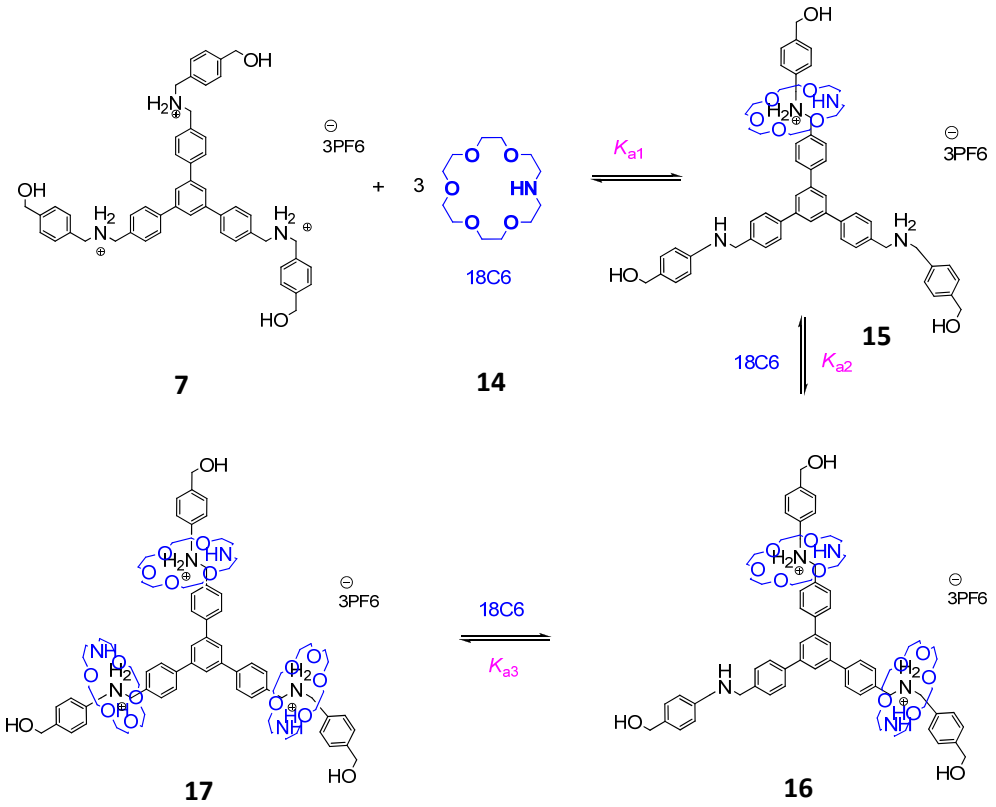
For our initial investigations on multivalency we have chosen, as the matching components:

i) a monotopic receptor in the form of a commercially crown ether derivative **14**

ii) the trifurcated trication **6**, as its hexafluorophosphate salt.

This thread is able to pass through the centre of macrocycle **14**, forming a pseudorotaxane precursor, that is held together solely by charge assisted $NH_2^+ \cdots O$ hydrogen bonds. Once in place, the axel may be capped by bulky substituents, so preventing the macrocycle from slipping.

Matching the components may gives rise (**Scheme 11**) to the formation of a 1:3 face to face interaction (**15**) in the shape of a triply threaded, two-component supramolecular bundle or superbundle.



Scheme 11.

3.3.2. Absorbtion Spectra

The electronic absorbtion spectra for the triaxle **7** and ether aza-18-crown-6 in CH_3CN solution show no change when a solution of **7** (5 x 10^{-5} M) and **14** are mixed in the UV couvette in a 1 to 6 proportion. In the visible region ether aza-18-crown-6 has no absorbtion.

4. CONCLUSIONS

To conclude, we have shown that starting from bromoacetophenone we generate a C_3-symmetric building block with potential for application the synthesis of new pseudorotaxanes and rotaxanes.

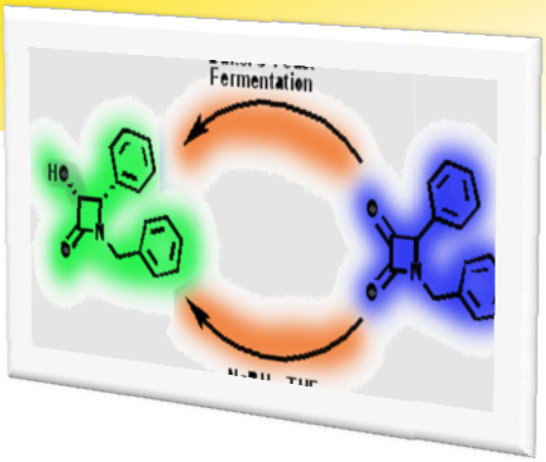
We have also synthesized a series of phenyl-substituted tpy derivatives and evaluated their fluorescence properties. Introduction of fluorescence properties to the tpy derivatives might open the way for further application as a new series of photofunctional compounds.

Also a macrocyclic derivative of tpy was scarcely characterized, numerous intents to prepare macrocyclic derivatives from amine substituted tpy failed.

Initial synthetic studies towards rotaxane formation indicated that triaxle complexation with commercial macrocycle aza 18C6 shown the formation of face to face interactions. Using UV-Vis measurement the interactions could not be detected while NMR spectroscopy proved to be a better method, but formation of the assembly still rise questions. Further investigations towards the interaction of triaxle with different crown ethers which have a larger cavity are currently under investigation.

Part 3

SYNTHESIS OF *α*-KETO-*β*-LACTAMS AS INTERMEDIATES IN TAXOL SYNTHESIS



Contents

2. OBJECTIVES

Reductions of α-keto esters catalyzed by Baker's Yeast are experimentally simple and avoid the yield limitations associated with kinetic resolutions. The major drawback is less-than-optimal stereoselectivity, the result of multiple reductase enzymes produced simultaneously by the yeast.

Therefore the *goal consisted in the synthesis of different α-keto-β-lactams as starting materials for bioreductions*. Bakers' Yeast (*Saccharomyces cerevisiae*) mediated reductions were planned to be investigated for the potential of a fermentation approach towards *α*-keto-*β*-lactams.

Our *goals in this study were to investigate further the yeast-mediated reductions of α-keto carbonyl compounds* and apply this knowledge to synthesize the paclitaxel side chain.

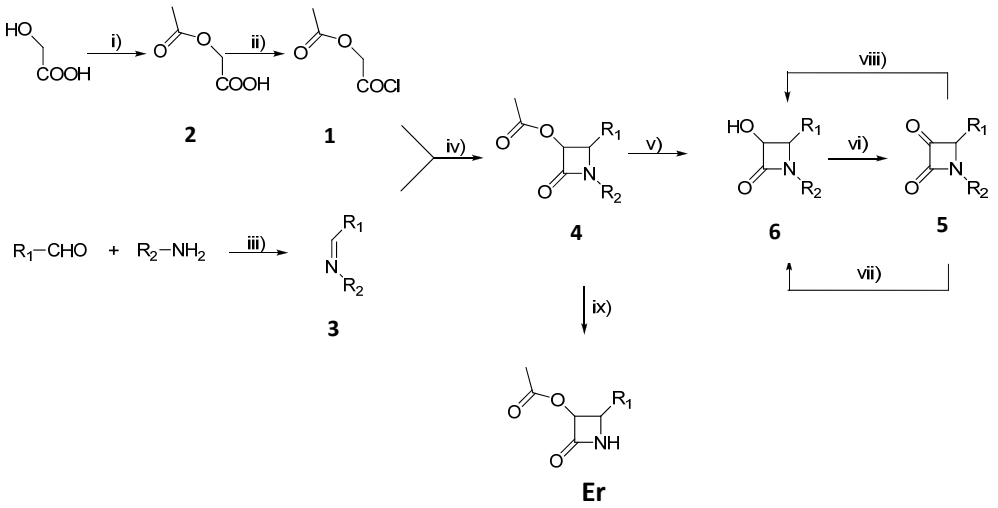
3. RESULTS AND DISCUSSIONS

While *α*-keto acids and derivatives thereof have received relatively less attention than *β*-keto esters as substrates for yeast reductions, the resulting α-hydroxy carbonyl compounds are equally valuable chiral building blocks and several routes to these compounds have been devised. Among a number of biologically interesting targets microbial reduction of *α*-keto-*β*-lactams allows access to the paclitaxel side chain.

Although numerous *α*-keto-*β*-lactams have been successfully prepared, the reported methods were optimized for specific compounds and lacked generality. Usually cyclizations to the lactam ring have been achieved by condensations of activated carboxylic acids with protected imines in *Staudinger* type reactions.[1] Acetoxyacetyl chloride was treated with NEt_3 and then was condensed with imines to obtain acetoxy protected *β*-lactams. Cainelli et al. in an alternative approach treated ketal or thioketal protected glyoxylic acid esters with a strong base such as *tert*-BuOK or BuLi providing anions that were condensed with imines to ketal or thioketal protected *β*-lactams.[2]

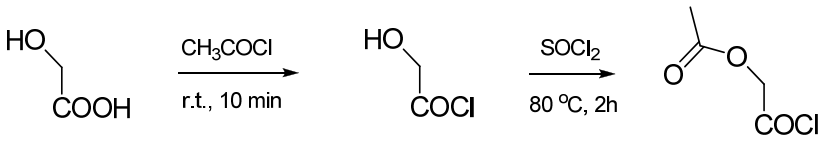
We chose a milder and more general three-step procedure[3] adapted for the preparation of *α*-keto-*β*-lactams. The protocol is based on the cyclization of an imine with a carboxychloride in the presence of NEt_3, followed by hydrolysis of the acetate and oxidation of the resulting alcohol (**Scheme 1**).

[1] Mukerjee, A. K.; Singh, A. K. *Tetrahedron* **1978**, *34,* 1731-1767.
[2] Cainelli, G.; Panunzio, M.; Giacomini, D.; Di Simone, B.; Camerini, R. *Synthesis* **1994**, 805-808.
[3] Mihovilovic, M. D.; Feicht, A.; Kayser, M. M. *J. Prakt. Chem.* **2000**, *342*, 585-590.



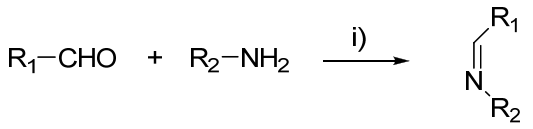
Scheme 1. *Reagents and conditions*: **3a**-**6a**: R_1= Ph, R_2= PMP; **3b**-**6b**, R_1= Ph, R_2= Bn; **3c**-**6c**, R_1= 2-Furyl, R_2= Bn; **3d**-**6d**, R_1= 2-Thienyl, R_2= Bn; **3e**, R_1= Ph, R_2= Ts; i) CH_3COCl, r.t., 10 min; ii) $SOCl_2$, 80 °C, 2h; iii) Na_2SO_4, dry CH_2Cl_2, r.t.; 24-48 h; iv) NEt_3, dry toluene, N_2, 100 °C, 30 min, r.t. overnight; v) 2N KOH, THF; vi) P_2O_5, dry DMSO, 48-72h; vii) Baker's Yeast reduction; viii) $NaBH_4$, dry ethanol, r.t.; ix) CAN, CH_3CN, 5 °C, 1-2 h.

For the preparation of the acetoxyacetyl chloride we used commercially available glyoxalic acid as starting material. The acid was converted to acetylglyoxalic acid **2** in reaction with an excess of acetyl chloride. Further, the white solid was recrystallized from toluene and refluxed in $SOCl_2$ for approximately 2 hours. The excess of $SOCl_2$ was distilled off and the acetoxyacetyl chloride **1** (**Scheme 2**) was obtained as a colorless liquid after distillation at reduced pressure at rotavapour (23 mbar, 60-70 °C). All the spectral data confirmed the formation of acetoxyacetyl chloride **1**.



Scheme 2.

Imines **3a**, **3b**, **3d** and **3e** were readily accessible by reacting appropriate amines with aldehydes (**Scheme 3**) in the presence of Na_2SO_4.[4] The reaction mixtures were allowed to stir at r.t. until the reaction was completed, the progress of the reaction being monitored by TLC. The only exception from the general preparation method was tosylated imine **3c** which was prepared by boiling benzaldehyde and tosylamide in toluene in the presence of catalytic amounts of BF_3-Et_2O. A Dean-Stark trap was used to collect the water formed.



3a, b, d, e

Scheme 3. *Reagents and Conditions*: i) **3a, b, d, e** Na_2SO_4, dry CH_2Cl_2, r.t., 24-48 h;
3c: BF_3-Et_2O, toluene, 100 ^oC, ca. 2h.

The products were isolated in good to very good yields (**TABLE 1**) and could be used in subsequent transformations without purification.

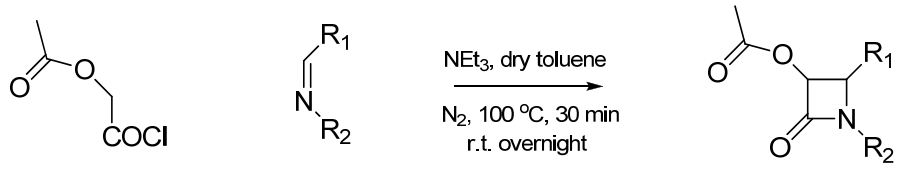
TABLE 1. Preparation of imines **3a-e**

Entry	R_1	R_2	Imine	Yield (%)
1	Phenyl	PMP	**3a**	97
2	Phenyl	Bn	**3b**	94
3	Phenyl	Ts	**3c**	85
4	2-Furyl	Bn	**3d**	87
5	2-Thienyl	Bn	**3e**	92

In the following step a solution of acetylglyoxylic chloride **1** and **3a-e** were cyclized according to **GP II** (see the experimental part) to afford lactams **4a-e** in moderate yields after recrystallization or flash

[4] (a) De Kimpe, N.; Nagy, M.; Boeykens, M.; Van der Schueren, D. *J. Org. Chem.* **1992**, *57*, 5761-5764; (b) De Kimpe, N.; De Smaele, D. *Tetrahedron Lett.* **1994**, *35,* 8023-8026.

chromatography (**Scheme 4**). For a better conversion we preferred not to prepare the acylchloride *in situ*. In this way the cyclization step can be easily controlled and scaled up.

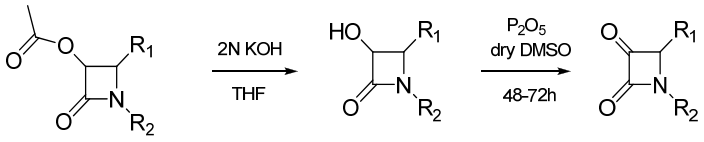


1 **3a-e** **4a-e**

Scheme 4. 4a: R_1 = Ph, R_2 = PMP; **4b**: R_1 = Ph, R_2 = Bn; **4c**: R_1 = Ph, R_2 = Ts; **4d**: R_1 = Furyl, R_2 = Bn; **4e**: R_1 = Thienyl, R_2 = Bn.

Lactams **4a-d** can be obtained as *cis*- and *trans*-isomers in the crude mixtures. Usually the major diastereoisomer in cyclization is the *cis* isomer. In this case compounds were isolated here are only the *cis*-form, exclusively. Assignment of diastereomers is based on previous studies of coupling constants for azetidine protons H_3 and H_4.

α-Acetoxy-β-lactams (**4a-b**) were hydrolyzed to alcohols (**6a**-**b**) in excellent yields under very mild conditions.[5] Subsequent oxidations were performed by treatment with DMSO in the presence of phosphorous pentoxide[6] to give the α-keto-β-lactams (**5a-d**) in good yields as shown in (**Scheme 5**).



4a-b **6a-b** **5a-b**

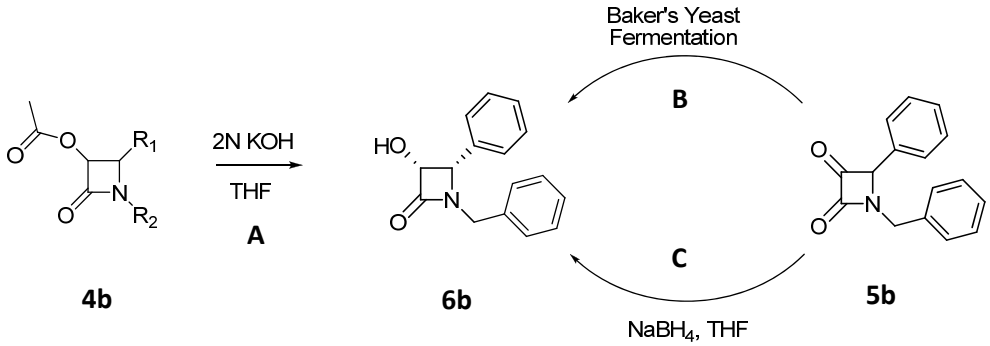
Scheme 5. a: R_1 = Ph, R_2 = PMP; **b**: R_1 = Ph, R_2 = Bn

Due to the poor solubility of the alcohols crude acetoxy lactams were employed in the deprotection step. In this way we were able to obtain a good overall yield for the two steps of the synthesis

[5] Brieva, R.; Crich, J. Z.; Sih, C. J. *J. Org. Chem.* **1993**, *58,* 1068-1075.
[6] (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Carreaux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M. *J. Org. Chem.* **1994**, *59,* 3123-3130; (b) Palomo, C.; Aizpurua, J. M.; Cossio, F. P.; Garcia, J. M.; Lopez, M. C.; Oiarbide, M. *J. Org. Chem.* **1990**, *55,* 2070-2078.

Oxidations of alcohols **6a-b** were performed by treatment with DMSO in the presence of phosphorous pentoxide.[6] The reaction time proved to be an essential factor for the obtaining of *α*-keto-*β*-lactams **5a-b** in good yields.

Reduction of prochiral carbonyl groups by Baker's Yeast is a well-known process and *β*-ketoesters are unquestionably the compounds of reference.[7] The reduction was made on *α*-keto-*β*-lactam **5b** substrate and also with sodium borohydride to compare ^{1}H NMR data with those of bioreductions (**Scheme 6**).



Scheme 6.

As it is clearly outlined in **Scheme 6** there are three possibilities to synthesize compound **6b**:

- **A** - Beaker's Yeast fermentation;
- **B** - $NaBH_4$ reduction of *α*-keto-*β*-lactam **5b**;
- **C** - Hydrolysis of the acetoxy group of compound **4b**.

α-Keto-*β*-lactam **5b** was submitted to yeast reduction, bioreductions with commercial Bakers' Yeast being carried out in 10% glucose solution supplemented by 1 equiv of *β*-cyclodextrine to improve solubility and membrane penetration of the substrates and to decrease toxicity *vis-à-vis* the living cells.[8] Biotransformations required 2-5 days at 30 °C in an orbital shaker to reach completion. Alcohol **6b** was obtained in good chemical yields as *cis*-isomer (**A**), with traces of *trans*- isomer, when using ordinary Bakers' Yeast obtained at a local supermarket.

Separately we performed a reduction with $NaBH_4$ (**B**) as we knew about its diastereoselectivity. The isomer formed was the *cis*- compound.

Finally the third pathway (**C**) is it represented by the hydrolysis of the acetoxy group from compound **4b**.

---

[7] (a) Servi, S. *Synthesis,* **1990**, 1-25; (b) Csuk, R.; Glanzer, B. I. *Chem. Rev*. **1991**, *91*, 49-97; (c) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev*. **1992**, *92*, 1071-1140; (d) Csuk, R.; Glanzer, B.I. In *Stereoselective Biocatalysis*; Patel R. N., Ed.; Marcel Dekker: NY-Basel, 2000; Chapter 19; (e) Faber, K. *Biotransformation in Organic Chemistry*; Springer: Berlin, 5th Ed., 2004.

[8] Bar, R. *Trends Biotechnol.* **1989**, *7*, 2-4.

4. CONCLUSIONS

Different *α*-keto-*β*-lactams were prepared with good yields. Synthesis of correspondingly substituted *α*-keto-*β*-lactam compounds as biotransformation precursors was carried out following a straightforward strategy involving Staudinger [2+2] cyclization.

Bakers' Yeast (*Saccharomyces cerevisiae*) mediated reductions were investigated for the potential of a fermentation approach towards *α*-keto-*β*-lactams. Bioreductions were carried out using growing whole-cells of *S. cerevisiae* and the diaselectivity of the process was studied.

Taken together, our results show that yeast-mediated reduction of α-keto carbonyl compounds provides a simple route to optically active alcohols.