

**SYNTHESIS OF CARBOLINES AND ANALOGUES
VIA RHODIUM-CATALYZED [2+2+2] CYCLOADDITION WITH
ALKYNYL-YNAMIDES
- APPLICATION TO THE TOTAL SYNTHESIS OF ALKALOIDS -**

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Hiermit versichere ich gemäß § 10 Abs. 3d der Promotionsordnung vom 24.07.2007, dass ich die als Dissertation vorgelegte Arbeit selbst angefertigt und alle benutzten Hilfsmittel (Literatur, Apparaturen, Material) in der Arbeit angegeben habe.

*Meinen Eltern und meiner Frau
In Dankbarkeit gewidmet*

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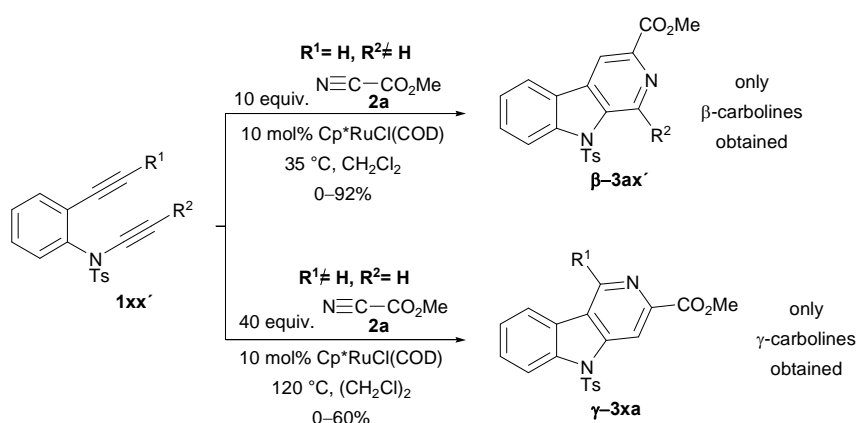
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I/ INTRODUCTION

Ynamides have become well-known synthons in a variety of organic syntheses. Their chemistry has exploded during the last two decades and ynamides were shown to be suitable substrates for a wide array of reactions comprising rearrangements, radical cyclizations or metal-catalyzed cycloadditions.^[1] This attracting reactivity offers notably a new potential access to important *N*-heterocycles like indole derivatives.

For example, 2-alkynyl-*N*-alkynylbenzenesulfonamides **1xx'** - called “diynes” in the present work - were recently shown to be powerful building blocks for the synthesis of highly substituted carbazoles via rhodium-catalyzed [2+2+2] cycloaddition with alkynes.^[2] This work was recently extended to the synthesis of β - and γ -carbolines when the participating alkyne was replaced by an electron-deficient nitrile and when Cp^{*}RuCl(COD) was used as a catalyst.^[3] The regioselectivity of the reaction was mainly controlled by the substitution pattern of the diynes.



Scheme I-1: Synthesis of β - and γ -carbolines via ruthenium-catalyzed [2+2+2] cycloaddition of diynes with methylcyanoformate^[3]

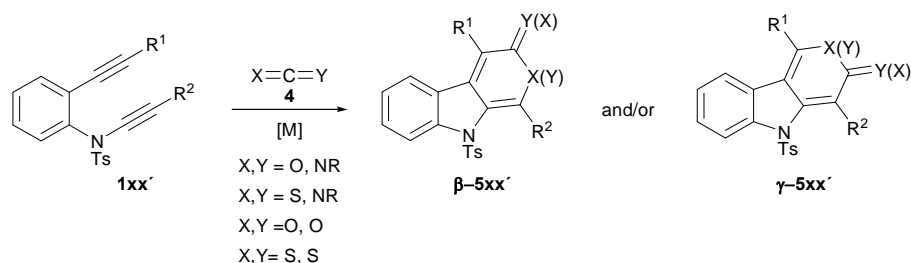
One aim of this thesis is to explore the reaction conditions:

- to facilitate the formation of the γ -carboline core,
- to control the regioselectivity of the reaction.

* for convenience reasons, diynes are numbered **1xx'** ($x = R^1$, $x' = R^2$; $a = H$, $b = TMS$, etc.).

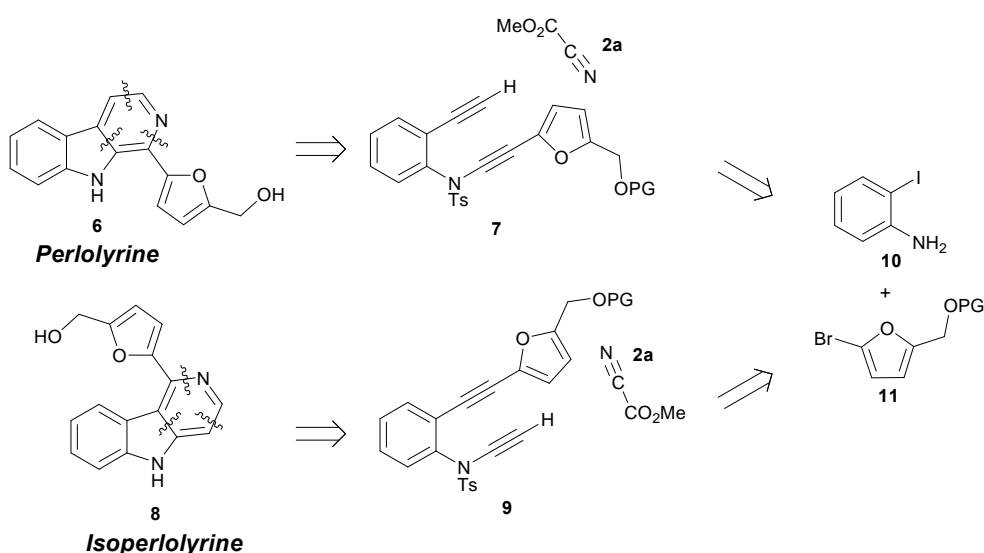
The same codification is used to describe the carbolines.

A further aim of this study is to enlarge the [2+2+2] cycloaddition strategy to various heterocumulenes as cycloaddition partners like iso(thio)cyanates, carbon dioxide or carbon disulfide .



Scheme I-2: Potential products for the cycloaddition of diynes with different heterocumulenes

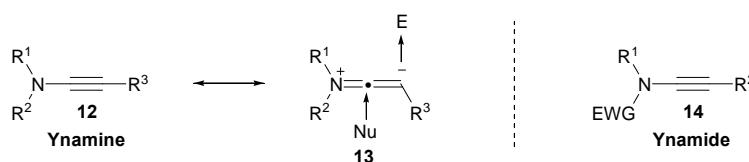
Finally, the following work aims at achieving the total syntheses of *Perlolyrine* **6** and *Isoperlolyrine* **8**, two natural products possessing respectively a β - and a γ -carboline core from the readily available 2-iodoaniline **10** and a derivative of furfuryl alcohol **11**. These syntheses, which rely on the [2+2+2] cycloaddition of the diynes **7** or **9** with methylcyanoformate as key-step, would highlight the utility in natural product synthesis of this new approach of synthesis of β - and γ -carbolines.



Scheme I-3: Retro-synthetic approach for the syntheses of *Perlolyrine* and *Isoperlolyrine*

II/ GENERAL PART**II.1. Synthesis of ynamides**

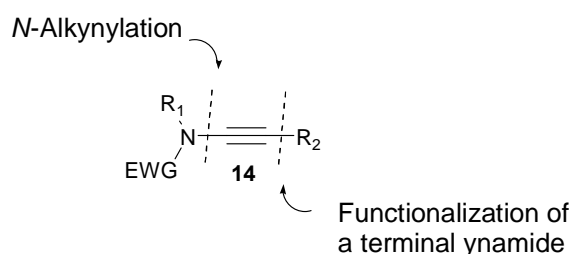
“Ynamide” is the usual name given to molecules possessing as functional group a protected amine bearing an alkynyl substituent. Contrary to the analogous ynamines **12**, ynamides **14** are much more stable compounds. They are less prone to nucleophilic attack, e.g. addition of water that enables them to withstand aqueous work-up and to be purified by chromatography on silica gel. Furthermore, they are often air-stable solids, easy to handle and can be stored for long periods at $-20\text{ }^{\circ}\text{C}$.



Scheme II-1: Ynamine and ynamide.

Though such an ynamide was reported for the first time in 1972, the chemistry of ynamides received only a growing interest in the two last decades. This increasing attention is mainly due to the novel possibilities offered by this moiety. Ynamides are suitable substrates for a large variety of reactions such as 3,3-rearrangements, radical cyclizations or metal-catalyzed cycloadditions.^[1] This expansion was also facilitated by the recent development of novel methods of synthesis of ynamides which offer nowadays an easier access to a larger scope of substituted ynamides.

Two ways have to be considered for the synthesis of substituted ynamides: the *N*-alkynylation of an amide or the functionalization of a terminal ynamide:



Scheme II-2: Approach of synthesis of ynamides.

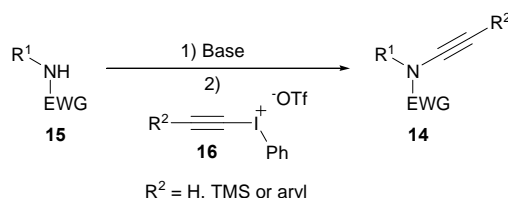
II.1.1. *N*-Alkynylation of amides

Three general methods are known for the synthesis of ynamides from amides:

- *N*-alkynylation with an iodonium salt,
- Synthesis via β,β -dichloroenamides
- Copper-catalyzed *N*-alkynylation with alkynyl bromides

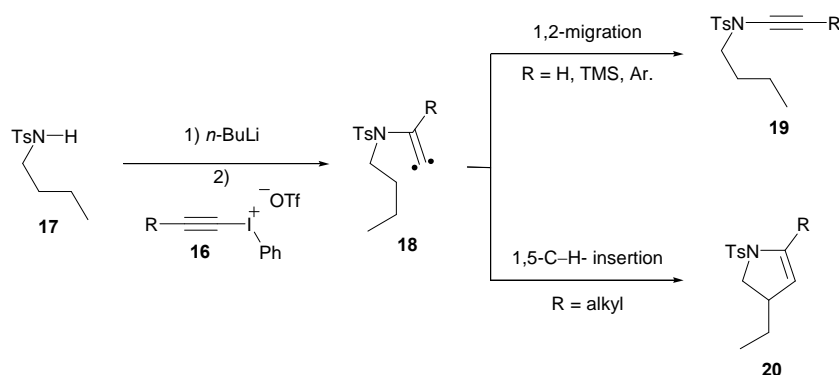
II.1.1.1. *N*-Alkynylation with iodonium salts

The first reliable and general method for the synthesis of ynamides consists in the *N*-alkynylation of amides with alkynyliodonium triflates (iodonium salts). Although the first examples were reported by Feldman and co-workers in 1996^[4], the methodology was extensively developed by Witulski and co-workers a few years later^[5]. Deprotonation of an amide **15** with a base such as *n*-BuLi, KHMDS or Cs₂CO₃ and addition of an iodonium salt **16** leads to the corresponding ynamide **14**.



Scheme II-3: Synthesis of ynamides with iodonium salts.

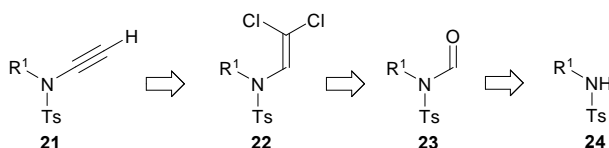
The method is suitable for amides with a variety of substituents but is however limited to TMS-, H- or aryl-substituted alkynyliodonium salts **16**. Other substituents can be introduced via further functionalization of the terminal ynamide. The reason of the limitation of the reaction stems from the reaction mechanism. The amid anion adds to the alkynyliodonium salt generating an intermediate alkylidene carbene **18** that can follow two different pathways depending on the nature of the substituent R on the alkylidene carbene. The reaction proceeds either with a 1,2-migration of the substituent to give the ynamide **19** (R= H, TMS, Ar.) or with a 1,5-C–H insertion leading to a 2,3-dihydropyrrole **20** (R= alkyl).



Scheme II-4: Mechanism of synthesis of ynamides with iodonium salts.

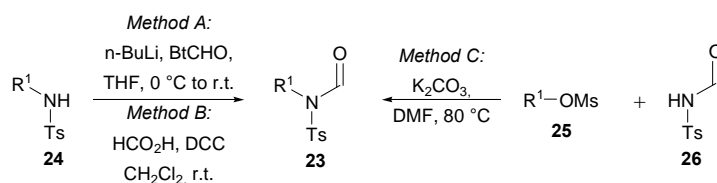
II.1.1.2. Synthesis via β,β -dichloroenamides

The Corey-Fuchs reaction was successfully adapted to the synthesis of ynamides by Brückner.^[6] Terminal ynamides **21** can be synthesized via β,β -dichloroenamides **22**.



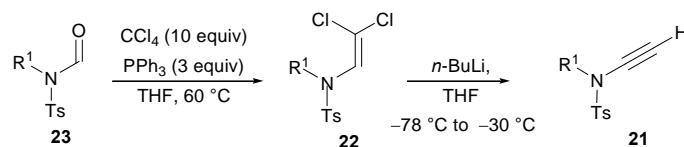
Scheme II-5: Corey-Fuchs approach for the synthesis of ynamides from amides.

The formanilide **23** can be prepared via different ways depending on the substitution of the nitrogen atom.



Scheme II-6: Formylation of amides.

The second step, the dichloromethylenation of the formanilide can be achieved by treating the latter with an excess of tetrachloromethane in presence of triphenylphosphine. The reaction proceeds generally in good to excellent yields. Subsequent dehalogenation of the resulting dichloroenamides with *n*-butyllithium and quenching the reaction by addition of methanol leads to the corresponding terminal ynamide **21**. With dichloroenamides bearing an alkyl, benzyl or phenyl substituent, the yields of this last step are generally higher than 80%.



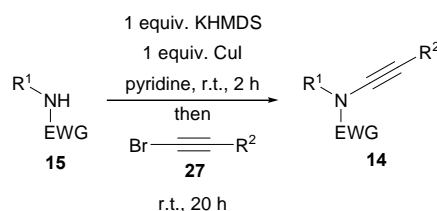
Scheme II-7: Synthesis of terminal ynamides from formamides

II.1.1.3. Copper-catalyzed *N*-alkynylation with alkynyl bromides

The copper-catalyzed *N*-alkynylation of amides with alkynyl bromides was simultaneously developed by several groups. This strategy aims at offering a more direct access to substituted ynamides with the advantage of using relatively cheaper and safer reagents. Inspired by the Buchwald's method of *N*-arylation of amides, the two complementary methods rely on different conditions that offer a noticeable choice of conditions suitable for a multitude of substrates.

- Danheiser's method

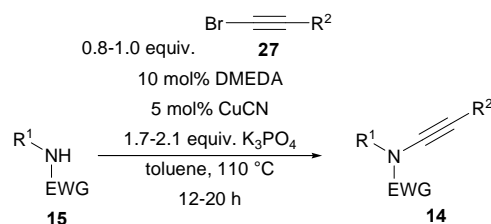
Looking for an alternative access to ynamides using cheaper reactants and being more flexible than the alkynyliodonium salt method, Danheiser developed a copper-mediated *N*-alkynylation of carbamates, ureas, and sulfonamides with alkynyl bromides.^[7] Treatment of these amides with KHMDS and an equimolar amount of CuI, followed by the addition of two equivalents of the alkynyl bromide leads to the corresponding ynamides **14** with moderate to good yields (40-78%). The reaction works smoothly at room temperature for different classes of amides (cyclic carbamates, sulfonamides, ureas, etc.). It allows the synthesis ynamides with different substitution patterns and, notably, gives access to alkyl substituted ynamides, which can not be directly obtained by the iodonium salt strategy.



Scheme II-8: Alkynylation of amides with alkynyl bromides

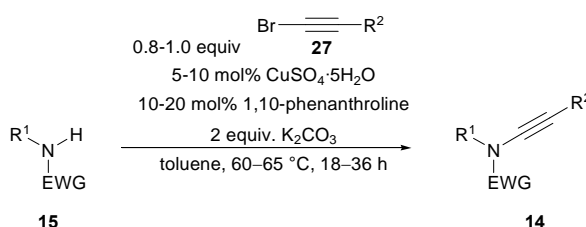
- Hsung's method

In the same time, the groups of Sato and Hsung proposed a similar methodology but using only a catalytic amount of CuCN (5 mol%) with dimethylethylenediamine (DMEDA) (10 mol%) as a ligand and two equivalent of K₃PO₄.^[8] However, the reaction needs a relatively high reaction temperature of 110 °C to give a satisfying conversion, which can be fatal for some ynamides.



Scheme II-9: Copper-catalyzed alkylation of amides with bromo-alkynes

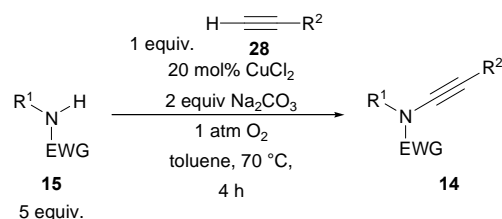
The methodology was re-examined and an improved catalytic system was found.^[9] These new conditions (5-20 mol% CuSO₄·5H₂O, 2 equiv. to copper of 1,10-phenanthroline and 2 equiv. of K₃PO₄ in toluene, 60-65 °C) was also successfully extended to other types of amides (sulfonamides, urethanes, etc.) and indoles with good to excellent yields.^[10]



Scheme II-10: Copper-catalyzed alkylation of amides with bromo-alkynes

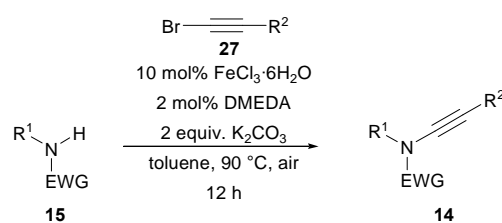
- alternative conditions

A few recent works proposed interesting alternative conditions. Stahl and co-workers reported the direct copper-catalyzed oxidative amidation of terminal alkynes.^[11] This method avoids the preparation of the alkynyl bromides but uses an excess of the amide and requires to work under an oxygen atmosphere. The reaction supports different substitution patterns on the alkyne (alkyl, aryl, silyl) and gives very good yields for various types of amides.



Scheme II-11: Copper-catalyzed alkylation of amides with terminal alkynes

Another promising study is the recent work of Zhang et al.^[12], who proposed an environmentally friendly iron-catalytic system (10 mol% FeCl₃·6H₂O, 20 mol% DMEDA and 2 equiv. K₂CO₃). This catalytic system can be recovered and re-used up to ten times with only a small loss of efficiency. The coupling works very well with several types of amides and bromo alkynes. Furthermore, the reaction tolerates hydroxyl groups on the substrate as well as on the bromo alkyne and does not need to be performed under an inert atmosphere.

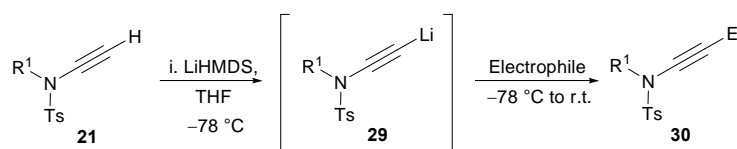


Scheme II-12: Iron-catalyzed alkylation of amides with bromo-alkynes.

II.1.2. Functionalization of terminal ynamides

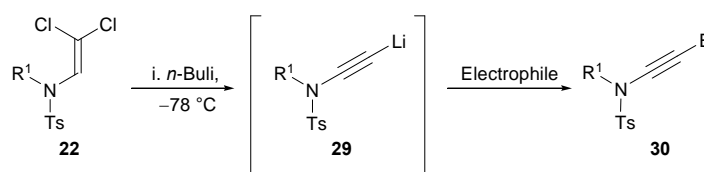
II.1.2.1. Via nucleophilic substitution

Fredericks and co-workers reported that substituted ynamides can be obtained from terminal ynamides by a deprotonation/nucleophilic substitution sequence.^[8b] The terminal ynamides **21** are deprotonated at $-78\text{ }^{\circ}\text{C}$ with LiHMDS and subsequent trapping of the resulting lithium acetylide **29** with diverse electrophiles (haloalkanes, acid chlorides, etc.) affords the substituted ynamides **30**.



Scheme II-13: Functionalization of terminal ynamides by nucleophilic substitution.

An analogous methodology was developed by Saá and co-workers by modification of the last step of Brückner's method of synthesis of ynamides.^[13] The intermediate lithium acetylide **29**, obtained by treatment of the β,β -dichloroenamides **22**, was trapped by different electrophiles to give access to various substituted ynamides. According to the electrophile used, it is possible to obtain ynamides with alkyl, hydroxyalkyl, silyl or carbonyl substituents in good to excellent yields (53-96%). The reaction can be applied to *N*-phenyl sulfonamides as well as to *N*-alkyl or *N*-allyl sulfonamides.

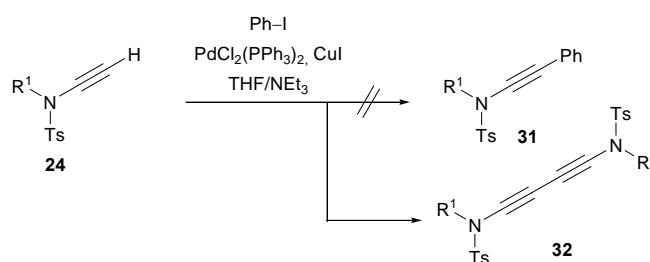


Scheme II-14: Synthesis of substituted ynamides from β,β -dichloroenamides.

II.1.2.2. Via cross-coupling reactions

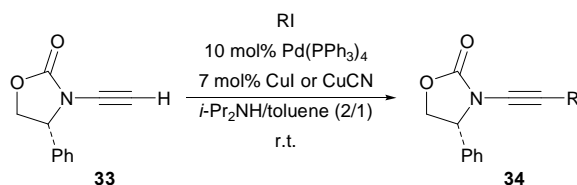
- Sonogashira coupling

The Sonogashira cross-coupling is actually the most popular route for the functionalization of a terminal alkyne. But, as reported by Saá and co-workers, the Sonogashira coupling of ynamides with aryl halides fails under standard conditions giving the homo-coupling product **32** as major product.^[14]



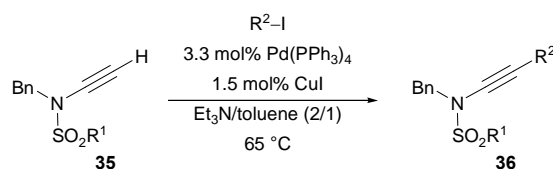
Scheme II-15: Homo-coupling of terminal ynamides under standard Sonogashira conditions.

Hsung and co-workers investigated the reaction in detail.^[15] They found two similar methods, depending on the type of ynamide, that allow the desired coupling with (hetero)aryl iodides and vinyl iodides. In the case of urethane-based ynamides, the coupling can be performed with 10 mol% of $\text{Pd}(\text{PPh}_3)_4$ and 7 mol% of CuI or CuCN in *i*- Pr_2NH /toluene (2:1) at room temperature with satisfying to excellent yields (57-93%).



Scheme II-16: Sonogashira coupling of terminal ynamides.

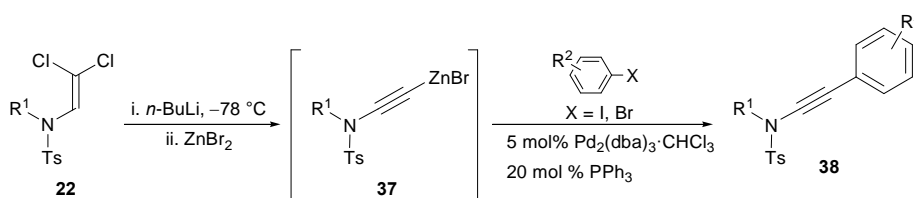
However, these conditions give only poor to moderate results in the case of acyclic, sulfonyl-substituted ynamides. Small modifications of the conditions were found to improve the reaction notably. Switching from the diisopropylamine to triethylamine and delaying the addition of CuI enhances the reaction rate and enable to perform the cross-coupling with relatively good yields (44-96%) for different types of sulfonamides **35** ($R^1 = \text{Ar, Me}$) and (hetero)aryl iodides:



Scheme II-17: Sonogashira coupling with sulfonyl-protected ynamides.

- Negishi coupling

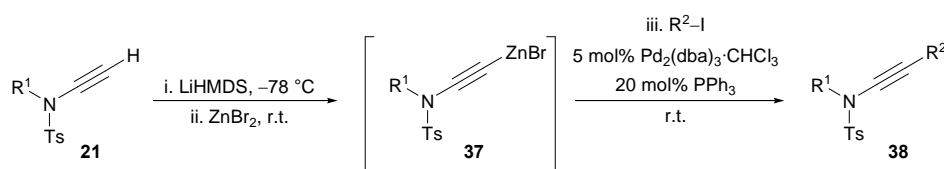
A successful alternative to the Sonogashira coupling is the Negishi coupling adapted to the synthesis of substituted ynamides by Saá and co-workers.^[16] The last step of Brückner's method of synthesis of ynamides was modified to form a zinc acetylide **37**. Addition of the latter to a solution of an (hetero)aryl halogenide, $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, and PPh_3 leads to the desired coupling product as major compound. The reaction proceeds with moderate to good yields depending on the coupling halogenide used and works with *N*-phenyl as well as *N*-alkyl substituted sulfonamides.



Scheme II-18: Synthesis of (hetero)aryl substituted ynamines from β,β -dichloroenamides.

The reaction was adapted to terminal ynamides by our group.^[3] Deprotonation of the terminal ynamides **21** with LiHMDS, followed by the addition of ZnBr_2 and addition of the resulting

zinc acetylide **37** to a solution of 5 mol% $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, 20 mol% PPh_3 and 1.2 equivalent of the iodo- or bromo-(hetero)arene affords the substituted ynamides **38** with good yields.



Scheme II-19: Functionalization of terminal ynamides via a Negishi coupling.^[3]

II.2. Heteroannulated indoles

II.2.1. Carbolines

Pyrido[*x,y-b*]indoles, better known under the common name carbolines, can be sub-divided in four different classes, according to the position of the nitrogen atom in the pyridine ring.

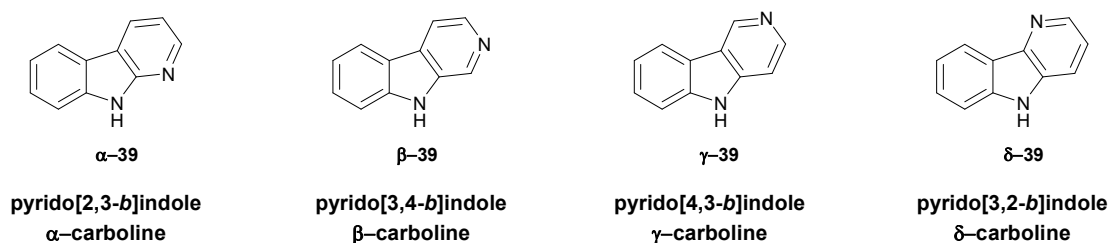
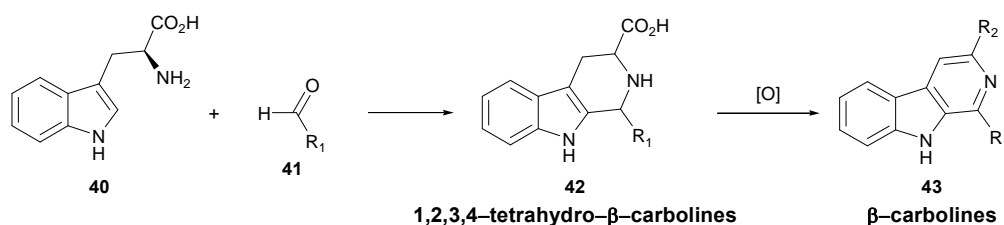


Figure II-20: The four isomeric carbolines.

Carbolines appear as central heterocyclic units in many natural products, either in their fully aromatic form or as partially hydrogenated systems. The β -carboline core is by far the most frequently isomer found in the nature.^[17] This natural occurrence is easily explained by the facile *in vivo* synthesis of the β -carboline core via a Pictet-Spengler cyclization of a tryptophan or tryptamine with an aldehyde or another carbonyl derivative. The resulting 1,2,3,4-tetrahydro- β -carboline **42** is then oxidized to the fully aromatic β -carboline **43**.



Scheme II-21: Biological synthesis of β -carbolines.

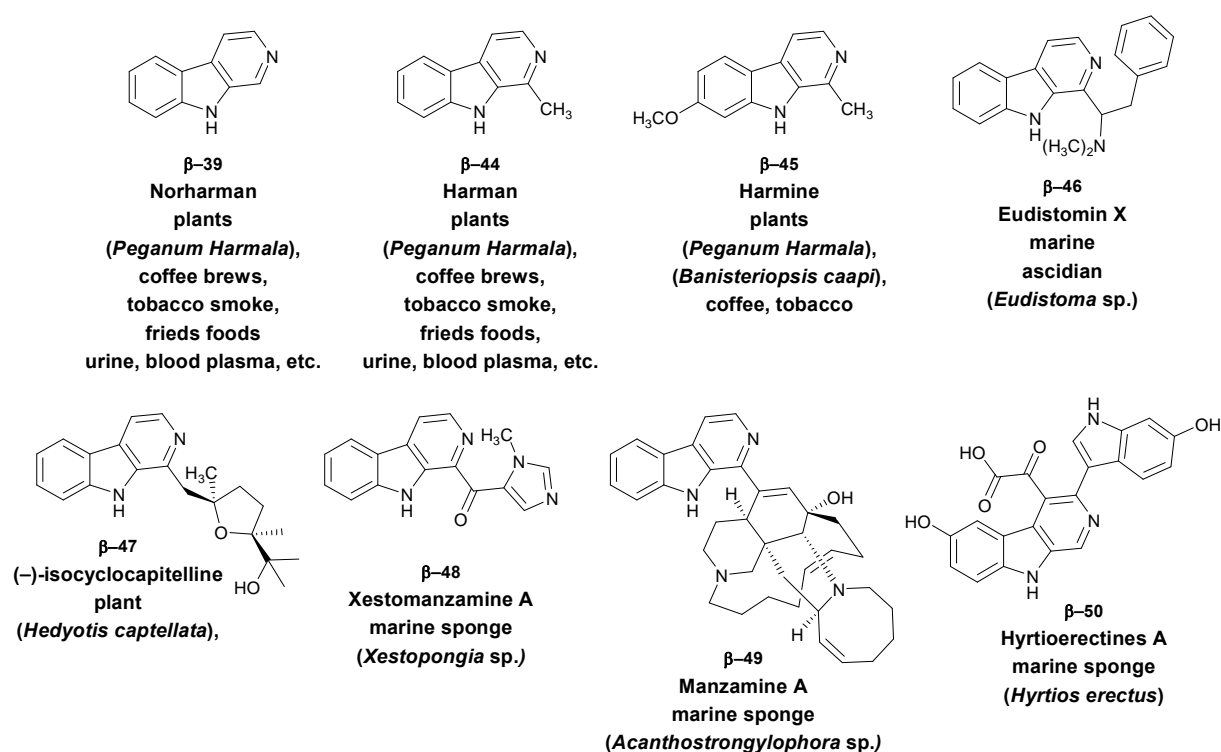
The other carboline cores are much less represented in nature but present also interesting biological activities. However, the following overview will be restricted to β - and γ -carbolines, subjects of this thesis.

II.2.1.1. β -Carbolines

Among the different carbolines, β -carbolines are by far the most extensively studied isomers. This interest is mainly due to their numerous biological and pharmacological properties.^[18] Though β -carbolines are often found in the nature and can be rapidly formed via a Pictet-Spengler cyclization, their synthesis was the subject of large number of studies.^[19]

II.2.1.1.1. Natural occurrence

Alkaloids with a β -carboline core or partially hydrogenated derivatives can be found in numerous plants, fruits and vegetables, but also in animals.^[20] Furthermore, some β -carbolines occur in alcoholic beverages (beer, wine, sake, whisky), tobacco smoke or the human body (plasma, urine).^[21]



Scheme II-22: Selected examples of naturally occurring β -carbolines.

II.2.1.1.2. Biological activities

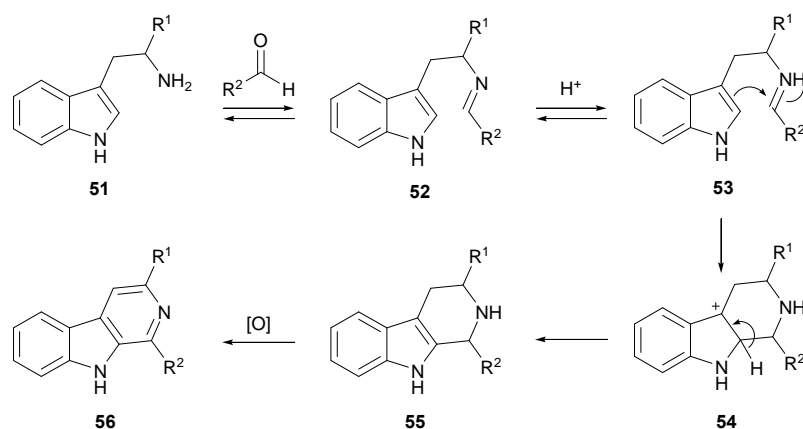
β -Carbolines exhibit a wide range of biological and pharmacological activities. Some of them act on the central nervous (CNS), muscular or cardiovascular systems. These activities go notably from enzyme inhibition (monoamine oxidase MAO^[22]) to suppression of the activity of the topoisomerase^[23]. Some β -carbolines are able to bind to benzodiazepine (BZR)s^[24] or 5-HT₂ serotonin receptors^[25]. Some of them are the main physiologically active components of plants used for a long time by African or Asian tribes for their therapeutic effects. Many have effectively shown a wide range of pharmacological properties such as antidepressive, anxiolytic or anticonvulsant effects. Some of them were also shown to possess antitumor properties^[26] or, more recently, anti-HIV activity^[27]. However, their use is limited due to inconvenient side effects such as hallucinogenic effects. Furthermore, some carbolines can interact with DNA, conferring them mutagenic^[28] or carcinogenic properties.

II.2.1.1.3. Synthesis of β -carbolines

The Pictet-Spengler and the Bischler-Napieralski condensations are the two classical methods for the synthesis of β -carbolines. But, these two well-known methods do not lead directly to the fully aromatic carbolines but respectively to their tetrahydro- or dihydro derivatives. However, the dehydrogenation of these compounds is however sometimes hard to perform. Furthermore, these methodologies start from tryptophan derivatives which are not always easy to prepare when a multi-substituted β -carboline is desired. Recently, alternative methods leading directly to fully aromatic β -carbolines have been developed.

- The Pictet-Spengler reaction

The Pictet-Spengler reaction consists in the condensation of a tryptamine derivative **51** with an aldehyde or another carbonyl derivative. This leads to the intermediate iminium ion **53** which cyclizes under mild acidic conditions to the tetrahydro- β -carboline **55**.

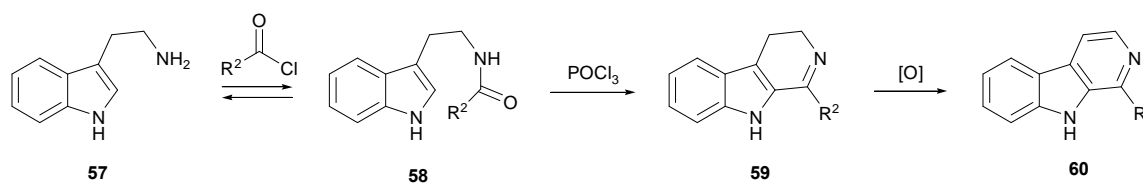


Scheme II-23: Synthesis of β -carbolines via the Pictet-Spengler reaction.

Aromatization to the desired β -carbolines can be completed by oxidation of the resulting tetrahydro- β -carbolines using a variety of reagents such as Pd/C, sulfur in refluxing xylenes or manganese oxide but this step is sometimes difficult.

- The Bischler-Napieralski

The Bischler-Napieralski reaction is similar to the Pictet-Spengler reaction but differs by the fact that the tryptamine derivative is first acylated to give the amide **58**. The latter is dehydrated to an active iminium species which then cyclises to give a dihydro- β -carboline **59**. Oxidation of this intermediate gives finally the desired β -carboline **60**. Though the oxidation step of the dihydro- β -carboline is much easier to perform than in the case of the tetrahydro- β -carbolines, the dehydration step requires vigorous reaction conditions, limiting the use of this method.

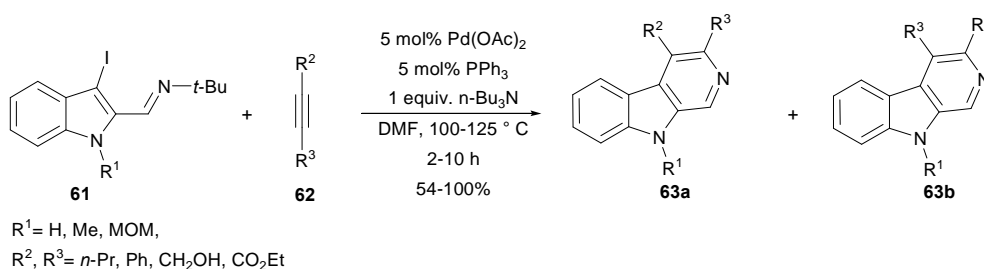


Scheme II-24: Synthesis of β -carbolines via the Bischler-Napieralski reaction.

- alternative approaches

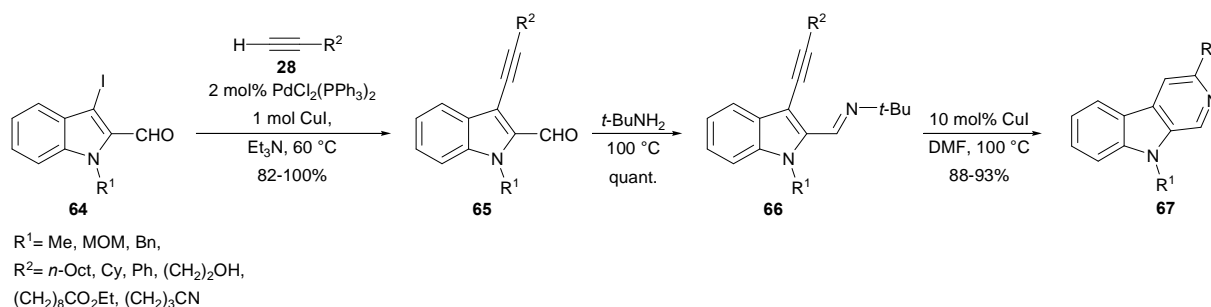
The synthesis of the β -carboline core can be done according to alternative strategies to avoid the problematic steps encountered in the two previously described ways.

Larock and Zhang have reported the synthesis of β -carbolines via palladium-catalyzed iminoannulation of the *t*-butylimines of 2-formyl-3-iodoindoles **61** with internal alkynes.^[29a] The reaction leads to 1,3,4-trisubstituted carbolines with relatively good yields when *N*-protected indoles are used. Reactions with non-protected indoles were also successful but gave lower yields. However, a poor regioselectivity was observed when unsymmetrical alkynes were used, giving both isomers in similar amounts.



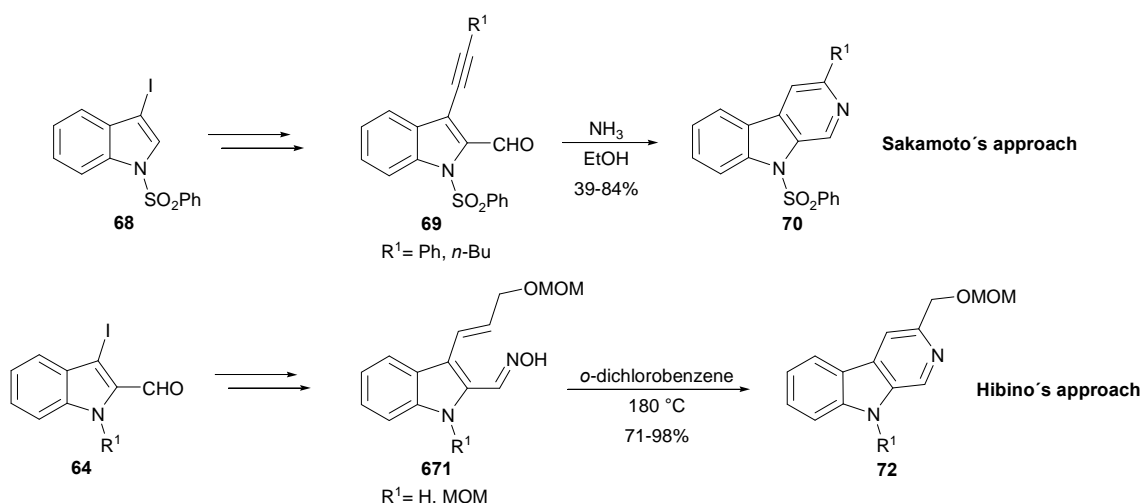
Scheme II-25: Synthesis of β -carbolines via palladium-catalyzed iminoannulation.

The synthesis of 3-substituted β -carbolines was also studied by switching from internal to terminal alkynes as coupling partners.^[29b] In this case, the reaction did not work under the usual conditions and the reaction sequence had to be modified. The terminal alkynes **26** were first coupled to the iodo-indoles **64** to give the 3-alkynyl-2-formyl-indoles **65** which were then converted into their *t*-butylimino derivatives **66**. These imino-indoles were subjected to a copper-catalyzed cyclization to afford the desired β -carbolines **67**. The reaction was however restricted to protected indoles and unactivated alkynes, electron-deficient or electron-rich alkynes failed to give 3-alkynylindoles.



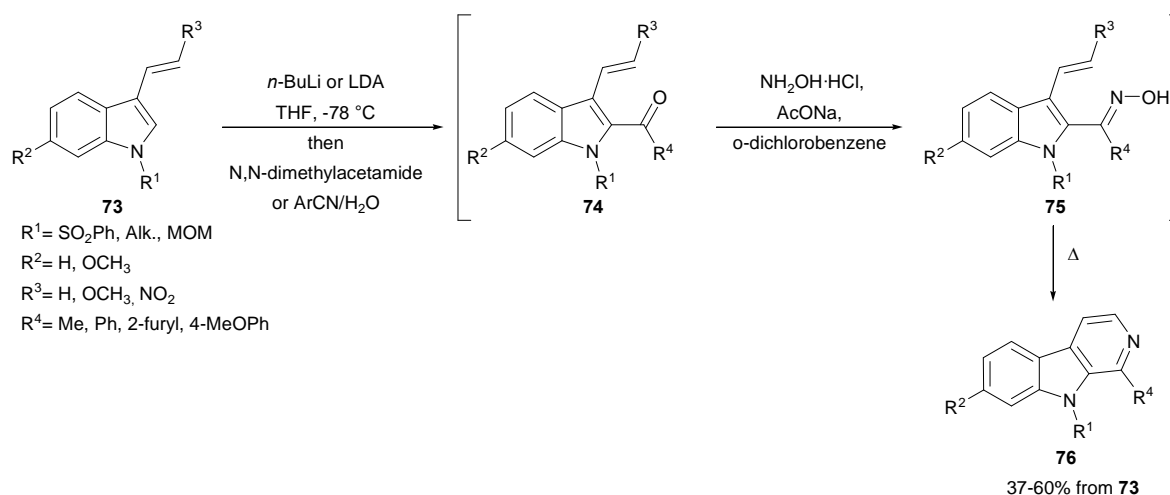
Scheme II-26: Synthesis of β -carbolines via copper-catalyzed iminoannulation.

Analogous methodologies were already proposed by the groups of Hibino^[30] and Sakamoto^[31], but these works diverge by the compounds or conditions employed for the cyclization step.



Scheme II-27: Synthesis of β -carbolines via thermal iminoannulation.

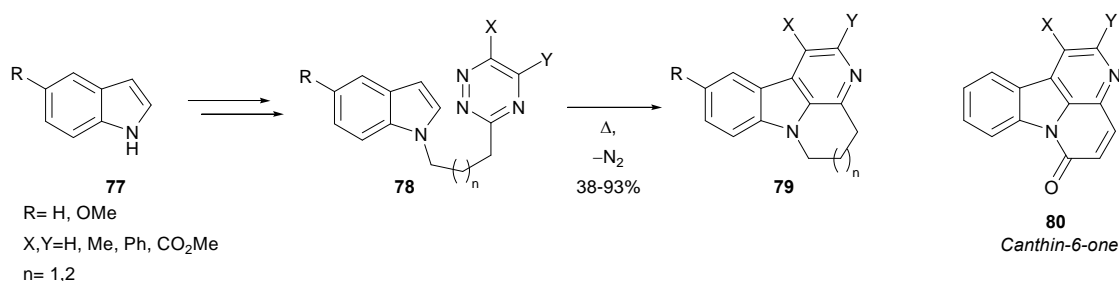
Similarly, Kusurkar and Goswami reported a one-pot strategy involving the thermal electrocyclization of azahexatrienes **75**.^[32] This approach is very close to the one developed by Hibino few years earlier but differs in the fact that the reaction allows the synthesis of 1-substituted β -carbolines. Contrary to Hibino's method, the reaction does not start from 2-formyl-indoles **64** but from 3-alkenyl-indoles **73** which after acylation afford the indoles **74**. These are directly converted to their imino-derivatives to give the β -carbolines **76** after thermal-induced cyclization.



Scheme II-28: Synthesis of a β -carboline via electrocyclizations of hexatrienes.

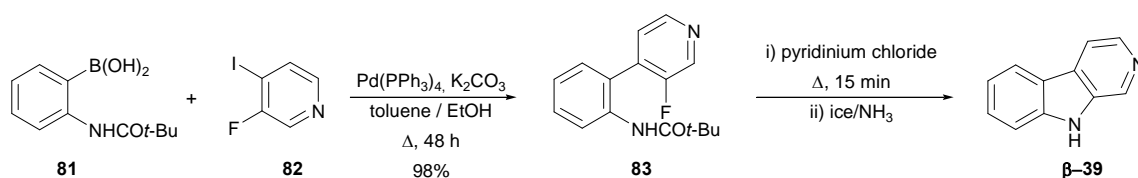
Snyder and co-workers reported a synthesis of β -carbolines by thermal intra-molecular cycloaddition of indolyl-1,2,4-triazines **78** but this method suffers from a lack of

regioselectivity.^[33a] The reaction proved however to be efficient for the synthesis of the Canthine skeleton when the triazine moiety is tethered to the indole.^[33b]



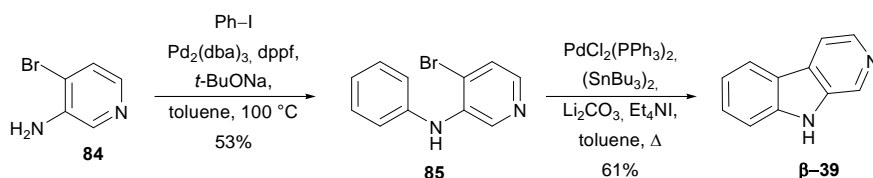
Scheme II-29: Synthesis of a β -carboline via electrocyclizations of hexatrienes.

Although most works rely on the pyridine-ring formation starting from indole derivatives, few groups have considered the synthesis of β -carboline via different approaches. Queguiner and co-workers developed a method for the synthesis all four parent carboline cores that has the formation of the pyrrole ring as final step.^[34] Using this strategy, *Norharman* β -39 was prepared in two steps from the phenyl boronic acid **81** and the pyridine **82**.



Scheme II-30: Synthesis of a β -carboline via ring-closure of a 3-fluoro-4-(anilino)pyridine.

A similar ring-closure approach was reported by Sakamoto and co-workers.^[35] In their strategy, the pyrrole ring of the β -carboline was formed by a palladium-catalyzed ring closure of the 3-anilino-4-bromopyridine **85**.

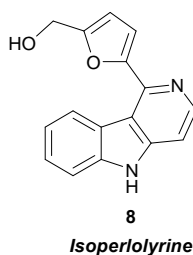


Scheme II-31: Synthesis of a β -carboline via a palladium-catalyzed ring closure of a 3-anilino-4-bromopyridine.

II.2.1.2. γ -Carbolines

II.2.1.2.1. Natural occurrence

Contrary to β -carbolines, γ -carbolines are very rare in nature, the only example known up to now is *Isoperlolyrine*, isolated from the seeds of *Gloriosa superba* L..^[36]



Scheme II-32: *Isoperlolyrine*, unique natural product reported to possess a γ -carboline core.

Despite the lack of naturally occurring γ -carbolines, their field of biological activity has already been well investigated. Many synthetic γ -carboline derivatives showed physiological or pharmacological properties.

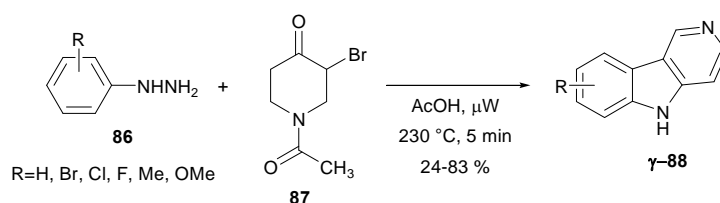
II.2.1.2.2. Biological activities

Like β -carbolines, γ -carbolines were shown to possess various biological activities. Some γ -carbolines were found for example to act as cardiovascular agents^[37] or as 5-HT₃/5-HT_{5a}/5-HT₆ receptors antagonists^[38]. Other γ -carboline showed antidepressant^[39] or anti-inflammatory activity^[40] in addition to enhanced neuroleptic activity^[41]. Recently, simple γ -carbolines were described to have a potent activity against bovine viral diarrhea virus.^[42] Furthermore, some γ -carbolines were shown to be more efficient than their β -carboline or carbazole analogues as selective cysLT₁ receptor antagonists.^[43]

II.2.1.2.3. Synthesis of γ -carbolines

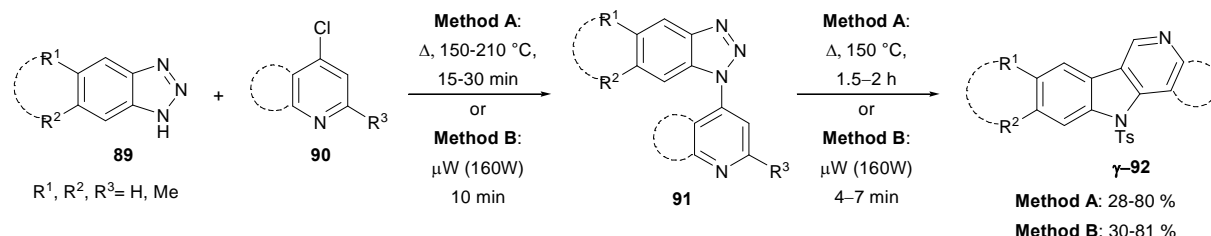
Unlike β -carbolines, γ -carbolines were for a long time hardly accessible. Adaptation of the Fischer synthesis proved to be inefficient, leading with difficulty to the desired γ -carbolines unless drastic thermal conditions were used.^[44] The reaction was recently shown to be facilitated by microwave irradiations but was limited to the synthesis of γ -carbolines

substituted only on the phenyl ring.^[45] Moreover, the reaction suffers from a poor regioselectivity and gives dehalogenated carbolines as by-products when halogeno-hydrazines are used.



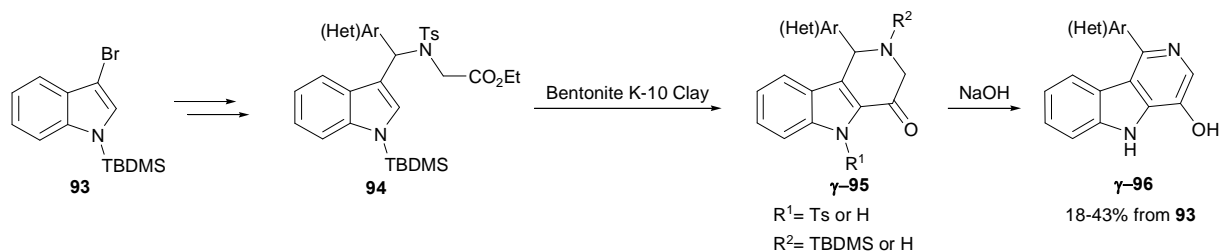
Scheme II-33: Microwave-enhanced Fischer synthesis of γ -carbolines.

γ -Carbolines were also successfully obtained by application of the Graebe–Ullman reaction to *N*-pyridinyl-benzotriazoles **91**.^{[44],[46]} Alvarez-Builla and co-workers showed that microwave irradiation enhances the reaction rate dramatically but remains without any noticeable influence on the yields. Additionally, the reaction was limited to the coupling of few substituted benzotriazoles or naphotriazoles and pyridines (or quinolines). A similar approach starting from *N*-phenyltriazolo[4,5-*b*]pyridines was studied simultaneously by Parrick and co-workers but did not furnish better results.^[47]



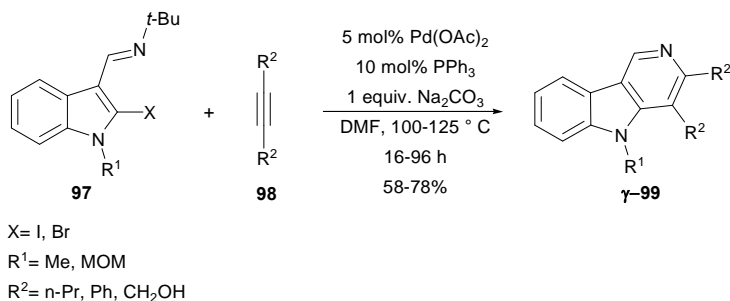
Scheme II-34: Synthesis of γ -carbolines via *N*-pyridinyl-benzotriazoles

The synthesis of γ -carbolines via lewis-acid-catalyzed intramolecular cyclizations of 3-aminomethyl indole derivatives was recently reported by Wynne and Stalick.^[48] This procedure was illustrated by the synthesis of wide array of 1-(hetero)aryl-4-hydroxy- γ -carbolines from the protected 3-bromo indole **93**. Treatment of the indoles **94** with Bentonite K-10 Clay leads to a mixture of protected and deprotected 1,2-dihydro- γ -carbolines γ -95 which give the carbolines γ -96 after reaction with sodium hydroxide.



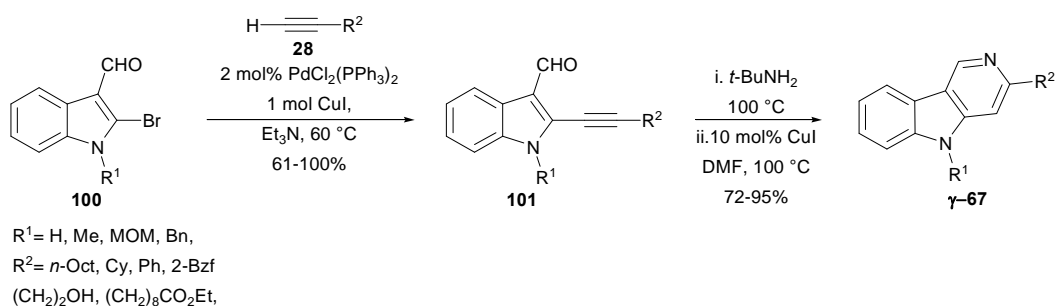
Scheme II-35: Synthesis of γ -carbolines via 3-aminomethyl indole derivatives.

Larock and Zhang adapted their aforementioned strategy of palladium-catalyzed annulation of imino-halogeno-indoles to the synthesis of γ -carbolines.^[29a] The reaction proved to be more difficult than in the case of β -carbolines. Other reaction conditions and a longer reaction time were required to give the desired carbolines with only slightly lower yields than in the case of β -carbolines.



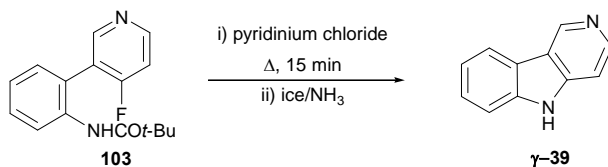
Scheme II-36: Synthesis of γ -carbolines via palladium-catalyzed annulation of imino-halogeno-indoles.

In a parallel way to their synthesis of 3-substituted β -carbolines, the same authors described the synthesis of 3-substituted γ -carbolines via a palladium/copper-catalyzed coupling and cyclization sequence with terminal alkynes.^[29b] Palladium-catalyzed coupling of a wide array of terminal alkynes to the 2-bromo-3-formyl-indoles **100** gives the 2-alkynyl indoles **101** with generally excellent yields. Imination of these indoles with *t*-butylamine and subsequent thermal cyclization *in situ* affords the 3-substituted γ -carbolines γ -**67**.



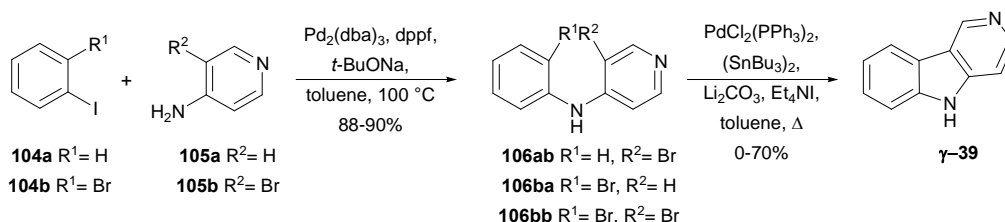
Scheme II-37: Synthesis of 3-substituted γ -carbolines via a palladium/copper-catalyzed coupling and cyclization sequence with terminal alkynes.

Queguiner and co-workers applied their strategy for the synthesis of the carboline core via final formation of the pyrrole ring to the synthesis of a γ -carboline.^[34] However, the method appears to be limited to this unique example since no substituted derivatives were described until now.



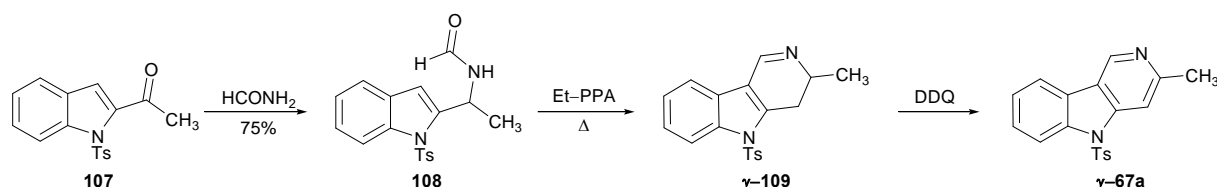
Scheme II-38: Synthesis of a γ -carboline via ring-closure of a 3-anilino-4-fluoropyridine.

Similarly, Sakamoto and co-workers applied their palladium-promoted β -carboline synthesis to the formation of the γ -isomer.^[35] The study showed that the 4-(2-bromoanilino)pyridine **106ba** was the best precursor for the synthesis of the γ -carboline core. This aniline underwent the palladium-promoted ring closure in a good yield of 70% whereas its regioisomer **106ab** afforded the desired carboline γ -39 in a lower yield of 47%. On the other hand, the dibromo compound **106bb** did not afford any γ -carboline product.



Scheme II-39: Synthesis of a γ -carboline via a palladium-catalyzed ring-closure of a 4-(2-bromoanilino)pyridine.

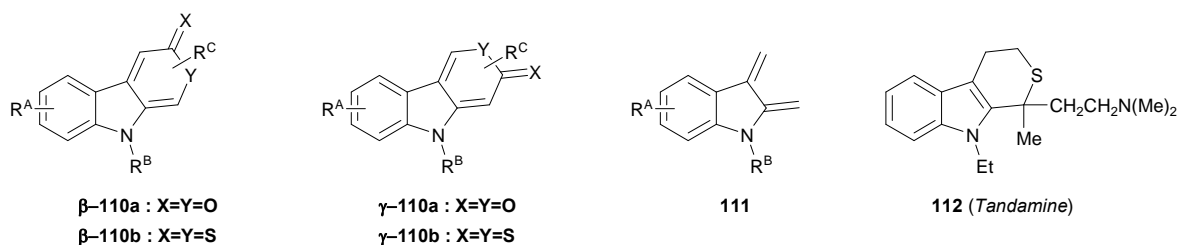
Preliminary results on a novel synthesis of γ -carbolines based on the application of the Bischler-Napieralski reaction were recently reported by Butin and co-workers.^[49] A Leuckart-Wallach type reductive amination of the indole **107** gave the amide **108**. The latter was heated in ethyl polyphosphate to afford a mixture of the dihydro γ -carbolines γ -**109** and the fully aromatic γ -carbolines γ -**67a**. Complete aromatization of γ -**109** was achieved by treatment with DDQ.



Scheme II-40: Synthesis of γ -carbolines via a Bischler-Napieralski variant.

II.2.2. Pyranoindolones

Pyrano[3,4-*b*]indol-3-ones β -**110a** and pyrano[4,3-*b*]indol-3-ones γ -**110a** (pyranoindolones) are known since the pioneering works of Plieninger and co-workers in 1964.^[50] They are notably known as stable synthetic equivalents of the highly reactive indoloquinodimethanes **111** making them interesting Diels-Alder adducts. Like α -pyrones, indolopyrones can react in Diels-Alder-reactions as a diene, a subsequent retro-Diels-Alder reaction liberates CO_2 resulting in an overall ring transformation from indolopyrones to (dihydro)carbazoles or heterocyclic analogues. On the contrary, their sulphur derivatives β -**110b** and γ -**110b** are still unprecedented, the closest similar compound reported is *Tandamine* **112**, which is considered as a potential antidepressant agent.^[51]

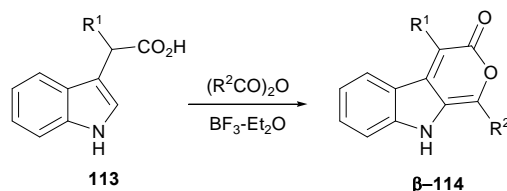


Scheme II-41: Selected indoloquinodimethane derivatives and *Tandamine*

II.2.2.1. Synthesis

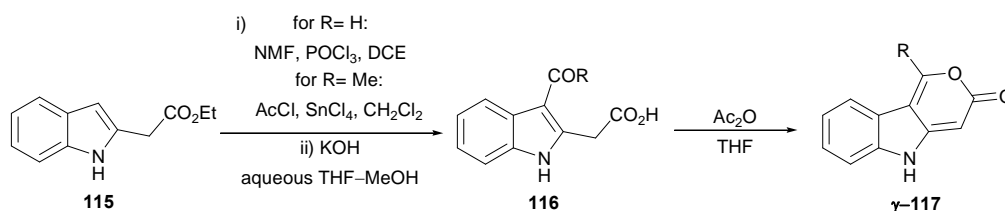
Few syntheses of pyrano[3,4-*b*]indol-3-ones are described in the literature, probably due to the efficiency of the straightforward method described by Plieninger.^[50] 1,4-disubstituted

pyrano[3,4-*b*]indol-3-ones are easily accessible from commercially available indol-3-ylacetic acid derivatives **113**. Their treatment with an acid anhydride and boron trifluoride-diethylether gives the resulting 1,4-disubstituted-pyrano[3,4-*b*]indol-3-ones β -**114** in moderate to good yields.



Scheme II-42: Synthesis of pyrano[3,4-*b*]indol-3-ones from indol-3-ylacetic acid derivatives.

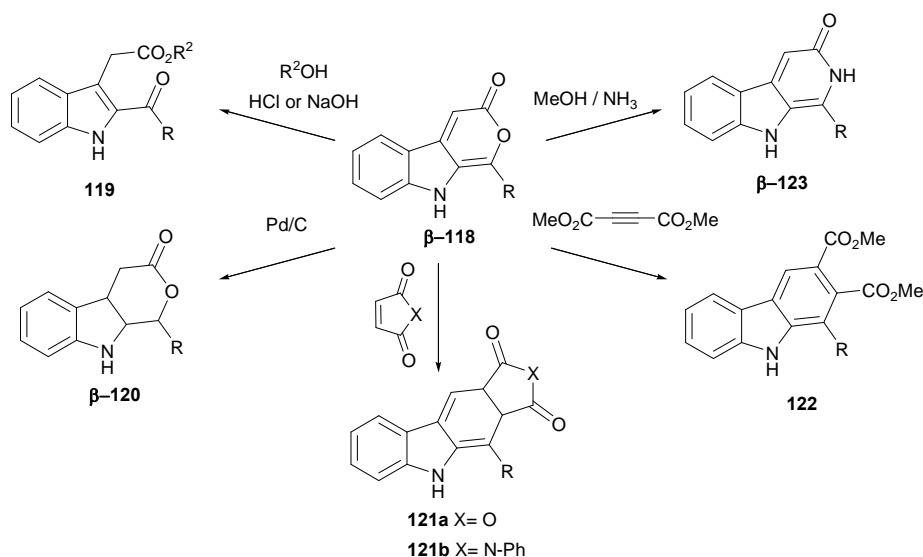
Similarly, only few synthetic routes to the isomeric pyrano[4,3-*b*]indol-3-ones have been reported up to now. According to Moody, the ester **115**, prepared in 2 steps from 2-nitrophenylacetyl chloride, is treated with *N*-methylformanilide and phosphorus oxychloride in 1,2-dichloroethane to give a 3-formylindole which is then hydrolyzed to the acid **116**.^[52f] Cyclodehydration of this compound by reaction with acetic anhydride gives the desired pyrano[4,3-*b*]indoles γ -**117** with an overall yield of 60% based on the ester **115**.



Scheme II-43: Synthesis of pyrano[4,3-*b*]indol-3-ones.

II.2.2.2. Reactivity

Pyrano[3,4-*b*]indol-3-ones and their [4,3-*b*] isomers possess a reactivity similar to α -pyrones. As shown by the pioneering work of Plieninger, treatment of β -**118** with alcoholic solution under base or acid catalysis leads in a ring opening to 2,3-disubstituted indoles **119**.^[50] They can also be reduced to the dihydro derivatives β -**120** with palladium on charcoal or react with an alcoholic solution of ammonia to give the indolopyridones β -**123**. They react as Diels-Alder dienes with maleic acid, *N*-phenyl-maleinimid or dimethyl acetylenedicarboxylate with concomitant loss of carbon dioxide to give respectively the carbazoles **121a**, **121b** and **122**.

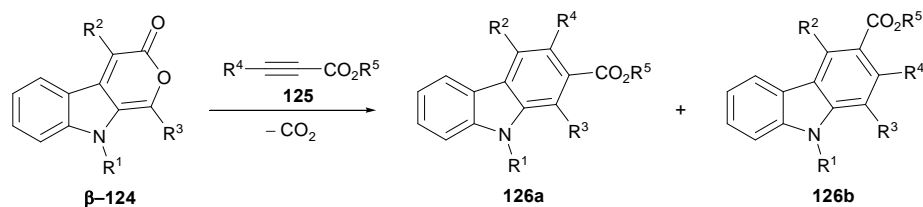


Scheme II-44: Pyranoindolones as important intermediates.

Since this study, the chemistry of indolopyrones remained almost unexploited until 1984 and the extensive work in their application as Diels-Alder dienes by the groups of Moody^[52], Pindur^[53] or Hoornaert^[54] or the more recent works on their reactivity towards nucleophiles by Stephanidou-Stephanatou and co-workers^[55].

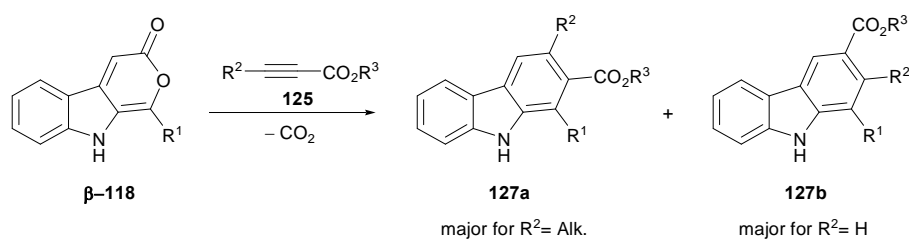
II.2.2.2.1. Diels-Alder reaction

Pyrano[3,4-*b*]indol-3-ones readily react with acetylenic esters in boiling bromobenzene to give the carbazoles **126a-b**.^[52a] The reaction proved however not to work with electron-rich acetylenes and to be more difficult with unactivated triple-bonds except in the case of intramolecular reactions.^[52c]



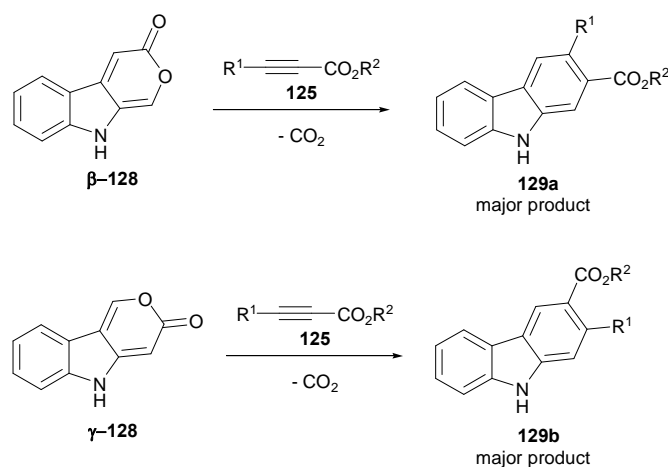
Scheme II-45: Reaction of pyranoindolones with electron-deficient alkynes.

The regioselectivity of the reaction with unsymmetrical alkynes depends on the substitution patterns of the alkyne. Reactions with mono-substituted alkynes ($R^2 = H$) lead mainly to the 1,3-substituted carbazoles **127b**, whereas the opposite regioselectivity is observed when the proton is replaced by an alkyl group.^[52d]



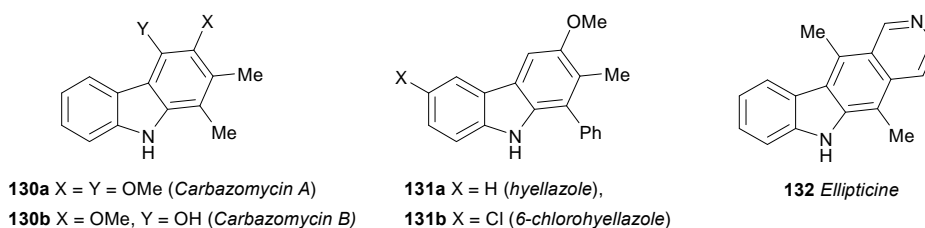
Scheme II-46: Reaction of pyranoindolones with electron-deficient alkynes.

Pyrano[4,3-*b*]indol-3-ones are less reactive and give the opposite regioselectivity than their isomers.^[52f] However, their reactivity can be enhanced by substitution of the nitrogen with a *t*-butyl group.



Scheme II-47: Reaction of pyranoindolones with electron-poor alkynes.

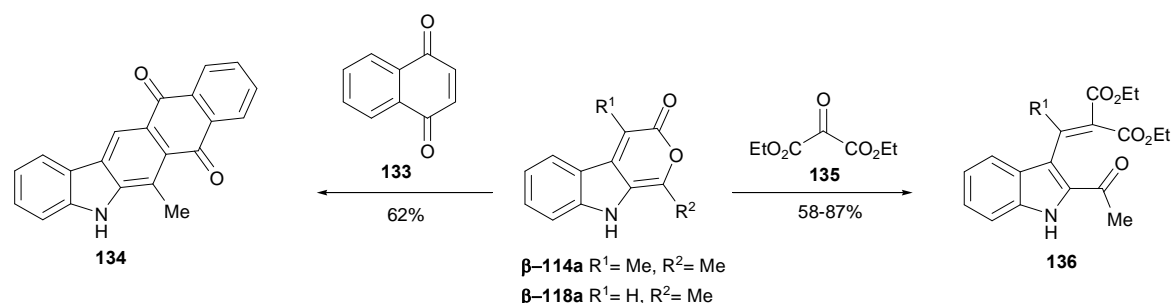
This strategy was successfully applied to the synthesis of different naturally occurring carbazoles such as *Carbazomycin A* **130a** and *B* **130b** or *Hyellazole* **131a**^[52e], and the well-known *Ellipticine* **132**^[52a].



Scheme II-48: Carbazoles obtained from Diels-Alder reaction of indolopyrones.

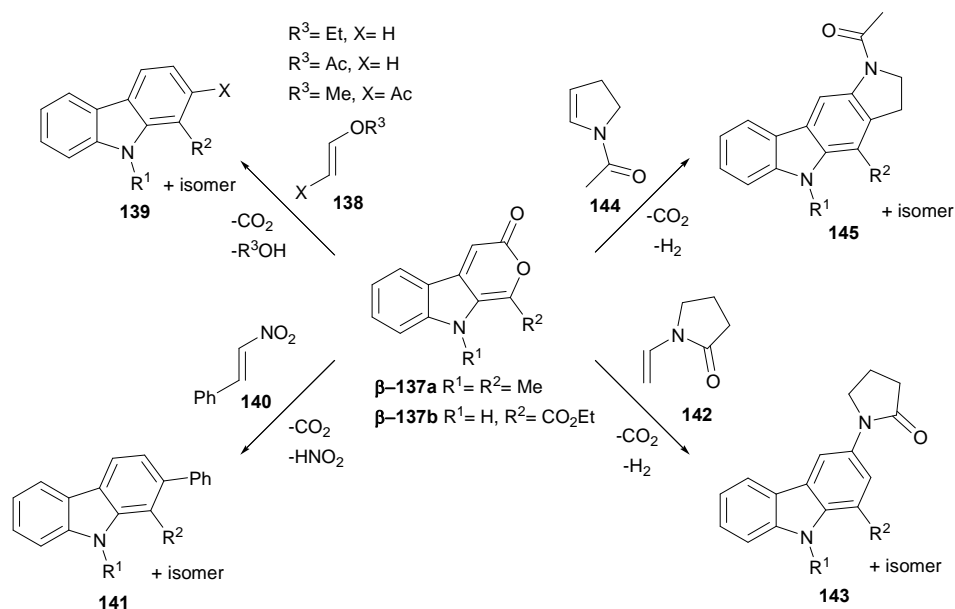
Pindur and Erfanian-Abdoust have extended the reaction to acrylonitriles, carbonyl dienophiles like diethyl mesoxalate^[53b] or to cyclic dienophiles such as benzyne, *p*-

napthoquinone^[53a]. Reaction with the latter did not lead to the expected cycloaddition product but to 2,3-disubstituted indoles **136**.



Scheme II-48: Reaction of indolopyrones with *p*-naphthoquinone or diethyl mesoxalate.

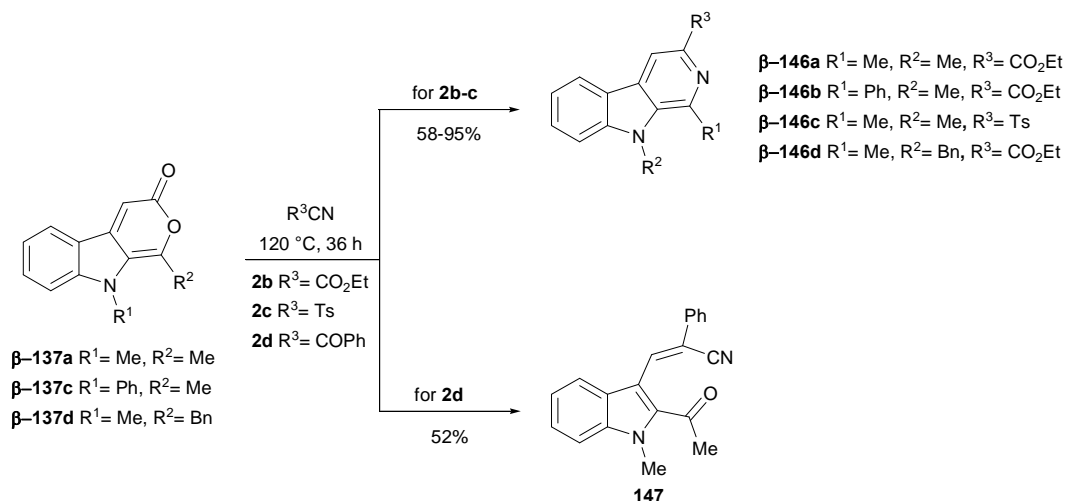
The reaction was later applied by Hoornaert and coworkers to electron-rich dienophiles, i.e. heterosubstituted olefins.^[54c] Surprisingly, the resulting carbazoles differed according to the hetero-substituent. When *N*-substituted olefins were used, the reaction led to the expected carbazoles **144** or **146** whereas use of *O*-substituted olefins **139** (enol, vinyl ether, etc.) or a nitroalkene did not lead to the expected carbazoles. The resulting carbazoles did not arise from dehydrogenation of the intermediate but from elimination of the hetero-substituent.



Scheme II-50: Reaction of pyranoindolones with electron-rich olefins.

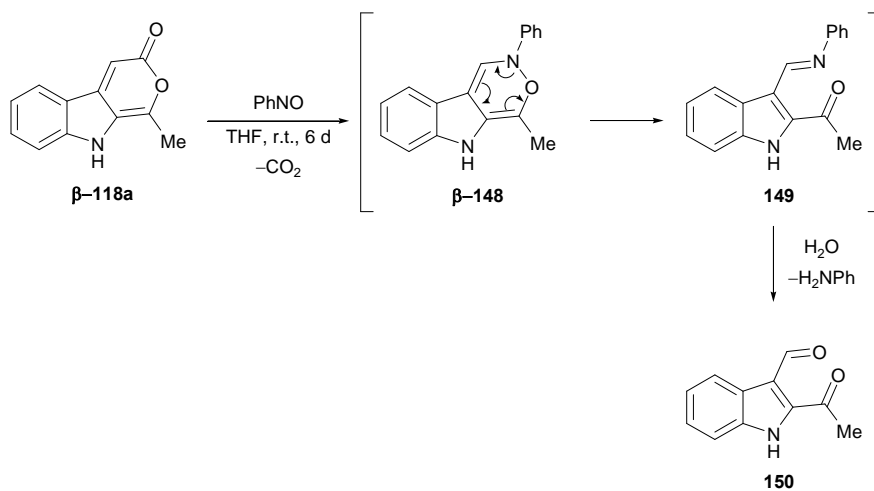
Pyranoindolones can also react with electron-deficient nitriles.^[54d] Different classes of products are obtained depending on the nitrile used. The reaction leads to β -carbolines

β -146a-d when ethylcyanoformate or *p*-toluenesulfonylcyanide are used, whereas the reaction with benzoyl cyanide gives the acylated derivative **147**.



Scheme II-51: Reaction of pyranoindolones with nitriles.

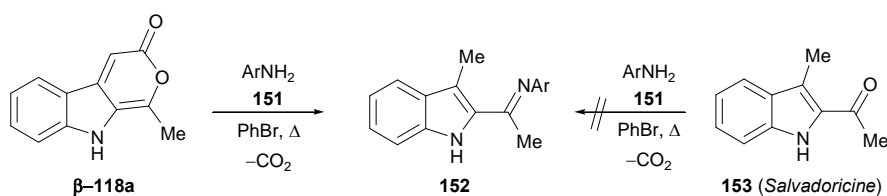
The reaction of pyrano[3,4-*b*]indol-3-ones with nitrosobenzene or oxygen provides 2,3-diacylindoles with moderate yields (30-40 %).^[53c]



Scheme II-52: Reaction of pyranoindolones with nitrosobenzene.

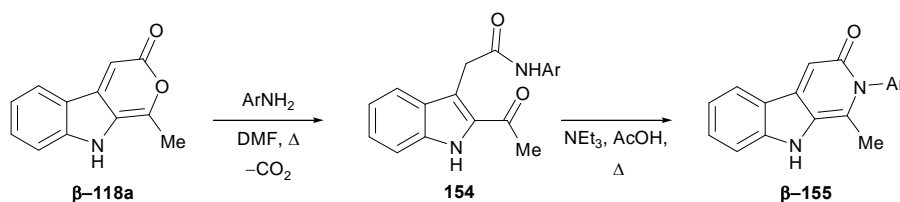
II.2.2.2.2. Reaction with nucleophiles

The reaction of pyranoindolones with diverse nucleophiles leads to numerous indole derivatives. For example, addition of aromatic amines to pyranoindolones leads to Salvadoricine Schiff bases **152** which cannot be obtained by simple condensation of these amines with *Salvadoricine* **153**.^[56]



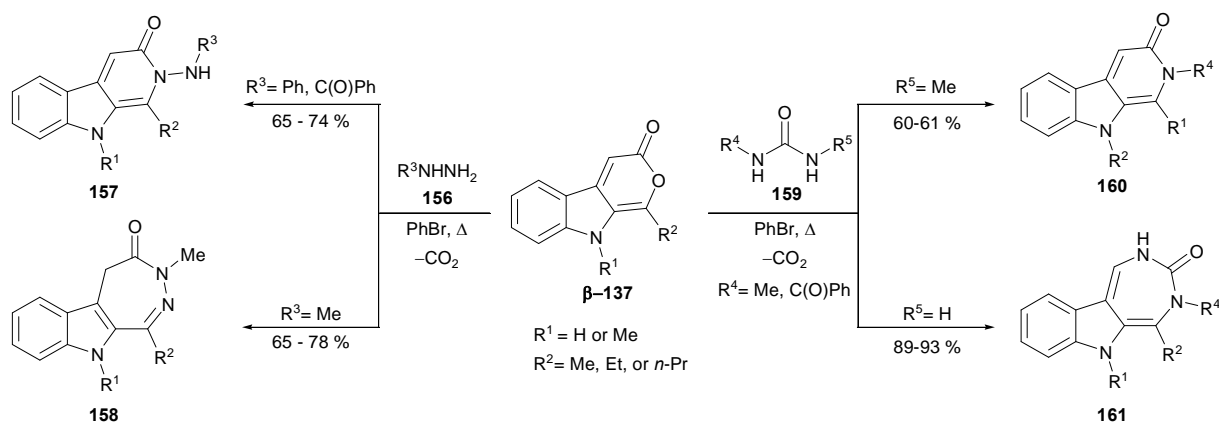
Scheme II-53: Reaction of pyranoindolones with aromatic amines.

The reaction depends considerably on the solvent used as shown by Dulenko.^[57] When the bromo-benzene is replaced by DMF, the reaction leads to the indole **154** which can be then converted into the β -carbolinones **β -155**.



Scheme II-54: Reaction of pyranoindolones with aromatic amines in DMF.

More recently, Stephanidou-Stephanatou and co-workers used indolopyrones as intermediates for the synthesis of indolo-fused azacycles. Reactions of the pyranoindolones with phenyl- or benzoylhydrazine lead to β -carbolinones **157** in good yields (65-74%)^[55a] whereas the reaction with methylhydrazine gives access to [1,2]-diazepino[4,5-*b*]indoles **158**.^[55b] The reaction was extended to ureas and, depending on the degree of substitution of the ureas, different products were obtained.^[55c] Whereas mono-substituted ureas **159** lead to 1,3-diazepinindolone **161** in excellent yields (89-93%), the reaction with disubstituted ureas **160** gives β -carbolinones **160** in moderate yields (60-61%).



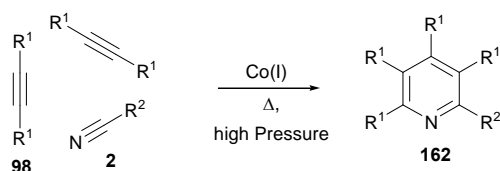
Scheme II-55: Reaction of pyranoindolones with hydrazines and ureas.

II.3. Synthesis of heterocycles via [2+2+2] cycloadditions

Among the numerous possible reactions for the synthesis of heterocycles, [2+2+2] cycloadditions of two alkynes with a carbon-heteroatom multiple bond receives a growing attention in organic chemistry. Specially, this strategy has known a spectacular development in the last thirty years. Its attraction is mainly due to the fact that the reaction leads via an atom-economical one-pot synthesis to various substituted heterocycles.

II.3.1. [2+2+2] Cycloaddition of alkynes with nitriles: synthesis of pyridine rings

The first result of [2+2+2] cycloadditions of alkynes with nitriles to the pyridine ring comes from the works of Sir William Ramsay in 1876 who obtained a small amount of pyridine from acetylene and hydrogen cyanide with help of a red-hot iron tube.^[58] The reaction remained unexplored for nearly a century until the pioneering works of Yamasaki and Wakatsuki^[59] in the early 1970's, followed by the works of Bönemann and Brijoux^[60] and Vollhardt and co-workers^[61] were reported.

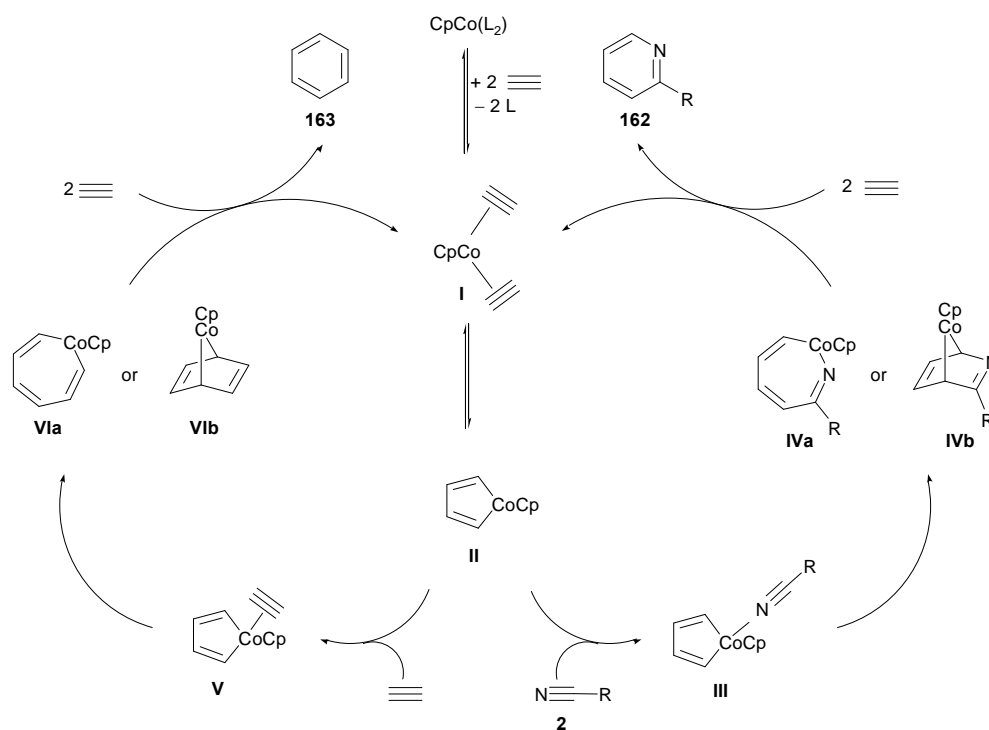


Scheme II-56: Synthesis of pyridines via [2+2+2] cycloaddition of two alkynes and a nitrile.

However, these cobalt(I)-based cotrimerizations required often drastic conditions – high temperature and pressure – to complete the reaction. Moreover, the reaction produces an important amount of benzenes as by-product from the undesired homo-trimerization. These drawbacks have limited the development of the reaction. Oehme and co-workers in 1989 partially solved the problem by developing photochemical conditions that allows to perform the reaction under milder conditions.^[62] Since then, the reaction has known a spectacular development and presents now a large choice of catalysts.^[63] Among them, cobalt-catalysts are by far the most used. Nevertheless, very interesting results have been obtained in the last decade with ruthenium and rhodium catalysts.^{[64],[65]} Several other metals like Ti^[66], Ni^[67], Fe^[68], Ta^[69], Zr^[70] (Zr/Ni or Zn/Cu) also catalyse the reaction efficiently. However, they present more disadvantages like the necessity of a stoichiometric amount of catalyst or drastic conditions of reaction.

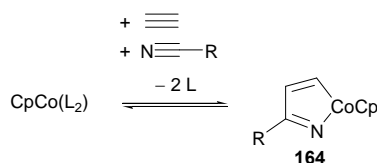
II.3.1.1. Cobalt-catalyzed reactions

The first representative syntheses of pyridines rings via metal-catalyzed [2+2+2] cycloadditions of alkynes with nitriles came from the successful applications of (η^5 -cyclopentadienyl)cobalt(I) complex derivatives [CpCo(L_x)] where the ligand is olefinic (L_x= C₂H₄, COD) or carbonyl (L_x= (CO)₂)^{[59]-[61]}. The commonly accepted mechanism starts with the exchange of the two labile ligands by the acetylene bonds followed by an oxidative cyclization to give the cobaltacyclopentadiene **II**. The nitrile coordinates then to the cobalt(III) by help of his lone pair and inserts into the cycle to lead to an azacobaltacycloheptatriene **IVa**. Reductive elimination of the cobalt center gives the resulting pyridine **162**. The same cycle runs parallel with a third alkyne moiety to give a benzene ring **163** as by-product. This side-reaction remains however less important due to the lower affinity of the alkyne for the metal center in comparison of the nitrile.



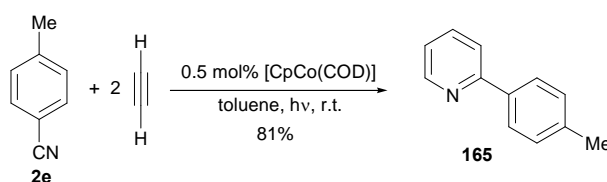
Scheme II-57: Plausible mechanism for the cobalt-catalyzed [2+2+2] cycloaddition of alkynes with nitriles.

This plausible mechanism was strengthened by several studies where some cobaltacyclopentadienes **II** were isolated. Furthermore, the formation of the azacobaltacyclopentadiene **164** was ruled out by kinetic studies.



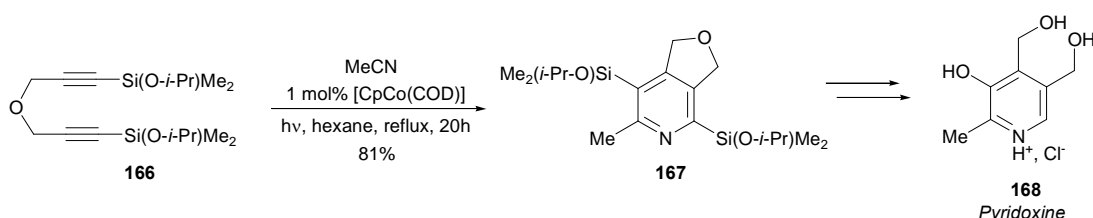
Scheme II-58: [2+2+2] Cycloaddition catalyzed by [CpCo(COD)].

Heller and Oehme have reported recent improvements on the cobalt-catalyzed trimerization by developing photochemical conditions enabling the use of mildest conditions without requiring any extensive heating.^[71a-b]



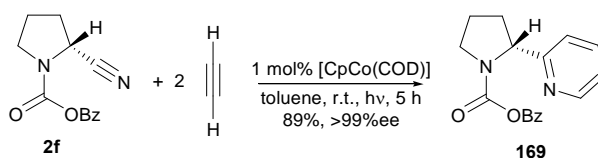
Scheme II-59: [2+2+2] Cycloaddition catalyzed by [CpCo(COD)].

These photochemical conditions were applied to the synthesis of *Pyridoxine* **168** (Vitamin B₆)^[71c]. The key-step is the [2+2+2] cycloaddition of acetonitrile to the diyne **166** with 1 mol% of [CpCo(COD)]. The resulting pyridine **167** can be then converted into *Pyridoxine* in 4 subsequent steps.



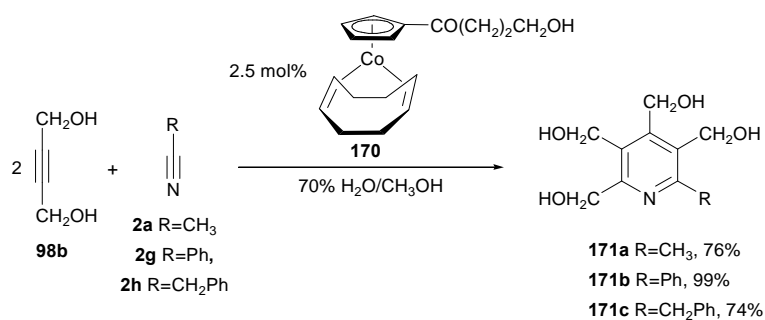
Scheme II-60: Key-step of the new synthesis of the *Pyridoxine*.

[2+2+2] Cycloadditions can be also carried out with chiral nitriles without loss of optical purity as demonstrated by the cycloaddition of the enantiopure nitrile **2f** with acetylene. The desired pyridine **169** is obtained without any detectable traces of racemization.^[71d]



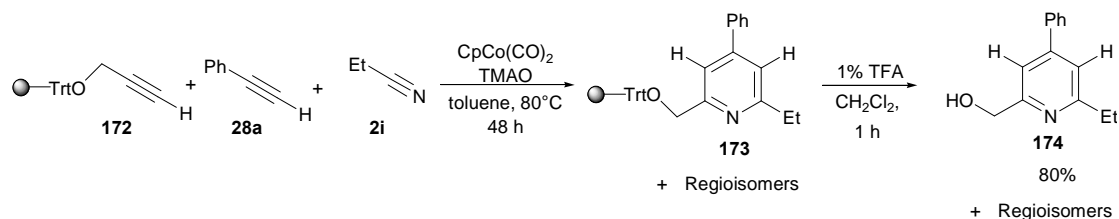
Scheme II-61: [2+2+2] cycloaddition with an enantiopure nitrile.

Fatland and co-workers have described a modified [CpCo(COD)] catalyst with substituents on the Cp-ring.^[72] This water-soluble complex allows the synthesis of pyridines with the use of only a stoichiometric amount of the nitrile and without the undesired formation of the homo-coupling trimers of the alkyne.



Scheme II-62: [2+2+2] Cycloaddition catalyzed by a water-soluble cobalt complex.

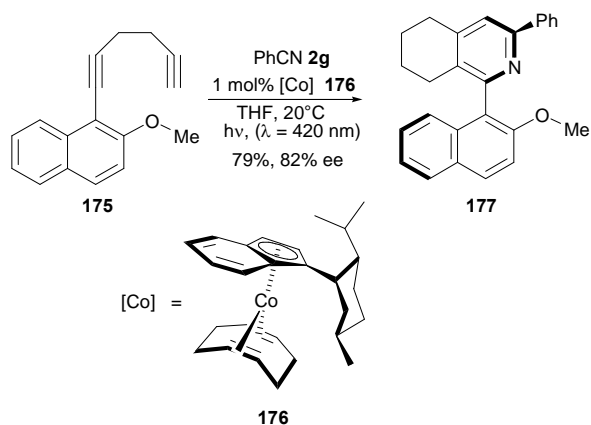
Another interesting recent result is the first solid-supported three-components cyclotrimerization communicated by Deiters et al..^[73] They developed this strategy to solve the problem of *homo*-trimerization of the alkynes by immobilizing one of them on a resin. The reaction tolerates a wide range of substituents on the free alkyne (alkyl, aryl, hydroxyl, alkoxy and carbamates).



Scheme II-63: Solid supported synthesis of pyridines.

The reactions proceeds in toluene at 80 °C with 10 equivalents of nitrile in the presence of 20 mol% of CpCo(CO)₂ and tetramethylammonium oxide (TMAO) as catalyst additive. It leads in relatively good yields (43-85%) to 2,4,6-pyridines as major regioisomer together with small amounts of the minor regioisomers. This strategy is still under investigation.

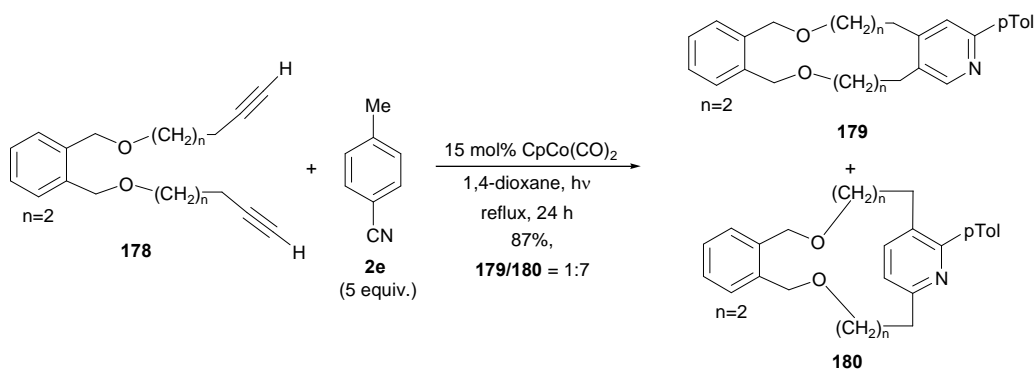
Heller and co-workers extended their research on the Co(I)-catalyzed photochemical [2+2+2] cycloaddition by performing the first asymmetric synthesis of atropisomers of 2-arylpyridines from diynes and nitriles.^[71e] The reaction is completed at 20°C with low to good enantioselectivities as proved by the synthesis of **177** from the diyne **175**.



Scheme II-64: Enantioselective synthesis of 2-arylpyridines.

However, yields and enantioselectivities remain very low when less hindered substrates are used. In these cases, better enantioselectivities can be reached if the temperature of reaction is lowered but the yields decrease strongly in counterpart.

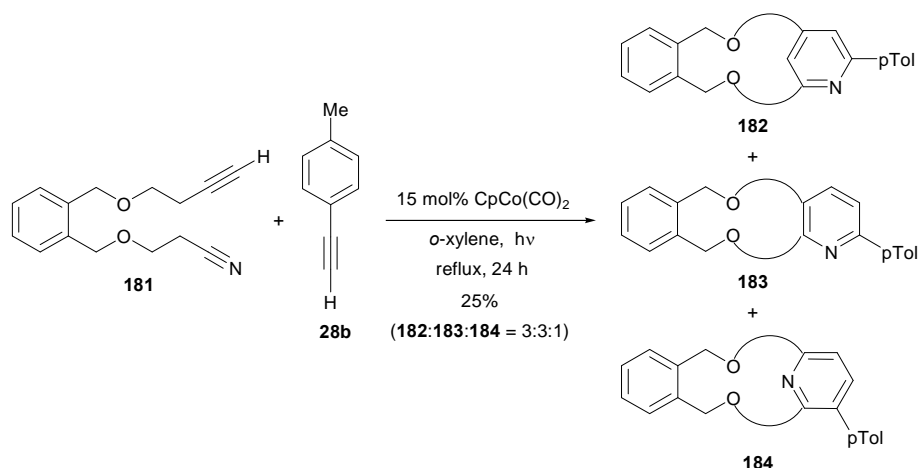
A synthesis of macrocycles was developed by Maryanoff and co-workers.^[74a-b] They use the $\text{CpCo}(\text{CO})_2$ complex for the synthesis of a series of pyridinophanes - macrocycles containing a pyridine moiety - from either diynes or tethered alkyne-nitriles in moderate to good yield (generally 30% to 60%).^[74b]



Scheme II-65: Synthesis of pyridinophanes via [2+2+2] cycloaddition.

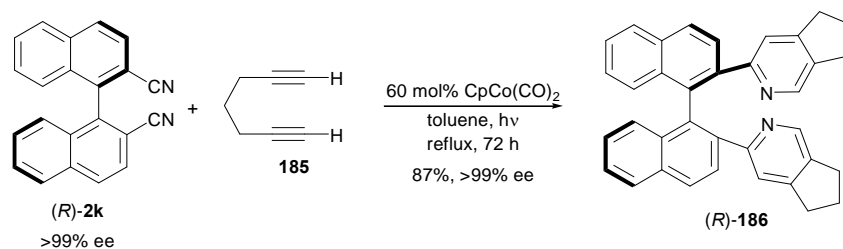
The reaction works with a wide variety of nitriles (conjugated to an arene, heteroarene, alkene group) but proved to be inefficient with nitriles linked to cyclic or acyclic alkyls or silylated nitriles, where only traces of products were observed. The reaction leads to a mixture of regioisomers which depends on the length and type of the tethered diyne used. The stereo-electronic effects play also an important role, i.e. electron-withdrawing groups on the conjugated arene favour the formation of the meta-isomer. The study showed that the concentration was an important factor since it influences greatly the yield of the macrocyclization, highly diluted solutions (0.005M) giving the best results. Analogously, the

nitrile can also be tethered to one of the alkynes (ω -alkynyl nitriles). Maryanoff noticed that contrary to the macrocyclization with a diyne and a nitrile, no para-isomers were observed.^[74b]



Scheme II-66: Synthesis of macrocycles from an ω -alkynyl nitrile and an alkyne.

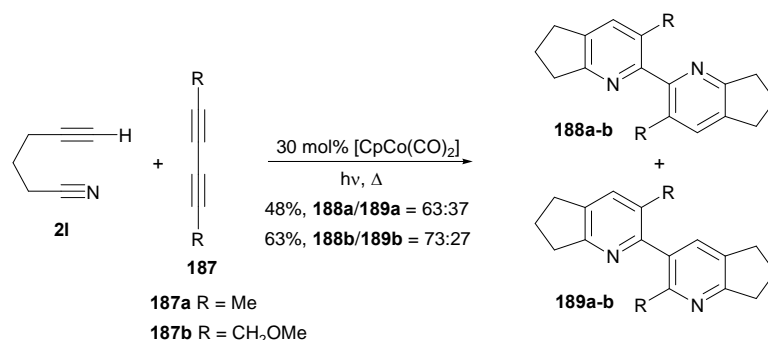
The synthesis of axially enantiopure bipyridines or biaryls having pyridinyl substituents is receiving a growing interest in the past few years. Hoshi and co-workers^[75] have reported the first resolution-free synthesis of such compounds. The use of enantiopure dicyanobinaphthyl **2k**, synthesized from the readily available enantiopure dibromo derivative, and a diyne like **185** enables indeed to get the desired product **186** without any loss of enantiopurity. This method avoids the difficult and fastidious resolution of these compounds that was previously necessary.



Scheme II-67: Synthesis of 2,2'-bis(pyridine-2-yl)-1,1'-binaphthyl ligands.

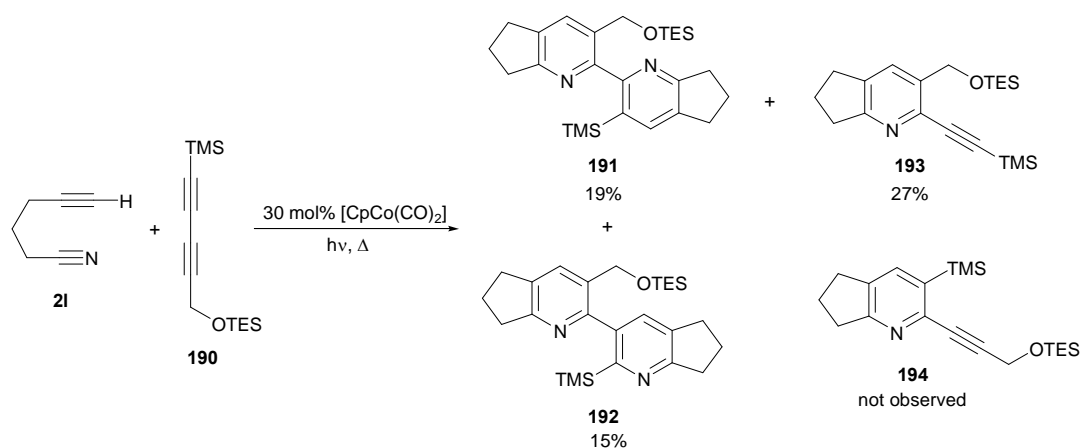
This reaction, which has only been successfully performed with terminal diynes, requires yet special conditions like indispensable irradiation and an important amount of catalyst (60 mol%) which has to be introduced with the diyne in three fractions every 24h in order to keep a high diluted solution to limit the competitive inter-molecular side reactions. Although the yields obtained in these cases are low, the reaction gives regioisomers which can not be synthesized from diynes.

ω -Alkynyl nitriles were also used by Saà and co-workers for the synthesis of symmetric 3,3'-substituted terpyridines, annulated 3-substituted bipyridines^[76a] or a one-step synthesis of 2,2'-bipyridines from acyclic precursors.^[76b] This method remains interesting though the regioselectivity of the reaction and the yields obtained are only moderate.



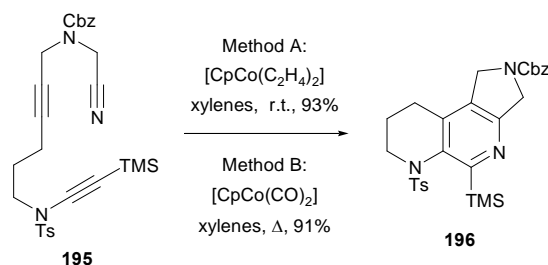
Scheme II-68: Synthesis of 2,2'-bipyridines from ω -alkynyl nitriles and diynes.

Later, they reported a more detailed study with symmetrical and unsymmetrical diynes where several factors like the steric and electronic effects were studied.^[76c] They found that electronic factors have a higher influence on the regioselectivity observed than steric factors which have an opposite regiodirective influence. The choice of the diyne partner has also a strong influence on the reaction, e.g. too bulky substituents like a trimethylsilyl group avoids the formation of the second heterocycle. Furthermore, the results obtained with unsymmetrical diynes suggest that the first cycloaddition is highly chemoselective since the reaction of the ω -alkynyl nitrile **2I** with the diyne **190** did not give the pyridine **194**.



Scheme II-69: Synthesis of 2,2'-bipyridines from ω -alkynyl nitriles and unsymmetrical diynes.

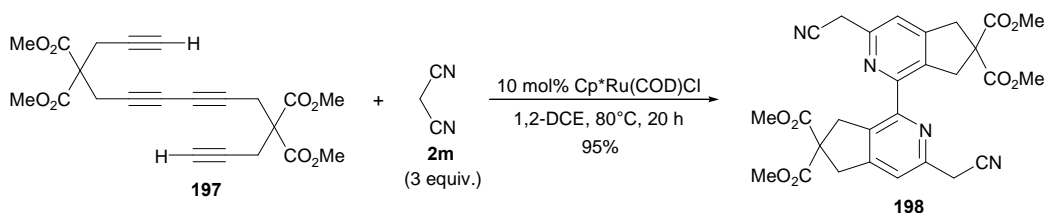
Malacria and co-workers reported recently the first [2+2+2] cycloaddition where the three cycloaddition partners are tethered.^[77] This unprecedented reaction leads to various tricyclic pyridines such as the novel 2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,4-*f*][1,7]naphthyridine **196**.



Scheme II-70: Intra-molecular [2+2+2] cycloaddition between an ynamide, an alkyne and a nitrile.

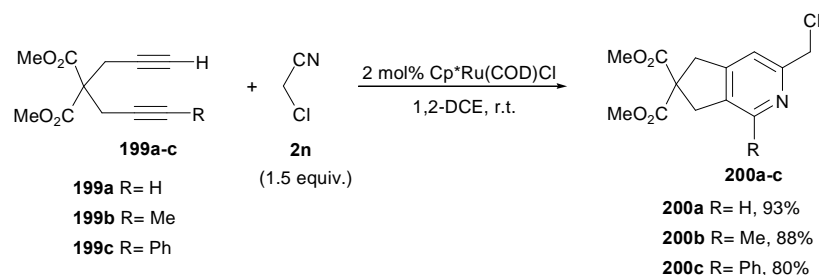
II.3.1.2. Ruthenium-catalyzed reactions

In the last decade, the Cp^{*}Ru(COD)Cl complex was shown to be a complementary alternative to cobalt complexes as demonstrated by the initiating work of Yamamoto and co-workers.^[64] But the reaction is limited to a small range of activated nitriles like electron-deficient nitriles or dicyanides. In the last case, only one nitrile group participates in a trimerization.



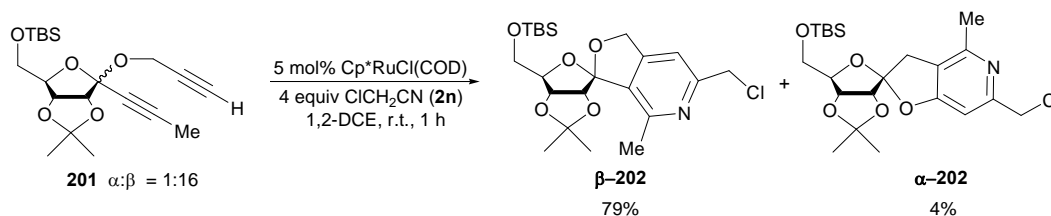
Scheme II-71: [2+2+2] Cycloaddition catalyzed by a ruthenium complex.

The reaction was then extended to α -halogenonitriles^[64c]. These nitriles were shown to react at room temperature with diynes to give the corresponding pyridines. The study showed that the position of the halogen was very important for the reaction since β -halogenonitriles were unable to give the expected cycloaddition product. Moreover, when the reaction is performed with a diyne having a terminal and an internal triple bond, the formation of only one regioisomer is observed. The reaction gives the pyridine with the substituent positioned α to the nitrogen atom as illustrated by the reaction of diynes **199a-c** with the α -halogenonitrile **2n**.



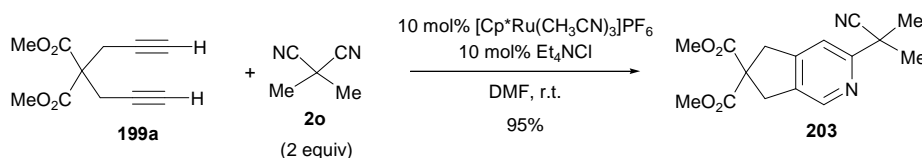
Scheme II-72: [2+2+2] Cycloaddition of diynes with α -halogenonitriles.

This method was successfully applied to the synthesis of a spirocyclic *C*-Arylriboside derivative β -**202** from the diyne **201** and chloroacetonitrile.^[64d] This furanose derivative possesses a spirocyclic *C*-arylriboside skeleton, and is expected to have a biological activity similarly to some of its papulacandins analogues.



Scheme II-73: Synthesis of a spirocyclic *C*-arylriboside via [2+2+2] cycloaddition of diynes with α -halogenonitriles.

Varela and co-workers achieved cycloadditions with a cationic ruthenium complex, $[\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3]\text{PF}_6$ ^[78]. But, similarly to the $\text{Cp}^*\text{RuCl}(\text{COD})$ complex used by Yamamoto and co-workers^[64], the reaction did not work with most of the nitriles tested like (hetero)arylcyanides, but led to the desired pyridines only with dicyanides and few other nitriles.

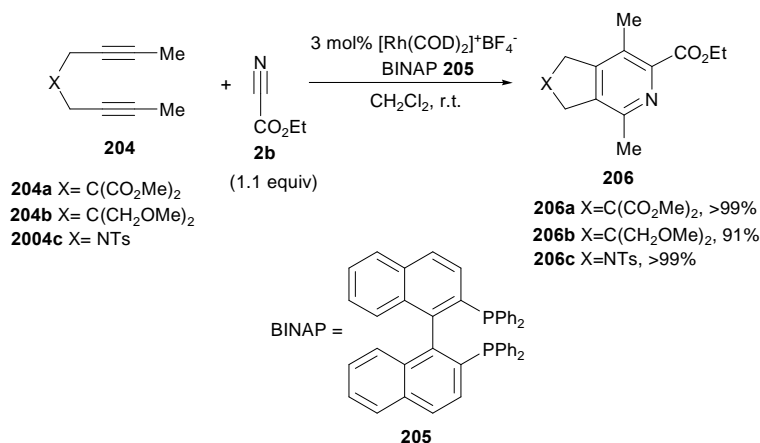


Scheme II-74: Synthesis of pyridines with a cationic ruthenium complex.

II.3.1.3. Rhodium-catalyzed reactions

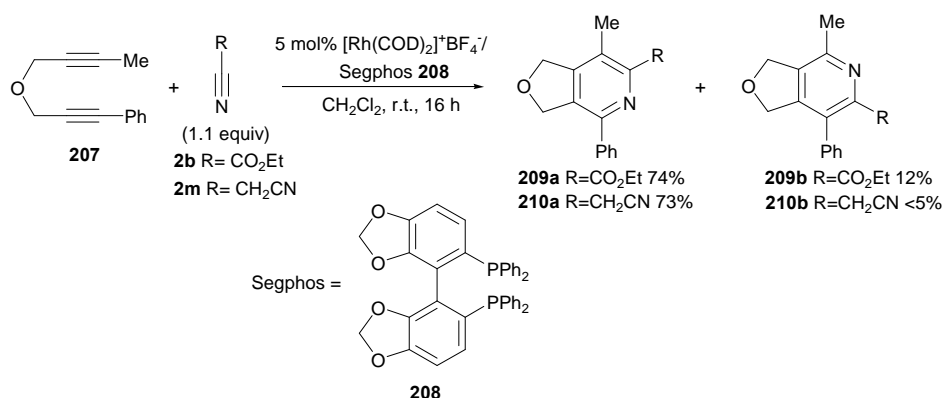
Tanaka and co-workers recently reported that rhodium/phosphine complexes catalyze the trimerization of alkynes entities efficiently.^[79a] Some of these $[\text{Rh}(\text{cod})_2]^+\text{BF}_4^-$ /phosphine (BINAP, modified-BINAP, Segphos or (*R*)-Solphos) catalytic systems were successfully

applied to the formation of pyridines with nitriles as cycloaddition partners^[79c]. Contrary to previously reported rhodium-catalyzed trimerizations^[65], which required high temperatures and gave a large amount of benzene by-products, the reaction is more chemoselective and proceeds under milder conditions. Pyridines are obtained in excellent yields at room temperature with electron-deficient nitriles without the benzene by-products resulting from *homo*-trimerization.



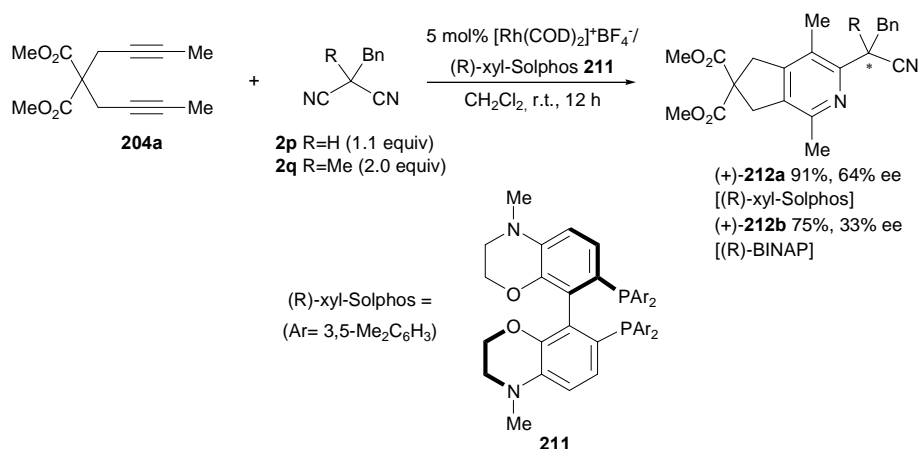
Scheme II-75: Trimerization of 1,6-diynes with nitriles.

Whereas electron-deficient nitriles are quite good substrates (35-87%), the reaction is less effective with other types of nitriles like alkyl, aryl or heteroatom substituted nitriles. In these cases, heating to 60°C or 80°C and longer reaction times are needed. Reactions with an unsymmetrical diyne were also performed which gave the pyridines **209a-b** and **210a-b** with a good regioselectivity.



Scheme II-76: Trimerization with unsymmetrical diynes.

An enantioselective cycloaddition with disubstituted malodinitriles was also performed to give bicyclic pyridines **212a-b** possessing a quaternary stereocenter.



Scheme II-77: Enantioselective cycloadditions of 1,6-diynes with disubstituted malodinitriles.

*C*₂-symmetric and non symmetric tetra-*ortho*-substituted axially chiral biaryls were synthesized by Tanaka with the cationic rhodium complex $[Rh(COD)_2]^+BF_4^-$.^[7d] These compounds have been obtained with excellent enantioselectivities (up to >99% ee). For example, the coupling of the tetrayne **213** and the electron-deficient nitrile **2b** leads to the bipyridine (+)-**214** with an enantioselectivity of 98%.

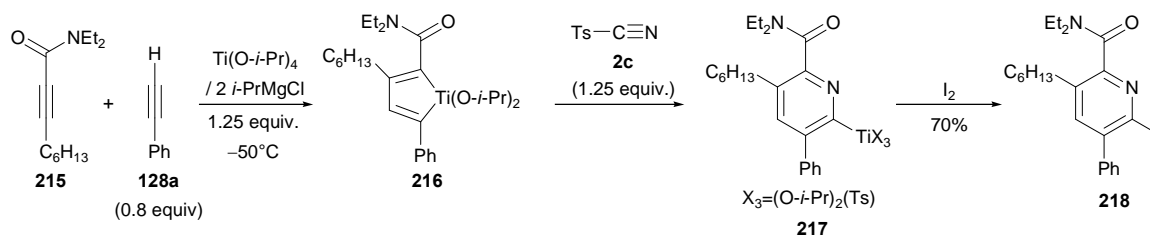


Scheme II-78: Enantioselective synthesis of axially chiral bipyridines.

II.3.1.4. Other metal catalysts

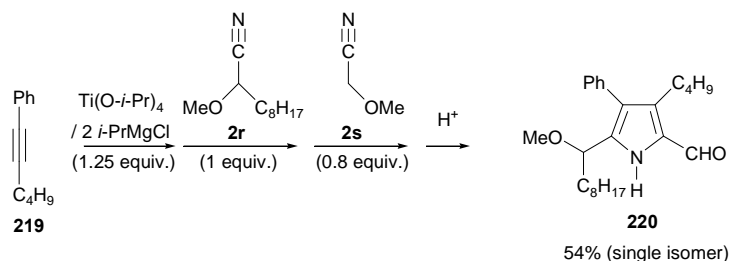
- Titanium-based catalysts

Sato and co-workers have developed a synthesis of metalated pyridines based on catalysis by a titanium(II) alkoxyde.^[66] They have recently presented an one-pot synthesis of various metalated pyridines from different types of alkynes (unsymmetrical internal alkynes, terminal alkynes, ynamides or acetylenic amides) and various types of nitriles.^[80a] These metalated pyridines can either be hydrolysed or, more interestingly, be converted to useful functionalized pyridines by addition of diverse reagents like iodine or propargyl bromide.



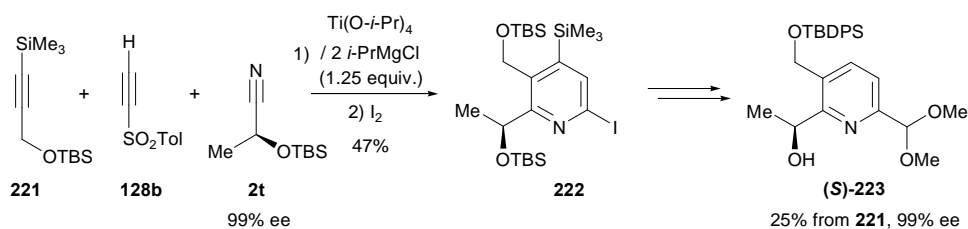
Scheme II-79: Examples of synthesis and conversion of metalated pyridines.

Although this method requires a stoichiometric amount of titanium, it has some interesting advantages: it allows not only the synthesis of pyridines but also of other *N*-heterocyclic products like pyrrolicarboxaldehydes **220** substituted by three other different groups. They can be synthesized via a regioselective manner from two different nitriles and an alkyne.



Scheme II-80: Examples of synthesis a pyrrolicarboxaldehyde.

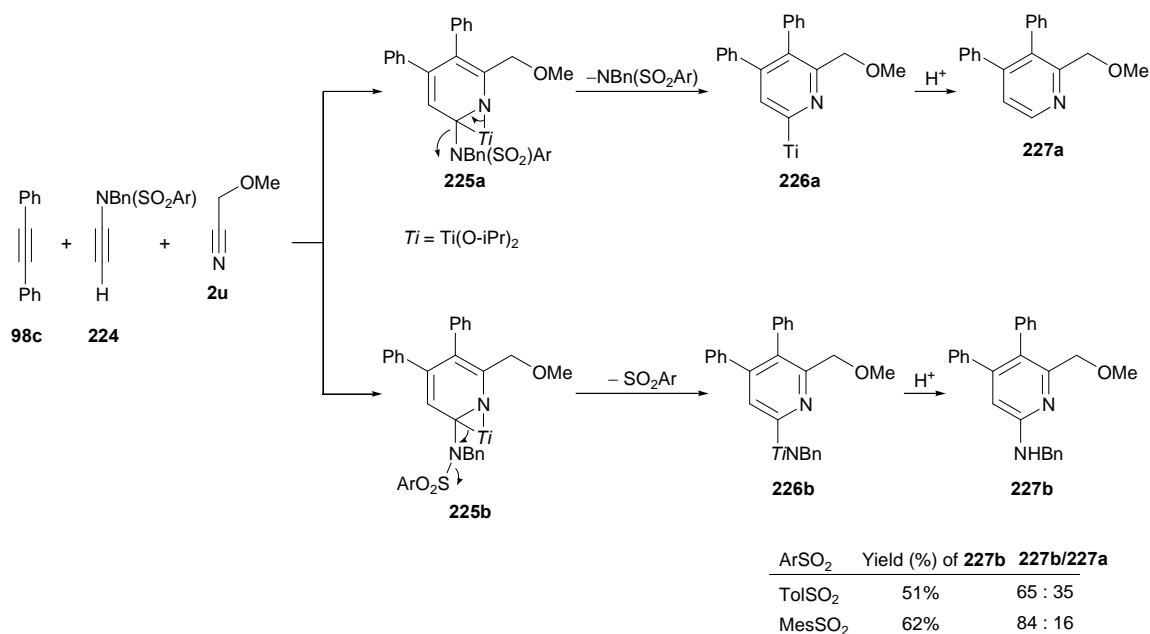
However, the nitriles have to be functionalized in the α -position with an alkoxy group or a chlorine atom.^[80b] The reaction conditions were also suitable for reactions with enantiopure nitriles with conservation of the chirality as demonstrated by the key-step of the synthesis of **223**, a possible intermediate for the total synthesis of *Cyclothiazomin*^[80a]



Scheme II-81: Synthesis of the pyridine (*S*)-**223**.

In their work on the synthesis of metalated pyridines catalyzed by a titanium(II) alkoxyde^[80b], Sato and co-workers observed that ynamides were suitable partners for the [2+2+2] cycloaddition with another alkyne and a nitrile. Additionally, they observed that in this case two products were obtained: the desired pyridine **227a** and the 2-aminopyridine **227b** coming

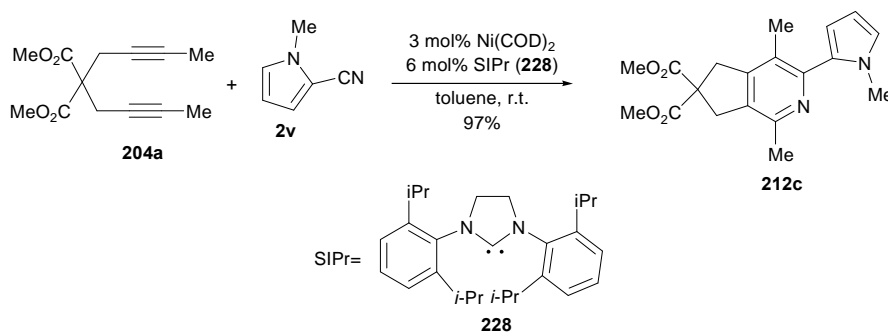
from the elimination of the sulfonyl group. The product ratio depends on the protecting group of the ynamide, a bulky sulfonyl group favors the formation of the 2-aminopyridine **227b**.



Scheme II-82: Synthesis of pyridines from an ynamide, an alkyne and a nitrile.

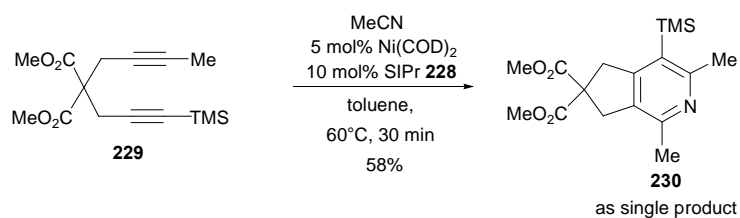
- Nickel-based catalysts

Nickel complexes also catalyze cycloadditions of diynes and nitriles as demonstrated by Louie and co-workers^[67] who used *N*-heterocyclic carbene ligands like **250** with nickel complexes for the trimerization of tethered diynes with nitriles at room temperature or gentle heating (60°C). These catalytic systems gave moderate to excellent yields as demonstrated by the trimerization of the diyne **204a** with 2-cyanopyrrole **2v** to give the pyridine **232c** in a yield of 97%. This method uses air-stable and readily available precursors and is applicable to diynes possessing symmetrical or unsymmetrical substitution patterns. A wide range of nitriles like electron-rich and electron-deficient (hetero)arylnitriles or alkylnitriles can be used as well as sterically hindered nitriles.



Scheme II-83: Nickel-catalyzed cycloaddition of diynes to nitriles.

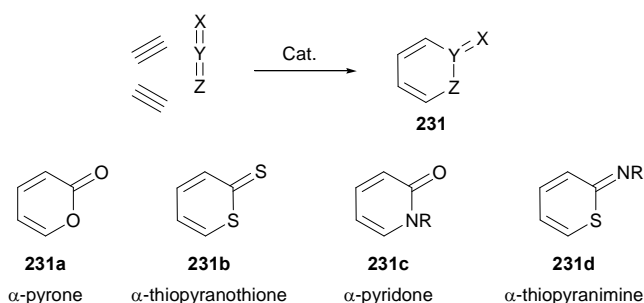
Furthermore, an excellent regioselectivity can be achieved with unsymmetrical diynes when the substituents differ largely in size, e.g. in the diene **229**.



Scheme II-84: Nickel-catalyzed cycloaddition of unsymmetrical diynes to nitriles.

II.3.2. [2+2+2] Cycloaddition of alkynes with heterocumulenes

The [2+2+2] cycloaddition of alkynes with diverse heterocumulenes is an attractive strategy for the synthesis of various heterocycles. For example, reactions with carbon dioxide or carbon disulfide give access to α -pyrone or α -thiopyranothione derivatives **231a-b**. Likewise, reactions with isocyanates lead generally to 2-pyridones **231c** whereas reactions with isothiocyanates give typically α -thiopyranimines **231d**.

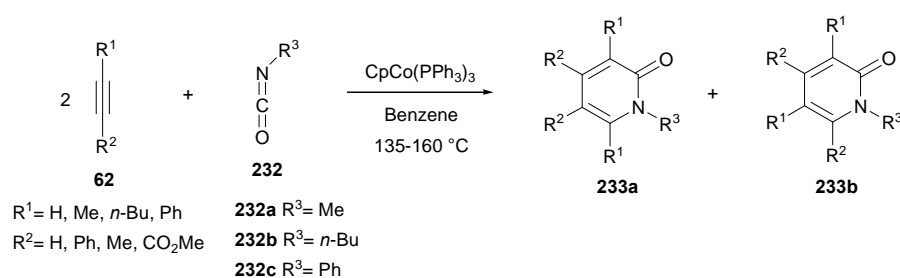


Scheme II-85: Synthesis of heterocycles via [2+2+2] cycloaddition of alkynes with heterocumulenes.

II.3.2.1. Cycloadditions with isocyanates

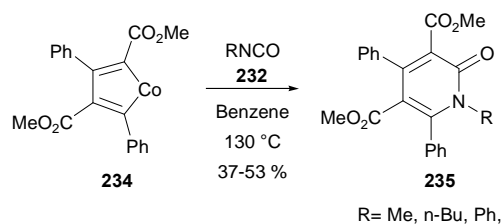
The [2+2+2] cycloaddition of alkynes with isocyanates represents a straightforward and efficient strategy for the synthesis of 2-oxo-1,2-dihydropyridines (2-pyridones). These 2-pyridones are receiving increasing interest as they show a broad variety of biological and pharmacological properties including anticancer, antiviral or antibacterial activity.^[81]

The first example for the synthesis of 2-pyridones via [2+2+2] cycloadditions of alkynes with isocyanates was reported by Yamazaki and Hong.^[82]



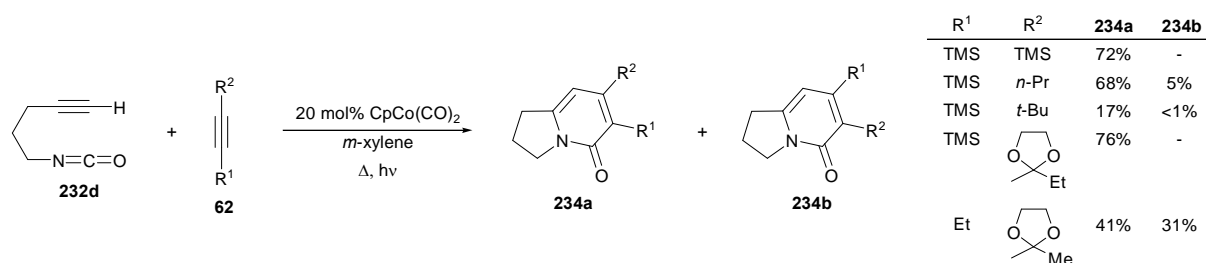
Scheme II-86: First synthesis of 2-pyridones via [2+2+2] cycloadditions with isocyanates.

They performed also the reaction from various cobaltacyclopentadienes. However, the reaction requires a temperature of 130 °C to be completed and an equimolar amount of cobalt catalyst. The reaction is regioselective when an unsymmetrical cobaltacyclopentadiene like **234** is employed to give the pyridone **235** as unique regioisomer.



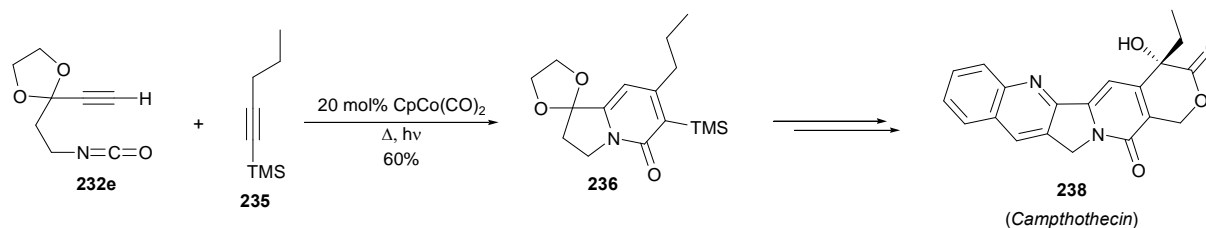
Scheme II-87: cycloaddition of an unsymmetrical cobaltacyclopentadiene with isocyanates.

An intramolecular variant was developed by Vollhardt and co-workers.^[83] The reaction, catalyzed by CpCo(CO)₂ in boiling *m*-xylene under irradiation, gave only disappointing results when tethered alkynes were reacted with isocyanates. Nevertheless, coupling of isocyanatopentyne **232d** with various internal alkynes **62** to 2,3-dihydro-5(1*H*)-indolizinones **234a-b** gave better yields.



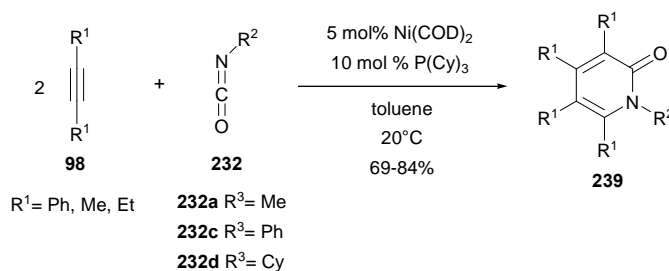
Scheme II-88: cycloaddition of isocyanatopentyne with internal mono-alkyne

This intramolecular approach was successfully applied to the synthesis of the tumor agent *Camptothecin* **238**.



Scheme II-89: Cobalt-catalyzed [2+2+2] cycloaddition as key-step in the synthesis of *Camptothecin*

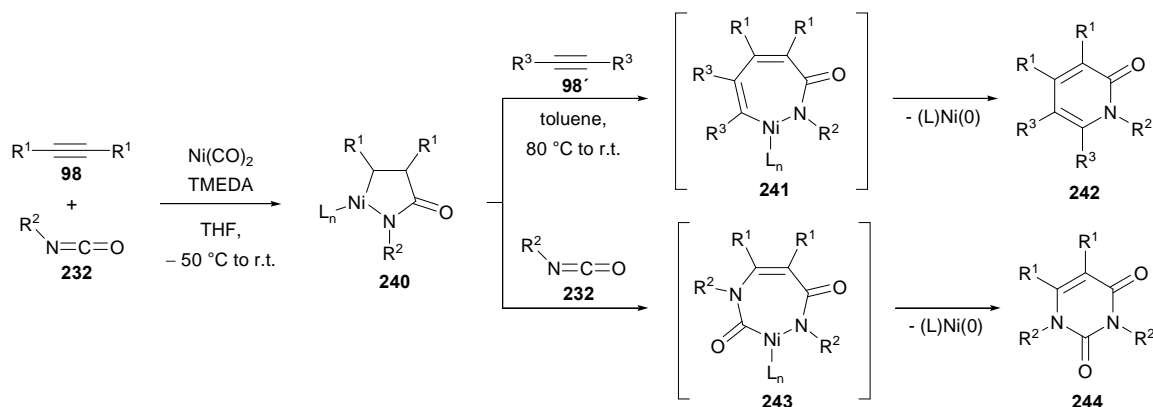
Few years after Yamazaki and Hong, Hoberg and Oster reported a nickel-catalyzed cycloaddition of alkynes and isocyanates.^[84] In contrast to the cobalt-catalyzed reaction, the reaction proceeds readily at ambient temperature with 5 mol% of the nickel catalyst (Ni(COD)₂/P(Cy)₃) to give the corresponding pyridones **239** in good yields.



Scheme II-90: Nickel-catalyzed [2+2+2] cycloaddition of internal alkynes with isocyanates.

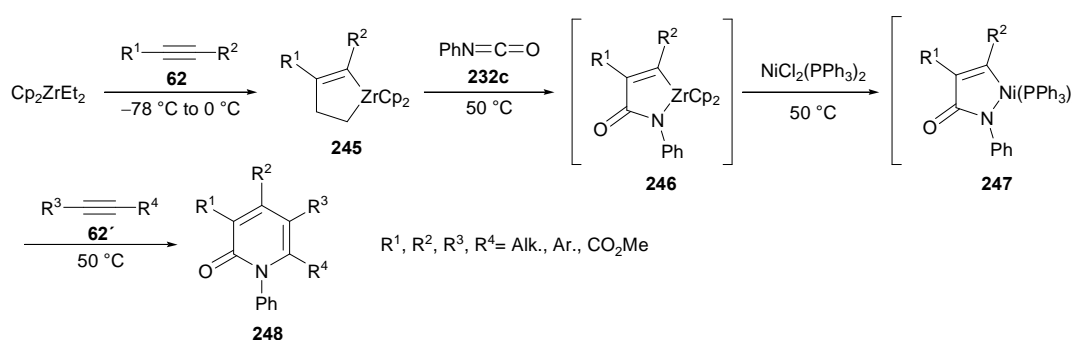
Mechanistic studies of the reaction showed clearly that the reaction starts with the formation of an azanickelacyclopentenone **240** which further reacts with a second alkyne to form an azanickelaheptacycle **241**.^[84b-d] Reductive elimination of the nickel center leads finally to the pyridones **242**. The chemoselectivity of the reaction can be tuned by selecting the reaction conditions. The use of strong basic and chelating ligands (tetramethylethylenediamine, 2,2'-bipyridine) allows even to isolate the intermediate azanickelacyclopentenones **240**. These can

react with a second alkyne or a second isocyanate to give the pyridones **242** or pyrimidinediones **244** respectively.



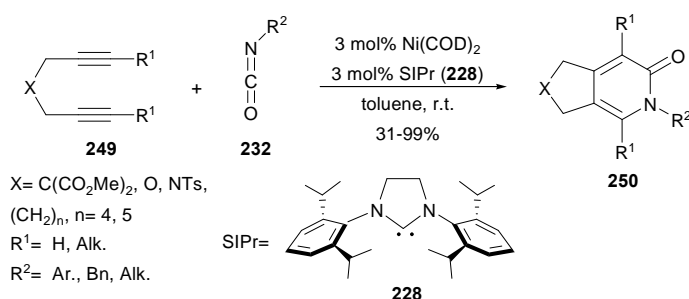
Scheme II-91: Reactivity of the nickelacyclopentenone with alkynes or isocyanates.

An analogous approach was developed by Takahashi and co-workers who synthesized first azazirconacycles from an alkyne and an isocyanates which reacts in presence of a nickel-catalyst in a second step with another alkyne.^[85] Though this method requires stoichiometric amounts of zirconium and nickel complexes, the advantage of this reaction is the possibility to synthesize fully substituted pyridones with an excellent regioselectivity. A simple choice of the sequence of introduction of the reactants to the reaction mixture determines the regioisomer obtained.



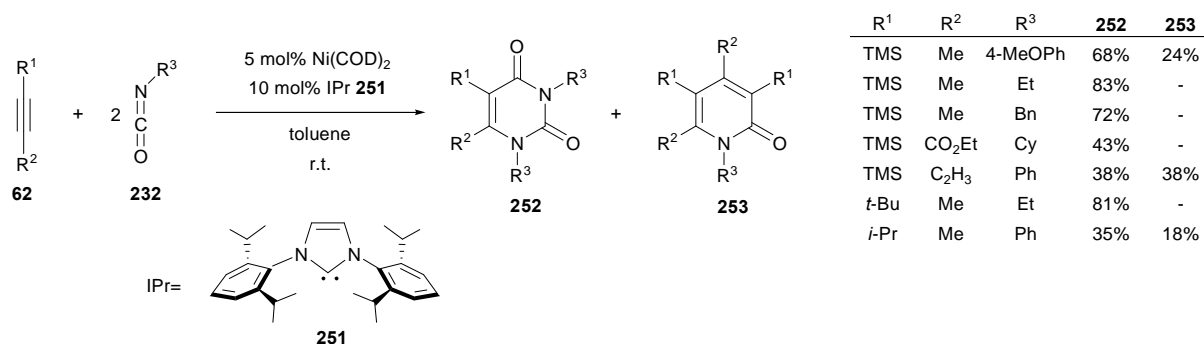
Scheme II-92: Synthesis of pyridone via azazirconacycles.

The nickel-catalyzed reaction was re-investigated later by Louie and co-workers.^[86a-c] A Nickel/*N*-heterocyclic carbene catalytic system was described to catalyse efficiently the cycloaddition of tethered alkynes with both aryl and alkyl isocyanates. The reaction works with terminal or internal alkynes and with differently tethered diynes.



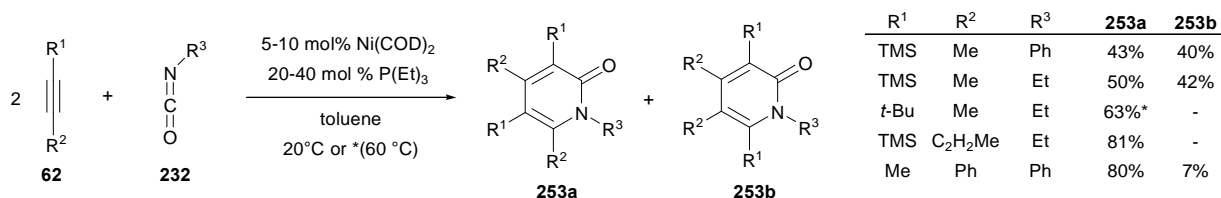
Scheme II-93: Nickel-catalyzed cycloaddition of tethered alkynes with isocyanates.

However, when this catalytic system was applied to asymmetrical substituted monoalkynes, the reaction did not lead to the expected pyridones **253** but to the pyrimidine-diones **252** as major products^[86b] This chemoselectivity of the reaction is emphasized when the alkynes possess bulky substituents (TMS, *t*-Bu).



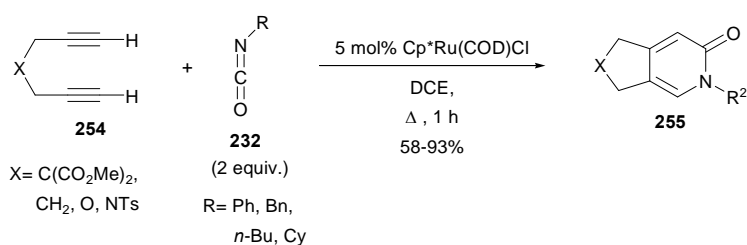
Scheme II-94: Nickel-catalyzed cycloaddition of an alkyne with two isocyanates.

Nevertheless, the pyridones **253a-b** could be obtained by switching the carbene ligand **251** by triethylphosphine.^[86c]



Scheme II-95: Nickel-catalyzed cycloaddition of asymmetrical monoalkynes with isocyanates.

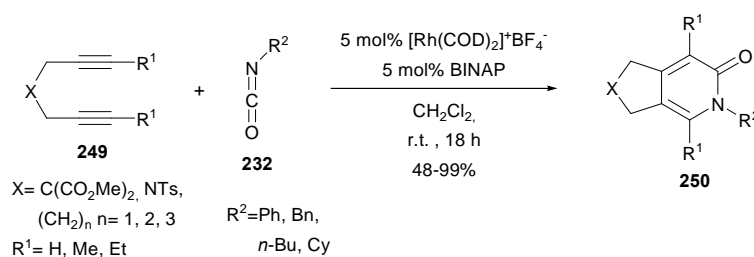
Yamamoto and co-workers applied successfully their previously described ruthenium-catalyzed synthesis of bicyclic pyridines to the synthesis of bicyclic pyridones by replacing the nitriles by isocyanates.^[87]



Scheme II-96: Ruthenium-catalyzed [2+2+2] cycloaddition of tethered alkynes with isocyanates.

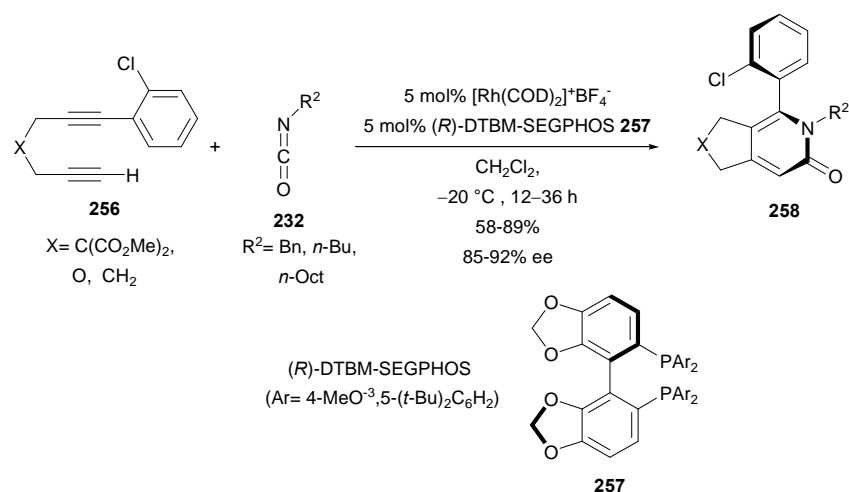
Several types of isocyanates (alkyl, (het)aryl) underwent the cycloaddition in good to excellent yields. The reaction requires tethered diynes but allows a multitude of connecting units.

Tanaka and co-workers showed that the reaction is also catalyzed by rhodium complexes, however reactions with terminal alkynes remained disappointing.^[88] In this case, different isomers were obtained in low yields depending on the substitution pattern of the alkyne. Very interesting results were obtained when tethered alkynes were used. The reaction can be applied to internal alkynes as well as terminal alkynes and accept differently substituted isocyanates.



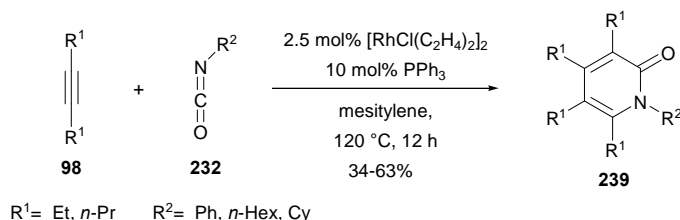
Scheme II-97: Rhodium-catalyzed [2+2+2] cycloaddition of tethered alkynes with isocyanates.

This method was successfully applied to the enantioselective synthesis of axially chiral 2-pyridones when 2-chlorophenyl-substituted alkynes **256** were used. The chiral 2-pyridones **258** were obtained in good yields and high enantiomeric excesses.



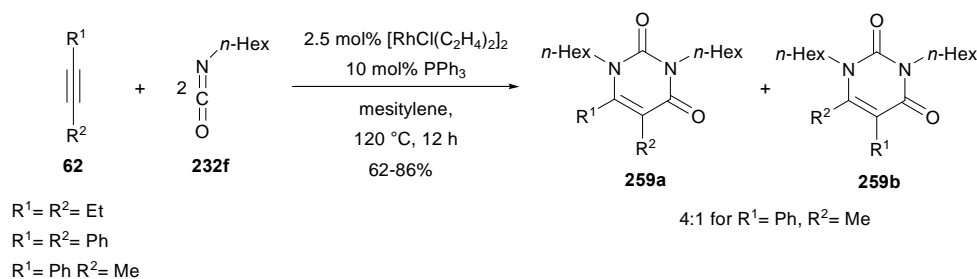
Scheme II-98: Enantioselective rhodium-catalyzed [2+2+2] cycloaddition of unsymmetrical tethered alkynes with isocyanates.

Kondo and co-workers developed a similar rhodium/phosphine-based catalytic system.^[89] The active catalytic complex formed from the neutral rhodium dimer $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ and triphenylphosphine is presumed to be “ $\text{RhCl}(\text{PPh}_3)_2$ ”. The reaction works without significant difference with alkyl- or aryl-substituted isocyanates to give the 2-pyridones **239** in moderate yields but gives no product when bulky substituents (*t*-butyl, adamantly) were used and was limited to a small range of internal alkynes.



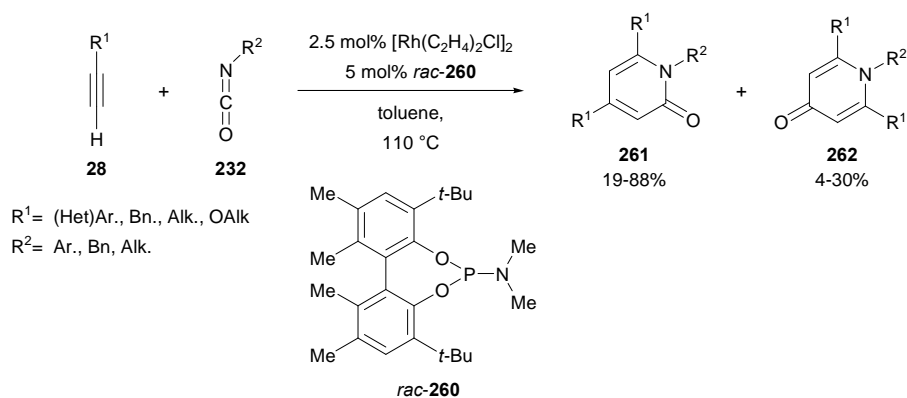
Scheme II-99: Rhodium-catalyzed [2+2+2] cycloaddition of monoalkynes with isocyanates.

Inverting the molar ratio of the alkynes and isocyanates to 1:2 resulted in the selective formation of pyrimidine-2,4-diones **259a-b**.



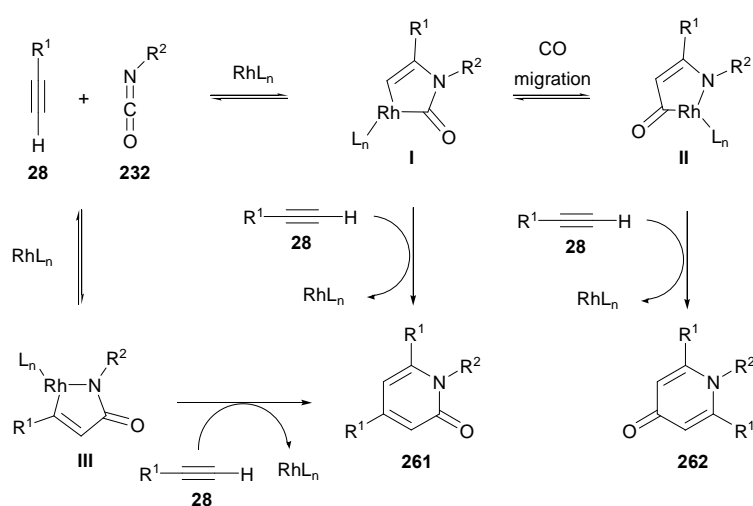
Scheme II-100: Rhodium-catalyzed cycloaddition of a monoalkyne with two isocyanates.

Rovis and co-workers solved very recently the problem of regioselectivity of the reaction with terminal monoalkynes by using another rhodium-based catalytic system.^[90] However, this rhodium-catalyzed cycloaddition remained limited to terminal alkynes. A wide range of isocyanates was tolerated, but unexpected 4-pyridones **262** appeared as minor products. However, this catalytic system was not suitable for tethered diynes: unseparable mixtures or no product at all were obtained.



Scheme II-101: Rhodium-catalyzed [2+2+2] cycloaddition of terminal alkynes with isocyanates.

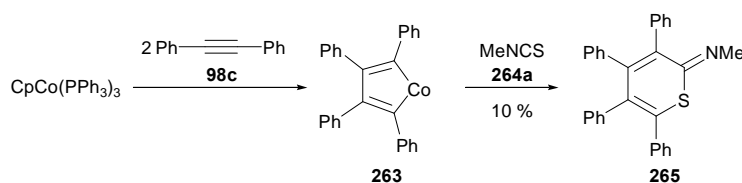
The formation of the 4-pyridone results presumably from the migration of the carbonyl from the azarhodacyclopentadiene **I** to **II**. The ratio between the two isomers is mainly controlled by the character of the isocyanate used: increasing the electron-withdrawing character of this substituent increases the amount of the minor isomer **262**.



Scheme II-102: Possible mechanisms for the rhodium-catalyzed [2+2+2] cycloaddition of terminal alkynes with isocyanates.

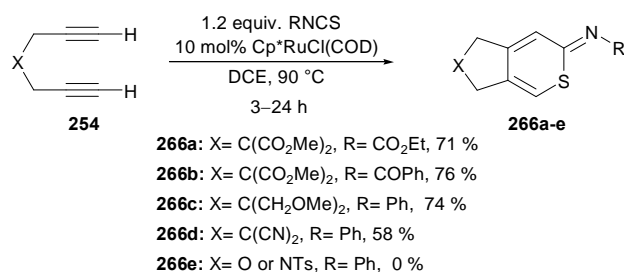
II.3.2.2. Cycloadditions with isothiocyanates

In contrast to isocyanates, cycloadditions with isothiocyanates do not lead to the corresponding thiopyridones but typically to thiopyranimines. The intermediate metallacycles react preferentially with the C–S double bond as the sulfur atom strongly coordinates to the metal center. The first example of such a reaction was reported by Wakatsuki and Yamazaki in 1973. The cobalt-mediated cycloaddition of the cobaltacycle **263** with methylisothiocyanate gave a small amount of the thiopyranimine **265**.^[91]



Scheme II-103: First synthesis of a thiopyranimine via a [2+2+2] cycloaddition with an isothiocyanate.

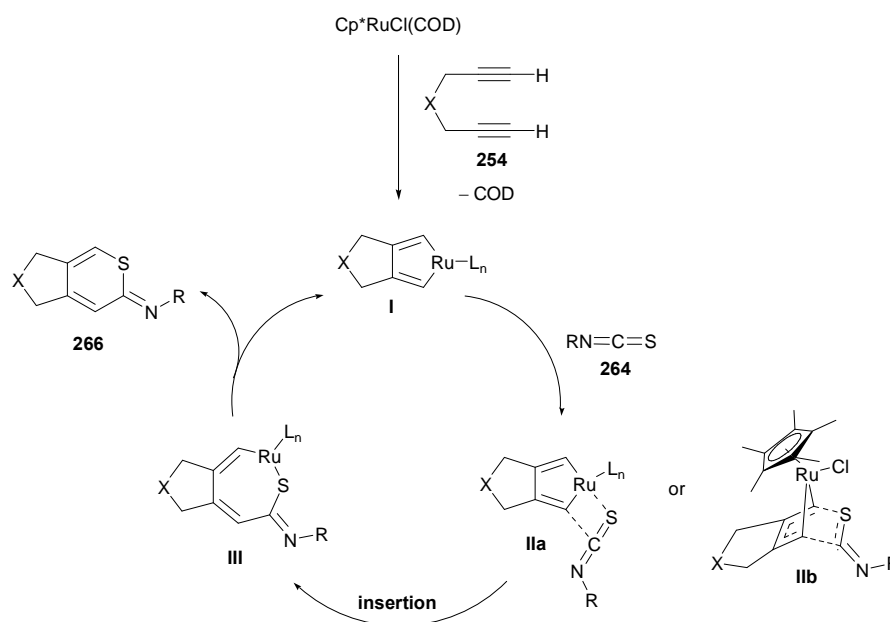
The reaction was later intensively investigated by Yamamoto and co-workers who synthesized different bicyclic thiopyranimines **266a-e** via this approach.^[92]



Scheme II-104: Ruthenium-catalyzed synthesis of bicyclic thiopyranimines.

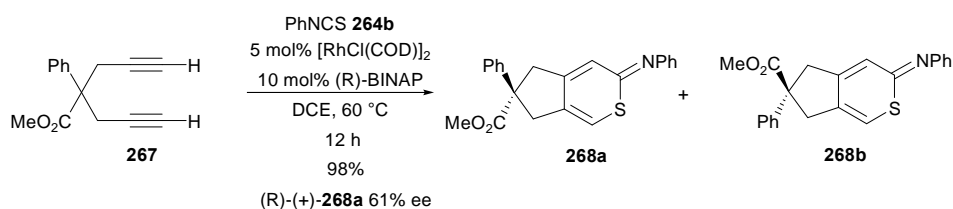
The chemoselectivity of the reaction is good since only a slight excess of isothiocyanates is sufficient to give the desired thiopyranimines as major product together with a small amount of the dimer as by-product. The reaction works with differently substituted isothiocyanates, although alkyl-substituted isothiocyanates give lower yields as aryl- or carbonyl- substituted ones. Furthermore, the presence of a tertiary center at the 4-position of the alkyne was crucial for the reaction since no reaction was observed as the carbon atom was replaced by an oxygen or a nitrogen. The reaction was however limited to symmetric terminal alkynes. The suggested mechanism for the reaction starts with the synthesis of the ruthenacyclopentadiene **I**. Coordination of the sulfur atom to the ruthenium facilitates the insertion of the C=S double

bond to form the seven-membered cycle **III** which gives the thiopyranimine **266** after reductive elimination of the metal center. An alternative mechanism could involve a Diels-Alder reaction of the ruthenacyclopentadiene **I** with the isothiocyanate via **IIIb**.



Scheme II-105: Plausible mechanism for the ruthenium-catalyzed formation of thiopyranimines.

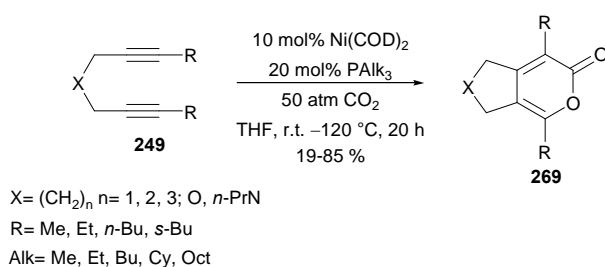
A few years later, Tanaka and co-workers reported a rhodium-catalyzed variant of this reaction.^[93] A screening of different rhodium and iridium catalysts showed that the active species formed *in situ* from the neutral rhodium dimer $[\text{RhCl}(\text{COD})]_2$ and BINAP efficiently promotes the reaction. This catalytic system was used for the synthesis of several thiopyranimines. Under similar conditions, but with the advantage of lower catalyst loadings (5 mol% $[\text{Rh}]$) the yields obtained are slightly higher as in Yamamoto's ruthenium-catalyzed reaction. Tanaka reported also an asymmetric variant of the reaction by addition of the diyne **297** to phenylisothiocyanate yielding the thiopyranimines **298a-b** with a good enantiomeric excess.



Scheme II-106: Enantioselective rhodium-catalyzed synthesis of bicyclic thiopyranimines.

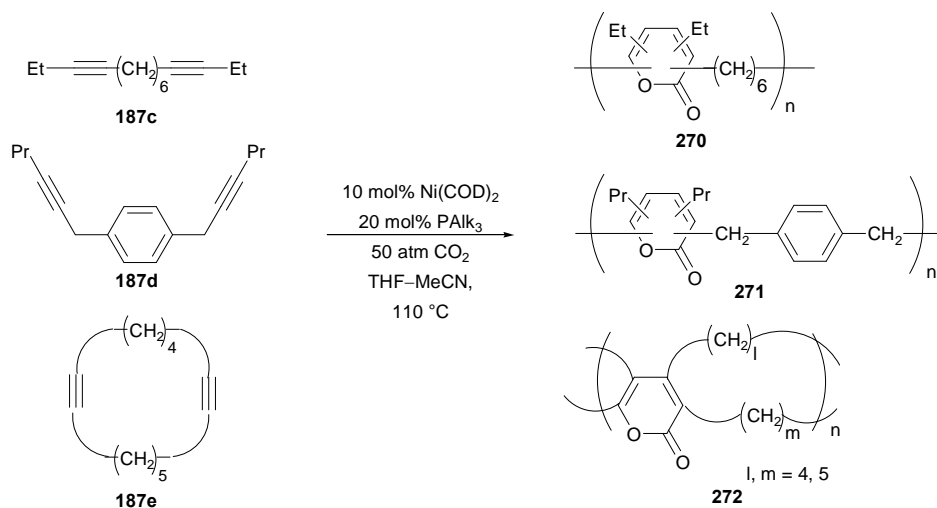
II.3.2.3. Cycloadditions with carbon dioxide

[2+2+2] cycloadditions of alkynes with CO₂ are not well documented as a consequence of the low reactivity of the C=O double bonds towards the reaction. Inoue and co-workers described first in 1977 a nickel-based catalytic systems but the reaction required harsh conditions of temperature and pressure of carbon dioxide (120 °C, 50 atm CO₂) in addition to a small range of suitable substrates.^[94] A decade later, Tsuda and co-workers described a Ni(COD)₂/trialkylphosphine catalytic system for the cycloaddition of CO₂ to tethered alkynes.^[95] However, the reaction was restricted to symmetrical, alkyl substituted alkynes **249**.



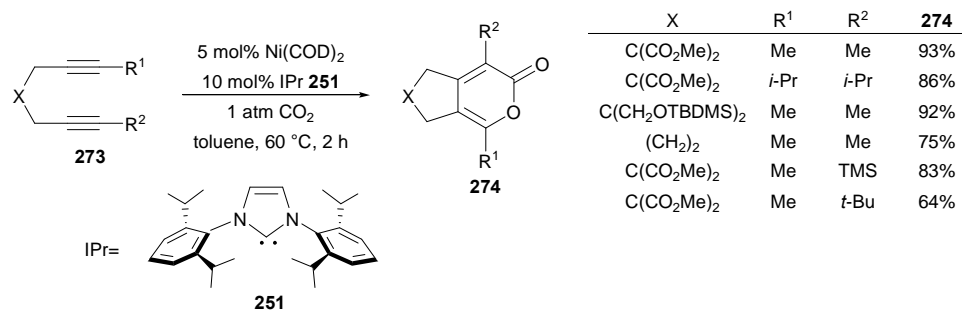
Scheme II-107: Nickel-catalyzed synthesis of α -pyrones.

This strategy was successfully applied to the synthesis of novel soluble ladder polymers with different patterns.^[95c]



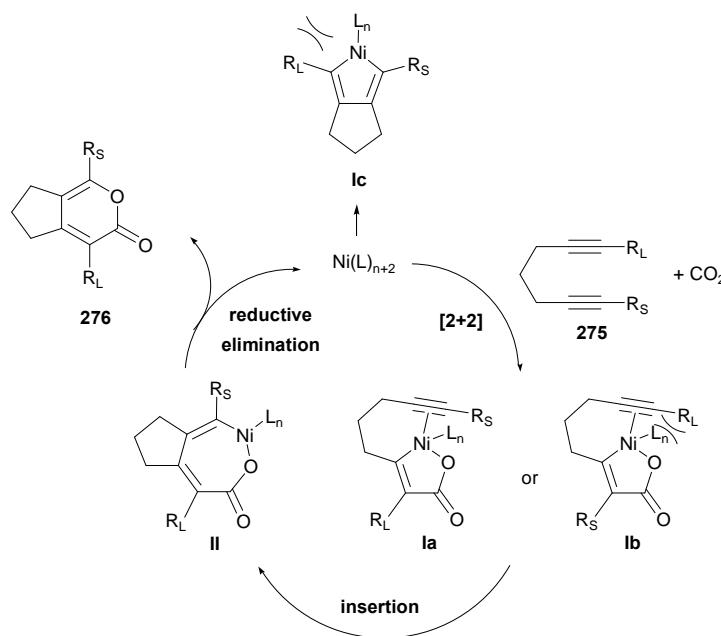
Scheme II-108: Nickel-catalyzed synthesis of a ladder polymer with an α -pyrone unit.

Louie and co-workers recently improved the methodology by using the imidazolidene-based ligand IPr **251** that allows to use milder conditions.^[96] The reaction proceeds rapidly in toluene at 60 °C with 5 mol% of Ni(COD)₂ and 10 mol% of the ligand.



Scheme II-109: Nickel-catalyzed synthesis of pyranones.

The mechanism of the reaction is thought to differ from the general pathway for the [2+2+2] cycloaddition of alkynes with carbon-heteroatom multiple bonds as previously described. As earlier reported by the mechanistic study of Hoberg^[84b], the reaction would start in this case from the initial cycloaddition of the carbon dioxide with one alkyne to form the nickelacycle **Ia** or **Ib**. Coordination of the second alkyne and its subsequent insertion gives the seven-member nickelacycle **II**, which, after reductive elimination leads to the corresponding pyranones **276**.

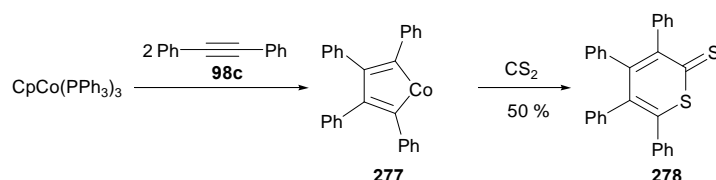


Scheme II-110: Plausible mechanism for the nickel-catalyzed formation of pyranone.

Among the two possible intermediate nickelacycles **Ia-b**, the one resulting from the cycloaddition of the smallest alkynyl unit and CO₂ (**Ib**) is thought to be disfavoured. The reason is attributed to the steric hindrance between the ligand and the substituent on the second alkyne that inhibits the coordination of the latter to the nickel centre. This mechanism would explain the excellent regioselectivity observed in the case of bulky substituents where only one isomer is obtained.

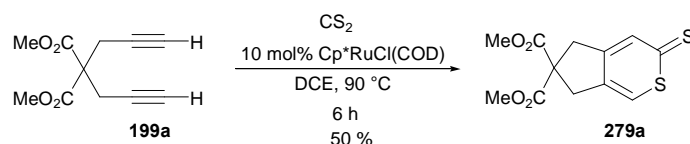
II.3.2.4. Cycloadditions with carbon disulfide

Similarly to cycloadditions with CO₂, the use of CS₂ as cycloaddition partner has been scarcely described. The first example comes from the works of Wakatsuki and Yamazaki in 1973 with the synthesis of the thiopyranothione **278**.^[91] CS₂ adds to the cobaltacyclopentadiene **277** formed from diphenylacetylene and the CpCo(PPh₃)₃ catalyst.



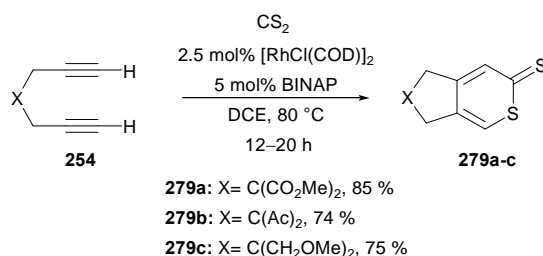
Scheme II-111: First synthesis of a thiopyranothione via a [2+2+2] cycloaddition with CS₂.

This cycloaddition was followed by rare other examples until that Yamamoto and co-workers applied the efficient Cp*RuCl(COD) catalyst to the synthesis of bicyclic thiopyranothiones like **279a**.^[92]



Scheme II-112: Ruthenium-catalyzed synthesis of a bicyclic thiopyranothione.

Similar results were recently reported by Tanaka and co-workers but using a rhodium-based catalyst.^[93] The reaction of various 1,6-diynes with carbon disulfide was catalyzed by a complex formed *in situ* from the rhodium dimer [RhCl(COD)]₂ and BINAP to give the resulting bicyclic thiopyranothiones **279a-c** in slightly higher yields (74-85%)

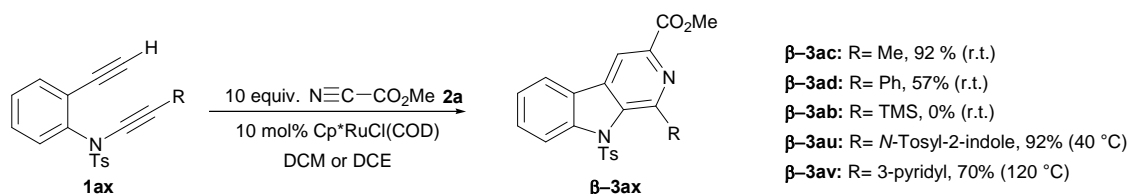


Scheme II-113: Rhodium-catalyzed synthesis of bicyclic thiopyranothiones.

III / RESULTS**III.1. [2+2+2] Cycloaddition with diynes**

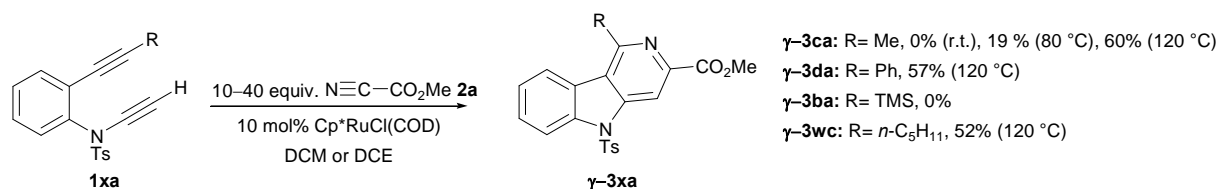
In a previous work in our group, it was demonstrated that the [2+2+2] cycloaddition of tethered alkynyl-ynamides (called “diynes” in the following work) with electron-deficient nitriles like methylcyanoformate was efficiently catalyzed by the Cp**RuCl(COD)* catalyst.^[3] The method was successfully applied to the synthesis of β- and γ-carbolines with excellent regioselectivities. The regioselectivity of the reaction was shown to be controlled by the type of diynes (**1ax** or **1xa**) used:

- Cycloadditions with diynes having a substituted ynamide moiety **1ax** lead to the corresponding β-carbolines **β-3ax** as single products. The reaction proceeds readily at ambient temperature to give the β-carbolines in good to excellent yields.



Scheme III-1: Synthesis of β-carbolines via ruthenium-catalyzed [2+2+2] cycloaddition of a diyne with methylcyanoformate.^[3]

- On the other hand, γ-carbolines **γ-3xa** were obtained as single products when the cycloadditions were performed with diynes having a terminal ynamide moiety **1xa**. However, the reaction proved to be much more difficult. In this case, the reaction required a much higher reaction temperature to give the corresponding γ-carbolines **γ-3xa** in satisfying yields.



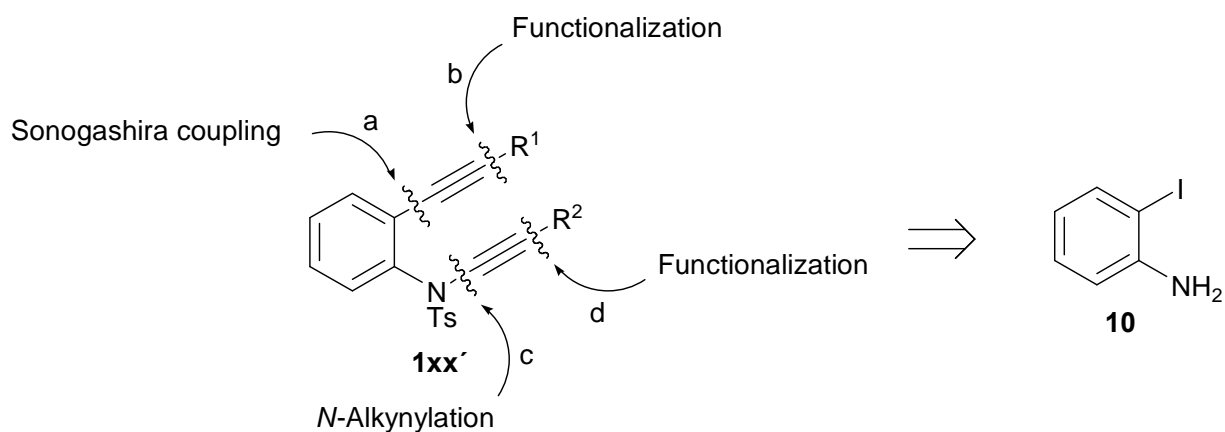
Scheme III-2: Synthesis of γ-carbolines via ruthenium-catalyzed [2+2+2] cycloaddition of a diyne with methylcyanoformate.^[3]

One objective of this work is to extend the reaction to the synthesis of a larger range of carbolines. For this purpose, the use of another catalytic system was envisaged. The main improvements of this catalytic system should lead to:

- the synthesis of γ -carbolines under milder conditions in satisfying yields,
- the synthesis of β -carbolines and γ -carbolines with the opposite regioselectivity,
- a larger scope of reactive nitriles,
- a broader variability of substituents on the diyne

III.1.1. Synthesis of diynes

A short retro-synthetic study of the diyne **1xx'** led to the idea that various diynes could be obtained from the derivatization of 2-iodoaniline **10**.

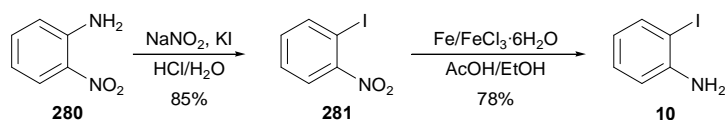


Scheme III-3: Retro-synthetic analysis of diynes **1xx'**.

This approach has been successfully developed previously in our group.^{[2],[3]} The *N*-ethynylation with the iodonium salt methodology proved to be well-adapted to phenyl-substituted sulfonamides. One aim of the present study was to extend this methodology to the synthesis of a larger library of diynes.

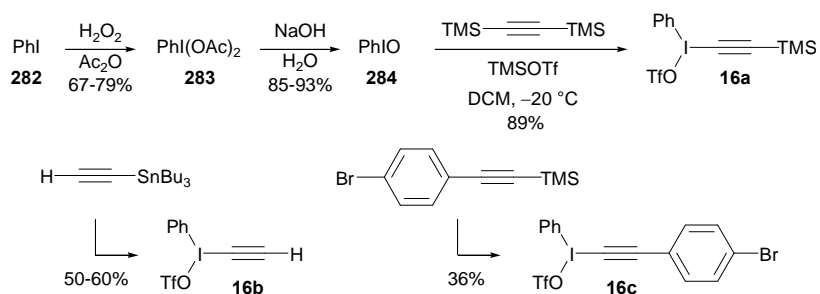
III.1.1.1. Synthesis of the precursors

2-Iodoaniline **10** is commercially available, but can also be synthesized in a large scale (100 g) in two steps from 2-nitroaniline **280**^[97]:



Scheme III-4: Synthesis of the 2-iodoaniline from 2-nitroaniline.

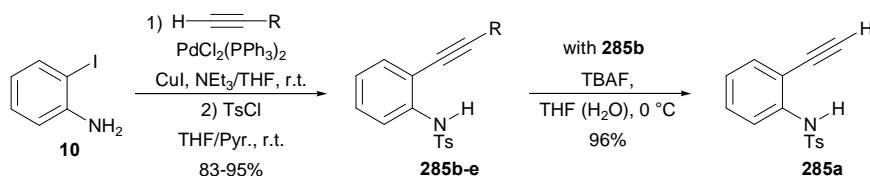
The required iodonium salts were prepared via oxidation of iodobenzene according to the Varvoglis' procedure^[98]:



Scheme III-5: Synthesis of the iodonium salts.

III.1.1.2. Synthesis of diynes with a terminal ynamide moiety

A good and general method to synthesize diynes with a terminal ynamide moiety **1xa** is to start with a Sonogashira coupling with 2-iodoaniline **10** followed by tosylation of the amino group which affords the 2-alkynyl-*N*-tosylanilines **285b-e**. This sequence works generally in good to excellent yields at a multi-gram scale. Moreover, the products are typically air-stable, crystalline compounds which can be stored for a long time without any special conditions.



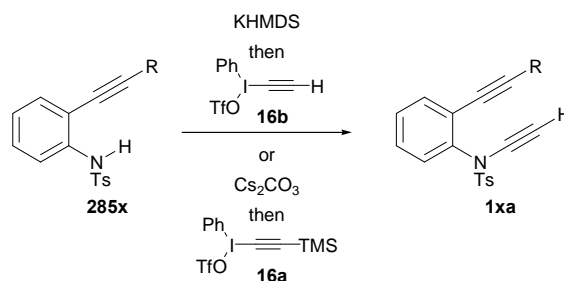
Scheme III-6: Synthesis of the sulfonamides **285a-e**.

Table III-1: Synthesis of the sulfonamides **285b-e**

Entry	Sulfonamide	R	yield ^a
1	285b	TMS	95%
2	285c	Me	90%
3	285d	Ph	92%
4	285e	<i>n</i> -Bu	83%

a) isolated yield

The next step, the *N*-ethynylation to the terminal ynamides **1xa** is performed by deprotonation of the sulfonamides **285b-e** by KHMDS followed by addition of the iodonium salt **16b**. The same result can be obtained by using the TMS-substituted iodonium salt **16a** but using Cs₂CO₃ as the base.



Scheme III-7: Synthesis of diyne via the method A.

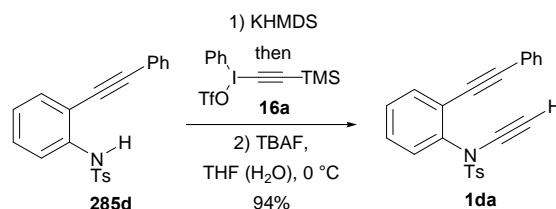
Table III-2: Synthesis of the diyne **1ba-ea**

Entry	Diyne	R	yield ^{a, b}
1	1ba	TMS	70%
2	1ca	Me	84%
3	1da	Ph	74%
4	1ea	<i>n</i> -Bu	82%

a) isolated yield; b) reaction with KHMDS as base and **16b**

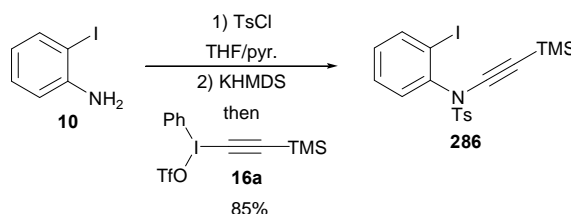
However, the reactions are often incomplete and give a difficultly separable mixture of the desired product and the unreacted sulfonamide. A convenient solution relies on performing the reaction in two steps: first *N*-alkynylation to the TMS-substituted ynamide followed by desilylation. This reaction sequence avoids the synthesis of the terminally substituted iodonium salts **16b** and so the use of the toxic tributylstannyl acetylene required for its

synthesis. Furthermore, reactions with the TMS-substituted iodonium salt **16a** work generally with a much better conversion of the sulfonamides, facilitating the purification of the product.



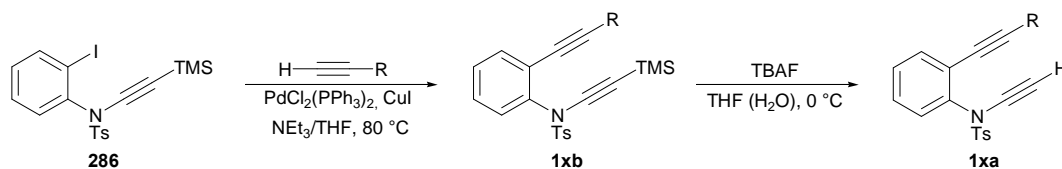
Scheme III-8: Alternative synthesis of the diyne **1da**.

Though this general method works efficiently, the three-step sequence reveals to be fastidious and time-requiring when a series of diynes is desired. In this case, two complementary methods exist to get a larger scope of diynes. The first alternative method relies on the synthesis of the ynamide **286** in two steps from 2-iodoaniline **10** (Method B).



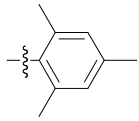
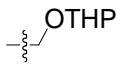

Scheme III-9: Synthesis of the ynamide **286**

The reaction sequence gives good yields and can be easily performed on a multi-gram scale. This ynamide offers an easy access to a large scope of diynes with a terminal ynamide moiety in a two-step sequence. The first step, a Sonogashira coupling of this ynamide with alkynes allows the synthesis of different diynes **1xb** which can be desilylated with TBAF in a second step to give the terminal ynamides **1xa**. Nevertheless, the Sonogashira reaction is limited to electron-rich alkyne or non-activated alkynes.



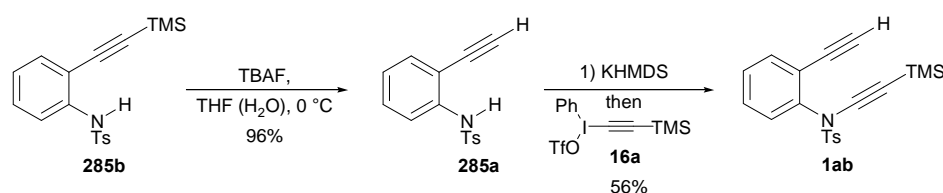
Scheme III-10: Synthesis of a diyne via the method B.

Table III-3: Synthesis of the diynes **1ea-ia**

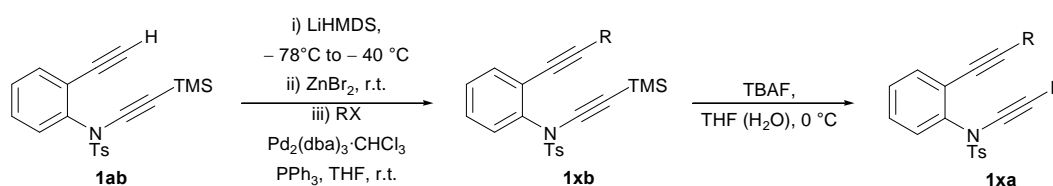
Entry	Diyne	R	yield Sonogashira ^{a)}	yield desilylation ^{a)}
1	1ea	<i>n</i> -Bu	83%	>34%
2	1fa	<i>t</i> -Bu	99%	64
3	1ga		95%	65%
4	1ha		56%	82%
5	1ia		0%	-

^{a)} isolated yield

The other alternative method relies on a functionalization-desilylation sequence of the diyne **1ab** (method C) which can be synthesized from **285b**.

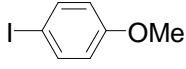
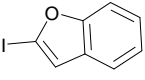
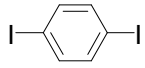
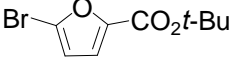
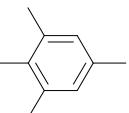
Scheme III-11: Synthesis of diynes **1ab**.

The first step of functionalization can be performed via a Negishi coupling of the diyne **1ab** with a halogeno arene to give the disubstituted diynes **1xb** which can be then desilylated to the diynes **1xa**.



Scheme III-12: Synthesis of diynes via the method C.

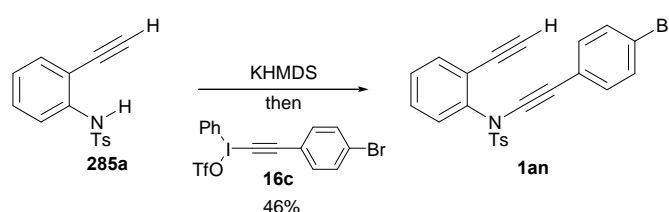
Table III-4: Synthesis of diynes **1xa** via method C

Entry	Diyne	RX	Yield Negishi ^a	Yield desilylation ^a
1	1ja		35%	-
2	1ka		87%	83%
3	1la		81% ^b	>51% ^b
4	1ma		85%	95%
5	1ga		0%	-

a) isolated yield; b) based on the twofold reaction

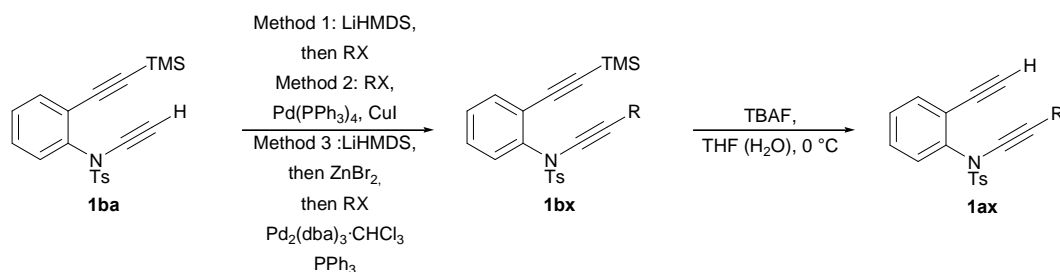
III.1.1.3. Synthesis of diynes with a terminal alkyne moiety

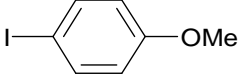
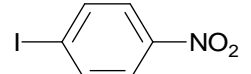
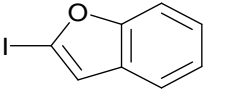
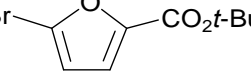
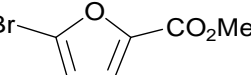
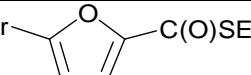
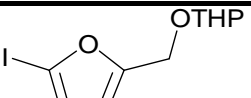
A general method of synthesis of diynes with a terminal ynamide consists in the application of the method A (*N*-alkynylation with iodonium salts) to the 2-ethynyl-*N*-tosylaniline **285a**.



Scheme III-13: Example of synthesis of a diyne **1ax** via the method A.

However, the small scope of alkynyliodonium salts available for the *N*-alkynylation reaction limits the use of this methodology. Alternatively, this kind of diynes can be obtained in a two-step sequence from the diyne **1ba** (Method C). As described in the introduction, the ynamide moiety of the diyne **1ba** can be functionalized either via nucleophilic substitution or by a palladium-catalyzed cross-coupling with (hetero)arenes (Sonogashira, Negishi). Application of these functionalization procedures to the diyne **1ba** allows the synthesis of diynes **1bx**. Desilylation of these diynes afford the desired diynes with one terminal alkyne moiety **1ax**.

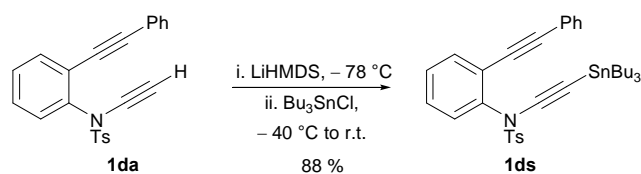
Scheme III-14: Synthesis of diynes **1ax** via the method C.Table II-5: Synthesis of diynes **1ax**

Entry	Diyne	RX	Method	Yield functionalization ^a	Yield desilylation ^a
1	1ac	MeI	1	91%	68%
2	1ad	PhI	2	63%	97%
3	1aj		3	83%	-
4	1ao		3	71%	-
5	1ak		3	85%	79%
6	1am		3	70-84% ^b	92%
7	1ap		3	78%	80%
8	1aq		3	70%	88%
9	1ar		3	34-56% ^b	77-86% ^b

a) isolated yield; b) a variable amount of intramolecular cycloaddition product was obtained as by-product

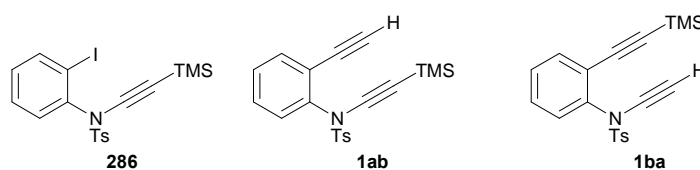
III.1.1.4. Synthesis of disubstituted diynes

Though numerous possibilities exist for the synthesis of disubstituted diynes, it is often more convenient to synthesize in a first part the diynes with a terminal ynamide moiety **1xa** according to one of the aforementioned methods followed by the functionalization of the ynamide moiety in a second part.



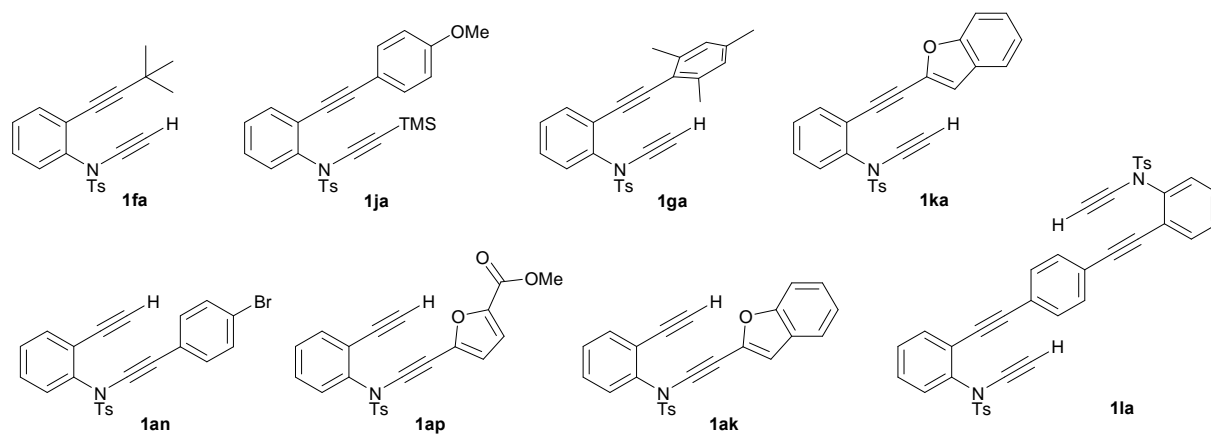
Scheme III-15: Example of synthesis of a disubstituted diyne.

To summarize, variously substituted diynes can be synthesized according to several complementary methods. Furthermore, the synthesis on a multi-gram scale of the three ynamides **286**, **1ab** and **1ba** is notably highly relevant since they offer a rapid access to a multitude of diynes.



Scheme III-16: Three strategic ynamides for the synthesis of a wide library of diynes.

Use of the different methods of synthesis of diynes during this study allowed notably the synthesis of the following unprecedented (bis)diynes*:

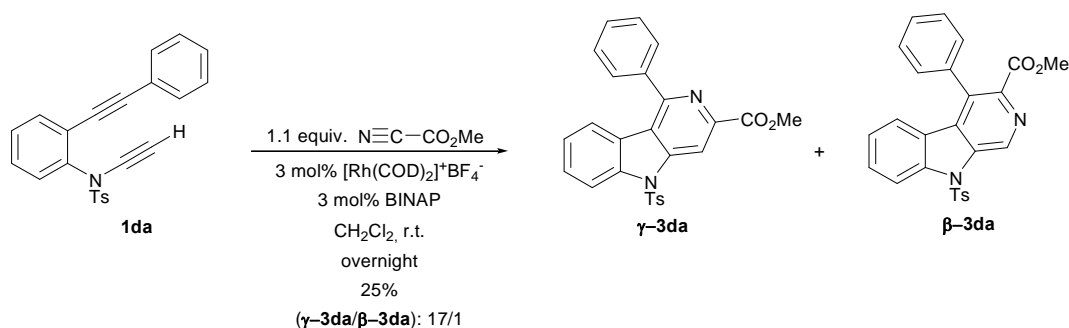


Scheme III-17: New diynes synthesized during this study.

* Beilstein and SciFinder researches gave no hits for these diynes

III.1.2. [2+2+2] Cycloaddition with nitriles: synthesis of γ - and β -carbolines

During the overview of the different catalytic systems reported to catalyze [2+2+2] cycloadditions, we got inspired by the recent works of Tanaka and co-workers. They reported rhodium-catalyzed [2+2+2] cycloadditions of alkynes with different types of cycloaddition partners.^[79a] Among them, the synthesis of pyridine rings via [2+2+2] cycloadditions of two alkynes with a nitrile was described to proceed efficiently under mild conditions if $[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-/\text{BINAP}$ is used as a catalytic system.^[79c] Attracted by these results, this catalyst was selected for a test reaction with our diyne substrates. Fortunately, the first experiment with the model diyne **1da** was promising since the desired reaction proceeded smoothly at room temperature. Addition of a mixture of the model diyne and the nitrile to the catalyst solution gave a mixture of the two carbolines γ -**3da** and β -**4da** together with some unreacted diyne. After purification by column chromatography on silica gel, a mixture of carbolines with a yield of 25% and a ratio γ : β of 17/1 was isolated.



Scheme III-18: Model [2+2+2] cycloaddition of a diyne with a nitrile.

The assignment of the main isomer to be the γ -carboline was easily ascertained by $^1\text{H-NMR}$ spectroscopy of the product mixture. The proton of the pyridine ring of the γ -carboline gives a characteristic singlet at 9.09 ppm whereas the pyridinyl proton of the β -carboline gives a signal at 9.74 ppm.^[3] Even the methyl signals of the tosyl and of the ester groups of both carbolines are well separated.

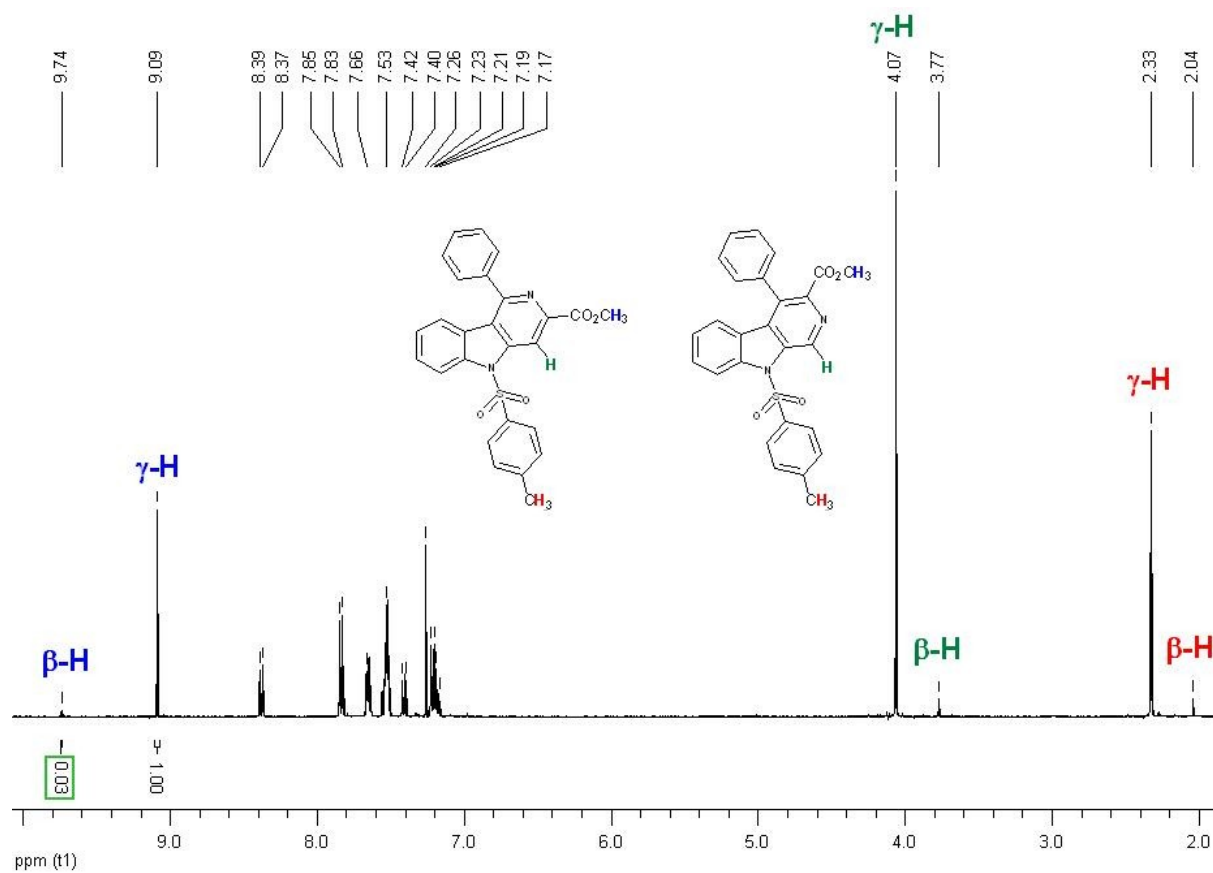


Figure III-1: $^1\text{H-NMR}$ spectrum of a mixture of β - and γ -carbolines and characteristic shifts.

Encouraged by this positive result, it was decided to study this rhodium-catalyzed [2+2+2] cycloaddition more in details.

III.1.2.1. Optimization of the reaction

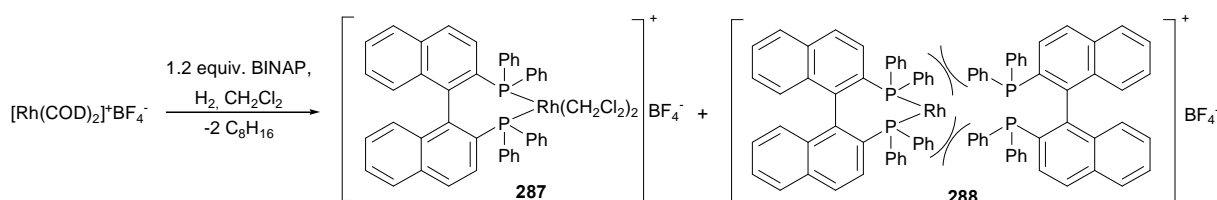
Increasing the load of catalyst to 5 mol%*, the amount of nitrile to 10 equivalents and the reaction time to three days led to a small increase of the total yield but also to a small decrease of the regioselectivity (entry 2). Doubling the catalyst loading to 10 mol% increased the yield up to 48% (entry 4). Moreover, changing the sequence of addition of the cycloaddition partners showed that pre-mixing the nitrile and the catalyst before addition of the diyne had a negative influence on the regioselectivity (entry 2 and 3).

Table III-6: Study of the load of catalyst on the model reaction in CH₂Cl₂

Entry	Load Catalyst	Equiv. Nitrile	T (°C)	Time	Yield ^a	Ratio γ : β ^b
1	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 3 mol% / 3 mol%	1,1	r.t.	overnight	25%	1.00:0.06 (17/1)
2	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	10	r.t.	3 days	36%	1.00:0.11 (9/1)
3	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	10 ^c	r.t.	3 days	23%	1.00:0.31 (3/1)
4	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 10 mol% / 12 mol%	10	r.t.	3 days	54%	1.00:0.13 (12/1)

a) isolated yield (mixture of both isomers); b) determined by ¹H-NMR of the isolated product; c) the diyne was added to a mixture of the catalyst and nitrile

* from this point on, a small excess of BINAP (1.2 equivalent to rhodium catalyst) was used to ensure the complete formation of the presumed effective catalyst **287**. This small excess could lead to the formation of a Rh(BINAP)₂ complex **288**, but the potential steric hindrance between the two BINAP ligands let assume that this complex should unlikely be formed.



Scheme III-19: *in situ* formation of the presumed active catalyst **287**.

The reaction conditions were optimized by a study of the reaction temperature. An elevation of the reaction temperature to 40 °C led to an increase of the yield to 49% with a similar selectivity (entry 2). Further elevation of the reaction temperature resulted in even higher yields (60 °C – 67%, 80 °C – 68%), but led to a drop of the regioselectivity down to 4/1 at 80 °C (entry 4). Furthermore, a too high reaction temperature revealed to be negative for the reaction as observed when the reaction was conducted at 100 °C that is probably due to decomposition of the diyne.

Table III-7: Study of the reaction temperature on the model reaction

Entry	Load Catalyst	Equiv. Nitrile	T (°C)	Time	Yield ^a	Ratio γ : β ^b
1	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	10	r.t.	3 days	36%	1.00:0.11 (9/1)
2	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	10	40 °C	3 days	49%	1.00:0.08 (12/1)
3	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	10	60 °C	3 days	67%	1.00:0.20 (5/1)
4	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	10	80 °C	3 days	68%	1.00:0.25 (4/1)
5	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	10	100 °C	3 days	57%	1.00:0.23 (4/1)

a) isolated yield (mixture of both isomers); b) determined by ¹H-NMR of the isolated product

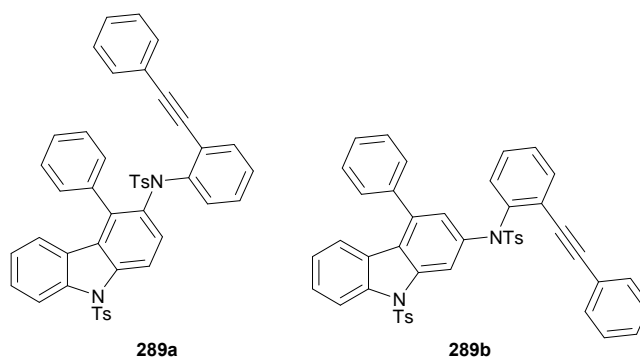
A screening of different solvents revealed that CH₂Cl₂ gives the highest isomer ratio (9/1 at r.t., entry 1) in a good total yield if the reaction is conducted at 60 °C but with a reduced regioselectivity. The use of a protic solvent like ethanol dramatically reduced the yield whereas the use of a non-polar solvent like toluene led to a loss of the regioselectivity to give the two carbolines in an equimolar ratio.

Table III-8: Study of the influence of the solvent on the [2+2+2] cycloaddition reaction

Entry	Solvent	T (°C)	Time	Yield ^a	Ratio γ : β ^b
1	DCM	r.t.	3 days	36%	1.00:0.11 (9/1)
2	DCM	60 °C	3 days	67%	1.00:0.20 (5/1)
3	THF	r.t.	3 days	69%	1.00:0.14 (7/1)
4	THF	60 °C	3 hours	72%	1.00:0.26 (4/1)
5	Toluene	r.t.	3 days	53%	1.00:1.09 (1/1)
6	Toluene	60 °C	3 hours	44%	1.00:0.93 (1/1)
7	EtOH	r.t.	3 days	11%	1.00:0.20 (5/1)
8	EtOH	60 °C	3 days	18%	1.00:0.16 (6/1)
9	Dioxane	60 °C	3 hours	68%	1.00:0.17 (6/1)
10	Acetonitrile	60 °C	3 hours	65%	1.00:0.42 (5/2)

a) isolated yield (mixture of both isomers); b) determined by ¹H-NMR of the crude product

The most interesting results come from the use THF or dioxane as solvent (Table III-8, entry 3 and 9). Total conversion of the diyne was observed after only three hours of reaction at 60 °C, giving a similar yield as in CH₂Cl₂ but in a slightly lower regioselectivity. However, this rapid consumption of the diyne is not only due to its reaction with the nitrile but also to its dimerization in the carbazoles **289a** and **289b**. A new product was isolated and assigned to be in fact a mixture of the dimers. IR and NMR analyses showed the absence of any terminal alkyne that indicates that these carbazoles result from the cycloaddition of one diyne moiety with the ynamide moiety of another diyne. This hypothesis was further supported by a FD-mass analysis of the product which gave a single peak at the mass corresponding to the double value of the molecular weight of the diyne. All these observation let us propose the two structures **289a** and **289b**. However, the complexity of the NMR spectra did not able us to say which carbazole is the major isomer.



Scheme III-20: Possible structures for the dimerization products of the model diyne.

Finally, reaction in acetonitrile led also to the desired carbolines with a similar total yield as in CH_2Cl_2 , however with a lower selectivity (Table III-8, entry 9).

As it was observed that the diyne is more prone to dimerization when THF is used as solvent, attempts to reduce the amount of this side-reaction by a slow addition of the diyne to a solution of catalyst and nitrile were considered. Intriguingly, this method resulted in a noticeable increase of the reaction time. In fact, only a small conversion was observed after three days in the case of a 2 hours addition and more than the half amount of diyne was recovered (Table III-9, entry 2). The conversion was even worse with a slower addition time of four hours where only one fourth of the starting material had reacted (Table III-9, entry 2). In both cases, no formation of the dimer was observed. This decrease of reactivity could be due to deactivation of the catalyst by complexation of the nitrile to the metal center. This would also explain why pre-mixing the nitrile and the catalyst before the addition of the diyne gave a worse result.

Table III-9: Study of the addition time on the model reaction

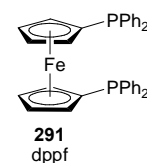
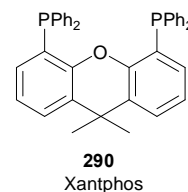
Entry	Addition time	Time ^a	Yield ^b	Ratio $\gamma:\beta^c$	Diyne recovered	Dimer
1	-	3 hours	72%	1.00:0.26 (4/1)	-	27%
2	2 hours	3 days	30%	1.00:0.12 (8/1)	57%	-
3	4 hours	3 days	20%	1.00:0.08 (12/1)	75%	-

a) reactions performed at 60 °C; b) isolated yield (mixture of both isomers); c) determined by ¹H-NMR of the crude product

Finally, a study of the ligand used showed that BINAP was essential for the reaction since no reaction occurred as BINAP was omitted (Table III-10, entry 1). The reaction worked also with dppf as ligand but with a much lower selectivity (Table 3, entry 4), whereas no reaction occurred when Xantphos was used (Table 3, entry 3).

Table III-10: Study of the ligand influence on the model reaction

Entry	Catalytic system ^a	Time	Yield ^b	Ratio γ : β ^c
1	$[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-$ 5 mol%	3 days	no reaction	-
2	$[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-/\text{BINAP}$ 5 mol% / 6 mol%	3 hours	72%	1.00:0.26 (4/1)
3	$[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-/\text{Xantphos}$ 5 mol% / 6 mol%	2 days	no reaction	-
4	$[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-/\text{dppf}$ 5 mol% / 6 mol%	overnight	36%	1.00:0.81 (5/4)



a) reactions in THF at 60 °C; b) isolated yield (mixture of both isomers);
c) determined by ¹H NMR of the crude product

Surprisingly, as we tried the neutral rhodium catalyst $[\text{RhCl}(\text{C}_8\text{H}_{14})_2]_2$, we observed a loss of the selectivity to give an almost equimolar mixture, however with a low yield (Table III-11, entry 1). The main reaction in this case is the dimerization of two diyne entities leading to a mixture of dimers as major products. A similar result in yield was obtained when THF was used as solvent but with a change of the regioselectivity was observed to give the β -isomer as main isomer. Switching from THF to toluene as solvent did not have any influence on the selectivity as observed in the case of the $[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-/\text{BINAP}$ complex.

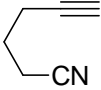
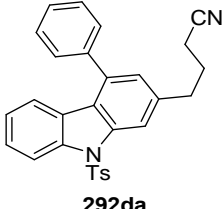
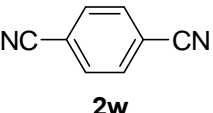
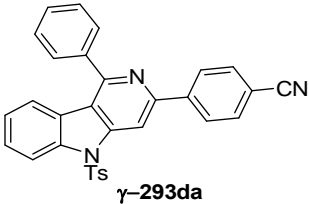
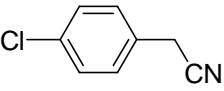
Table III-11: Study of the $[\text{RhCl}(\text{C}_8\text{H}_{14})_2]_2/2\text{BINAP}$ catalytic system

Entry	Catalytic system	Solvent	T (°C)	Time	Yield ^a	Ratio γ : β ^b	Dimer
1	$[\text{RhCl}(\text{C}_8\text{H}_{14})_2]_2/2\text{BINAP}$ 2.5 mol% / 6 mol%	DCM	60	3 days	24%	1.00:0.93 (1/1)	61%
2	$[\text{RhCl}(\text{C}_8\text{H}_{14})_2]_2/2\text{BINAP}$ 2.5 mol% / 6 mol%	THF	60	3 hours	21%	1.00:2.26 (1/2)	62%
3	$[\text{RhCl}(\text{C}_8\text{H}_{14})_2]_2/2\text{BINAP}$ 2.5 mol% / 6 mol%	Toluene	60	2 days	19%	1.00:2.04 (1/2)	71%

a) isolated yield (mixture of both isomers); b) determined by ¹H-NMR of the crude product

Finally, the cycloaddition of the model diyne **1da** with various nitriles was investigated.

Table III-12: Study of the reaction with other types of nitriles

Entry	Nitrile	Time	Major product	Yield ^{a, b}	Ratio γ : β ^c
1	Br-CN 2v	overnight	dimers	0%	-
2	 2l	overnight	 292da	81%	0.92:1.00 \approx 1/1
3	 2w	overnight	 γ - 293da	not determined ^d	(1.00:0.00)
4	 2x	overnight	dimers	0%	-

a) reaction performed with 5 mol% of $[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-$, 6 mol% of BINAP and 10 equiv. of nitrile in CH_2Cl_2 ; b) isolated yield (mixture of both isomers); c) determined by $^1\text{H-NMR}$ of the crude product; d) the product was obtained together with a non-estimable amount of reacting nitrile that did not allowed to determine the yield

Cycloadditions with different types of nitrile showed that the reaction was possible neither with bromine cyanide (Table III-12, entry 1) nor with the 4-chlorobenzyl cyanide (Table III-12, entry 4), leading in both cases to the dimers as unique products. The cycloaddition with 1,4-dicyanobenzene led to the γ -carboline γ -**293da** as main product (confirmed by a FD-mass analysis) in an excellent regioselectivity together with a small amount of dimers of the diyne. However, the yield in this case could not be determined as the carboline could not be separated from the dimers and the remaining 1,4-dicyanobenzene. Finally, the cycloaddition with the 5-cyanopentyne led chemoselectively to the formation of the carbazole γ -**292da** and its regioisomer in almost equal amounts in 82% total yield.

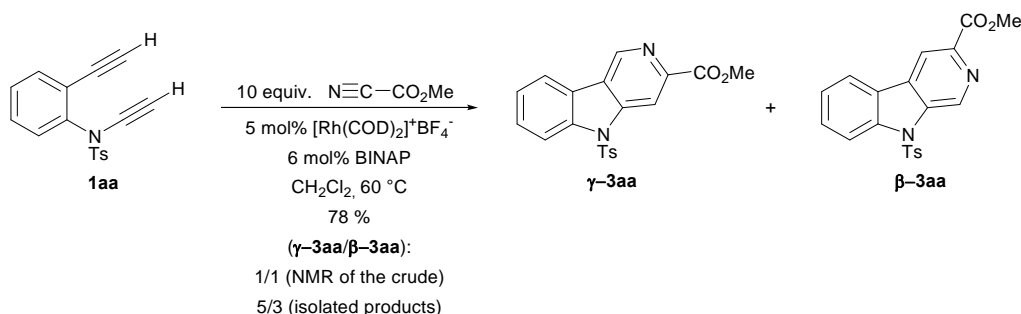
III.1.2.2. Application of the reaction to various diynes

According to the different results obtained during the study of the model reaction, standard conditions were selected for the synthesis of differently substituted carbolines:

- 5 mol%/6 mol% of $[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-/\text{BINAP}$ as catalytic system,
- 10 equivalents of nitrile,
- addition of the cycloaddition partners mixture to the catalyst solution in a rapid, but dropwise manner,
- CH_2Cl_2 or THF as solvent,
- a reaction temperature of 60 °C

III.1.2.2.1. Reaction with the non-substituted diyne

The optimized conditions were first applied to the reaction of the non-substituted diyne **1aa**.



Scheme III-21: [2+2+2] cycloaddition with a non-substituted diyne.

The reaction worked very well, a complete conversion was observed after few hours and ^1H -NMR analysis of the crude product showed only the two carbolines. The reaction proceeded with a total lack of selectivity, the two regioisomers appearing in a 1:1 ratio.

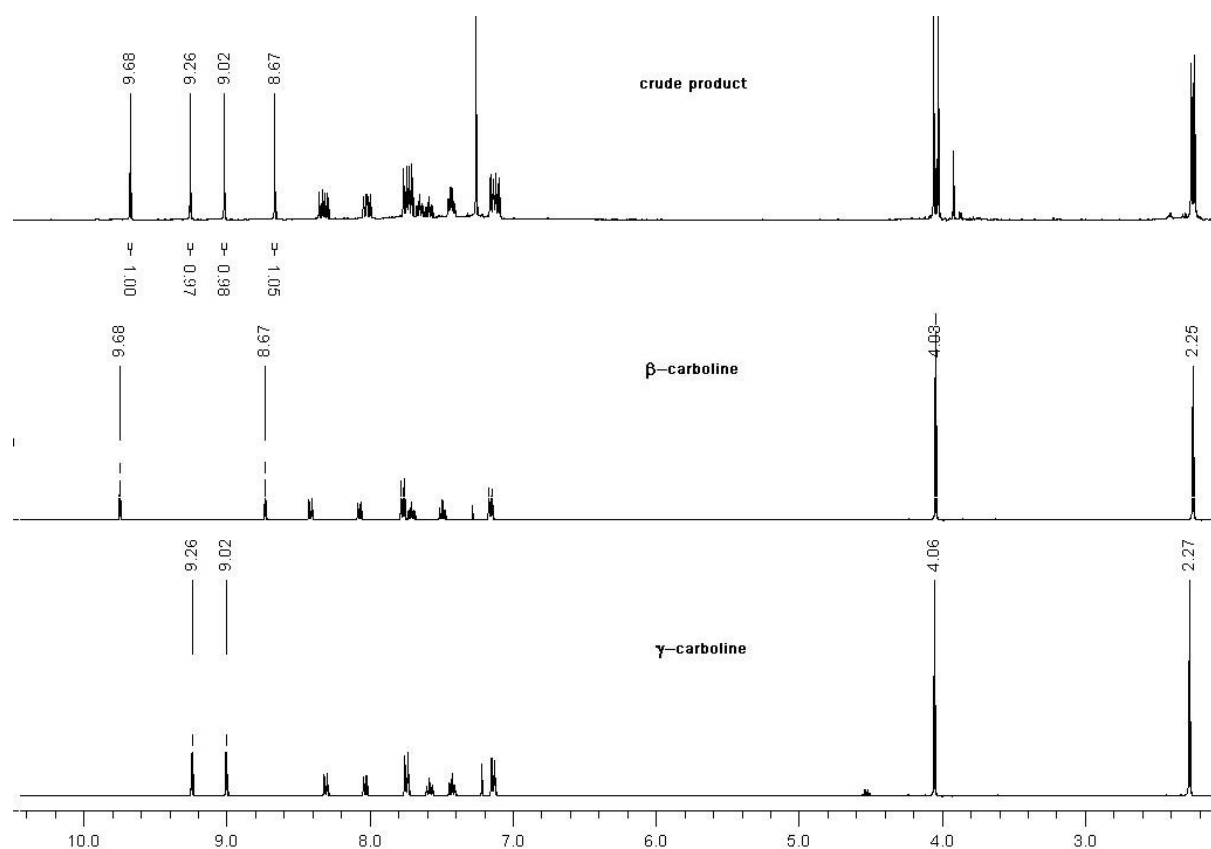


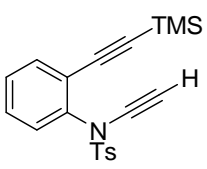
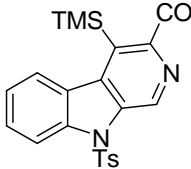
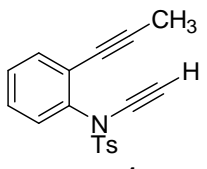
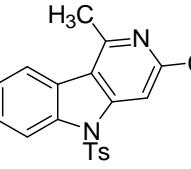
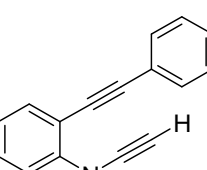
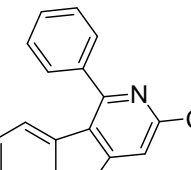
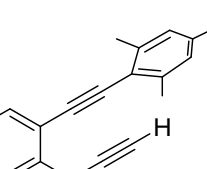
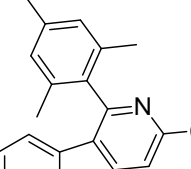
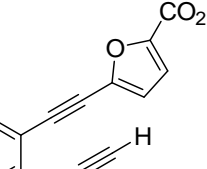
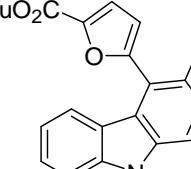
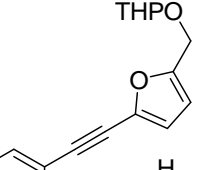
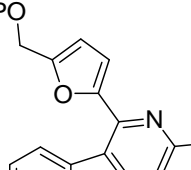
Figure III-2: ^1H -NMR spectra of the non-substituted carbolines β -3aa and γ -3aa

However, after purification of the reaction mixture by column chromatography, the two regioisomers were not obtained in equal amounts but in a ratio of β : γ = 5:3 (50%/28%). This difference could come from the fact that the γ -carboline, which is relatively polar, could have partially crystallized on the column and could not be totally eluted.

III.1.2.2.2. Reaction with diynes having a terminal ynamides moiety

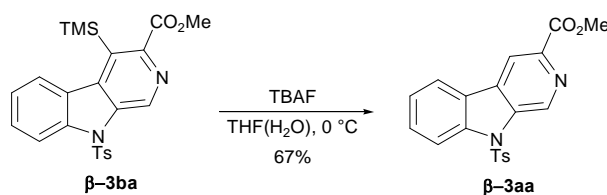
In a second part, the catalytic system was applied to the [2+2+2] cycloaddition of diynes possessing a terminal ynamide with methylcyanoformate. The cycloadditions worked in moderate to excellent yield, giving generally the corresponding γ - and β -carbolines as main products.

Table III-13: Synthesis of carbolines from terminal ynammides

Entry	Diyne	Main product	Yield ^{a,b}	Ratio γ : β ^c
1	 1ba	 β-3ba	50-62% ^e	only β
2	 1ca	 γ-3ca	64% 76% ^d	1.00:0.42 (5/2) 1.00:1.88 (1/2) ^d
3	 1da	 γ-3da	67% 72% ^d	1.00:0:20 (5/1) 1.00:0.26 (4/1) ^d
4	 1ga	 γ-3ga	97%	only γ
5	 1ma	 β-3ma	49% ^d	1.00:2.88 (1/3) ^d
6	 1ra	 γ-3ra	<22% <64% ^d	1.00:0:30 (3/1) 1.00:1.96 (1/2) ^d

a) reaction performed with 5 mol% of $[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-$, 5 mol% of BINAP and 10 equiv. of nitrile in CH_2Cl_2 at 60 °C; b) isolated yield ; c) determined by $^1\text{H-NMR}$ of the crude product ; d) reaction in THF; e) 5-10% of desilylated carbolines were obtained

According to these results, it appears that the regioselectivity of the reaction seems to depend on different factors. On one hand, the steric hindrance seems to have an effect on the regioselectivity since the selectivity for the formation of the γ -carboline increases with the size of the substituent (H < methyl < phenyl \approx furyl < mesityl). However, this observation was contradicted by the cycloaddition with the TMS-substituted diyne **1ba**. In this case, the reaction proceeded with a totally inverted regioselectivity to give only the β -carboline **β -3ba** together with desilylated carbolines as by-products. The structure of this carboline **β -3ba** was further confirmed by desilylation by treatment with TBAF to give the desilylated β -carboline **β -3aa**.



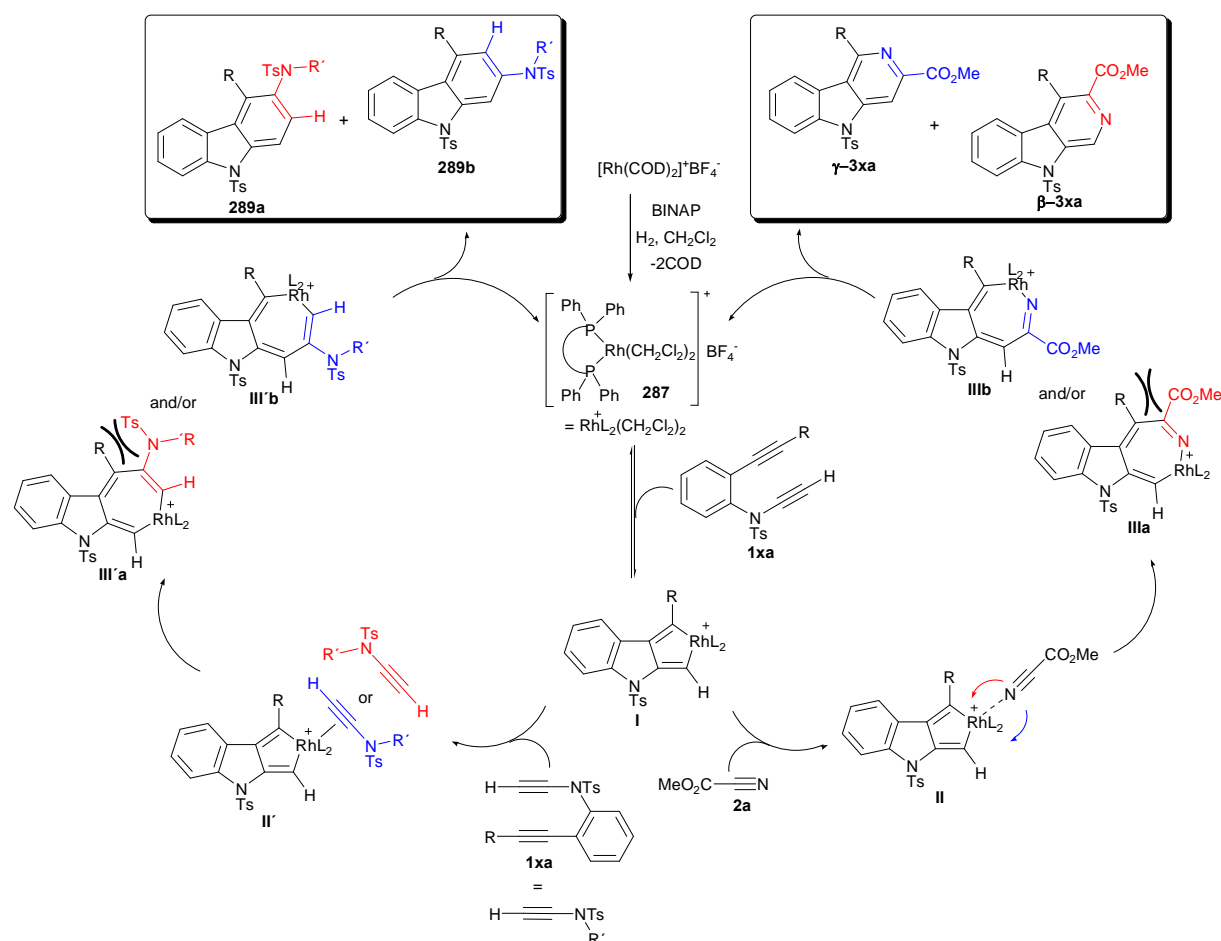
Scheme III-22: Verification of the structure of the β -carboline **β -3ba**.

On the other hand, as observed during the optimization of the reaction conditions, the choice of the solvent used for the cycloaddition has a decisive influence on the regioselectivity. Whereas DCM as a solvent facilitates the formation of the γ -carbolines (e.g. entry 2: γ -3ca: β -3ca = 5/2; entry 6: γ -3ra: β -3ra = 3/1) this regioselectivity can be inverted by the use of THF as a solvent (e.g. entry 2: γ -3ca: β -3ca = 1/2; entry 6: γ -3ra: β -3ra = 1/2)

- mechanistic considerations

From these results, a first discussion about a possible mechanism for the reaction can be made. As proposed in several works, the [2+2+2] cycloaddition of alkynes with nitriles can start either by the formation of a rhodacyclopentadiene (mechanism A) or by an azarhodacyclopentadiene (mechanism B). However, the success of the synthesis of β - and γ -carbolines supports undoubtedly the rhodacyclopentadiene route. The most plausible mechanism of the reaction would start by the formation of a rhodacyclopentadiene **I** from the active catalyst and the diyne. This can further react by coordination of the nitrile to the rhodium center followed by its insertion into the cycle to give the azarhodacycloheptatrienes **IIIa** and **IIIb**. However the formation of the cycle **IIIa** would be gradually disfavored with the increase of the size of the alkynyl substituent that was experimentally observed.

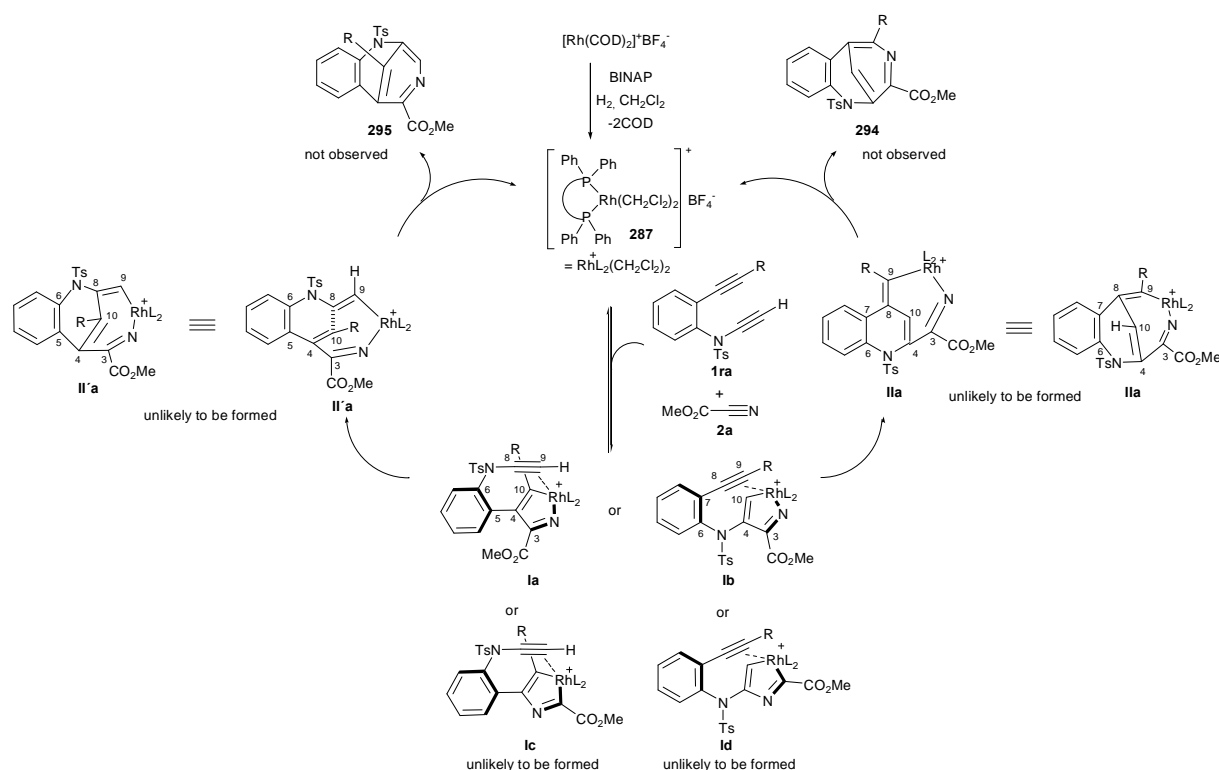
Reductive elimination of the metal center from the rhodacycloheptatriene leads to the formation of the corresponding β - and γ -carbolines **β -3xa** and **γ -3xa**.



Scheme III-23: Possible mechanism for the [2+2+2] cycloaddition of diynes with a nitrile.

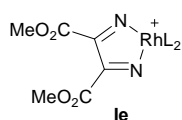
This mechanism offers a good explanation for the course of the cycloaddition reaction and explains notably the regioselectivity of the reaction but also the formation of the dimers as by-products. As previously shown by the reaction of the model diyne with 5-cyanopentyne **2i**, the diyne can also react with alkynes. In the same way, the intermediate rhodacyclopentadiene **I** can react with a triple bond of a second diyne. From the two alkyne units of this second diyne, the ynamide triple bond appears to be particularly more reactive, probably due to a higher affinity of the terminal acetylene to the metal center. Insertion of this one in the rhodacyclopentadiene leads to a mixture of rhodacycloheptatrienes **III'a** and **III'b**. Coordination and insertion of the other triple bond of the diyne in the cycle could be also considered but would lead to carbazoles which were not observed in these reactions.

An alternative mechanism (mechanism B) starting with the formation of an azarhodacyclopentadiene should also be considered. But, this mechanism appears to be less probable for the formation of β - and γ -carbolines since none of the four different possible azarhodacyclopentadienes **Ia-d** can further react in a simple way to give the carbolines formed in the reaction. For example, if the azarhodacyclopentadiene **Ia** and **Ib** would react intra-molecularly with the remaining alkyne, the insertion of the triple bond in the azarhodacyclopentadiene would give bicyclic azarhodanonacycles which are unlikely to be formed for sterical reasons.



Scheme III-24: Alternative mechanism for the [2+2+2] cycloaddition of diynes with a nitrile.

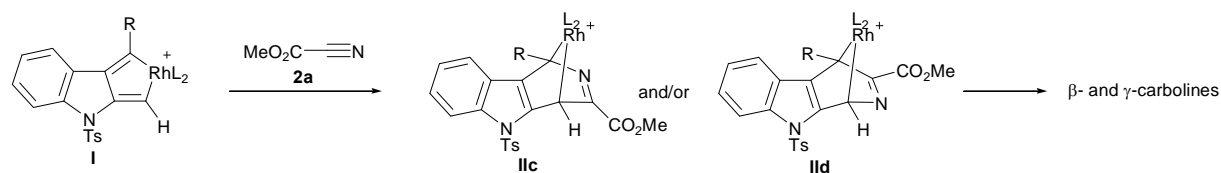
On the contrary, mechanism B can give an explanation for the poor yield of carbolines obtained when the diyne is slowly added to a mixture of the catalyst and the nitrile. In this case, the formation of one or several of the azarhodacyclopentadiene **Ia-d** or the potential formation of a bis-azarhodacyclopentadiene **Ie** would inhibit the reaction by trapping the rhodium center.



Scheme III-25: Possible bis-azarhodacyclopentadiene.

However, neither mechanism A nor mechanism B can explain the influence of the solvent on the reaction or the reversal of regioselectivity for the reaction with the TMS-substituted diyne. This result indicates that other effects than steric effects play a role in the regioselectivity. For example, electronic effects could have an impact on the regioselectivity. Therefore, further reactions are required to give a more detailed account of these effects. An evaluation of these electronic effects would be the study of cycloadditions of (hetero)aryl substituted diynes with various electron-accepting or electron-donating substituents on para-position.

Another possible mechanism (mechanism A') could be that the rhodacyclopentadiene **I** - which can be regarded as a reactive indoloquinodimethane - does not further react with the insertion of the reacting nitrile into the rhodacyclopentadiene but reacts rather in a Diels-Alder type reaction with the nitrile. This reaction would give the bicyclic compounds **IIc** and **II d** which would give the γ - and β -carbolines after elimination of the rhodium center.



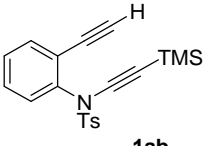
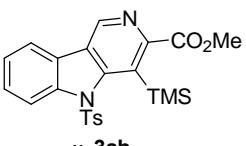
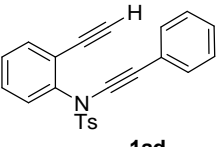
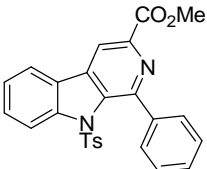
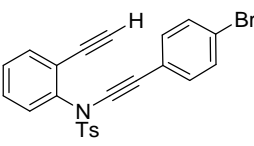
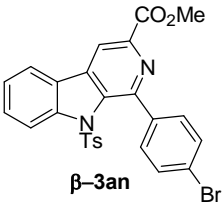
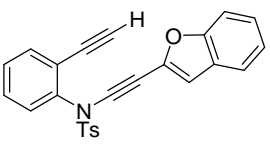
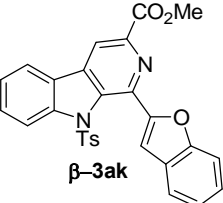
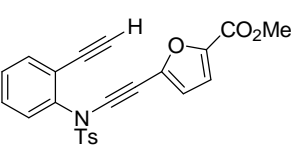
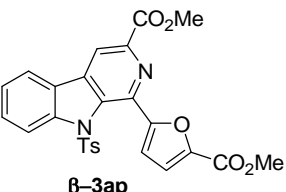
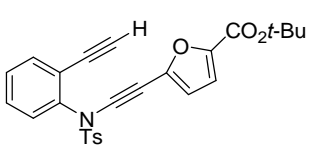
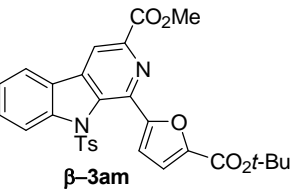
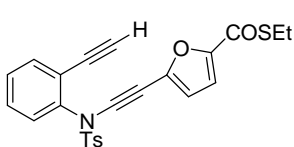
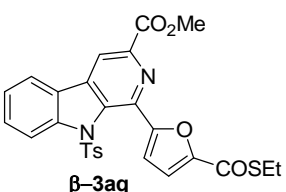
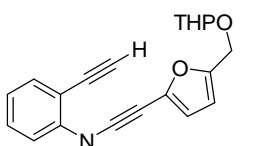
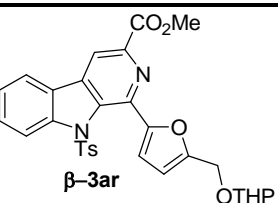
Scheme III-26: Alternative mechanism for the [2+2+2] cycloaddition.

A more precise study of this possible mechanism would be to perform a frontier molecular orbital study (FMO study) of the butadiene moiety of the rhodacyclopentadiene **I**. However, such a study will be complex due to the presence of the rhodium center and cannot be part of a synthetic project.

III.1.2.2.3. Reaction with diynes having a terminal alkyne moiety

Similarly, the reactivity of diynes substituted on the ynamide unit was investigated. The [2+2+2] cycloaddition led typically to the corresponding β -carbolines as major products in good to excellent yields.

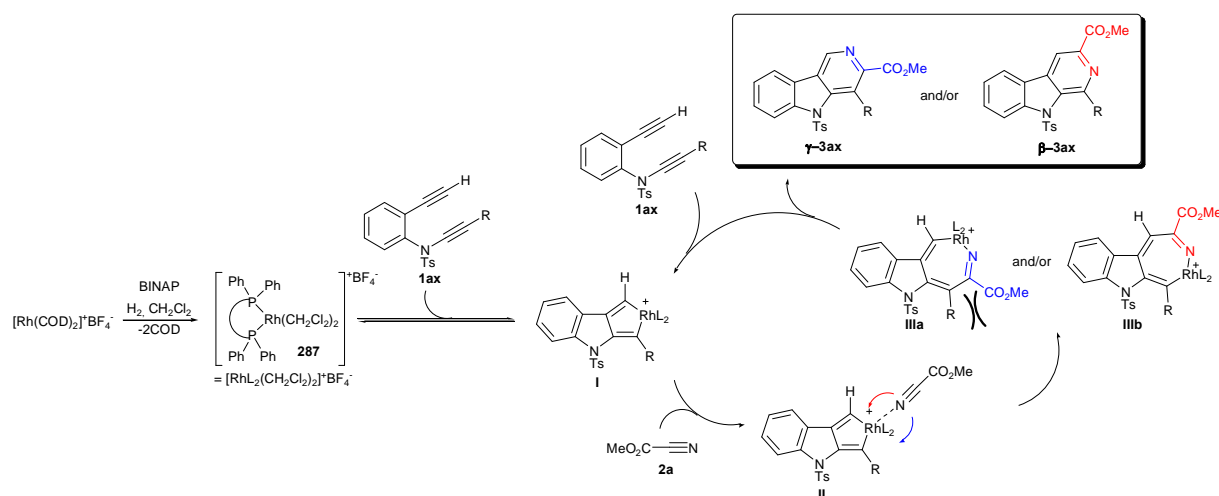
Table II-14: Synthesis of carbolines from substituted ynamides

Entry	Diyne	Main product	Yield ^{a, b}	Ratio $\beta:\gamma^c$
1	 1ab	 γ - 3ab	41-57% ^e	only γ
2	 1ad	 β - 3ad	91% 88% ^d	1.00:0.08 (12/1) 1.00:0.04 (20/1) ^d
3	 1an	 β - 3an	80%	1.00:0.14 (7/1)
4	 1ak	 β - 3ak	68%	1.00:0.51 (2/1)
5	 1ap	 β - 3ap	92%	1.00:0.20 (5/1)
6	 1am	 β - 3am	99% ^d	1.00:0.12 (8/1) ^d
7	 1aq	 β - 3aq	80%	1.00:0.21 (5/1)
8	 1ar	 β - 3ar	27% 78% ^d	1.00:0.13 (8/1) 1.00:0.10 (10/1) ^d

a) reaction performed with 5 mol% of $[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-$, 5 mol% of BINAP and 10 equiv. of nitrile in CH_2Cl_2 at 60 °C; b) isolated yield; c) determined by $^1\text{H-NMR}$ of the crude product; d) reaction in THF; e) 5-10% of desilylated carbolines were obtained

Contrary to the reactions with terminal ynamides, the influence of the solvent on the regioselectivity is only small. The β -carbolines were effectively obtained as major product when the reactions were performed in CH_2Cl_2 or THF with relatively similar isomer ratios (entry 2, 8). Moreover, the reaction with the diyne **1ar** was considerably enhanced by switching from CH_2Cl_2 to THF (entry 8). But again, the cycloaddition with the TMS-substituted diyne gave the opposite regioselectivity with the corresponding γ -carboline γ -**3ab** as main product in addition of small amounts of the desilylated carbolines (entry 1).

According to the synthetic results and taking into account of the mechanism discussion of the cycloaddition with terminal ynamides, the following mechanism is thought to be the most possible:



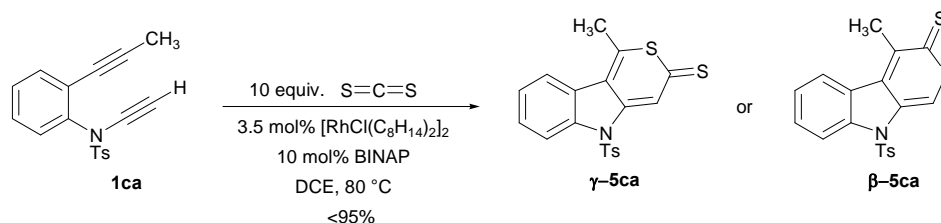
Scheme III-27: Possible mechanism for the [2+2+2] cycloaddition of diynes with a nitrile.

III.1.3. [2+2+2] cycloadditions with heterocumulenes

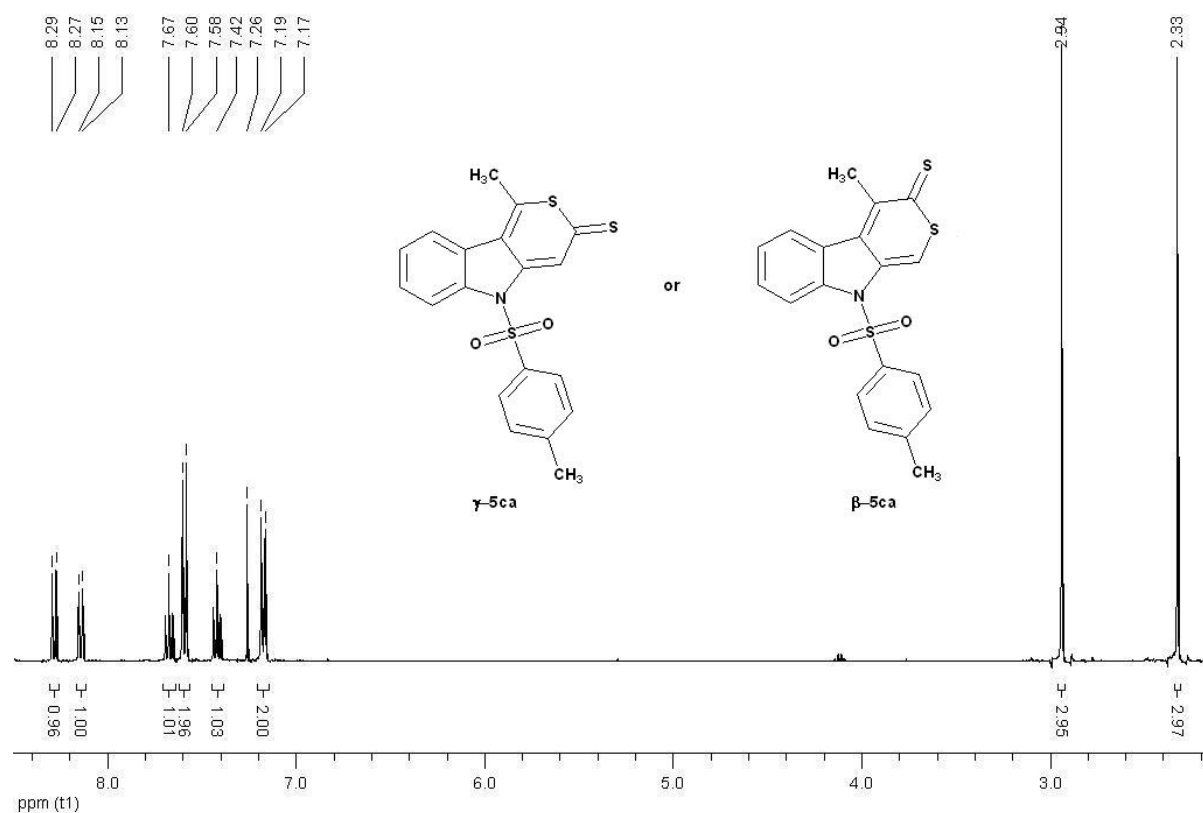
The [2+2+2] cycloaddition strategy was also extended to heterocumulenes as cycloaddition partners. To test the reactions, the diyne **1ca** was selected as model and each reaction was performed with the rhodium catalytic system described in Tanaka's works that gave the best results, i.e. the cationic rhodium $[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-$ for the reaction with isocyanates^[88] and the neutral rhodium catalyst $[\text{RhCl}(\text{COD})]_2$ for the others^[93]. However, the reaction conditions were slightly modified.*

* $[\text{RhCl}(\text{C}_8\text{H}_{14})_2]_2$ was used as pre-catalyst and ten equivalents of the heterocumulenes were used in the following study. Furthermore, as in the case of the cycloaddition with nitriles, a small excess of BINAP to the rhodium pre-catalyst was used.

III.1.3.1. Test cycloadditions

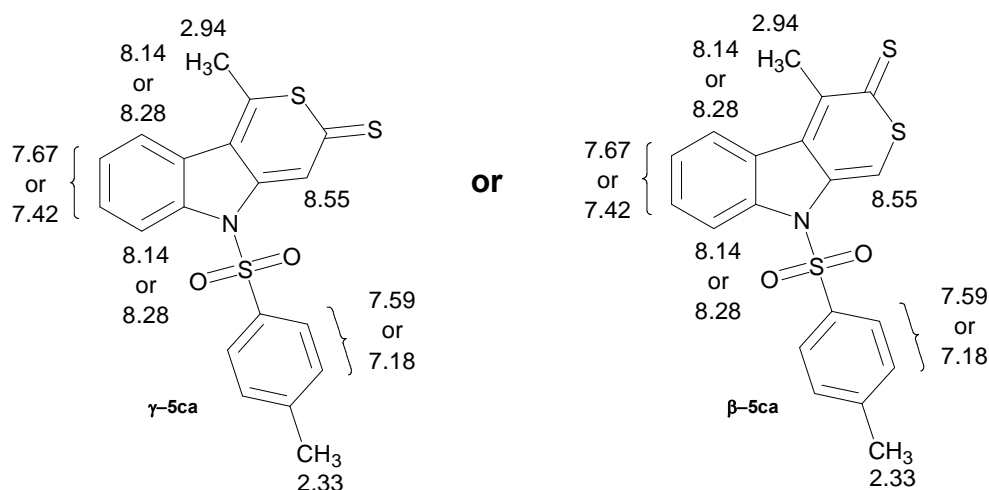
III.1.3.1.1. Cycloaddition with CS₂Scheme III-28: Test reaction with CS₂.

The initially yellowish reaction mixture turned rapidly violet after the addition of few drops of the reagent mixture. A complete conversion of the diyne was observed after three hours. Purification of the reaction mixture led to the isolation of a dark violet solid. A FD-mass analysis of the product confirmed the potential addition of CS₂ to the diyne **1ca** by giving a single peak at the expected mass.

* ¹H NMR analysis:Figure III-3: ¹H-NMR of the isolated product.

The $^1\text{H-NMR}$ of the isolated product shows a singlet at 8.55 ppm corresponding to the single proton on the thiopyranothione ring. Two other singlets appear on the spectrum corresponding to the methyl substituents. Supposing that the chemical shift of the methyl of the tosyl group does not vary from its typical value (~ 2.30 ppm) allows to attribute the singlet at 2.94 ppm to the methyl substituent of the thiopyranothione ring. The two doublets at 7.18 ppm and 7.59 ppm, integrating for two protons each, correspond to the aromatic protons of the tosyl group. The protons of the annulated benzene ring are represented by the remaining doublets and triplets.

From this spectrum, a first assignment of the signals is possible:



Scheme III-29: Partial assignment of the proton signals.

To assign completely the signals, NOESY and COSY analyses were done.

* Nuclear Overhauser Effect Spectroscopy (NOESY):

The NOESY analysis showed that the methyl group of the thiopyranothione ring is spatially close to the proton giving a doublet at 8.14 ppm, which allows to attribute the two doublets of the phenyl ring to their corresponding protons.

* Homonuclear correlation spectroscopy (COSY) analysis

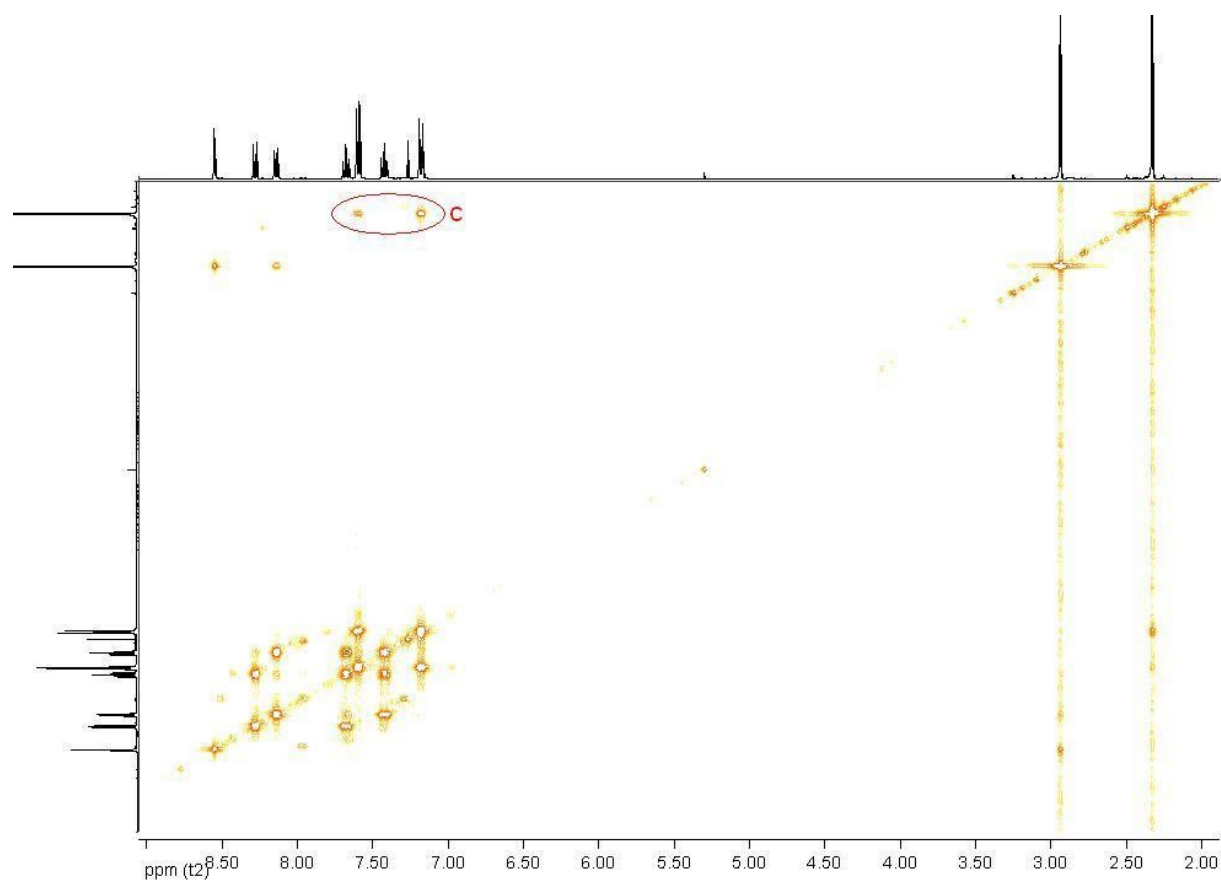


Figure III-4: COSY spectrum of the isolated product.

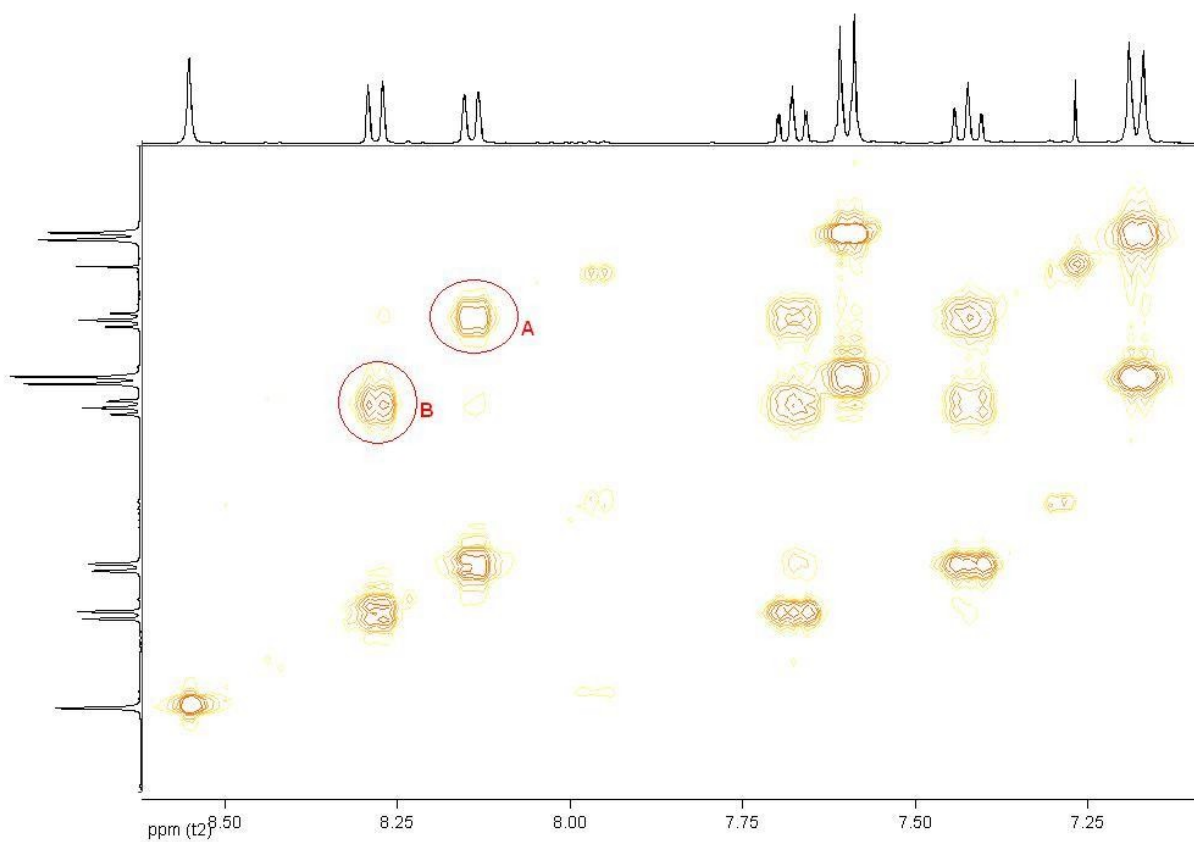
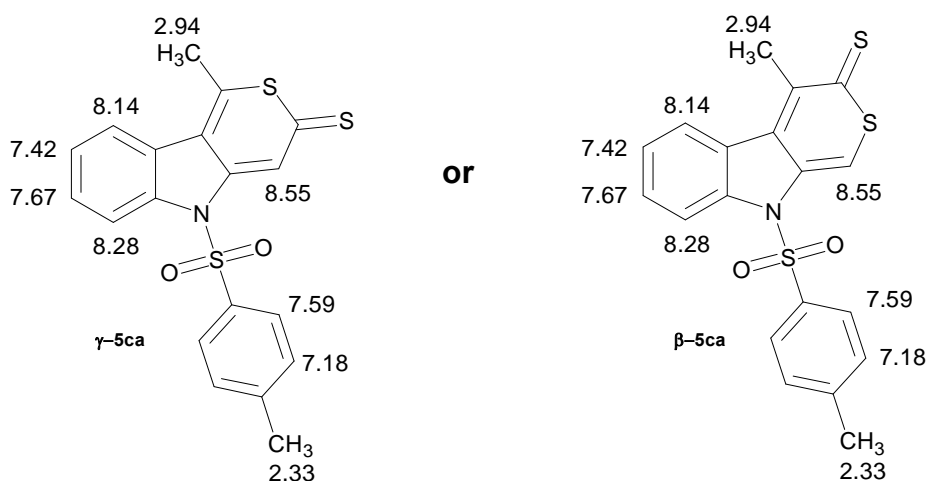


Figure III-5: Enlargement of the aromatic area of the COSY spectrum.

The COSY spectrum allows to assign the two triplets of the benzene ring. As illustrated by Figure III-5, a coupling between the proton giving the doublet at 8.14 ppm and the proton giving the triplet at 7.42 ppm (A) proves their vicinal positions. Furthermore, the proton giving the doublet at 8.28 ppm couples to the vicinal proton giving the triplet at 7.67 ppm (B). The COSY confirmed also the aforementioned hypothesis about the chemical shift of the methyl of the tosyl group as shown by the relation between the signal at 2.33 ppm and those at 7.18 and 7.59 ppm (C). Moreover, a difference of intensity in these correlations enables to complete the assignment of the signals as follow:



Scheme III-30: Assignment of the $^1\text{H-NMR}$ signals to their corresponding protons.

^{13}C NMR analysis:

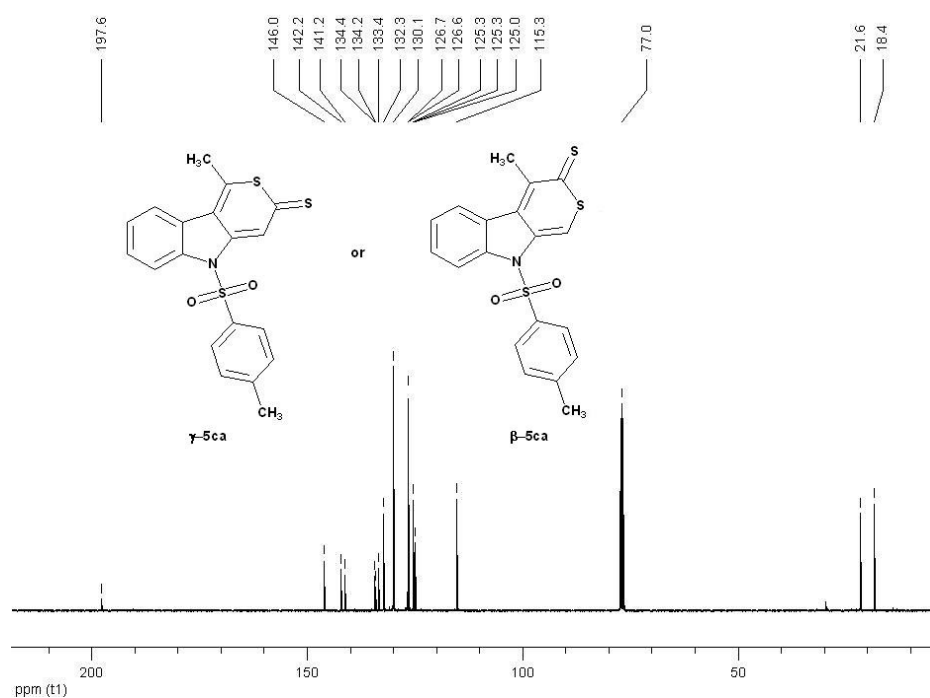


Figure III-6: $^{13}\text{C-NMR}$ of the isolated product.

The presence of a carbon-sulfur double bond is confirmed by the corresponding peak at 197.6 ppm. As expected, the two methyl substituents are represented by the peaks at 21.6 ppm and 18.4 ppm. An enlargement of the aromatic area shows clearly seven aromatic CH-peaks and the remaining seven quaternary carbons. A precise assignment of the primary and tertiary carbons could be done with help of an HSQC analysis.

* Heteronuclear Single Quantum Coherence (HSQC) analysis:

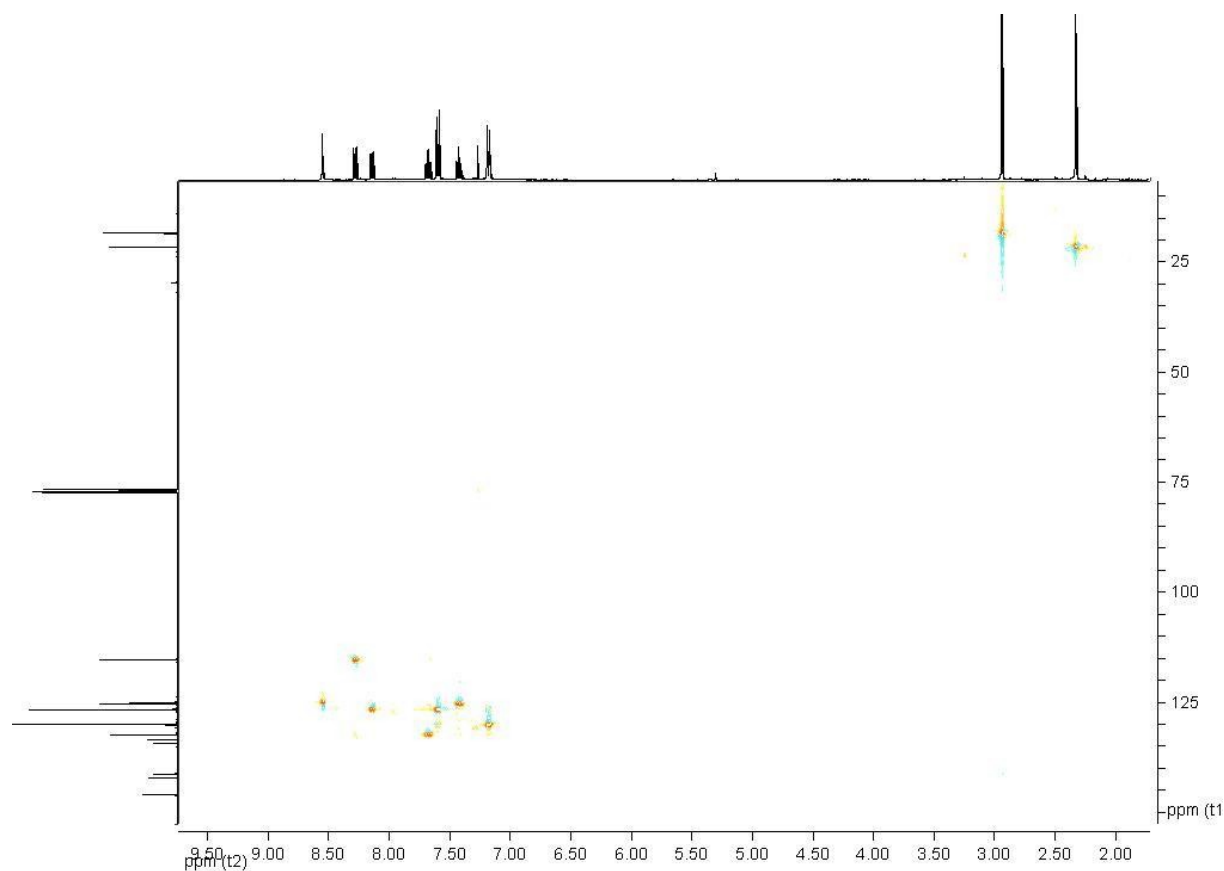


Figure III-7: HSQC spectrum of the isolated product.

As illustrated by the above HSQC spectrum, the correlation of each C-H bond can be observed that allows to complete partially the signal assignments. An additional HMBC analysis was required to complete the assignment of the signals totally and to determine the more plausible structure of the product.

* Heteronuclear Multiple Bond Coherence (HMBC) analysis:

The HMBC analysis gives information on the long distance correlations between the different protons and carbons (especially J^3 coupling information).

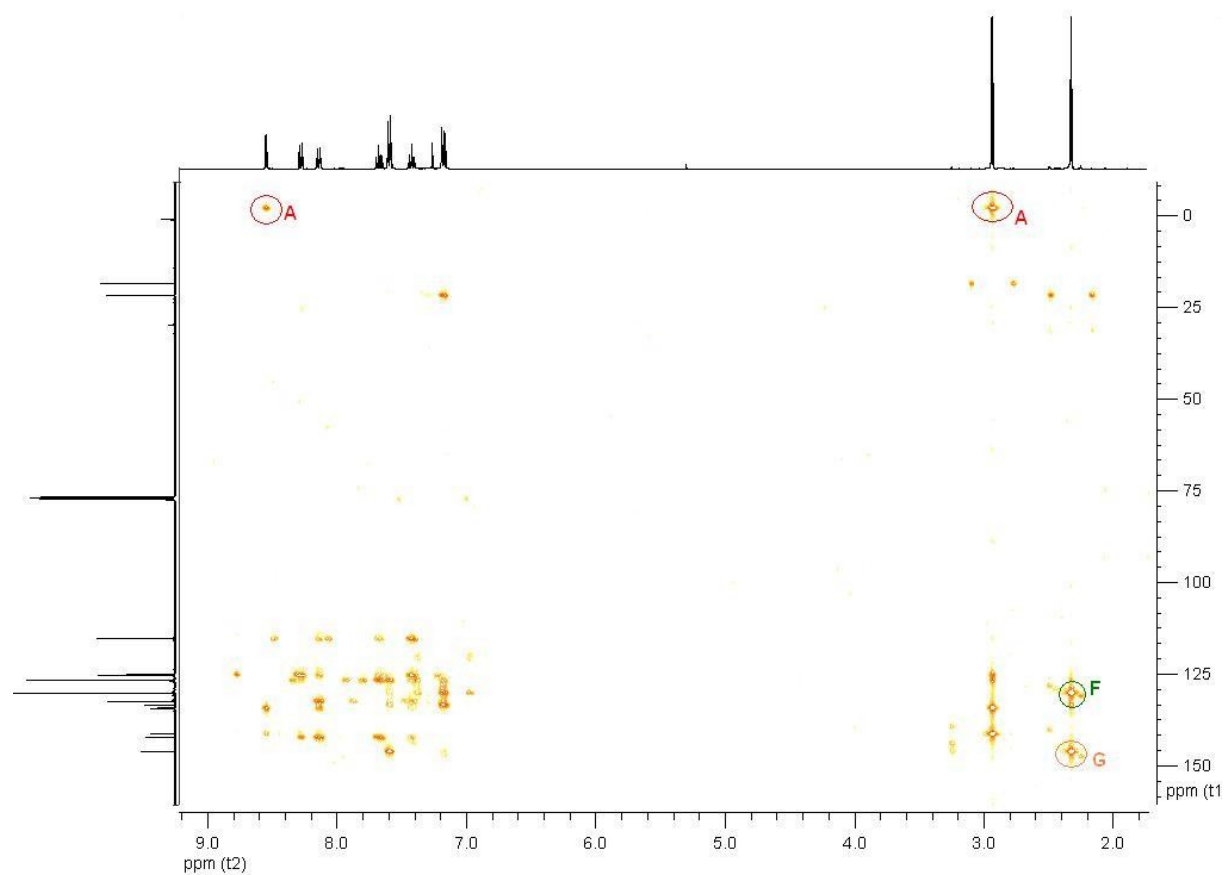


Figure III-8: HMBC spectrum of the isolated product.

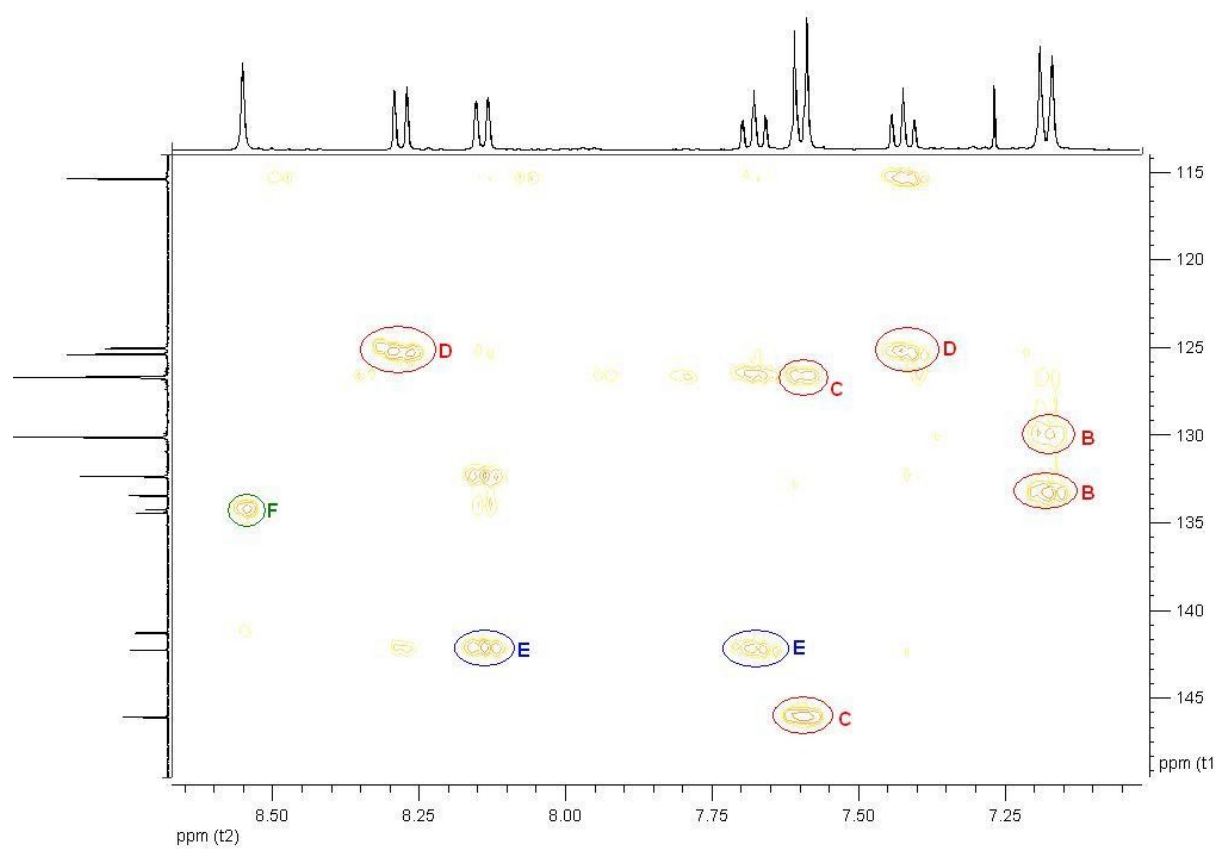
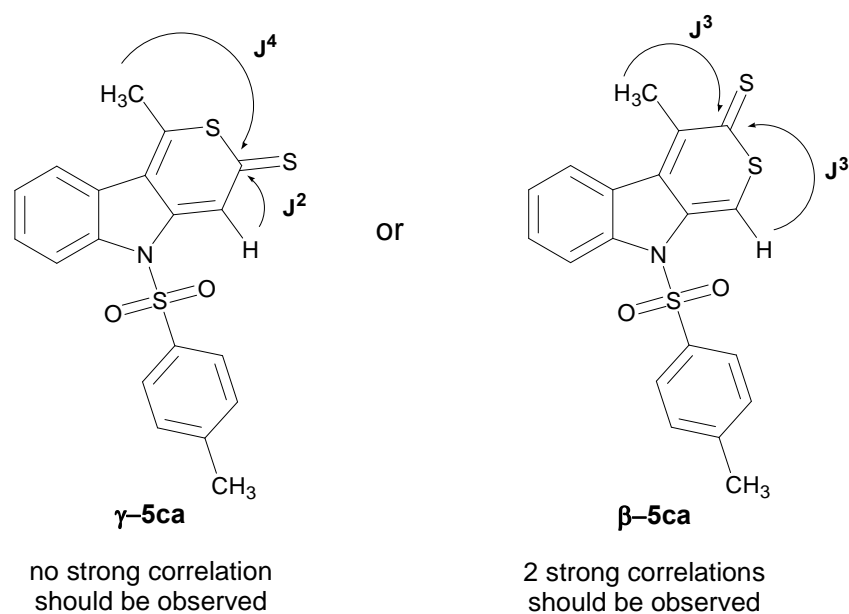


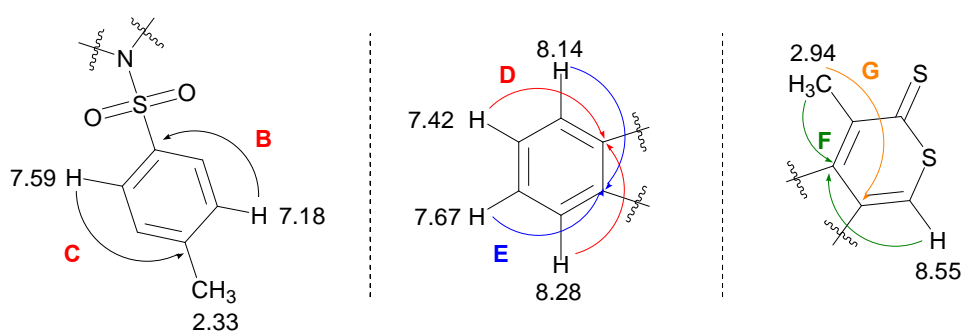
Figure III-9: Enlargement of the HMBC spectrum.

The most important information brought by the HMBC spectrum is the position of the carbon-sulfur double bond in the product. As shown by the spectrum, a coupling exists between the carbon of the carbon-sulfur double bond and the methyl group of the thiopyrone ring (**A**), but also with the thiopyronyl proton. As a consequence, the structure γ -5ca can be undoubtedly rejected.



Scheme III-31: Expected difference in HMBC.

Moreover, the spectrum enables us to assign the remaining signals to the corresponding quaternary carbons:



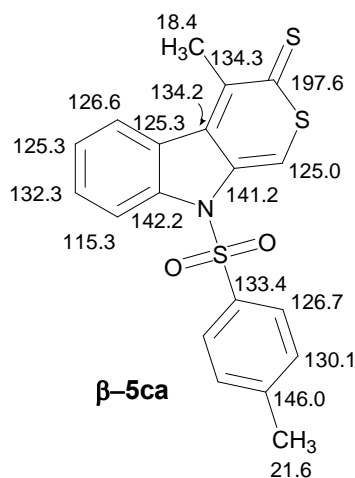
Scheme III-32: Information brought by the HMBC experiment.

- assignment of the quaternary carbons of the tosyl group: the proton at 7.18 ppm gives notably a coupling with the carbon at 133.4 ppm (**B**) whereas the other proton at 7.59 ppm gives a coupling with the carbon at 146.0 ppm (**C**). These observations allow the assignment of these signals to the corresponding quaternary carbons.

- assignment of the quaternary carbons of the benzene ring: the carbon giving a signal at 125.3 ppm couples with the protons which gives the doublet at 8.28 ppm and with the triplet at 7.42 (D). Similarly the carbon giving a signal at 142.2 ppm couples with the protons which give the doublet at 8.14 ppm and the triplet at 7.67 (E).

- assignment of the quaternary carbons of the thiopyranothione ring : the carbon giving a signal at 134.2 ppm couples with the dithiopyronyl proton and the protons of the methyl substituent. This is only possible for the quaternary carbon adjacent of the methyl group (F). Moreover, the protons of the methyl substituent couple also with the carbon giving the signal at 141.2 ppm allowing to assign this signal as the last unidentified pyrrole carbon (G). Finally, the last signal at 134.3 ppm should represent the carbon bearing the methyl substituent.

So, the complete assignment of the signals has been completed and is summarized in the following scheme:



Scheme III-33: Final assignment of the ^{13}C -NMR signals.

Finally, a crystal structure analysis was successfully obtained and confirmed the supposed structure of the molecule:

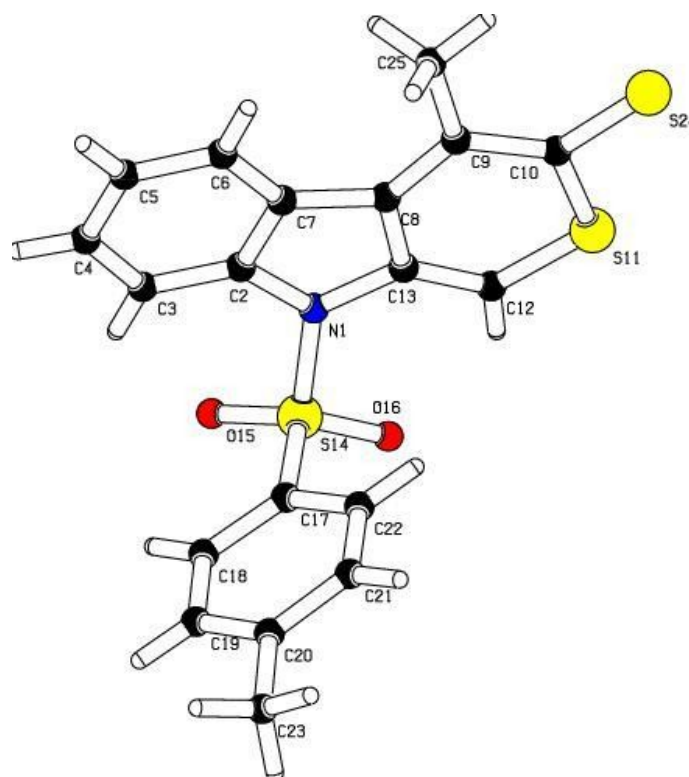
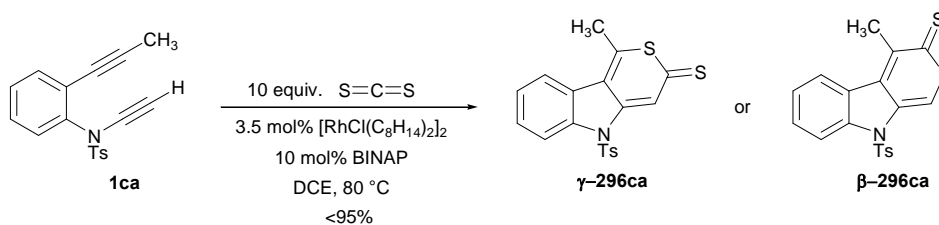


Figure III-10: X-ray structure of the isolated product

This new indoloannulated thiopyranothione is unprecedented up to now. The thiopyranothione β -5ca can be stored for a long period at $-26\text{ }^{\circ}\text{C}$ but is sensitive to air and light. The question arises if the [2+2+2] cycloaddition of diynes and carbon disulfide is a reaction with a broad scope and if the other isomer can be obtained with a suitable catalyst and conditions.

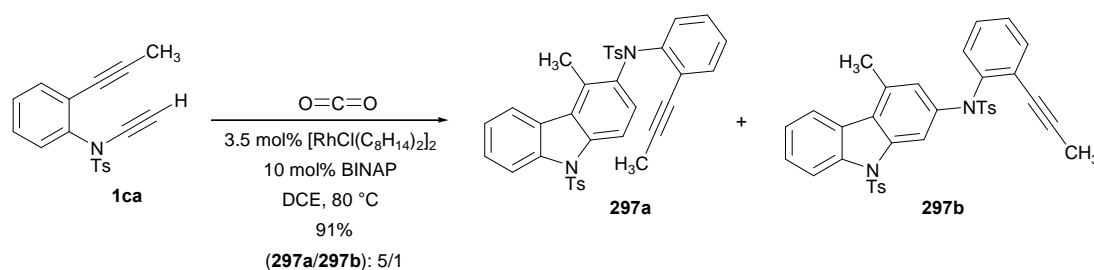
III.1.3.1.2. Cycloaddition with CO_2

Similarly to the reaction with CS_2 , the reactivity of CO_2 toward the cycloaddition reaction was investigated. For this purpose, the reaction was performed under a carbon dioxide atmosphere.



Scheme III-34: Test reaction with CO_2 .

Complete conversion of the diyne was observed after four hours. Purification of the reaction mixture led to the isolation of two products which could not be totally separated. $^1\text{H-NMR}$ -analysis of the major product showed four methyl peaks and several doublets and triplets in the aromatic area (for a total of eighteen aromatic protons). The formation of a dimer of **1ca** is the most probable hypothesis which was confirmed by a FD-mass analysis giving a single peak at $m/z = 618.7$, twice the mass of the starting material (309.4). The second product appears to be probably its regioisomer **297b**.

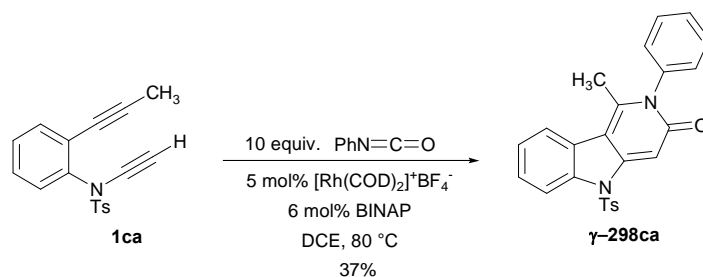


Scheme III-35: Result of the test reaction with CO_2 .

The reaction was also tried by addition of a large excess of dry ice to the reaction mixture but led to the same result. A further study would be to perform the reaction under a carbon dioxide pressure or in supercritical carbon dioxide.

III.1.3.1.3. Cycloaddition with an isocyanate

The reaction with isocyanates was tested with the reaction of the model diyne **1ca** with phenylisocyanate in presence of the cationic rhodium $[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-/\text{BINAP}$ catalytic system.

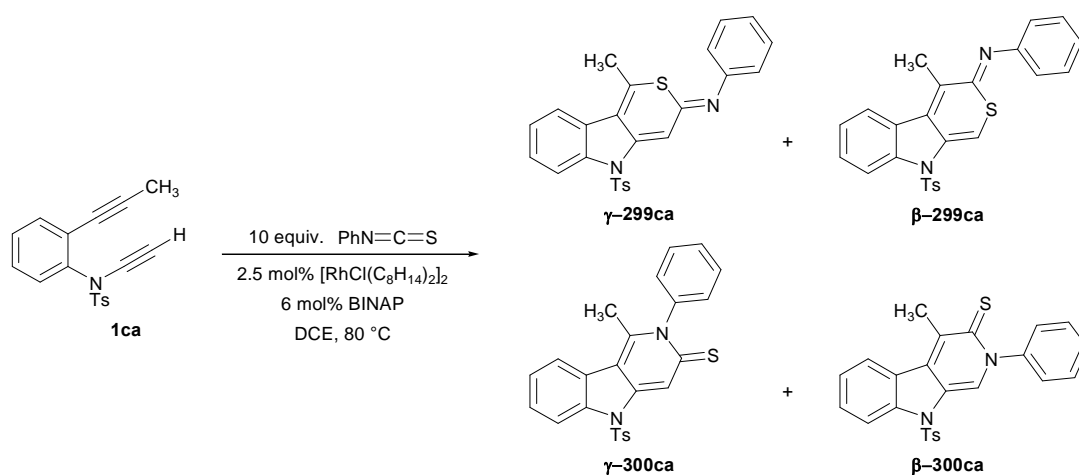


Scheme III-36: Test reaction with phenylisocyanate.

Complete disappearance of the starting material was observed after four hours at 80°C . Purification of the reaction mixture by column chromatography led to the isolation of the γ -carbolinone γ -298ca as single product in 37% yield.

III.1.3.1.4. Cycloaddition with an isothiocyanate

Like CS₂ and isocyanates, the related isothiocyanates are interesting heterocumulenes for the [2+2+2] cycloaddition reaction. The reaction of phenylisothiocyanate with the diyne **1ca** was used as a model to elucidate the possibility of the reaction. This could potentially lead to four different products depending on the reacting double-bond of the isocyanate. However, according to previously reported works on similar reaction, the carbon-sulfur double bond is expected to react chemoselectively that would give the two thiopyranoimines γ -**299ca** and β -**299ca** as cycloaddition products.



Scheme III-37: Test reaction with phenylisothiocyanate as cycloaddition partner.

Complete disappearance of the starting material was observed after stirring overnight at 80 °C. ¹H-NMR analysis of the crude product indicated the probable success of the reaction: the spectrum was very close to the spectrum corresponding to the thiopyranothione β -**5ca** obtained by the cycloaddition with CS₂. Notably, a singlet and two doublets with chemical shifts very close to those of the thiopyranothione β -**5ca** were observed (Figure III-11). However, purification of the reaction mixture by column chromatography on silica gel led to the isolation as unique product of a compound which surprisingly presented a different ¹H-NMR spectrum with many signals that did not appear in the crude product analysis (Figure III-12). An FD-mass spectrum of this compound gives m/z= 444.3 as a single signal, corresponding to an addition product of the diyne with the isothiocyanate.

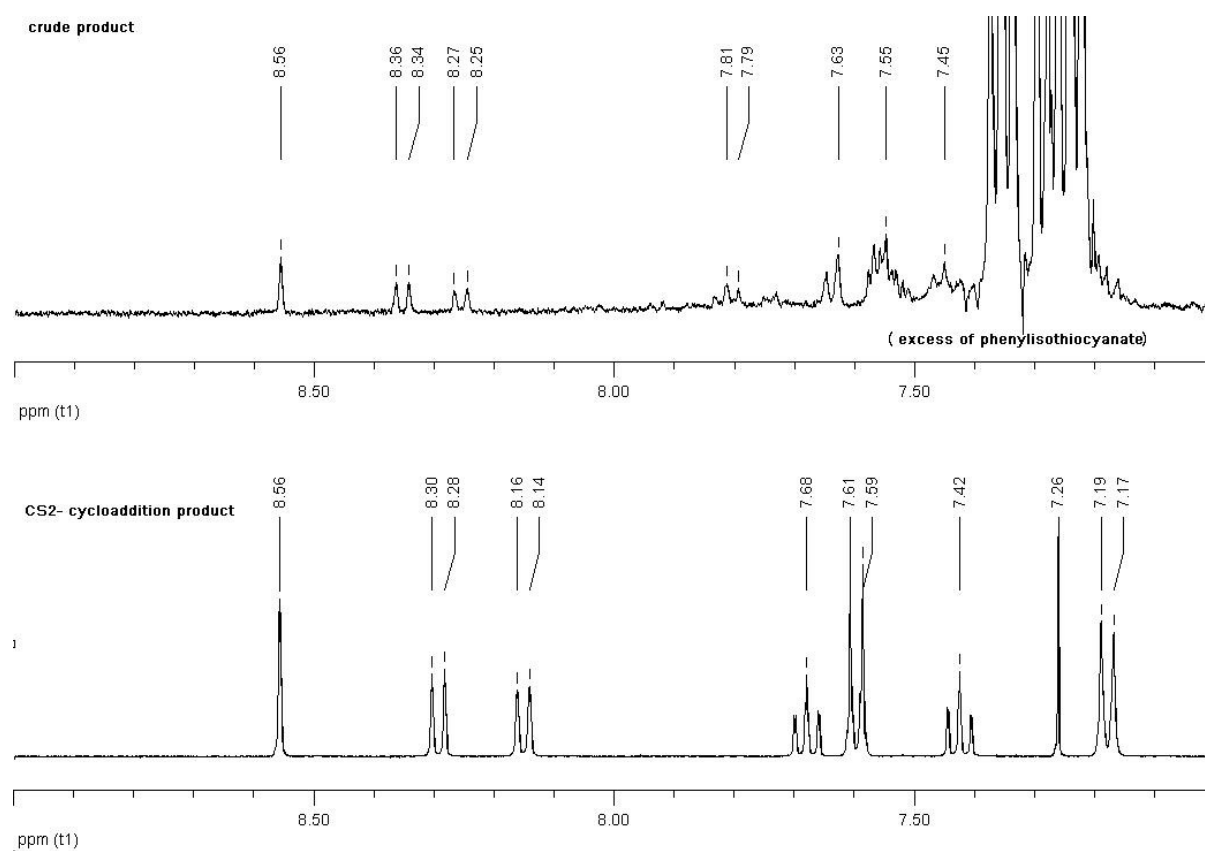


Figure III-11: $^1\text{H-NMR}$ of the crude product.

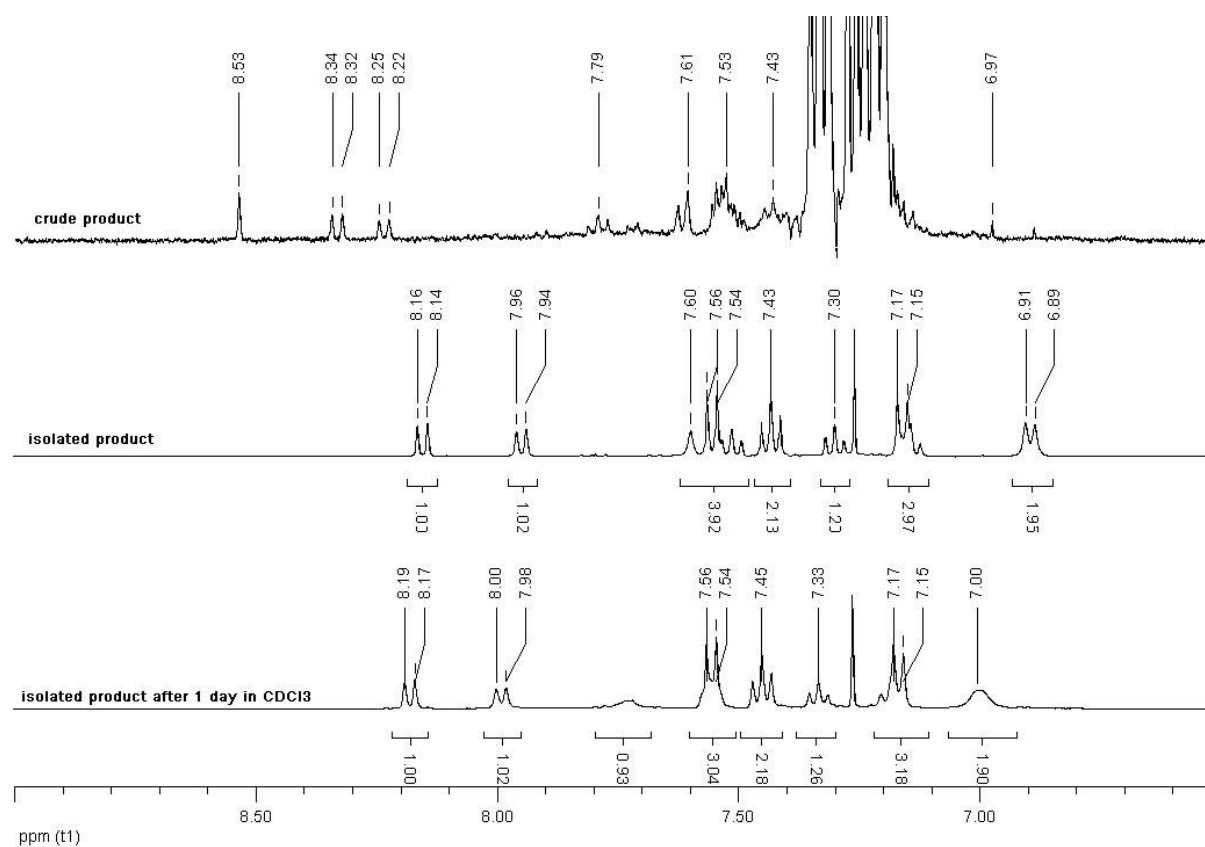


Figure III-12: Comparison between the $^1\text{H-NMR}$ spectra of the crude and the isolated product.

However, a X-ray analysis of the isolated product confirmed the structure of the isolated product to be the thiopyranoimine β -299ca.

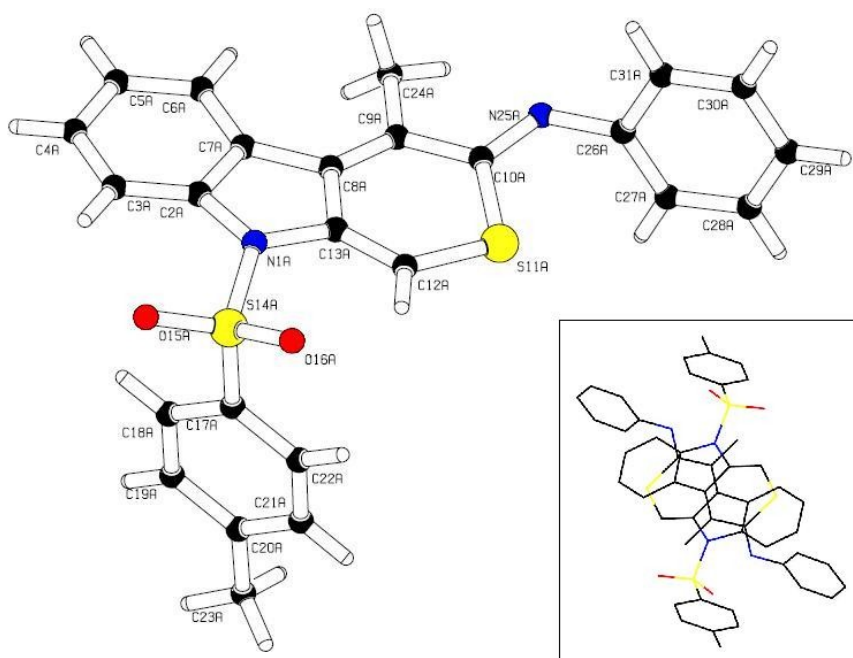


Figure III-13: X-Ray structure of the thiopyranoimine β -299ca.

The differences observed in the $^1\text{H-NMR}$ spectra of the crude and the isolated product are still not clear but could come from a dynamical phenomenon, e.g. rapid E/Z isomerization of the imine moiety and/or a potential rotation hindrance of the tosyl and/or the phenyl groups.

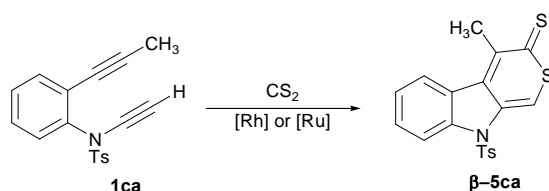
III.1.3.2. Extension of the study of the reaction with CS_2

The remarkable result obtained from the test reaction with carbon disulfide prompted us to investigate the reaction more in details.

III.1.3.2.1. Optimization of the reaction

- Catalytic system

In a first part, different catalytic systems were examined



Scheme III-38: Test of different catalytic systems on the cycloaddition with CS_2 .

Table III-15: Study of the catalytic system of the [2+2+2] cycloaddition with CS₂

Entry	Catalytic system	Solvent	T (°C)	Time	Yield ^a
1	[RhCl(C ₈ H ₁₄) ₂] ₂ /3BINAP 3.5 mol% / 10 mol%	DCE	80 °C	3 hours	>95%
2	[RhCl(C ₈ H ₁₄) ₂] ₂ /3BINAP 2 mol% / 6 mol%	DCE	80 °C	3 hours	67%
3	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	DCE	80 °C	6 hours	0% decomposition
4	Cp [*] RuCl(COD) 5 mol%	DCE	80 °C	6 hours	no reaction
5	[RhCl(C ₈ H ₁₄) ₂] ₂ /3Xantphos 3.5 mol% / 10 mol%	DCE	80 °C	6 hours	no reaction

a) isolated yield

As shown by Table III-15, the cycloaddition proceeded only with the [RhCl(C₈H₁₄)₂]₂/3BINAP as catalytic system. The cationic rhodium-based catalyst was inefficient as the reaction led only to decomposition of the diyne (entry 3) whereas the use of the ruthenium catalyst did not give any reaction (entry 4). Furthermore, the use of another ligand such as Xantphos instead of BINAP did not give any reaction (entry 5). Lowering the catalyst amount to 2 mol% led to a notable decrease in yield and regioselectivity (entry 2).

- Reaction temperature

In a second part, the reaction temperature was subjected to a short study.

Table III-16: Influence of the reaction temperature

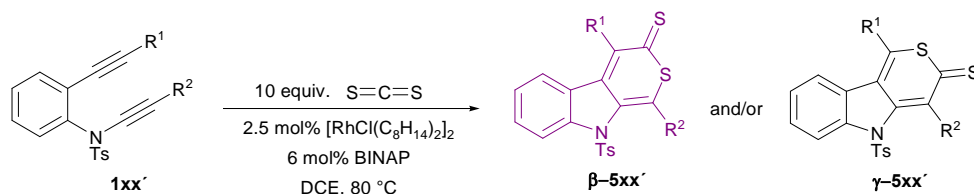
Entry	Catalytic system	Solvent	T (°C)	Time	Yield ^a
1	[RhCl(C ₈ H ₁₄) ₂] ₂ /3BINAP 3.5 mol% / 10 mol%	DCE	80 °C	3 hours	>95%
2	[RhCl(C ₈ H ₁₄) ₂] ₂ /3BINAP 3.5 mol% / 10 mol%	DCE	r.t.	overnight	56%
3	[RhCl(C ₈ H ₁₄) ₂] ₂ /3BINAP 3.5 mol% / 10 mol%	DCE	40 °C	3 hours	84%

a) isolated yield

As shown by Table III-16, the reaction proceeds also at room temperature but with a slower reaction rate, giving the thiopyranothione in a 56% yield. A raise of the reaction temperature to 40 °C led to an increase of the yield to 84%.

III.1.3.2.2. Application of the reaction to various diynes

The reaction was applied to the synthesis of differently substituted diynes with the following conditions:



Scheme III-39: Cycloaddition of various diynes with CS₂.

Surprisingly, TLC analyses of cycloadditions with diynes bearing a larger substituent on the alkyne moiety such as **1da** or **1ea** showed an additional red spot. Isolation and analyses of the corresponding product showed that this product is the second regioisomer as undoubtedly confirmed by an X-ray analysis of **γ-5da**.

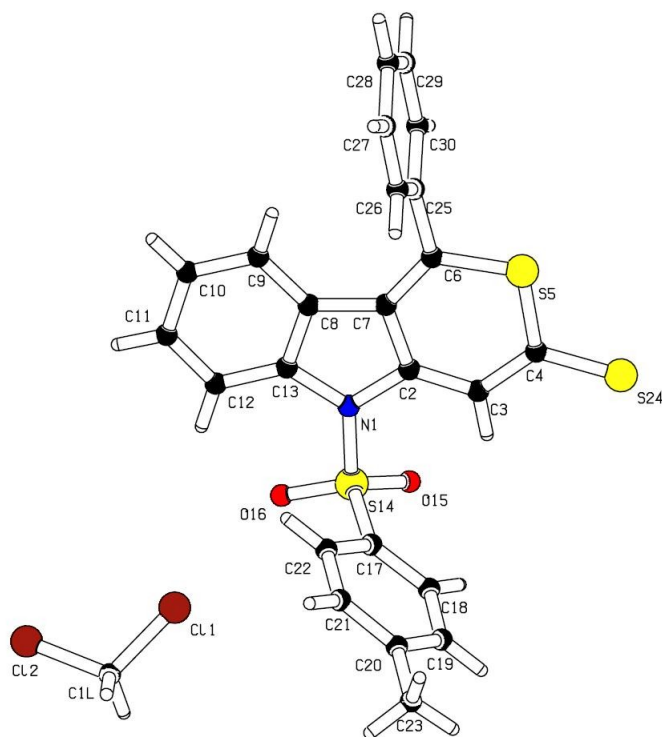
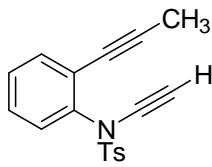
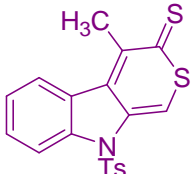
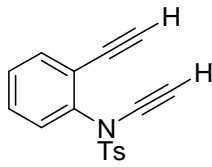
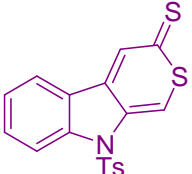
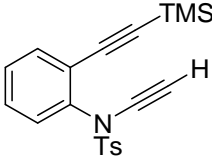
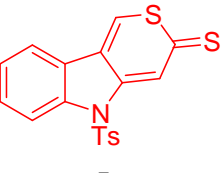
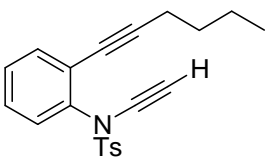
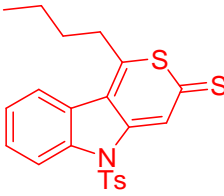
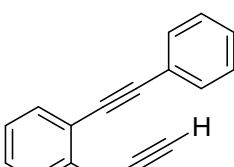
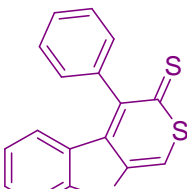
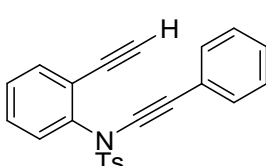
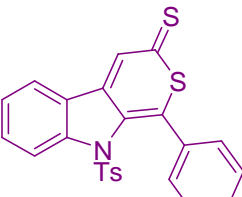


Figure III-14: X-ray structure of the red isomer **γ-5da**.

Table III-17: Cycloaddition with various diynes

Entry	Diyne	Main product	Yield ^a	Ratio $\beta:\gamma^c$
1	 1ca	 β-5ca	95% ^f	1.00:0.03 (33/1)
2	 1aa	 β-5aa	(84%) ^d	1.00:0.30 (3/1)
3	 1ba	 γ-5aa	31%	1.00:2.31 (1/2)
4	 1ea	 β-5ea	71% ^f	1.00:1.09 (10/11)
5	 1da	 β-5da	92% ^f	1.00:0.78 (5/4)
6	 1ad	 β-5ad	68%	only violet ^e

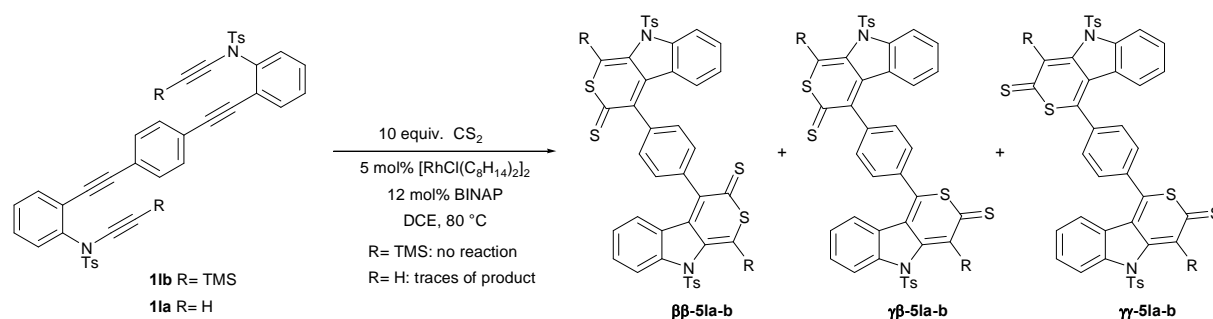
a) isolated yield (total yield); b) determined by ¹H-NMR of the isolated product; c) determined by ¹H-NMR of the crude product; d) 87% of product was isolated but was partially decomposed; e) only β -5ad was isolated; f) catalyst loading of 3.5 mol% [Rh]₂/10 mol% BINAP

Contrary to the cycloaddition with the methyl-substituted diyne **1ca**, the reactions in these cases proceeded almost without regioselectivity (entry 4 and 5). However, a second analysis of the NMR spectra of the reactions performed with the diyne **1ca** showed the presence of a small amount of the red isomer (<3%), but which was not previously isolated.

Moreover, the reaction with the non-substituted diyne led presumably to the thiopyranothiones β -**5aa** and γ -**5aa** as indicated by $^1\text{H-NMR}$ of the crude product and the two colored spots observed on the TLC. However, isolation of these two spots did not give pure products due to partial decomposition (entry 2). The reactivity of these compounds towards light and/or air was further observed by a rapid change of the color of the solution in CDCl_3 . Similarly to the cycloaddition with a nitrile, the reaction with the TMS-substituted diyne **1ba** gave a reversed regioselectivity with the desilylated thiopyranothione γ -**5aa** as major product (entry 3).

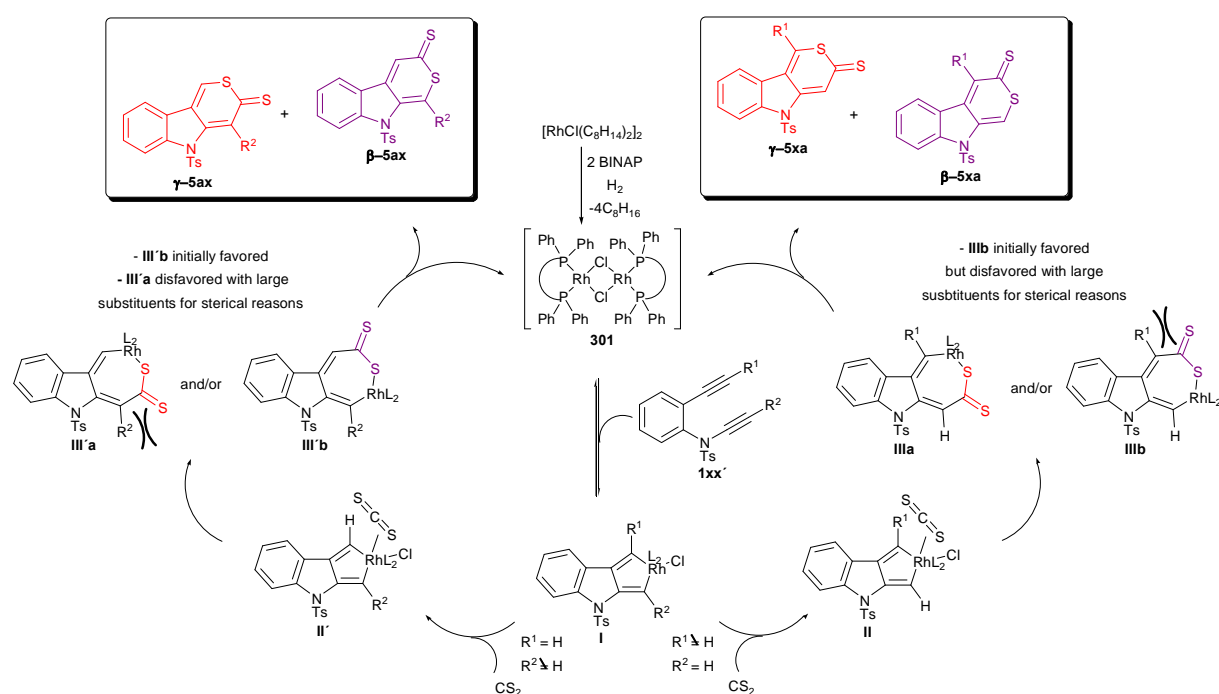
The reaction with a diyne having a substituted ynamide proceeded surprisingly with an excellent regioselectivity as only the thiopyranothione **1da** was obtained (entry 6). This result is in contrast to the expected isomer where the carbon-sulfur double bond would be on the α -position of the substituent. This implies that the regioselectivity of the reaction would generally favor the formation of the “violet” regioisomer if the ynamide is substituted. However, it is difficult to draw a conclusion with only this example.

Two cycloadditions with the tetraynes **11b** and **11a** were performed to study the possibility of the formation of bis-thiopyranothiones. The reaction with the TMS-disubstituted tetrayne **11b** did not give any reaction whereas the reaction with the terminal ynamides **11a** led to a violet mixture of several products. FD-mass analysis showed that at least one of the expected bis-thiopyranothiones was probably formed.



Scheme III-40: Attempts of cycloaddition with tetraynes.

From these few examples, a first outline of a possible mechanism can be done. Similarly to the cycloaddition with nitriles, the mechanism would probably start with the formation of a rhodacyclopentadiene **I**. Then, CS₂ would insert into the metallacycle to give preferentially the rhodacycloheptadienes **IIIb** or **IIIb'** according to the type of substitution. But, in the case of terminal ynarnides, the formation of this rhodacycloheptadienes **IIIb** would be disfavoured for steric reasons whereas the formation of **III'a** would be more disfavoured for the same steric reasons in the case of substituted ynarnides. Reductive elimination of the rhodium center gives finally the resulting thiopyranothiones.



Scheme III-41: Possible mechanism for the [2+2+2] cycloaddition of diynes with CS₂.

However, the detailed mechanism will be probably more complicated. As for the mechanism of reaction of the reaction with nitriles, a Diels-Alder reaction of the rhodacyclopentadiene **I** with CS₂ can not be excluded.

III.1.3.2.3. UV-Vis and fluorescence spectroscopy of thiopyranothiones

- study of thiopyranof[3,4-*b*]indole-3-thiones

The UV-spectra of the violet thiopyranothiones β -5ca, β -5da and β -5ad were recorded in CH_2Cl_2 :

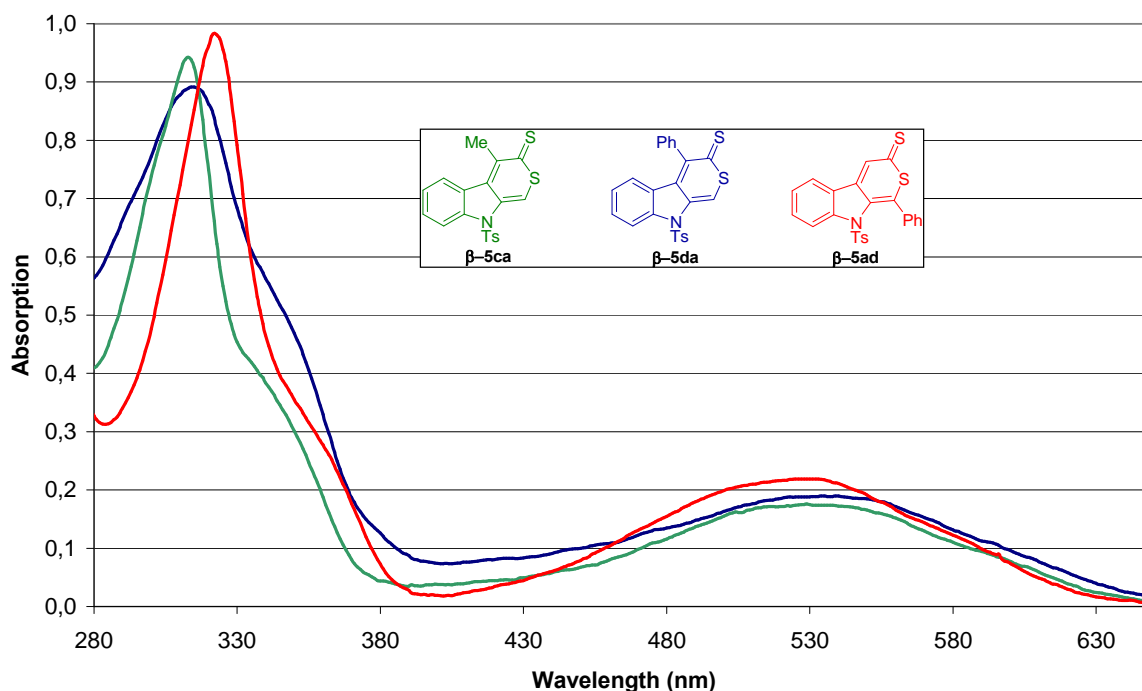


Figure III-15: UV-Spectra of the violet thiopyranothiones β -5ca, β -5da and β -5ad.

Table II-18: UV-Properties of the violet thiopyranothiones β -5ca, β -5da and β -5ad

Entry	Thiopyranothione	R ¹	R ²	C _m (mmol/mL)	λ_{max}	A _{max}	ϵ_1	log ϵ_1	$\lambda_{\text{max}2}$	A _{max2}	ϵ_2	log ϵ_2
1	β -5da	Ph	H	4,47E-05	535	0,1894	4240	3,63	313	0,9427	21099	4,32
2	β -5ca	Me	H	4,46E-05	529	0,1752	3927	3,59	312	0,8912	19974	4,30
3	β -5ad	H	Ph	4,47E-05	527	0,2187	4895	3,69	322	0,9836	22013	4,34

The UV-spectroscopy of the three violet thiopyranothiones β -5ca, β -5da and β -5ad gave similar spectra, showing in each case two maxima of absorption. A low energy maximum appears at about 531 nm, probably corresponding to a $n \rightarrow \pi^*$ transition of the C=S bond. A second maximum appears in the UV at about 317 nm, probably corresponding to the $\pi \rightarrow \pi^*$ transition of the whole conjugated system together with a $n \rightarrow \sigma^*$ transition of the C-S-C system.

- study of thiopyrano[4,3-*b*]indole-3-thiones

Similarly, UV-spectra of the red thiopyranothiones γ -5aa and γ -5da were recorded in CH_2Cl_2 :

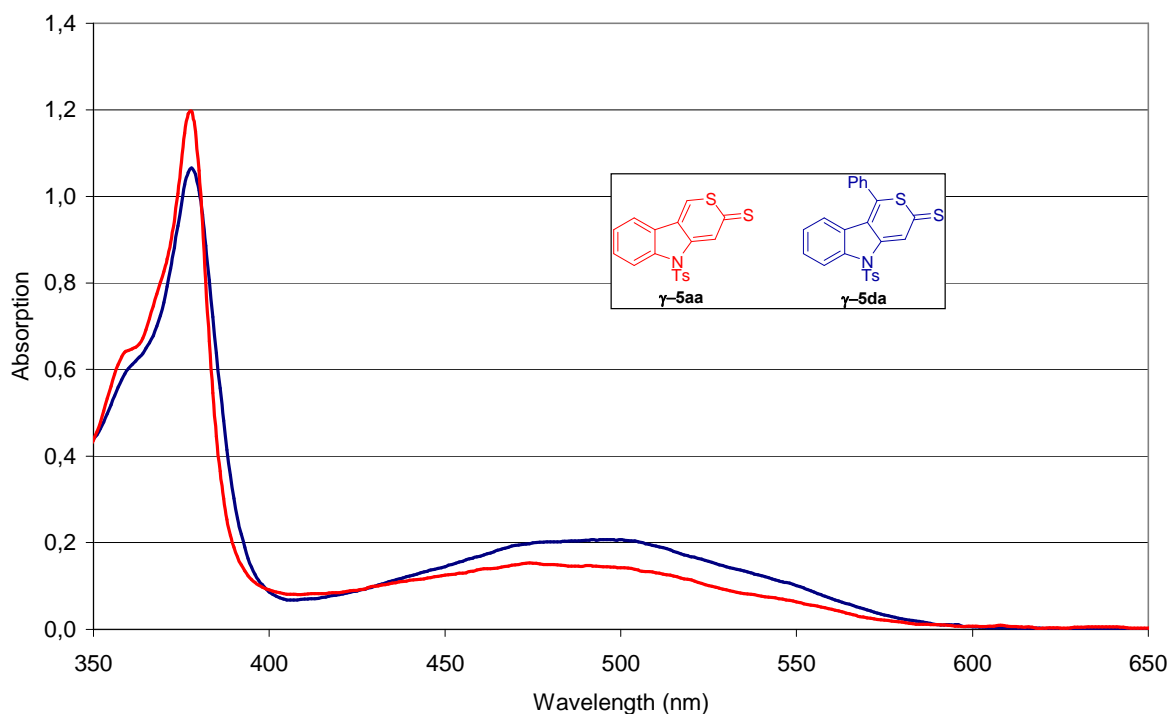


Figure III-16: UV-spectra of the red thiopyranothiones γ -5aa and γ -5da.

Table II-19: UV-Properties of the red thiopyranothiones γ -5aa and γ -5da

Entry	Thiopyranothione	R ¹	R ²	C _m (mmol/mL)	λ_{max}	A _{max}	ϵ_1	log ϵ_1	$\lambda_{\text{max}2}$	A _{max2}	ϵ_2	log ϵ_2
1	γ -5aa	H	H	4,31E-05	474	0,1534	3562	3,55	378	1,1960	27770	4,44
2	γ -5da	Ph	H	4,47E-05	497	0,2069	4631	3,67	378	1,0653	23841	4,38

The UV-spectroscopy of the red thiopyranothiones γ -5aa and γ -5da gave similar curves with two maxima. A broad band appears in the visible part with $\lambda_{\text{max}} = 474$ nm and 497 nm respectively, probably corresponding to the $n \rightarrow \pi^*$ transition of the C=S bond. A second band appears at 378 nm for both molecules, probably corresponding to a $\pi \rightarrow \pi^*$ transition of the whole conjugated system together with a $n \rightarrow \sigma^*$ transition of the C-S-C system. Both molar extinction coefficients of γ -5da ($\epsilon_1 = 4631$ and $\epsilon_2 = 23841$) are of the same order than those of its violet isomer β -5da ($\epsilon_1 = 4240$ and $\epsilon_2 = 21099$). The two isomeric forms are differentiated by a significant shift of the C=S $n \rightarrow \pi^*$ transition of about 40 nm.

- solvatochromie of the thiopyranothiones β -5da and γ -5da

The influence of solvent polarity on the absorption spectra of β -5da and γ -5da was studied.

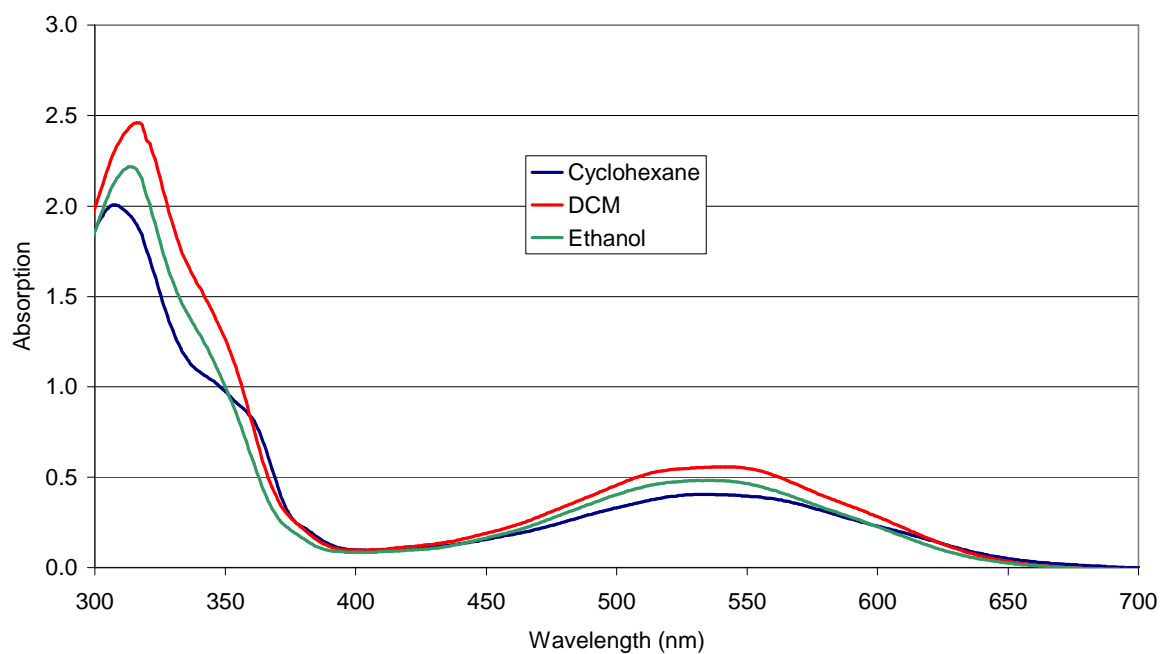


Figure III-17: UV-spectrum of the violet thiopyranothione β -5da in different solvents.

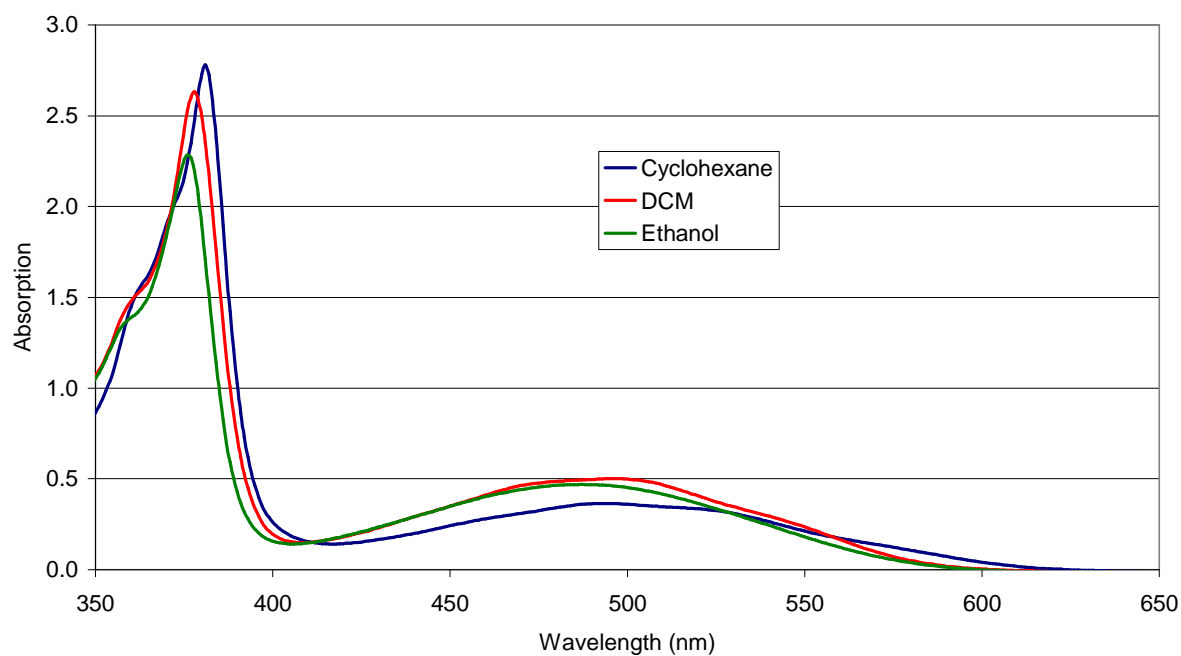


Figure III-18: UV-spectrum of the red thiopyranothione γ -5da in different solvents.

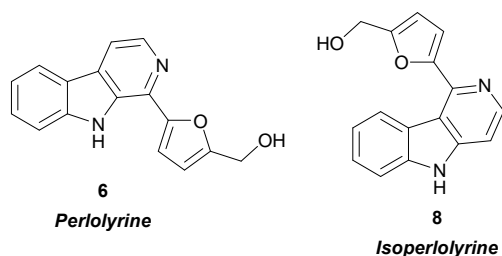
Table II-20: Solvatochromy of the thiopyranothiones β -5da and γ -5da

Entry	Thiopyranothione	Solvent	C _m (mmol/mL)	$\lambda_{\max 1}$	A _{max1}	ϵ_1	log ϵ_1	$\lambda_{\max 2}$	A _{max2}	ϵ_2	log ϵ_2
1	β -5da	Cyclohexane	1,12E-04	535	0,4052	3628	3,56	307	0,9427	17963	4,25
2	β -5ca	CH ₂ Cl ₂	1,12E-04	54	0,5583	4998	3,70	317	0,8912	22016	4,34
3	β -5ad	Ethanol	1,12E-04	535	0,4824	4319	3,64	313	0,9836	19845	4,30
4	γ -5da	Cyclohexane	1,12E-04	494	0,3646	3263	3,51	381	2,7803	24889	4,40
5	γ -5da	CH ₂ Cl ₂	1,12E-04	497	0,5004	4480	3,65	378	2,6323	23564	4,37
6	γ -5da	Ethanol	1,12E-04	487	0,4691	4200	3,62	376	2,2850	20456	4,31

In both case, the solvent has only small effects on the UV-spectrum, giving only a small difference of few nanometers for the maxima of absorption.

III.2. Total syntheses of *Isoperlolyrine* and *Perlolyrine*

The novel strategy for the synthesis of β - and γ -carboline cores appears to be very interesting for the total synthesis of natural products. In order to prove this, the total syntheses of the β -carboline *Perlolyrine* **6** and its structural isomer γ -carboline *Isoperlolyrine* **8** were investigated.

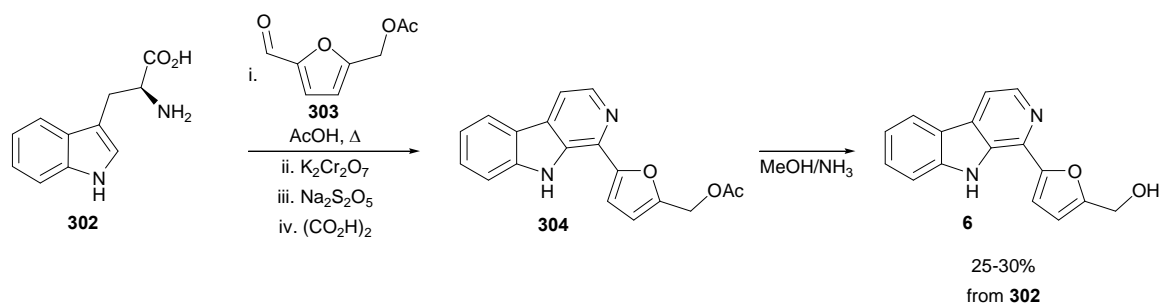


Scheme III-41: *Perlolyrine* and *Isoperlolyrine*.

III.2.1. Presentation

Isoperlolyrine is, to the best of our knowledge, the only natural product possessing a γ -carboline core. *Isoperlolyrine* was isolated in 1984 from the seeds of *Gloriosa superba* L.^[36] but was curiously not subjected to further investigation. Its total synthesis has notably never been reported up to now, making it a challenging subject. On the contrary, *Perlolyrine* is much better known. It was first isolated in 1970 by Jeffreys in perennial rye-grass (*Lolium perenne* L.)^[99] and found later in several other plants (*Panax ginseng*^[100], *Codonopsis lanceolata*^[101] *Codonopsis pilosula*^[102], *Lycium chinense*^[103]) but also in Japanese sake^[104] and soy sauce^[105]. *Perlolyrine* is also known as “yellow substance, YS” due to its high

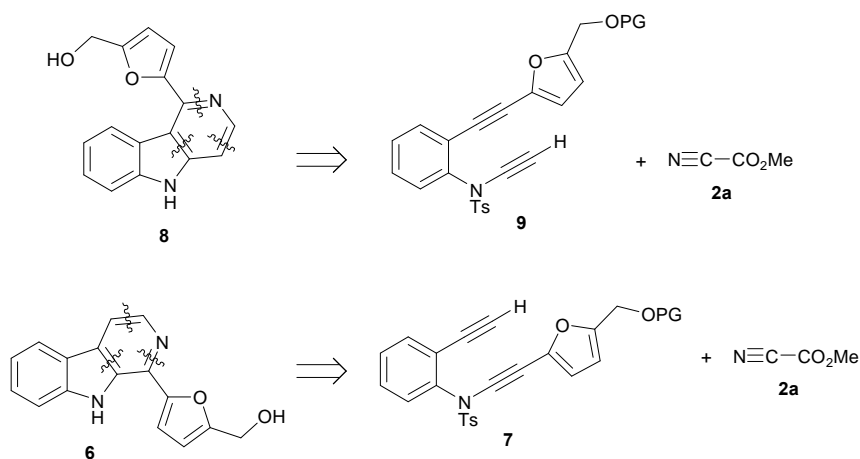
fluorescence properties.^[105] *Perlolyrine* was already successfully synthesized in few steps from tryptophane^[99] or tryptamine^[106].



Scheme III-42: Synthesis of *Perlolyrine* by Jeffreys.^[99]

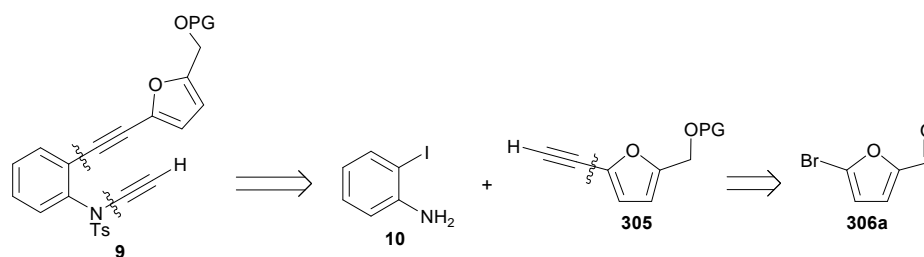
III.2.2. Retro-synthetic approach

The total syntheses of *Isoperlolyrine* and *Perlolyrine* were envisaged to use the [2+2+2] cycloaddition as a key-step.



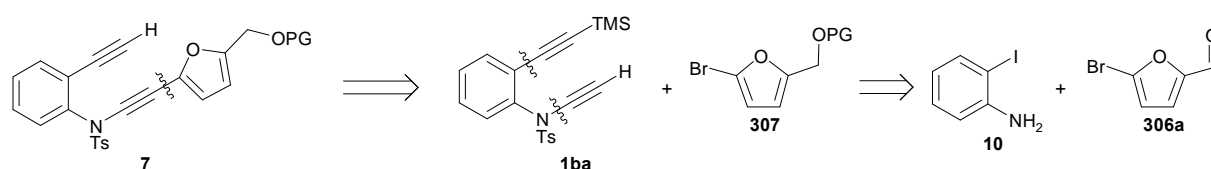
Scheme III-43: Retro-synthesis of *Isoperlolyrine* and *Perlolyrine*.

The diyne required for the synthesis of *Isoperlolyrine* should be synthesized from 2-iodoaniline **10** and 5-bromo-furan-2-aldehyde **306a** via one of the previously described methods for the synthesis of diynes with a terminal ynamide moiety.



Scheme III-44: Retro-synthesis of the required diyne for the synthesis of *Isoperlolyrine*.

Similarly, the diyne required for the synthesis of *Perlolyrine* should be obtained by the functionalization of the diyne **1ba** with a derivative **307** of the 5-bromo-furan-2-aldehyde **306a**.



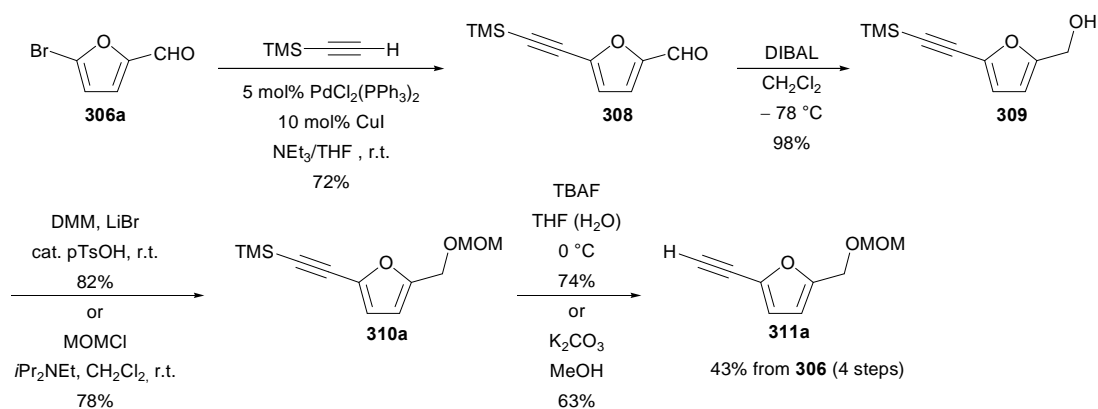
Scheme III-45: Retro-synthesis of the required diyne for the synthesis of *Perlolyrine*.

III.2.3. Total synthesis of *Isoperlolyrine* – first approach

In a first approach, the hydroxymethyl group on the furane ring was introduced at an early stage and protected as a methoxymethyl-ether (MOM route).

III.2.3.1. Methoxymethyl route (MOM route)

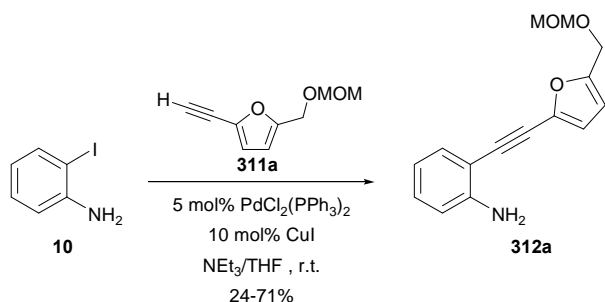
III.2.3.1.1. Synthesis of the alkyne



Scheme III-46: Synthesis of the terminal alkyne **311a**.

The reaction sequence afforded the terminal alkyne **311a** in a satisfying yield of 43% from 5-bromo-furfural **306a**. However, the yields decreased when the reaction was performed at the gram-scale (≈ 5 mmol). Moreover, both alkynes **310a** and **311a** revealed to be unstable, decomposing rapidly to a black tar, the terminal alkyne **311a** decomposed rapidly even by storing at (-26 °C).

III.2.3.1.2. Synthesis of the diyne

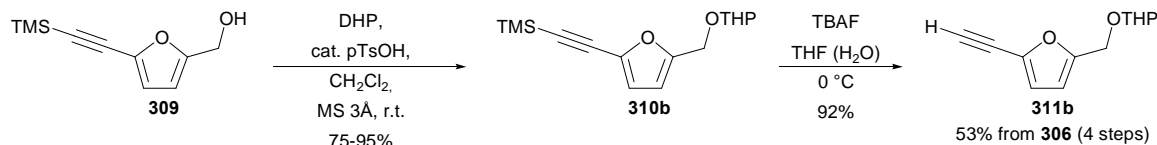


Scheme III-47: Sonogashira-coupling of 2-iodoaniline with the terminal alkyne **311a**.

Nevertheless, the Sonogashira coupling of the terminal alkyne was achieved in a satisfying yield of 71%. But here again, up-scaling the reaction led to a drastic decrease of the yield in product (24%). Moreover, the product **312a** decomposed within a few hours in the fridge. As a consequence, another protecting group (THP) was selected for the reaction sequence. Å

III.2.3.2. Tetrahydropyranyl route (THP route)

III.2.3.2.1. Synthesis of the alkyne

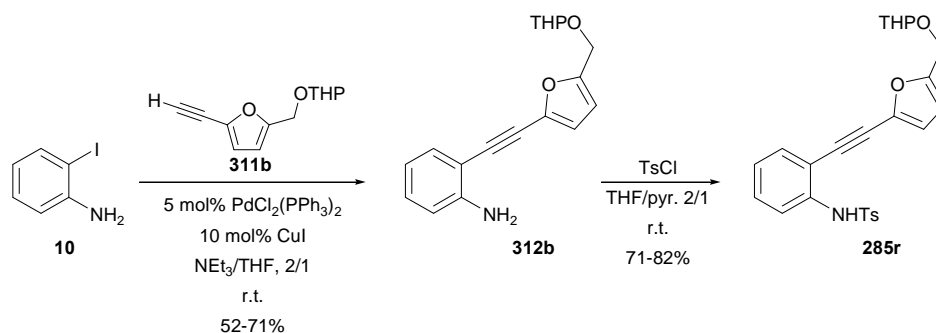


Scheme III-48: Synthesis of the terminal alkyne **311b**.

Protection of the alcohol function of **309** by a THP group followed by desilylation led to the terminal alkyne **311b** in a satisfying yield of about 53% from the 5-bromo-furfural **306**. Similarly to the MOM-protected alkyne **311a**, the THP-protected alkyne **311b** is prone to decomposition but can be kept for a few days at -26 °C.

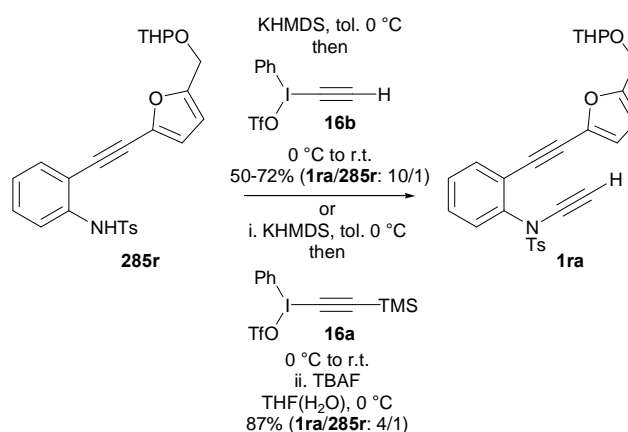
III.2.3.2.2. Synthesis of the diyne

The diyne **1ra** was synthesized according the method A starting with a Sonogashira coupling of 2-iodoaniline **10** to the terminal alkyne **311b** followed by tosylation of the resulting amine **312b**.



Scheme III-49: Synthesis of the sulfonamide **285r**.

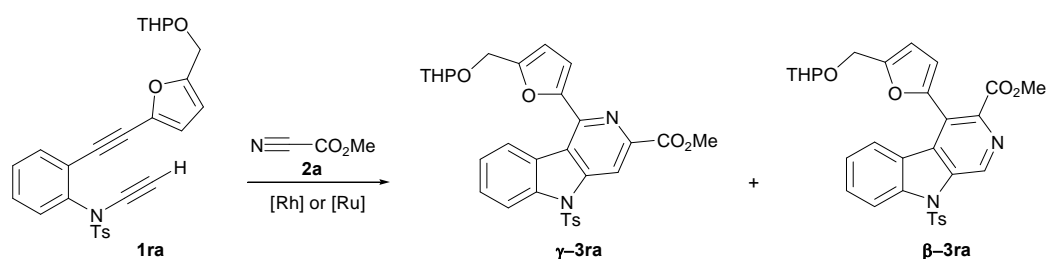
The next step, the *N*-ethynylation proved to be difficult, leading to a mixture of the desired product and unreacted starting material which could not be well separated. Similar results were obtained when the reaction was performed in a two-step sequence via the TMS-substituted diyne. Use of a larger excess of iodonium salt allowed to get a complete conversion and to increase the yield up to 72%. But, the resulting diyne proved to be unstable and decomposed readily in a few hours. It can be kept in solution at $-26\text{ }^{\circ}\text{C}$ for a short period.



Scheme III-50: Synthesis of the diyne **1ra**.

III.2.3.2.3. Key-step of [2+2+2] cycloaddition

With the required diyne **1ra** in hand, the key-step of the synthesis was investigated



Scheme III-51: Attempted synthesis of the γ -carboline γ -3ra.

Table III-21: [2+2+2] cycloaddition of the diyne **1ra** with methylcyanoformate

Entry	Catalytic system	Solvent	Temperature	Duration	Yield ^a	Ratio γ : β ^b
1	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 10 mol% / 12 mol%	DCM	r.t.	overnight	<7%	1:0.22 5/1
2	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 10 mol% / 12 mol%	DCM	r.t.	3 days	<16%	1:0.48 2/1
3	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	DCM	60 °C	3 days	<22%	1:0.30 3/1
4	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 10 mol% / 12 mol%	THF	60 °C	3 days	<64%	1:1.96 1/2
5	Cp* <i>Ru</i> Cl(COD) 10 mol%	DCM	r.t.	overnight	traces	-
6	Cp* <i>Ru</i> Cl(COD) 10 mol%	DCM	120 °C	overnight	traces	-

a) isolated yield (mixture of both isomers); b) determined by ¹H NMR of the isolated product

As illustrated by Table III-21, the reaction proved to be difficult. Cycloadditions in DCM gave disappointing results: a slow conversion was observed to give only small amounts of the desired carbolines even after three days of reaction. Moreover, the two regioisomers could not be separated. Increasing the catalyst loading and switching from DCM to THF enhanced the reaction but led to a reversal of the regioselectivity to give the β -carboline β -3ra as major product (entry 4). Experiments with Cp**Ru*Cl(COD) as a catalyst gave poor results: reaction at room temperature showed almost no conversion to carboline whereas a reaction at 120 °C led only to the decomposition of the diyne.

As this first approach of synthesis of *Isoperloloyrine* suffered from chemical instabilities of most intermediates, dropping yields upon up-scaling and poor yields of the cycloaddition, an

other strategy has to be considered. The synthesis was left aside and our attention turned to the synthesis of *Perlolyrine*.

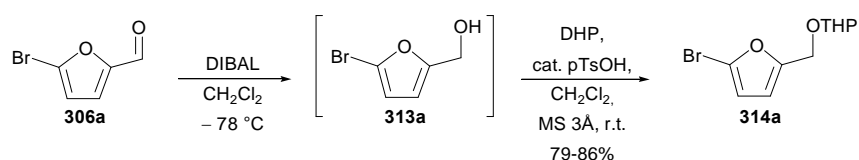
III.2.3.2. Total synthesis of *Perlolyrine*

The first approach to synthesize *Perlolyrine* was similar to the one used for *Isoperlolyrine*.

III.2.3.2.1. Tetrahydropyranyl route (THP route)

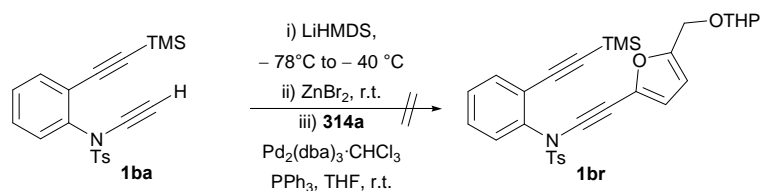
III.2.3.2.1.1. Synthesis of the diyne

The bromo-furane required for the functionalization of the diyne **1ar** was synthesized in a two-step sequence from the 5-bromo-furfural in a 79-86% yield. Attempts to isolate the hydroxyl- intermediate were unsuccessful, leading to a rapid decomposition of the product. The protected alcohol is more stable but also decomposed rapidly upon standing, it can be stored for a few days at $-26\text{ }^{\circ}\text{C}$.



Scheme III-52: Synthesis of the THP-protected hydroxymethyl-furane **314a**.

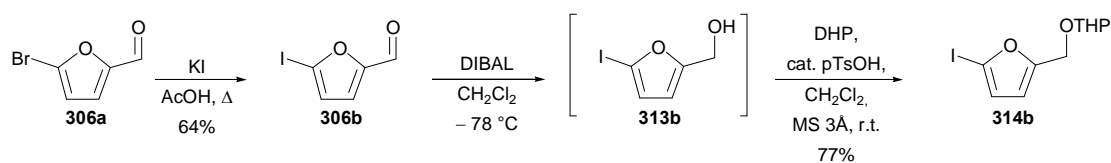
The functionalization of the diyne **1ba** was tried via a Negishi coupling with the freshly prepared bromo-furane **314a** but no reaction was observed.



Scheme III-53: Attempt of Negishi coupling of the bromo-furane **314a** with the diyne **1ba**.

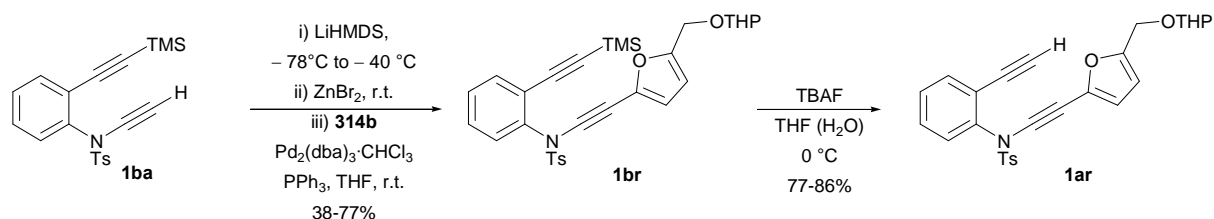
This result is probably due to the poor reactivity of the bromo-compound towards the coupling. As a result, the coupling with its iodo-derivate came in consideration. For this purpose, the synthesis of 5-iodofurfural was performed according to a known procedure^[107]

and the resulting 5-iodo-furfural **306b** was subjected to the same reduction/protection sequence to give the desired protected alcohol **314b**.



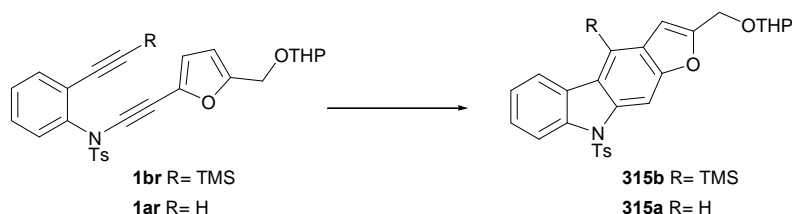
Scheme III-54: Synthesis of the THP-protected hydroxymethyl-furane **314b**.

Fortunately, the Negishi coupling of the latter with the diyne **1ba** was successful, giving the diyne **1br** which was desilylated to the expected diyne **1ar**.



Scheme III-55: Synthesis of the diyne **1ar**.

However, both coupling and desilylation reactions gave the carbazoles **315a-b** as by-products.

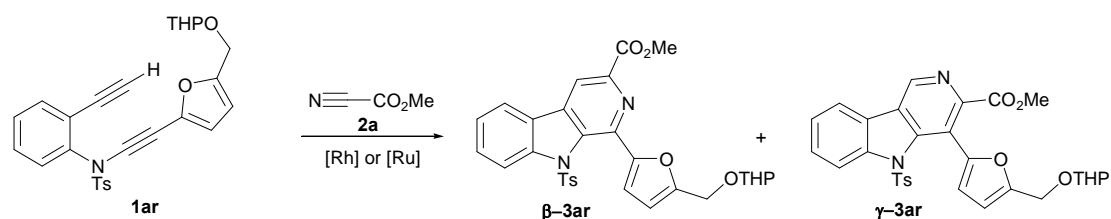


Scheme III-56: Side-reaction of intramolecular cyclization.

This tricky intramolecular cyclization – which was already studied with aryl-substituted diynes and described as a “dehydro Diels-Alder reaction”^[108] – made the Negishi coupling particularly hard to control. An extended reaction time led to larger amounts of by-product whereas a shortened reaction time gave an incomplete conversion of the starting diyne. The progress of the reaction was difficult to control since the starting diyne **1ba** and the by-product **315b** could not be differentiated by TLC analysis. A possible solution would be to follow the conversion of the starting material by HPLC or ¹H-NMR at regular intervals.

III.2.3.2.1.2. Key-step of [2+2+2] cycloaddition

The [2+2+2] cycloaddition of the diyne **1ar** with methylcyanoformate led to the desired β -carboline **β -3ar** as major product in moderate to good yields.



Scheme III-57: Cycloaddition of the diyne **1ar** with methylcyanoformate.

Table III-22: Study of the key-step of the synthesis of *Perlolryne*

Entry	Catalytic system	Solvent	Temperature	Duration	Yield ^a	Ratio β : γ ^b
1	Cp*RuCl(COD) 10 mol%	DCM	r.t.	overnight	45%	1:0.22 3/1
2	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	DCM	r.t.	2 days ^c	12%	1:0.04 25/1
3	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	DCM	60 °C	overnight	27%	1:0.13 7/1
4	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	THF	r.t.	6 days ^c	48%	1:0.8 12/1
5	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 10 mol% / 12 mol%	THF	r.t.	6 days ^c	80%	1:0.10 10/1
6	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	THF	60 °C	overnight	78%	1:0.09 11/1

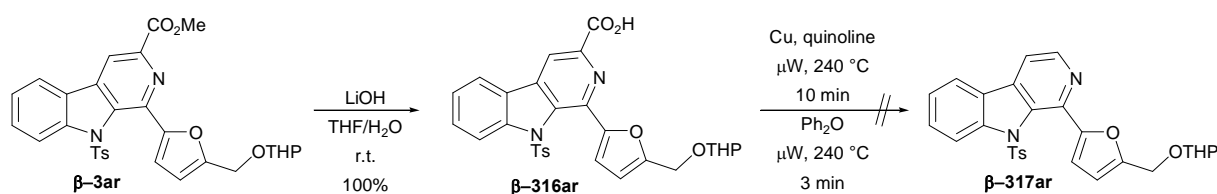
a) isolated yield (mixture of both isomers); b) determined by ¹H NMR of the crude product;
c) incomplete conversion

Table III-22 shows that the yield and regioselectivity depend strongly on the catalyst and on the conditions used. The ruthenium-catalyzed cycloaddition gave a mixture of the isomeric carbolines in a moderate yield of 45% and an unexpected regioselectivity of β : γ = 3/1 (entry 1). The rhodium-catalyzed [2+2+2] cycloaddition gave a higher regioselectivity but in a much lower total yield under the same conditions, albeit with a lower loading of catalyst (entry 2). A raise of the reaction temperature to 60 °C led to an increase of the yield to 27% but had a negative effect on the regioselectivity. Again, switching from DCM to THF had a remarkable influence on the reaction since the carbolines could be obtained with a satisfying yield of 78%

and a very good regioselectivity (entry 6). A similar result was obtained when the reaction was performed at room temperature using a double amount of catalyst (entry 5).

III.2.3.2.1.3. Completion of the synthesis

With the synthesis of the β -carboline **β -3ar**, an important step was completed and few steps remained to obtain the *Perlolyrine*. In a first approach, the cleavage of the methyl ester and decarboxylation of the resulting acid, followed by deprotection and detosylation was envisaged.



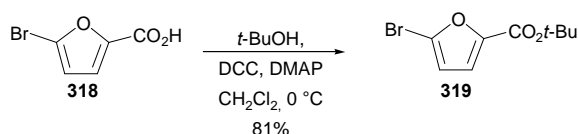
Scheme III-58: Attempts to the decarboxylation of the β -carboline **β -316ar**.

Unfortunately, attempts to decarboxylate the acid to give the desired carboline **β -317ar** failed and led to the decomposition of the acid. Alternative ways were tried such as first deprotection of the alcohol or detosylation of the indole nitrogen but these reactions did not lead to satisfying results. As the protected furfuryl-alcohol was supposed to be the source of the difficulty of the decarboxylation step, other strategies which would mask the furfuryl-alcohol function were investigated. Or, in parallel of the study of *Perlolyrine*'s synthesis, it was observed that 5-bromo-furyl compounds bearing an electron-attracting group ((thio)ester) were excellent substrates for the functionalization of ynamides as well as for the rhodium-catalyzed [2+2+2] cycloaddition reaction. Moreover, these derivatives are much easier to handle as they were often obtained as stable solids. As a consequence, such a compound was envisaged to be used for the synthesis of *Perlolyrine*. However, this ester group would have to be later differentiated from the methyl ester group brought by the cycloaddition with the methylcyanofornate. After careful consideration, the use of a *tert*-butyl ester group was selected for the new synthesis approach.

III.2.3.2.2. *tert*-Butyl ester route

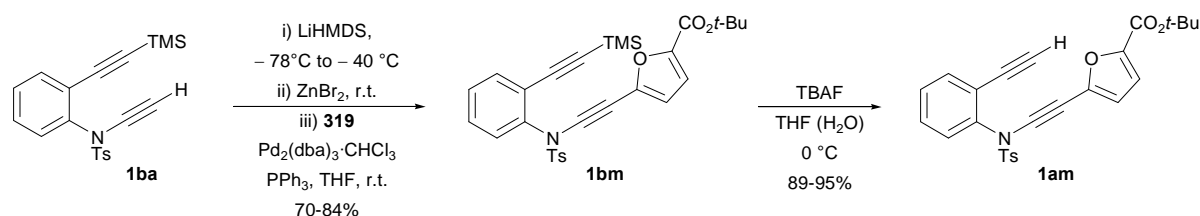
III.2.3.2.2.1. Synthesis of the diyne

The synthesis starts with the preparation of the *tert*-butyl ester **319** required for the functionalization of the diyne **1ba**. This bromo-ester was easily obtained as a stable solid by esterification of the 5-bromo-furoic acid **318** in 81% yield.



Scheme III-59: Synthesis of the ester **319**.

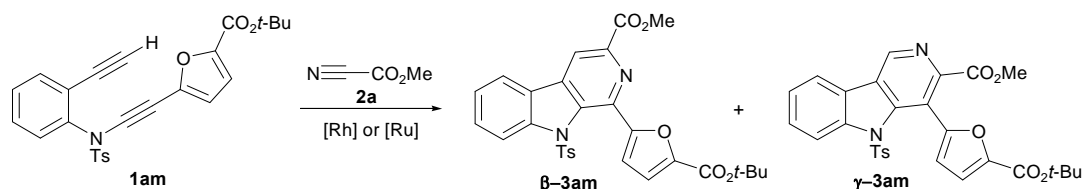
Coupling of this bromo-furane with the diyne **1ba** led to the diyne **1bm** which afforded the desired diyne **1am** after desilylation together with small amounts of the intramolecular cycloaddition by-products.



Scheme III-60: Synthesis of the diyne **1am**.

III.2.3.2.2.2. Key-step of [2+2+2] cycloaddition

The [2+2+2] cycloaddition of the diyne **1am** with methylcyanoformate led to the desired β -carboline β -**3am** as major product in excellent yields and high regioselectivities with the rhodium-based catalyst as well as with the ruthenium catalyst.



Scheme III-61: Cycloaddition of the diyne **1am** with methylcyanoformate.

Table III-23: Study of the key-step of the synthesis of *Perlolyrine*

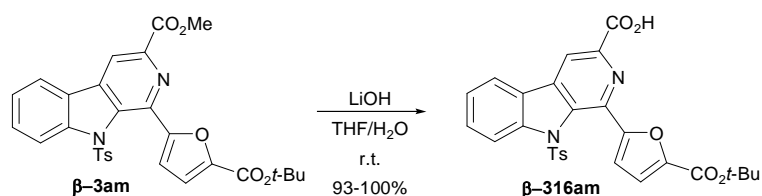
Entry	Catalytic system	Solvent	Temperature	Duration	Yield ^a	Ratio β : γ ^b
1	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 10 mol% / 12 mol%	THF	r.t.	1 week	26%	1:0.23 4/1
2	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	THF	60 °C	3 hours	99%	1:0.12 8/1
3	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 3 mol% / 3.6 mol%	THF	60 °C	6 hours	98%	1:0.10 10/1
4	Cp [*] RuCl(COD) 10 mol%	DCE	r.t.	3 hours	69%	only β
5	Cp [*] RuCl(COD) 10 mol%	DCE	60 °C	3 hours	82%	only β
6	Cp [*] RuCl(COD) 10 mol%	DCM	40 °C	overnight ^c	97%	only β

a) isolated yield (both isomers); b) determined by ¹H NMR of the crude product; c) addition of the diyne in 6 hours

The cycloaddition with the ruthenium catalyst proceeded smoothly at room temperature to give the desired β -carboline in 69% yield together with a small amount of the dimers and the intramolecular cyclization by-product (entry 4). Raising the reaction temperature to 60 °C led to a slight increase of the yield to 82% (entry 5). Addition of the diyne in a period of 6 hours almost suppressed the side-reactions and gave the desired β -carbolines in an excellent yield of 97% (entry 6). The cycloaddition with the rhodium-based catalyst proved to proceed slowly at room temperature but showed a complete conversion after 3 hours at 60 °C to give a mixture of easily separable isomers in an excellent yield and with a satisfying regioselectivity (entry 2). The catalyst loading could be even reduced to 3 mol% without significant changes in yield and in regioselectivity (entry 3).

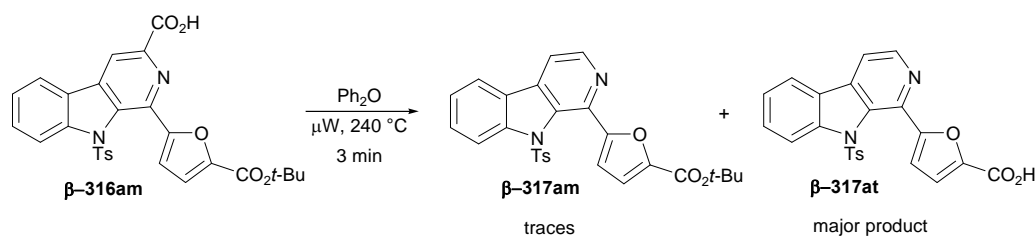
III.2.3.2.2.3. Completion of the synthesis

Encouraged by the excellent results of the cycloaddition step, the completion of the synthesis was examined. In a first step, the methyl ester group was cleaved almost quantitatively to give the acid β -**316am**, which was then subjected to decarboxylation.



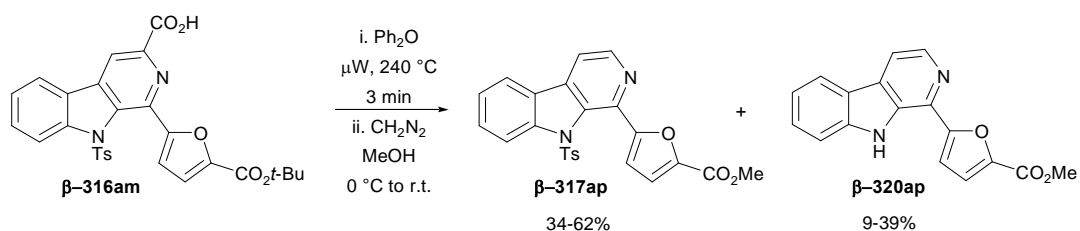
Scheme III-62: Cleavage of the methyl ester of $\beta\text{-3am}$.

The first experiment to decarboxylate the picolinic acid led to an unexpected result since a thermal cleavage of the *tert*-butyl ester was observed as a parallel reaction to give the β -carboline $\beta\text{-317at}$ as main product. A precise yield could however not be obtained due to the contamination of the product by diphenylether.



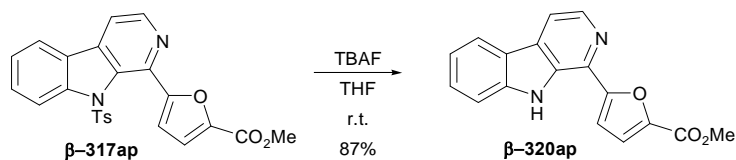
Scheme III-63: Decarboxylation of the picolinic acid.

Unfortunately, attempts to reduce this acid directly with $\text{BH}_3\cdot\text{THF}$ or LiAlH_4 were not successful. To circumvent this problem, the crude mixture from the decarboxylation reaction was directly subjected to methylation with a diazomethane solution to give the furyl ester $\beta\text{-317ap}$ together with variable amounts of the detosylated carboline $\beta\text{-320ap}$.



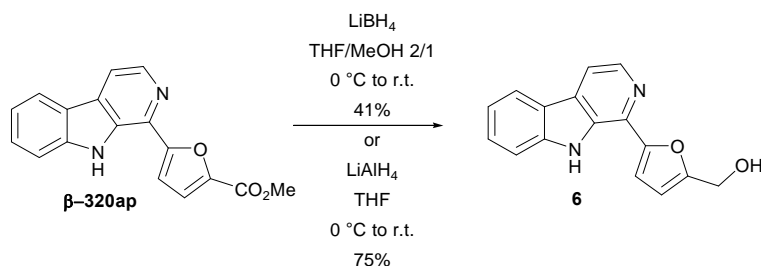
Scheme III-64: Synthesis of the carboline $\beta\text{-317ap}$.

Detosylation of the β -carboline $\beta\text{-317ap}$ was achieved by addition of TBAF via a known procedure.^[109]



Scheme III-65: Detosylation of the carboline $\beta\text{-317ap}$.

The last step, the reduction of the methyl ester was initially examined in a first experiment by reaction with LiBH_4 but a total conversion was not possible even though a large excess of the reducing agent was used (20 equiv.). Nevertheless, purification of the reaction mixture led to *Perlolyrine* **6** in a yield of 41% and 49% of the ester was recovered. LiAlH_4 as reducing agent gave better results but the reaction required 6 equivalents of LiAlH_4 for a complete conversion. *Perlolyrine* could be obtained in 75% yield.



Scheme III-66: Last step of reduction of the methyl ester of $\beta\text{-320ap}$.

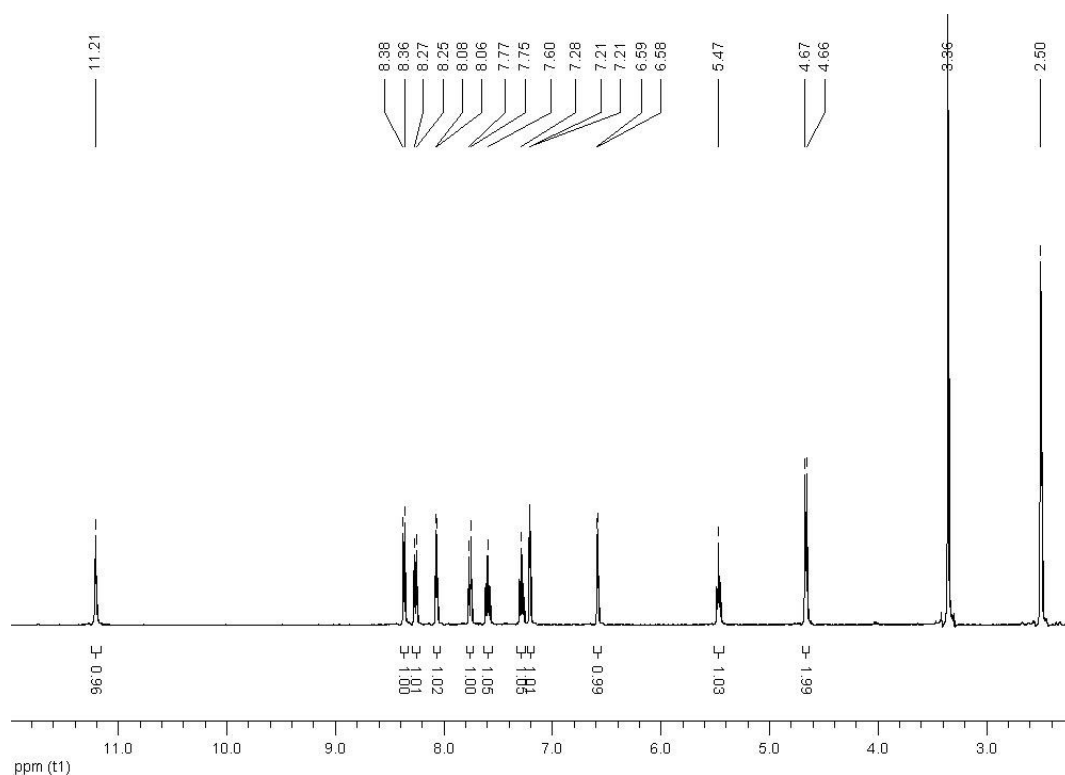


Figure III-19: $^1\text{H-NMR}$ spectrum of *Perlolyrine* in DMSO-d_6 .

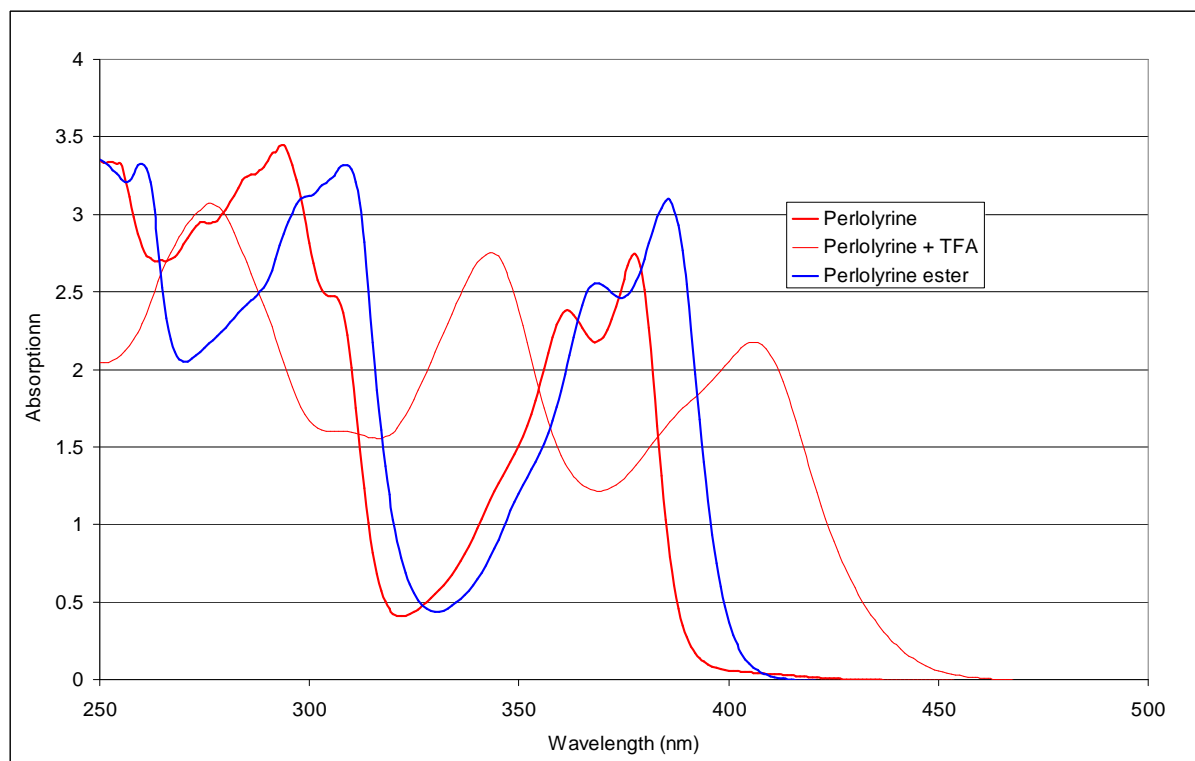
III.2.3.2.2.4. UV-Vis and fluorescence spectroscopy of *Perlolyrine*

Figure III-20: UV-spectra of *Perlolyrine 6* and its ester derivative β -320ap

Table III-24: UV-Vis Properties of *Perlolyrine 6* and its methyl ester derivative β -320ap

Entry	Substance	Cm (mmol/mL)	λ_{\max}	A_{\max}	ϵ	$\log \epsilon$	$\lambda_{\max 2}$	$A_{\max 2}$	ϵ_2	$\log \epsilon_2$
1	Perlolyrine ester β -320ap	1.71E-04	386	3.0914	18072	4.26	309	3.3186	19401	4.29
2	Perlolyrine 6	1.85E-04	378	2.7422	14790	4.17	294	3.4451	18581	4.27
3	Perlolyrine 6 + TFA	1.85E-04	406	2.1751	11731	4.07	343	2.7508	14836	4.17

As depicted by the Figure III-20, *Perlolyrine* and the ester β -320ap give similar absorption spectra with two maxima of absorption corresponding to the $\pi \rightarrow \pi^*$ transition of the whole conjugated system. A maximum of absorption appears at 378 nm for *Perlolyrine* and 386 nm for the ester. These transitions are allowed as shown by the molar extinction coefficients of both substances, the coefficient of the ester (~18000) being slightly higher as the one of *Perlolyrine* (~15000). A second maximum is observed in each case at 294 nm for *Perlolyrine* and 309 nm for the ester with similar molar extinction coefficients (~19000). Protonation of *Perlolyrine* by TFA led to drastic changes in the UV-spectrum. A third absorption maximum appeared at 276 nm in addition to noticeable bathochromic shifts of the two other maxima of 28 nm for the first maximum (378 nm to 406 nm) and 49 nm for the second one (294 nm to 343 nm).

- fluorescence spectroscopy

The fluorescence properties of *Perlolyrine 6* and the ester β -320ap were studied:

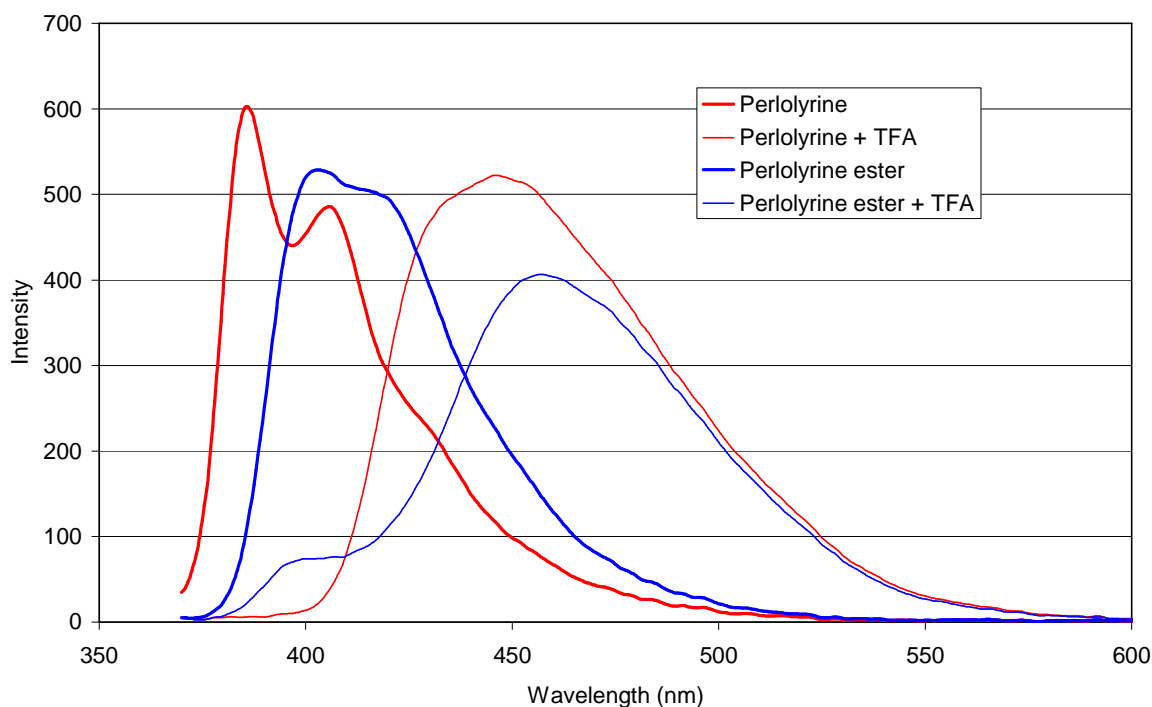


Figure III-21: Fluorescence-spectra of *Perlolyrine 6* and its ester derivative β -320ap

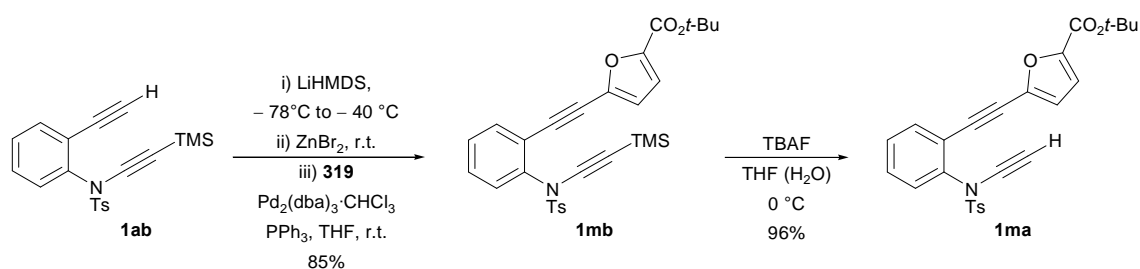
As depicted by Figure III-21, *Perlolyrine* presents a fluorescence maximum at 386 nm whereas the ester β -320ap presents a maximum at 403 nm. Protonating the two substances by TFA results in bathochromic shifts of the fluorescence, the maxima are shifted about 60 nm towards longer wavelengths.

So, *Perlolyrine* was successfully obtained using a [2+2+2] cycloaddition of a diyne and a nitrile as key-step with an overall yield of about 15-20% from 2-iodoaniline. This success was encouraging and brought us to apply this “*tert*-butyl ester” strategy to the synthesis of *Isoperlolyrine*.

III.2.3.3. Total synthesis of *Isoperlolyrine* – second approach

III.2.3.3.1. Synthesis of the diyne

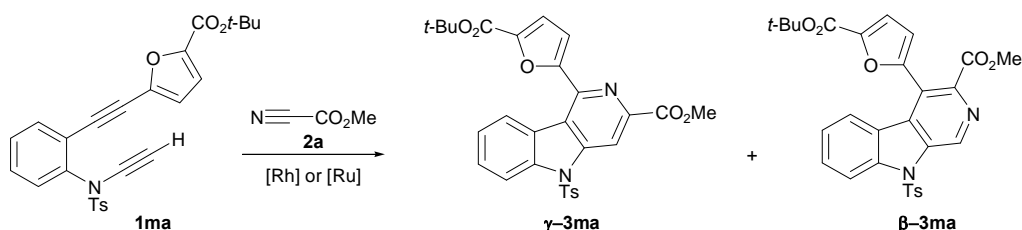
Following the same strategy as for *Perlolyrine*, the diyne **1mb** was prepared in 85% yield by a Negishi-coupling of the 5-bromofurane *tert*-butyl ester **319** with the terminal alkyne **1ab**. Desilylation of the resulting diyne gave the diyne **1ma** in a 96% yield.



Scheme III-67: Synthesis of the diyne **1ma**

III.2.3.3.2. Key-step of [2+2+2] cycloaddition

With the diyne **1ma** in hand, the key-step, the cycloaddition with methylcyanoformate was investigated. Unfortunately, the cyclizations in the *Isoperlolyrine* synthesis proved to be much more difficult than in the *Perlolyrine* synthesis. In the case of the rhodium-catalysed cycloaddition, the expected carbolines were obtained in a 49% yield but the desired isomer was obtained as minor isomer (γ -**3ma**/ β -**3ma** = 1/3) (reaction in THF, entry 1). Cycloaddition with the ruthenium catalyst led to the desired isomer as sole product but in a relatively low yield of 26% when the reaction performed at room temperature. A raise of the reaction temperature to 60°C led to a moderate yield of 46% (entry 3) whereas performing a higher raise of the reaction temperature led mostly to decomposition of the diyne. Increasing the amount of catalyst to 50 mol% allowed to get the γ -carboline γ -**3ma** in a satisfying yield of 69% (entry 6).



Scheme III-68: Cycloaddition of the diyne **1ma** with methylcyanoformate.

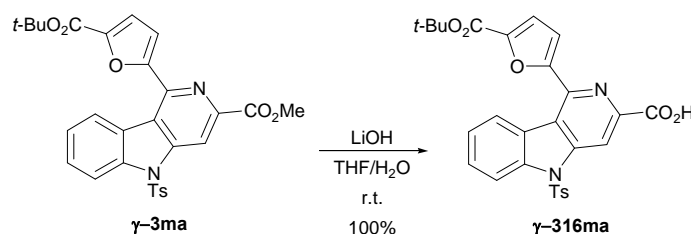
Table III-25: Key-step of the synthesis of *Isoperlolyrine*

Entry	Catalytic system	Solvent	Temperature	Duration	Yield ^a	Ratio γ : β ^b
1	[Rh(COD) ₂] ⁺ BF ₄ ⁻ /BINAP 5 mol% / 6 mol%	THF	60 °C	3 hours	48%	1:2.88 1/3
2	Cp [*] RuCl(COD) 10 mol%	DCM	r.t.	overnight ^{c, d}	26%	only γ
3	Cp [*] RuCl(COD) 10 mol%	DCM	60 °C	overnight ^c	46%	only γ
4	Cp [*] RuCl(COD) 10 mol%	DCE	80 °C	overnight ^{c, d}	traces	only γ
5	Cp [*] RuCl(COD) 20 mol%	DCM	40 °C	overnight ^d	40%	only γ
6	Cp [*] RuCl(COD) 50 mol%	DCM	40 °C	6 hours ^d	69%	only γ

a) isolated yield (both isomers); b) determined by ¹H NMR of the crude product; c) incomplete conversion; d) addition of the diyne in 4 hours

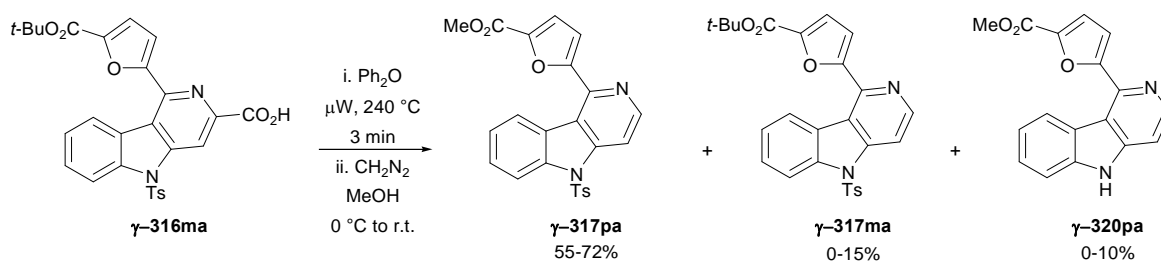
III.2.3.3.3. Completion of the synthesis

Following the same strategy as for *Perlolyrine*, the methyl ester was cleaved with LiOH to give quantitatively the acid γ -316ma.



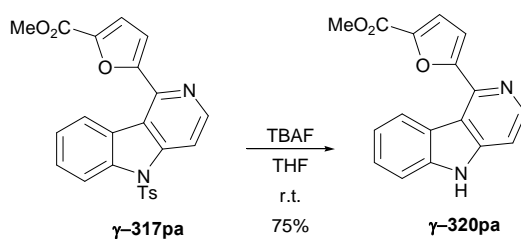
Scheme III-69: Cleavage of the methyl ester of β -3ma.

As decarboxylation of this compound led to the concomitant thermal cleavage of the *t*-butylester, the crude reaction mixture was directly subjected to methylation with a diazomethane solution to give the methyl ester γ -317pa as major product in a 55-72% yield together with variable amounts of the *tert*-butyl ester γ -316ma and the detosylated methyl ester γ -318pa.



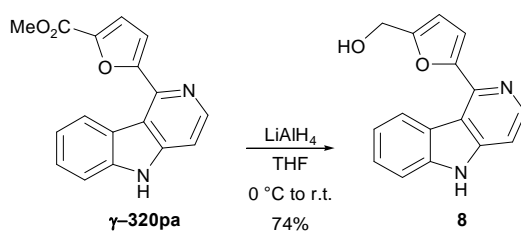
Scheme III-70: Decarboxylation of the carboline **γ -316ma**.

Further detosylation with TBAF led to the carboline **γ -317pa** in a good yield of 75%.



Scheme III-71: Detosylation of the carboline **γ -317pa**.

The final step of reduction of the ester group required a large excess LiAlH_4 to give the desired *Isoperloyrine* **8** in a yield of 74% and an overall yield of about 10 % from 2-iodoaniline **10**.



Scheme III-72: Last step of reduction to *Isoperloyrine*.

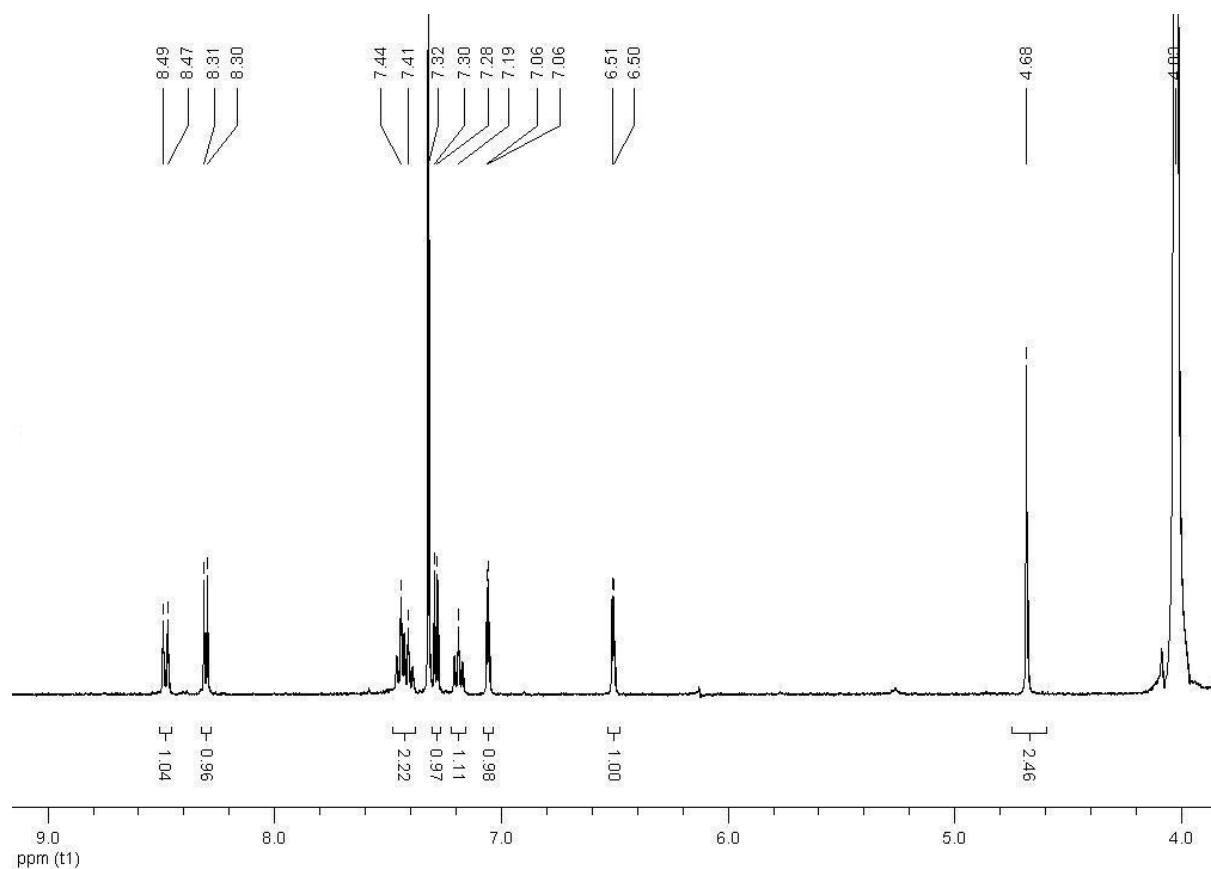


Figure III-22: $^1\text{H-NMR}$ spectrum of Isoperlolyrine in $\text{CDCl}_3/\text{MeOD}$ 4/1.

Surprisingly, the melting point (measured $241\text{ }^\circ\text{C}$, literature $186\text{ }^\circ\text{C}$ ^[36]) as well as the $^1\text{H-NMR}$ chemical shifts of the synthesized *Isoperlolyrine* did not fit to the literature data as shown in the Table III-26.

Table III-26: Comparison of the measured chemical shifts in $^1\text{H-NMR}$ with the literature^[36]

<i>Isoperlolyrine</i>		
"Natural" ^[36] Literature shifts in ppm (coupling constant, Hz)	Synthetic Measured shifts in ppm (coupling constant, Hz)	
$\text{CDCl}_3/\text{CD}_3\text{OD}$ 4/1	$\text{CDCl}_3/\text{CD}_3\text{OD}$ 4/1 (400)	DMSO (400)
		11.94 s, br.
8.34, d (6)	8.57, d (8)	8.76, d (8.2)
8.22 d (8)	8.38, d (6)	8.42, d (5.5)
8.10 d (6)	7.53 m	7.57, d (8.0)
7.79 td (8, 1.2)	7.37, d (6)	7.49, t (7.3)
7.70 td (8, 1.2)	7.27, td (8, 1.3)	7.43, d (5.5)
7.62 d (3.8)	7.15, d (3.3)	7.24, t (7.3)
7.39 td (8, 1.2)		7.14, d (3.2)
6.61 d (3.8)	6.59, d (3.3)	6.6, d (3.2)
4.71 s	4.77, s	5.5, s, br.
		4.64, d (3.2)

Recrystallization of the *Isoperlolyrine* afforded suitable crystals for an X-ray analysis:

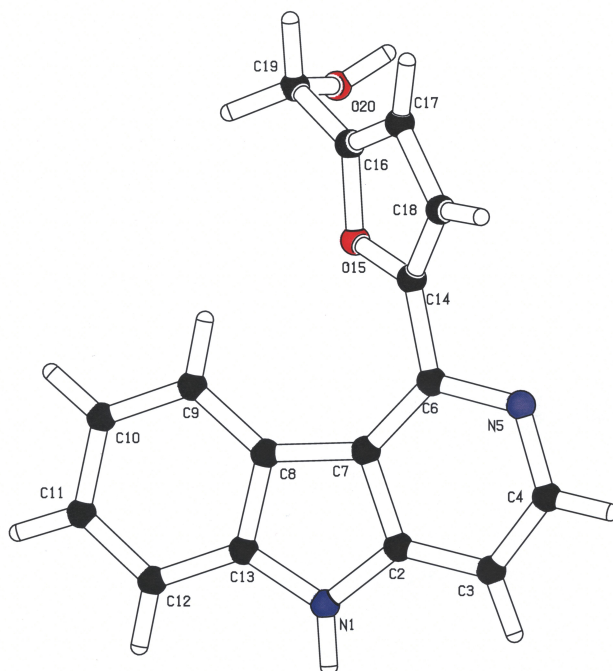
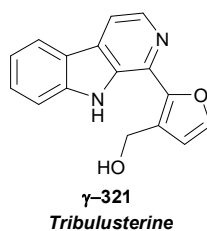


Figure III-23: X-Ray structure of the synthesized *Isoperlolyrine*.

Unquestionable confirmation of the structure of the synthesized *Isoperlolyrine* by the X-ray crystallography analysis and the differences observed in $^1\text{H-NMR}$ and melting points let us suppose that the alkaloid isolated by Dvořáčková et al. and assigned to be *Isoperlolyrine* could be an isomeric compound. According to the data described by Dvořáčková et al., their isolated compound is possibly the β -carboline β -**321**, known as *Tribulusterine* which has a similar melting point of 178-179 °C (EtOH).^[110]



Scheme III-73: Structure of Tribulusterine

However, no $^1\text{H-NMR}$ data of *Tribulusterine* using the same solvent mixture have ever been reported which could confirm or revoke this hypothesis. A solution would be to synthesize *Tribulusterine* using the [2+2+2] cycloaddition approach or by an already known procedure.^[111] This could unfortunately not be done in the present work due to a lack of time.

III.2.3.3.4. UV-Vis and fluorescence spectroscopy of *Isoperlolyrine*

- UV-VIS spectroscopy

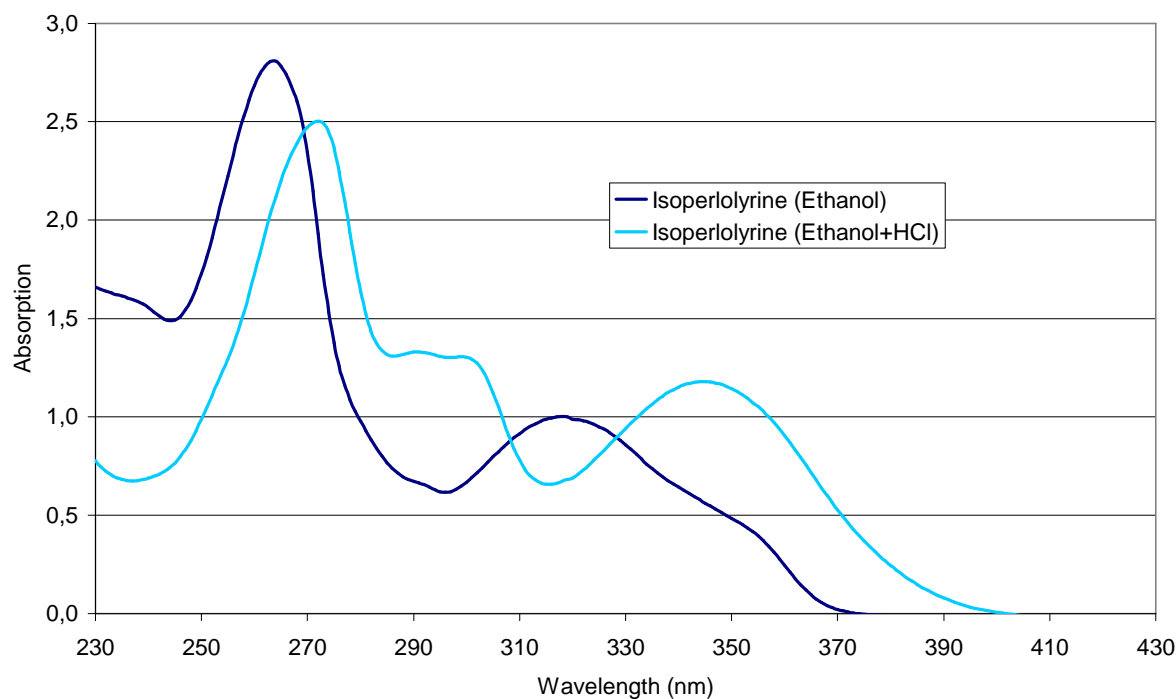


Figure III-24: UV-spectra of *Isoperlolyrine 8* in ethanol

Table III-27: UV-Properties of *Isoperlolyrine* in ethanol

	Cm (mmol/mL)	λ_{\max}	A_{\max}	ϵ	$\log \epsilon$	$\lambda_{\max 2}$	$A_{\max 2}$	ϵ_2	$\log \epsilon_2$
<i>Isoperlolyrine</i>	9.84E-05	318	1.0009	10174	4.01	264	2.8079	28541	4.46
<i>Isoperlolyrine</i> + HCl	9.84E-05	345	1.1792	11986	4.08	272	2.5020	25431	4.41

As depicted by Figure III-24 and presented in Table III-27, the UV-Vis spectrum of *Isoperlolyrine* presents two maxima of absorption at 318 nm and 264 nm corresponding to the $\pi \rightarrow \pi^*$ transition of whole aromatic system. Small bathochromic shifts were observed when *Isoperlolyrine* was protonated by addition of HCl as shown by the shifts of 27 nm of the first maximum and 8 nm for the second.

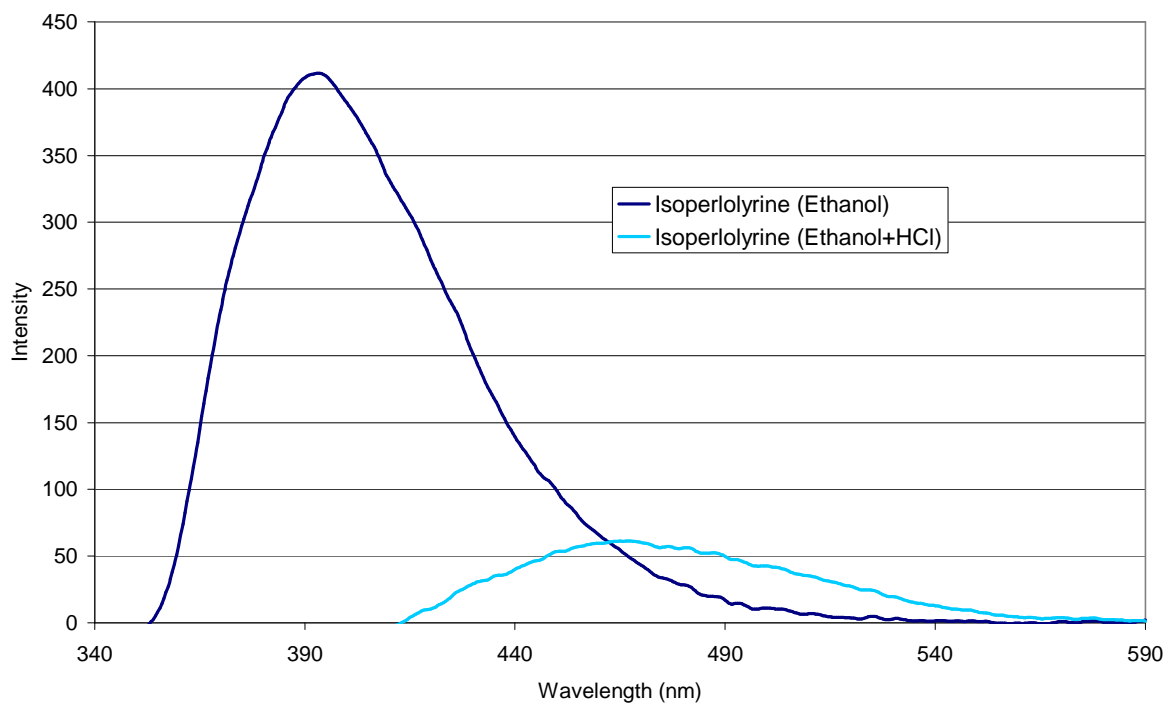
- Fluorescence spectroscopy

Figure III-25: Fluorescence spectrum of *Isoperlolyrine 8*

As shown by Figure III-25, *Isoperlolyrine* gives a fluorescence maximum at 394 nm. Addition of HCl to *Isoperlolyrine* leads to a drastic decrease of the intensity of the fluorescence together with a bathochromic shift of the maximum to 467 nm.

Figure III-26 depicts the UV-Vis spectra of *Perlolyrine* and *Isoperlolyrine* in ethanol and in ethanol/hydrochloric acid. Compared to the β -carboline *Perlolyrine*, the absorption maxima of the γ -isomer *Isoperlolyrine* appear at significant higher energies. A comparison of these spectra and the UV-Vis spectra of the “natural” *Isoperlolyrine* isolated by Dvořáčková et al. strengthen that the natural compound is not a γ -carboline but probably a β -carboline.

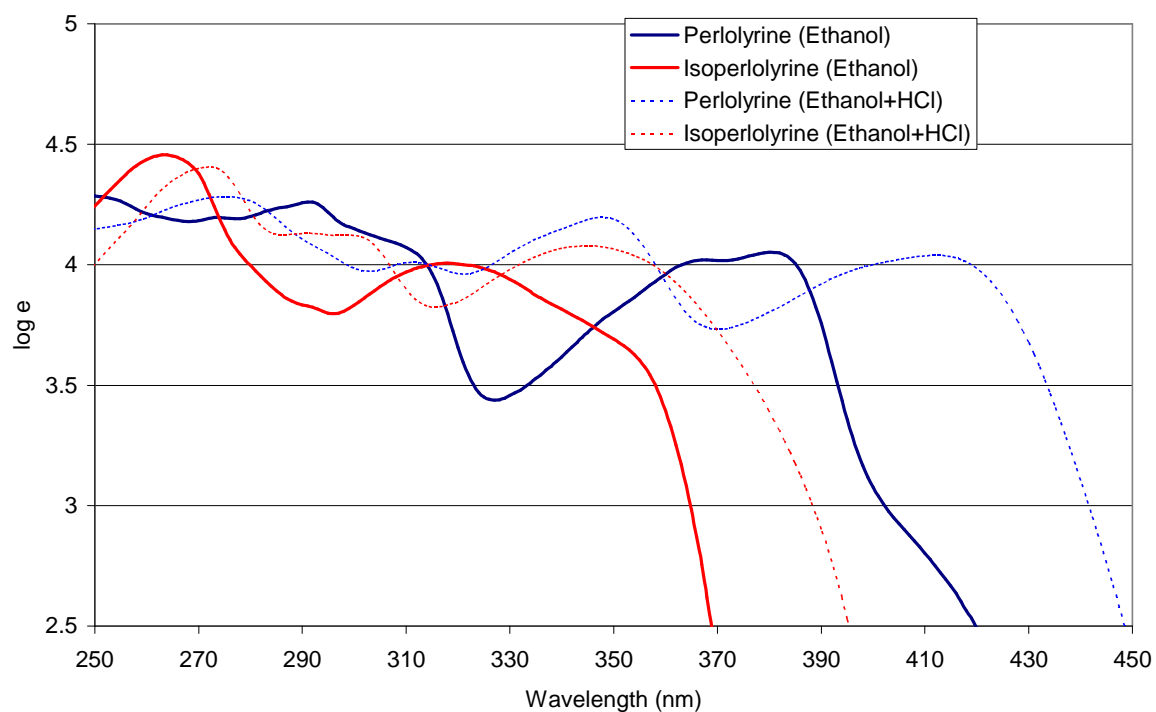


Figure III-26: Comparison of the UV-spectra of *Isoperlolyrine 8* and *Perlolyrine 6*

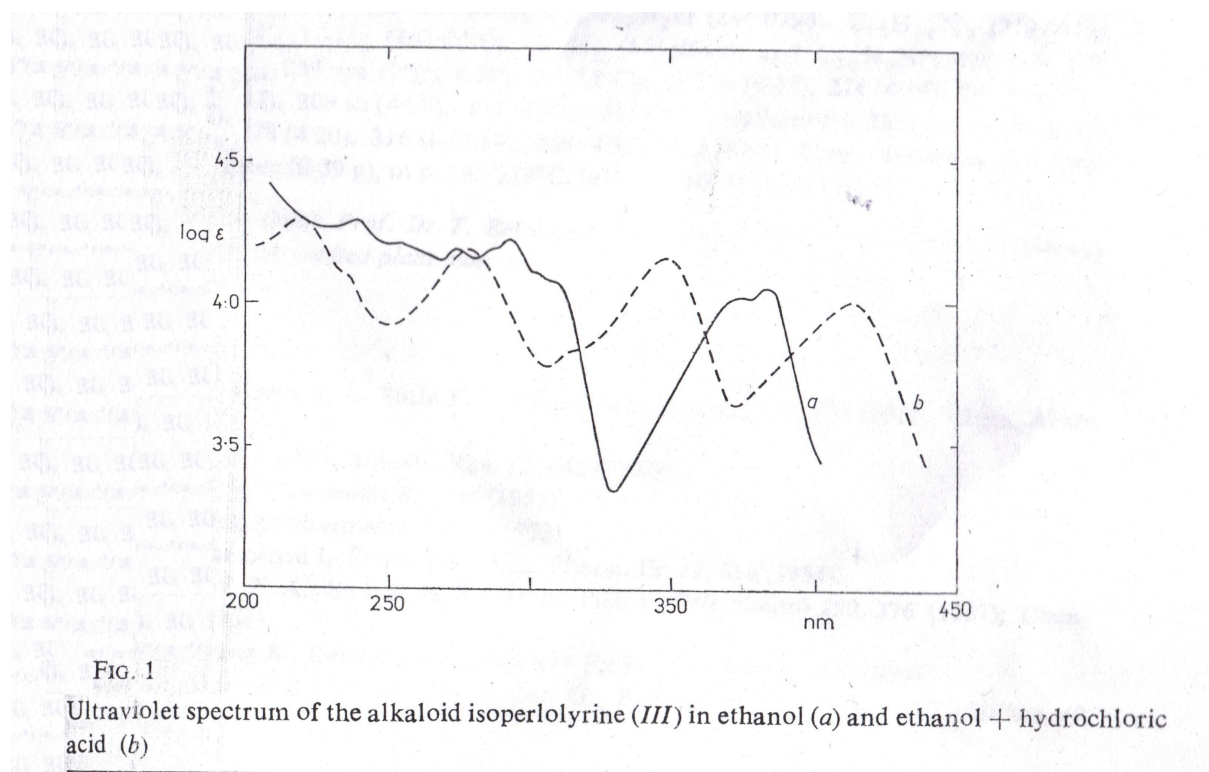


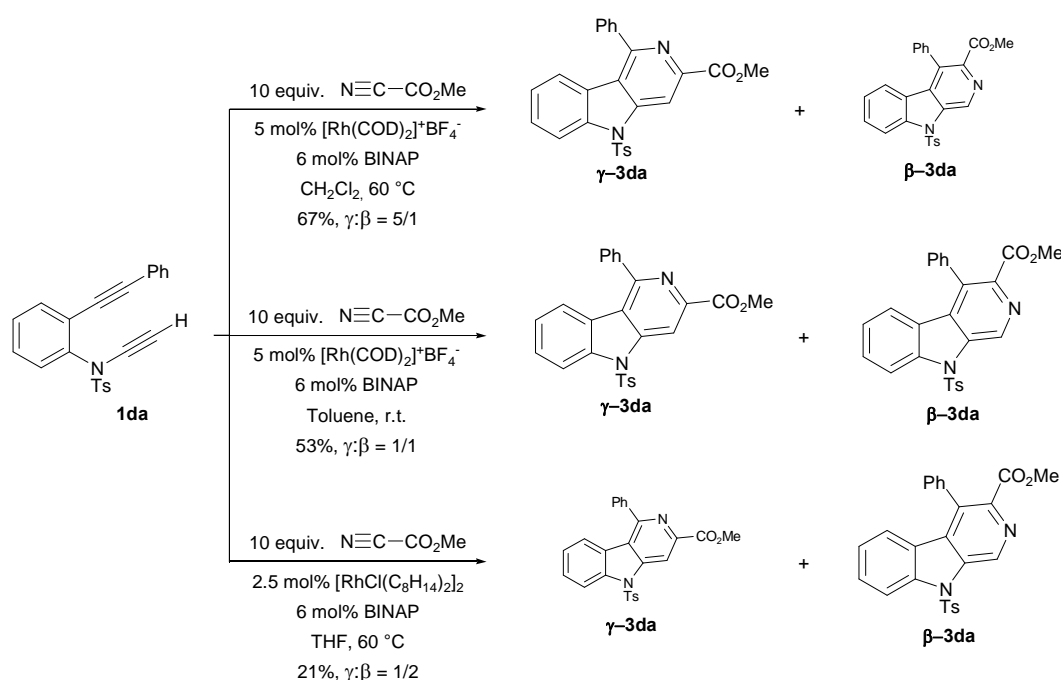
FIG. 1

Ultraviolet spectrum of the alkaloid isoperlolyrine (*III*) in ethanol (*a*) and ethanol + hydrochloric acid (*b*)

Figure III-27: UV-spectra of *Isoperlolyrine* reported by Dvořáčková et al.^[36]

IV/ SUMMARY

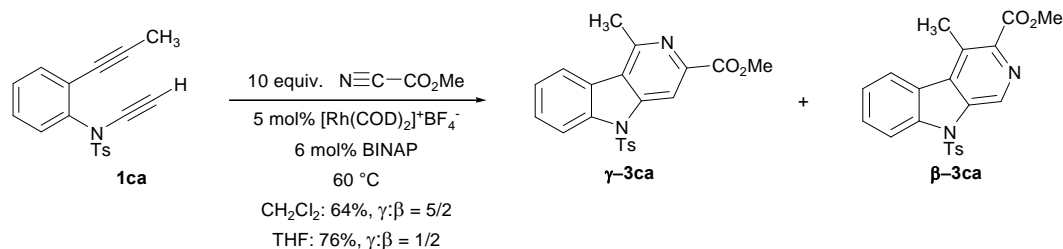
The synthesis of γ -carbolines was developed using a rhodium-catalyzed [2+2+2] cycloaddition strategy of diynes with methylcyanoformate. The study with the model diyne **1da** showed that the reaction proceeds at room temperature with a slow conversion and can be enhanced by a moderate heating (60 °C). The reaction leads to a mixture of the corresponding γ - and β -carbolines γ -**3da** and β -**3da**. Optimization of the reaction conditions showed that the regioselectivity of the reaction can be controlled by the choice of the solvent or by the catalytic system used.



Scheme IV-1: Control of the regioselectivity of the [2+2+2] cycloaddition of a diyne and methylcyanoformate

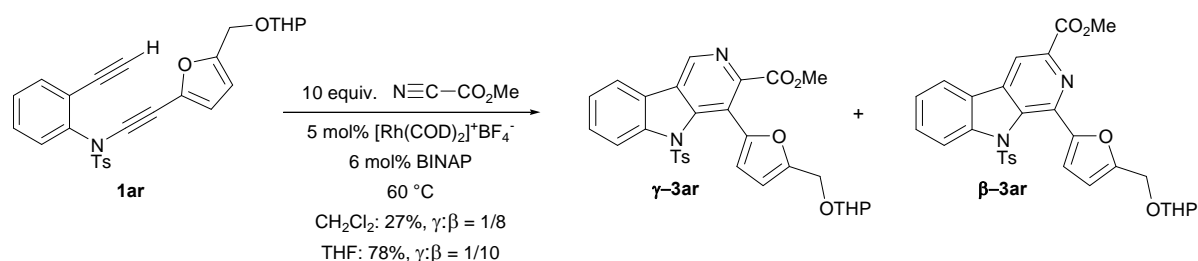
Application of the optimized reaction conditions to a larger scope of diynes showed that the regioselectivity strongly depends on the type of substitution of the alkynyl moiety, giving regioselectivities in the range $\gamma:\beta = 1/0$ to $\gamma:\beta = 0/1$.

Moreover, except the diyne **1da**, performing the cycloaddition in THF instead of CH_2Cl_2 permits to reverse the regioselectivity of the reaction to give the corresponding β -carboline as major product as showed by the cycloadditions with **1ca**.



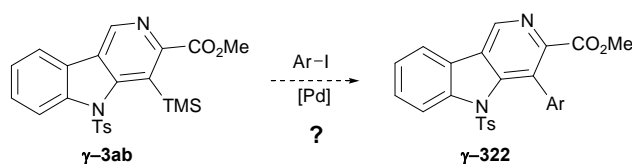
Scheme IV-2: Inversion of the regioselectivity by a change of the solvent used for the cycloaddition

This catalytic system also allows cycloadditions with substituted ynamides in good to excellent yields. In this case, the reaction leads typically to the corresponding β -carbolines as major products with good regioselectivities. In several cases, the use of THF as solvent accelerates the reaction rate without modifying the regioselectivity as shown by the reaction with the diyne **1ar**.



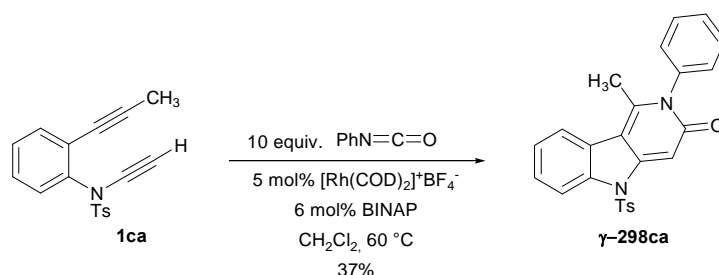
Scheme IV-3: [2+2+2] Cycloaddition with the diyne **1ar** in CH_2Cl_2 and in THF

The cycloaddition with the TMS-substituted diyne **1ab** is highly interesting since this reaction gives the γ -carboline **$\gamma\text{-}3ab$** as main product. It would be interesting to investigate the Hiyama coupling of this carboline with aryl iodide that could potentially offer an access to the γ -carboline **$\gamma\text{-}322$** .



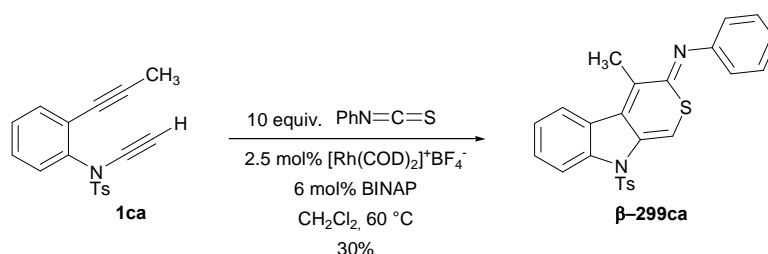
Scheme IV-4: Hiyama coupling as potential access to the γ -carbolines **$\gamma\text{-}322$**

Extension of the [2+2+2] cycloaddition strategy to heterocumulenes as cycloaddition partners allowed the synthesis of the γ -carboline **$\gamma\text{-}298ca$** when phenylisocyanate was used whereas all attempts to cycloadditions with carbon dioxide remained unsuccessful.



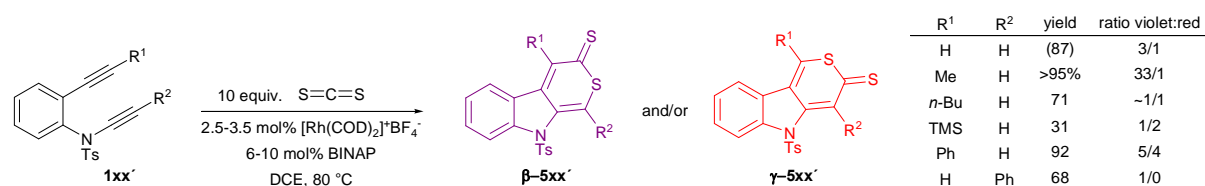
Scheme IV-5: [2+2+2] cycloaddition of the diene **1ca** with phenylisocyanate

Furthermore, cycloaddition with phenylisothiocyanate was also successful. In this case, the diene reacted chemoselectively and regioselectively with the C–S double bond to lead to a new class of indole derivatives – i. e. thiopyrano[3,4-*b*]indol-3-imine.



Scheme IV-6: [2+2+2] cycloaddition of the diene **1ca** with phenylisothiocyanate

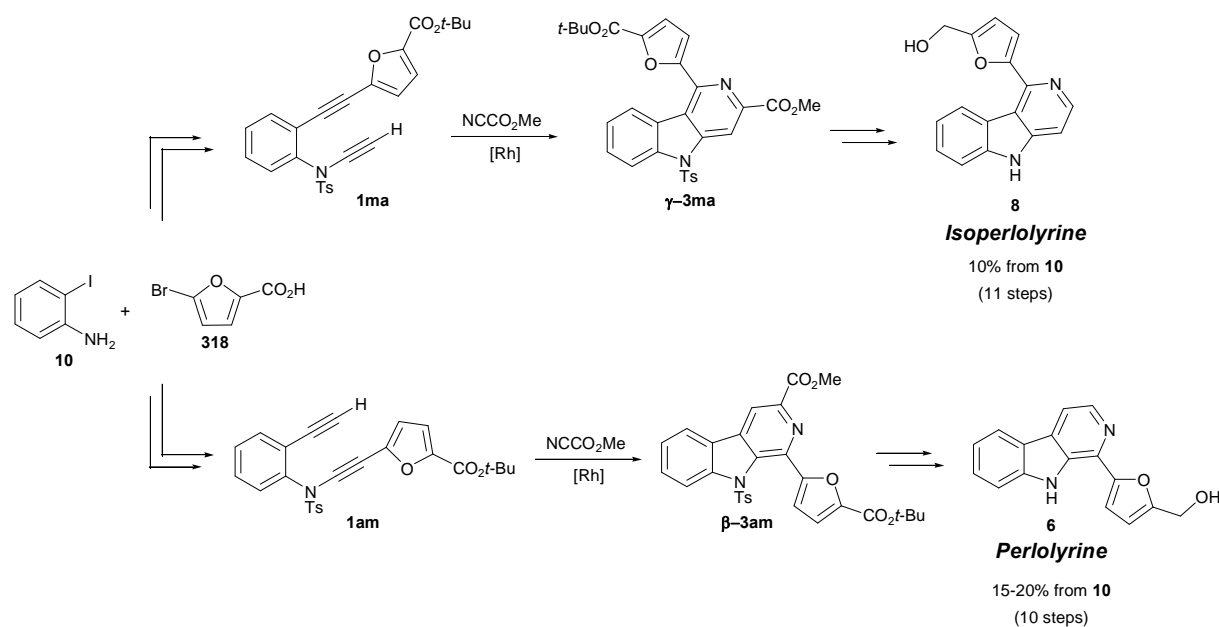
Probably, the most interesting results come from the use of carbon disulfide as cycloaddition partner. With this heterocumulene, cycloadditions with various diynes led to the synthesis of a series of the sulfur derivatives of the well known pyranoindolones. These new thiopyronothiones are remarkably colored, each regioisomer giving intensively colored solutions, either violet or red.



Scheme IV-7: [2+2+2] cycloadditions with CS₂ as cycloaddition partner

Finally, the [2+2+2] cycloaddition approach for the synthesis of the γ - and β -carboline cores was successfully applied to the first total synthesis of *Isoperlolyrine* and the total synthesis of *Perlolyrine*. Both syntheses rely on the [2+2+2] cycloaddition of the diynes **1ma** and **1am** with methylcyanoformate as a key-step to give the γ - and β -carbolines **γ -3ma** and **β -3am**

respectively. Both synthesis start from 2-iodoaniline **10** and *Perlolyrine* was synthesized in a 15-20% overall yield whereas *Isoperlolyrine* was obtained in a 10% overall yield.



Scheme IV-8: Total syntheses of *Isoperlolyrine* and *Perlolyrine*

Analyses of the synthetic *Isoperlolyrine* showed several differences (NMR, melting point, UV-spectra) with the properties reported by Dvořáčková et al.^[36]. Confirmation of the structure of the synthetic by an X-Ray structure implies that the natural product isolated by Dvořáčková is not the *Isoperlolyrine* but is more probably an alkaloid possessing a β -carboline core as suggested by the analogy of its UV-spectrum with the one of *Perlolyrine*.

V / EXPERIMENTAL PART**V.1. General methods**

All reactions were carried out under dry argon or nitrogen unless otherwise indicated. Commercially available reagents were used without further purification unless otherwise indicated; solvents and gases were dried by standard procedures. Solvents were dried according to general procedure and kept under inert atmosphere.^[112]

Acetone	CaCl ₂
Acetonitrile	K ₂ CO ₃
Dichloromethane	CaH ₂
1,2-Dichlorethane	CaH ₂
Diethylether	Na/K-alloy
1,4-Dioxane	Na
<i>N, N</i>-Dimethylformamide	P ₂ O ₅
Tetrahydrofuran	Na/K-alloy
Toluene	Na
Triethylamine	CaH ₂
Pyridine	CaH ₂

- Analytic methodes and measurement equipement**Thin-Layer Chromatography:**

Thin-layer chromatography was performed using commercially pre-coated plastic sheets for TLC POLYGRAM[®] SIL G/UV₂₅₄, aluminium sheets for TLC ALUGRAM[®] SIL G/UV₂₅₄, or pre-coated plastic sheets for TLC POLYGRAM[®] ALOX N/UV₂₅₄, layer thickness 200 µm from Macherey-Nagel. Compounds on TLC were visualized under UV light (254 and 366 nm).

Flash chromatography:

Flash chromatography was performed using Merck silica gel 60, particle size 40-63 μm or aluminium oxide MP EcoChromTM from MP Biomedicals Germany GmbH. In this case, aluminium oxide was deactivated by addition of water prior to use (activity grade III, 7% w/w water addition)

NMR-Spectra:

^1H and ^{13}C NMR spectra were performed in CDCl_3 or $\text{DMSO-}d_6$ on either:

„Bruker ARX400“ ^1H NMR (400 MHz); ^{13}C NMR (100 MHz)

„Bruker AC300“ ^1H NMR (300 MHz); ^{13}C NMR (75 MHz).

„Bruker AV400“ ^1H NMR (400 MHz); ^{13}C NMR (100 MHz).

^1H and ^{13}C NMR spectra were calibrated to the ^1H or ^{13}C residue signal of the solvent: 7.26 ppm (CDCl_3) and 77.0 ppm (CDCl_3) respectively or 2.49 ($\text{DMSO-}d_6$) and 39.7 ($\text{DMSO-}d_6$).

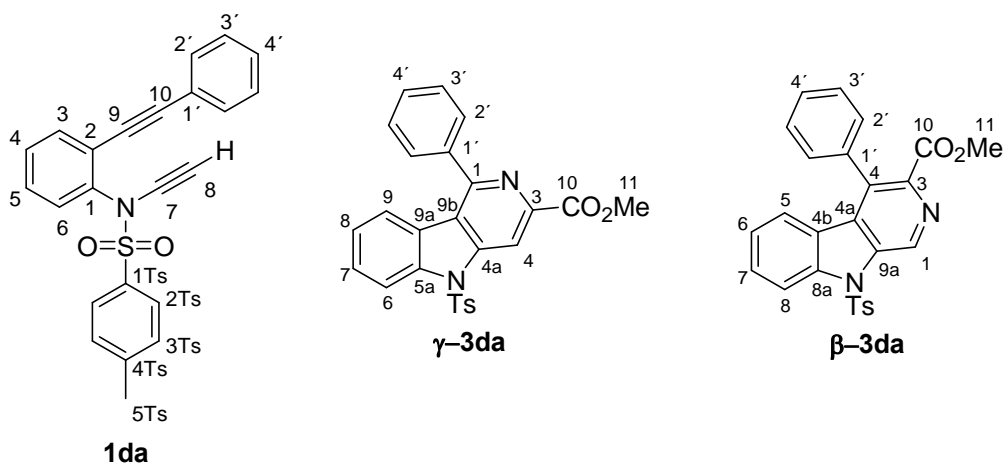
^1H NMR data are presented as follows: chemical shift (δ , in ppm), multiplicity (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J , Hz), integration (number of H), assignment.

^{13}C NMR data are presented as follows: chemical shift (δ , in ppm), order of carbon (CH_3 = primary carbon, CH_2 = secondary carbon, CH = tertiary carbon, C_q = quaternary carbon), assignment.

The sign “*” means that assignment of the signals to their corresponding proton or carbon were done with help of COSY, DEPT135, HSQC and HMBC analyses. Otherwise, assignments were done by comparison with known assignments of similar molecules or with help of tables^[113].

Numbering and naming

Numbering and naming of the different products do not always respect the IUPAC rules for convenience reasons. Numbering of diynes and indole derivatives was based on the numbering of the diyne **1da** and the carbolines **3da** as depicted by Scheme IV-1. Numbering of the tosyl group always corresponds to the numbering on diyne **1da**.



Scheme V-1 Numbering of diynes and indole derivatives

Infrared Spectra:

Infrared spectra were recorded in the range 4000–650 cm^{-1} on an ATR-Unit (Zn-Se-Crystal) JASCO 4100 FT/IR Fourier Transform Infrared Spectrometer (Jasco). The intensity of the IR-bands is described as follow:

vs = very strong, s = strong, m = medium, w = weak, br. = broad.

Melting points:

Melting points (mp) were determined on a Büchi HWS SG 2000 apparatus and are uncorrected.

Mass analyses:

FD-MS spectra were obtained on a Mat 95 (Finnigan); HR-ESI spectra were obtained on a Q-TOF-ULTIMA 3 with Lock Spray device (Waters-Micromass) and NaICsI Standard as reference.

MS data are presented as follows: m/z (relative intensity)

Elemental analyses:

Elemental analyses were performed on a CHN equipment Vario EL (Elementar Analysensysteme GmbH).

X-Ray analysis:

X-Ray analyses were performed on a Turbo CAD-4 with Cu- $K\alpha$ radiation and data collection with CAD-4 Software (Enraf –Nonius, 1989); Structure solution: SIR97 (direct methods); Structure refinement: SHELXL97; Molecular graphics: PLATON.

UV-vis spectra:

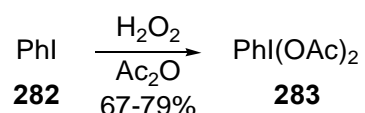
Measurements of UV-vis spectra were performed on a Perkin-Elmer Lambda 16 UV-Spectrometer with Perkin-Elmer Software UV-Winlab. Analyses of the measurements and graphic representations were performed with Microsoft Excel. Analyses were performed with HPLC-grade solvents (Acros)

Fluorescence spectra:

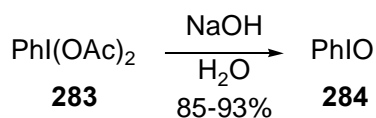
Measurements of fluorescence spectra were performed on a Perkin-Elmer LS 50B-Spectrometer with Perkin-Elmer Software FL-Winlab. Analyses of the measurements and graphic representations were performed with Microsoft Excel. Analyses were performed with HPLC-grade solvents (Acros)

V.2. Experimental section**V.2.1. [2+2+2] Cycloaddition with diynes****V.2.1.1. Synthesis of iodonium salts**

- General procedure for the synthesis of iodonium salts 16 (GPI)^[98]

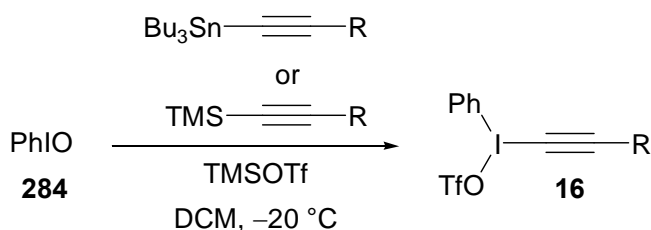


A stirred mixture of acetic anhydride (305 mL) and 30% hydrogen peroxide (70 mL) was kept at exactly 40 °C for 4 h; the use of a thermostated bath is strongly recommended. To the resulting peracetic acid solution, iodobenzene (52 g, 28.5 mL) was added with stirring over 15 min and the clear reaction mixture was kept overnight at room temperature. A part of DIB crystallized out and was collected; then ice-water (~ 400 mL) was added to the filtrate and a further crop of crystals obtained. The combined material was washed with cold water and petroleum ether and was dried in a desiccator over sodium hydroxide to yield 55–65 g (67–79%) of crude DIB, m.p. 156–159 °C (recrystallized from chloroform, m.p. 163–165 °C); this purity is satisfactory in most cases.



Finely ground DIB (32.2 g, 100 mmol) was placed in a 250 mL beaker and 150 mL of 3N sodium hydroxide was added over 5 min with vigorous stirring. The mixture was triturated with a spatula for 15 min in order to become homogeneous. After standing for 45 min, water was added (100 mL) with vigorous stirring and the solid collected on a Buchner funnel; it was returned to the beaker and triturated in water (200 mL), collected again, washed with water (3 x 200 mL) and dried by maintaining suction. Further purification was effected by triturating this solid in chloroform (75 mL). After air-drying, iodosylbenzene (18.7–20.5 g, 85–93%) was obtained, m.p. 210 °C.

HAZARD: the compound explodes at its melting point. In some reactions best results were obtained when it was well-crushed and kept over P₄O₁₀ for 2-3 weeks. When left at room temperature for long periods of time, iodosylbenzene disproportionates to iodobenzene and iodylbenzene.



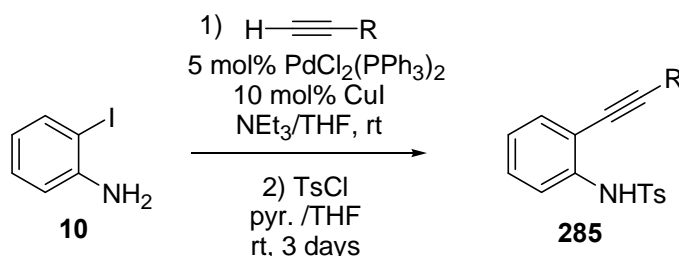
To a stirred suspension of PhIO (8.8 g, 40 mmol) in dry CH₂Cl₂ (60 mL) at –20 °C under N₂ was added dropwise, 7.75 mL (40 mmol) of Me₃SiOTf. A bright yellow suspension of the μ -oxo-bis-triflate, formed immediately after completion of the addition of the Me₃SiOTf. With the reaction mixture at –20 °C, the appropriate sila- or tin-acetylene (RC≡CSiMe₃ or RC≡CSnR'₃, 40 mmol) was added dropwise over approximately 30 min. The mixture was allowed to warm to room temperature and concentrated to about 25 mL, and cold dry ether (5 mL) and then dried in vacuo. Use of *n*-Bu₃SnC≡CH gave the parent HC≡C⁺OTf in 50–60 % yield, m.p. 100–101 °C (dec), Me₃SiC≡CSiMe₃ gave Me₃SiC≡C⁺OTf in 89% yield, m.p. 138–139 °C (dec)

According to this procedure, 4-BrPhC≡C⁺OTf **16c** was prepared from 4-BrPhC≡CTMS in 36% yield.^[114]

V.2.1.2. Synthesis of diynes

V.2.1.2.1. Synthesis of diynes with a terminal ynamide moiety

- General procedure for the synthesis of sulfonamides **285** (GP2)^{[2],[3]}

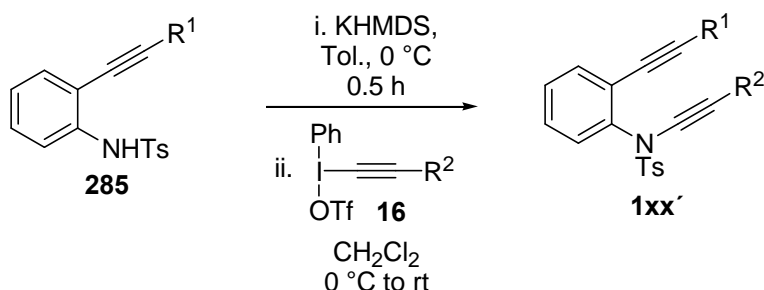


In a dried Schlenk under Argon (or N_2) are placed the 2-iodoaniline **10** (219 mg, 1.00 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (35 mg, 0,05 mmol, 5 mol%), CuI (19 mg, 0,10 mmol, 10 mol%), 6 mL NEt_3 and 3 mL DMF (or THF). Then the alkyne (0.2 mL, 1.40 mmol, 1.4 equiv.) is added dropwise. The mixture is stirred at room temperature until completion of the reaction (TLC). The solvent is removed, the residue dissolved with 10 mL of CH_2Cl_2 and 10 mL water. The aqueous layer is extracted 3 times with 10 mL CH_2Cl_2 . The combined organic layers are washed with 50 mL brine, dried over MgSO_4 , filtered on celite and the solvent is evaporated. The crude product is purified by a column chromatography or directly tosylated. To a solution of this amine dissolved in 40 mL pyridine and 40 mL THF is added the dropwise a solution of TsCl (1.4 equiv.) in 40 mL THF. The mixture is stirred 36h at room temperature until completion of the reaction (TLC). The solvent is removed, the residue dissolved with 20 mL of CH_2Cl_2 and 20 mL water. The aqueous layer is extracted 3 times with 20 mL CH_2Cl_2 . The combined organic layers are washed with 50 mL brine, dried over MgSO_4 , filtered and the solvent is evaporated. The crude product is purified by a column chromatography.

Sulfonamides **285b-e** ($\text{R} = \text{TMS}, \text{Me}, \text{Ph}, n\text{-Bu}$) were prepared according to this procedure. Analyses of these sulfonamides fit with the literature.^{[2],[3]}

V.2.1.2.1.1. Synthesis of diynes via *N*-alkynylation of sulfonamides (method A)

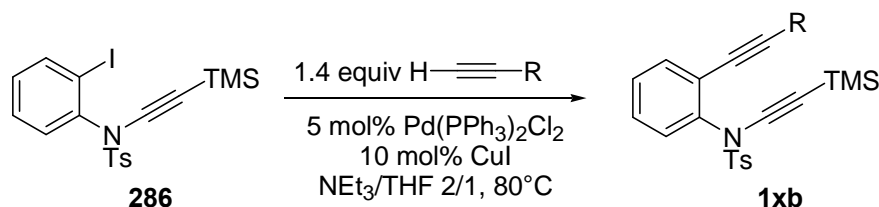
- General procedure for ethynylation of sulfonamides with iodonium salts (GP3)^{[2],[3]}



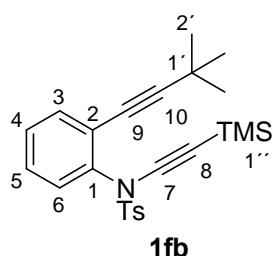
To a solution of the sulphonamide **285** (1.5 mmol) in 100 mL of toluene under N₂ at 0 °C is added dropwise a solution of KHMDS (3.6 mL, 0.5 M in toluene, 1.2 eq.). The solution is stirred 30 minutes at 0 °C. Then, a solution of the iodonium salt **16** (1.95 mmol, 1.3 equiv.) in 50 mL CH₂Cl₂ is added dropwise via a cannula to the solution*, the ice-bath is removed and the solution is stirred overnight at room temperature. After completion of the reaction (TLC), the solvent is removed and the residue is dissolved in 60 mL of CH₂Cl₂ and 60 mL of brine. The aqueous layer is extracted twice with 40 mL of CH₂Cl₂. The combined organic layers are dried over MgSO₄, filtered and the solvent is evaporated. The crude product is purified by a column chromatography.

* For a reaction with the iodonium salt **16b** (R²=TMS) or **16c** (R²=4-BrPh), the iodonium salt is added in 4 portions as a solid over 20 minutes.

Diynes **1ba-ea** and **1bb-eb** (R¹= TMS, Me, Ph, *n*-Bu, R²= H or TMS) were prepared according to this procedure. Analyses of these diynes fit with the literature.^{[2],[3]}

V.2.1.2.1.2. Synthesis of diynes via functionalization of the ynamide **286** (method B)- General procedure for the Sonogashira coupling with ynamide **286** (GP4)^[2]

In a dried Schlenk under Argon (or N₂) are placed the ynamide **286**^[2] (939 mg, 2 mmol), PdCl₂(PPh₃)₂ (70 mg, 0.1 mmol, 5 mol%), CuI (38 mg, 0.2 mmol, 10 mol%), 20 mL NEt₃ and 10 mL DMF (or THF). Then the alkyne (1.4 mmol, 1.4 equiv.) is added dropwise. The mixture is heated at 80 °C until completion of the reaction (TLC). The solvent is removed, the residue dissolved with 30 mL of CH₂Cl₂ and 30 mL water. The aqueous layer is extracted 3 times with 20 mL CH₂Cl₂. The combined organic layers are washed with 50 mL brine, dried over MgSO₄, filtered on celite and the solvent is evaporated. The crude product is purified by column chromatography.

2-(3,3-Dimethylpropynyl)-N-(2-trimethylsilylethynyl)-N-tosylbenzenamine 1fb

Prepared from **286** and 3,3-dimethylpropyne

Yield = 99%, pale orange solid, m.p. = 87-88 °C

Purified by column chromatography (SiO₂, PE/EtOAc 95/5)

R_f = 0.72 (PE/EtOAc 90/10)

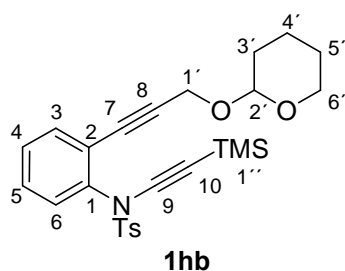
¹H NMR (CDCl₃) δ ppm: 7.73 (d, J = 8.3 Hz, 2H, H^{2Ts}), 7.43 (dd, J = 7.7 Hz, J = 1.7 Hz, 1H, H³), 7.30 (d, J = 8.1 Hz, 2H, H^{3Ts}), 7.24 (m, 2H, H⁴⁺⁵), 7.13 (dd, J = 7.7 Hz, J = 1.1 Hz, 1H, H⁶), 2.45 (s, 1H, H^{5Ts}), 1.24 (s, 9H, H^{2'}), 0.15 (s, 9H, H^{1''});

¹³C NMR (CDCl₃) δ ppm: 144.6 (C_q, C^{4Ts}), 138.6 (C_q, C¹), 134.8 (C_q, C^{1Ts}), 133.4 (CH, C³), 129.4 (CH, C^{3Ts}), 128.8 (CH, C⁶), 128.5 (CH, C^{2Ts}), 128.4 (CH, C⁴), 128.0 (CH, C⁵), 124.3 (C_q, C²), 104.8 (C_q, C¹⁰), 94.6 (C_q, C⁷), 74.8 (C_q, C⁹), 72.2 (C_q, C⁸), 30.6 (CH₃, C^{2''}), 28.0 (C_q, C^{1''}), 21.6 (CH₃, C^{5Ts}), 0.1 (CH₃, C^{1'});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2973.70 (s), 2163.74 (vs), 1597.73 (w), 1477.21 (m), 1369.21 (vs), 1242.90 (m), 1173.47 (vs), 1095.37 (w), 845.63 (vs), 761.74 (s), 703.89 (s), 655.68 (s);

FD-MS: m/z (%) = 423.4 (100) [M]⁺, 424.4 (33), 425.4 (13), 426.4 (2)

2-(Tetrahydropyranylalkoxypropynyl)-N-(2-trimethylsilylethynyl)-N-tosylbenzenamine 1hb



Prepared from **286** and 3-(tetrahydropyranyloxy)propyne

Yield = 56%, orange oil

Purified by column chromatography (SiO₂, PE/EtOAc 95/5)

R_f = 0.54 (PE/EtOAc 80/20)

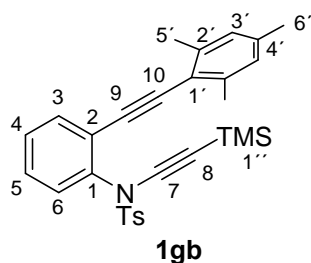
¹H NMR (CDCl₃) δ ppm: 7.70 (d, J = 8.3 Hz, 2H, H^{2Ts}), 7.46 (m, 1H, H³), 7.28 (m, 4H, H^{3Ts+4+5}), 7.19 (m, 1H, H⁶), 4.86 (t, J = 3.7 Hz, 1H, H^{2'}), 4.24 (s, 2H, H^{1'}), 3.86 (m, 1H, H^{6'a}), 3.58 (m, 1H, H^{6'b}), 2.45 (s, 3H, H^{5Ts}), 1.78 (m, 2H, H^{3'}), 1.59 (m, 4H, H^{4'+5'}), 0.14 (s, 9H, H^{1''});

¹³C NMR (CDCl₃) δ ppm: 144.8 (C_q, C^{4Ts}), 138.9 (C_q, C¹), 134.1 (C_q, C^{1Ts}), 133.7 (CH, C³), 129.3 (CH, C^{3Ts}), 129.0 (CH, C^{4,5 or 6}), 128.9 (CH, C^{4,5 or 6}), 128.8 (CH, C^{4,5 or 6}), 128.6 (CH, C^{2Ts}), 122.6 (C_q, C²), 96.8 (CH, C^{2'}), 94.6 (C_q, C⁷), 91.3 (C_q, C⁹), 81.2 (C_q, C¹⁰), 72.8 (C_q, C⁸), 62.2 (CH₂, C^{6'}), 54.4 (CH₂, C^{1'}), 30.3 (CH₂, C^{3'}), 25.3 (CH₂, C^{5'}), 21.6 (CH₃, C^{5Ts}), 19.2 (CH₂, C^{4'}), 0.0 (CH₃, C^{1''});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2949.59 (s, br.), 2867.63 (w), 2163.74 (vs), 1594.84 (w), 1488.78 (w), 1442.49 (w), 1372.10 (s), 1254.47 (w), 1169.62 (vs), 1120.44 (s), 1024.98 (vs), 904.45 (w), 840.81 (vs), 755.96 (w), 656.64 (w);

FD-MS: m/z (%) = 481.2 (100) [M]⁺, 482.2 (32), 483.2 (12).

2-(Mesitylethynyl)-N-(2-trimethylsilylethynyl)-N-tosylbenzenamine 1gb



Prepared from **286** and mesitylethyne

Yield = 95%, orange oil

Purified by column chromatography (SiO₂, PE/EtOAc 95/5)

R_f = 0.40 (PE/EtOAc 90/10).

¹H NMR (CDCl₃) δ ppm: 7.76 (d, J= 8.3 Hz, 2H, H^{2Ts}), 7.61 (dd, J= 7.7 Hz, J= 1.4 Hz, 1H, H³), 7.37 (td, J= 7.5 Hz, J= 1.4 Hz, 1H, H^{4 or 5}), 7.31 (td, J= 7.9 Hz, J= 1.5 Hz, 1H, H^{4 or 5}), 7.20 (d, J= 8.0 Hz, 1H, H⁶), 7.15 (d, J= 8.2 Hz, 2H, H^{3Ts}), 6.89 (s, 2H, H^{3'}), 2.43 (s, 6H, H^{5'}), 2.32 (s, 3H, H^{5Ts}), 2.27 (s, 3H, H^{6'}), 0.16 (s, 9H, H^{1''});

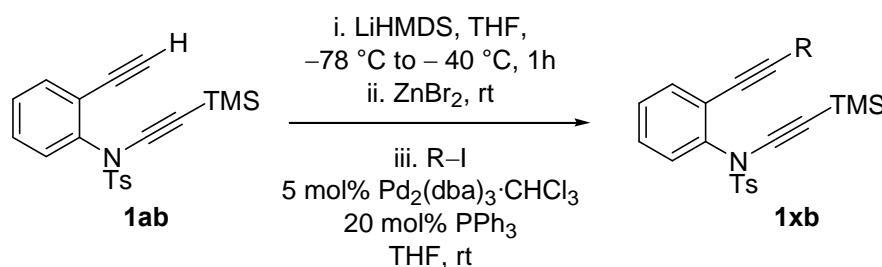
¹³C NMR (CDCl₃) δ ppm: 144.7 (C_q, C^{4Ts}), 140.6 (C_q, C^{2'}), 138.3 (C_q, C¹), 138.0 (C_q, C^{4'}), 134.4 (C_q, C^{1Ts}), 133.6 (CH, C³), 129.2 (CH, C^{3Ts}), 129.1 (CH, C⁶), 128.8 (CH, C⁴), 128.6 (CH, C⁵), 128.4 (CH, C^{2Ts}), 127.4 (CH, C^{3'}), 124.4 (C_q, C^{2 or 1'}), 119.7 (C_q, C^{2 or 1'}), 95.0 (C_q, C¹⁰), 93.1 (C_q, C⁷), 92.7 (C_q, C⁹), 72.4 (C_q, C⁸), 21.4 (CH₃, C^{5Ts}), 21.3 (CH₃, C^{6'}), 21.1 (CH₃, C^{5'}), -0.0 (CH₃, C^{1''});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2952.48 (s, br.), 2206.17 (w), 2160.85 (vs), 1594.84 (w), 1495.53 (w), 1446.35 (w), 1375.00 (s), 1243.86 (w), 1173.47 (vs), 1095.37 (w), 1031.73 (w), 844.67 (vs), 759.82 (s), 702.93 (w), 664.36 (w);

FD-MS: m/z (%) = 485.2 (100) [M]⁺, 486.2 (36), 487.2 (16), 488.2 (4).

V.2.1.2.1.3. Synthesis of diynes via functionalization of the diyne **1ab** (method C)

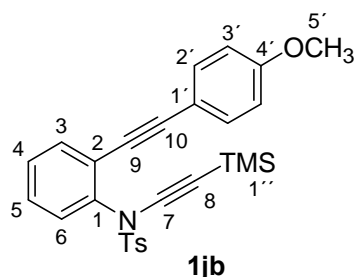
- General procedure for the functionalization of the diyne **1ab** via Negishi coupling (GP5)^[3]



A freshly prepared LiHMDS solution (6.0 mL, 0.5M in THF, 1.5 equiv.) is added slowly to a solution of the diyne **1ab**^{[2], [3]} (735 mg, 2 mmol) in dry THF (10 mL) cooled at -78 °C and the mixture is stirred for 1 h. A solution of ZnBr₂ (1.5 mL, 1.5M in THF, 1.1 equiv.) is added via syringe and, after stirring for 20 additional minutes at room temperature, the reaction mixture is transferred via cannula to a solution of Pd₂(dba)₃·CHCl₃ (103.5 mg, 0.1 mmol, 5 mol%), PPh₃ (104.9 mg, 0.4 mmol, 20 mol%) and the corresponding halo(hetero)aryl (2.4 mmol, 1.2 equiv.) in dry THF (4 mL) and the reaction is let stirred overnight at room temperature. The solvent is removed, the residue dissolved with 30 mL of CH₂Cl₂ and 30 mL water. The aqueous layer is extracted 3 times with 20 mL CH₂Cl₂. The combined organic layers are washed with 50 mL

brine, dried over MgSO_4 , filtered on celite and the solvent is evaporated. The crude product is purified by column chromatography.

***N*-2-(2-(trimethylsilyl)ethynyl)-2-(2-(4-methoxyphenyl)ethynyl)-*N*-tosylbenzenamine 1jb**



Prepared from **1ab** and 4-iodoanisole

Yield = 35%, orange solid, m.p.= 117 °C

Purified by column chromatography (Silica gel, PE/Et₂O 90/10)

R_f = 0.34 (PE/EtOAc 90/10).

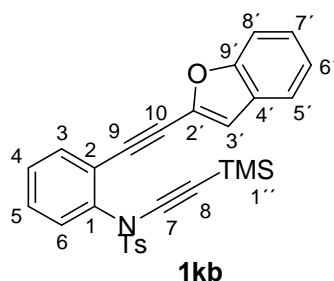
¹H NMR (CDCl₃) δ ppm: 7.73 (d, J= 8.3 Hz, 2H, H^{2Ts}), 7.48 (m, 1H, H³), 7.38 (m, 1H, H⁵), 7.34 (m, 2H, H⁴⁺⁶), 7.23 (dt, J= 8.2 Hz, J= 2.7 Hz, 2H, H^{2'}), 7.14 (d, J= 8.3 Hz, 2H, H^{3Ts}), 6.80 (dt, J= 8.8 Hz, J= 2.7 Hz, 2H, H³), 3.83 (s, 3H, H^{5'}), 2.23 (s, 3H, H^{5Ts}), 0.11 (s, 9H, H^{1''});

¹³C NMR (CDCl₃) δ ppm: 159.8 (C_q, C^{4'}), 144.7 (C_q, C^{4Ts}), 138.3 (C_q, C¹), 134.6 (C_q, C^{1Ts}), 133.2 (CH, C^{2'}), 133.0 (CH, C³), 129.8 (CH, C^{4 or 5}), 129.4 (CH, C^{3Ts}), 128.9 (CH, C^{4 or 5}), 128.6 (CH, C^{2Ts}), 128.5 (CH, C⁶), 123.0 (C_q, C²), 115.0 (C_q, C¹), 113.5 (CH, C³), 95.6 (C_q, C¹⁰), 94.4 (C_q, C⁷), 83.9 (C_q, C⁹), 73.1 (C_q, C⁸), 55.3 (CH₃, C^{5'}), 21.5 (CH₃, C^{5Ts}), 0.1 (CH₃, C^{1''});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2946.70 (w, br.), 2837.74 (w), 2211.95 (m), 2163.74 (vs), 1597.73 (s), 1510.95 (vs), 1444.42 (w), 1363.43 (vs), 1288.22 (s), 1248.68 (vs), 1170.58 (vs), 1086.69 (m), 1028.84 (m), 929.52 (w), 827.31 (s), 754.99 (m), 703.89 (m), 662.43 (s);

FD-MS: m/z (%) = 473.3 (100) [M]⁺, 474.3 (33), 475.3 (14), 476.3 (3).

2-(2-(Benzofuran-2-yl)ethynyl)-*N*-(2-(trimethylsilyl)ethynyl)-*N*-tosylbenzenamin 1kb



Prepared from **1ab** and 2-iodobenzofuran^[114]

Yield = 87%, pale yellow solid, m.p.= 103-104 °C

Purified by column chromatography (Silica gel, PE/Et₂O 90/10)

R_f = 0.36 (PE/EtOAc 90/10)

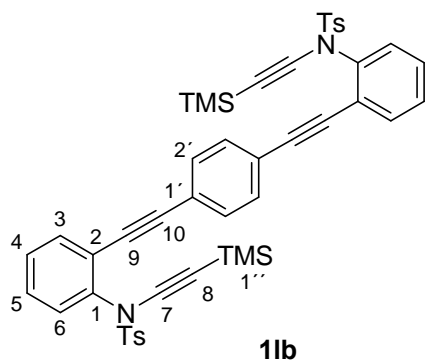
$^1\text{H NMR}$ (CDCl_3) δ ppm: 7.76 (d, $J = 8.3$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.57 (m, 2H, $\text{H}^{5'+8'$ or 3), 7.46 (m, 2H, H^{bzf} or $3-6$), 7.39 (m, 3H, H^{bzf} or $4-6$), 7.28 (t, $J = 7.3$ Hz, 1H, H^{bzf} or $4-6$), 7.17 (d, $J = 8.4$ Hz, 2H, $\text{H}^{3\text{Ts}}$), 6.83 (s, 1H, $\text{H}^{3'}$), 2.10 (s, 3H, $\text{H}^{5\text{Ts}}$), 0.18 (s, 9H, $\text{H}^{1''}$);

$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 154.7 (C_q , $\text{C}^{9'}$), 144.7 (C_q , $\text{C}^{4\text{Ts}}$), 138.6 (C_q , $\text{C}^{2'}$), 138.2 (C_q , C^1), 134.1 (C_q , $\text{C}^{1\text{Ts}}$), 133.3 (CH, C^3), 130.1 (CH, C^4), 129.7 (CH, C^6), 129.4 (CH, $\text{C}^{3\text{Ts}}$), 129.0 (CH, C^5), 128.5 (CH, $\text{C}^{2\text{Ts}}$), 127.4 (C_q , $\text{C}^{4'}$), 125.8 (CH, $\text{C}^{7'}$), 123.3 (CH, $\text{C}^{6'}$), 121.1 (CH, $\text{C}^{5'}$), 121.1 (C_q , C^2), 112.2 (CH, $\text{C}^{8'}$), 111.0 (CH, $\text{C}^{3'}$), 94.0 (C_q , C^7), 90.4 (C_q , C^9), 85.3 (C_q , C^{10}), 73.6 (C_q , C^8), 21.3 (CH_3 , $\text{C}^{5\text{Ts}}$), -0.1 (CH_3 , $\text{C}^{1''}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 2964.05 (w), 2160.85 (vs), 1441.53 (w), 1366.32 (vs), 1248.68 (s), 1170.58 (vs), 842.74 (vs), 809.96 (s), 749.21 (s);

FD-MS: m/z (%) = 483.3 (100) [$\text{M}]^+$, 484.3 (34), 485.3 (13), 486.3 (2).

2-(2-(4-(2-(2-(*N*-(2-(Trimethylsilyl)ethynyl)-*N*-tosylamino)phenyl)ethynyl)phenyl)ethynyl)-*N*-(2-(trimethylsilyl)ethynyl)-*N*-tosylbenzenamine **1b**



Prepared from **1ab** and 1,4-diiodobenzene,

Yield = 81%, orange solid, m.p. = 191-193 °C

Purified by column chromatography (SiO_2 , PE/ Et_2O 80/20)

$R_f = 0.37$ (PE/ EtOAc 80/20)

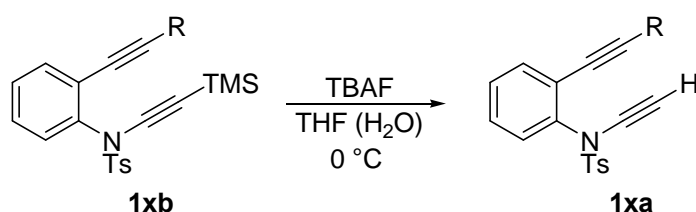
$^1\text{H NMR}$ (CDCl_3) δ ppm: 7.73 (d, $J = 8.0$ Hz, 4H, $\text{H}^{2\text{Ts}}$), 7.55 (m, 2H, H^3), 7.38 (m, 6H, H^{4+5+6}), 7.26 (s, 4H, $\text{H}^{2'}$), 7.17 (d, $J = 8.0$ Hz, 4H, $\text{H}^{3\text{Ts}}$), 2.27 (s, 6H, $\text{H}^{5\text{Ts}}$), 0.14 (s, 18H, $\text{H}^{1''}$);

$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 144.9 (C_q , $\text{C}^{4\text{Ts}}$), 138.7 (C_q , C^1), 134.3 (C_q , $\text{C}^{1\text{Ts}}$), 133.3 (CH, C^3), 131.2 (CH, $\text{C}^{2'}$), 129.5 (CH, C^5), 129.4 (CH, $\text{C}^{3\text{Ts}}$), 129.2 (CH, C^4 or 6), 129.0 (CH, C^4 or 6), 128.5 (CH, $\text{C}^{2\text{Ts}}$), 122.9 (C_q , $\text{C}^{1'}$), 122.5 (C_q , C^2), 94.9 (C_q , C^{10}), 94.5 (C_q , C^7), 87.1 (C_q , C^9), 73.1 (C_q , C^8), 21.5 (CH_3 , $\text{C}^{5\text{Ts}}$), 0.1 (CH_3 , $\text{C}^{1''}$);

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2952.48 (w), 2156.99 (vs), 1601.59 (w), 1512.88 (w), 1361.50 (vs), 1251.58 (s), 1173.47 (vs), 1031.73 (w), 834.06 (vs), 763.67 (s);

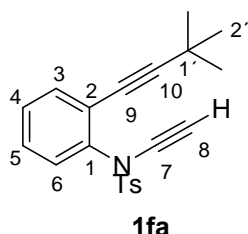
FD-MS: m/z (%) = 809.3 (100) [M]⁺, 810.2 (49), 811.2 (32), 812.3 (6), 813.2 (3).

- General procedure for desilylation of silylated alkynes with TBAF (GP6)



To a solution of the silylated alkyne (1.0 mmol) in 10 mL THF and two drops of water is added dropwise at 0 °C 1.2 mL of a 1M THF solution of TBAF (1.2 mmol, 1.2 equiv.). The solution is stirred at 0°C. After completion of the reaction (TLC), 20 mL of EtOAc and 20 mL of brine are added. The aqueous layer is extracted twice with 20 mL of EtOAc. The combined organic layers are dried over MgSO₄, filtered and the solvent is evaporated. The crude product is purified by a column chromatography.

***N*-ethynyl-2-(3,3-dimethylpropynyl)-*N*-tosylbenzenamine 1fa**



Yield= 64%, orange oil

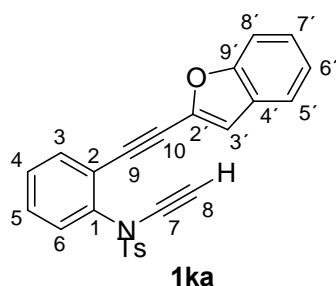
Purified by column chromatography (SiO₂, PE/EtOAc 95/5)

R_f = 0.72 (PE/EtOAc 80/20)

¹H NMR (CDCl₃) δ ppm: 7.68 (d, J = 8.3 Hz, 2H, H^{2Ts}), 7.40 (dd, J = 7.7 Hz, J = 1.9 Hz, 1H, H³), 7.28 (d, J = 7.9 Hz, 2H, H^{3Ts}), 7.24 (m, 2H, H⁴⁺⁵), 7.18 (td, J = 7.5 Hz, J = 1.7 Hz, 1H, H⁶), 2.80 (s, 1H, H⁸), 2.41 (s, 1H, H^{5Ts}), 1.18 (s, 9H, H^{2'});

¹³C NMR (CDCl₃) δ ppm: 144.7 (C_q, C^{4Ts}), 138.1 (C_q, C¹), 134.7 (C_q, C^{1Ts}), 133.5 (CH, C³), 129.6 (CH, C^{3Ts}), 128.9 (CH, C^{4,5 or 6}), 128.7 (CH, C^{4,5 or 6}), 128.3 (CH, C^{2Ts}), 128.0 (CH, C^{4,5 or 6}), 123.9 (C_q, C²), 105.0 (C_q, C¹⁰), 75.7 (C_q, C^{7 or 9}), 74.6 (C_q, C^{7 or 9}), 58.6 (CH, C⁸), 30.5 (CH₃, C^{2'}), 28.0 (C_q, C^{1'}), 21.6 (CH₃, C^{5Ts});

The product decomposed before all analyses were performed

2-(2-(Benzofuran-2-yl)ethynyl)-*N*-ethynyl-*N*-tosylbenzenamine 1ka

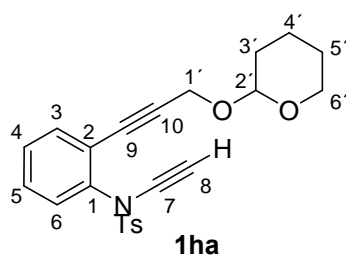
Yield= 83%, orange oil

Purified by column chromatography (SiO₂, PE/EtOAc 95/5) $R_f = 0.60$ (PE/EtOAc 80/20)

¹H NMR (CDCl₃) δ ppm: 7.73 (d, J= 8.2Hz, 2H, H^{2Ts}), 7.56 (m, 2H, H^{5'+3} or 8'), 7.45 (m, 2H⁴⁻⁶ or bzf), 7.39 (m, 3H⁴⁻⁶ or bzf), 7.27 (m, 1H, H⁶ or bzf), 7.14 (d, J= 8.2 Hz, 2H, H^{3Ts}), 6.88 (s, 1H, H^{3'}), 2.97 (s, 1H, H⁸), 2.15 (s, 3H, H^{5Ts});

¹³C NMR (CDCl₃) δ ppm: 154.8 (C_q, C^{9'}), 145.2 (C_q, C^{4Ts}), 138.4 (C_q, C¹ or 2'), 138.3 (C_q, C¹ or 2'), 134.1 (C_q, C^{1Ts}), 133.3 (CH, C³), 130.1 (CH, C^{4,5} or 6), 130.0 (CH, C^{4,5} or 6), 129.6 (CH, C^{3Ts}), 129.3 (CH, C^{4,5} or 6), 128.4 (CH, C^{2Ts}), 127.5 (C_q, C^{4'}), 125.9 (CH, C^{7'}), 123.4 (CH, C^{6'}), 121.4 (C_q, C²), 121.3 (CH, C^{5'}), 112.5 (CH, C^{8'}), 111.2 (CH, C^{3'}), 90.4 (C_q, C¹⁰), 85.5 (C_q, C⁹), 75.6 (C_q, C⁷), 59.4 (CH, C⁸), 21.4 (CH₃, C^{5Ts});

The product decomposed before that all analyses were performed

2-(Tetrahydropyranylalkoxypropynyl)-*N*-ethynyl -*N*-tosylbenzenamine 1hb

Yield = 82%, orange oil

Purified by column chromatography (Al₂O₃, PE/EtOAc 90/10) $R_f = 0.25$ (PE/EtOAc 90/10)

¹H NMR (CDCl₃) δ ppm: 7.69 (d, J= 8.3 Hz, 2H, H^{2Ts}), 7.43 (m, 1H, H³), 7.29 (m, 4H, H^{3Ts+4+5}), 7.22 (m, 1H, H⁶), 4.87 (t, J= 3.0 Hz, 1H, H^{2'}), 4.24 (d, J= 4.3 Hz, 2H, H^{1'}), 3.84 (m, 1H, H^{6'a}), 3.56 (m, 1H, H^{6'b}), 2.82 (s, 1H, H⁸), 2.42 (s, 3H, H^{5Ts}), 1.76 (m, 2H, H^{3'}), 1.56 (m, 4H, H^{4'+H'5});

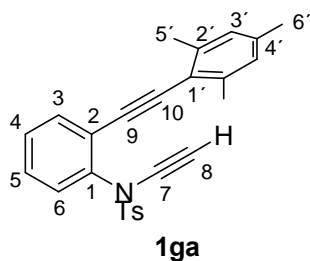
¹³C NMR (CDCl₃) δ ppm: 144.9 (C_q, C^{5Ts}), 138.4 (C_q, C¹), 134.1 (C_q, C^{1Ts}), 133.6 (CH, C³), 129.5 (CH, C^{3Ts}), 129.0 (CH, C⁴⁺⁵⁺⁶), 128.3 (CH, C^{2Ts}), 122.5 (C_q, C²), 96.5 (CH, C^{2'}), 91.4

(C_q, C¹⁰), 80.9 (C_q, C⁹), 75.7 (C_q, C⁷), 62.1 (CH₂, C^{6'}), 58.6 (CH, C⁸), 54.1 (CH₂, C^{1'}), 30.2 (CH₂, C^{3'}), 25.2 (CH₂, C^{5'}), 21.5 (CH₃, C^{5Ts}), 19.1 (CH₂, C^{4'});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3295.75 (s), 2946.70 (vs, br.), 2858.95 (m), 2133.85 (s), 1591.95 (m), 1486.85 (m), 1444.42 (m), 1369.21 (vs), 1261.22 (w), 1170.58 (vs), 1116.58 (s), 1083.80 (m), 1020.16 (vs), 902.52 (m), 869.74 (m), 809.96 (m), 752.10 (s), 700.99 (w), 671.11 (s);

FD-MS: m/z (%) = 409.4 (21) [M]⁺, 410.4 (10)

2-(2-Mesitylethynyl)-N-ethynyl-N-tosylbenzenamine **1ga**



Yield = 82%, orange solid, m.p. = 121-122 °C

Purified by column chromatography (Silica gel, PE/EtOAc 95/5)

R_f = 0.68 (PE/EtOAc 80/20)

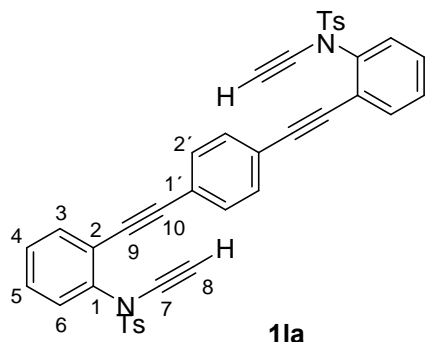
¹H NMR (CDCl₃) δ ppm: 7.73 (d, J = 8.2 Hz, 2H, H^{2Ts}), 7.59 (d, J = 7.6 Hz, 1H, H³), 7.37 (t, J = 7.4 Hz, 1H, H⁴ or ⁵), 7.31 (t, J = 7.8 Hz, 1H, H⁴ or ⁵), 7.21 (d, J = 8.1 Hz, 1H, H⁶), 7.13 (d, J = 8.2 Hz, 2H, H^{3Ts}), 6.88 (s, 2H, H^{3'}), 2.87 (s, 1H, H⁸), 2.43 (s, 6H, H^{5'}), 2.31 (s, 3H, H^{5Ts}), 2.21 (s, 3H, H^{6'});

¹³C NMR (CDCl₃) δ ppm: 144.9 (C_q, C^{4Ts}), 140.5 (C_q, C^{2'}), 138.1 (C_q, C¹ or ^{1'}), 137.8 (C_q, C¹ or ^{1'}), 134.5 (C_q, C^{1Ts}), 133.8 (CH, C³), 129.4 (CH, C^{3Ts}), 129.3 (CH, C^{4,5} or ⁶), 129.1 (CH, C^{4,5} or ⁶), 128.6 (CH, C^{4,5} or ⁶), 128.2 (CH, C^{2Ts}), 127.4 (CH, C^{3'}), 124.2 (C_q, C² or ^{1'}), 119.6 (C_q, C² or ^{1'}), 93.3 (C_q, C¹⁰), 92.3 (C_q, C⁹), 76.4 (C_q, C⁷), 58.6 (CH, C⁸), 21.3 (CH₃, C^{4Ts}), 21.3 (CH₃, C^{6'}), 21.1 (CH₃, C^{5'});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3268.75 (vs), 2203.27 (m), 2130.96 (m), 1594.84 (m), 1492.63 (m), 1366.32 (s), 1221.6668 (w), 1170.58 (s), 1089.58 (w), 920.84 (w), 845.63 (w), 749.21 (m), 703.89 (m), 652.79 (m);

FD-MS: m/z (%) = 413.2 (100) [M]⁺, 414.2 (24), 415.2 (9);

2-(2-(4-(2-(2-(*N*-Ethynyl-*N*-tosylamino)phenyl)ethynyl)phenyl)ethynyl)-*N*-ethynyl-*N*-tosylbenzenamine 11a



Yield >51%, orange solid

Purified by column chromatography (SiO₂, PE/EtOAc 2/1)

R_f = 0.16 (PE/EtOAc 80/20)

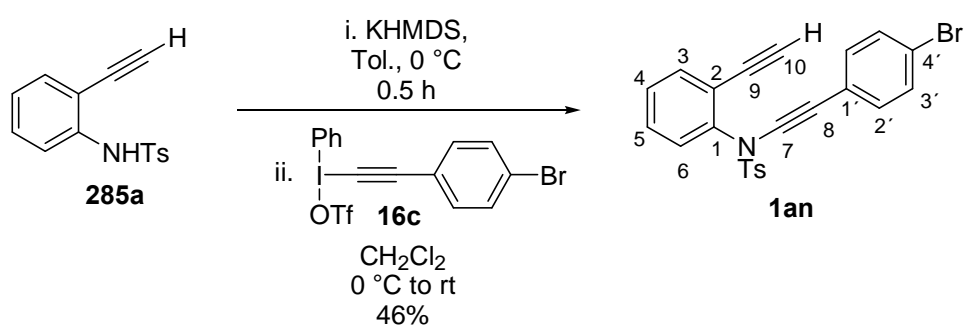
¹H NMR (CDCl₃) δ ppm: 7.72 (d, J = 8.2 Hz, 4H, H^{2Ts}), 7.56 (m, 2H, H³), 7.38 (m, 6H, H⁴⁻⁶), 7.32 (s, 4H, H^{2'}), 7.17 (d, J = 8.2 Hz, 4H, H^{3Ts}), 2.93 (s, 2H, H⁸), 2.27 (s, 6H, H^{5Ts});

¹³C NMR (CDCl₃) δ ppm: 145.1 (C_q, C^{4Ts}), 138.5 (C_q, C¹), 134.4 (C_q, C^{1Ts}), 133.3 (CH, C³), 131.3 (CH, C^{2'}), 129.7 (CH, C^{3Ts}), 129.6 (CH, C⁵), 129.3 (CH, C^{4 or 6}), 129.2 (CH, C^{4 or 6}), 128.4 (CH, C^{2Ts}), 122.9 (C_q, C^{2 or 1'}), 122.7 (C_q, C^{2 or 1'}), 95.0 (C_q, C¹⁰), 86.9 (C_q, C⁹), 76.0 (C_q, C⁷), 59.0 (CH, C⁸), 21.6 (CH₃, C^{5Ts});

V.2.1.2.2. Synthesis of diynes with a terminal alkyne moiety

V.2.1.2.2.1. Synthesis of diynes via *N*-alkynylation of sulfonamide **285a** (method A)

2-(Ethynyl)-*N*-(4-bromophenylethynyl)-*N*-tosylbenzenamine 1an



According to the general procedure of *N*-alkynylation of sulfonamides with iodonium salts **GP3**, 542.7 mg (2 mmol) of **285a**^{[2], [3]} and 1.49 g (2.4 mmol, 1.4 equiv.) of **16c** led after column chromatography (SiO₂, PE/EtOAc 90/10, R_f = 0.54 (80/20)) to 415 mg (0.92 mmol, 46%) of the diene **1an** as a white solid of m.p. = 99-100 °C (PE/CH₂Cl₂).

$^1\text{H NMR}$ (CDCl_3) δ ppm: 7.74 (d, $J = 8.4$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.52 (m, 1H, H^3), 7.37 (m, 7H, $\text{H}^{4-6+2'+3'}$), 7.22 (d, $J = 8.6$ Hz, 2H, $\text{H}^{3\text{Ts}}$), 3.02 (s, 1H, H^{10}), 2.46 (s, 3H, $\text{H}^{5\text{Ts}}$);

$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 145.1 (C_q , $\text{C}^{4\text{Ts}}$), 139.6 (C_q , C^1), 134.2 (CH, C^3), 134.0 (C_q , $\text{C}^{1\text{Ts}}$), 132.8 (CH, $\text{C}^{3'}$), 131.4 (CH, $\text{C}^{2'}$), 129.6 (3CH, $\text{C}^{3\text{Ts}+5}$), 129.2 (CH, C^4), 129.1 (CH, C^6), 128.6 (CH, $\text{C}^{2\text{Ts}}$), 122.1 (C_q , $\text{C}^{1'}$), 121.9 (2 \times C_q , $\text{C}^{2+4'}$), 83.6 (C_q , C^7), 83.1 (CH, C^{10}), 78.7 (C_q , C^9), 69.5 (C_q , C^8), 21.7 (CH_3 , $\text{C}^{5\text{Ts}}$);

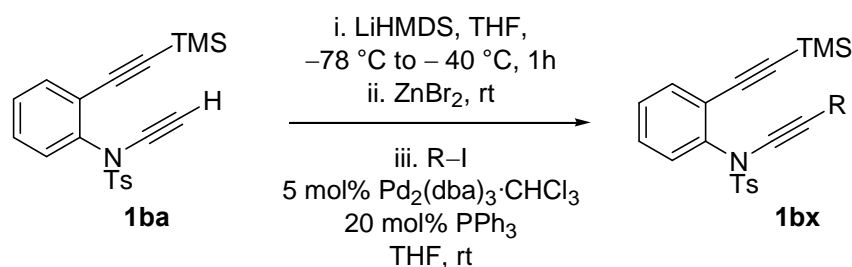
IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3267.79 (vs), 2365.26 (s), 2245.70 (w), 1590.99 (w), 1474.31 (s), 1357.64 (vs), 1162.87 (vs), 1081.87 (w), 1018.23 (w), 915.06 (w), 819.59 (w), 755.96 (w);

FD-MS: m/z (%) = 449.2 (83) $[\text{M}]^+$, 450.2 (22), 451.2 (100), 452.3 (33), 453.2 (2);

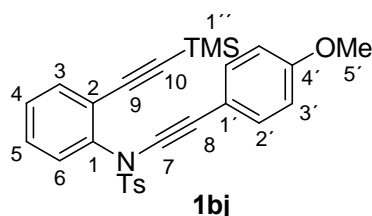
Elemental analysis (%) for $\text{C}_{23}\text{H}_{16}\text{BrNO}_2\text{S}$ (450.35) calcd: C 61.34, H 3.58, N 3.11, S 7.12; found C 62.06, H 3.62, N 2.86, S 7.38

V.2.1.2.2.2. Synthesis of diynes via functionalization of the diyne **1ba** (method C)

- General procedure for the functionalization of the diyne **1ba** via a Negishi coupling (GP7)^[3]



A freshly prepared LiHMDS solution (6.0 mL, 0.5M in THF, 1.5 equiv.) is added slowly to a solution of the diyne **1ba** (735 mg, 2 mmol) in dry THF (10 mL) cooled at $-78\text{ }^\circ\text{C}$ and the mixture is stirred for 1 h. A solution of ZnBr_2 (1.5 mL, 1.5M in THF, 1.1 equiv.) is added via syringe and, after stirring for 20 additional minutes at room temperature, the reaction mixture is transferred via cannula to a solution of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (103.5 mg, 0.1 mmol), PPh_3 (104.9 mg, 0.4 mmol) and the corresponding halo(hetero)aryl in dry THF (4 mL) and the reaction is stirred overnight. The solvent is removed, the residue dissolved with 30 mL of CH_2Cl_2 and 30 mL water. The aqueous layer is extracted 3 times with 20 mL CH_2Cl_2 . The combined organic layers are washed with 50 mL brine, dried over MgSO_4 , filtered on celite and the solvent is evaporated. The crude product is purified by column chromatography.

2-(2-Trimethylsilylethynyl)-*N*-(2-(4-methoxyphenyl)ethynyl)-*N*-tosylbenzenamine **1bj**Prepared from **1ba** and 4-iodoanisole

Yield = 83%, yellow oil

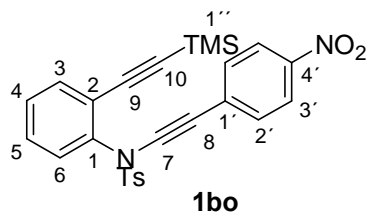
Purified by column chromatography (SiO₂, PE/EtOAc 95/5)R_f = 0.33 (PE/EtOAc 90/10)

¹H NMR (CDCl₃) δ ppm: 7.75 (d, J = 8.3 Hz, 2H, H^{2Ts}), 7.52 (d, J = 5.7 Hz, 1H, H³), 7.32 (m, 7H, H^{3Ts+4-6+2'}), 6.80 (d, J = 8.9 Hz, 2H, H^{3'}), 3.78 (s, 3H, H^{6'}), 2.45 (s, 3H, H^{5Ts}), 0.14 (9H, H^{1''});

¹³C NMR (CDCl₃) δ ppm: 159.2 (C_q, C^{4'}), 144.6 (C_q, C^{4Ts}), 139.5 (C_q, C¹), 134.6 (C_q, C^{1Ts}), 134.0 (CH, C³), 133.0 (CH, C^{2'}), 129.5 (CH, C^{3Ts}), 129.1 (CH, C^{4,5 or 6}), 128.9 (CH, C^{4,5 or 6}), 128.6 (CH, C^{4,5 or 6}), 128.4 (CH, C^{2Ts}), 122.8 (C_q, C²), 114.9 (C_q, C^{1'}), 113.7 (CH, C^{3'}), 101.1 (C_q, C¹⁰), 100.0 (C_q, C⁹), 81.0 (C_q, C⁷), 70.0 (C_q, C⁸), 55.2 (CH₃, C^{6'}), 21.6 (CH₃, C^{5Ts}), -0.4 (CH₃, C^{1''});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2958.27 (m,br.), 2837.74 (m), 2238.95 (s), 2157.95 (m), 1600.63 (s), 1567.84 (w), 1508.06 (vs), 1486.85 (s), 1444.42 (m), 1366.32 (vs), 1291.11 (m), 1245.79 (vs), 1173.47 (vs), 1089.58 (m), 1032.69 (m), 923.74 (w), 830.21 (vs), 764.64 (s), 706.78 (s), 658.57 (m);

FD-MS: m/z (%) = 473.4 (100) [M]⁺, 474.4 (26), 475.4 (5).

2-(2-Trimethylsilylethynyl)-*N*-(2-(4-nitrophenyl)ethynyl)-*N*-tosylbenzenamine **1bo**Prepared from **1ba** and 1-nitro-4-iodobenzene

Yield = 71%, yellow oil

Purified by column chromatography (SiO₂ PE/EtOAc 95/5)R_f = 0.40 (PE/EtOAc 90/10)

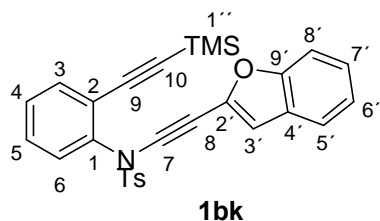
¹H NMR (CDCl₃) δ ppm : 8.13 (d, J = 9.0 Hz, 2H, H^{3'}), 7.71 (d, J = 8.3 Hz, 2H, H^{2Ts}), 7.61 (m, 1H, H³), 7.50 (m, 1H, H⁶), 7.40 (m, 4H, H^{2'+4-5}), 7.26 (d, J = 8.5 Hz, 2H, H^{3Ts}), 2.44 (s, 3H, H^{5Ts}), 0.01 (9H, H^{1''});

^{13}C NMR (CDCl_3) δ ppm: 146.0 (C_q , $\text{C}^{4'}$), 145.2 (C_q , $\text{C}^{4\text{Ts}}$), 138.3 (C_q , C^1), 134.3 (C_q , $\text{C}^{1\text{Ts}}$), 134.1 (CH , C^3), 130.6 (C_q , $\text{C}^{1'}$), 130.5 (CH , $\text{C}^{2'}$), 129.8 (CH , $\text{C}^{3\text{Ts}}$), 129.3 (CH , $\text{C}^{4,5}$ or 6), 129.1 (CH , $\text{C}^{4,5}$ or 6), 128.9 (CH , $\text{C}^{4,5}$ or 6), 128.4 (CH , $\text{C}^{2\text{Ts}}$), 123.5 (CH , $\text{C}^{3'}$), 122.4 (C_q , C^2), 101.7 (C_q , C^{10}), 99.2 (C_q , C^9), 88.5 (C_q , C^7), 70.8 (C_q , C^8), 21.7 (CH_3 , $\text{C}^{5\text{Ts}}$), -0.5 (CH_3 , $\text{C}^{1''}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3055.66 (w, br.), 2956.34 (w, br.), 2237.99 (vs), 2153.13 (w), 1594.84 (s), 1502.28 (s), 1481.06 (m), 1435.74 (w), 1382.71 (s), 1336.43 (vs), 1243.86 (m), 1177.33 (vs), 1067.41 (s), 918.91 (w), 844.67 (s), 766.57 (m), 688.46 (s);

FD-MS: m/z (%) = 488.3 (100) $[\text{M}]^+$, 489.3 (36), 490.3 (15), 491.3 (3).

2-(2-Trimethylsilylethynyl)-*N*-(2-(benzofuran-2-yl)ethynyl)-*N*-tosylbenzenamine **1bk**



Prepared from **1ba** and 2-iodobenzofuran^[115]

Yield= 85%, yellow oil

Purified by column chromatography (SiO_2 , PE/EtOAc 95/5)

R_f = 0.58 (PE/EtOAc, 80/20)

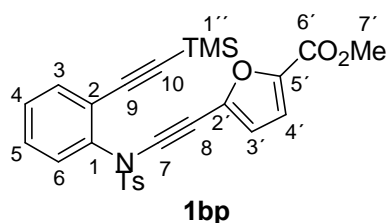
^1H NMR (CDCl_3) δ ppm: 7.71 (d, J = 8.2 Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.47 (m, 2H, $\text{H}^{5'+3}$), 7.34 (m, 7H, $\text{H}^{3\text{Ts}+4-5+\text{bfz}}$), 7.23 (t, J = 6.9 Hz, 1H, $\text{H}^{7'}$ or $6'$), 6.91 (s, 1H, $\text{H}^{3'}$), 2.46 (s, 3H, $\text{H}^{5\text{Ts}}$), 0.19 (s, 9H, $\text{H}^{1''}$);

^{13}C NMR (CDCl_3) δ ppm: 154.9 (C_q , $\text{C}^{9'}$), 145.0 (C_q , $\text{C}^{4\text{Ts}}$), 138.7 (C_q , C^1 or $2^{1'}$), 138.6 (C_q , C^1 or $2'$), 134.6 (C_q , $\text{C}^{1\text{Ts}}$), 134.5 (CH , C^3), 130.2 (CH , $\text{C}^{3\text{Ts}}$), 129.6 (CH , $\text{C}^{2\text{Ts}}$), 129.5 (CH , $\text{C}^{4,5}$ or 6), 128.9 (CH , $\text{C}^{4,5}$ or 6), 127.7 (C_q , $\text{C}^{4'}$), 125.9 (CH , $\text{C}^{7'}$), 123.4 (CH , $\text{C}^{6'}$), 122.9 (C_q , C^2), 121.5 (CH , $\text{C}^{5'}$), 113.0 (CH , $\text{C}^{8'}$), 111.5 (CH , $\text{C}^{3'}$), 102.3 (C_q , C^{10}), 99.9 (C_q , C^9), 87.8 (C_q , C^7), 62.1 (C_q , C^8), 22.25 (CH_3 , $\text{C}^{5\text{Ts}}$), 0.1 (CH_3 , $\text{C}^{1''}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3070.12 (w), 2960.20 (w), 2227.38 (vs), 2160.85 (s), 1601.59 (s), 1478.17 (s), 1442.49 (s), 1372.10 (vs), 1247.72 (s), 1173.47 (vs), 1092.48 (s), 844.67 (s), 812.85 (s), 753.07 (s);

FD-MS: m/z (%) = 482.8 (100) $[\text{M}]^+$, 483.8 (40), 484.8 (15), 485.8 (3), 486.8 (1).

2-(2-Trimethylsilylethynyl)-N-(2-(methylfuran-2-carboxylate-5-yl)ethynyl)-N-tosylbenzenamine 1bp



Prepared from **1ba** and methyl 5-bromofuran-2-carboxylate,

Yield= 78%, yellow oil

Purified by column chromatography (SiO₂, PE/EtOAc 95/5)

R_f= 0.85 (PE/EtOAc 50/50)

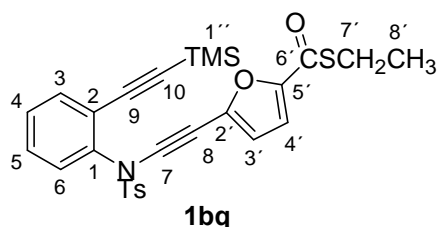
¹H NMR (CDCl₃) δ ppm: 7.71 (d, J= 8.4Hz, 2H, H^{2Ts}), 7.50 (m, 1H, H³), 7.33 (m, 5H, H^{3Ts+4-6}), 7.13 (d, J= 3.7 Hz, 1H, H^{4'}), 6.62 (d, J= 3.7Hz, 1H, H^{3'}), 3.87 (s, 3H, H⁷), 2.46 (s, 3H, H^{5Ts}), 0.18 (s, 9H, H^{1''});

¹³C NMR (CDCl₃) δ ppm: 158.1 (C_q, C^{6'}), 145.0 (C_q, C^{5'}), 144.2 (C_q, C^{4Ts}), 140.0 (C_q, C^{2'}), 138.1 (C_q, C¹), 134.2 (C_q, C^{1Ts}), 133.8 (CH, C³), 129.6 (CH, C^{3Ts}), 129.1 (CH, C^{4,5 or 6}), 129.0 (CH, C^{4,5 or 6}), 128.9 (CH, C^{4,5 or 6}), 128.2 (CH, C^{2Ts}), 122.6 (C_q, C²), 118.6 (CH, C^{4'}), 117.4 (CH, C^{3'}), 101.7 (C_q, C¹⁰), 99.2 (C_q, C⁹), 87.2 (C_q, C⁷), 60.5 (C_q, C⁸), 52.0 (CH₃, C⁷), 21.5 (CH₃, C^{5Ts}), -0.6 (CH₃, C^{1''});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2956.34 (br.), 2235.09 (vs), 2163.74 (w), 1725.01 (vs), 1375.00 (s), 1296.89 (vs), 1173.47 (s), 1137.80 (s), 1084.76 (s), 918.91 (w), 848.53 (s), 755.96 (s), 699.07 (s);

FD-MS: m/z (%) = 490.8 (100) [M]⁺, 491.8 (32), 492.8 (13), 493.8 (3).

2-(2-Trimethylsilylethynyl)-N-(2-(5-((ethylsulfanyl)carbonyl)furan-2-yl)ethynyl)-N-tosylbenzenamine 1bq



Prepared from **1ba** and

Ethylsulfanyl 5-bromo-2-furan carboxylate^[116]

Yield= 70%, yellow oil

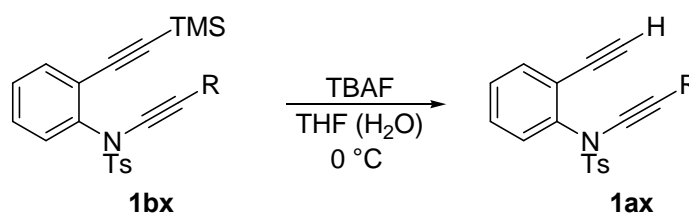
Purified by column chromatography (SiO₂, PE/Et₂O 95/5)

R_f= 0.23 (PE/Et₂O 90/10)

$^1\text{H NMR}$ (CDCl_3) δ ppm: 7.73 (d, $J=8.0$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.50 (m, 1H, H^3), 7.35 (m, 5H, $\text{H}^{3\text{Ts}+4-6}$), 7.11 (d, $J=3.5$ Hz, 1H, $\text{H}^{4'}$), 6.63 (d, $J=4.1$ Hz, 1H, $\text{H}^{3'}$), 3.05 (q, $J=7.4$ Hz, 2H, $\text{H}^{7'}$), 2.46 (s, 3H, $\text{H}^{5\text{Ts}}$), 1.32 (t, $J=7.4$ Hz, 3H, $\text{H}^{8'}$), 0.18 (s, 9H, $\text{H}^{1''}$).

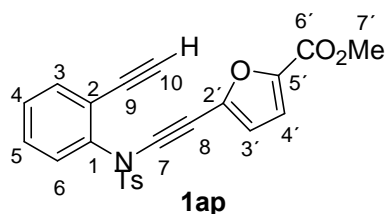
$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 180.0 (C_q , $\text{C}^{6'}$), 150.7 (C_q , $\text{C}^{5'}$), 145.2 (C_q , $\text{C}^{4\text{Ts}}$), 140.0 (C_q , $\text{C}^{2'}$), 138.3 (C_q , C^1), 134.4 (C_q , $\text{C}^{1\text{Ts}}$), 134.0 (CH, C^3), 129.8 (CH, $\text{C}^{3\text{Ts}}$), 129.3 (CH, $\text{C}^{4,5}$ or 6), 129.2 (CH, $\text{C}^{4,5}$ or 6), 129.1 (CH, $\text{C}^{4,5}$ or 6), 128.5 (CH, $\text{C}^{2\text{Ts}}$), 122.9 (C_q , C^2), 117.9 (CH, $\text{C}^{4'}$), 115.9 (CH, $\text{C}^{3'}$), 101.9 (C_q , C^{10}), 99.4 (C_q , C^9), 87.7 (C_q , C^7), 60.9 (C_q , C^8), 22.6 (CH_2 , $\text{C}^{7'}$), 21.7 (CH_3 , $\text{C}^{5\text{Ts}}$), 14.7 (CH_3 , $\text{C}^{8'}$), -0.3 (CH_3 , $\text{C}^{1''}$);

- General procedure for desilylation of silylated ynamides with TBAF (GP8)



To a solution of the silylated ynamide (1.0 mmol) in 10 mL THF and two drops of water is added dropwise at 0 °C 1.2 mL of a 1M THF solution of TBAF (1.2 mmol, 1.2 equiv.). The solution is stirred at 0°C. After completion of the reaction (TLC), 20 mL of EtOAc and 20 mL of brine are added. The aqueous layer is extracted twice with 20 mL of EtOAc. The combined organic layers are dried over MgSO_4 , filtered and the solvent is evaporated. The crude product is purified by a column chromatography.

2-Ethynyl-*N*-(2-(methylfuran-2-carboxylate-5-yl)ethynyl)-*N*-tosylbenzenamine 1ap



Prepared from **1bp**,

Yield= 82%, white solid, m.p.= 113-114 °C

Purified by column chromatography (SiO_2 , PE/EtOAc 90/10)

$R_f= 0.29$ (PE/EtOAc 80/20)

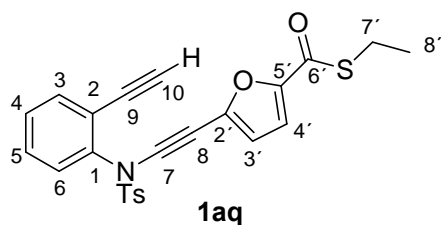
$^1\text{H NMR}$ (CDCl_3) δ ppm: 7.74 (d, $J=8.4$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.52 (m, 1H, H^3), 7.36 (m, 4H, $\text{H}^{3\text{Ts}+4+5}$), 7.26 (m, 1H, H^6), 7.13 (d, $J=3.5$ Hz, 1H, $\text{H}^{4'}$), 6.64 (d, $J=3.7$ Hz, 1H, $\text{H}^{3'}$), 3.89 (s, 3H, $\text{H}^{7'}$), 3.10 (s, 1H, H^{10}), 2.48 (s, 3H, $\text{H}^{5\text{Ts}}$);

^{13}C NMR (CDCl_3) δ ppm: 158.4 (C_q , $\text{C}^{6'}$), 145.4 (C_q , $\text{C}^{4\text{Ts}}$), 144.4 (C_q , $\text{C}^{5'}$), 140.2 (C_q , $\text{C}^{2'}$), 139.0 (C_q , C^1), 134.2 (CH , C^3), 133.9 (C_q , $\text{C}^{1\text{Ts}}$), 129.8 (CH , $\text{C}^{3\text{Ts}}$), 129.7 (CH , C^5), 129.4 (CH , C^4), 129.1 (CH , C^6), 128.5 (CH , $\text{C}^{2\text{Ts}}$), 122.3 (C_q , C^2), 118.8 (CH , $\text{C}^{4'}$), 118.0 (CH , $\text{C}^{3'}$), 87.7 (C_q , C^7), 83.5 (CH , C^{10}), 78.5 (C_q , C^9), 60.5 (C_q , C^8), 52.02 (CH_3 , $\text{C}^{7'}$), 21.7 (CH_3 , $\text{C}^{5\text{Ts}}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3278.39 (vs), 2241.84 (s), 1711.51 (vs), 1375.00 (vs), 1330.64 (s), 1290.14 (vs), 1166.72, (vs), 1131.05 (w), 1078.01 (w), 922.77 (w), 755.96 (w);

FD-MS: m/z (%) = 419.3 (100) $[\text{M}]^+$, 420.2 (23), 421.3 (6);

2-Ethynyl-*N*-(2-(5-((ethylsulfanyl)carbonyl)furan-2-yl)ethynyl)-*N*-tosylbenzenamine **1aq**



Prepared from **1bq**,

Yield=88%, white solid, m.p.: 60-61°C

Purified by column chromatography (SiO_2 , PE/ Et_2O 90/10)

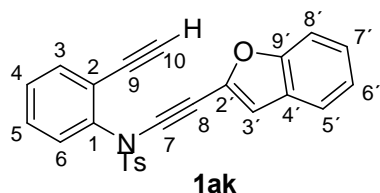
R_f = 0.42 (PE/ EtOAc 80/20)

^1H NMR (CDCl_3) δ ppm: 7.73 (d, J = 8.2Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.50 (m, 1H, H^3), 7.35 (m, 4H, $\text{H}^{3\text{Ts}+4+5}$), 7.29 (m, 1H, H^6), 7.11 (d, J =3.7 Hz, 1H, $\text{H}^{4'}$), 6.64 (d, J =3.7 Hz, 1H, $\text{H}^{3'}$), 3.11 (s, 1H, H^{10}), 3.05 (q, J =7.4 Hz, 2H, $\text{H}^{7'}$), 2.47 (s, 3H, $\text{H}^{5\text{Ts}}$), 1.32 (t, J = 7.4 Hz, 3H, $\text{H}^{8'}$);

* ^{13}C NMR (CDCl_3) δ ppm: 180.0 (C_q , $\text{C}^{6'}$), 150.7 (C_q , $\text{C}^{5'}$), 145.4 (C_q , $\text{C}^{4\text{Ts}}$), 139.8 (C_q , $\text{C}^{2'}$), 138.8 (C_q , C^1), 134.1 (CH , C^3), 133.7 (C_q , $\text{C}^{1\text{Ts}}$), 129.7 (CH , $\text{C}^{3\text{Ts}}$), 129.6 (CH , $\text{C}^{5'}$), 129.3 (CH , C^4), 129.0 (CH , C^6), 128.5 (CH , $\text{C}^{2\text{Ts}}$), 122.1 (C_q , C^2), 118.1 (CH , $\text{C}^{3'}$), 115.9 (CH , $\text{C}^{4'}$), 88.1 (C_q , C^7), 83.5 (C_q , C^{10}), 78.3 (C_q , C^9), 60.7 (C_q , C^8), 22.6 (CH_2 , $\text{C}^{7'}$), 21.7 (CH_3 , $\text{C}^{5\text{Ts}}$), 14.7 (CH_3 , $\text{C}^{8'}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3271.64 (vs), 2213.88 (s), 1644.02 (vs), 1509.99 (w), 1481.06 (w), 1446.35 (w), 1357.64 (s), 1169.62 (s), 1014.37 (w), 859.13 (m), 806.10 (m), 685.57 (m);

FD-MS: m/z (%)= 449.2 (100) $[\text{M}]^+$, 450.2 (10), 451.2 (49);

2-Ethynyl-*N*-(2-(benzofuran-2-yl)ethynyl)-*N*-tosylbenzenamine 1akPrepared from **1bk**,

Yield= 79%, White solid, m.p.: 127 °C

Purified by column chromatography (SiO₂, PE/EtOAc 90/10)R_f= 0.28 (PE/EtOAc 90/10)

¹H NMR (CDCl₃) δ ppm: 7.76 (d, J= 8.3 Hz, 2H, H^{2Ts}), 7.54 (m, 2H, H^{5'+3 or 8'}), 7.36 (m, 7H, H^{4-6+bzf}), 7.23 (t, J= 7.2 Hz, 1H, H^{6'}), 6.94 (s, 1H, H^{3'}), 3.10 (s, 1H, H¹⁰), 2.48 (s, 3H, H^{5Ts});

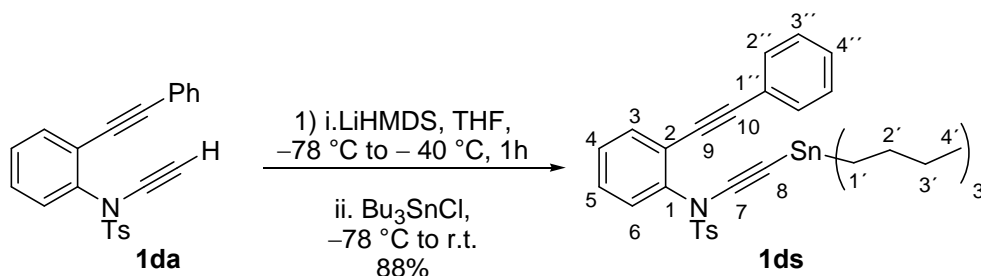
¹³C NMR (CDCl₃) δ ppm: 154.9 (C_q, C^{9'}), 145.3 (C_q, C^{4Ts}), 139.2 (C_q, C¹), 138.6 (C_q, C^{2'}), 134.2 (CH, C³), 134.0 (C_q, C^{1Ts}), 129.8 (CH, C^{3Ts}), 129.7 (CH, C^{4 or 5 or 6}), 129.3 (CH, C^{4 or 5 or 6}), 129.2 (CH, C^{4 or 5 or 6}), 128.6 (CH, C^{2Ts}), 127.7 (C_q, C^{4'}), 125.6 (CH, C^{7'}), 123.1 (CH, C^{6'}), 122.2 (C_q, C²), 121.1 (CH, C^{5'}), 113.0 (CH, C^{8'}), 111.2 (CH, C^{3'}), 87.6 (C_q, C⁷), 83.4 (CH, C¹⁰), 78.5 (C_q, C⁹), 61.6 (C_q, C⁸), 21.77 (CH₃, C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3262.00 (vs), 2233.16 (s), 1600.63 (w), 1474.31 (w), 1447.31 (w), 1366.32 (vs), 1258.32 (w), 1170.58 (s), 1062.59 (w), 923.74 (w), 818.63 (w), 754.99 (s), 689.43 (w);

FD-MS: m/z (%) = 411.1 (100) [M]⁺, 412.1 (26), 413.1 (8), 414.1 (1);

V.2.1.2.3 Synthesis of disubstituted diynes

- General Procedure for the functionalization of a diyne via nucleophilic substitution (GP9)^[3]

2-(2-Phenylethynyl)-*N*-(2-tris(tributylstannyl)ethynyl)-*N*-tosylbenzenamine 1ds

A freshly prepared LiHMDS solution (6.0 mL, 0.5M in THF, 1.5 equiv.) is added slowly to a solution of the diyne **1da** (743 mg, 2 mmol) in dry THF (15 mL) cooled at $-78\text{ }^{\circ}\text{C}$ and the mixture is stirred for 1 h. A solution of Bu_3SnCl (650 μL in 5 mL THF, 2.4 mmol, 1.2 equiv.) is added dropwise over 10 min. The reaction is let warm to room temperature and stirred overnight. The reaction is then quenched by addition of EtOAc (20 mL) and brine (20 mL). The aqueous layer is extracted twice with 10 mL of EtOAc. The combined organic layers are washed by 20 mL brine, dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue is purified by a column chromatography (SiO_2 , PE/Et₂O 80/20, $R_f = 0.35$) to give 1.16 g (1.76 mmol, 88%) of the diyne **1ds** as a pale yellow oil

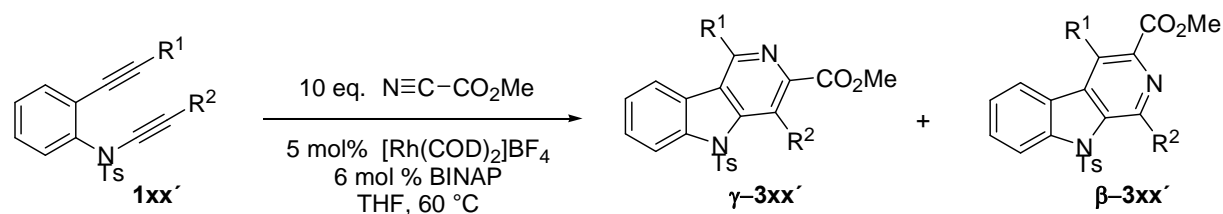
$^1\text{H NMR}$ (CDCl_3) δ ppm: 7.74 (d, $J = 8.3$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.52 (m, 1H, H^3), 7.33 (m, 8H, $\text{H}^{4-6+2''-4''}$), 7.12 (d, $J = 8.2$ Hz, 2H, $\text{H}^{3\text{Ts}}$), 2.21 (s, 3H, $\text{H}^{5\text{Ts}}$), 1.47 (quint., $J = 7.6$ Hz, 6H, H^3), 1.26 (sext., $J = 7.4$ Hz, 6H, $\text{H}^{2'}$), 1.91 (t, $J = 8.2$ Hz, 6H, $\text{H}^{1'}$), 0.83 (t, $J = 7.3$ Hz, 9H, $\text{H}^{4'}$);

$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 144.4 (C_q , $\text{C}^{4\text{Ts}}$), 139.4 (C_q , C^1), 134.8 (C_q , $\text{C}^{1\text{Ts}}$), 133.20 (CH, C^3), 131.7 (CH, $\text{C}^{2''}$), 129.7 (CH, $\text{C}^{4,5}$ or 6), 129.3 (CH, $\text{C}^{3\text{Ts}}$), 128.8 (CH, $\text{C}^{4,5}$ or 6), 128.7 (CH, $\text{C}^{4,5,6}$ or $4''$), 128.5 (CH, $\text{C}^{2\text{Ts}}$), 128.3 (CH, $\text{C}^{4,5,6}$ or $4''$), 127.9 (CH, $\text{C}^{3''}$), 123.0 (C_q , $\text{C}^{1''}$ or 2), 122.8 (C_q , $\text{C}^{1''}$ or 2), 97.8 (C_q , C^7), 95.2 (C_q , C^9), 85.4 (C_q , C^{10}), 71.0 (C_q , C^8), 28.8 (CH_2 , $\text{C}^{2'}$), 27.0 (CH_2 , C^3), 21.5 (CH_3 , $\text{C}^{5\text{Ts}}$), 13.6 (CH_3 , $\text{C}^{4'}$), 11.2 (CH_2 , $\text{C}^{1'}$).

Diyne **1bc** ($\text{R}^1 = \text{TMS}$, $\text{R}^2 = \text{Me}$) was prepared according to this procedure using methyl iodide as alkylating agent. Analyses of this diyne fit with the literature.^{[2],[3]}

V.2.1.3 [2+2+2] Cycloaddition with nitriles: synthesis of γ - and β -carbolines

- General procedure for the [2+2+2] cycloaddition of alkynes with nitriles (**GP10**)^[79c, modified]



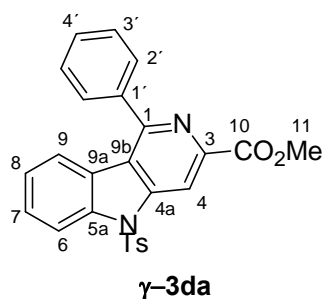
Under Argon, BINAP (7.5 mg, 0.012 mmol) and $[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-$ (4.9 mg, 0.010 mmol) are dissolved in CH_2Cl_2 (3.0 mL) in a Schlenk tube, and the mixture is stirred at room temperature for 5 min. H_2 is then introduced to the resulting solution. After stirring at room temperature for

0.5 h, the resulting solution is concentrated to dryness and the residue dissolved in CH₂Cl₂ (THF) (3.0 mL). To this solution is added dropwise over 1 min a solution of diyne (0.2 mmol) and nitrile (2.0 mmol) in CH₂Cl₂ (THF) (5.0 mL). Undissolved substrate is dissolved by addition of CH₂Cl₂ (THF) (2x1.0 mL), added to the solution and the mixture is heated at 60 °C. After completion of the reaction (TLC), the solvent is removed and the residue is purified by column chromatography.

- Cycloaddition with the diyne 1da (R¹= Ph, R²= H) and methylcyanoformate 2a

According to the general procedure **GP10**, 74.3 mg (0.2 mmol) of the diyne **1da** led after column chromatography to 61.2 mg (0.134 mmol, 67%) of a mixture of the carbolines γ -**3da** and γ -**3da**. (CH₂Cl₂ as solvent)

Methyl 1-phenyl-5-tosyl-5H-pyrido[4,3-b]indole-3-carboxylate γ -**3da**



White solid, m.p.= 198-199 °C

Purified by column chromatography (SiO₂, PE/EtOAc 80/20)

R_f= 0.16 (PE/EtOAc 80/20)

¹H NMR (CDCl₃) δ ppm: 9.10 (s, 1H, H⁴), 8.39 (d, J= 8.4 Hz, 1H, H⁶), 7.84 (d, J= 8.2 Hz, 2H, H^{2Ts}), 7.66 (m, 2H, H^{2'} or 3'), 7.54 (m, 4H, H^{7+8+2'} or 3'), 7.40 (d, J= 7.5 Hz, 1H, H^{4'}), 7.21 (d, J= 8.2 Hz, 2H, H^{3Ts}), 7.19 (d, J= 7.4 Hz, 1H, H⁹), 4.07 (s, 3H, H¹¹), 2.33 (s, 3H, H^{5Ts});

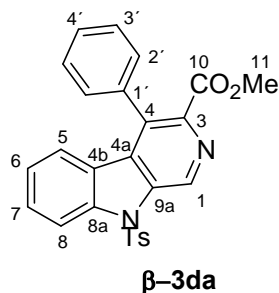
¹³C NMR (CDCl₃) δ ppm: 166.0 (C_q, C¹⁰), 155.2 (C_q, C¹), 145.9 (C_q, C^{4Ts}), 144.8 (C_q, C³), 144.4 (C_q, C^{4a}), 139.1 (C_q, C^{5a}), 139.0 (C_q, C^{1'}), 134.5 (C_q, C^{1Ts}), 130.1 (CH, C^{3Ts}), 129.3 (CH, C^{4'}), 129.0 (3CH, H^{2'} or 3'+7), 128.7 (CH, H^{2'} or 3'), 126.7 (CH, C^{2Ts}), 124.2 (CH, C⁸), 123.4 (C_q, C^{9a}), 123.0 (CH, C⁹), 122.1 (C_q, C^{1a}), 114.5 (CH, C⁶), 110.2 (CH, C⁴), 53.1 (CH₃, C¹¹), 21.6 (CH₃, C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3034.44 (w), 1739.48 (vs), 1718.26 (vs), 1563.02 (s), 1368.25 (vs), 1343.18 (s), 1254.47 (s), 1222.65 (vs), 1177.33 (vs), 1152.26 (vs), 1010.52 (s), 766.57 (s);

FD-MS: m/z (%) = 455.71 (100) [M]⁺, 456.71 (29), 457.72 (7), 458.73 (1);

Analyses in agreement with the literature^[3]

Methyl 4-phenyl-9-tosyl-9H-pyrido[3,4-b]indole-3-carboxylate β -3da



White solid, m.p.= 211-212 °C

Purified by column chromatography (SiO₂, PE/EtOAc 80/20)

R_f= 0.15 (PE/EtOAc 90/10)

¹H NMR (CDCl₃) δ ppm: 9.74 (s, 1H, H¹), 8.38 (d, J= 8.4 Hz, 1H, H⁸), 7.81 (d, J= 8.2 Hz, 2H, H^{2Ts}), 7.53 (m, 4H, H^{7+3'+4'}), 7.33 (m, 2H, H^{2'}), 7.17 (d, J= 7.6 Hz, 2H, H^{3Ts}), 7.10 (t, J= 7.4 Hz, 1H, H⁶), 6.67 (d, J= 8.0 Hz, 1H, H⁵), 3.78 (s, 3H, H¹¹), 2.33 (s, 3H, H^{5Ts});

¹³C NMR (CDCl₃) δ ppm: 166.2 (C_q, C¹⁰), 145.9 (C_q, C^{4Ts}), 141.5 (C_q, C³), 139.2 (C_q, C^{8a}), 136.0 (C_q, C⁴), 135.5 (CH, C¹), 135.3 (C_q, C^{9a}), 134.4 (C_q, C^{1Ts}), 133.0 (C_q, C^{4a}), 131.8 (C_q, C^{1'}), 130.1 (CH, C^{3Ts}), 130.0 (CH, C⁷), 128.8 (CH, C^{2' or 3'}), 128.5 (CH, C^{4'}), 128.3 (CH, C^{2' or 3'}), 126.7 (CH, C^{2Ts}), 124.2 (CH, C⁶), 124.1 (C_q, C^{4b}), 123.7 (CH, C⁵), 114.7 (CH, C⁸), 52.6 (CH₃, C¹¹), 21.6 (CH₃, C^{5Ts});

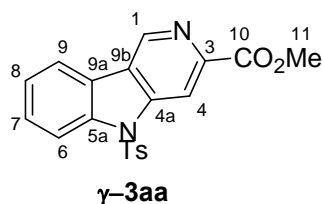
IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3005.52 (w), 1735.62 (vs), 1587.13 (w), 1421.28 (w), 1375.00 (vs), 1254.47 (s), 1173.47 (vs), 1052.94 (s), 971.95 (s), 816.71 (w), 763.67 (vs), 696.18 (s), 660.50 (s);

FD-MS: m/z (%) = 455.6 (100) [M]⁺, 456.6 (29), 457.6 (9), 458.6 (2);

Elemental analysis (%) for C₂₆H₂₀N₂O₄S calcd: C 68.41, H 4.42, N 6.14, S 7.02; found C 68.27, H 4.42, N 6.12, S 7.03

- Cycloaddition with the diyne **1aa ($R^1=H$, $R^2=H$) and methylcyanoformate **2a****

According to the general procedure **GP10**, 59.1 mg (0.2 mmol) of the diyne **1aa** led after column chromatography to 38.0 mg (0.1 mmol, 50%) of the carboline β -**3aa** and 21.3 mg (0.056 mmol, 28%) of the carboline γ -**3aa**. (CH_2Cl_2 as solvent)

Methyl 5-tosyl-5H-pyrido[4,3-b]indole-3-carboxylate γ -3aa****

White solid, m.p.= 197-198 °C

Purified by column chromatography (Silica gel, PE/EtOAc 1/1)

R_f = 0.08 (PE/EtOAc 2/1)

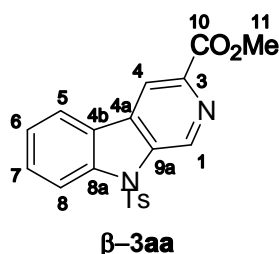
¹H NMR (CDCl_3) δ ppm: 9.29 (s, 1H, H^1), 9.05 (s, 1H, H^4), 8.35 (d, $J=8.5$ Hz, 1H, H^6), 8.08 (d, $J=7.8$ Hz, 1H, H^9), 7.79 (d, $J=8.4$ Hz, 2H, $H^{2\text{Ts}}$), 7.63 (t, $J=7.9$ Hz, 1H, H^7), 7.47 (t, $J=7.8$ Hz, 1H, H^8), 7.18 (d, $J=8.4$ Hz, 2H, $H^{3\text{Ts}}$), 4.09 (s, 3H, H^{11}), 2.30 (s, 3H, $H^{5\text{Ts}}$);

¹³C NMR (CDCl_3) δ ppm: 165.8 (C_q , C^{10}), 145.9 (C_q , $C^{4\text{Ts}}$), 145.4 (C_q , C^3), 143.6 (C_q , C^{4a}), 142.5 (CH, C^1), 139.1 (C_q , C^{5a}), 134.5 (C_q , $C^{1\text{Ts}}$), 130.1 (CH, $C^{3\text{Ts}}$), 129.5 (CH, C^7), 126.7 (CH, $C^{2\text{Ts}}$), 124.8 (CH, C^8), 124.6 (C_q , C^{9a}), 123.0 (C_q , C^{9b}), 121.2 (CH, C^9), 114.9 (CH, C^6), 111.6 (CH, C^4), 53.1 (CH_3 , C^{11}), 21.6 (CH_3 , $C^{5\text{Ts}}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 2931.28 (m, br.), 1721.16 (vs), 1591.95 (w), 1456.96 (m), 1405.85 (m), 1366.31 (m), 1294.00 (s), 1230.36 (m), 1170.58 (s), 1089.58 (m), 969.05 (m), 821.53 (w), 761.74 (m), 668.21 (m);

FD-MS: m/z (%)= 380.2 (100) [M]⁺, 381.2 (22), 382.2 (7), 383.2 (1);

Analyses in agreement with the literature^[3]

Methyl 9-tosyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate β -3aa

White solid, m.p.= 212-213 °C

Purified by column chromatography (SiO₂, PE/EtOAc 2/1)

R_f= 0.27 (PE/EtOAc 2/1),

¹H NMR (CDCl₃) δ ppm: 9.71 (s, 1H, H¹), 8.71 (s, 1H, H⁴), 8.40 (d, J= 8.5 Hz, 1H, H⁸), 8.06 (d, J= 7.8 Hz, 1H, H⁵), 7.75 (d, J= 8.4 Hz, 2H, H^{2Ts}), 7.70 (t, J= 7.3 Hz, 1H, H⁷), 7.48 (t, J= 7.4 Hz, 1H, H⁶), 7.15 (d, J= 8.2 Hz, 2H, H^{3Ts}), 4.07 (s, 3H, H¹¹), 2.29 (s, 3H, H^{5Ts});

¹³C NMR (CDCl₃) δ ppm: 165.8 (C_q, C¹⁰), 145.9 (C_q, C^{4Ts}), 142.0 (C_q, C³), 139.3 (C_q, C^{8a}), 136.8 (CH, C¹), 136.3 (C_q, C^{9a}), 134.3 (C_q, C^{1Ts}), 133.1 (C_q, C^{4a}), 130.6 (CH, C⁷), 130.0 (CH, C^{3Ts}), 126.6 (CH, C^{2Ts}), 124.7 (CH, C⁶), 123.9 (C_q, C^{4b}), 121.8 (CH, C⁵), 116.9 (CH, C⁴), 115.2 (CH, C⁸), 53.0 (CH₃, C¹¹), 21.6 (CH₃, C^{5Ts});

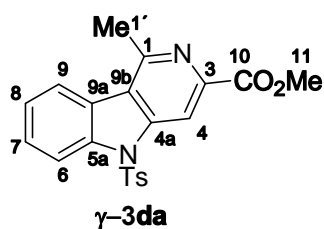
IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3021.91 (w, br.), 1742.37 (vs), 1594.84 (w), 1432.85 (m), 1366.32 (s), 1302.68 (m), 1248.68 (m), 1176.36 (vs), 1128.15 (m), 980.63 (s), 896.74 (w), 779.10 (w), 749.21 (w), 668.21 (s);

FD-MS: m/z (%) = 380.3 (100) [M]⁺, 381.3 (34);

Analyses in agreement with the literature^[3]

- Cycloaddition with the diyne 1ca (R¹= Me, R²= H) and methylcyanofornate 2a

According to the general procedure **GP10**, 61.8 mg (0.2 mmol) of the diyne **1ca** led after column chromatography to 16.4 mg (0.042 mmol, 22%) of the carboline **β -3aa** and 32.9 mg (0.083 mmol, 42%) of the carboline **γ -3aa**. (CH₂Cl₂ as solvent)

Methyl 1-methyl-5-tosyl-5*H*-pyrido[4,3-*b*]indole-3-carboxylate γ -3ca

Orange solid, m.p.= 246-247 °C

Purified by column chromatography (SiO₂, PE/EtOAc 2/1) R_f = 0.16 (PE/EtOAc 2/1),

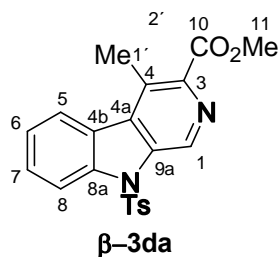
¹H NMR (CDCl₃) δ ppm: 8.98 (s, 1H, H⁴), 8.41 (d, J= 9.5 Hz, 1H, H⁶), 8.10 (d, J= 7.9 Hz, 1H, H⁹), 7.78 (d, J= 7.9 Hz, 2H, H^{3Ts}), 7.62 (t, J= 8.0 Hz, 1H, H⁷), 7.49 (t, J= 7.5 Hz, 1H, H⁸), 7.17 (d, J= 8.5 Hz, 2H, H^{2Ts}), 4.08 (s, 3H, H¹¹), 3.06 (s, 3H, H¹), 2.30 (s, 3H, H^{5Ts});

*¹³C NMR (CDCl₃) δ ppm: 166.0 (C_q, C¹⁰), 153.7 (C_q, C¹), 145.8 (C_q, C^{4Ts}), 144.4 (C_q, C³), 143.7 (C_q, C^{4a}), 139.0 (C_q, C^{5a}), 134.5 (C_q, C^{1Ts}), 130.0 (CH, C^{3Ts}), 128.7 (CH, C⁷), 126.7 (CH, C^{2Ts}), 124.7 (CH, C⁹), 124.0 (C_q, C^{9b}), 123.0 (CH, C⁸), 122.7 (C_q, C^{9a}), 114.8 (CH, C⁶), 109.8 (CH, C⁴), 53.1 (CH₃, C¹¹), 24.4 (CH₃, C¹), 21.6 (CH₃, C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2922.59 (s, br.), 2858.95 (m), 1715.37 (vs), 1594.84 (w), 1465.63 (m), 1438.64 (m), 1366.32 (s), 1329.68 (s), 1296.89 (m), 1248.68 (m), 1234.22 (m), 1170.58 (s), 1092.48 (s), 936.27 (w), 806.10 (w), 754.99 (m), 662.43 (m);

FD-MS: m/z (%) = 394.4 (100) [M]⁺, 395.4 (25), 396.4 (5);

Analyses in agreement with the literature^[3]

Methyl 4-methyl-9-tosyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate β -3ca

Orange solid, m.p.= 196-197 °C

Purified by column chromatography (SiO₂, PE/EtOAc 80/20) R_f = 0.35 (PE/EtOAc 2/1)

¹H NMR (CDCl₃) δ ppm: 9.59 (s, 1H, H¹), 8.47 (d, J= 8.5 Hz, 1H, H⁸), 8.22 (d, J= 8.0 Hz, 1H, H⁵), 7.74 (d, J= 8.3 Hz, 2H, H^{2Ts}), 7.68 (t, J= 8.0 Hz, 1H, H⁷), 7.48 (t, J= 8.0 Hz, 1H, H⁶), 7.14 (d, J= 8.3 Hz, 2H, H^{3Ts}), 4.03 (s, 3H, H¹¹), 3.02 (s, 3H, H¹), 2.28 (s, 3H, H^{5Ts});

^{13}C NMR (CDCl_3) δ ppm: 166.9 (C_q , C^{10}), 145.8 (C_q , $\text{C}^{4\text{Ts}}$), 142.1 (C_q , C^3), 139.1 (C_q , C^{8a}), 135.3 (C_q , C^{9a}), 134.3 (C_q , $\text{C}^{1\text{Ts}}$), 134.1 (CH , C^1), 132.2 (C_q , C^4), 130.3 (C_q , C^{4a}), 130.0 (CH , $\text{C}^{3\text{Ts}}$), 129.6 (CH , C^7), 126.6 (CH , $\text{C}^{2\text{Ts}}$), 125.0 (C_q , C^{4b}), 124.6 (CH , C^6), 124.2 (CH , C^5), 115.1 (CH , C^8), 52.8 (CH_3 , C^{11}), 21.6 (CH_3 , $\text{C}^{5\text{Ts}}$), 16.3 (CH_3 , $\text{H}^{1'}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 2922.59 (s, br.), 2843.52 (s), 1715.37 (vs), 1591.95 (w), 1435.74 (m), 1369.21 (s), 1309.43 (m), 1248.68 (s), 1224.58 (m), 1167.69 (vs), 1125.26 (m), 1068.33 (s), 1032.69 (m), 936.27 (m), 806.10 (w), 752.10 (m), 673.99 (m), 655.68 (m);

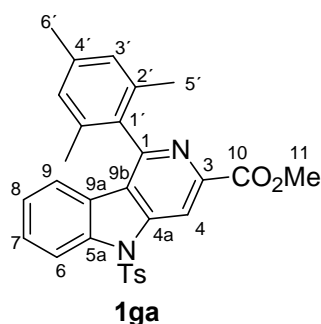
FD-MS: m/z (%) = 394.3 (100) $[\text{M}]^+$, 395.3 (10), 396.3 (5);

Analyses in agreement with the literature^[3]

- Cycloaddition with the diyne **1ga** ($\text{R}^1 = \text{mesityl}$, $\text{R}^2 = \text{H}$) and methycyanofomate **2a**

According to the general procedure **GP10**, 82.7 mg (0.2 mmol) of the diyne **1ga** led after column chromatography to 97.3 mg (0.195 mmol, 97%) of the carboline γ -**3ga**. (CH_2Cl_2 as solventt)

Methyl 1-(2,4,6-trimethylphenyl)-5-tosyl-5H-pyrido[4,3-b]indole-3-carboxylate γ -3ga



White solid, m.p.= 136-137 °C

Purified by column chromatography (SiO_2 , PE/EtOAc 2/1)

$R_f = 0.57$ (PE/EtOAc 2/1)

^1H NMR (CDCl_3) δ ppm: 9.04 (s, 1H, H^4), 8.31 (d, $J = 8.5$ Hz, 1H, H^6), 7.84 (d, $J = 8.3$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.51 (t, $J = 8.4$ Hz, 1H, H^7), 7.22 (d, $J = 8.5$ Hz, 2H, $\text{H}^{3\text{Ts}}$), 7.15 (t, $J = 7.9$ Hz, 1H, H^8), 6.97 (s, 2H, $\text{H}^{3'}$), 6.74 (d, $J = 8.0$ Hz, 1H, H^9), 4.05 (s, 3H, H^{11}), 2.36 (s, 3H, $\text{H}^{5\text{Ts}}$), 2.32 (s, 3H, H^6), 1.79 (s, 6H, $\text{H}^{5'}$);

^{13}C NMR (CDCl_3) δ ppm: 166.2 (C_q , C^{10}), 155.1 (C_q , C^1), 145.8 (C_q , $\text{C}^{4\text{Ts}}$), 145.4 (C_q , C^3), 143.9 (C_q , C^{4a}), 139.0 (C_q , C^{5a}), 138.3 (C_q , $\text{C}^{1'}$), 135.6 (C_q , $\text{C}^{2'}$), 134.9 (C_q , $\text{C}^{4'}$), 134.6 (C_q ,

C^{1Ts} , 130.1 (CH, C^{3Ts}), 128.9 (CH, C^7), 128.7 (CH, $C^{3'}$), 126.7 (CH, C^{2Ts}), 124.8 (CH, C^9), 123.5 (C_q , C^{9b}), 122.9 (C_q , C^{9a}), 122.1 (CH, C^8), 114.3 (CH, C^6), 110.1 (CH, C^4), 53.0 (CH_3 , C^{11}), 21.6 (CH_3 , C^{5Ts}), 21.2 (CH_3 , $C^{6'}$), 19.5 (CH_3 , $C^{5'}$);

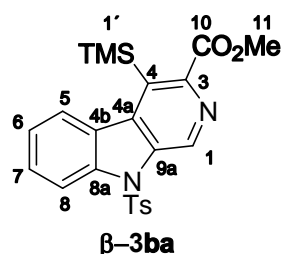
IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 2952.48 (w, br.), 1718.26 (vs), 1607.38 (w), 1564.95 (m), 1456.96 (m), 1438.64 (m), 1381.75 (s), 1326.79 (s), 1258.32 (m), 1224.58 (s), 1176.36 (vs), 1128.15 (m), 1089.58 (w), 1035.59 (m), 1014.37 (m), 971.95 (m), 842.74 (w), 781.99 (w), 740.53 (m), 665.32 (m);

FD-MS: m/z (%) = 498.1 (100) $[M]^+$, 499.1 (34), 500.1 (9), 501.1 (2);

- Cycloaddition with the diyne 1ba ($R^1 = TMS$, $R^2 = H$) and methylcyanofomate 2a

According to the general procedure **GP10**, 73.7 mg (0.2 mmol) of the diyne **1ba** led after column chromatography to 56.5 mg (0.125 mmol, 62%) of the carboline β -**3ba**. (CH_2Cl_2 as solvent)

Methyl 4-trimethylsilyl-9-tosyl-9H-pyrido[3,4-b]indole-3-carboxylate β -3ba



White solid, m.p.= 158-159 °C

Purified by column chromatography (SiO_2 , PE/EtOAc 80/20)

$R_f = 0.68$ (PE/EtOAc 2/1),

1H NMR ($CDCl_3$) δ ppm: 9.65 (s, 1H, H^1), 8.46 (d, $J = 8.6$ Hz, 1H, H^8), 8.14 (d, $J = 8.0$ Hz, 1H, H^5), 7.73 (d, $J = 8.0$ Hz, 2H, H^{2Ts}), 7.66 (td, $J = 7.4, 1.2$ Hz, 1H, H^7), 7.43 (td, $J = 8.2, 1.0$ Hz, 1H, H^6), 7.14 (d, $J = 8.0$ Hz, 2H, H^{3Ts}), 4.01 (s, 3H, H^{11}), 2.29 (s, 3H, H^{5Ts}), 0.48 (s, 9H, $H^{1'}$);

^{13}C NMR ($CDCl_3$) δ ppm: 169.1 (C_q , C^{10}), 150.8 (C_q , C^3), 145.7 (C_q , C^{4Ts}), 139.5 (C_q , C^{8a}), 138.2 (C_q , C^4), 136.2 (CH, C^1), 134.4 (C_q , C^{1Ts} or $9a$), 134.3 (C_q , C^{1Ts} or $9a$), 130.0 (CH, C^{3Ts}), 129.8 (CH, C^7), 128.8 (C_q , C^{4a}), 126.6 (CH, C^{2Ts}), 125.7 (CH, C^6), 125.0 (C_q , C^{4b}), 123.5 (CH, C^5), 115.0 (CH, C^8), 53.0 (CH_3 , C^{11}), 21.5 (CH_3 , C^{5Ts}), 0.8 (CH_3 , $C^{1'}$);

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2940.91 (w), 1723.09 (vs), 1602.56 (w), 1452.14 (s), 1364.39 (vs), 1287.25 (s), 1249.65 (vs), 1222.65 (s), 1186.01 (s), 1166.72 (vs), 1087.66 (s), 1055.84 (s), 1003.77 (w), 927.59 (s), 840.81 (vs), 754.99 (vs), 671.11 (vs);

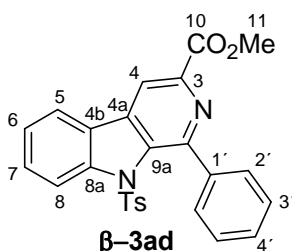
FD-MS: m/z (%) = 452.1 (100) [M]⁺, 453.2 (4);

Elemental analysis (%) for C₂₃H₂₄N₂O₄SSi calcd: C 61.04, H 5.349, N 6.19, S 7.08; found C 60.73, H 5.33, N 6.21, S 7.11.

- Cycloaddition with the diyne **1ad** (R¹= H, R²= Ph) and methylcyanofornate **2a**

According to the general procedure **GP10**, 74.3 mg (0.2 mmol) of the diyne **1ad** led after column chromatography to 82.1 mg (0.18 mmol, 90%) of the carboline **β-3ad** and 4.2 mg (0.083 mmol, 1%) of the carboline **γ-3ad**. (CH₂Cl₂ as solvent)

Methyl 1-phenyl-9-tosyl-9H-pyrido[3,4-b]indole-3-carboxylate β-3ad



White solid, m.p. = 208-209 °C

Purified by column chromatography (SiO₂, PE/EtOAc 80/20)

R_f = 0.62 (PE/EtOAc 2/1)

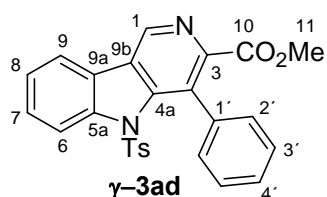
¹H NMR (CDCl₃) δ ppm: 8.42 (s, 1H, H⁴), 8.27 (d, J= 8.3 Hz, 1H, H⁸), 8.12 (d, J= 7.1 Hz, 2H, H^{2'}), 7.84 (d, J= 7.7 Hz, 1H, H⁵), 7.61 (t, J= 7.8 Hz, 1H, H⁷), 7.52 (t, J= 7.1 Hz, 2H, H^{3'}), 7.42 (m, 2H, H^{6+4'}), 6.96 (d, J= 8.3 Hz, 2H, H^{2Ts}), 6.83 (d, J= 8.3 Hz, 2H, H^{3Ts}), 4.05 (s, 3H, H¹¹), 2.17 (s, 3H, H^{5Ts});

***¹³C NMR** (CDCl₃) δ ppm: 165.6 (C_q, C¹⁰), 151.2 (C_q, C¹), 144.8 (C_q, C^{4Ts}), 143.7 (C_q, C³), 142.3 (C_q, C^{8a}), 140.3 (C_q, C^{1'}), 139.2 (C_q, C^{4a}), 136.5 (C_q, C^{9a}), 131.9 (C_q, C^{1Ts}), 130.2 (CH, C⁷), 128.9 (CH, C^{3Ts+4'}), 128.6 (CH, C^{2'}), 128.3 (CH, C^{3'}), 126.8 (C_q, C^{4b}), 126.7 (CH, C^{2Ts}), 126.0 (CH, C⁶), 121.3 (CH, C⁵), 119.4 (CH, C⁸), 114.5 (CH, C⁴), 53.0 (CH₃, C¹¹), 21.4 (CH₃, C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3073.01 (w), 2949.59 (w), 2220.63 (w), 1715.37 (vs), 1613.16 (w), 1562.06 (w), 1375.00 (vs), 1357.64 (s), 1278.57 (w), 1242.90 (s), 1207.22 (s), 1173.47 (vs), 1149.37 (s), 1047.16 (w), 923.74 (w), 722.21 (w), 662.43 (w);

FD-MS: m/z (%)= 456.2 (100) [M]⁺, 457.2 (34), 458.2 (5);

Methyl 4-phenyl-5-tosyl-5H-pyrido[4,3-b]indole-3-carboxylate γ -3ad



White solid, m.p.= 177-178 °C

Purified by column chromatography (SiO₂, PE/EtOAc 2/1)

R_f= 0.30 (PE/EtOAc 2/1)

¹H NMR (CDCl₃) δ ppm: 9.11 (s, 1H, H¹), 8.24 (d, J= 8.4 Hz, 1H, H⁶), 7.96 (d, J= 7.7 Hz, 1H, H⁹), 7.56 (t, J= 7.4 Hz, 1H, H⁷), 7.45 (t, J= 7.6 Hz, 1H, H⁸), 7.39 (m, 5H, H^{2'-4'}), 7.07 (d, J= 8.3 Hz, 2H, H^{2Ts}), 6.96 (d, J= 8.4 Hz, 2H, H^{3Ts}), 3.64 (s, 3H, H¹¹), 2.27 (s, 3H, H^{5Ts});

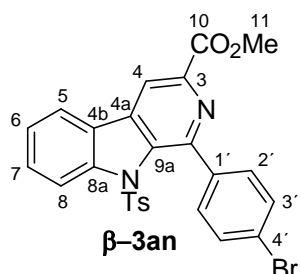
¹³C NMR (CDCl₃) δ ppm: 167.9 (C_q, C¹⁰), 150.0 (C_q, C^{4a}), 144.8 (C_q, C^{4Ts}), 144.2 (C_q, C³), 141.5 (C_q, C^{5a}), 140.9 (CH, C¹), 136.0 (C_q, C^{1'}), 133.8 (C_q, C^{1Ts}), 129.4 (CH, C^{3Ts,2'} or 3'), 129.3 (CH, C^{3Ts,2'} or 3'), 128.9 (CH, C⁷), 128.1 (CH, C^{4'}), 128.0 (CH, C^{2'} or 3'), 126.6 (2*C_q, C^{9a+4}), 126.2 (CH, C^{2Ts}), 125.7 (CH, C⁸), 125.0 (C_q, C^{9b}), 120.5 (CH, C⁹), 118.5 (CH, C⁶), 52.6(CH₃, C¹¹), 21.5 (CH₃, C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2922.59 (s, br.), 2861.84 (m), 1733.69 (vs), 1583.27 (w), 1462.74 (w), 1402.00 (m), 1360.53 (s), 1312.32 (s), 1170.58 (s), 1089.58 (w), 1001.84 (m), 950.73 (m), 800.31 (m), 754.99 (w), 662.43 (m);

FD-MS: m/z (%)= 456.4 (100) [M]⁺, 457.4 (12);

- Cycloaddition with the diyne 1an (R¹= H, R²= 4-BrPh) and methylcyanoformate 2a

According to the general procedure **GP10**, 90.1 mg (0.2 mmol) of the diyne **1an** led after column chromatography to 75.4 mg (0.14 mmol, 71%) of the carboline **β -3an** and 10.0 mg (0.019 mmol, 9%) of the carboline **γ -3an**. (CH₂Cl₂ as solvent)

Methyl 1-(4-bromophenyl)-9-tosyl-9H-pyrido[3,4-*b*]indole-3-carboxylate β -3an

White solid, m.p.= 197-198 °C

Purified by column chromatography (SiO₂, PE/EtOAc 80/20)R_f = 0.60 (PE/EtOAc 2/1)

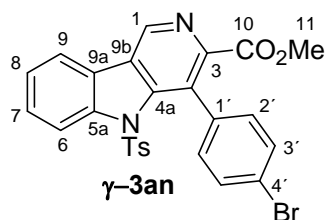
¹H NMR (CDCl₃) δ ppm: 8.43 (s, 1H, H⁴), 8.27 (d, J= 8.5 Hz, 1H, H⁸), 7.98 (d, J= 8.5 Hz, 2H, H^{3'}), 7.86 (d, J= 7.7 Hz, 1H, H⁵), 7.64 (m, 3H, H^{7+2'}), 7.44 (t, J= 7.7 Hz, 1H, H⁶), 6.97 (d, J= 8.5 Hz, 2H, H^{2Ts}), 6.87 (d, J= 8.5 Hz, 2H, H^{3Ts}), 4.05 (s, 3H, H¹¹), 2.20 (s, 3H, H^{5Ts});

¹³C NMR (CDCl₃) δ ppm: 165.6 (C_q, C¹⁰), 149.9 (C_q, C¹), 145.0 (C_q, C^{4Ts}), 143.8 (C_q, C³), 142.3 (C_q, C^{8a}), 139.3 (C_q, C^{4a} or 1'), 139.2 (C_q, C^{4a} or 1'), 136.4 (C_q, C^{9a}), 131.9 (C_q, C^{1Ts}), 131.4 (CH, C^{3'}), 130.4 (CH, C⁷), 130.3 (CH, C^{2'}), 129.0 (CH, C^{3Ts}), 126.6 (CH, C^{2Ts}), 126.1 (CH, C⁶), 123.3 (C_q, C^{4'}), 121.4 (CH, C⁵), 119.3 (CH, C⁸), 114.8 (CH, C⁴), 53.0 (CH₃, C¹¹), 21.4 (CH₃, C^{5Ts}), 1 C_q signal misses due to overlapping (probably 4b, at 126.6 ppm).

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3046.98 (w), 2951.52 (w), 1731.76 (vs), 1613.16 (w), 1557.24 (w), 1487.81 (w), 1383.68 (vs), 1359.57 (s), 1233.25 (s), 1184.08 (s), 1170.58 (vs), 1157.08 (s), 1115.62 (w), 1049.09 (w), 952.66 (w), 831.17 (w), 763.67 (s), 668.21 (s);

FD-MS: m/z (%) = 534.1 (89) [M]⁺, 535.1 (26), 536.1 (100), 537.1 (27), 538.1 (8), 538.1 (1);

Elemental analysis (%) for C₂₆H₁₉BrN₂O₄S (535.41): C 58.33, H 3.58, N 5.23, S 5.99; found C 58.42, H 3.65, N 5.08, S 6.07

Methyl 4-(4-bromophenyl)-*N*-tosyl-5H-pyrido[4,3-*b*]indole-3-carboxylate γ -3an

White solid, m.p.= 193-194 °C

Purified by column chromatography (SiO₂, PE/EtOAc 2/1)R_f = 0.26 (PE/EtOAc 2/1)

¹H NMR (CDCl₃) δ ppm: 9.16 (s, 1H, H¹), 8.22 (d, J=8.5Hz, 1H, H⁶), 8.01 (d, J=7.4Hz, 1H, H⁹), 7.58 (t, J= 7.4 Hz, 1H, H⁷), 7.47 (t, J= 7.4 Hz, 1H, H⁸), 7.38 (d, J= 8.5 Hz, 1H, H^{2Ts}), 7.16 (m, 4H, H^{2'+3'}), 7.05 (d, J= 8.1 Hz, 2H, H^{3Ts}), 3.69 (s, 3H, H¹¹), 2.34 (s, 3H, H^{5Ts});

^{13}C NMR (CDCl_3) δ ppm: 167.3 (C_q , C^{10}), 149.3 (C_q , C^{4a}), 144.9 (C_q , $\text{C}^{4\text{Ts}}$), 144.2 (C_q , C^3), 141.6 (C_q , C^{5a}), 141.2 (CH , C^1), 134.7 (C_q , C^4), 134.4 (C_q , $\text{C}^{1\text{Ts}}$), 131.3 (CH , $\text{C}^{3'}$), 130.9 (CH , $\text{C}^{2'}$), 129.4 (CH , $\text{C}^{3\text{Ts}}$), 129.1 (CH , C^7), 126.6 (C_q , $\text{C}^{1'}$), 125.8 (CH , $\text{C}^{2\text{Ts}}$), 125.7 (CH , C^8), 125.4 (C_q , C^{9b}), 124.6 (C_q , C^{9a}), 122.7 (C_q , $\text{C}^{4'}$), 120.6 (CH , C^9), 118.3 (CH , C^6), 52.7 (CH_3 , C^{11}), 21.6 (CH_3 , $\text{C}^{5\text{Ts}}$);

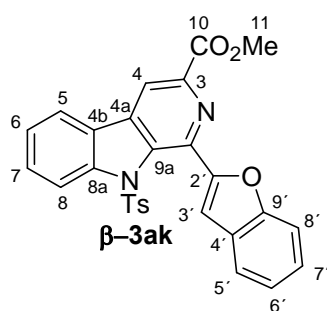
IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3066.26 (w), 2952.48 (w), 1735.62 (vs), 1580.38 (w), 1463.71 (w), 1361.50 (vs), 1304.61 (m), 1180.22 (s), 1152.26 (s), 989.30 (s), 946.88 (m), 830.21 (m), 806.10 (m), 755.96 (m);

FD-MS: m/z (%) = 534.3 (97) $[\text{M}]^+$, 535.3 (26), 536.3 (100), 537.3 (27), 538.3 (8), 539.3 (1);

- Cycloaddition with the diyne 1ak ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{benzofuran-2-yl}$) and methylcyanoformate 2a

According to the general procedure **GP10**, 82.3 mg (0.2 mmol) of the diyne **1ak** led after column chromatography to 48.7 mg (0.098 mmol, 49%) of the carboline β -**3ak** and 20.4 mg (0.041 mmol, 20%) of the carboline γ -**3ak**. (CH_2Cl_2 as solvent)

Methyl 1-(benzofuran-2-yl)-9-tosyl-9H-pyrido[3,4-*b*]indole-3-carboxylate β -3ak



Orange solid, m.p.: 216-217 °C

Purified by column chromatography (SiO_2 , PE/EtOAc 80/20)

$R_f = 0.44$ (PE/EtOAc 2/1)

^1H NMR (CDCl_3) δ ppm: 8.48 (s, 1H, H^4), 8.19 (d, $J = 8.5$ Hz, 1H, H^8), 7.85 (d, $J = 7.7$ Hz, 1H, H^5), 7.68-7.54 (m, 4H, $\text{H}^{7+\text{bzf}}$), 7.41-7.25 (m, 3H, $\text{H}^{6+\text{bzf}}$), 7.09 (d, $J = 8.1$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 6.89 (d, $J = 8.1$ Hz, 2H, $\text{H}^{3\text{Ts}}$), 4.09 (s, 3H, H^{11}), 2.20 (s, 3H, $\text{H}^{5\text{Ts}}$);

^{13}C NMR (CDCl_3) δ ppm: 165.5 (C_q , C^{10}), 155.3 (C_q , $\text{C}^{9'}$), 154.3 (C_q , C^1), 144.9 (C_q , $\text{C}^{4\text{Ts}}$), 143.7 (C_q , C^3), 142.5 (C_q , C^{8a}), 141.3 (C_q , $\text{C}^{2'}$), 139.2 (C_q , C^{4a}), 135.7 (C_q , C^{9a}), 132.8 (C_q , $\text{C}^{1\text{Ts}}$), 130.5 (CH , C^7), 129.1 (CH , $\text{C}^{3\text{Ts}}$), 128.5 (C_q , $\text{C}^{4'}$), 126.8 (CH , $\text{C}^{2\text{Ts}}$), 126.2 (C_q , C^{4b}),

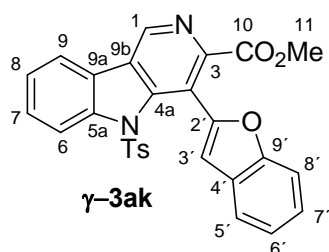
^{13}C NMR (CDCl₃) δ ppm: 125.9 (CH, C⁶), 125.3 (CH, C⁷), 123.0 (CH, C⁶), 121.9 (CH, C⁵), 121.5 (CH, C⁵), 119.0 (CH, C⁸), 115.3 (CH, C⁴), 111.7 (CH, C³), 107.5 (CH, C⁸), 53.1 (CH₃, C¹¹), 21.5 (CH₃, C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3034.44 (w), 2952.48 (w), 1732.73 (vs), 1565.92 (w), 1449.24 (w), 1375.00 (s), 1258.32 (s), 1222.65 (w), 1166.72 (vs), 1099.23 (m), 975.80 (w), 925.66 (w), 812.85 (w), 745.35 (s), 674.96 (s);

FD-MS: m/z (%) = 496.1 (100) [M]⁺, 497.1 (31), 498.1 (9), 499.1 (2);

Exact masse: [M+H]⁺ calcd: 497.1171; found 497.1177.

Methyl 4-(benzofuran-2-yl)-5-tosyl-5H-pyrido[4,3-b]indole-3-carboxylate γ -3ak



Orange solid, m.p.: 178-179 °C

Purified by column chromatography (Silica gel, PE/EtOAc 80/20)

R_f = 0.22 (PE/EtOAc 2/1)

¹H NMR (CDCl₃) δ ppm: 9.18 (s, 1H, H¹), 8.21 (d, J= 8.5 Hz, 1H, H⁶), 7.97 (d, J= 7.7 Hz, 1H, H⁹), 7.60 (m, 2H, H⁷ or ⁸ or bzf), 7.45 (m, 2H, H⁷ or ⁸ or bzf), 7.26 (m, 4H, H^{2Ts+bzf}), 6.97 (d, J= 8.8 Hz, 3H, H^{3Ts+3'}), 3.79 (s, 3H, H¹¹), 2.26 (s, 3H, H^{5Ts});

¹³C NMR (CDCl₃) δ ppm: 167.2 (C_q, C¹⁰), 155.1 (C_q, C^{9'}), 149.7 (C_q, C^{4a}), 145.0 (C_q, C^{4Ts}), 144.3 (C_q, C³), 142.2 (CH, C¹), 141.3 (C_q, C^{5a}), 133.9 (C_q, C^{1Ts}), 129.3 (CH, C^{3Ts}), 129.2 (CH, C⁷), 128.6 (C_q, C^{2'}), 126.5 (C_q, C^{4'}), 126.5 (CH, C^{2Ts}), 125.7 (CH, C⁸), 124.7 (CH, C^{7'}), 124.3 (C_q, C^{9a}), 122.9 (CH, C^{6'}), 121.4 (CH, C^{5'}), 120.6 (CH, C⁹), 118.1 (CH, C⁶), 116.1 (C_q, C^{9b}), 111.3 (CH, C^{3'}), 107.4 (CH, C^{8'}), 53.0 (CH₃, C¹¹), 21.6 (CH₃, C^{5Ts});

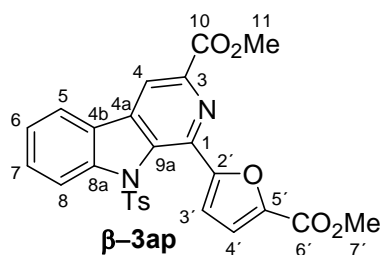
IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3059.51 (w), 2941.88 (w), 1728.87 (vs), 1590.99 (w), 1446.35 (w), 1368.25 (s), 1296.89 (m), 1169.62 (vs), 997.02 (m), 808.99 (m), 749.21 (s);

FD-MS: m/z (%) = 496.1 (100) [M]⁺, 497.1 (32), 498.1 (10), 499.1 (2);

- Cycloaddition with the diyne **1ap ($R^1 = H$, $R^2 = 5$ -(methoxycarbonyl)furan-2-yl) and methylcyanofomate **2a****

According to the general procedure **GP10**, 83.9 mg (0.2 mmol) of the diyne **1ap** led after column chromatography to 76.6 mg (0.152 mmol, 76%) of the carboline **β -3ap** and 16.3 mg (0.032 mmol, 16%) of the carboline **γ -3ap**. (CH_2Cl_2 as solvent)

Methyl 1-(5-(methoxycarbonyl)furan-2-yl)-9-tosyl-9H-pyrido[3,4-b]indole-3-carboxylate
 β -3ap



White solid, m.p.= 208-209 °C

Purified by column chromatography (SiO_2 , PE/EtOAc 80/20)

$R_f = 0.23$ (PE/EtOAc 2/1),

$^1\text{H NMR}$ (CDCl_3) δ ppm: 8.47 (s, 1H, H^4), 8.16 (d, $J = 8.5$ Hz, 1H, H^8), 7.82 (d, $J = 7.7$ Hz, 1H, H^5), 7.60 (t, $J = 7.4$ Hz, 1H, H^7), 7.40 (m, 3H, $\text{H}^{6+3'+4'}$), 7.06 (d, $J = 8.1$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 6.89 (d, $J = 7.7$ Hz, 2H, $\text{H}^{3\text{Ts}}$), 4.07 (s, 3H, H^{11}), 3.95 (s, 3H, $\text{H}^{7'}$), 2.19 (s, 3H, $\text{H}^{5\text{Ts}}$);

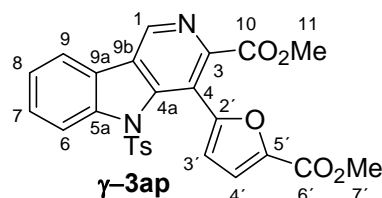
$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 165.3 (C_q , C^{10}), 159.1 (C_q , $\text{C}^{6'}$), 155.7 (C_q , $\text{C}^{2'}$), 145.0 (C_q , $\text{C}^{4\text{Ts}}$), 144.5 (C_q , $\text{C}^{5'}$), 143.6 (C_q , C^1), 142.4 (C_q , C^{8a}), 140.0 (C_q , C^3), 139.3 (C_q , C^{4a}), 135.7 (C_q , C^{9a}), 132.3 (C_q , $\text{C}^{1\text{Ts}}$), 130.6 (CH, C^7), 129.1 (CH, $\text{C}^{3\text{Ts}}$), 126.8 (CH, $\text{C}^{2\text{Ts}}$), 126.0 (C_q , C^{4b}), 126.0 (CH, C^6), 121.4 (CH, C^5), 119.5 (CH, C^4), 119.0 (CH, C^8), 115.7 (CH, C^4), 112.4 (CH, $\text{C}^{3'}$), 53.1 (CH_3 , C^{11}), 52.0 (CH_3 , $\text{C}^{7'}$), 21.4 (CH_3 , $\text{C}^{5\text{Ts}}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 2966.95 (w), 1715.37 (vs), 1576.52 (w), 1441.53 (w), 1372.10 (s), 1348.00 (m), 1282.43 (s), 1242.90 (m), 1164.79 (s), 987.38 (w), 761.74 (m);

FD-MS: m/z (%) = 504.3 (100) [$\text{M}]^+$, 505.4 (29), 506.4 (5), 507.4 (2);

Elemental analysis (%) for $\text{C}_{26}\text{H}_{20}\text{N}_2\text{O}_7\text{S}$ (504.51): C 61.90, H 4.00, N 5.55, S 6.36; found C 61.84, H 4.04, N 5.53, S 6.39.

Methyl 4-(5-(methoxycarbonyl)furan-2-yl)-*N*-tosyl-5H-pyrido[4,3-*b*]indole-3-carboxylate γ -3ap



White solid, m.p.= 149-150 °C

Purified by column chromatography (SiO₂, PE/EtOAc 60/40)

R_f= 0.11 (PE/EtOAc 2/1)

¹H NMR (CDCl₃) δ ppm: 9.17 (s, 1H, H¹), 8.22 (d, J=8.1 Hz, 1H, H⁶), 7.96 (d, J= 7.4 Hz, 1H, H⁹), 7.57 (t, J= 7.4 Hz, 1H, H⁷), 7.45 (t, J= 7.4 Hz, 1H, H⁸), 7.30 (m, 3H, H^{2Ts+4'}), 7.00 (d, J= 8.1 Hz, 2H, H^{3Ts}), 6.71 (d, J= 3.3 Hz, 1H, H^{3'}), 3.92 (s, 3H, H^{7'}), 3.88 (s, 3H, H¹¹), 2.26 (s, 3H, H^{5Ts});

*¹³C NMR (CDCl₃) δ ppm: 166.7 (C_q, C¹⁰), 159.1 (C_q, C^{6'}), 151.4 (C_q, C^{2'}), 149.2 (C_q, C^{4a}), 145.3 (C_q, C^{4Ts}), 144.4 (2C_q, C^{4'+3}), 142.5 (CH, C¹), 141.2 (C_q, C^{5a}), 133.4 (C_q, C^{1Ts}), 129.5 (CH, C^{3Ts}), 129.4 (CH, C⁷), 126.7 (C_q, C⁴), 126.7 (CH, C^{2Ts}), 125.8 (CH, C⁸), 124.3 (C_q, C^{9a}), 120.6 (CH, C⁹), 119.4 (CH, C⁶), 118.1 (CH, C^{4'}), 115.5 (C_q, C^{9b}), 112.6 (CH, C^{3'}), 53.1 (CH₃, C¹¹), 51.9 (CH₃, C^{7'}), 21.5 (CH₃, C^{5Ts});

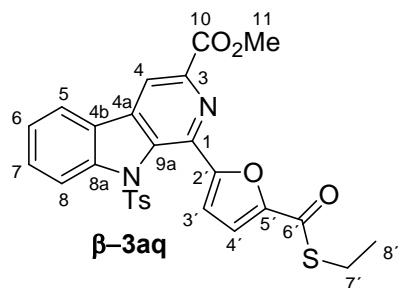
IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2952.48 (w), 1743.33 (vs), 1718.26 (vs), 1565.92 (w), 1520.60 (w), 1364.39 (s), 1304.61 (vs), 1180.22 (s), 1148.40 (m), 1127.19 (m), 1010.52 (m), 738.60 (w);

FD-MS: m/z (%) = 504.1 (100) [M]⁺, 505.1 (31), 506.1 (9), 507.1 (1).

- Cycloaddition with the diyne 1aq (R¹= H, R²= 5-(ethylsulfanylcarbonyl)furan-2yl) and methylcyanofornate 2a

According to the general procedure **GP10**, 85.9 mg (0.19 mmol) of the diyne **1aq** led after column chromatography to 66.1 mg (0.123 mmol, 65%) of the carboline **β -3aq** and 14.1 mg (0.026 mmol, 13%) of the carboline **γ -3aq**. (CH₂Cl₂ as solvent)

Methyl 1-(5-((ethylsulfanyl)carbonyl)furan-2-yl)-9-tosyl-9H-pyrido[3,4-b]indole-3-carboxylate β -3aq



White solid, m.p.= 193-194 °C

Purified by column chromatography (SiO₂, PE/EtOAc 80/20)

R_f= 0.36 (PE/EtOAc 2/1)

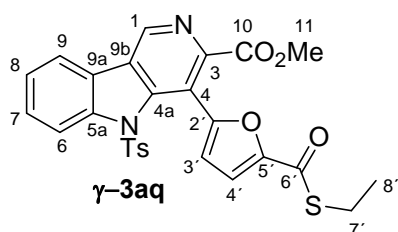
¹H NMR (CDCl₃) δ ppm: 8.47 (s, 1H, H⁴), 8.24 (d, J= 8.4 Hz, 1H, H⁸), 7.82 (d, J= 7.4 Hz, 1H, H⁵), 7.61 (d, J= 7.8 Hz, 1H, H⁷), 7.38 (m, 3H, H^{6+3'+4'}), 7.05 (d, J= 8.2 Hz, 2H, H^{2Ts}), 6.86 (d, J= 8.2 Hz, 2H, H^{3Ts}), 4.07 (s, 3H, H¹¹), 3.12 (q, J= 7.4 Hz, 2H, H^{6'}), 2.19 (s, 3H, H^{5Ts}), 1.39 (t, J= 7.4 Hz, 3H, H^{7'});

¹³C NMR (CDCl₃) δ ppm: 180.9 (C_q, C^{6'}), 165.3 (C_q, C¹⁰), 155.5 (C_q, C^{2'}), 150.9 (C_q, C^{5'}), 145.0 (C_q, C^{4Ts}), 143.7 (C_q, C¹), 142.7 (C_q, C^{8a}), 140.0 (C_q, C³), 139.4 (C_q, C^{4a}), 135.7 (C_q, C^{9a}), 132.3 (C_q, C^{1Ts}), 130.6 (CH, C⁷), 129.1 (CH, C^{3Ts}), 126.8 (CH, C^{2Ts}), 126.1 (C_q, C^{4b}), 126.0 (CH, C⁶), 121.5 (CH, C⁵), 119.1 (CH, C⁸), 116.6 (CH, C^{4'}), 115.7 (CH, C⁴), 112.7 (CH, C^{3'}), 53.1 (CH₃, C¹¹), 22.8 (CH₂, C^{7'}), 21.4 (CH₃, C^{5Ts}), 14.8 (CH₃, C^{8'});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2942.84 (w, br.), 1721.16 (vs), 1643.05 (vs), 1597.73 (m), 1508.06 (w), 1444.42 (m), 1405.85 (w), 1366.32 (s), 1350.89 (s), 1240.00 (vs), 1207.22 (m), 1161.90 (vs), 1110.80 (s), 1089.58 (m), 1062.59 (m), 971.95 (w), 933.38 (m), 863.95 (s), 806.10 (m), 767.53 (s), 752.10 (m), 671.11 (s);

FD-MS: m/z (%) = 534.1 (100) [M]⁺, 535.1 (29), 536.1 (14);

Methyl 4-(5-((ethylsulfanyl)carbonyl)furan-2-yl)-5-tosyl-5H-pyrido[4,3-b]indole-3-carboxylate γ -3aq



White solid, m.p.= 168-169 °C

Purified by column chromatography (SiO₂, PE/Et₂O 50/50)

R_f= 0.18 (PE/EtOAc 2/1)

¹H NMR (CDCl₃) δ ppm: 9.17 (s, 1H, H¹), 8.24 (d, J= 8.4 Hz, 1H, H⁶), 7.95 (d, J= 7.8 Hz, 1H, H⁹), 7.57 (t, J= 8.4 Hz, 1H, H⁷), 7.45 (t, J= 7.6 Hz, 1H, H⁸), 7.31 (d, J= 3.7 Hz, 1H, H⁴), 7.25 (d, J= 8.5 Hz, 2H, H^{2Ts}), 6.99 (d, J= 8.6 Hz, 2H, H^{3Ts}), 6.73 (d, J= 3.5 Hz, 1H, H³), 3.89 (s, 3H, H¹¹), 3.09 (q., J= 7.4 Hz, 2H, H⁷), 2.25 (s, 3H, H^{5Ts}), 1.36 (t, J= 7.4 Hz, 3H, H⁸);

¹³C NMR (CDCl₃) δ ppm: 180.5 (C_q, C^{6'}), 166.7 (C_q, C¹⁰), 151.1 (C_q, C^{2'}), 150.9 (C_q, C^{5'}), 149.1 (C_q, C^{4a}), 145.3 (C_q, C^{4Ts}), 144.5 (C_q, C³), 142.5 (CH, C¹), 141.3 (C_q, C^{5a}), 133.3 (C_q, C^{1Ts}), 129.5 (CH, C^{3Ts}), 129.4 (CH, C⁷), 126.7 (CH, C^{2Ts}), 125.9 (CH, C⁸), 124.3 (C_q, C^{9a}), 120.7 (CH, C⁹), 118.3 (CH, C⁷), 116.7 (CH, C⁴), 113.0 (CH, C³), 53.2 (CH₃, C¹¹), 22.7 (CH₂, C^{7'}), 21.6 (CH₃, C^{5Ts}), 14.8 (CH₃, C⁸). Two C_q miss due to overlapping;

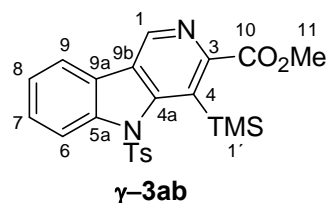
IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2955.38 (w, br.), 1745.26 (s), 1640.16 (vs), 1594.84 (w), 1505.17 (s), 1369.21 (m), 1299.79 (s), 1254.47 (m), 1170.58 (s), 1155.15 (s), 1089.58 (w), 990.27 (s), 861.06 (s), 757.89 (w), 658.57 (m);

FD-MS: m/z (%) = 534.4 (100) [M]⁺, 535.4 (30), 536.4 (12), 537.3 (2);

- Cycloaddition with the diyne **1ab** (R¹= H, R²= TMS) and methylcyanoformate **2a**

According to the general procedure **GP10**, 73.9 mg (0.2 mmol) of the diyne **1ab** led after column chromatography to 51.2 mg of a mixture of the carbolines γ -**3ab** and β -**3aa** (γ -**3ab**: β -**3aa** = 1.00:0.15, \approx 46 mg of γ -**3ab**, 50%). (CH₂Cl₂ as solvent)

Methyl 4-trimethylsilyl-5-tosyl-5H-pyrido[4,3-b]indole-3-carboxylate γ -3ab



White solid, m.p.= 134-135 °C (to check)

Purified by column chromatography (SiO₂, PE/EtOAc 80/20)

R_f= 0.18 (PE/EtOAc 2/1)

¹H NMR (CDCl₃) δ ppm: 9.01 (s, 1H, H¹), 8.20 (d, J= 8.2 Hz, 1H, H⁶), 7.78 (d, J= 7.8 Hz, 1H, H⁹), 7.51 (t, J= 8.4 Hz, 1H, H⁷), 7.36 (t, J= 7.8 Hz, 1H, H⁸), 6.93 (d, J= 8.4 Hz, 2H, H^{2Ts}), 6.82 (d, J= 8.4 Hz, 2H, H^{3Ts}), 4.08 (s, 3H, H¹¹), 2.17 (s, 3H, H^{5T}), 0.54 (s, 9H, H¹);

^{13}C NMR (CDCl_3) δ ppm: 168.1 (C_q , C^{10}), 154.0 (C_q , C^3 or $4a$), 152.8 (C_q , C^3 or $4a$), 145.0 (C_q , $\text{C}^{4\text{Ts}}$), 141.3 (C_q , C^{5a}), 141.2 (CH , C^1), 131.7 (C_q , $\text{C}^{1\text{Ts}}$ or 4), 130.4 (C_q , $\text{C}^{1\text{Ts}}$ or 4), 128.9 (3CH , $\text{C}^{3\text{Ts}+7}$), 126.9 (CH , $\text{C}^{2\text{Ts}}$), 126.9 (C_q , C^{9b}), 126.1 (CH , C^8), 125.9 (C_q , C^{9a}), 120.8 (CH , C^9), 118.8 (CH , C^6), 53.1 (CH_3 , C^{11}), 21.4 (CH_3 , $\text{C}^{5\text{Ts}}$), 2.9 (CH_3 , $\text{C}^{1'}$);

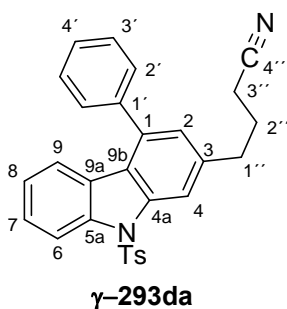
IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 2945.73 (w), 1739.48 (vs), 1718.26 (vs), 1449.24 (m), 1357.64 (s), 1294.0 (vs), 1247.72 (s), 1166.72 (vs), 1137.80 (vs), 989.30 (m), 936.27 (w), 848.53 (s), 766.57 (s), 660.50 (m);

FD-MS: m/z (%) = 452.1 (100) $[\text{M}]^+$, 453.2 (25), 454.1 (2);

- Cycloaddition with the diyne **1da** ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$) and 5-cyanopent-1-yne **2l**

According to the general procedure **GP10**, 74.3 mg (0.2 mmol) of the diyne **1da** and 210 mL (2 mmol, 10 equiv.) of the nitrile **2l** led after column chromatography to 75.2 mg (0.162 mmol, 81%) of a mixture of the carbazoles γ -**3da** and γ -**3da**. (CH_2Cl_2 as solvent)

1-Phenyl-3-(3-cyanopropyl)-5-tosyl-carbazole γ -292da



White solid, m.p.= 136-137 °C

Purified by column chromatography (SiO_2 , PE/EtOAc 90/10)

$R_f = 0.38$ (PE/EtOAc 80/20)

^1H NMR (CDCl_3) δ ppm: 8.34 (d, $J = 8.5$ Hz, 1H, H^6), 8.20 (d, $J = 1.4$ Hz 1H, H^4), 7.74 (d, $J = 7.9$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.45 (m, 5H, $\text{H}^{2'-4'}$), 7.39 (t, $J = 7.2$ Hz, 1H, H^7), 7.16 (t, $J = 7.9$ Hz, 3H, $\text{H}^{3\text{Ts}+9}$), 7.06 (t, $J = 7.6$ Hz, 1H, H^8), 7.04 (d, $J = 1.4$ Hz, 1H, H^2), 2.99 (t, $J = 7.5$ Hz, 2H, $\text{H}^{1''}$), 2.38 (t, $J = 7.1$ Hz, 2H, $\text{H}^{3''}$), 2.31 (s, 3H, $\text{H}^{5\text{Ts}}$), 2.12 (quint., $J = 7.3$ Hz, 2H, $\text{H}^{2''}$);

^{13}C NMR (CDCl_3) δ ppm: 145.0 (C_q , $\text{C}^{4\text{Ts}}$), 139.9 (C_q , C^1), 139.0 (C_q , C^{4a}), 138.9 (C_q , C^3), 138.7 (C_q , C^{5a}), 137.1 (C_q , $\text{C}^{1'}$), 135.1 (C_q , $\text{C}^{1\text{Ts}}$), 129.8 (CH , $\text{C}^{3\text{Ts}}$), 129.0 (CH , $\text{C}^{2''}$ or $3''$), 128.6 (CH , $\text{C}^{2''}$ or $3''$), 128.0 (CH , C^4), 126.9 (CH , C^7), 126.5 (CH , $\text{C}^{2\text{Ts}}$), 126.1 (CH , C^2), 125.8 (C_q ,

C^{9b}), 123.4 (CH, C^8), 122.3 (C_q , C^{9a}), 122.0 (CH, C^9), 119.4 (C_q , $C^{4''}$), 114.8 (CH, C^6), 113.5 (CH, C^4), 34.9 (CH_2 , $C^{1''}$), 27.2 (CH_2 , $C^{2''}$), 21.5 (CH_3 , C^{5Ts}), 16.5 (CH_2 , $C^{3''}$);

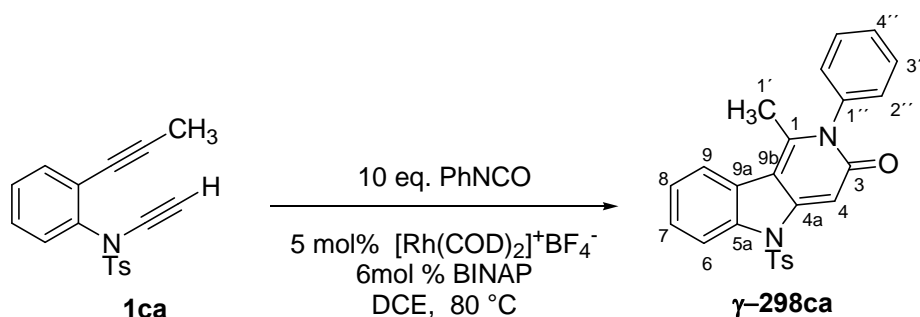
IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3054.69 (w, br.), 2955.38 (w, br.), 1591.95 (m), 1438.64 (m), 1372.10 (vs), 1213.01 (w), 1173.47 (vs), 1122.37 (m), 977.73 (m), 812.85 (m), 752.10 (s), 703.89 (s), 665.32 (m);

FD-MS: m/z (%) = 464.4 (100) $[M]^+$, 465.4 (31), 466.3 (9), 467.3 (2).

The second isomer was not isolated pure enough for analyses.

V.2.1.4 [2+2+2] Cycloaddition with an isocyanate

1-Methyl-5-tosyl-2-phenyl-2,5-dihydro-3H-pyrido[4,3-b]indol-3-one γ -298ca



According to the general procedure **GP10**, cycloaddition of 77.0 mg of **1aa** (0.25 mmol) and 270 μ L of phenylisothiocyanate (2.49 mmol) led after purification by column chromatography (SiO_2 , PE/EtOAc 80/20 then EtOAc 100%, R_f = 0.48 (EtOAc 100%)) to 39.9 mg (0.093 mmol, 37%) of γ -**298ca** as a brown oil.

1H NMR ($CDCl_3$) δ ppm: 8.25 (d, J = 8.3 Hz, 1H, H^6), 7.87 (d, J = 8.4, 2H, H^{2Ts}), 7.67 (d, J = 7.6 Hz, 1H, H^9), 7.56 (m, J = 8.5 Hz, 2H, $H^{3''}$), 7.51 (m, 1H, $H^{4''}$), 7.42 (td, J = 7.7 Hz, J = 1.2 Hz, 1H, H^7), 7.38 (s, 1H, H^4), 7.30 (td, J = 7.7 Hz, J = 1.0 Hz, 1H, H^8), 7.25 (d, J = 8.0 Hz, 2H, H^{3Ts}), 7.23 (m, 2H, $H^{2''}$), 2.39 (s, 3H, $H^{1'}$), 2.36 (s, 3H, H^{5Ts});

^{13}C NMR ($CDCl_3$) δ ppm: 163.2 (C_q , C^3), 148.5 (C_q , C^{4a}), 145.6 (C_q , C^{4Ts}), 141.8 (C_q , C^1), 139.6 (C_q , C^{5a}), 138.3 (C_q , $C^{1''}$), 134.4 (C_q , C^{1Ts}), 130.0 (CH, $C^{3''}$), 129.9 (CH, C^{3Ts}), 129.1

(CH, C^{4''}), 128.1 (CH, C^{2''}), 127.1 (CH, C⁷), 127.0 (CH, C^{2Ts}), 124.7 (C_q, C^{9a}), 124.5 (CH, C⁸), 121.1 (CH, C⁹), 114.6 (CH, C⁶), 109.6 (C_q, C^{9b}), 98.0 (CH, C⁴), 21.6 (CH₃, C^{5Ts}), 18.9 (CH₃, C^{1'});

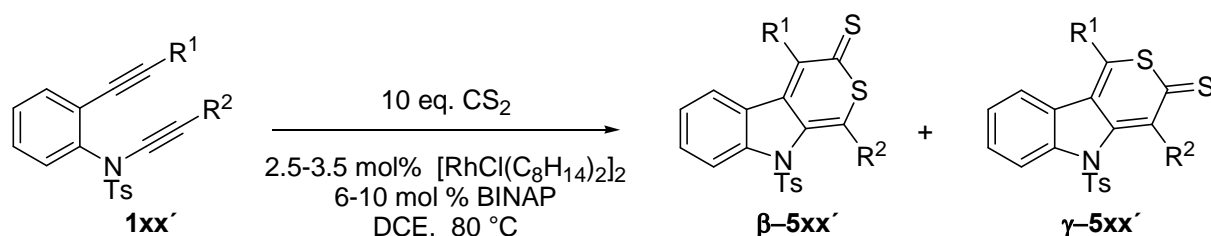
IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3060.48 (w), 2925.48 (w), 1655.59 (vs), 1597.73 (w), 1562.06 (m), 1492.63 (m), 1462.74 (m), 1381.75 (m), 1267.00 (w), 1173.47 (s), 1095.37 (w), 944.95 (w), 909.27 (w), 812.85 (w), 730.89 (m), 662.43 (m);

FD-MS: m/z (%) = 428.2 (100) [M]⁺, 429.3 (31), 430.3 (6), 431.3 (1).

Exact masse: [M+Na]⁺ calcd: 451.1092; found 451.1105.

V.2.1.5. [2+2+2] Cycloadditions with CS₂

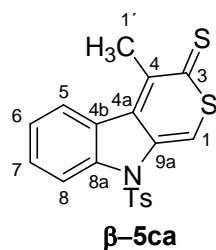
- General procedure for the [2+2+2] cycloaddition of alkynes with CS₂ (GP11)^[93, modified]



Under Argon (N₂), BINAP (15.6 mg, 0.025 mmol, 10 mol%) and [RhCl(C₈H₁₄)₂]₂ (6.1 mg, 0.0087 mmol, 3.5 mol%) are dissolved in degazed CH₂Cl₂ (3.0 mL) in a Schlenk tube, and the mixture is stirred at room temperature for 5 min. H₂ is then introduced to the resulting solution. After stirring at room temperature for 0.5 h, the resulting solution is concentrated to dryness and the residue dissolved in DCE (3.0 mL). To this solution is added dropwise over 1 min a solution of the diyne (0.25 mmol) and CS₂ (150 μ L, 2.5 mmol, 10 equiv.) in DCE (5.0 mL). Undissolved substrate is dissolved by addition of DCE (2x1.0 mL), added to the solution and the mixture is heated at 80 $^\circ$ C. After completion of the reaction (TLC), the solvent is removed and the residue is purified by column chromatography.

- Cycloaddition with the diyne 1ca (R¹ = Me, R² = H) and methylcyanofomate 2a

According to the general procedure **GP11**, 77.3 mg (0.25 mmol) of **1ca** with CS₂ led to 91.6 mg (0.237 mmol, 95%) of **\beta-5ca** as a violet solid. (3.5 mol% [Rh]₂)

4-Methyl-9-tosyl-thiopyrano[3,4-*b*]indole-3(9H)-thione β -5ca:

Violet solid, m.p. = 175-176 °C (decomposition)

Purified by column chromatography (Al₂O₃, PE/EtOAc 95/5)

R_f = 0.46 (Al₂O₃, PE/EtOAc 90/10).

¹H NMR (CDCl₃) δ ppm: 8.55 (s, 1H, H¹), 8.28 (d, J = 8.3 Hz, 1H, H⁸), 8.14 (d, J = 8.0, 1H, H⁵), 7.67 (t, J = 7.9 Hz, 1H, H⁷), 7.59 (d, J = 8.5 Hz, 2H, H^{2Ts}), 7.42 (t, J = 7.5 Hz, 1H, H⁶), 7.18 (d, J = 8.4 Hz, 2H, H^{3Ts}), 2.94 (s, 3H, H^{1'}), 2.33 (s, 3H, H^{5Ts});

¹³C NMR (CDCl₃) δ ppm: 197.6 (C_q, C³), 146.0 (C_q, C^{4Ts}), 142.2 (C_q, C^{8a}), 141.2 (C_q, C^{9a}), 134.3 (C_q, C⁴), 134.2 (C_q, C^{4a}), 133.4 (C_q, C^{1Ts}), 132.3 (CH, C⁷), 130.1 (CH, C^{3Ts}), 126.7 (CH, C^{2Ts}), 126.6 (CH, C⁵), 125.3 (CH, C⁶), 125.3 (C_q, C^{4b}), 125.0 (CH, C¹), 115.3 (CH, C⁸), 21.6 (CH₃, C^{5Ts}), 18.4 (CH₃, C^{1'});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2925.48 (s, br.), 1600.63 (m), 1508.06 (m), 1456.96 (m), 1369.21 (s), 1345.11 (vs), 1269.90 (s), 1188.90 (s), 1155.15 (vs), 1089.58 (m), 1028.84 (vs), 936.27 (s), 788.74 (m), 743.42 (m), 703.89 (w), 668.21 (vs);

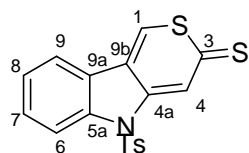
FD-MS: m/z (%) = 385.2 (100.0) [M]⁺, 386.2 (19.6), 387.2 (9.4), 388.2 (1.6).

Elemental analysis (%) for C₁₉H₁₅NO₂S₃ (385.52): C 59.19, H 3.92, N 3.63, S 24.95; found C 59.35, H 3.94, N 3.58, S 24.43.

UV-Vis (CH₂Cl₂): $\lambda_{\max 1}$ = 529 nm, ϵ_1 = 3927 cm²/mmol, $\lambda_{\max 2}$ = 312 nm, ϵ_2 = 19974 cm²/mmol;

- Cycloaddition with the diyne 1aa (R¹ = H, R² = H) and CS₂

According to the general procedure **GP11**, cycloaddition of 74.2 mg of **1aa** (0.25 mmol) with CS₂ led to 15.9 mg (partially decomposed, <0.043 mmol, <17%) of γ -**5ca** as a red solid together with 62.3 mg (partially decomposed, <0.168 mmol, <67%) of β -**5aa** as a violet solid. (2.5 mol% [Rh]₂)

5-Tosyl-thiopyrano[4,3-*b*]indole-3(5H)-thione γ -5aa: **γ -5aa**

Red solid, m.p.: 172-173 °C (decomposition)

Purified by column chromatography (SiO₂, PE/CH₂Cl₂/EtOAc 6/3/1)R_f = 0.43 (PE/CH₂Cl₂/EtOAc 6/3/1),

¹H NMR (CDCl₃) δ ppm: 8.58 (s, 1H, H⁴), 8.22 (d, J = 8.4 Hz, 1H, H⁶), 8.15 (s, 1H, H¹), 7.81 (d, J = 8.3 Hz, H^{2Ts}), 7.68 (d, J = 7.7 Hz, 1H, H⁹), 7.54 (t, J = 7.5 Hz, 1H, H⁷), 7.36 (t, J = 7.5 Hz, 1H, H⁸), 7.27 (d, J = 8.5 Hz, H^{3Ts}), 2.37 (s, 3H, H^{5Ts});

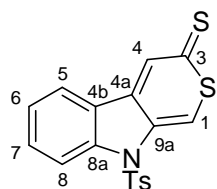
¹³C NMR (CDCl₃) δ ppm: 199.1 (C_q, C³), 146.3 (C_q, C^{4Ts}), 144.9 (C_q, C^{4a}), 139.8 (C_q, C^{5a}), 134.6 (CH, C¹), 134.0 (C_q, C^{1Ts}), 130.4 (CH, C⁷), 130.3 (CH, C^{3Ts}), 127.0 (C_q, C^{9b}), 127.0 (CH, C^{2Ts}), 125.3 (CH, C₈), 123.0 (CH, C⁹), 122.9 (C_q, C^{9a}), 120.3 (CH, C⁴), 115.3 (CH, C⁶); 21.5 (CH₃, C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 1586.16 (s), 1510.95 (vs), 1453.10 (m), 1402.00 (w), 1372.10 (vs), 1224.58 (m), 1170.58 (vs), 1092.48 (w), 987.38 (vs), 944.95 (m), 866.85 (w), 806.10 (m), 752.10 (s), 668.21 (s);

FD-MS: m/z (%) = 371.2 (100) [M]⁺, 372.2 (21), 373.2 (11), 374.2 (2);

Exact masse: [M+H]⁺ calcd: 372.0181; found 372.0189.

UV-Vis (CH₂Cl₂): $\lambda_{\max 1}$ = 474 nm, ϵ_1 = 3562 cm²/mmol, $\lambda_{\max 2}$ = 378 nm, ϵ_2 = 27770 cm²/mmol;

9-Tosyl-thiopyrano[3,4-*b*]indole-3(5H)-thione β -5aa: **β -5aa**

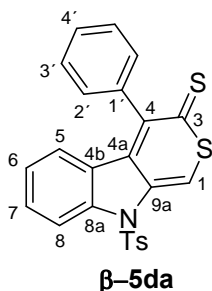
Violet solid

Purified by column chromatography (SiO₂, PE/CH₂Cl₂/EtOAc 6/3/1)R_f = 0.43 (PE/EtOAc 80/20)

The product β -5aa was partially decomposed before all analyses were performed.

- Cycloaddition with the diyne **1da ($R^1 = \text{Ph}$, $R^2 = \text{H}$) and CS_2**

According to the general procedure **GP11**, cycloaddition of 94.3 mg of **1da** (0.25 mmol) with CS_2 led to 102.9 mg (0.23 mmol, 92%) of a mixture of γ -**5da** and β -**5da**. (3.5 mol% $[\text{Rh}]_2$)

4-Phenyl-9-tosyl-thiopyrano[3,4-*b*]indole-3(9H)-thione β -5da

Violet solid, m.p.= 167-168 °C

Purified by column chromatography (Al_2O_3 , PE/ CHCl_3 / EtOAc 7/2/1)

$R_f = 0.54$ (PE/ EtOAc 80/20)

* ^1H NMR (CDCl_3) δ ppm: 8.61 (s, 1H, H^1), 8.16 (d, $J = 8.5$ Hz, 1H, H^8), 7.66 (d, $J = 8.4$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.54 (m, 4H, $\text{H}^{7+3'+5'}$), 7.24 (d, $J = 8.5$ Hz, 2H, $\text{H}^{3\text{Ts}}$), 7.14 (d, $J = 7.7$ Hz, 2H, $\text{H}^{2'}$), 6.94 (t, $J = 8.7$ Hz, 1H, H^6), 6.11 (d, $J = 8.2$ Hz, 1H, H^5), 2.38 (s, 3H, $\text{H}^{5\text{Ts}}$);

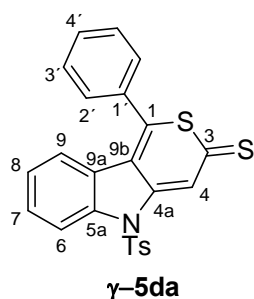
* ^{13}C NMR (CDCl_3) δ ppm: 197.8 (C_q , C^3), 146.1 (C_q , $\text{C}^{4\text{Ts}}$), 143.6 (C_q , C^{9a}), 142.4 (C_q , C^{8a}), 136.6 (C_q , $\text{C}^{1'}$), 134.8 (C_q , C^4), 134.6 (C_q , C^{4a}), 133.5 (C_q , $\text{C}^{1\text{Ts}}$), 132.6 (CH, C^7), 130.1 (CH, $\text{C}^{3\text{Ts}}$), 129.8 (CH, $\text{C}^{3'}$), 128.8 (CH, C^4), 128.5 (CH, $\text{C}^{2'}$), 126.7 (CH, $\text{C}^{2\text{Ts}}$), 126.6 (CH, H^1), 126.2 (CH, C^5), 124.9 (CH, C^6), 124.2 (C_q , C^{4b}), 114.8 (CH, C^8), 21.6 (CH_3 , $\text{C}^{5\text{Ts}}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3084.58 (w), 2988.16 (w), 1594.84 (s), 1513.85 (s), 1447.31 (s), 1375.00 (s), 1342.21 (vs), 1282.43 (m), 1251.58 (m), 1167.69 (vs), 1159.01 (vs), 1092.48 (w), 1041.37 (s), 953.63 (s), 899.63 (m), 839.85 (w), 809.96 (m), 749.21 (s), 695.21 (m), 665.32 (s);

FD-MS: m/z (%) = 447.2 (100) $[\text{M}]^+$, 448.2 (26), 449.2 (17), 450.2 (2);

Exact masse: $[\text{M}+\text{H}]^+$ calcd: 448.0494; found 448.0495.

UV-Vis: (CH_2Cl_2): $\lambda_{\text{max}1} = 535$ nm, $\epsilon_1 = 4240$ cm^2/mmol , $\lambda_{\text{max}2} = 313$ nm, $\epsilon_2 = 21099$ cm^2/mmol ;

1-Phenyl-5-tosyl-thiopyrano[4,3-*b*]indole-3(5H)-thione γ -5da

Red solid, m.p.= 146-147 °C

Purified by column chromatography (Al₂O₃, PE/CHCl₃/EtOAc 7/2/1)

R_f= 0.48 (PE/EtOAc 80/20)

¹H NMR (CDCl₃) δ ppm: 8.66 (s, 1H, H⁴), 8.26 (d, J= 8.4 Hz, 1H, H⁶), 7.86 (d, J= 8.4Hz, 2H, H^{2Ts}), 7.56 (m, 3H, H^{3'+4'}), 7.42 (m, 3H, H^{7+2'}), 7.31 (d, J= 8.0 Hz, 2H, H^{3Ts}), 7.01 (t, J= 8.0 Hz, 1H, H⁸), 6.78 (d, J= 8.0 Hz, 1H, H⁹), 2.40 (s, 3H, H^{5Ts});

¹³C NMR (CDCl₃) δ ppm: 198.9 (C_q, C³), 154.5 (C_q, C¹), 146.3 (C_q, C^{4Ts}), 145.9 (C_q, C^{4a}), 139.9 (C_q, C^{5a}), 134.0 (C_q, C^{1Ts}), 133.2 (C_q, C^{1'}), 130.8 (CH, C^{4'}), 130.3 (CH, C^{3Ts}), 129.93 (CH, C⁷), 129.5 (CH, C^{3'}), 128.5 (CH, C^{2'}), 127.0 (CH, C^{2Ts}), 124.8 (CH, C⁸), 123.9 (C_q, C^{9b}), 122.8 (C_q, C^{9a}), 122.38 (CH, C⁹), 121.4 (CH, C⁴), 115.0 (CH, C⁶), 21.7 (CH₃, C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2973.70 (w), 1583.27 (m), 1519.63 (s), 1456.96 (m), 1363.43 (vs), 1176.36 (s), 1155.15 (s), 1086.69 (w), 984.48 (vs), 942.06 (m), 809.96 (w), 746.32 (m), 695.21 (w), 671.11 (m);

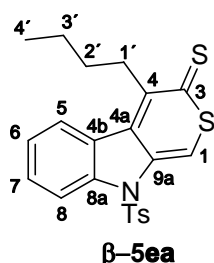
FD-MS: m/z (%) = 447.2 (100) [M]⁺, 448.3 (29), 449.2 (17), 450.2 (4), 451.2 (1);

Exact masse: [M+H]⁺ calcd: 448.0494; found 448.0513;

UV-Vis: (CH₂Cl₂): $\lambda_{\max 1}$ = 497 nm, ϵ_1 = 46310 cm²/mmol, $\lambda_{\max 2}$ = 378 nm, ϵ_2 = 23841 cm²/mmol.

- Cycloaddition with the diyne 1ea (R¹= *n*-Bu, R²= H) and CS₂

According to the general procedure **GP11**, cycloaddition of 84.3 mg of **1ea** (0.24 mmol) with carbon disulfide led to 72.8 mg (0.17 mmol, 71%) of a mixture of γ -**5ea** and β -**5ea**. (3.5 mol% [Rh]₂)

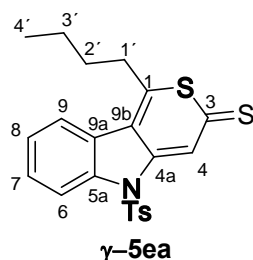
4-*n*-Butyl-9-tosyl-thiopyrano[3,4-*b*]indole-3(9H)-thione β -5ea

Violet solid

Purified by column chromatography (Al₂O₃, PE/EtOAc 90/10)R_f = 0.65 (SiO₂, PE/EtOAc 80/20)

¹H NMR (CDCl₃) δ ppm: 8.54 (s, 1H, H¹), 8.30 (d, J = 8.4 Hz, 1H, H⁸), 7.99 (d, J = 7.8 Hz, 1H, H⁵), 7.67 (t, J = 8.4 Hz, 1H, H⁷), 7.60 (d, J = 8.4 Hz, 2H, H^{2Ts}), 7.43 (t, J = 8.2 Hz, 1H, H⁶), 7.19 (d, J = 8.2 Hz, 2H, H^{3Ts}), 2.34 (s, 3H, H^{5Ts}), 1.69 (m, 2H, H^{1'}), 1.57 (m, 2H, H^{2'}), 1.25 (m, 2H, H^{3'}), 1.00 (t, J = 6.9 Hz, 3H, H^{4'});

The product β -5ea was decomposed before all analyses were performed.

1-*n*-Butyl-5-tosyl-thiopyrano[4,3-*b*]indole-3(5H)-thione γ -5ea

Red solid

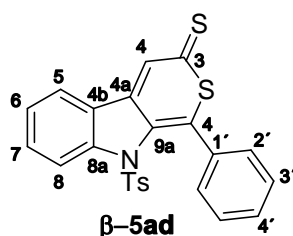
Purified by column chromatography (Al₂O₃, PE/EtOAc 90/10)R_f = 0.48 (SiO₂, PE/EtOAc 80/20)

¹H NMR (CDCl₃) δ ppm: 8.59 (s, 1H, H⁴), 8.32 (d, J = 8.4 Hz, 1H, H⁶), 7.80 (d, J = 8.6 Hz, 2H, H^{2Ts}), 7.73 (d, J = 8.0 Hz, 2H, H^{2Ts}), 7.54 (t, J = 8.4 Hz, 1H, H⁷), 7.39 (t, J = 8.0 Hz, 1H, H⁸), 7.27 (d, J = 8.4 Hz, 2H, H^{3Ts}), 3.05 (t, J = 7.8 Hz, 2H, H^{1'}), 2.37 (s, 3H, H^{5Ts}), 1.74 (m, 2H, H^{2'}), 1.50 (m, 2H, H^{3'}), 0.98 (t, J = 7.3 Hz, 3H, H^{4'});

FD-MS: m/z (%) = 427.3 (100) [M]⁺, 428.3 (22), 429.3 (15), 430.3 (3), 431.3 (1).

- Cycloaddition with the diyne 1ad (R¹ = H, R² = Ph) and CS₂

According to the general procedure **GP11**, cycloaddition of 92.9 mg of **1ad** (0.25 mmol) with carbon disulfide led to 76.3 mg (0.17 mmol, 68%) of β -5ad as a violet solid. (2.5 mol% [Rh]₂)

4-Phenyl-9-tosyl-thiopyrano[3,4-*b*]indole-3(9H)-thione β -5ad

Violet solid, m.p.= 175-176 °C

Purified by column chromatography (Al₂O₃, PE/EtOAc/CHCl₃ 80/10/10), R_f= 0.46 (PE/EtOAc 80/20),

*¹H NMR (CDCl₃) δ ppm: 8.08 (d, J= 8.2 Hz, 1H, H⁸), 7.75 (m, 2H, H^{2'}), 7.70 (s, 1H, H⁴), 7.63 (m, 2H, H⁵⁺⁶), 7.54 (m, 3H, H^{3'+4'}), 7.37 (t, J= 7.2 Hz, 1H, H⁷), 7.06 (d, J= 8.3 Hz, H^{2Ts}), 6.97 (d, J= 8.3 Hz, 2H, H^{3Ts}), 2.26 (s, 3H, H^{5Ts});

*¹³C NMR (CDCl₃) δ ppm: 201.0 (C_q, C³), 149.8 (C_q, C¹), 145.4 (C_q, C^{4Ts}), 144.8 (C_q, C^{8a}), 141.6 (C_q, C^{4a}), 135.7 (C_q, C^{1'}), 133.6 (C_q, C^{9a}), 132.9 (CH, C⁵), 131.2 (C_q, C^{1Ts}), 130.5 (CH, C^{4'}), 129.3 (CH, C^{3Ts}), 129.1 (CH, C^{3'}), 128.3 (CH, C^{2'}), 127.6 (CH, C⁴), 127.2 (C_q, C^{4b}), 127.1 (CH, C^{2Ts}), 127.0 (CH, C⁷), 122.4 (CH, C⁶), 120.1 (CH, C⁸), 21.6 (CH₃, C^{5Ts});

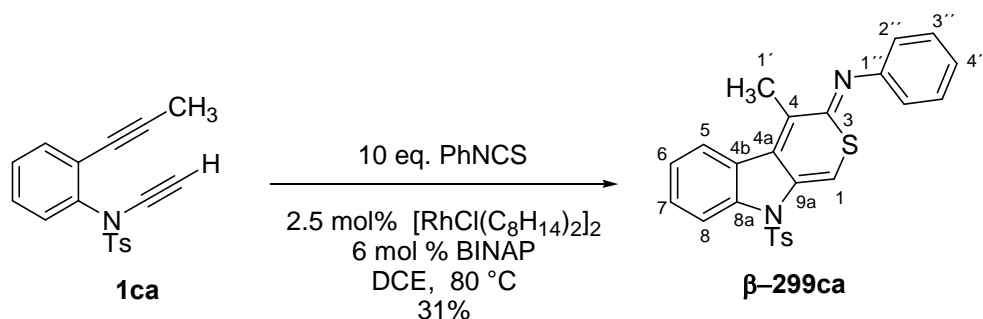
IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3042.16 (w, br.), 1600.63 (m), 1516.74 (s), 1486.85 (m), 1453.10 (w), 1372.10 (s), 1207.22 (m), 1167.69 (vs), 1110.80 (m), 1047.16 (s), 905.42 (m), 818.63 (m), 773.32 (m), 662.43 (s);

FD-MS: m/z (%) = 447.3 (100) [M]⁺, 448.3 (38), 449.3 (7), 450.3 (3);

UV-Vis (CH₂Cl₂): $\lambda_{\max 1}$ = 527 nm, ϵ_1 = 4895 cm²/mmol, $\lambda_{\max 2}$ = 322 nm, ϵ_2 = 22013 cm²/mmol.

V.2.1.6. [2+2+2] Cycloaddition with an isothiocyanate

- Cycloaddition with the diyne 1ca (R¹= Me, R²= H) and phenylisothiocyanate



According to the general procedure **GP11**, cycloaddition of 78.8 mg of **1aa** (0.255 mmol) and 210 μL of phenylisothiocyanate (2.55 mmol) with 4.6 mg (0.0064 mmol, 2.5 mol%) and 9.6 mg (0.0153 mmol, 6 mol%) led to 35.2 mg (0.079 mmol, 31%) of **β -299ca** as a red-orange solid.

4-Methyl-9-tosyl-9H-thiopyrano[3,4-*b*]indol-(3*Z*)-iminophenyl **β -299ca**

Red-orange solid, purified by column chromatography (SiO_2 , PE/EtOAc 90/10), $R_f = 0.46$ (PE/EtOAc 90/10), m.p. = 183-184 $^\circ\text{C}$

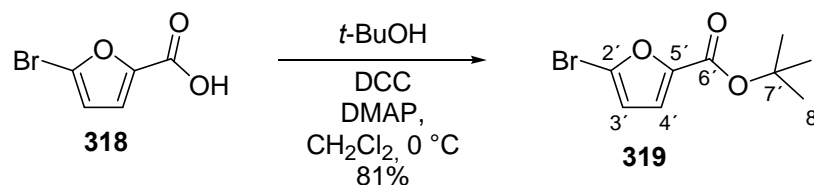
$^1\text{H NMR}$ (CDCl_3) δ ppm: 8.15 (d, $J = 8.2$ Hz, 1H, H^8), 7.95 (d, $J = 7.9$ Hz, 1H, H^5), 7.60 (br. s, 1H, H^1), 7.55 (d, $J = 8.4$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.51 (t, $J = 7.4$ Hz, 1H, H^7), 7.43 (t, $J = 7.6$ Hz, 2H, $\text{H}^{3'}$), 7.30 (t, $J = 8.1$ Hz, 1H, H^6), 7.16 (d, $J = 8.2$ Hz, 2H, $\text{H}^{3\text{Ts}}$), 7.14 (t, $J = 9.7$ Hz, 1H, $\text{H}^{4'}$), 6.90 (d, $J = 7.7$ Hz, 2H, $\text{H}^{2'}$), 2.36 (s, 3H, $\text{H}^{1'}$), 2.34 (s, 3H, $\text{H}^{5\text{Ts}}$);

$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 145.5 (C_q , $\text{C}^{4\text{Ts}}$), 142.0 (C_q , C^{8a}), 133.5 (C_q , $\text{C}^{1\text{Ts}}$), 131.2 (CH, C^7), 130.7 (C_q , C^4), 130.3 (CH, $\text{C}^{2'}$), 129.9 (CH, $\text{C}^{3\text{Ts}}$), 128.7 (C_q , $\text{C}^{1''}$), 126.9 (CH, $\text{C}^{2\text{Ts}}$), 126.8 (C_q , C^{4b}), 126.2 (CH, C^5), 125.1 (CH, C^6), 124.8 (CH, $\text{C}^{4'}$), 120.1 (CH, $\text{C}^{3'}$), 115.7 (CH, C^8), 109.0 (CH, C^1), 21.6 (CH_3 , $\text{C}^{5\text{Ts}}$), 15.8 (CH_3 , $\text{C}^{1'}$). C_q miss due to overlapping.

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 2922.27 (vs), 2850.27 (s), 1733.69 (w), 1532.17 (m), 1456.96 (m), 1372.10 (w), 1264.11 (m), 1095.35 (s), 800.31 (m);

FD-MS: m/z (%) = 444.3 (100) $[\text{M}]^+$, 445.3 (34), 446.3 (17).

Exact masse: $[\text{M}+\text{H}]^+$ calcd: 445.1044; found 445.1039.

V.2.2. Total syntheses of *Perlolyrine* and *Isoperlolyrine*V.2.2.1. Total synthesis of *Perlolyrine**tert*-Butyl 5-bromofuran-2-carboxylate **319**

To a solution of 3.42 g (17.9 mmol) of 5-bromo-2-furoic acid **318** in 50 mL of dry CH_2Cl_2 under N_2 are added 10 mL of *t*-BuOH. The mixture is cooled to 0 °C and 131 mg (1.07 mmol, 6 mol%) of DMAP and 5.06 mg (24.5 mmol, 1.4 equiv) of DCC are added and the reaction is stirred at 0 °C for 6 hours and let warmed overnight to room temperature. The mixture is filtered over Celite and washed with 50 mL of CH_2Cl_2 . The filtrate is extracted twice with 50 mL of saturated NaHCO_3 , one time with 50 mL of H_2O and one time with 50 mL of brine. The combined organic layers are dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude product is purified by column chromatography (SiO_2 , PE/EtOAc 98/2, $R_f = 0.76$ (90/10)) to give 3.58 g (14.5 mmol, 81 %) as a colorless oil which solidifies in the fridge.

White solid of m.p. = 34-35 °C

$^1\text{H NMR}$ (CDCl_3) δ ppm: 7.02 (d, $J = 3.5$ Hz, 1H, $\text{H}^{4'}$), 6.42 (d, $J = 3.5$ Hz, 1H, $\text{H}^{3'}$), 1.57 (s, 9H, H^8);

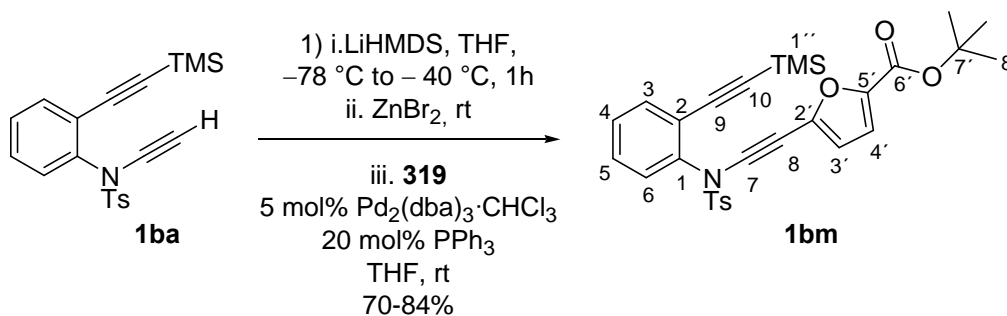
$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 156.9 (C_q , C^6), 147.5 (C_q , C^5), 126.6 (C_q , C^2), 119.0 (CH, $\text{C}^{4'}$), 113.6 (CH, $\text{C}^{3'}$), 82.3 (C_q , C^7), 28.1 (CH_3 , C^8).

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3151.11 (w), 3129.90 (m), 3009.37 (m), 2982.37 (s), 2928.38 (m), 1730.80 (vs), 1715.37 (vs), 1570.74 (m), 1465.63 (vs), 1387.53 (w), 1369.21 (s), 1302.68 (vs), 1213.01 (w), 1146.47 (s), 1122.37 (vs), 1017.27 (s), 915.06 (m), 848.53 (m), 812.85 (m), 757.89 (m);

FD-MS: m/z (%): 246.0 (100) $[\text{M}]^+$, 247.0 (6), 248.0 (94), 249.0 (9);

Exact masse: $[M+Na]^+$ calcd for $(C_9H_{11}NO_3NaBr)$: 268.9789; found 268.9802.

2-(2-(Trimethylsilyl)ethynyl)-N-(2-(5-(*tert*-butoxycarbonyl)furan-2-yl)ethynyl)-N-tosylbenzenamine 1bm



Following the general procedure for the Negishi coupling **GP7**, 919 mg (2.5 mmol) of the diyne **1ba** led after column chromatography (SiO_2 , PE/EtOAc 90/10, $R_f = 0.74$ (80/20)), to 1.01 g (1.88 mmol, 75%) of the diyne **1bm** as a yellow oil.

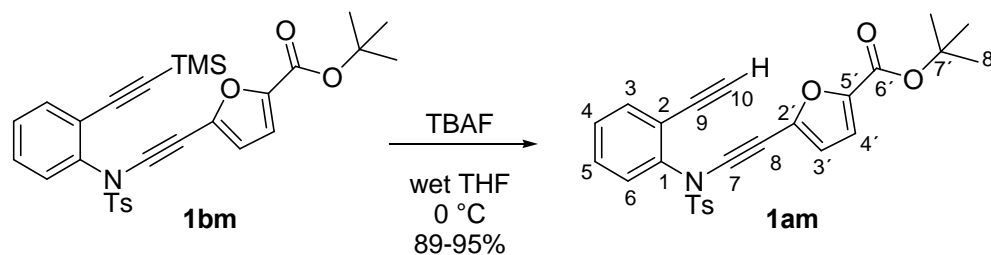
1H NMR ($CDCl_3$) δ ppm: 7.68 (d, $J = 8.1$ Hz, 2H, H^{2Ts}), 7.43 (m, 1H, H^3), 7.29 (m, 5H, H^{3Ts+4^6}), 6.99 (d, $J = 3.3$ Hz, 1H, H^{4^1}), 6.55 (d, $J = 3.3$ Hz, 1H, H^{3^1}), 2.42 (s, 3H, H^{5Ts}), 1.52 (s, 9H, H^{8^1}), 0.15 (s, 9H, H^{1^1});

^{13}C NMR ($CDCl_3$) δ ppm: 157.2 (C_q , C^{6^1}), 145.8 (C_q , C^{5^1}), 145.0 (C_q , C^{4Ts}), 139.5 (C_q , C^{2^1}), 138.4 (C_q , C^1), 134.4 (C_q , C^{1Ts}), 133.8 (CH, C^3), 129.7 (CH, C^{3Ts}), 129.1 (CH, C^5), 129.1 (CH, C^6), 128.9 (CH, C^4), 128.3 (CH, C^{2Ts}), 122.8 (C_q , C^2), 117.8 (CH, C^{4^1}), 117.6 (CH, C^{3^1}), 101.7 (C_q , C^{10}), 99.4 (C_q , C^9), 87.0 (C_q , C^7), 82.0 (C_q , C^{7^1}), 60.8 (C_q , C^8), 28.1 (CH_3 , C^{8^1}), 21.6 (CH_3 , C^{5Ts}), -0.4 (CH_3 , C^{1^1});

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 2977.55 (s), 2235.09 (vs), 2167.60 (s), 1707.66 (vs), 1590.99 (m), 1491.67 (m), 1372.10 (s), 1300.75 (vs), 1173.47 (vs), 1134.90 (vs), 840.81 (vs);

FD-MS: m/z (%) = 532.7 (100) $[M]^+$, 533.7 (37), 534.7 (15), 535.7 (4), 536.7 (1).

Elemental analysis (%) for $C_{26}H_{23}NO_5S$ calcd: C 65.26, H 5.85, N 2.62, S 5.26; found C 65.14, H 5.38, N 2.43, S 2.63

2-Ethynyl-*N*-(2-(5-(*tert*-butoxycarbonyl)furan-2-yl))ethynyl)-*N*-tosyl-benzenamine **1am**

Following the general procedure for the desilylation of silylated alkynes or ynamides **GP8**, 448 mg (0.84 mmol) of the diene **1bm** led after column chromatography (SiO₂, PE/EtOAc 90/10, R_f= 0.52 (80/20)) to 357.2 mg (0.77 mmol, 92%) of the diene **1am** as a white solid of m.p.= 98-98 °C

¹H NMR (CDCl₃) δ ppm: 7.72 (d, J= 8.3 Hz, 2H, H^{2Ts}), 7.51 (m, 1H, H³), 7.35 (m, 5H, H^{3Ts+4-6}), 7.02 (d, J= 3.5 Hz, H^{4'}), 6.60 (d, J= 3.5 Hz, 1H, H^{3'}), 3.10 (s, 1H, H¹⁰), 2.47 (s, 3H, H^{5Ts}), 1.56 (s, 9H, H^{8'});

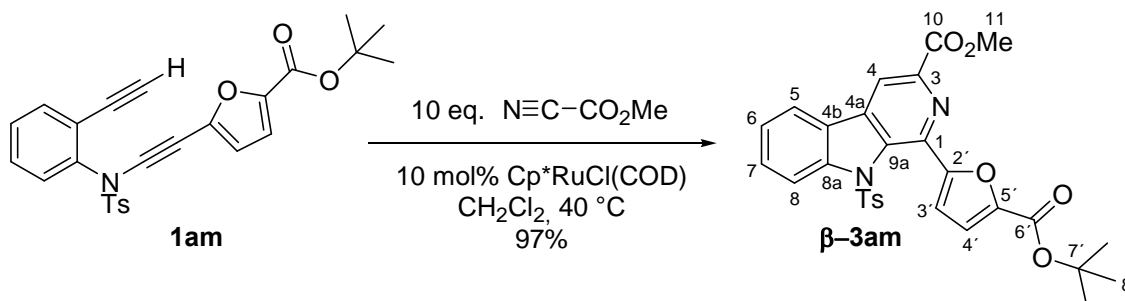
*¹³C NMR (CDCl₃) δ ppm: 157.3 (C_q, C^{6'}), 145.9 (C_q, C^{5'}), 145.3 (C_q, C^{4Ts}), 139.4 (C_q, C^{2'}), 138.9 (C_q, C¹), 134.0 (CH, C³), 133.8 (C_q, C^{1Ts}), 129.7 (CH, C^{3Ts}), 129.57 (CH, C⁵), 129.3 (CH, C⁴), 128.9 (CH, C⁶), 128.4 (CH, C^{2Ts}), 122.1 (C_q, C²), 117.9 (CH, C^{4'}), 117.7 (CH, C^{3'}), 87.3 (C_q, C⁷), 83.4 (CH, C¹⁰), 82.1 (C_q, C^{7'}), 78.4 (C_q, C⁹), 60.7 (C_q, C⁸), 28.0 (CH₃, C^{8'}), 21.6 (CH₃, C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3257.18 (vs), 2984.30 (s), 2231.24 (s), 1711.51 (vs), 1368.25 (vs), 1304.61 (vs), 1166.72 (vs), 1124.30 (s) 816.71 (s);

FD-MS: m/z (%) = 460.7 (100) [M]⁺, 461.7 (25), 462.7 (6);

Elemental analysis (%) for C₂₆H₂₃NO₅S calcd: C 67.66, H 5.02, N 3.03, S 6.95; found C 67.51, H 5.10, N 3.02, S 7.05.

Methyl 1-(5-(*tert*-butoxycarbonyl)furan-2-yl)-9-tosyl-9H-pyrido[3,4-*b*]indole-3-carboxylate β -3am



To a solution of 25.9 mg of $\text{Cp}^*\text{RuCl}(\text{COD})$ (0.068 mmol, 10 mol%) and methylcyanoformate (540 μL , 6.83 mmol, 10 equiv.) in 20 mL degazed CH_2Cl_2 at $40\text{ }^\circ\text{C}$ is added a solution of 315 mg (0.683 mmol) of the diyne **1am** in 20 mL degazed CH_2Cl_2 over 6 hours and the reaction is let stirred overnight at $40\text{ }^\circ\text{C}$. The CH_2Cl_2 is removed and the residue purified by column chromatography (SiO_2 , PE/EtOAc 2/1, $R_f = 0.16$ (80/20)) to give 361.5 mg (0.66 mmol, 97%) of β -3am as a white solid of m.p.: $177\text{-}178\text{ }^\circ\text{C}$ (PE/ CH_2Cl_2)

$^1\text{H NMR}$ (CDCl_3) δ ppm: 8.45 (s, 1H, H^4), 8.17 (d, $J = 8.2$ Hz, 1H, H^8), 7.83 (d, $J = 7.6$ Hz, 1H, H^5), 7.60 (t, $J = 8.4$ Hz, 1H, H^7), 7.39 (t, $J = 7.8$ Hz, 1H, H^6), 7.33 (d, $J = 3.5$ Hz, 1H, $\text{H}^{4'}$), 7.27 (d, $J = 3.9$ Hz, 1H, $\text{H}^{3'}$), 7.07 (d, $J = 8.3$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 6.86 (d, $J = 8.3$ Hz, 2H, $\text{H}^{3\text{Ts}}$), 4.07 (s, 3H, H^{11}), 2.19 (s, 3H, $\text{H}^{5\text{Ts}}$), 1.64 (s, 9H, $\text{H}^{8'}$);

$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 165.3 (C_q , C^{10}), 158.0 (C_q , $\text{C}^{6'}$), 155.0 (C_q , $\text{C}^{2'}$), 146.0 (C_q , $\text{C}^{5'}$), 144.9 (C_q , $\text{C}^{4\text{Ts}}$), 143.6 (C_q , C^1), 142.5 (C_q , C^{8a}), 140.4 (C_q , C^3), 139.3 (C_q , C^{4a}), 135.6 (C_q , C^{9a}), 132.4 (C_q , $\text{C}^{1\text{Ts}}$), 130.4 (CH, C^7), 129.0 (CH, $\text{C}^{3\text{Ts}}$), 126.9 (CH, $\text{C}^{2\text{Ts}}$), 126.1 (C_q , C^{4b}), 125.9 (CH, C^6), 121.4 (CH, C^5), 118.9 (CH, $\text{C}^{4'}$), 118.4 (CH, C^8), 115.4 (CH, C^4), 112.3 (CH, $\text{C}^{3'}$), 81.9 (C_q , $\text{C}^{7'}$), 53.1 (CH_3 , C^{11}), 28.2 (CH_3 , $\text{C}^{8'}$), 21.4 (CH_3 , $\text{C}^{5\text{Ts}}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 2955.38 (br), 1745.26 (vs), 1724.05 (vs), 1367.28 (s), 1350.89 (s), 1303.64 (s), 1245.79 (s), 1132.01 (s), 1115.65 (s);

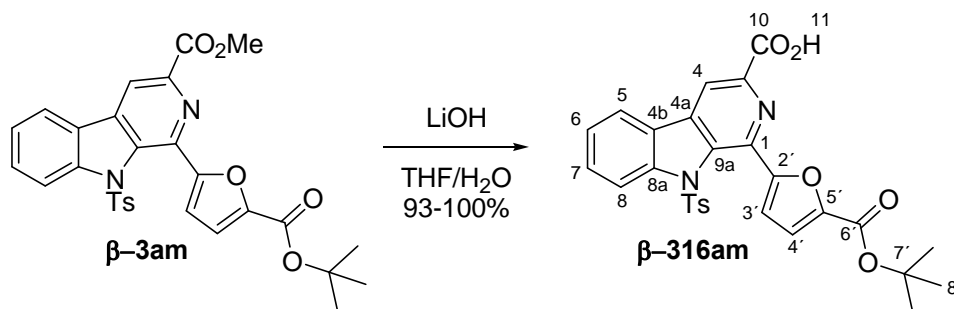
FD-MS: m/z (%) = 546.2 (100) [$\text{M}]^+$, 547.2 (31), 548.2 (8), 549.2 (1);

Elemental analysis (%) for $C_{29}H_{26}N_2O_7S$ calcd: C 63.72, H 4.79, N 5.13; found C 63.41, H 4.91, N 5.15.

Exact masse: $[M+Na]^+$ calcd for $(C_{29}H_{26}N_2NaO_7S^+)$: 569.1353; found 569.1381.

1-(5-(*tert*-butoxycarbonyl)furan-2-yl)-9-tosyl-9H-pyrido[3,4-*b*]indole-3-carboxylic acid

β -316am



To a solution of 280.7 mg (0.514 mmol) of the methyl ester β -3am in 15 mL of THF/H₂O (2/1) are added 37 mg (1.54 mmol, 3 equiv.) of LiOH. The solution is stirred 1 hour and then acidified to pH 1-2 with 5 mL of HCl 1N. 20 mL of CH₂Cl₂ and 20 mL of H₂O are added, the layers separated and the aqueous layer is extracted three times with 10 mL of CH₂Cl₂. The combined organic layers are washed with 20 mL of brine, dried over MgSO₄, filtered and the solvent removed *in vacuo* to give the acid as a white solid of mp: 182-183 °C (PE/CH₂Cl₂)

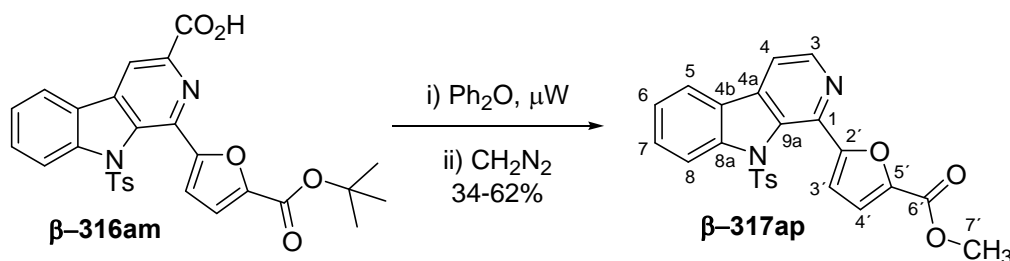
¹H NMR (CDCl₃) δ ppm: 8.51 (s, 1H, H⁴), 8.15 (d, J= 8.1 Hz, 1H, H⁸), 7.84 (d, J= 7.7 Hz, 1H, H⁵), 7.61 (t, J=8.1 Hz, 1H, H⁷), 7.42 (t, J= 7.7 Hz, 1H, H⁶), 7.28 (m, 2H, H, H^{3'+4'}), 7.07 (d, J= 8.1 Hz, 2H, H^{2Ts}), 6.90 (d, J= 8.1 Hz, 2H, H^{3Ts}), 2.21 (s, 3H, H^{5Ts}), 1.65 (s, 9H, H⁸);

¹³C NMR (CDCl₃) δ ppm: 163.9 (C_q, C¹⁰), 157.9 (C_q, C^{6'}), 153.9 (C_q, C^{2'}), 146.3 (C_q, C^{4Ts}), 145.3 (C_q, C^{5'}), 142.8 (C_q, C¹), 141.9 (C_q, C⁸), 140.6 (C_q, C³), 139.2 (C_q, C^{4a}), 136.4 (C_q, C^{9a}), 132.2 (C_q, C^{1Ts}), 131.0 (CH, C⁷), 129.2 (CH, C^{3Ts}), 126.9 (CH, C^{2Ts}), 126.2 (CH, C⁶), 125.9 (C_q, C^{4b}), 121.8 (CH, C⁵), 119.0 (CH, C⁸), 118.3 (CH, C^{4'}), 114.1 (CH, C⁴), 112.8 (CH, C^{3'}), 82.3 (C_q, H⁷), 28.2 (CH₃, H⁸), 21.3 (CH₃, C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3296.71 (br.), 2976.59 (br.), 1745.26 (vs), 1709.59 (vs), 1590.99 (s), 1518.67 (w), 1428.99 (w), 1347.03 (s), 1311.36 (vs), 1178.29 (s), 1138.76 (vs), 930.48 (w), 761.74 (s);

FD-MS: m/z (%) = 531.7 (100) $[M]^+$, 532.7 (33), 533.7 (11), 534.7 (2).

1-(5-(methoxycarbonyl)furan-2-yl)-9-tosyl-9H-pyrido[3,4-*b*]indole β -317ap



A solution of 108.9 mg (0.2 mmol) of the acid β -316am in 5 mL of Ph_2O is heated to 240 °C for 3 minutes (300W) in a microwave reactor. The cooled solution is diluted with 10 mL of methanol, cooled to 0 °C and a freshly prepared solution of diazomethane in Et_2O (prepared from *N*-methyl-*N*-nitroso-urea and a 40% KOH solution^[117]) is added slowly. The mixture is let warmed to room temperature and stirred overnight. The reaction is quenched by addition of few drops of AcOH. The solvent are removed, the residue dissolved with 20 mL of EtOAc and 20 mL of H_2O . The aqueous layer is extracted 3 times with 20 mL of EtOAc and the combined organic extracts washed twice with 30 mL of saturated NaHCO_3 and once with 30 mL of brine, dried over MgSO_4 , filtered and the solvent removed in vacuo. The crude product is purified by column chromatography (SiO_2 , PE/EtOAc 2/1, R_f = 0.21), to give the β -carboline β -317ap as a yellow solid of mp: 201-202 °C (PE/ CH_2Cl_2) together with 5.3 mg (0.018 mmol, 9%) of the detosylated β -carboline β -320ap.

* ^1H NMR (CDCl_3) δ ppm: 8.68 (d, J = 4.9 Hz, 1H, H^3), 8.19 (d, J = 8.4 Hz, 1H, H^8), 7.77 (d, J = 7.8 Hz, 1H, H^5), 7.62 (d, J = 4.9 Hz, 1H, H^4), 7.57 (t, J = 7.2 Hz, 1H, H^6), 7.39 (d, J = 3.7 Hz, 1H, $\text{H}^{4'}$), 7.37 (t, J = 7.6 Hz, 1H, H^7), 7.24 (d, J = 3.5 Hz, 1H, $\text{H}^{3'}$), 7.04 (d, J = 8.4 Hz, 2H, $\text{H}^{2\text{Ts}}$), 6.88 (d, J = 8.0 Hz, 2H, $\text{H}^{3\text{Ts}}$), 3.96 (s, 3H, $\text{H}^{7'}$), 2.20 (s, 3H, $\text{H}^{5\text{Ts}}$);

* ^{13}C NMR (CDCl_3) δ ppm: 159.2 (C_q , $\text{C}^{6'}$), 156.4 (C_q , $\text{C}^{2'}$), 145.4 (CH, C^3), 144.7 (C_q , $\text{C}^{4\text{Ts}}$), 144.3 (C_q , $\text{C}^{5'}$), 142.2 (C_q , C^{8a}), 140.5 (C_q , C^1), 138.7 (C_q , C^{4a}), 134.1 (C_q , C^{9a}), 132.21 (C_q , $\text{C}^{1\text{Ts}}$), 130.1 (CH, C^7), 128.9 (CH, $\text{C}^{3\text{Ts}}$), 127.0 (CH, $\text{C}^{2\text{Ts}}$), 126.7 (C_q , C^{4b}), 125.8 (CH, C^6), 121.2 (CH, C^5), 119.6 (CH, $\text{C}^{4'}$), 119.4 (CH, C^8), 113.8 (CH, C^4), 111.7 (CH, $\text{C}^{3'}$), 51.97 (CH_3 , $\text{C}^{7'}$), 21.5 (CH_3 , $\text{C}^{5\text{Ts}}$);

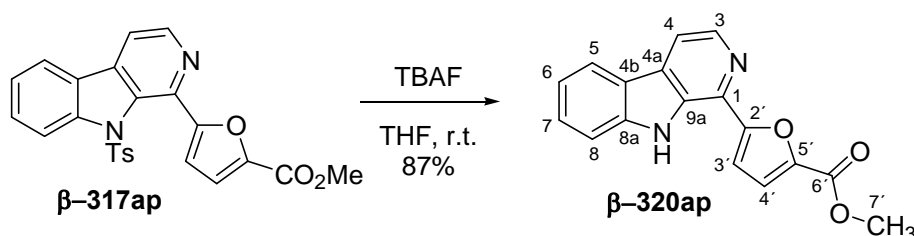
IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3104.83 (br), 1718.26 (vs), 1520.60 (w), 1378.85 (s), 1296.89 (s), 1173.47 (s), 1141.65 (s), 770.42 (s).

FD-MS: m/z (%) = 446.0 (100) [M]⁺, 447.0 (29), 448.0 (8), 449.0 (2);

Elemental analysis (%) for C₂₄H₁₈N₂O₅S calcd: C 64.56, H 4.06, N 6.27; found C 64.15, H 4.07, N 6.03.

Exact masse: [M+Na]⁺ calcd for (C₂₄H₁₈N₂NaO₅S⁺): 469.0829; found 469.0822.

1-(5-(methoxycarbonyl)furan-2-yl)-9H-pyrido[3,4-*b*]indole β -320ap



To a solution of 98 mg (0.22 mmol) of the tosylated product β -317ap in 20 mL of THF are added 1.5 mL of a TBAF solution (1.0M in THF, 1.5 mmol, 7 eq.) and the reaction is let stirred 2 hours at room temperature. After completion of the reaction (TLC), 10 mL of EtOAc and 10 mL of H₂O are added. The aqueous layer is extracted three times with 10 mL of EtOAc and the combined organic layers are washed with 20 mL of brine. The organic phase is dried over MgSO₄, filtered and the solvent removed *in vacuo*. The crude product is purified by column chromatography (SiO₂, PE/EtOAc 1/1, R_f= 0.54) to give 57.4 mg (0.196 mmol, 89 %) of the β -carboline β -320ap as a yellow solid of m.p.= 168-169 °C (PE/CH₂Cl₂)

¹H NMR (CDCl₃) δ ppm: 9.61 (s, 1H, NH), 8.50 (d, J= 5.1 Hz, 1H, H³), 8.14 (d, J= 7.8 Hz, 1H, H⁸), 7.96 (d, J= 5.3 Hz, 1H, H⁴), 7.66 (d, J= 8.2 Hz, 1H, H⁵), 7.61 (t, J= 5.8 Hz, 1H, H⁷), 7.39 (d, J= 3.5 Hz, 1H, H⁶), 7.36 (d, J= 3.7 Hz, 1H, H^{4'}), 7.32 (t, J= 6.8 Hz, 1H, H^{3'}), 4.01 (s, 3H, H^{7'});

***¹³C NMR** (CDCl₃) δ ppm: 159.2 (C_q, C^{6'}), 157.8 (C_q, C^{2'}), 143.7 (C_q, C^{5'}), 140.6 (C_q, C^{8a}), 139.0 (CH, C³), 131.9 (C_q, C^{9a}), 131.6 (C_q, C¹), 130.6 (C_q, C^{4a}), 128.8 (CH, C⁷), 121.5 (CH,

C^5), 120.9 (C_q , C^{4b}), 120.3 (CH, C^6), 119.9 (CH, $C^{4'}$), 114.8 (CH, C^4), 111.9 (CH, C^8), 109.7 (CH, C^3), 52.1 (CH_3 , $C^{7'}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3465.46 (vs), 3108.69 (w), 1722.12 (vs), 1509.99 (s), 1425.14 (s), 1375.00 (s), 1300.75 (vs), 1283.39 (vs), 1212.04 (s), 1134.90 (vs), 1021.12 (w), 755.96 (s);

FD-MS: m/z (%) = 292.0 (100) $[M]^+$, 293.0 (19);

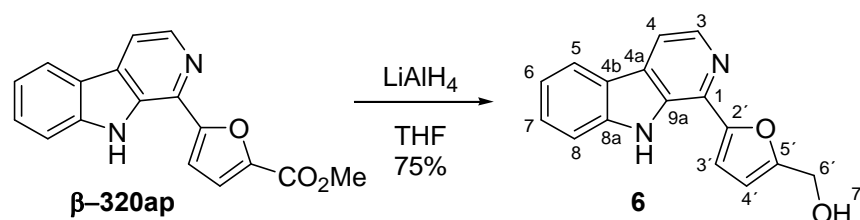
Elemental analysis (%) for $C_{17}H_{12}N_2O_3$ calcd: C 69.86, H 4.14, N 9.58; found C 69.72, H 3.86, N 9.55

Exact masse : $[M+H]^+$ calcd: 293.0921; found 293.0935.

UV-vis (CH_2Cl_2): λ_{max1} = 386 nm, ϵ_1 = 18072 $cm^2/mmol$, λ_{max2} = 309 nm, ϵ_2 = 19401 $cm^2/mmol$;

Fluorescence (CH_2Cl_2) : λ_{max} = 403 nm.

1-(5-(hydroxymethyl)furan-2-yl)-9H-pyrido[3,4-*b*]indole (*Perlolyrine*) **6**



To a solution of 29.7 mg (0.102 mmol) of the methyl ester **β -320ap** in 10 mL THF at 0 °C was slowly added a suspension of 23.2 mg of $LiAlH_4$ (0.612 mmol, 6 eq.) in 5 mL THF and the mixture was let warm to room temperature. After completion of the reaction (TLC), the reaction is quenched by addition of 1 mL of HCl 1N followed by 20 mL H_2O and 10 mL of EtOAc. The layers are separated and the aqueous layer is extracted three times with 10 mL of EtOAc. The combined organic layers are washed with 20 mL of brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product is purified by column chromatography (SiO_2 , PE/ EtOAc 1/1, R_f = 0.14) to give 19.9 mg (0.075 mmol, 75%) of *Perlolyrine* as a yellow solid of m.p. = 165-166 °C (PE, CH_2Cl_2) (Lit: 166 °C ($CHCl_3$)^[100])

*¹H NMR (DMSO-d₆) δ ppm: 11.21 (s, 1H, H⁹), 8.37 (d, J= 5.3 Hz, 1H, H³), 8.26 (d, J= 7.8 Hz, 1H, H⁵), 8.07 (d, J= 5.1 Hz, 1H, H⁴), 7.76 (d, J= 8.2 Hz, 1H, H⁸), 7.61 (t, J= 7.6 Hz, 1H, H⁷), 7.28 (t, J= 7.6 Hz, 1H, H⁶), 7.21 (d, J= 3.1 Hz, 1H, H^{3'}), 6.58 (d, J= 3.1 Hz, 1H, H^{4'}), 5.48 (t, J= 6.2 Hz, 1H, H^{7'}), 4.67 (d, J= 6.2 Hz, 1H, H^{6'});

*¹³C NMR (DMSO-d₆) δ ppm: 156.8 (C_q, C^{5'}), 152.1 (C_q, C^{2'}), 141.0 (C_q, C^{8a}), 138.2 (CH, C³), 133.2 (C_q, C¹), 130.5 (C_q, C^{9a}), 129.4 (C_q, C^{4a}), 128.4 (CH, C⁷), 121.7 (CH, C⁵), 120.6 (C_q, C^{4b}), 119.7 (CH, C⁶), 113.67 (CH, C⁴), 112.4 (CH, C⁸), 109.6 (CH, C^{3'}), 109.1 (CH, C^{4'}), 56.0 (CH₂, C^{6'});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3373.85 (br.), 2871.49 (w), 1629.55 (s), 1565.92 (s), 1431.89 (s), 1329.68 (s), 1010.52 (vs), 742.46 (vs);

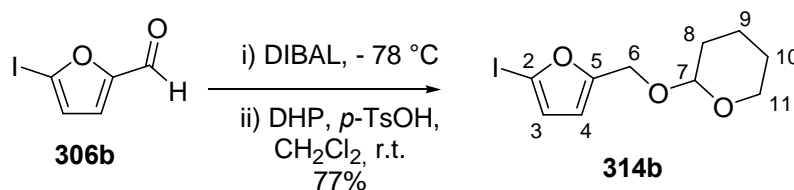
FD-MS: m/z (%) = 264.0 (100) [M]⁺, 265.0 (19), 266.0 (2);

UV-vis (CH₂Cl₂): $\lambda_{\max 1}$ = 378 nm, ϵ_1 = 14790 cm²/mmol; $\lambda_{\max 2}$ = 294 nm, ϵ_2 = 18581 cm²/mmol;

Fluorescence (CH₂Cl₂) : λ_{\max} = 386 nm.

- Other products

2-Iodo-5-(tetrahydropyranyloxymethyl)furan 306b



To a solution of 863 mg, (3.89 mmol) of 5-iodo-2-furaldehyde^[105] dissolved in 20 ml of CH₂Cl₂ and cooled to -78°C under N₂ is added dropwise a 5.2 mL of a ~1M solution of DIBAL in Toluene (5.2 mmol, 1.3 equiv.). The resulting mixture is stirred at -78°C for 2 hours and conversion of the starting material is checked by TLC. Then 20 mL of a mixture of CH₂Cl₂/Methanol 1:1 is added slowly with cooling to 0°C, followed by 10 mL of a 1N HCl solution and the resulting mixture is stirred 30 min at 0°C. The solid aluminium salts are filtered, the organic layer was separated, the aqueous layer was extracted 2 times with 20 mL of

CH₂Cl₂ and the combined organic layers are dried over MgSO₄, filtered and concentrated to about 10 mL. 20 mL of dry CH₂Cl₂ (20 mL) and few beads of molecular sieves (3Å) are added and 500 μL of 3,4-Dihydropyran (5.44 mmol, 1.4 equiv.) are added dropwise followed by 164 mg of *p*TsOH.H₂O (0.86 mmol, 20 mol%) and the resulting mixture is stirred at room temperature under N₂ until completion of the reaction. Then 10 mL CH₂Cl₂ and 20 mL water are added. The aqueous layer is extracted 3 times by 10 ml CH₂Cl₂. The combined organic layers are washed by 20 mL brine, dried over MgSO₄ and filtered. After evaporation of the solvent, the crude product is purified by column chromatography (Al₂O₃, PE 100%, R_f= 0.78 (SiO₂, 80/20)) to give 925.5 mg (3.00 mmol, 77%) of **314b** as a colourless oil.

¹H NMR (CDCl₃) δ ppm: 6.46 (d, J= 3.1 Hz, 1H, H³), 6.22 (d, J= 3.1 Hz, 1H, H⁴), 4.67 (t, J= 3.3 Hz, 1H, H⁷), 4.60 (d, J= 2.9 Hz, 1H, H⁶), 4.45 (d, J= 2.9 Hz, 1H, H^{6'}), 3.84 (m, 1H, H^{11a}), 3.49 (m, 1H, H^{11b}), 1.79 (m, 1H, H^{8a}), 1.68 (m, 1H, H^{8b}), 1.50 (m, 4H, H⁹⁺¹⁰);

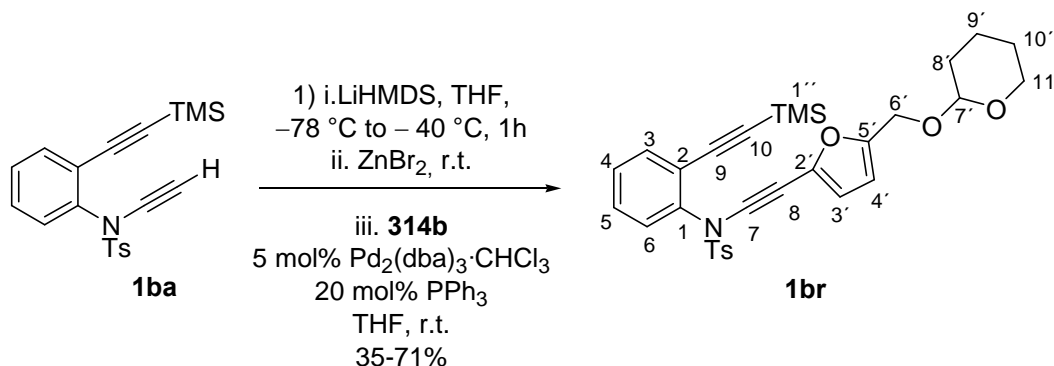
¹³C NMR (CDCl₃) δ ppm: 157.2 (C_q, C⁵), 120.7 (CH, C³), 112.1 (CH, C⁴), 97.1 (CH, C⁷), 87.9 (C_q, C²), 61.7 (CH₂, C⁶), 60.1 (CH₂, C¹¹), 30.1 (CH₂, C⁸), 25.2 (CH₂, C¹⁰), 18.9 (CH₂, C⁹);

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3445.21 (br.), 3124.12 (br.), 2939.95 (s), 2867.63 (s), 1482.99 (s), 1347.03 (s), 1200.47 (s), 1116.58 (s), 1011.48 (vs), 902.52 (s);

FD-MS: m/z (%) = 308.0 (100) [M]⁺, 309.1 (11);

Exact masse: [M+Na]⁺ calcd: 330.9802, found =330.9809.

2-(2-(Trimethylsilyl)ethynyl)-N-(2-(5-((tetrahydropyran-2-yloxy)methyl)furan-2-yl)ethynyl)-N-tosylbenzenamine 1br:



Following the general procedure for the Negishi coupling **GP7**, 919 mg (2.5 mmol) of the diyne **1ba** led after purification by column chromatography (Al_2O_3 , PE/EtOAc 95/5, $R_f=0.53$ (80/20)) to 973 mg (1.78 mmol, 77%) of the diyne **1br** as a yellow oil.

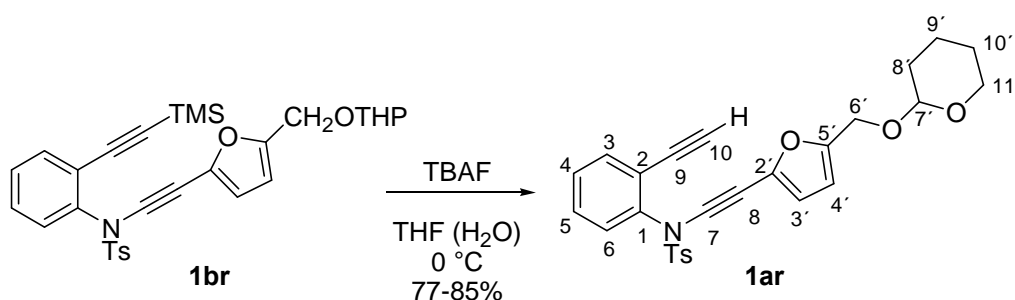
$^1\text{H NMR}$ (CDCl_3) δ ppm: 7.70 (d, $J=8.4$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.47 (m, 1H, H^3), 7.31 (m, 5H, $\text{H}^{3\text{Ts}+4^6}$), 6.54 (d, $J=3.3$ Hz, 1H, $\text{H}^{3'}$), 6.30 (d, $J=3.1$ Hz, 1H, $\text{H}^{4'}$), 4.68 (t, $J=3.3$ Hz, 1H, $\text{H}^{7'}$), 4.58 (d, $J=12.9$ Hz, 1H, $\text{H}^{6^{\text{a}}}$), 4.44 (d, $J=13.4$ Hz, 1H, $\text{H}^{6^{\text{b}}}$), 3.86 (m, 1H, $\text{H}^{11^{\text{a}}}$), 3.53 (m, 1H, $\text{H}^{11^{\text{b}}}$), 2.44 (s, 3H, $\text{H}^{5\text{Ts}}$), 1.79-1.50 (m, 6H, $\text{H}^{8'-10'}$), 0.19 (s, 9H, $\text{H}^{1''}$);

$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 153.1 (C_q , $\text{C}^{5'}$), 144.7 (C_q , $\text{C}^{4\text{Ts}}$), 138.7 (C_q , C^1), 136.6 (C_q , $\text{C}^{2'}$), 134.3 (C_q , $\text{C}^{1\text{Ts}}$), 133.6 (CH, C^3), 129.5 (CH, $\text{C}^{3\text{Ts}}$), 128.9 (CH, C^4), 128.8 (CH, C^5 or 6), 128.7 (CH, C^5 or 6), 128.1 (CH, $\text{C}^{2\text{Ts}}$), 122.5 (C_q , C^2), 117.7 (CH, $\text{C}^{3'}$), 110.2 (CH, $\text{C}^{4'}$), 101.3 (C_q , C^{10}), 99.4 (C_q , C^9), 97.0 (CH, $\text{C}^{7'}$), 85.9 (C_q , C^7), 61.5 (CH_2 , $\text{C}^{11'}$), 61.17 (C_q , C^8), 60.3 (CH_2 , $\text{C}^{6'}$), 30.0 (CH_2 , C^8), 25.1 (CH_2 , $\text{C}^{10'}$), 21.4 (CH_3 , $\text{C}^{5\text{Ts}}$), 18.8 (CH_2 , $\text{C}^{9'}$), -0.6 (CH_3 , $\text{C}^{1''}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 2951.52 (br.), 2869.56 (br.), 2227.38 (s), 2161.81 (s), 1736.58 (s), 1596.77 (s), 1482.03 (s), 1443.46(s), 1374.03 (vs), 1248.68 (s), 1172.51 (vs), 1117.55 (s), 1078.98 (s), 1017.27 (s), 842.74 (vs);

FD-MS: m/z (%) = 546.9 (100) $[\text{M}]^+$, 547.9 (32), 548.9 (15).

2-Ethynyl-N-(2-(5-((tetrahydropyran-2-yloxy)methyl)furan-2-yl)ethynyl)-N-tosylbenzenamine 1ar:



Following the general procedure for the desilylation of silylated alkynes or ynamides **GP8**, 973 mg (1.78 mmol) of the diyne **1br** led after column chromatography (Al_2O_3 , PE/EtOAc 90/10), $R_f=0.29$ (SiO_2 , 90/10)) to 647.7 mg (1.36 mmol, 77%) of the diyne **1ar** as a white solid of m.p.= 100-101 $^\circ\text{C}$

$^1\text{H NMR}$ (CDCl_3) δ ppm: 7.75 (d, $J = 8.2\text{ Hz}$, 2H, $\text{H}^{2\text{Ts}}$), 7.53 (m, 1H, H^3), 7.34 (m, 4H, $\text{H}^{3\text{Ts}+4^5}$), 7.27 (m, 1H, H^6), 6.55 (d, $J = 3.3\text{ Hz}$, 1H, $\text{H}^{3'}$), 6.30 (d, $J = 3.1\text{ Hz}$, 1H, $\text{H}^{4'}$), 4.70 (m, 1H, $\text{H}^{7'}$), 4.60 (d, $J = 12.9\text{ Hz}$, 1H, $\text{H}^{6^{\text{a}}}$), 4.47 (d, $J = 13.1\text{ Hz}$, 1H, $\text{H}^{6^{\text{b}}}$), 3.88 (m, 1H, $\text{H}^{11^{\text{a}}}$), 3.55 (m, 1H, $\text{H}^{11^{\text{b}}}$), 3.09 (s, 1H, H^{10}), 2.47 (s, 3H, $\text{H}^{5\text{Ts}}$), 1.85-1.50 (m, 6H, $\text{H}^{8^{\text{a}}-10^{\text{a}}}$);

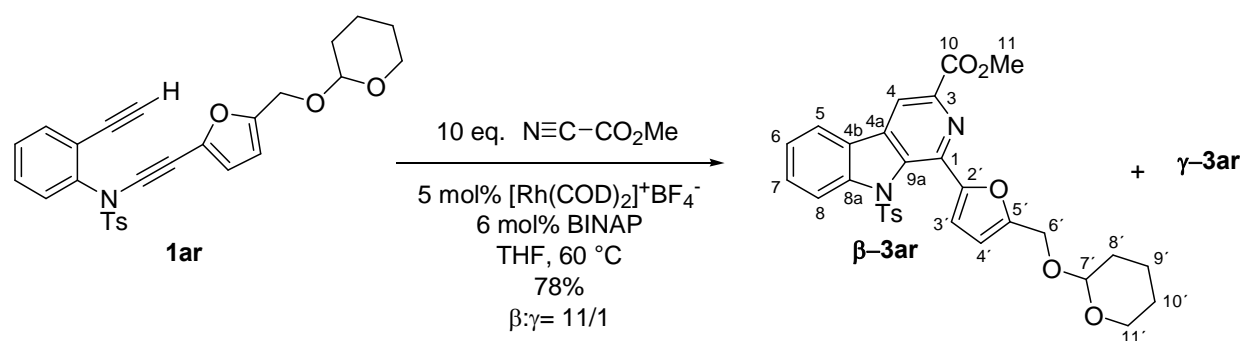
$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 159.4 (C_q , $\text{C}^{5'}$), 145.1 (C_q , $\text{C}^{4\text{Ts}}$), 139.6 (C_q , C^1), 136.8 (C_q , $\text{C}^{2'}$), 134.1 (CH, C^3), 129.7 (CH, $\text{C}^{3\text{Ts}}$), 129.6 (CH, C^5), 129.1 (CH, $\text{C}^{4\text{ or }6}$), 129.1 (CH, $\text{C}^{4\text{ or }6}$), 128.6 (CH, $\text{C}^{2\text{Ts}}$), 122.2 (C_q , C^2), 118.3 (CH, $\text{C}^{3'}$), 110.5 (CH, $\text{C}^{4'}$), 97.3 (CH, $\text{C}^{7'}$), 86.4 (C_q , C^7), 83.3 (CH, C^{10}), 78.7 (C_q , C^9), 62.0 (CH_2 , $\text{C}^{11'}$), 61.4 (C_q , C^8), 60.6 (CH_2 , $\text{C}^{6'}$), 30.3 (CH_2 , $\text{C}^{8'}$), 25.4 (CH_2 , $\text{C}^{10'}$), 21.7 (CH_3 , $\text{C}^{5\text{Ts}}$), 19.1 (CH_2 , $\text{C}^{9'}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3269.72 (vs), 2952.48 (br), 2232.20 (s), 1596.77 (s), 1541.81 (s), 1481.06 (s), 1443.46 (s), 1372.10 (vs), 1169.62 (vs), 118.51 (s), 1084.76 (s), 1013.41 (s), 721.76 (s);

FD-MS: m/z (%) = 473.2 (1) $[\text{M}]^+$, 475.2 (100), 476.2 (27), 477.2 (10), 478.2 (2);

Elemental analysis (%) for $\text{C}_{27}\text{H}_{25}\text{NO}_5\text{S}$ (475.56): C 68.19, H 5.30, N 2.95, S 6.74; found C 68.00, H 5.43, N 2.87, S 6.69

Methyl 1-(5-((tetrahydropyran-2-yl)oxy)methyl)furan-2-yl)-9-tosyl-9H-pyrido[3,4-*b*]indole-3-carboxylate β -3ar



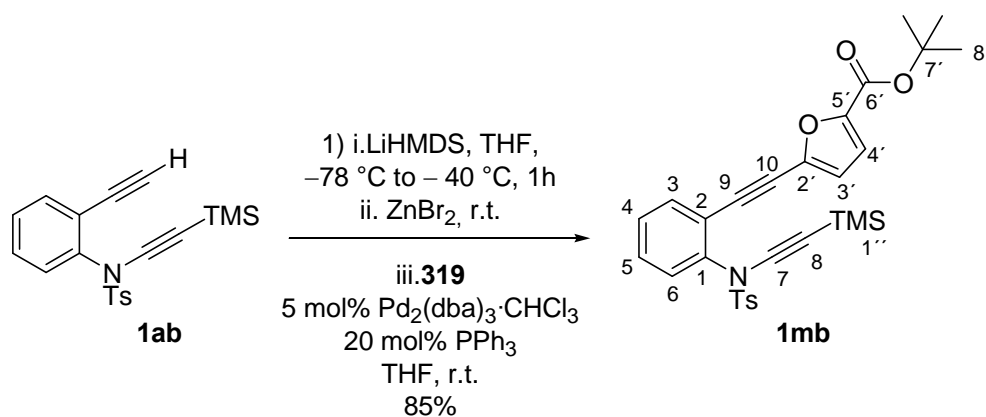
According to the general procedure **GP10**, 100.2 mg (0.21 mmol) of the diene **1ar** led after column chromatography (Al_2O_3 , PE/EtOAc 2/1, $R_f = 0.38$ (γ), 0.23 (β) (SiO_2 , 2/1)) to 93.6 mg (0.167 mmol, 78%) of a mixture of the carboline β -3ar and γ -3ar.

*¹H NMR (CDCl₃) δ ppm: 8.35 (s, 1H, H⁴), 8.18 (d, J=8.4 Hz, 1H, H⁸), 7.79 (d, J= 7.7 Hz, 1H, H⁵), 7.57 (t, J= 7.2 Hz, 1H, H⁷), 7.37 (t, J= 8.2 Hz, 1H, H⁶), 7.27 (d, J= 3.3 Hz, 1H, H^{3'}), 6.99 (d, J= 8.2 Hz, 2H, H^{2Ts}), 6.83 (d, J= 8.0 Hz, 2H, H^{3Ts}), 6.54 (d, J= 3.3 Hz, 1H, H^{4'}), 4.84 (t, J= 3.5 Hz, 1H, H^{7'}), 4.75 (d, J= 13.3 Hz, 1H, H^{6'a}), 4.69 (d, J= 13.3 Hz, 1H, H^{6'b}), 4.04 (s, 3H, H¹¹), 3.93 (m, 1H, H^{11'a}), 3.55 (m, 1H, H^{11'b}), 2.16 (s, 3H, H^{5Ts}), 1.87-1.54 (m, 6H, H^{8'}, H^{9'}, H^{10'});

*¹³C NMR (CDCl₃) δ ppm: 165.5 (C_q, C¹⁰), 153.1 (C_q, C^{5'}), 152.8 (C_q, C^{2'}), 144.8 (C_q, C^{4Ts}), 143.6 (C_q, C¹), 142.5 (C_q, C^{8a}), 141.6 (C_q, C³), 139.3 (C_q, C^{4a}), 135.0 (C_q, C^{9a}), 132.3 (C_q, C^{1Ts}), 130.3 (CH, C⁷), 128.9 (CH, C^{3Ts}), 126.8 (CH, C^{2Ts}), 126.4 (C_q, C^{4b}), 125.9 (CH, C⁶), 121.3 (CH, C⁵), 119.2 (CH, C⁸), 114.5 (CH, C⁴), 111.7 (CH, C^{3'}), 111.5 (CH, C^{4'}), 96.7 (CH, C^{7'}), 62.0 (CH₂, C^{11'}), 60.3 (CH₂, C^{6'}), 53.0 (CH₃, C¹¹), 30.3 (CH₂, C^{8'}), 25.5 (CH₂, C^{10'}), 21.4 (CH₃, C^{5Ts}), 19.1 (CH₂, C^{9'});

V.2.2.2. Total synthesis of *Isoperlolryine*

2-(2-(5-(*tert*-Butoxycarbonyl)furan-2-yl)ethynyl)-*N*-(2-(trimethylsilyl)ethynyl)-*N*-tosylbenzenamine **1mb**:



Following the general procedure for the Negishi coupling **GP5**, 920 mg (2.5 mmol) of the diyne **1ab** led after column chromatography (SiO₂, PE/EtOAc 95/5 then 90/10, R_f= 0.73 (80/20)), to 1.14 g (2.13 mmol, 85%) of the diyne **1mb** as a yellow solid of m.p. = 131-132 °C.

*¹H NMR (CDCl₃) δ ppm: 7.66 (d, J= 8.3 Hz, 2H, H^{2Ts}), 7.45 (d, J= 6.9 Hz, 1H, H³), 7.38 (m, 3H, H⁴⁻⁶), 7.20 (d, J= 8.3 Hz, 2H, H^{3Ts}), 7.02 (d, J= 3.5 Hz, 1H, H^{4'}), 6.44 (d, J= 3.5 Hz, 1H, H^{3'}), 2.26 (s, 3H, H^{5Ts}), 1.56 (s, 9H, H^{8'}), 0.07 (s, 9H, H^{1''});

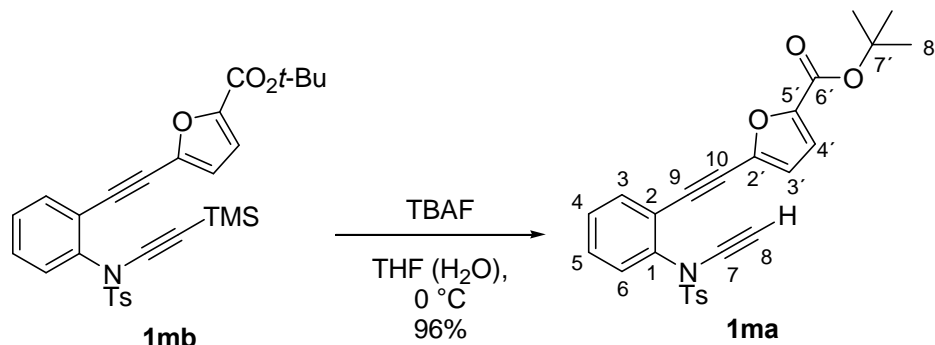
*¹³C NMR (CDCl₃) δ ppm: 157.2 (C_q, C^{6'}), 145.9 (C_q, C^{5'}), 144.9 (C_q, C⁴), 139.2 (C_q, C¹), 138.5 (C_q, C^{2'}), 134.0 (C_q, C^{1Ts}), 133.4 (CH, C³), 130.0 (CH, C⁴), 129.9 (CH, C⁶), 129.6 (CH, C^{3Ts}), 129.0 (CH, C⁵), 128.4 (CH, C^{2Ts}), 121.0 (C_q, C²), 117.7 (CH, C^{4'}), 117.1 (CH, C^{3'}), 94.0 (C_q, C⁷), 90.1 (C_q, C⁹), 84.4 (C_q, C¹⁰), 82.3 (C_q, C^{7'}), 73.4 (C_q, C⁸), 28.2 (CH₃, C^{8'}), 21.5 (CH₃, C^{5Ts}), -0.1 (CH₃, C^{1''});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2970.80 (w), 2163.74 (s), 1718.26 (vs), 1509.99 (s), 1368.25(s), 1304.61 (s), 1169.62 (s), 1131.05 (s), 837.92 (s);

FD-MS: m/z (%) = 533.0 (100) [M]⁺, 534.0 (28), 535.0 (11);

Elemental analysis (%) for C₂₉H₃₁NO₅SSi calcd: C 65.26, H 5.85, N 2.62, S 6.01; found C 65.26, H 5.89, N 2.62, S 5.72.

2-(2-(5-(*tert*-Butoxycarbonyl)furan-2-yl)ethynyl)-*N*-ethynyl-*N*-tosyl-benzenamine **1ma**



Following the general procedure for the desilylation of silylated alkynes or ynamides **GP8**, 267 mg (0.5 mmol) of the diyne **1mb** led after column chromatography (SiO₂, PE/Et₂O 2/1, R_f= 0.46 (PE/EtOAc 80/20)) to 222.1 mg (0.48 mmol, 96%) of the diyne **1ma** as a white solid of m.p.= 111-112 °C

¹H NMR (CDCl₃) δ ppm: 7.69 (d, J= 8.2 Hz, 2H, H^{2Ts}), 7.49 (d, J= 7.0 Hz, 1H, H³), 7.44 (m, 3H, H⁴⁻⁶), 7.21 (d, J= 8.2 Hz, 2H, H^{3Ts}), 7.05 (d, J= 3.5 Hz, 1H, H^{4'}), 6.54 (d, J= 3.5 Hz, 1H, H^{3'}), 2.91 (s, 1H, H⁸), 2.32 (s, 3H, H^{5Ts}), 1.61 (s, 9H, H^{8'});

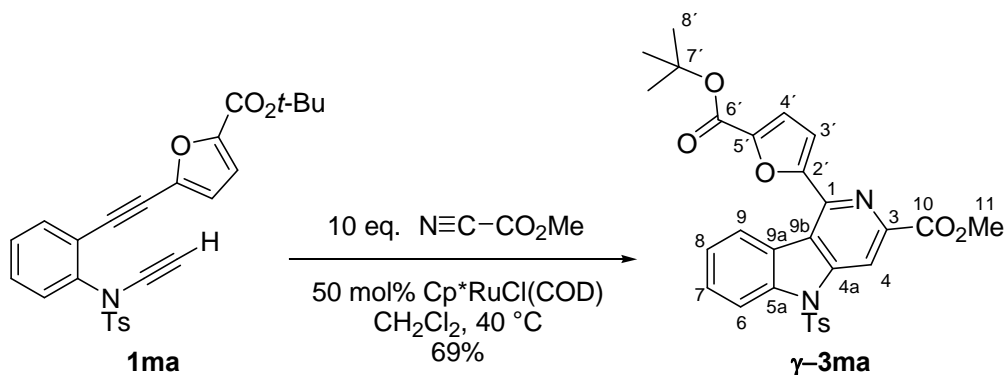
^{13}C NMR (CDCl_3) δ ppm: 157.2 (C_q , $\text{C}^{6'}$), 145.9 (C_q , $\text{C}^{5'}$), 145.1 (C_q , $\text{C}^{4\text{Ts}}$), 139.2 (C_q , C^1), 138.3 (C_q , $\text{C}^{2'}$), 133.9 (C_q , $\text{C}^{1\text{Ts}}$), 133.3 (CH , C^3), 130.1 (CH , C^4), 130.0 (CH , C^6), 129.7 (CH , $\text{C}^{3\text{Ts}}$), 129.2 (CH , C^5), 128.3 (CH , $\text{C}^{2\text{Ts}}$), 121.2 (C_q , C^2), 117.7 (CH , $\text{C}^{4'}$), 117.2 (CH , $\text{C}^{3'}$), 90.0 (C_q , C^{10}), 84.4 (C_q , C^9), 82.4 (C_q , $\text{C}^{7'}$), 75.4 (C_q , C^7), 59.3 (CH , C^8), 28.2 (CH_3 , $\text{C}^{8'}$), 21.5 (CH_3 , $\text{C}^{5\text{Ts}}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3289.00 (vs), 2988.16 (w), 2129.03 (s), 1722.12 (vs), 1516.74 (s), 1375.00 (vs), 1307.50 (s), 1173.47 (s), 1137.80 (s), 1010.52 (s), 766.57 (s);

FD-MS: m/z (%) = 461.0 (100) $[\text{M}]^+$;

Elemental analysis (%) for $\text{C}_{26}\text{H}_{23}\text{NO}_5\text{S}$ calcd: C 67.66, H 5.02, N 3.03, S 6.95; found C 67.43, H 4.92, N 3.03, S 6.78

Methyl 1-(5-(*tert*-butoxycarbonyl)furan-2-yl)-5-tosyl-5H-pyrido[4,3-*b*]indole-3-carboxylate γ -3ma



To a solution of 38 mg of $\text{Cp}^*\text{RuCl}(\text{COD})$ (0.1 mmol, 50 mol%) and methylcyanoformate (160 μL , 2 mmol, 10 equiv.) in 10 mL degazed CH_2Cl_2 at $40\text{ }^\circ\text{C}$ is added a solution 92.4 mg (0.2 mmol) of the diene **1ma** in 10 mL degazed CH_2Cl_2 over 4 hours and the reaction is heated for further 2 hours. The CH_2Cl_2 is removed and the residue purified by column chromatography (SiO_2 , PE/ CHCl_3 / EtOAc 70/20/10, $R_f = 0.33$) to give 69 mg (0.126 mmol, 69%) of the γ -carboline γ -3ma) as a white solid of m.p.: $178\text{-}179\text{ }^\circ\text{C}$ (PE/ CH_2Cl_2).

^1H NMR (CDCl_3) δ ppm: 9.05 (s, 1H, H^4), 8.99 (d, $J = 7.8$ Hz, 1H, H^9), 8.43 (d, $J = 8.4$ Hz, 1H, H^6), 7.74 (d, $J = 8.4$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.63 (td, $J = 7.8$ Hz, $J = 1.2$ Hz, 1H, H^7), 7.49 (td, $J = 7.8$ Hz,

$J = 1.0$ Hz, 1H, H^8), 7.45 (d, $J = 3.6$ Hz, 1H, $H^{4'}$), 7.31 (d, $J = 3.6$ Hz, 1H, $H^{3'}$), 7.15 (d, $J = 8.1$ Hz, 2H, H^{3Ts}), 4.08 (s, 3H, H^{11}), 2.28 (s, 3H, H^{5Ts}), 1.64 (s, 9H, $H^{8'}$);

^{13}C NMR ($CDCl_3$) δ ppm: 165.5 (C_q , C^{10}), 157.9 (C_q , $C^{6'}$), 155.5 (C_q , $C^{2'}$), 146.4 (C_q , $C^{5'}$), 146.0 (C_q , C^{4Ts}), 145.6 (C_q , C^3), 144.6 (C_q , C^1), 142.7 (C_q , C^{4a}), 139.5 (C_q , C^{5a}), 134.3 (C_q , C^{1Ts}), 130.1 (CH, C^{3Ts}), 129.6 (CH, C^7), 126.7 (CH, C^{2Ts}), 125.5 (CH, C^9), 125.0 (CH, C^8), 122.9 (C_q , C^{9a}), 121.3 (C_q , C^{9b}), 119.1 (CH, $C^{4'}$), 114.4 (CH, C^6), 114.3 (CH, $C^{3'}$), 110.6 (CH, C^4), 82.4 (C_q , $C^{7'}$), 53.1 (CH_3 , C^{11}), 28.4 (CH_3 , $C^{8'}$), 21.6 (CH_3 , C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3144.37 (w), 2966.95 (w), 1743.33 (vs), 1714.41 (vs), 1597.73 (w), 1453.10 (w), 1361.50 (w), 1304.61 (s), 1265.07 (s), 1233.25 (s), 1159.01 (vs), 1134.90 (s), 1014.37 (s), 943.9 ((w), 742.5 (s), 667.25 (s);

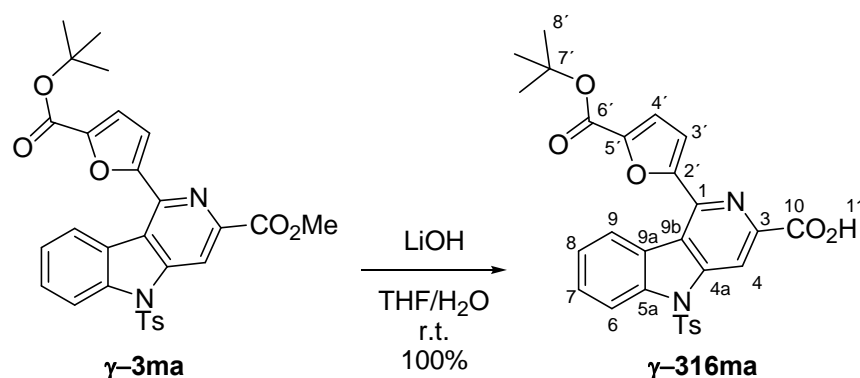
FD-MS: m/z (%) = 546.0 (100) $[M]^+$, 547.0 (31), 548.0 (10), 549.0 (2);

Elemental analysis (%) for $C_{29}H_{26}N_2O_7S$ calcd: C 63.72, H 4.79, N 5.13; found C 64.27, H 5.40, N 5.03.

Exact masse: $[M+Na]^+$ calcd: 569.1353; found 569.1373.

1-(5-(*tert*-Butoxycarbonyl)furan-2-yl)-5-tosyl-5H-pyrido[4,3-*b*]indole-3-carboxylic acid

γ -316ma



To a solution of 171 mg (0.31 mmol) of the methyl ester β -3ma in 15 mL of THF/ H_2O (2/1) are added 22.5 mg (0.93 mmol, 3 equiv.) of LiOH. The solution is stirred 1 hour and then acidified to pH 1-2 with 5 mL of HCl 1N. 20 mL of CH_2Cl_2 and 20 mL of H_2O are added, the layers separated and the aqueous layer is extracted three times with 10 mL of CH_2Cl_2 . The

combined organic layers are washed with 20 mL of brine, dried over MgSO_4 , filtered and the solvent removed *in vacuo* to give the acid as a white solid of mp = 170-171 °C (decomposition)

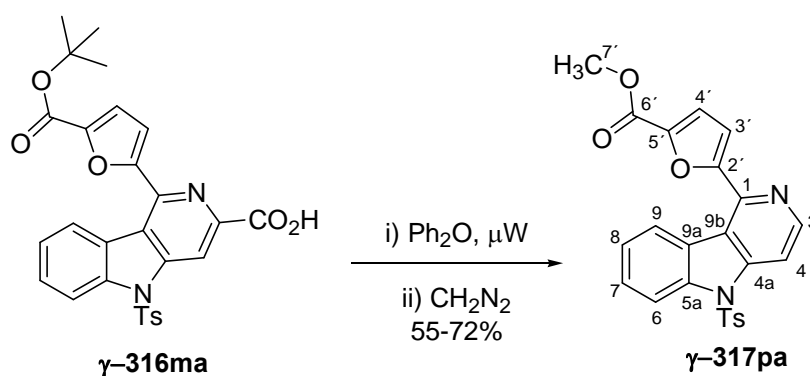
$^1\text{H NMR}$ (CDCl_3) δ ppm: 9.16 (s, 1H, H^4), 9.01 (d, $J = 8.3$ Hz, 1H, H^9), 8.48 (d, $J = 8.4$ Hz, 1H, H^6), 7.80 (d, $J = 8.4$ Hz, 2H, $\text{H}^{2\text{Ts}}$), 7.69 (t, $J = 7.4$ Hz, 1H, H^7), 7.52 (t, $J = 7.6$ Hz, 1H, H^8), 7.35 (d, $J = 3.4$ Hz, 1H, $\text{H}^{4'}$), 7.32 (d, $J = 3.4$ Hz, 1H, $\text{H}^{3'}$), 7.19 (d, $J = 8.4$ Hz, 2H, $\text{H}^{3\text{Ts}}$), 2.31 (s, 3H, $\text{H}^{5\text{Ts}}$), 1.65 (s, 9H, H^8);

$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 164.1 (C_q , C^{10}), 157.5 (C_q , $\text{C}^{6'}$), 154.2 (C_q , $\text{C}^{2'}$), 146.7 (C_q , C^3), 146.1 (C_q , $\text{C}^{4\text{Ts}}$ or $5'$), 146.0 (C_q , $\text{C}^{4\text{Ts}}$ or $5'$), 142.5 (C_q , C^1), 141.1 (C_q , C^{4a}), 139.4 (C_q , C^{5a}), 134.1 (C_q , $\text{C}^{1\text{Ts}}$), 130.1 (CH, $\text{C}^{3\text{Ts}}$), 130.0 (CH, C^7), 126.6 (CH, $\text{C}^{2\text{Ts}}$), 125.4 (CH, C^9), 125.0 (CH, C^8), 122.2 (C_q , C^{9a}), 121.6 (C_q , C^{9b}), 118.8 (CH, $\text{C}^{4'}$), 114.3 (CH, C^6), 114.2 (CH, $\text{C}^{3'}$), 108.8 (CH, C^4), 82.7 (C_q , C^7), 28.2 (CH_3 , $\text{C}^{8'}$), 21.5 (CH_3 , $\text{C}^{5\text{Ts}}$);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3144.37 (w, br.), 2977.55 (w), 1764.55 (vs), 1703.80 (vs), 1587.13 (w), 1431.89 (w), 1361.50 (s), 1300.75 (vs), 1166.72 (s), 1134.90 (vs), 1021.12 (s), 961.34 (s), 745.35 (s);

FD-MS: m/z (%) = 531.8 (100) $[\text{M}]^+$, 532.8 (32), 533.8 (12), 534.8 (2);

1-(5-(Methoxycarbonyl)furan-2-yl)-5-tosyl-5H-pyrido[4,3-*b*]indole γ -317pa



A solution of 83.3 mg (0.156 mmol) of the acid γ -316ma in 5 mL of Ph_2O is heated to 240 °C for 3 minutes (300W) in a microwave reactor. The cooled solution is diluted with 10 mL of methanol and a freshly prepared solution of diazomethane in Et_2O (prepared from *N*-methyl-*N*-nitroso-urea and a 40% KOH solution^[117]) is added slowly at 0 °C. The mixture is let warm to

room temperature and stirred overnight. The reaction is then quenched by addition of AcOH. The solvent are removed, the residue dissolved with 20 mL of EtOAc and 20 mL of H₂O. The aqueous layer is extracted 3 times with 20 mL of EtOAc and the combined organic extracts washed twice with 30 mL of saturated NaHCO₃ and once with 30 mL of brine, dried over MgSO₄, filtered and the solvent removed in vacuo. The crude product is purified by column chromatography (SiO₂, PE/EtOAc 2/1, R_f = 0.46), to give 50.5 mg (0.113 mmol, 72%) of the methyl ester **γ-317pa** as a white solid of mp: 193-194 °C (PE/CH₂Cl₂) together with 4.6 mg (0.016, 10%) of the detosylated product **γ-320pa**

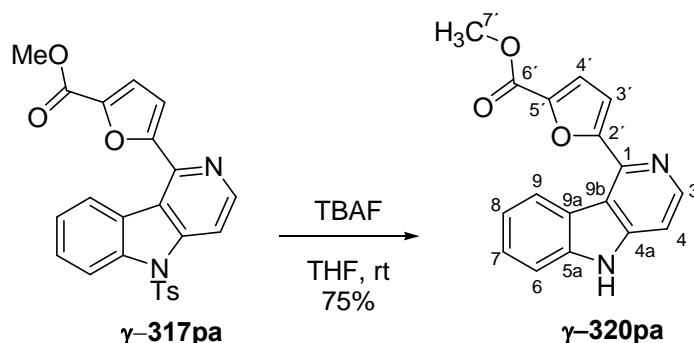
*¹H NMR (CDCl₃) δ ppm: 8.79 (d, J = 8.1 Hz, 1H, H⁹), 8.66 (d, J = 5.6 Hz, 1H, H³), 8.40 (d, J = 8.5 Hz, 1H, H⁶), 8.31 (d, J = 5.6 Hz, 1H, H⁴), 7.73 (d, J = 8.3 Hz, 2H, H^{2Ts}), 7.59 (t, J = 7.6 Hz, 1H, H⁷), 7.45 (t, J = 7.7 Hz, 1H, H⁸), 7.38 (d, J = 3.6 Hz, 1H, H^{4'}), 7.30 (d, J = 3.6 Hz, 1H, H^{3'}), 7.15 (d, J = 8.2 Hz, 2H, H^{3Ts}), 3.97 (s, 3H, H^{7'}), 2.30 (s, 3H, H^{5Ts});

*¹³C NMR (CDCl₃) δ ppm: 159.0 (C_q, C^{6'}), 156.8 (C_q, C^{2'}), 146.3 (CH, C³), 145.7 (C_q, C^{4Ts}), 145.1 (C_q, C^{4a}), 144.5 (C_q, C^{5'}), 142.74 (C_q, C¹), 138.43 (C_q, C^{5a}), 134.5 (C_q, C^{1Ts}), 130.0 (CH, C^{3Ts}), 128.8 (CH, C⁷), 126.6 (CH, C^{2Ts}), 124.7 (2xCH, C⁹ and C⁸), 123.4 (C_q, C^{9a}), 119.7 (CH, C^{4'}), 119.6 (C_q, C^{9b}), 114.3 (CH, C⁶), 113.1 (CH, C^{3'}), 109.4 (CH, C⁴), 52.1 (CH₃, C^{7'}), 21.5 (CH₃, C^{5Ts});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3136.65 (w), 3045.05 (w), 2966.95 (w), 1725.01 (vs, C=O), 1431.89 (s), 1382.71 (s), 1300.75 (s), 1177.33 (s), 1156.12 (s), 1021.12 (s), 742.46 (s);

FD-MS: m/z (%) = 445.8 (100) [M]⁺, 446.8 (26), 448.8 (2);

Elemental analysis (%) for C₂₄H₁₈N₂O₅S calcd: C 64.56, H 4.06, N 6.27; found C 64.52, H 4.07, N 6.28.

1-(5-(methoxycarbonyl)furan-2-yl)-5H-pyrido[4,3-*b*]indole γ -320pa

To a solution of 40.9 mg (0.092 mmol) of the tosylated carboline γ -317pa in 10 mL of THF are added 640 μ L of a TBAF solution (1.0M in THF, 0.64 mmol, 7 eq.) and the reaction let stirred at room temperature. After completion of the reaction (TLC), 10 mL of EtOAc and 10 mL of H₂O are added. The aqueous layer is extracted three times with 10 mL of EtOAc and the combined organic layers are washed with 20 mL of brine. The organic phase is dried over MgSO₄, filtered and the solvent removed *in vacuo*. The crude product is purified by column chromatography (SiO₂, PE/ EtOAc 1/1, R_f = 0.12 (2/1)) to give 20.2 mg (0.069 mmol, 75 %) of γ -320pa as a yellow solid of m.p. = 225-226 °C (decomposition)

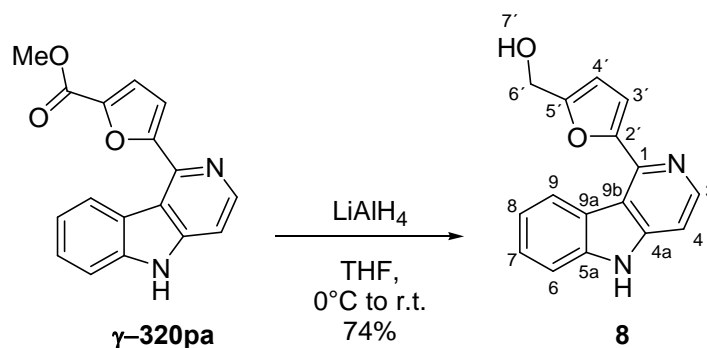
*¹H NMR (CDCl₃) δ ppm: 12.07 (s, 1H, H⁵), 9.08 (d, J = 8.2 Hz, 1H, H⁹), 8.50 (d, J = 5.5 Hz, 1H, H³), 7.57 (m, 4H, H^{4,6,7} and 4'), 7.40 (d, J = 3.6 Hz, 1H, H^{3'}), 7.30 (t, J = 7.9 Hz, 1H, H⁸), 3.94 (s, 3H, H^{7'});

*¹³C NMR (CDCl₃) δ ppm: 158.5 (C_q, C^{6'}), 157.7 (C_q, C^{2'}), 145.4 (C_q, C¹), 143.9 (CH, C³), 143.6 (C_q, C^{5'}), 141.3 (C_q, C^{4a}), 140.2 (C_q, C^{5a}), 127.2 (CH, C⁷), 124.5 (CH, C⁹), 120.2 (CH, C⁸), 120.0 (CH, C^{4'}), 119.7 (C_q, C^{9a}), 115.4 (C_q, C^{9b}), 112.3 (CH, C^{3'}), 111.3 (CH, C⁶), 106.5 (CH, C⁴), 52.1 (CH₃, C^{7'});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3331.43 (vs), 2928.38 (w), 1690.30 (vs), 1605.45 (s), 1559.17 (s), 1435.74 (s), 1319.07 (s), 1258.32 (s), 1028.84 (s), 742.46 (s);

FD-MS: m/z (%) = 291.8 (100) [M]⁺, 292.8 (29), 293.8 (1);

Exact masse: [M+H]⁺ calcd: 293.0921; found 293.0937.

1-(5-(hydroxymethyl)furan-2-yl)-5H-pyrido[4,3-*b*]indole (*Isoperlolryrine*) **8**

To a solution of 30.2 mg (0.103 mmol) of the methyl ester γ -**320pa** in 10 mL THF at 0 °C was slowly added a suspension of 23.4 mg of LiAlH₄ (0.62 mmol, 6 eq.) in 5 mL THF and the mixture was let warm to room temperature. After completion of the reaction (TLC), the reaction is quenched by addition of 1 mL of HCl 1N followed by 10 mL H₂O and 10 mL of EtOAc. The layers are separated and the aqueous layer is extracted three times with 10 mL of EtOAc. The combined organic layers are washed with 20 mL of brine, dried over MgSO₄, filtered and the solvent removed *in vacuo* to give 20.3 g (0.077 mmol, 74%) of **8** as a yellow solid of m.p.= 240-241 °C (decomposition) (lit.^[36]: 186 °C (decomposition)).

¹H NMR (CDCl₃) δ ppm: 11.94 (s, 1H, H⁵), 8.76 (d, J= 8.2 Hz, 1H, H⁹), 8.42 (d, J= 5.5 Hz, 1H, H³), 7.57 (d, J= 8.0 Hz, 1H, H⁶), 7.49 (t, J= 7.3 Hz, 1H, H⁷), 7.43 (d, J= 5.5 Hz, 1H, H⁴), 7.24 (t, J= 7.3 Hz, 1H, H⁸), 7.14 (d, J= 3.3 Hz, 1H, H^{3'}), 6.60 (d, J= 3.3 Hz, 1H, H^{4'}), 5.50 (s, 1H, H^{7'}), 4.64 (d, J= 3.3 Hz, 2H, H^{6'});

¹³C NMR (CDCl₃) δ ppm: 156.1 (C_q, C^{5'}), 153.5 (C_q, C^{2'}), 145.3 (C_q, C^{4a}), 143.8 (CH, C³), 143.1 (C_q, C¹), 140.0 (C_q, C^{5a}), 126.6 (CH, C⁷), 124.1 (CH, C⁹), 120.2 (C_q, C^{9a}), 120.0 (CH, C⁸), 114.7 (C_q, C^{9b}), 111.2 (CH, C^{3'}), 111.1 (CH, C⁶), 109.3 (CH, C^{4'}), 105.2 (CH, C⁴), 55.9 (CH₂, C^{6'});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3161.72 (br.), 2782.78 (br.), 2695.03 (br.), 1605.45 (vs), 1470.46 (s), 1205.29 (vs), 1014.37 (vs), 738.60 (s);

FD-MS: m/z (%) = 155.9 (100) [DMSO]₂, 263.8 (83) [M]⁺, 264.8 (14);

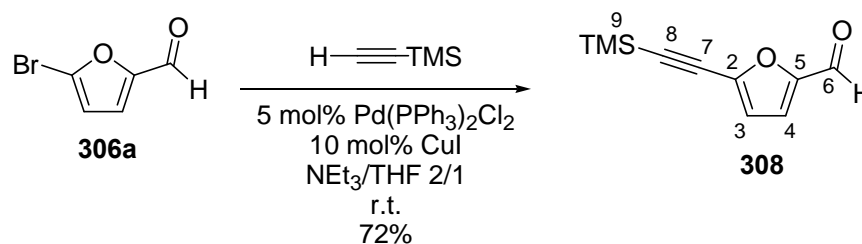
Exact masse: [M+H]⁺ calcd: 265.0972; found 265.0983.

UV-Vis (EtOH): $\lambda_{\max 1} = 318$ nm, $\epsilon_1 = 10174$ cm²/mmol; $\lambda_{\max 2} = 264$ nm, $\epsilon_2 = 28541$ cm²/mmol

Fluorescence (EtOH) : $\lambda_{\max} = 393$ nm.

- Other compounds

5-(Trimethylsilylethynyl)-2-furaldehyde **308**



In a dried Schlenk under N₂ are placed 1.75 g of the 5-bromo-2-furaldehyde **306a** (10.0 mmol), PdCl₂(PPh₃)₂ (351 mg, 0.5 mmol, 5 mol%), CuI (190 mg, 1.0 mmol, 10 mol%), 80 mL NEt₃ and 40 mL THF. Trimethylsilylacetylene (1.95 mL, 14.0 mmol, 1.4 equiv.) is then added dropwise. The mixture is stirred at room temperature overnight. The solvent is removed, the residue dissolved with 100 mL of CH₂Cl₂ and 100 mL water and filtered over a pad of celite. The aqueous layer is extracted twice with 50 mL CH₂Cl₂. The combined organic layers are washed with 50 mL brine, dried over MgSO₄, filtered on celite and the solvent is evaporated. The crude product is purified by column chromatography (SiO₂, PE/EtOAc 95/5, R_f = 0.49 (PE/EtOAc 90/10)) to give 1.38 g (7.2 mmol, 72%) as a yellow oil which crystallize upon standing. (m.p. = 60-61 °C)

¹H NMR (CDCl₃) δ ppm: 9.61 (s, 1H, H⁶), 7.21 (d, J = 3.7 Hz, 1H, H⁴), 6.71 (d, J = 3.7 Hz, 1H, H³), 0.27 (s, 9H, H⁹);

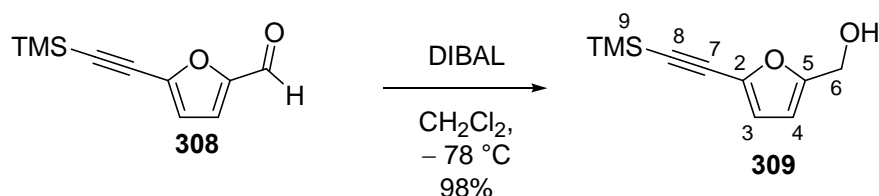
¹³C NMR (CDCl₃) δ ppm: 177.3 (CH, C⁶), 152.2 (C_q, C⁵), 141.5 (C_q, C²), 120.8 (CH, C⁴), 117.3 (CH, C³), 103.8 (C_q, C⁷), 92.8 (C_q, C⁸), 0.6 (CH₃, C⁹);

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 2964.05 (w), 2853.17 (w), 2157.95 (m), 1664.27 (vs), 1495.53 (s), 1384.64 (m), 1254.47 (s), 1194.69 (m), 1023.05 (s), 836.96 (s), 836.96 (vs), 757.89 (m), 716.43 (s);

FD-MS: m/z (%) = 192.3 (100) $[M]^+$, 193.4 (17), 194.3 (4);

Elemental analysis (%) for $C_{10}H_{12}O_2Si$ (322.31): C 62.46, H 6.29; found C 62.23, H 6.35.

5-(Trimethylsilylethynyl)-2-hydroxymethylfuran **309**



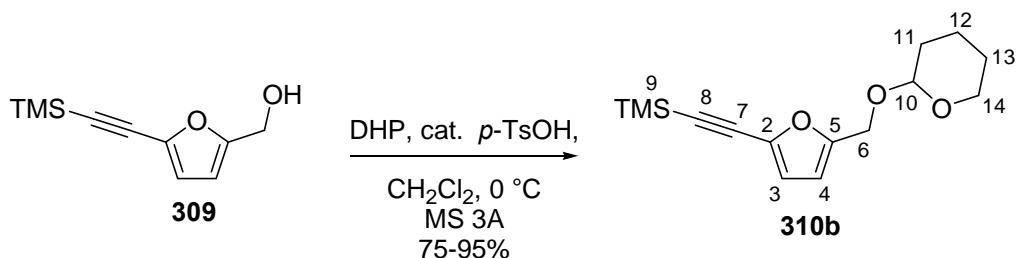
To a solution of the aldehyde **308** (1.923 g, 10 mmol) dissolved in 50 ml of CH_2Cl_2 and cooled to -78°C under N_2 is added dropwise 8 mL of a solution of DIBAL in toluene (12 mmol, 25% w/w in toluene, 1.2 equiv.). The resulting mixture is stirred at -78°C for 2 hours and conversion of the starting material is checked by TLC. Then 10 mL of a mixture of CH_2Cl_2 /Methanol 1:1 is added slowly with cooling to 0°C , followed by 10 mL of a 1N HCl solution and the resulting mixture is stirred 30 min at 0°C . The solid aluminium salts are filtered, the organic layer was separated, the aqueous layer was extracted 2 times with 20 mL of CH_2Cl_2 and the combined organic layers are dried over MgSO_4 , filtered and concentrated. The crude product is purified by column chromatography (SiO_2 , PE/EtOAc 80/20, $R_f = 0.35$) to give 1.87 g (9.8 mmol, 98%) of **309** as a white solid of m.p. = $29-30^\circ\text{C}$.

^1H NMR (CDCl_3) δ ppm: 6.56 (d, $J = 3.3$ Hz, 1H, H^3), 6.27 (d, $J = 3.3$ Hz, 1H, H^4), 4.58 (d, $J = 6.1$ Hz, 2H, H^6), 1.85 (t, $J = 6.3$ Hz, 1H, H^7), 0.25 (s, 9H, H^9);

^{13}C NMR (CDCl_3) δ ppm: 155.0 (C_q , C^5), 136.9 (C_q , C^2), 116.5 (CH, C^3), 108.7 (CH, C^4), 99.9 (C_q , C^7), 94.0 (C_q , C^8), 57.5 (CH_2 , C^6), -0.3 (CH_3 , C^9);

IR (neat, ATR) $\tilde{\nu}$ (cm^{-1}): 3259.11 (vs, br.), 2956.34 (m), 2898.49 (m), 2154.10 (vs), 1526.38 (w), 1365.35 (m), 1248.68 (vs), 1204.33 (m), 1010.52 (vs), 936.27 (m), 830.21 (vs), 791.64 (s), 755.96 (s), 724.14 (m);

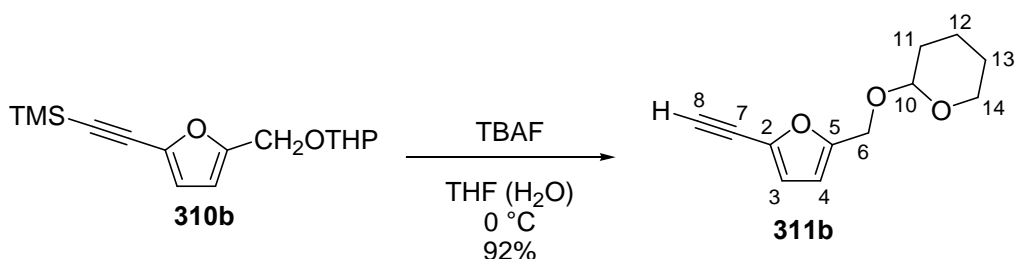
FD-MS: m/z (%) = 194.1 (100) $[M]^+$.

5-(Trimethylsilylethynyl)-2-((tetrahydropyranyloxy)methyl)furane **310b**

To a solution of 1.55g the alcohol **309** (8 mmol) in 40 mL of CH_2Cl_2 with few beads of molecular sieves (3Å) is added dropwise 880 μL of 3,4-Dihydropyran (9.6 mmol, 1.2 equiv.), followed by 304 mg of $p\text{-TsOH}\cdot\text{H}_2\text{O}$ (1.6 mmol, 20 mol%) and the resulting mixture is stirred at 0 °C under N_2 until completion of the reaction (followed by TLC). Then 20 mL distilled water are added. The aqueous layer is extracted 3 times by 10 ml CH_2Cl_2 . The combined organic layers are dried over MgSO_4 and filtered. After evaporation of the solvent, the crude product is purified by a column chromatography (Al_2O_3 , PE/EtOAc 98/2, $R_f=0.87$ (8/2)) to give 1.78g (6.4 mmol, 80%) of **310b** as a colorless oil.

$^1\text{H NMR}$ (CDCl_3) δ ppm: 6.56 (d, $J=3.3$ Hz, 1H, H^3), 6.29 (d, $J=3.3$ Hz, 1H, H^4), 4.70 (t, $J=3.5$ Hz, 1H, H^{10}), 4.63 (d, $J=13.0$ Hz, 1H, H^6), 4.45 (d, $J=13.0$ Hz, 1H, H^6), 3.88 (m, 1H, H^{14a}), 3.55 (m, 1H, H^{14b}), 1.83-1.52 (m, 6H, H^{11-13}), 0.24 (s, 9H, H^9);

$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 152.9 (C_q , C^5), 137.0 (C_q , C^2), 116.5 (CH, C^3), 110.2 (CH, C^4), 99.6 (C_q , C^7), 97.4 (CH, C^{10}), 94.3 (C_q , C^8), 61.9 (CH_2 , C^{14}), 60.6 (CH_2 , C^6), 30.3 (CH_2 , C^{11}), 25.3 (CH_2 , C^{13}), 19.1 (CH_2 , C^{12}), -0.3 (CH_3 , C^9).

2-Ethynyl-5-((tetrahydropyran-2-yloxy)methyl)furane **311b**

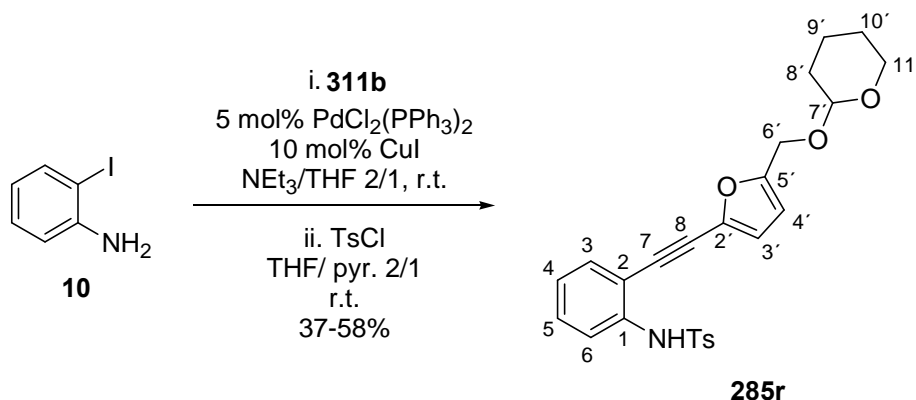
To a solution of the alkyne **310b** (1.26 g, 4.53 mmol) in 20 mL THF and two drops of distilled water is added dropwise at 0 °C 5.88 mL of a 1M THF solution of TBAF (1.2 equiv.). The solution is stirred 20 min at 0°C. After completion of the reaction, the reaction is quenched by addition of 20 mL EtOAc and 20 mL brine. The aqueous layer is extracted twice with 20 mL of

EtOAc. The combined organic layers are dried over MgSO_4 , filtered and the solvent is evaporated. The crude product is purified by a column chromatography (Al_2O_3 , PE/EtOAc 95/5, $R_f=0.64$ (9/1)) to give 859 mg (4.16 mmol, 92%) of **311b** as a pale yellow oil.

$^1\text{H NMR}$ (CDCl_3) δ ppm: 6.60 (d, $J=3.3\text{Hz}$, 1H, H^3), 6.32 (d, $J=3.3\text{Hz}$, 1H, H^4), 4.72 (t, $J=3.3\text{Hz}$, 1H, H^{10}), 4.62 (d, $J=13.0\text{ Hz}$, 1H, H^{6a}), 4.46 (d, $J=13.0\text{ Hz}$, 1H, H^{6b}), 3.89 (m, 1H, H^{6a}), 3.56 (m, 1H, H^{6b}), 3.39 (s, 1H, H^8), 1.81-1.55 (m, 6H, H^{11-14});

$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 153.2 (C_q , C^5), 136.1 (C_q , C^2), 116.9 (CH, C^3), 110.0 (CH, C^4), 97.4 (CH, C^{10}), 81.8 (CH, C^8), 73.9 (C_q , C^7), 61.9 (CH_2 , C^{14}), 60.5 (CH_2 , C^6), 30.2 (CH_2 , C^{11}), 25.3 (CH_2 , C^{13}), 19.0 (CH_2 , C^{12}).

2-(2-(5-((Tetrahydropyran-2-yloxy)methyl)furan-2-yl)ethynyl)-*N*-tosylbenzenamine **285r**



Following the general procedure for the synthesis of sulfonamides **GP2**, 669 mg (3 mmol) of the 2-iodoaniline **10** led after column chromatography (Al_2O_3 , PE/ Et_2O 80/20, $R_f=0.58$ (7/3)), to 568 mg (1.26 mmol, 42%) of the sulfonamide **285r** as a pale orange solid of m.p: 91-92 °C.

$^1\text{H NMR}$ (CDCl_3) δ ppm: 7.67 (d, $J=8.4\text{ Hz}$, 2H, $\text{H}^{2\text{Ts}}$), 7.60 (d, $J=7.6\text{ Hz}$, 1H, H^3), 7.33 (m, 2H, H^{4-5}), 7.17 (d, $J=8.4\text{ Hz}$, 2H, $\text{H}^{3\text{Ts}}$), 7.06 (td, $J=1.2\text{ Hz}$, $J=7.6\text{ Hz}$, 1H, H^6), 6.62 (d, $J=3.5\text{ Hz}$, 1H, $\text{H}^{3'}$), 6.40 (d, $J=3.5\text{ Hz}$, 1H, $\text{H}^{4'}$), 4.77 (t, $J=3.5\text{ Hz}$, 1H, $\text{H}^{7'}$), 4.70 (d, $J=13.1\text{ Hz}$, 1H, $\text{H}^{6'a}$), 4.52 (d, $J=13.1\text{ Hz}$, 1H, $\text{H}^{6'b}$), 3.92 (m, 1H, $\text{H}^{11'a}$), 3.60 (m, 1H, $\text{H}^{11'b}$), 2.33 (s, 3H, $\text{H}^{5\text{Ts}}$), 1.87-1.56 (m, 6H, $\text{H}^{8'-10'}$);

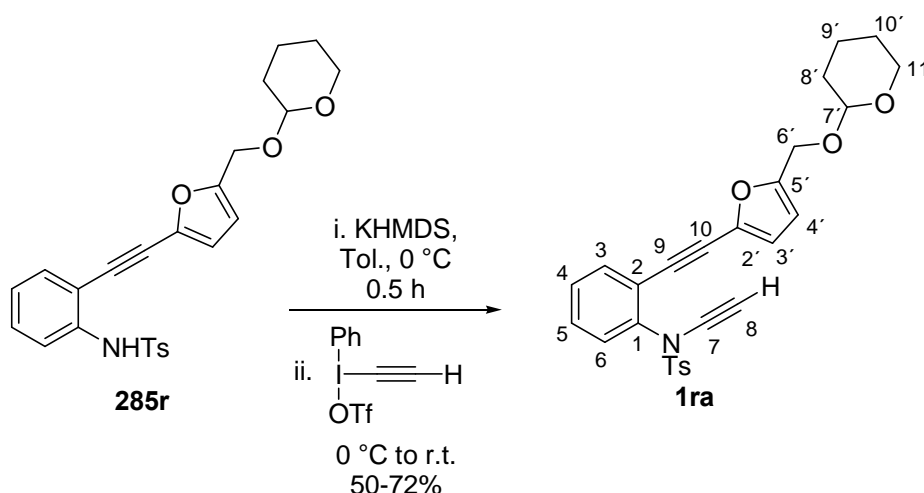
$^{13}\text{C NMR}$ (CDCl_3) δ ppm: 153.8 (C_q , $\text{C}^{5'}$), 143.9 (C_q , $\text{C}^{4\text{Ts}}$), 137.4 (C_q , C^1), 135.8 ($2\times\text{C}_q$, $\text{C}^{1\text{Ts}+2'}$), 131.9 (CH, C^3), 130.0 (CH, C^5), 129.5 (CH, $\text{C}^{3\text{Ts}}$), 127.2 (CH, $\text{C}^{2\text{Ts}}$), 124.7 (CH, C^4), 120.9 (CH, C^6), 117.0 (CH, C^3), 113.9 (C_q , C^2), 110.4 (CH, C^4), 97.5 (CH, $\text{C}^{7'}$), 87.8 (C_q , C^7),

85.8 (C_q, C⁸), 61.9 (CH₂, C^{11'}), 60.5 (CH₂, C^{6'}), 30.2 (CH₂, C^{8'}), 25.2 (CH₂, C^{10'}), 21.4 (CH₃, C^{5Ts}), 19.0 (CH₂, C^{9'});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3654.44 (s), 2946.70 (m, br.), 2216.77 (w), 1594.84 (w), 1480.10 (m), 1397.17 (m), 1333.53 (vs), 1163.83 (vs), 1112.73 (m), 1017.27 (s), 974.84 (w), 903.49 (m), 809.96 (s), 761.74 (m), 680.75 (m);

FD-MS: m/z (%) = 451.2 (100) [M]⁺, 452.2 (28), 453.2 (8), 454.2 (2), 455.2 (1);

2-(2-(5-((Tetrahydropyran-2-yloxy)methyl)furan-2-yl)ethynyl)-N-ethynyl-N-tosylbenzenamine 1ra



Following the general procedure for the *N*-alkynylation of sulfonamides **GP3**, 90.3 mg (0.2 mmol) of the sulfonamide **285r** led after column chromatography (Al₂O₃, PE/Et₂O 80/20, R_f= 0.58 (7/3)) to 68.6 mg (0.144 mmol, 72%) of the diyne **1ra** as a colourless oil.

¹H NMR (CDCl₃) δ ppm: 7.69 (d, J=8.2Hz, 2H, H^{2Ts}), 7.46 (m, 1H, H⁶), 7.41 (m, 1H, H³), 7.37 (m, 2H, H⁴⁺⁵), 7.20 (d, J= 8.6Hz, 2H, H^{3Ts}), 6.47 (d, J= 3.3 Hz, 1H, H^{3'}), 6.34 (d, J=3.3Hz, 1H, H^{4'}), 4.76 (t, J= 3.5Hz, 1H, H^{7'}), 4.66 (d, J= 13.0 Hz, 1H, H^{6'a}), 4.49 (d, J= 13.0Hz, 1H, H^{6'b}), 3.92 (m, 1H, H^{11'a}), 3.59 (m, 1H, H^{11'b}), 2.89 (s, 1H, H⁸), 2.32 (s, 3H, H^{5Ts}), 1.85-1.55 (m, 6H, H^{8'-10'});

¹³C NMR (CDCl₃) δ ppm: 153.3 (C_q, C^{5'}), 145.0 (C_q, C^{4Ts}), 137.9 (C_q, C^{2'}), 136.7 (C_q, C¹), 134.1 (C_q, C^{1Ts}), 133.0 (CH, C³), 129.9 (CH, C⁵), 129.6 (CH, C^{3Ts}), 129.4 (CH, C⁴), 129.1 (CH, C⁶), 128.3 (CH, C^{2Ts}), 121.9 (C_q, C²), 116.9 (CH, C^{3'}), 110.4 (CH, C^{4'}), 97.5 (CH, C^{7'}),

88.8 (C_q, C⁹), 85.4 (C_q, C¹⁰), 75.6 (C_q, C⁷), 62.0 (CH₂, C^{11'}), 60.6 (CH₂, C^{6'}), 59.1 (CH, C⁸), 30.3 (CH₂, C^{8'}), 25.3 (CH₂, C^{10'}), 21.5 (CH₃, C^{5Ts}), 19.1 (CH₂, C^{9'});

IR (neat, ATR) $\tilde{\nu}$ (cm⁻¹): 3654.44 (s), 2946.70 (m, br.), 2216.77 (w), 1594.84 (w), 1480.10 (m), 1397.17 (m), 1333.53 (vs), 1163.83 (vs), 1112.73 (m), 1017.27 (s), 974.84 (w), 903.49 (m), 809.96 (s), 761.74 (m), 680.75 (m).

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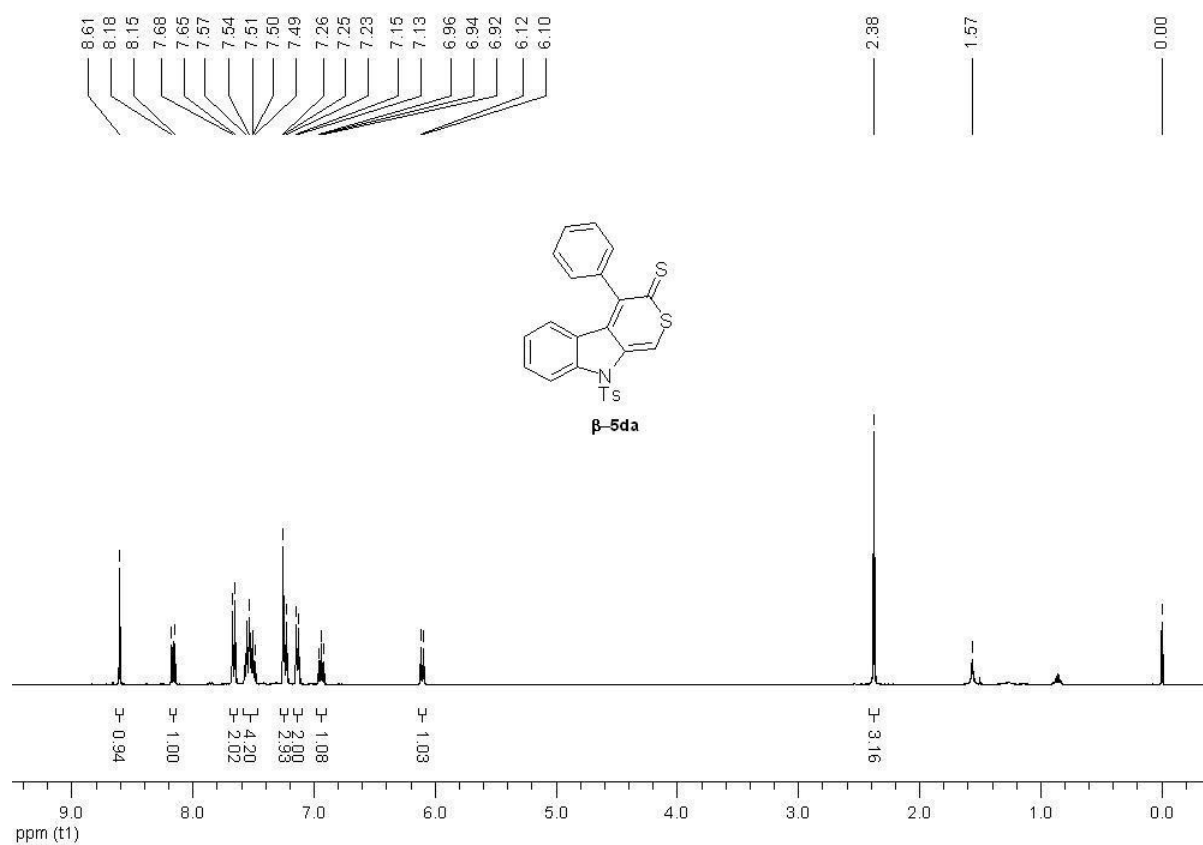
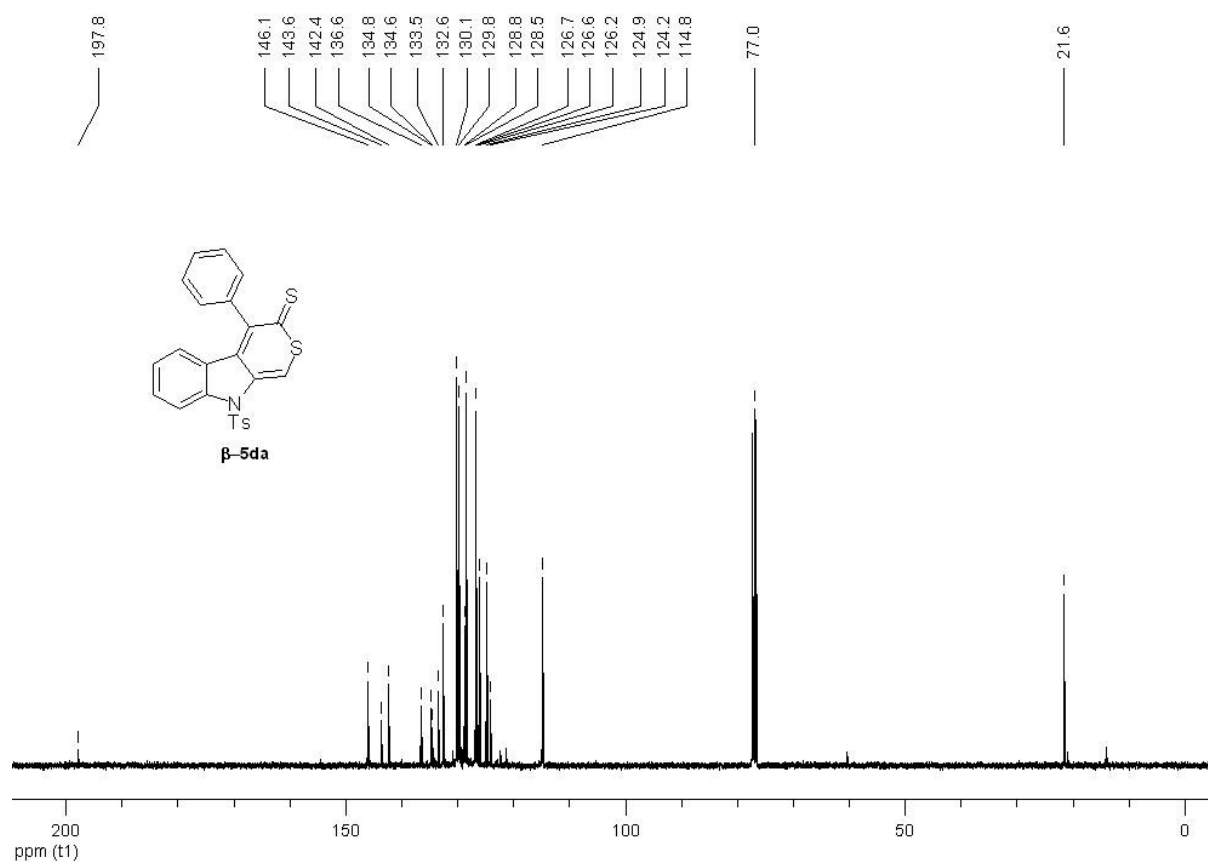
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VII / APPENDIX**VII.1. Abbreviations and acronyms**

Ac :	Acetyl
Alk :	Alkyl
Ar :	Aryl
Bn :	Benzyl
Bt :	Benzotriazole
Bz :	Benzoyl
Cbz :	Carboxybenzyl
COD :	Cyclooctadiene
COSY :	Correlation spectroscopy
Cp :	Cyclopentadienyl
Cp* :	entamethylcyclopentadienyl
Cy :	Cyclohexyl
cysLT ₁ :	Cysteinyl leukotriene receptor 1
dba :	Dibenzylideneacetone
DCC :	Dicyclohexylcarbodiimide
DCE :	1,2-Dichloroethane
DCM:	Dichloromethane
DDQ :	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL :	Diisobutylaluminium hydride
DMEDA :	Dimethylethylenediamine
dppf :	Diphenylphosphino ferrocene
Et :	Ethyl
Et-PPA :	Ethyl polyphosphate
EWG :	Electron-withdrawing group
HMBC :	Heteronuclear Multiple Bond Coherence
HSQC :	Heteronuclear Single Quantum Coherence
5-HT _i :	5-hydroxytryptamine
Hz :	Hertz
KHMDS :	Potassium hexamethyldisilazane
LDA :	Lithium diisopropylamide

LiHMDS :	Lithium hexamethyldisilazane
Me :	Methyl
MOM :	Methoxymethyl
Ms :	Mesyl, methylsulfonyl
NOESY :	Nuclear Overhauser Effect Spectroscopy
NMF :	<i>N</i> -Methylformamide
NMR :	Nuclear magnetic resonance
Ph :	Phenyl
PG :	Protecting group
ppm:	parts per million
pTol :	Para-methylbenzene
pyr. :	pyridine
TBS :	Tributylsilyl
TBDPS :	<i>t</i> -Butyldiphenylsilyl
TBDMS :	<i>t</i> -Butyldimethylsilyl
TES :	Triethylsilyl
Tf :	Triflate
TFA :	Trifluoroacetic acid
THF :	Tetrahydrofuran
TMAO :	Trimethylamine <i>N</i> -oxide
TMS :	Trimethylsilyl
Ts :	Tosyl

VII.2. Selected NMR spectra

Figure VII-1: ¹H-NMR spectrum of the thiopyrano-3-thione **β-5da** (CDCl₃, 400 MHz)Figure VII-2: ¹³C-NMR spectrum of the thiopyrano-3-thione **β-5da** (CDCl₃, 75 MHz)

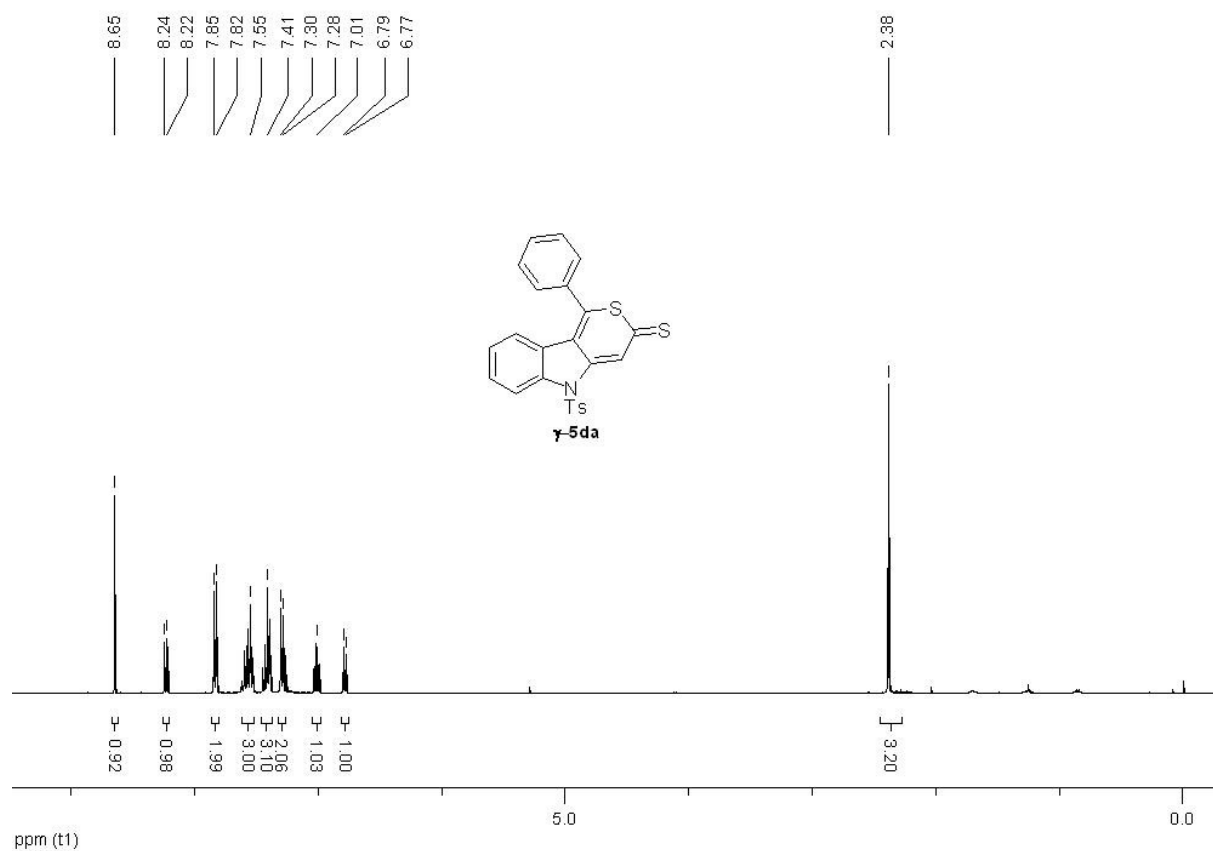


Figure VII-3: ¹H-NMR spectrum of the thiopyrano-3-thione **γ-5da** (CDCl₃, 400 MHz)

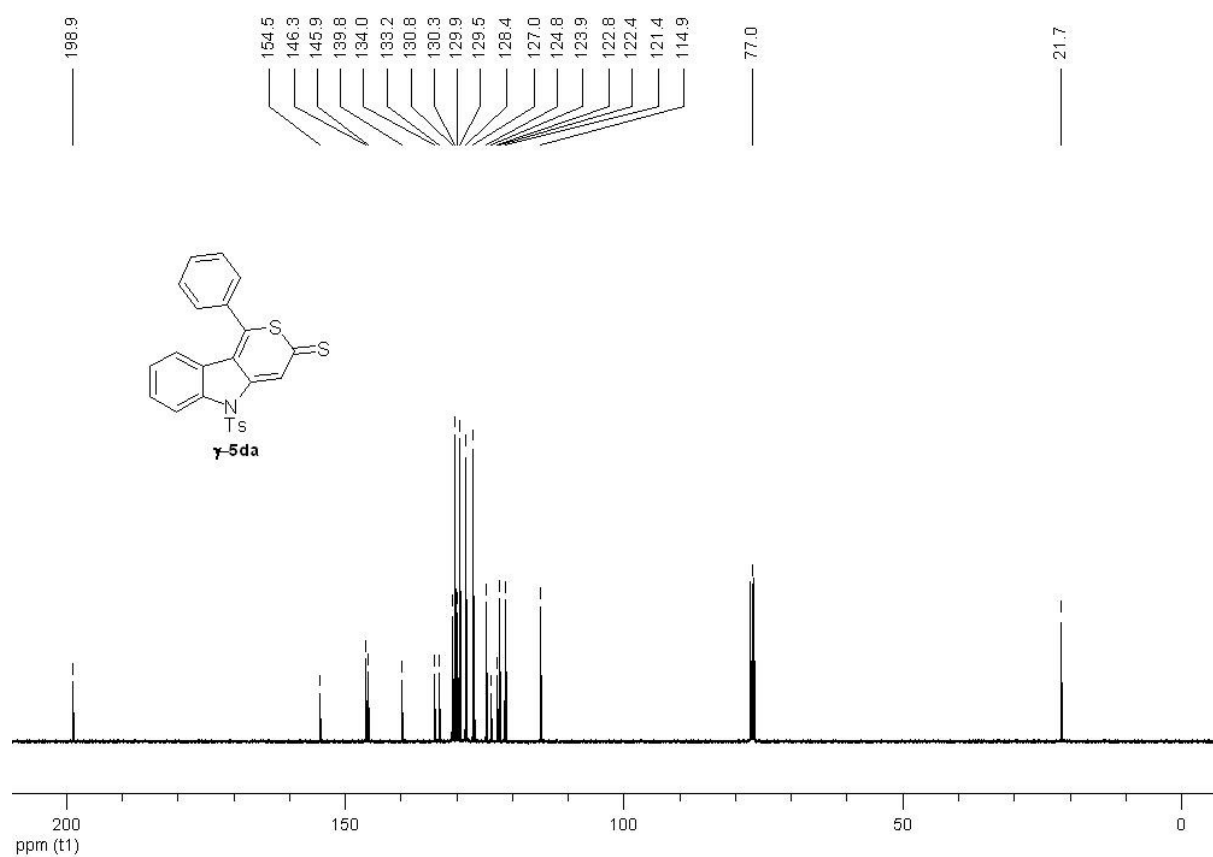


Figure VII-4: ¹³C-NMR spectrum of the thiopyrano-3-thione **γ-5da** (CDCl₃, 75 MHz)

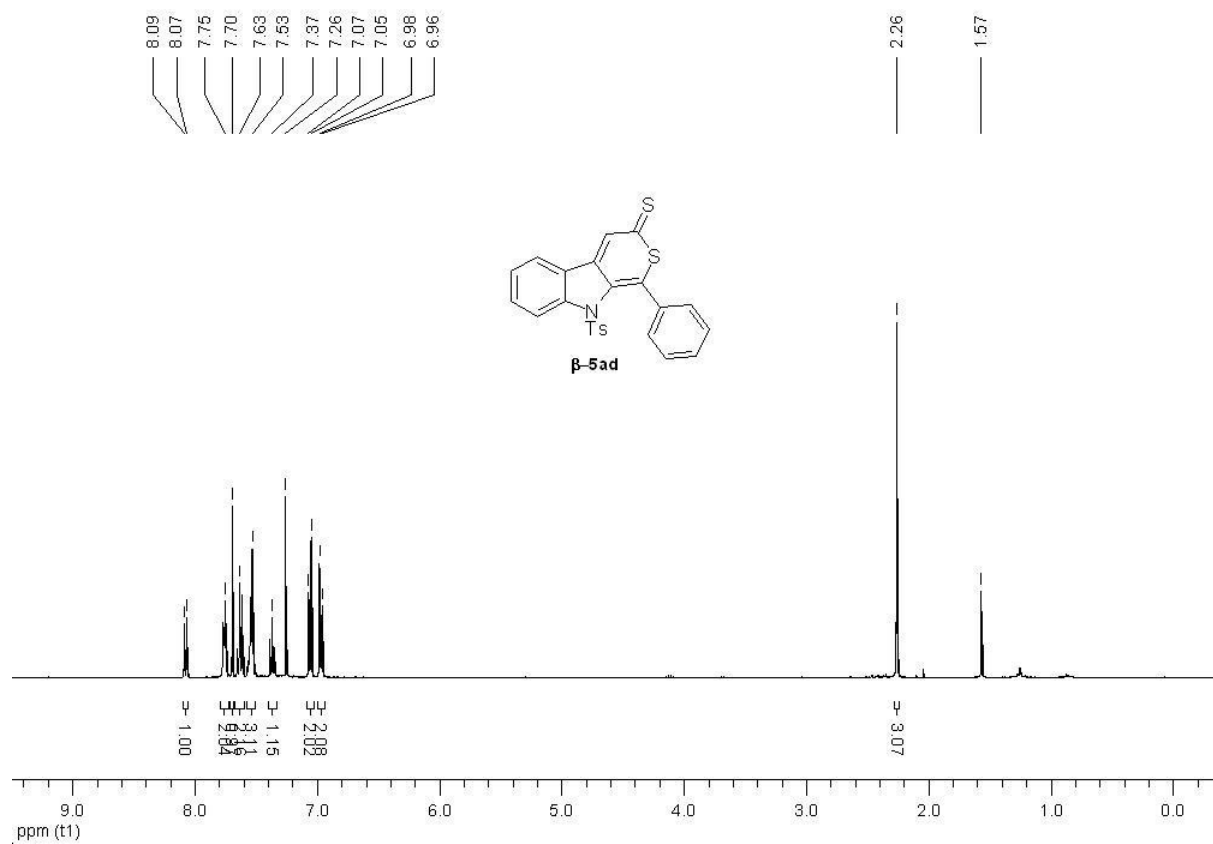


Figure VII-5: ¹H-NMR spectrum of the thiopyrano-3-thione **β-5ad** (CDCl₃, 400 MHz)

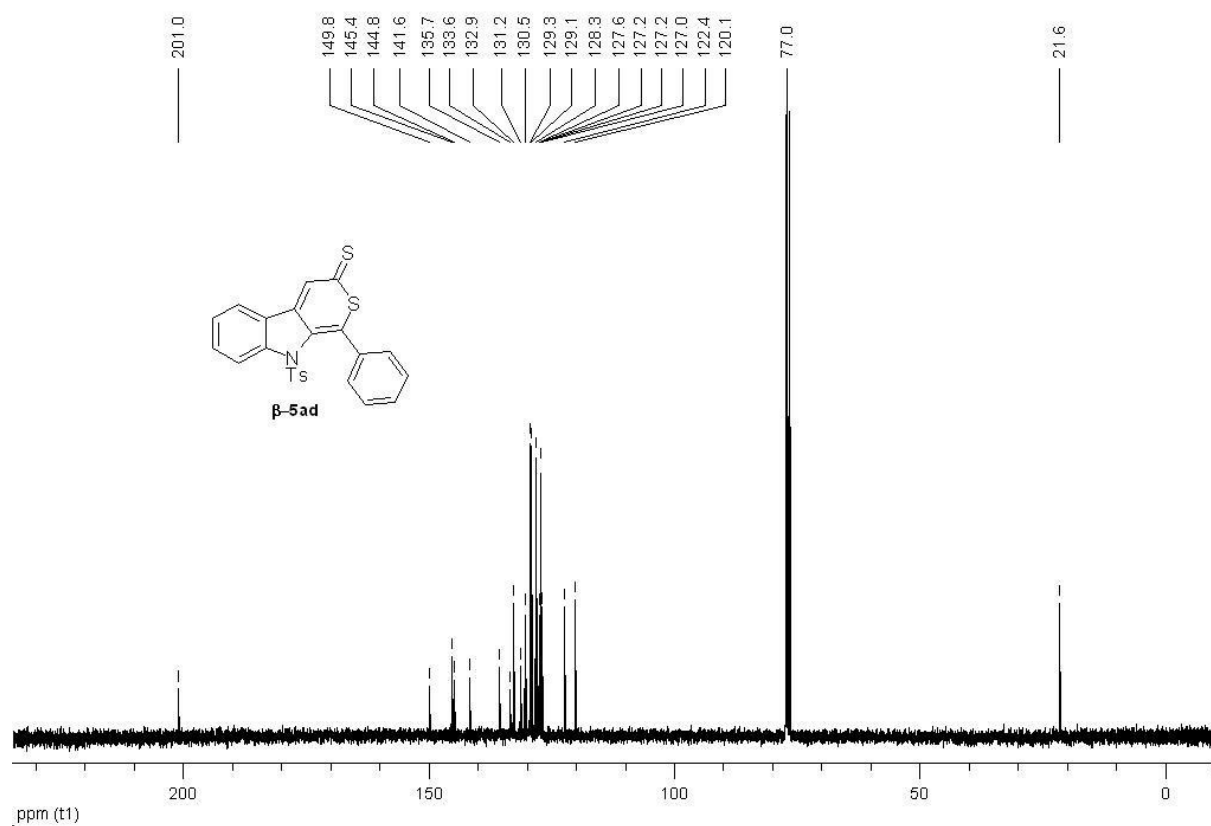


Figure VII-6: ¹³C-NMR spectrum of the thiopyrano-3-thione **β-5ad** (CDCl₃, 75 MHz)

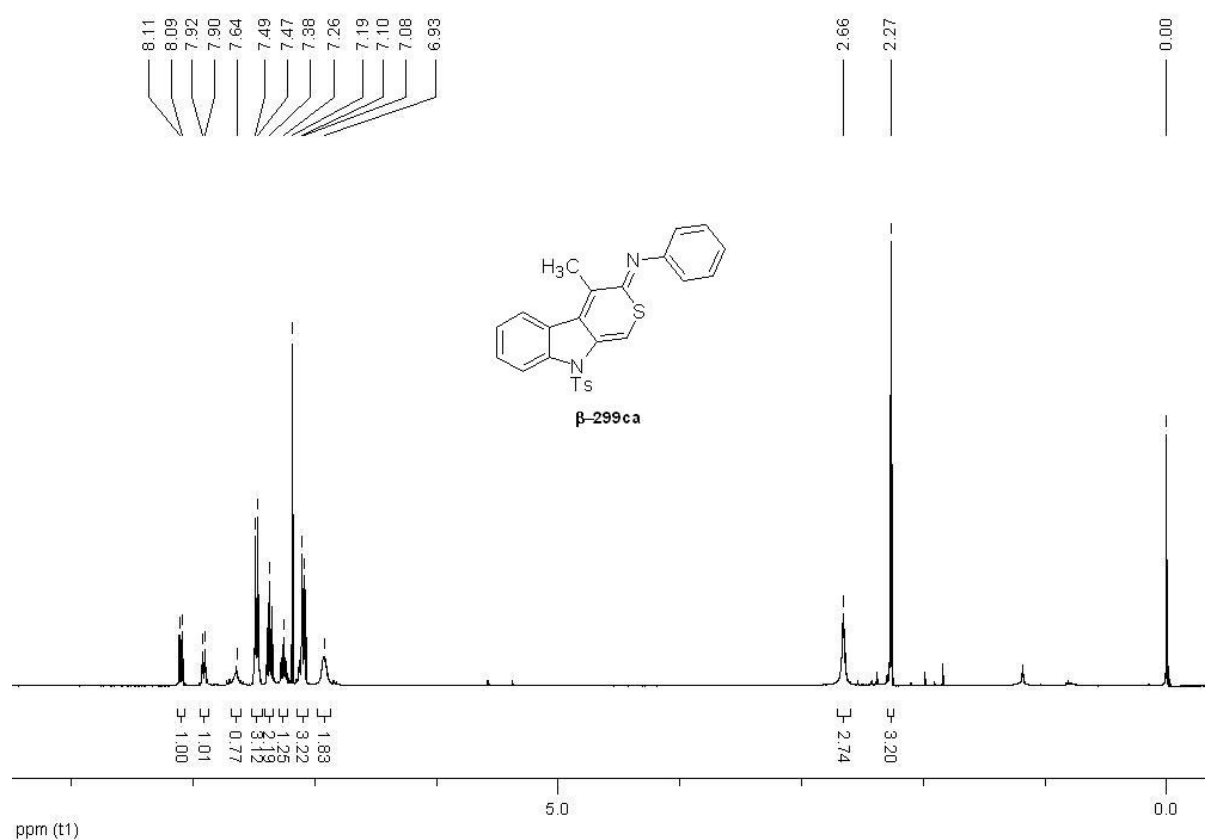


Figure VII-7: $^1\text{H-NMR}$ spectrum of the thiopyrano-3-imine β -299ca (CDCl₃, 400 MHz)

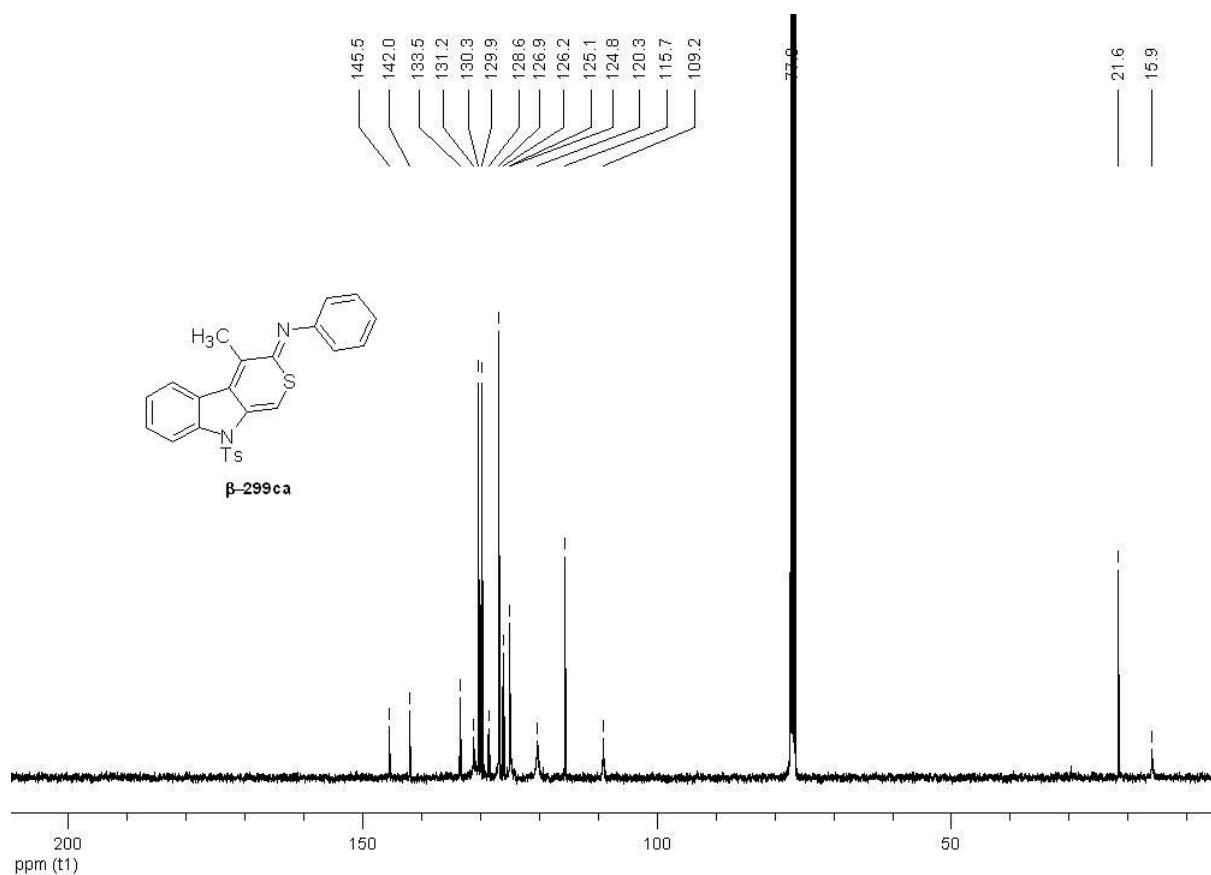


Figure VII-8: $^{13}\text{C-NMR}$ spectrum of the thiopyrano-3-imine β -299ca (CDCl₃, 75 MHz)

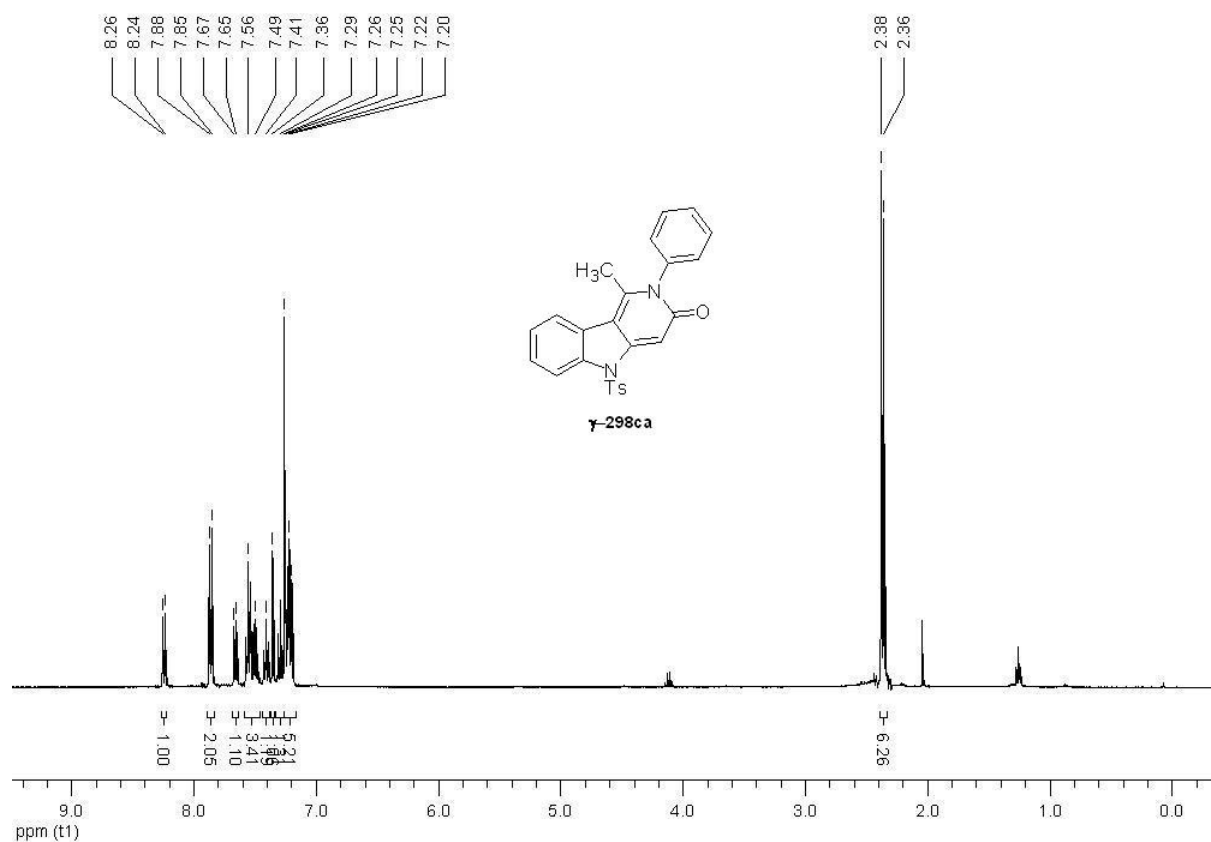


Figure VII-9: ¹H-NMR spectrum of the γ-carbolin-3-one γ-298ca (CDCl₃, 400 MHz)

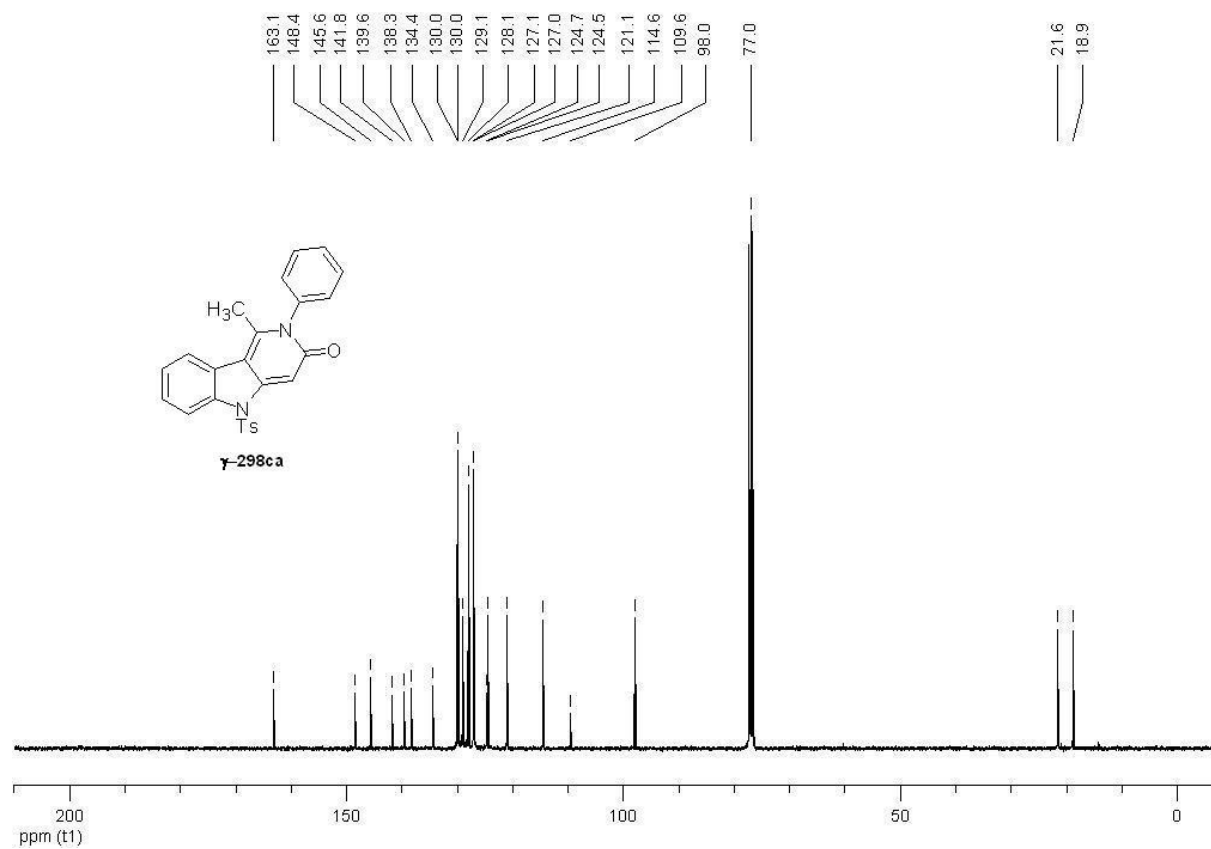


Figure VII-10: ¹³C-NMR spectrum of the γ-carbolin-3-one γ-298ca (CDCl₃, 75 MHz)

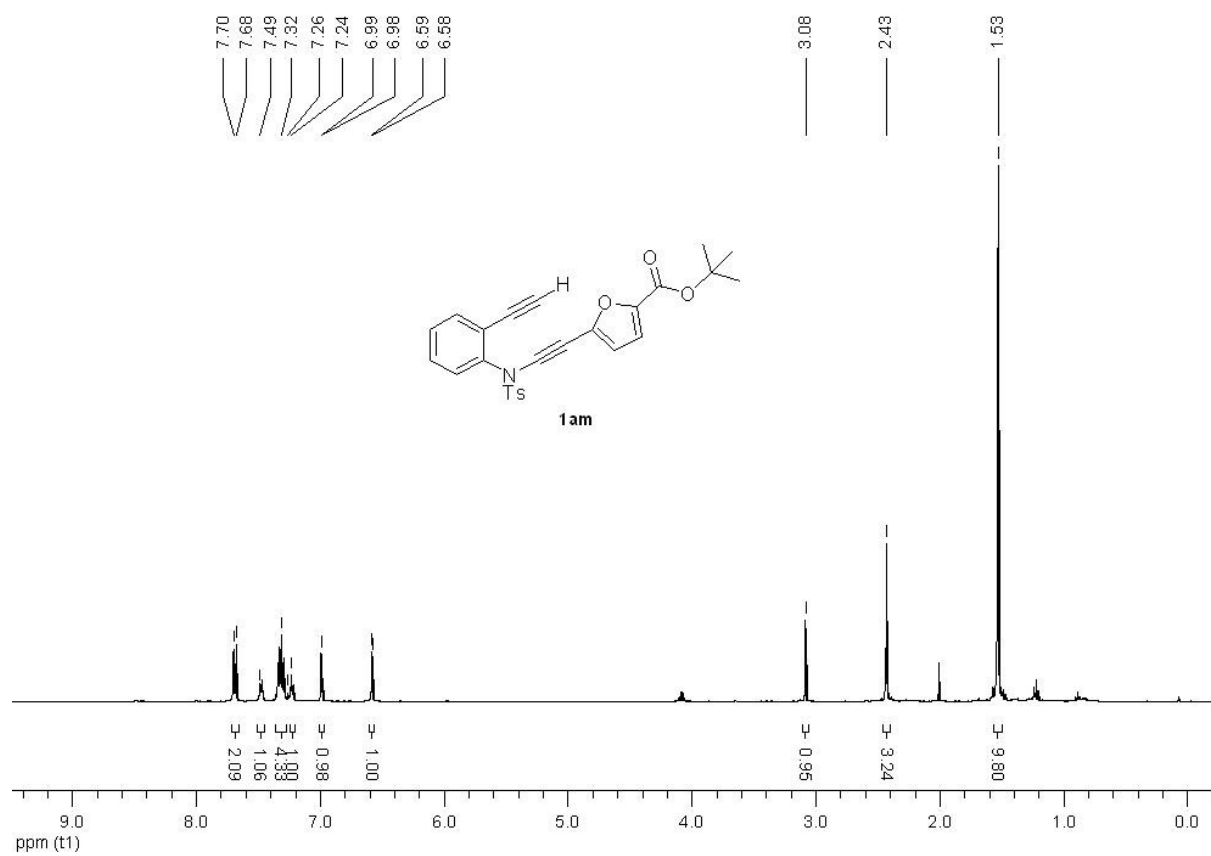


Figure VII-11: ¹H-NMR spectrum of the diene **1am** (CDCl₃, 400 MHz)

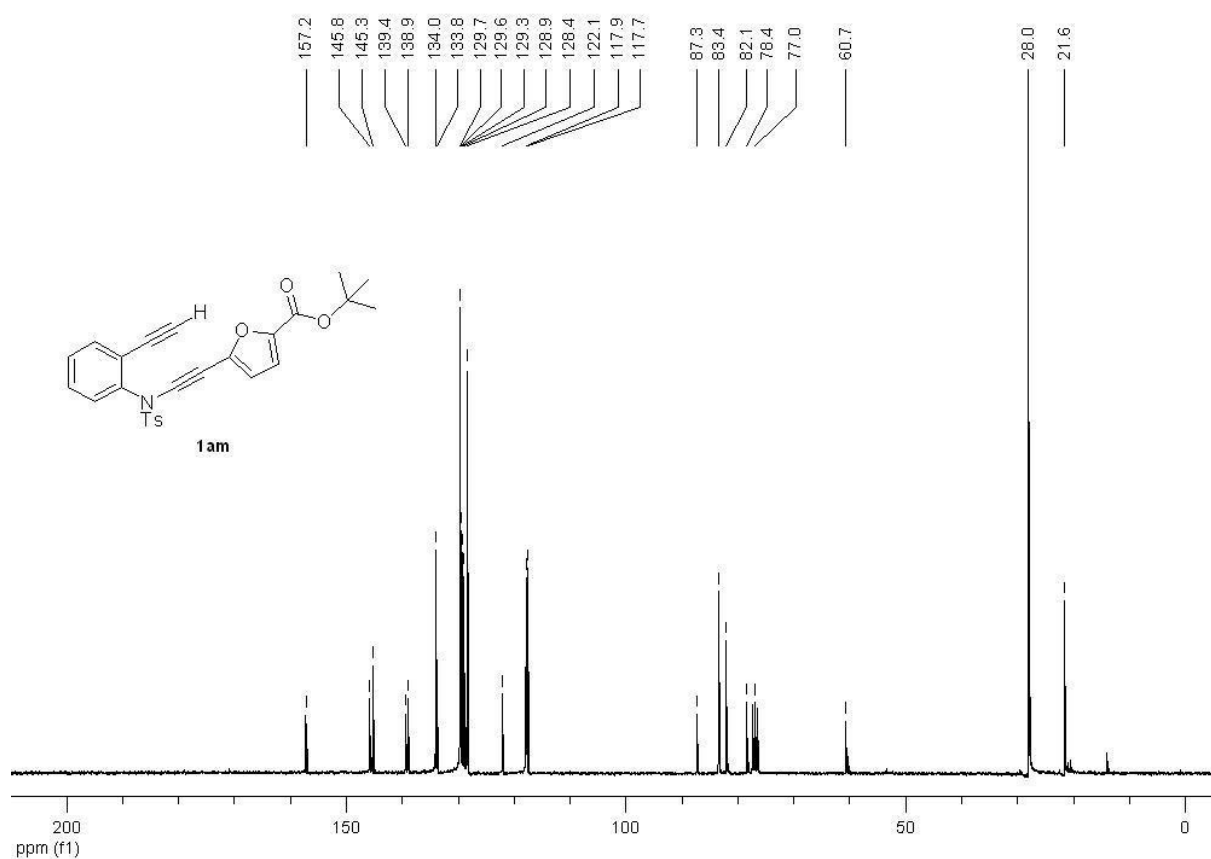


Figure VII-12: ¹³C-NMR spectrum of the diene **1am** (CDCl₃, 75 MHz)

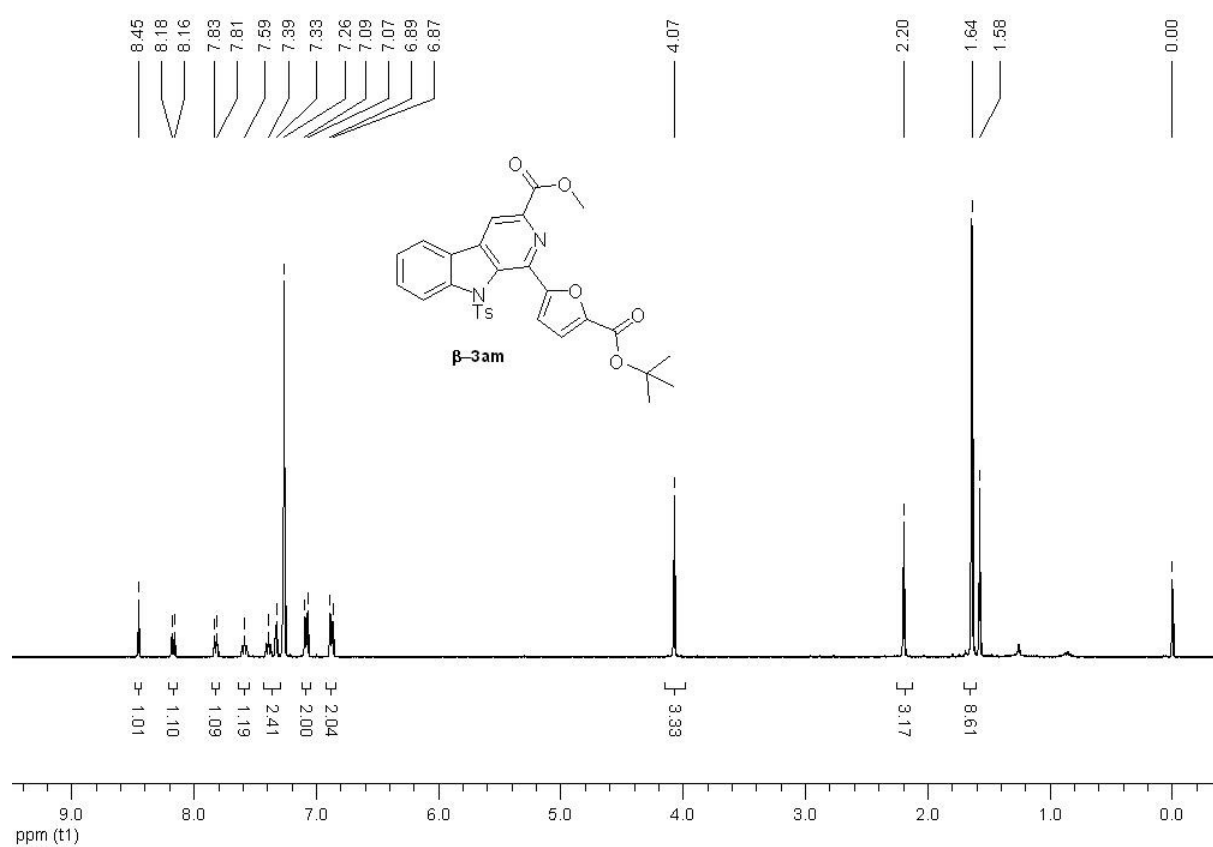


Figure VII-13: ¹H-NMR spectrum of the β-carboline β-3am (CDCl₃, 400 MHz)

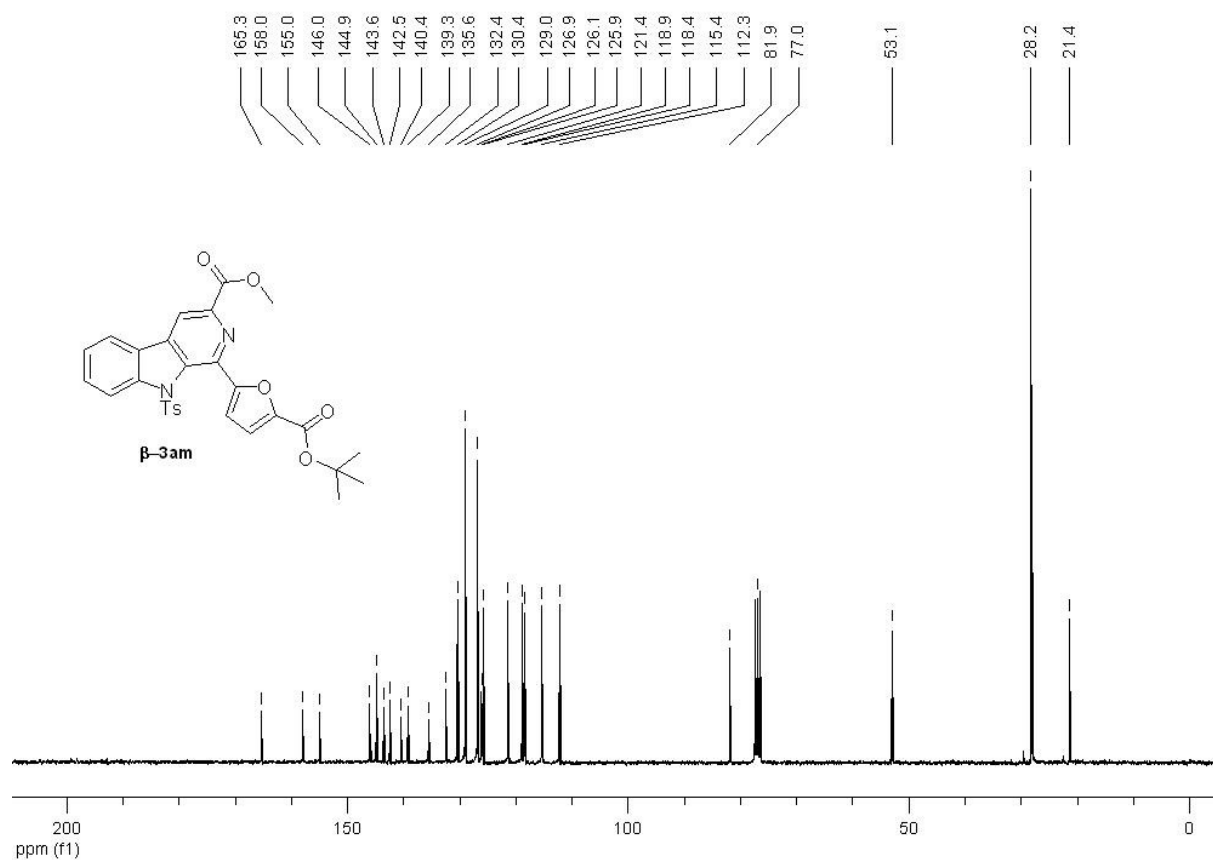
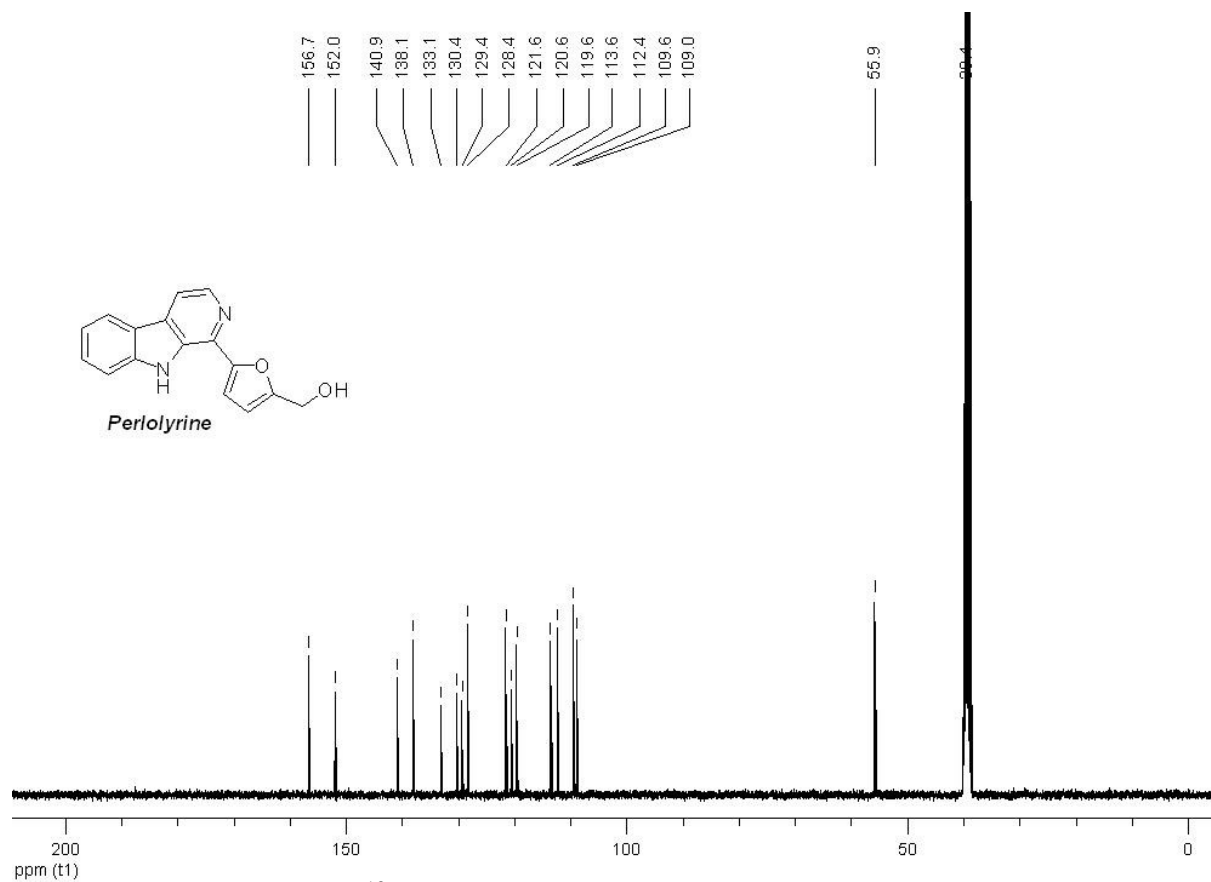
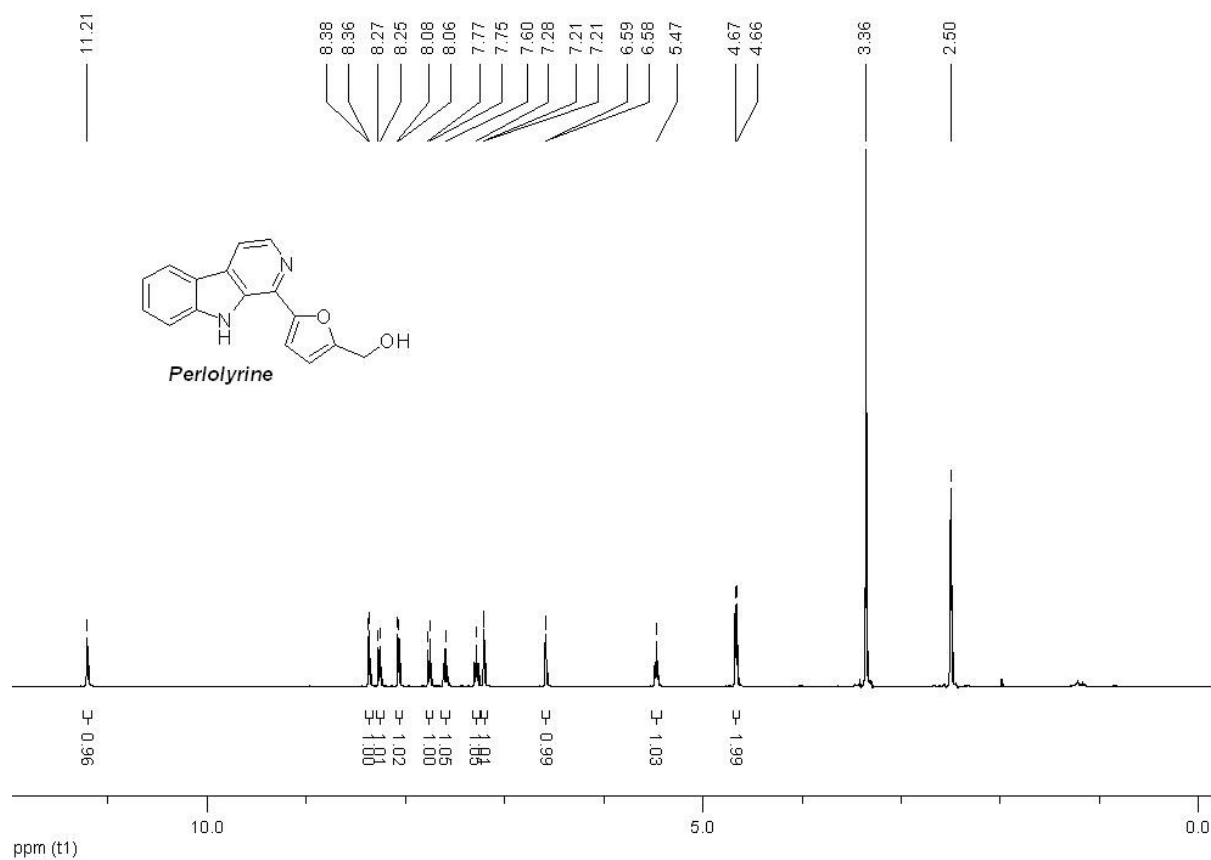


Figure VII-14: ¹³C-NMR spectrum of the β-carboline β-3am (CDCl₃, 75 MHz)



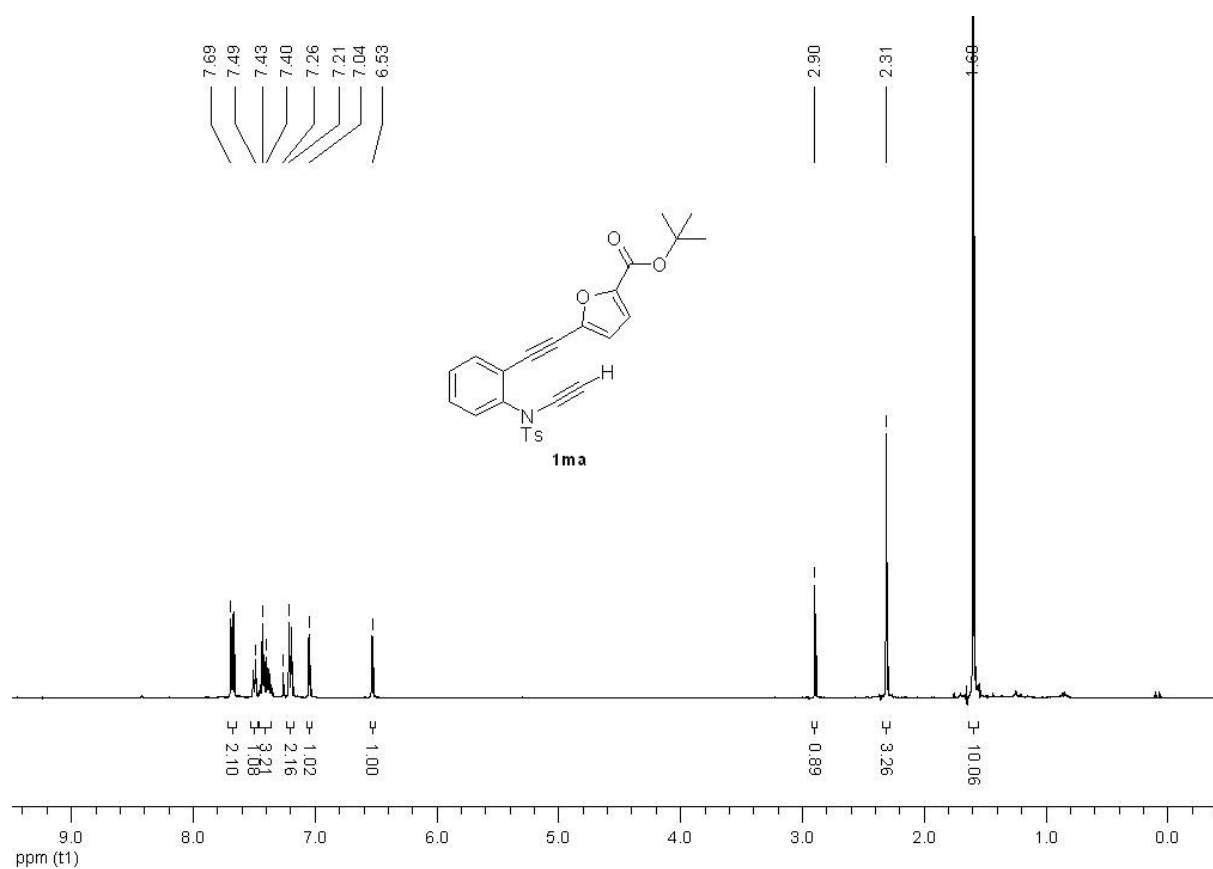


Figure VII-17: $^1\text{H-NMR}$ spectrum of the diene **1am** (CDCl_3 , 400 MHz)

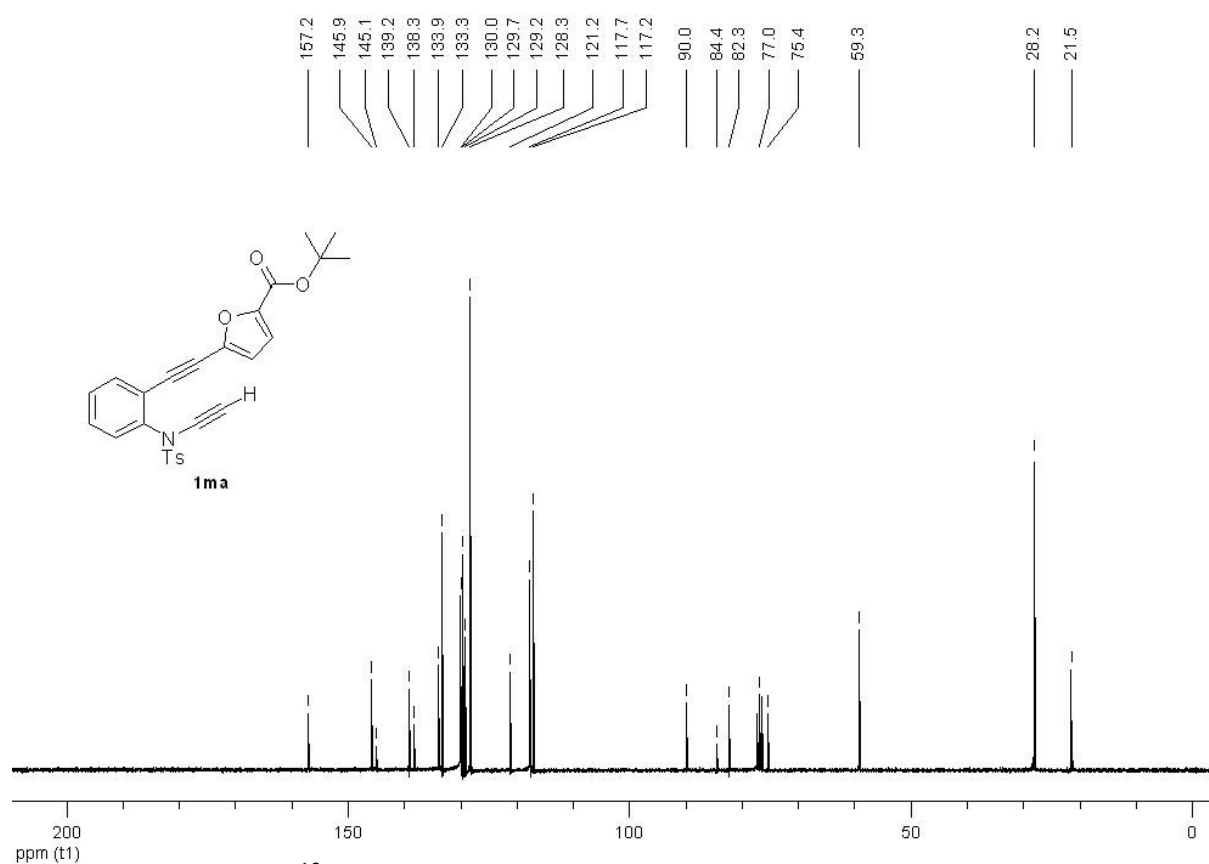


Figure VII-18: $^{13}\text{C-NMR}$ spectrum of the diene **1am** in CDCl_3 (CDCl_3 , 75 MHz)

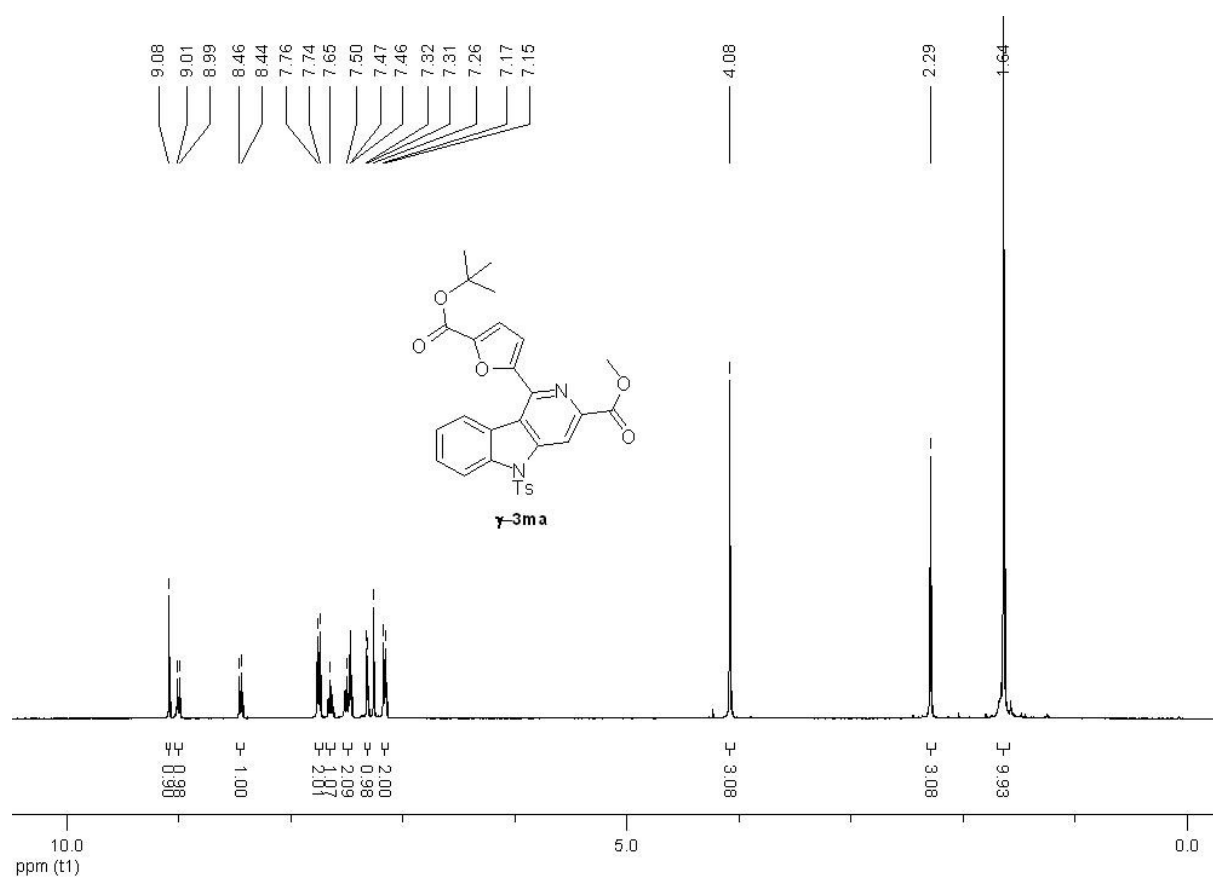


Figure VII-19: $^1\text{H-NMR}$ spectrum of the γ -carboline γ -3ma (CDCl₃, 400 MHz)

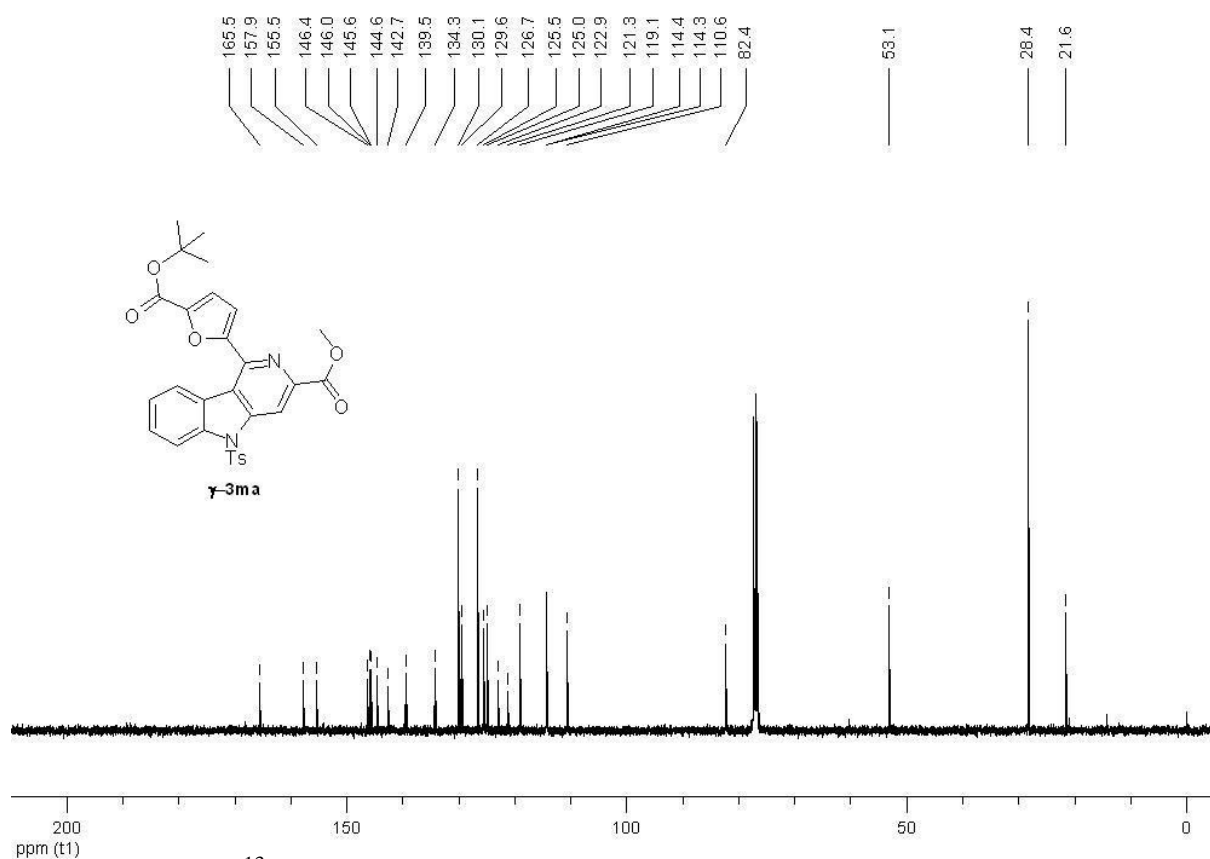
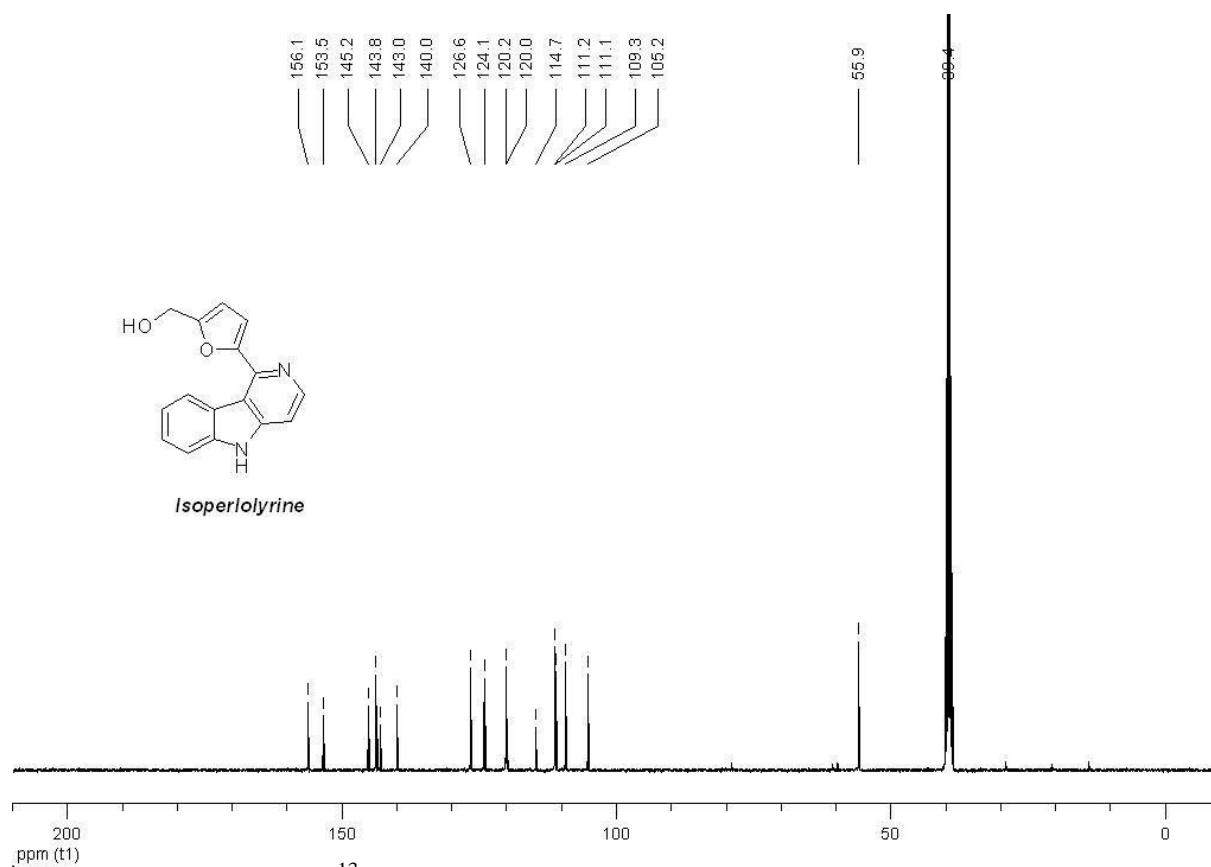
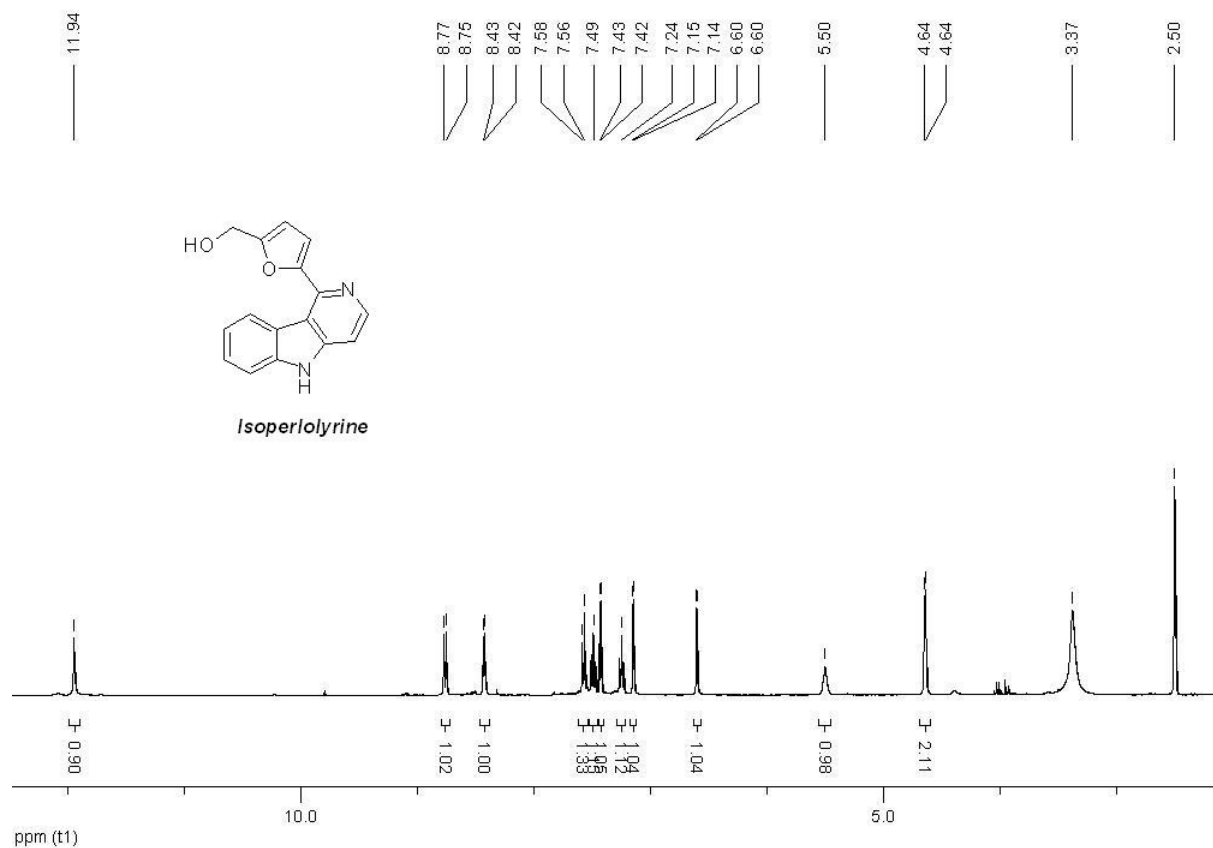


Figure VII-20: $^{13}\text{C-NMR}$ spectrum of the γ -carboline γ -3ma in CDCl₃ (CDCl₃, 75 MHz)



VII.3. X-Ray structures

VII.3.1. X-Ray structure of β -5ca

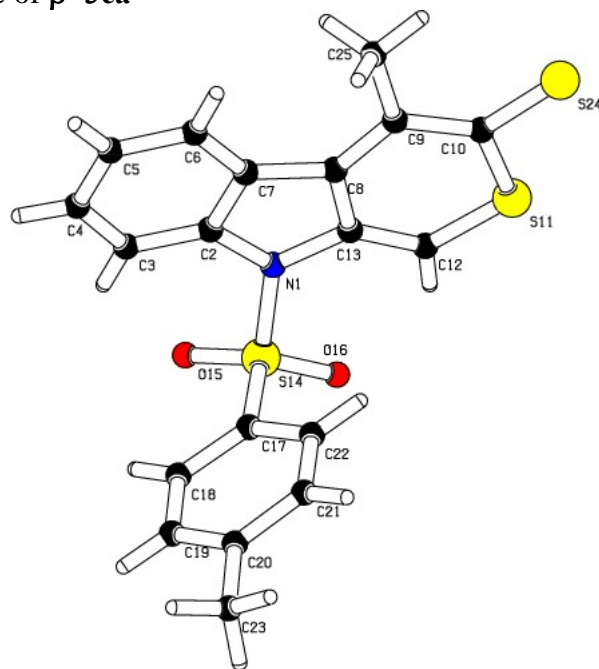


Figure VII-23: X-Ray structure of the thiopyrano-3-thione β -5ca.

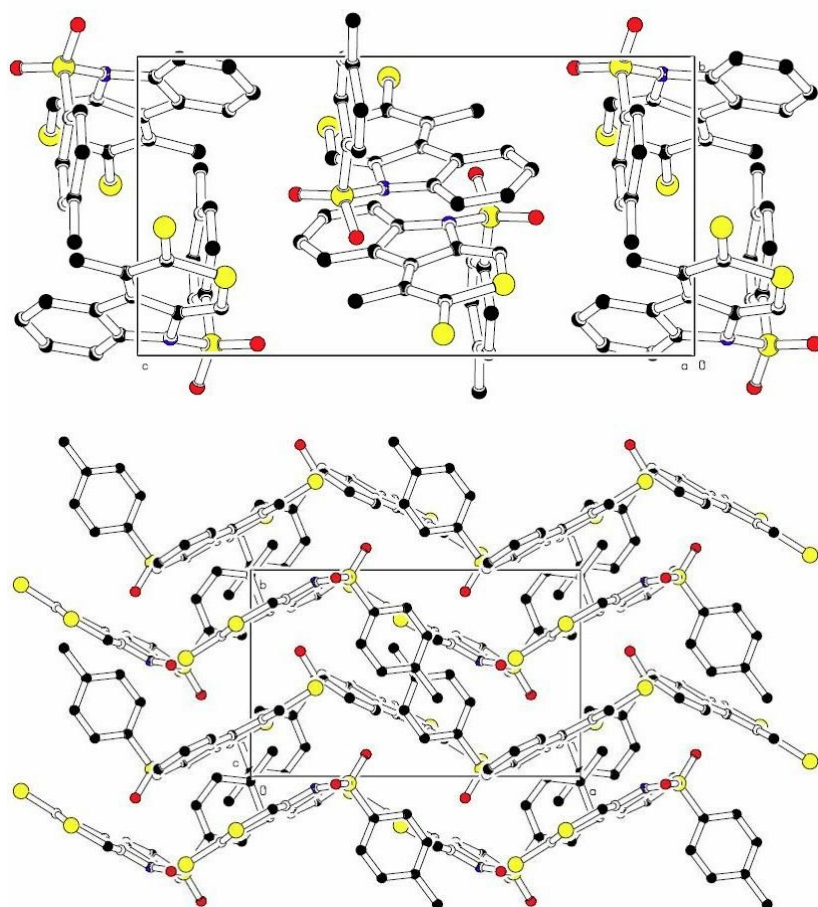


Figure VII-24: Crystalline packing of the thiopyrano-3-thione β -5ca.

Kristalldaten für β -5ca

Summenformel	$C_{19}H_{15}NO_2S_3$		
Molgewicht	385.5 $g\text{mol}^{-1}$		
Absorption	$\mu = 4.15 \text{ mm}^{-1}$ Korrektur mit 6 Flächen		
Transmission	$T_{\min}=0.42, T_{\max}=0.7$		
Kristallgröße	0.1 x 0.1 x 0.7 mm^3 dunkel rote Nadel		
Raumgruppe	P 2 ₁ /n (monoklin)		
Gitterkonstanten	a = 13.2530(4) Å		
(berechnet aus	b = 8.2423(3) Å	$\beta = 96.124(3)^\circ$	
25 Reflexen mit	c = 15.452(2) Å		
$60^\circ < \Theta < 70^\circ$)	V = 1678.1(2) Å ³	z = 4	F(000) = 800
Temperatur	-80°C		
Dichte	$d_{\text{rön}} = 1.526 \text{ gcm}^{-3}$		

Datensammlung

Diffraktometer	Turbo CAD4
Strahlung	Cu-K α Graphitmonochromator
Scan – Typ	$\omega/2\theta$
Scan – Breite	$0.9+0.14*\tan(\theta)^\circ$
Meßbereich	$1.5^\circ \leq \theta \leq 70^\circ$ $0 \leq h \leq 16 \quad 0 \leq k \leq 10 \quad -18 \leq l \leq 18$
Reflexzahl:	
gemessen	3167
unabhängige	3167 ($R_\sigma = 0.0325$)
beobachtete	2714 ($ F /\sigma(F) > 4.0$)

Datenkorrektur, Strukturlösung und -verfeinerung

Korrekturen	Lorentz- und Polarisationskorrektur. Intensitätsschwankungen mit kubischen Spline angegliedert.
Lösung	Programm: SIR-97(Direkte Methoden)
Verfeinerung	Programm: SHELXL-97 (Vollmatrixverfahren). 228 verfeinerte Parameter, gewichtete Verfeinerung: $w=1/[\sigma^2(F_o^2) + (0.053*P)^2+0.82*P]$ wobei $P=(\text{Max}(F_o^2,0)+2*F_o^2)/3$. Wasserstoffatome geometrisch eingefügt und reitend verfeinert. Nichtwasserstoffatome anisotrop verfeinert.
Diskrepanzfaktor	$wR2 = 0.1015$ ($R1=0.037$ für beobachtete Reflexe, 0.0453 für alle Reflexe)
Fitgüte	S = 1.040
maximale Änderung der Parameter	0.001 * e.s.d
maximale Peakhöhe in diff. Fouriersynthese	0.42, -0.36 $e\text{Å}^{-3}$

Table VII-1: Bond lengths [\AA] for β -5ca

N(1)-C(2)	1.422(3)	C(10)-S(24)	1.668(2)
N(1)-C(13)	1.425(3)	C(10)-S(11)	1.729(2)
N(1)-S(14)	1.6756(18)	S(11)-C(12)	1.702(2)
C(2)-C(3)	1.384(3)	C(12)-C(13)	1.352(3)
C(2)-C(7)	1.398(3)	S(14)-O(16)	1.4245(18)
C(3)-C(4)	1.381(3)	S(14)-O(15)	1.4265(17)
C(4)-C(5)	1.385(4)	S(14)-C(17)	1.754(2)
C(5)-C(6)	1.383(3)	C(17)-C(18)	1.383(3)
C(6)-C(7)	1.403(3)	C(17)-C(22)	1.390(3)
C(7)-C(8)	1.459(3)	C(18)-C(19)	1.388(3)
C(8)-C(9)	1.383(3)	C(19)-C(20)	1.390(3)
C(8)-C(13)	1.443(3)	C(20)-C(21)	1.389(3)
C(9)-C(10)	1.435(3)	C(20)-C(23)	1.505(3)
C(9)-C(25)	1.499(3)	C(21)-C(22)	1.385(3)

Table VII-2: Bond angles [deg] for β -5ca

C(2)-N(1)-C(13)	107.46(17)	C(12)-S(11)-C(10)	107.07(11)
C(2)-N(1)-S(14)	121.62(14)	C(13)-C(12)-S(11)	121.37(18)
C(13)-N(1)-S(14)	125.24(15)	C(12)-C(13)-N(1)	126.8(2)
C(3)-C(2)-C(7)	122.9(2)	C(12)-C(13)-C(8)	124.5(2)
C(3)-C(2)-N(1)	127.5(2)	N(1)-C(13)-C(8)	108.67(18)
C(7)-C(2)-N(1)	109.56(18)	O(16)-S(14)-O(15)	119.95(11)
C(4)-C(3)-C(2)	117.4(2)	O(16)-S(14)-N(1)	105.83(9)
C(3)-C(4)-C(5)	121.2(2)	O(15)-S(14)-N(1)	106.73(10)
C(6)-C(5)-C(4)	121.3(2)	O(16)-S(14)-C(17)	109.53(10)
C(5)-C(6)-C(7)	118.8(2)	O(15)-S(14)-C(17)	108.39(10)
C(2)-C(7)-C(6)	118.4(2)	N(1)-S(14)-C(17)	105.43(9)
C(2)-C(7)-C(8)	108.18(18)	C(18)-C(17)-C(22)	121.02(19)
C(6)-C(7)-C(8)	133.4(2)	C(18)-C(17)-S(14)	119.77(16)
C(9)-C(8)-C(13)	124.2(2)	C(22)-C(17)-S(14)	119.17(16)
C(9)-C(8)-C(7)	129.7(2)	C(17)-C(18)-C(19)	119.2(2)
C(13)-C(8)-C(7)	106.06(17)	C(18)-C(19)-C(20)	121.0(2)
C(8)-C(9)-C(10)	121.9(2)	C(21)-C(20)-C(19)	118.7(2)
C(8)-C(9)-C(25)	121.2(2)	C(21)-C(20)-C(23)	120.5(2)
C(10)-C(9)-C(25)	116.88(19)	C(19)-C(20)-C(23)	120.8(2)
C(9)-C(10)-S(24)	126.28(18)	C(22)-C(21)-C(20)	121.2(2)
C(9)-C(10)-S(11)	120.65(16)	C(21)-C(22)-C(17)	118.86(19)
S(24)-C(10)-S(11)	113.07(13)		

Table VII-3: Torsion angles [deg] for β -5ca

C(13)-N(1)-C(2)-C(3)	-178.6(2)	S(11)-C(12)-C(13)-C(8)	3.1(3)
S(14)-N(1)-C(2)-C(3)	-24.0(3)	C(2)-N(1)-C(13)-C(12)	-178.9(2)
C(13)-N(1)-C(2)-C(7)	1.1(2)	S(14)-N(1)-C(13)-C(12)	27.6(3)
S(14)-N(1)-C(2)-C(7)	155.80(15)	C(2)-N(1)-C(13)-C(8)	-2.3(2)
C(7)-C(2)-C(3)-C(4)	-1.5(3)	S(14)-N(1)-C(13)-C(8)	-155.83(15)
N(1)-C(2)-C(3)-C(4)	178.3(2)	C(9)-C(8)-C(13)-C(12)	0.7(3)
C(2)-C(3)-C(4)-C(5)	-0.3(3)	C(7)-C(8)-C(13)-C(12)	179.3(2)
C(3)-C(4)-C(5)-C(6)	1.5(4)	C(9)-C(8)-C(13)-N(1)	-176.00(19)
C(4)-C(5)-C(6)-C(7)	-0.9(4)	C(7)-C(8)-C(13)-N(1)	2.6(2)
C(3)-C(2)-C(7)-C(6)	2.1(3)	C(2)-N(1)-S(14)-O(16)	-177.20(16)
N(1)-C(2)-C(7)-C(6)	-177.71(18)	C(13)-N(1)-S(14)-O(16)	-27.17(19)
C(3)-C(2)-C(7)-C(8)	-179.74(19)	C(2)-N(1)-S(14)-O(15)	53.96(18)
N(1)-C(2)-C(7)-C(8)	0.5(2)	C(13)-N(1)-S(14)-O(15)	-156.01(17)
C(5)-C(6)-C(7)-C(2)	-0.8(3)	C(2)-N(1)-S(14)-C(17)	-61.18(18)
C(5)-C(6)-C(7)-C(8)	-178.5(2)	C(13)-N(1)-S(14)-C(17)	88.86(18)
C(2)-C(7)-C(8)-C(9)	176.6(2)	O(16)-S(14)-C(17)-C(18)	-124.30(18)
C(6)-C(7)-C(8)-C(9)	-5.6(4)	O(15)-S(14)-C(17)-C(18)	8.3(2)
C(2)-C(7)-C(8)-C(13)	-1.9(2)	N(1)-S(14)-C(17)-C(18)	122.24(18)
C(6)-C(7)-C(8)-C(13)	176.0(2)	O(16)-S(14)-C(17)-C(22)	53.38(19)
C(13)-C(8)-C(9)-C(10)	-5.5(3)	O(15)-S(14)-C(17)-C(22)	-174.07(17)
C(7)-C(8)-C(9)-C(10)	176.3(2)	N(1)-S(14)-C(17)-C(22)	-60.09(19)
C(13)-C(8)-C(9)-C(25)	175.0(2)	C(22)-C(17)-C(18)-C(19)	-1.2(3)
C(7)-C(8)-C(9)-C(25)	-3.2(3)	S(14)-C(17)-C(18)-C(19)	176.40(17)
C(8)-C(9)-C(10)-S(24)	-173.91(17)	C(17)-C(18)-C(19)-C(20)	-0.2(3)
C(25)-C(9)-C(10)-S(24)	5.6(3)	C(18)-C(19)-C(20)-C(21)	2.1(3)
C(8)-C(9)-C(10)-S(11)	5.9(3)	C(18)-C(19)-C(20)-C(23)	-177.8(2)
C(25)-C(9)-C(10)-S(11)	-174.60(17)	C(19)-C(20)-C(21)-C(22)	-2.5(3)
C(9)-C(10)-S(11)-C(12)	-2.1(2)	C(23)-C(20)-C(21)-C(22)	177.3(2)
S(24)-C(10)-S(11)-C(12)	177.70(12)	C(20)-C(21)-C(22)-C(17)	1.2(3)
C(10)-S(11)-C(12)-C(13)	-2.2(2)	C(18)-C(17)-C(22)-C(21)	0.8(3)
S(11)-C(12)-C(13)-N(1)	179.22(17)	S(14)-C(17)-C(22)-C(21)	-176.89(16)

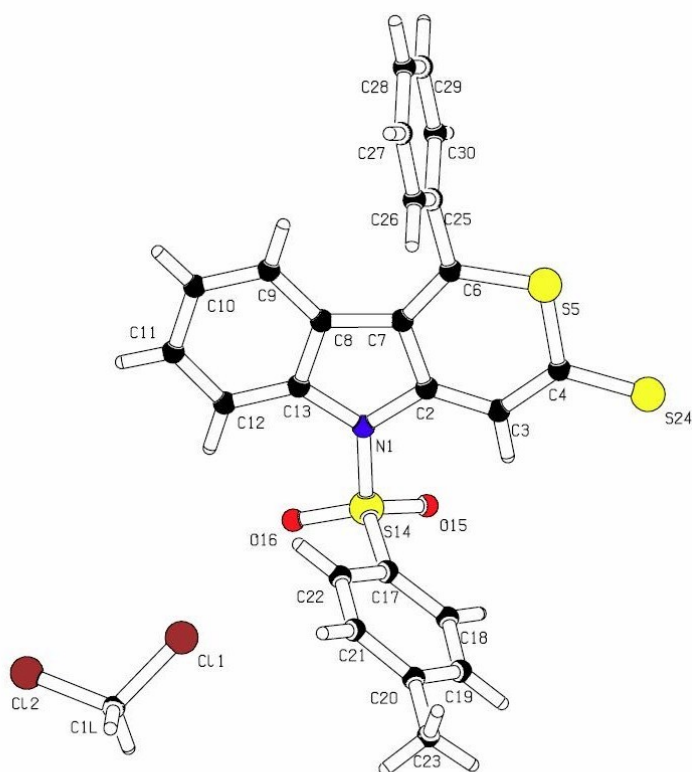
VII.3.2. X-Ray structure of γ -5da

Figure VII-25: X-Ray structure of the thiopyrano-3-thione γ -5ad.

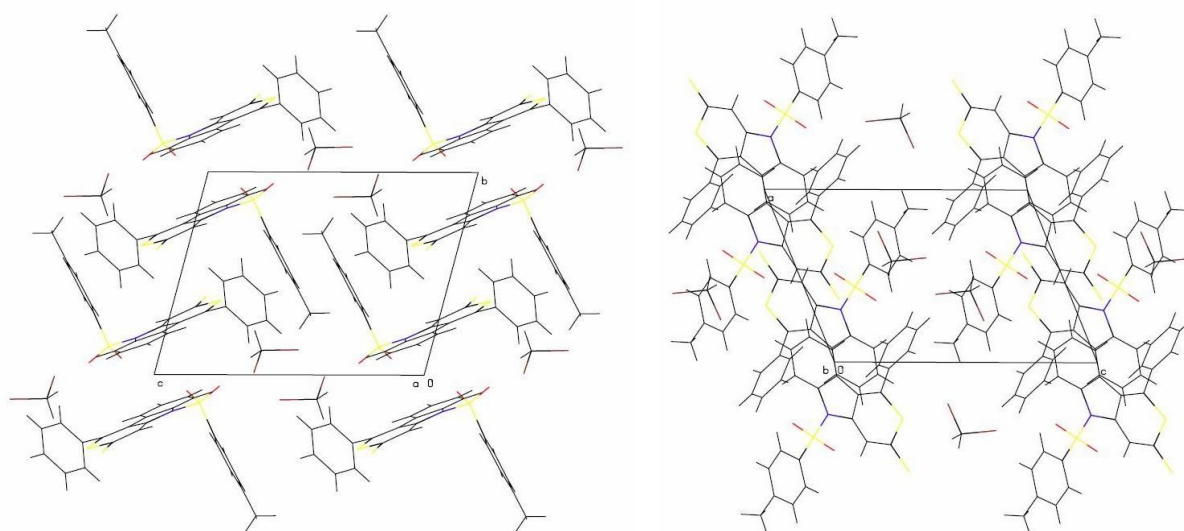


Figure VII-26: Crystalline packing of the thiopyrano-3-thione γ -5ad.

Kristalldaten für γ -5ad

Summenformel	$C_{24}H_{17}NO_2S_3 \cdot CH_2Cl_2$	
Molgewicht	532.49 g mol ⁻¹	
Absorption	$\mu = 5.19 \text{ mm}^{-1}$ Korrektur mit 6 Flächen	
Transmission	$T_{\min} = 0.24, T_{\max} = 0.68$	
Kristallgröße	0.08 x 0.2 x 0.4 mm ³ rote Platte	
Raumgruppe	P -1 (triklin)	
Gitterkonstanten	$a = 9.837(1) \text{ \AA}$	$\alpha = 97.689(9)^\circ$
(berechnet aus	$b = 10.278(2) \text{ \AA}$	$\beta = 108.305(8)^\circ$
25 Reflexen mit	$c = 13.286(2) \text{ \AA}$	$\gamma = 108.103(8)^\circ$
$65^\circ < \theta < 70^\circ$)	$V = 1171.6(3) \text{ \AA}^3$	$z = 2 \quad F(000) = 548$
Temperatur	-80°C	
Dichte	$d_{\text{rön}} = 1.509 \text{ g cm}^{-3}$	

Datensammlung

Diffraktometer	Turbo Cad4
Strahlung	Cu-K α Graphitmonochromator
Scan – Typ	$\omega/2\theta$ -scans
Scan – Breite	$0.9^\circ + 0.14 \cdot \tan(\theta)$
Meßbereich	$2^\circ \leq \theta < 70^\circ$ $-11 \leq h \leq 0 \quad -11 \leq k \leq 12 \quad -15 \leq l \leq 15$
Reflexzahl:	
gemessen	4706
unabhängige	4431 ($R_{\text{int}} = 0.0287$)
beobachtete	4040 ($ F /\sigma(F) > 4.0$)

Datenkorrektur, Strukturlösung und -verfeinerung

Korrekturen	Lorentz- und Polarisationskorrektur. Intensitätsschwankungen mit kubischen Spline korrigiert
Lösung	Programm: SIR-97 (Direkte Methoden)
Verfeinerung	Programm: SHELXL-97 (Vollmatrixverfahren). 299 verfeinerte Parameter, gewichtete Verfeinerung: $w = 1/[\sigma^2(F_o^2) + (0.0626 \cdot P)^2 + 0.83 \cdot P]$ wobei $P = (\text{Max}(F_o^2, 0) + 2 \cdot F_o^2)/3$. Wasserstoffatome geometrisch eingefügt und reitend verfeinert. Nichtwasserstoffatome anisotrop verfeinert.
Diskrepanzfaktor	$wR2 = 0.1065$ ($R1 = 0.0379$ für beobachtete Reflexe, 0.0414 für alle Reflexe)
Fitgüte	$S = 1.017$
maximale Änderung der Parameter	0.001 * e.s.d
maximale Peakhöhe in diff. Fouriersynthese	0.49, -0.42 e \AA^{-3}

Table VII-4: Bond lengths [\AA] for γ -5da

N(1)-C(2)	1.405(3)	C(18)-C(19)	1.389(3)
N(1)-C(13)	1.436(3)	C(18)-H(18)	0.9500
N(1)-S(14)	1.6771(17)	C(19)-C(20)	1.395(3)
C(2)-C(3)	1.367(3)	C(19)-H(19)	0.9500
C(2)-C(7)	1.446(3)	C(20)-C(21)	1.391(3)
C(3)-C(4)	1.412(3)	C(20)-C(23)	1.506(3)
C(3)-H(3)	0.9500	C(21)-C(22)	1.382(3)
C(4)-S(24)	1.665(2)	C(21)-H(21)	0.9500
C(4)-S(5)	1.732(2)	C(22)-H(22)	0.9500
S(5)-C(6)	1.721(2)	C(23)-H(23A)	0.9800
C(6)-C(7)	1.361(3)	C(23)-H(23B)	0.9800
C(6)-C(25)	1.494(3)	C(23)-H(23C)	0.9800
C(7)-C(8)	1.453(3)	C(25)-C(30)	1.386(3)
C(8)-C(9)	1.401(3)	C(25)-C(26)	1.388(3)
C(8)-C(13)	1.402(3)	C(26)-C(27)	1.388(3)
C(9)-C(10)	1.381(3)	C(26)-H(26)	0.9500
C(9)-H(9)	0.9500	C(27)-C(28)	1.385(3)
C(10)-C(11)	1.391(3)	C(27)-H(27)	0.9500
C(10)-H(10)	0.9500	C(28)-C(29)	1.380(3)
C(11)-C(12)	1.391(3)	C(28)-H(28)	0.9500
C(11)-H(11)	0.9500	C(29)-C(30)	1.391(3)
C(12)-C(13)	1.383(3)	C(29)-H(29)	0.9500
C(12)-H(12)	0.9500	C(30)-H(30)	0.9500
S(14)-O(15)	1.4257(16)	C(1L)-Cl(2)	1.757(3)
S(14)-O(16)	1.4274(16)	C(1L)-Cl(1)	1.761(2)
S(14)-C(17)	1.758(2)	C(1L)-H(1L1)	0.9900
C(17)-C(18)	1.384(3)	C(1L)-H(1L2)	0.9900
C(17)-C(22)	1.391(3)		

Table VII-5: Bond angles [deg] for γ -5da

C(2)-N(1)-C(13)	109.41(16)	C(17)-C(18)-C(19)	119.0(2)
C(2)-N(1)-S(14)	123.30(14)	C(17)-C(18)-H(18)	120.5
C(13)-N(1)-S(14)	127.27(14)	C(19)-C(18)-H(18)	120.5
C(3)-C(2)-N(1)	126.56(18)	C(18)-C(19)-C(20)	121.1(2)
C(3)-C(2)-C(7)	126.24(18)	C(18)-C(19)-H(19)	119.5
N(1)-C(2)-C(7)	107.19(17)	C(20)-C(19)-H(19)	119.5
C(2)-C(3)-C(4)	123.21(18)	C(21)-C(20)-C(19)	118.5(2)
C(2)-C(3)-H(3)	118.4	C(21)-C(20)-C(23)	120.8(2)
C(4)-C(3)-H(3)	118.4	C(19)-C(20)-C(23)	120.6(2)
C(3)-C(4)-S(24)	125.67(16)	C(22)-C(21)-C(20)	121.3(2)
C(3)-C(4)-S(5)	119.70(16)	C(22)-C(21)-H(21)	119.4
S(24)-C(4)-S(5)	114.63(12)	C(20)-C(21)-H(21)	119.4
C(6)-S(5)-C(4)	107.18(10)	C(21)-C(22)-C(17)	119.0(2)
C(7)-C(6)-C(25)	126.27(18)	C(21)-C(22)-H(22)	120.5
C(7)-C(6)-S(5)	121.92(15)	C(17)-C(22)-H(22)	120.5
C(25)-C(6)-S(5)	111.76(14)	C(20)-C(23)-H(23A)	109.5
C(6)-C(7)-C(2)	121.71(18)	C(20)-C(23)-H(23B)	109.5
C(6)-C(7)-C(8)	130.91(18)	H(23A)-C(23)-H(23B)	109.5
C(2)-C(7)-C(8)	107.38(17)	C(20)-C(23)-H(23C)	109.5
C(9)-C(8)-C(13)	119.53(19)	H(23A)-C(23)-H(23C)	109.5
C(9)-C(8)-C(7)	132.47(19)	H(23B)-C(23)-H(23C)	109.5
C(13)-C(8)-C(7)	108.00(17)	C(30)-C(25)-C(26)	120.25(19)
C(10)-C(9)-C(8)	118.6(2)	C(30)-C(25)-C(6)	120.14(18)
C(10)-C(9)-H(9)	120.7	C(26)-C(25)-C(6)	119.45(18)
C(8)-C(9)-H(9)	120.7	C(27)-C(26)-C(25)	119.8(2)
C(9)-C(10)-C(11)	120.9(2)	C(27)-C(26)-H(26)	120.1
C(9)-C(10)-H(10)	119.6	C(25)-C(26)-H(26)	120.1
C(11)-C(10)-H(10)	119.6	C(28)-C(27)-C(26)	120.1(2)
C(10)-C(11)-C(12)	121.6(2)	C(28)-C(27)-H(27)	120.0
C(10)-C(11)-H(11)	119.2	C(26)-C(27)-H(27)	120.0
C(12)-C(11)-H(11)	119.2	C(29)-C(28)-C(27)	120.0(2)
C(13)-C(12)-C(11)	117.3(2)	C(29)-C(28)-H(28)	120.0
C(13)-C(12)-H(12)	121.4	C(27)-C(28)-H(28)	120.0
C(11)-C(12)-H(12)	121.4	C(28)-C(29)-C(30)	120.3(2)
C(12)-C(13)-C(8)	122.10(19)	C(28)-C(29)-H(29)	119.8
C(12)-C(13)-N(1)	129.92(19)	C(30)-C(29)-H(29)	119.8
C(8)-C(13)-N(1)	107.98(17)	C(25)-C(30)-C(29)	119.5(2)
O(15)-S(14)-O(16)	120.02(10)	C(25)-C(30)-H(30)	120.2
O(15)-S(14)-N(1)	108.03(9)	C(29)-C(30)-H(30)	120.2
O(16)-S(14)-N(1)	105.28(9)	Cl(2)-C(1L)-Cl(1)	111.26(14)
O(15)-S(14)-C(17)	109.01(10)	Cl(2)-C(1L)-H(1L1)	109.4
O(16)-S(14)-C(17)	109.45(10)	Cl(1)-C(1L)-H(1L1)	109.4
N(1)-S(14)-C(17)	103.79(9)	Cl(2)-C(1L)-H(1L2)	109.4
C(18)-C(17)-C(22)	121.13(19)	Cl(1)-C(1L)-H(1L2)	109.4
C(18)-C(17)-S(14)	119.48(16)	H(1L1)-C(1L)-H(1L2)	108.0
C(22)-C(17)-S(14)	119.34(16)		

Table VII-6: Torsion angles [deg] for γ -5da

C(13)-N(1)-C(2)-C(3)	176.94(19)	C(2)-N(1)-C(13)-C(8)	2.0(2)
S(14)-N(1)-C(2)-C(3)	-1.4(3)	S(14)-N(1)-C(13)-C(8)	-179.75(14)
C(13)-N(1)-C(2)-C(7)	-2.0(2)	C(2)-N(1)-S(14)-O(15)	-39.63(18)
S(14)-N(1)-C(2)-C(7)	179.68(13)	C(13)-N(1)-S(14)-O(15)	142.36(17)
N(1)-C(2)-C(3)-C(4)	-178.83(18)	C(2)-N(1)-S(14)-O(16)	-169.00(16)
C(7)-C(2)-C(3)-C(4)	-0.1(3)	C(13)-N(1)-S(14)-O(16)	12.99(19)
C(2)-C(3)-C(4)-S(24)	178.86(16)	C(2)-N(1)-S(14)-C(17)	76.01(17)
C(2)-C(3)-C(4)-S(5)	-1.0(3)	C(13)-N(1)-S(14)-C(17)	-102.00(18)
C(3)-C(4)-S(5)-C(6)	0.5(2)	O(15)-S(14)-C(17)-C(18)	-10.2(2)
S(24)-C(4)-S(5)-C(6)	-179.37(11)	O(16)-S(14)-C(17)-C(18)	122.83(17)
C(4)-S(5)-C(6)-C(7)	1.1(2)	N(1)-S(14)-C(17)-C(18)	-125.19(17)
C(4)-S(5)-C(6)-C(25)	178.86(14)	O(15)-S(14)-C(17)-C(22)	172.41(16)
C(25)-C(6)-C(7)-C(2)	-179.66(18)	O(16)-S(14)-C(17)-C(22)	-54.52(19)
S(5)-C(6)-C(7)-C(2)	-2.2(3)	N(1)-S(14)-C(17)-C(22)	57.47(18)
C(25)-C(6)-C(7)-C(8)	-0.2(3)	C(22)-C(17)-C(18)-C(19)	1.0(3)
S(5)-C(6)-C(7)-C(8)	177.20(16)	S(14)-C(17)-C(18)-C(19)	-176.29(16)
C(3)-C(2)-C(7)-C(6)	1.9(3)	C(17)-C(18)-C(19)-C(20)	-0.1(3)
N(1)-C(2)-C(7)-C(6)	-179.21(17)	C(18)-C(19)-C(20)-C(21)	-1.3(3)
C(3)-C(2)-C(7)-C(8)	-177.69(19)	C(18)-C(19)-C(20)-C(23)	-179.6(2)
N(1)-C(2)-C(7)-C(8)	1.2(2)	C(19)-C(20)-C(21)-C(22)	1.7(3)
C(6)-C(7)-C(8)-C(9)	1.2(4)	C(23)-C(20)-C(21)-C(22)	-179.9(2)
C(2)-C(7)-C(8)-C(9)	-179.3(2)	C(20)-C(21)-C(22)-C(17)	-0.8(3)
C(6)-C(7)-C(8)-C(13)	-179.5(2)	C(18)-C(17)-C(22)-C(21)	-0.6(3)
C(2)-C(7)-C(8)-C(13)	0.0(2)	S(14)-C(17)-C(22)-C(21)	176.71(16)
C(13)-C(8)-C(9)-C(10)	0.5(3)	C(7)-C(6)-C(25)-C(30)	-100.3(3)
C(7)-C(8)-C(9)-C(10)	179.7(2)	S(5)-C(6)-C(25)-C(30)	82.0(2)
C(8)-C(9)-C(10)-C(11)	0.7(3)	C(7)-C(6)-C(25)-C(26)	84.2(3)
C(9)-C(10)-C(11)-C(12)	-1.1(3)	S(5)-C(6)-C(25)-C(26)	-93.4(2)
C(10)-C(11)-C(12)-C(13)	0.2(3)	C(30)-C(25)-C(26)-C(27)	0.4(3)
C(11)-C(12)-C(13)-C(8)	1.1(3)	C(6)-C(25)-C(26)-C(27)	175.86(19)
C(11)-C(12)-C(13)-N(1)	-178.4(2)	C(25)-C(26)-C(27)-C(28)	0.1(3)
C(9)-C(8)-C(13)-C(12)	-1.4(3)	C(26)-C(27)-C(28)-C(29)	-0.3(3)
C(7)-C(8)-C(13)-C(12)	179.21(18)	C(27)-C(28)-C(29)-C(30)	0.0(3)
C(9)-C(8)-C(13)-N(1)	178.17(17)	C(26)-C(25)-C(30)-C(29)	-0.7(3)
C(7)-C(8)-C(13)-N(1)	-1.2(2)	C(6)-C(25)-C(30)-C(29)	-176.1(2)
C(2)-N(1)-C(13)-C(12)	-178.4(2)	C(28)-C(29)-C(30)-C(25)	0.4(3)
S(14)-N(1)-C(13)-C(12)	-0.2(3)		

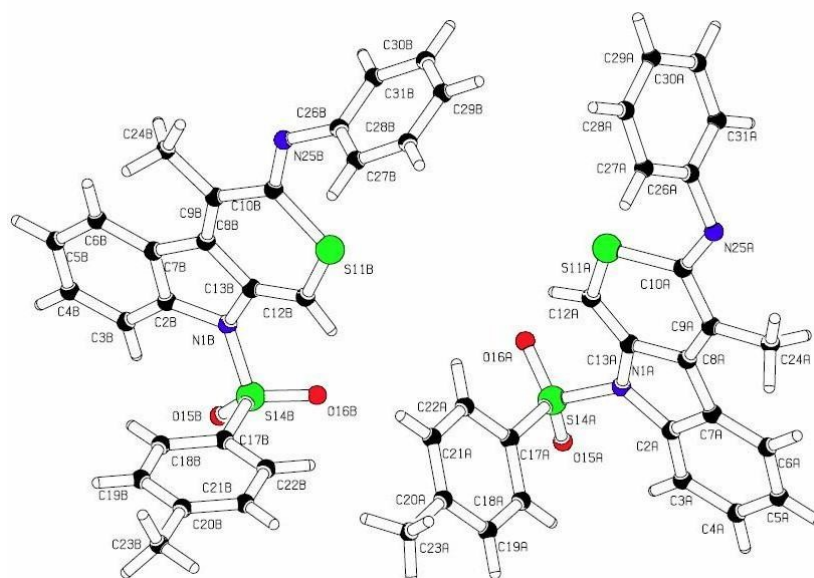
VII.3.2. X-Ray structure of β -299ca

Figure VII-27: X-Ray structure of the thiopyrano-3-imine β -299ca.

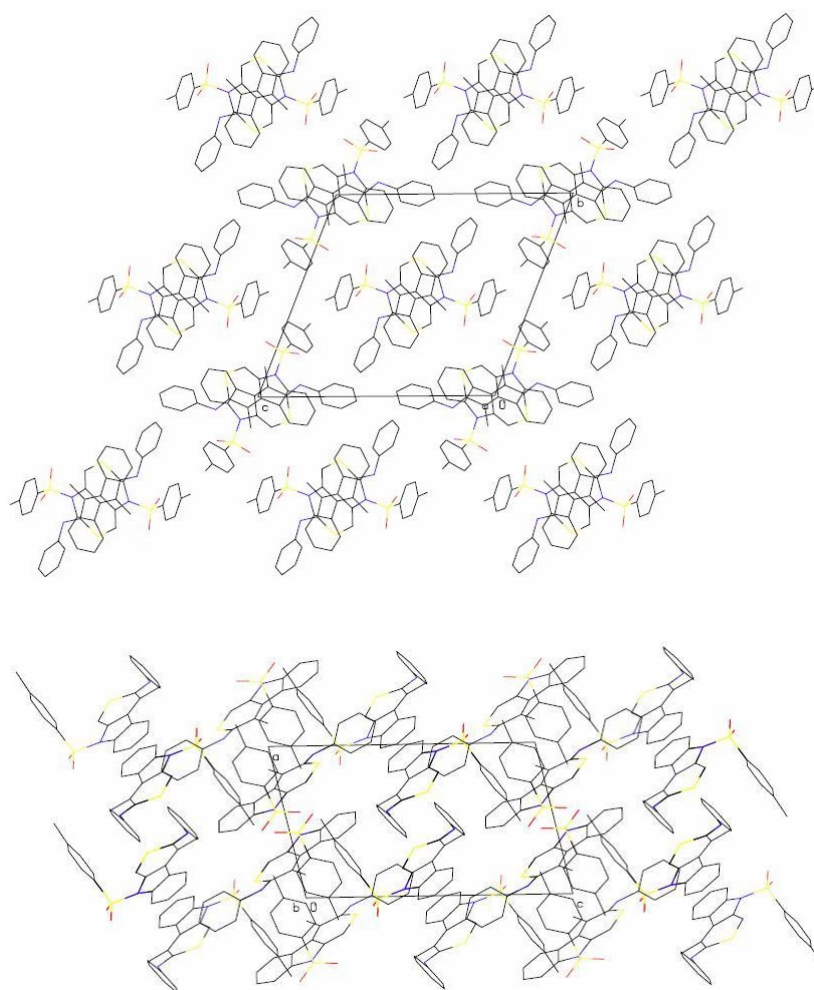


Figure VII-28: Crystalline packing of the thiopyrano-3-imine β -299ca.

Kristalldaten für β -299ca

Summenformel	$C_{25}H_{20}N_2O_2S_2$	
Molgewicht	444.6 $g\ mol^{-1}$	
Raumgruppe	P-1 (triklin)	
Absorption	$\mu = 0.28\ mm^{-1}$	
Kristallgröße	0.09 x 0.18 x 0.4 mm^3 orange Nadel	
Gitterkonstanten	$a = 9.1997(6)\ \text{\AA}$	$\alpha = 110.129(1)^\circ$
(berechnet aus 6518	$b = 15.1692(8)\ \text{\AA}$	$\beta = 100.749(2)^\circ$
Reflexen mit	$c = 16.7138(9)\ \text{\AA}$	$\gamma = 94.237(2)^\circ$
2.2 $^\circ < \theta < 27.5^\circ$)	$V = 2127.3(4)\ \text{\AA}^3$	$z = 4$ $F(000) = 928$
Temperatur	-100 $^\circ C$	
Dichte	$d_{r\ddot{o}n} = 1.388\ g\ cm^{-3}$	

Datensammlung

Diffraktometer	SMART CCD
Strahlung	Mo- K_α Graphitmonochromator
Scan – Typ	ω, φ scans
Scan – Breite	0.5 $^\circ$
Meßbereich	2 $^\circ \leq \theta \leq 28^\circ$ -12 $\leq h \leq 12$ -19 $\leq k \leq 19$ -20 $\leq l \leq 22$
Reflexzahl:	
gemessen	29569
unabhängige	10121 ($R_{int} = 0.0349$)
beobachtete	7293 ($ F /\sigma(F) > 4.0$)

Datenkorrektur, Strukturlösung und -verfeinerung

Korrekturen	Lorentz- und Polarisationskorrektur.
Lösung	Programm: SIR-97 (Direkte Methoden)
Verfeinerung	Programm: SHELXL-97 (Vollmatrixverfahren). 563 verfeinerte Parameter, gewichtete Verfeinerung: $w = 1/[\sigma^2(F_o^2) + (0.0548 * P)^2 + 0.71 * P]$ wobei $P = (\text{Max}(F_o^2, 0) + 2 * F_o^2) / 3$. Wasserstoffatome geometrisch eingefügt und reitend verfeinert, Nichtwasserstoffatome anisotrop verfeinert.
Diskrepanzfaktor	$wR2 = 0.1201$ ($R1 = 0.0441$ für beobachtete Reflexe, 0.0704 für alle Reflexe)
Fitgüte	$S = 1.014$
maximale Änderung der Parameter	0.001 * e.s.d
maximale Peakhöhe in diff. Fouriersynthese	0.78, -0.41 $e\ \text{\AA}^{-3}$

Table VII-7: Bond lengths [\AA] for β -299ca

N(1A)-C(2A)	1.429(2)	N(1B)-C(2B)	1.428(3)
N(1A)-C(13A)	1.436(2)	N(1B)-C(13B)	1.440(3)
N(1A)-S(14A)	1.6659(16)	N(1B)-S(14B)	1.6674(18)
C(2A)-C(3A)	1.385(3)	C(2B)-C(3B)	1.383(3)
C(2A)-C(7A)	1.402(3)	C(2B)-C(7B)	1.399(3)
C(3A)-C(4A)	1.385(3)	C(3B)-C(4B)	1.391(4)
C(3A)-H(3A)	0.9500	C(3B)-H(3B)	0.9500
C(4A)-C(5A)	1.380(3)	C(4B)-C(5B)	1.369(4)
C(4A)-H(4A)	0.9500	C(4B)-H(4B)	0.9500
C(5A)-C(6A)	1.383(3)	C(5B)-C(6B)	1.381(4)
C(5A)-H(5A)	0.9500	C(5B)-H(5B)	0.9500
C(6A)-C(7A)	1.396(3)	C(6B)-C(7B)	1.403(3)
C(6A)-H(6A)	0.9500	C(6B)-H(6B)	0.9500
C(7A)-C(8A)	1.468(3)	C(7B)-C(8B)	1.460(3)
C(8A)-C(9A)	1.364(3)	C(8B)-C(9B)	1.364(3)
C(8A)-C(13A)	1.455(3)	C(8B)-C(13B)	1.458(3)
C(9A)-C(10A)	1.465(3)	C(9B)-C(10B)	1.461(3)
C(9A)-C(24A)	1.503(3)	C(9B)-C(24B)	1.512(3)
C(10A)-N(25A)	1.283(3)	C(10B)-N(25B)	1.280(3)
C(10A)-S(11A)	1.769(2)	C(10B)-S(11B)	1.777(2)
S(11A)-C(12A)	1.721(2)	S(11B)-C(12B)	1.725(2)
C(12A)-C(13A)	1.339(3)	C(12B)-C(13B)	1.337(3)
C(12A)-H(12A)	0.9500	C(12B)-H(12B)	0.9500
S(14A)-O(15A)	1.4255(15)	S(14B)-O(15B)	1.4241(17)
S(14A)-O(16A)	1.4271(15)	S(14B)-O(16B)	1.4289(16)
S(14A)-C(17A)	1.751(2)	S(14B)-C(17B)	1.752(2)
C(17A)-C(18A)	1.386(3)	C(17B)-C(22B)	1.379(3)
C(17A)-C(22A)	1.389(3)	C(17B)-C(18B)	1.389(3)
C(18A)-C(19A)	1.380(3)	C(18B)-C(19B)	1.380(3)
C(18A)-H(18A)	0.9500	C(18B)-H(18B)	0.9500
C(19A)-C(20A)	1.391(3)	C(19B)-C(20B)	1.384(4)
C(19A)-H(19A)	0.9500	C(19B)-H(19B)	0.9500
C(20A)-C(21A)	1.387(3)	C(20B)-C(21B)	1.379(4)
C(20A)-C(23A)	1.502(3)	C(20B)-C(23B)	1.512(3)
C(21A)-C(22A)	1.380(3)	C(21B)-C(22B)	1.383(3)
C(21A)-H(21A)	0.9500	C(21B)-H(21B)	0.9500
C(22A)-H(22A)	0.9500	C(22B)-H(22B)	0.9500
C(23A)-H(23A)	0.9800	C(23B)-H(23D)	0.9800
C(23A)-H(23B)	0.9800	C(23B)-H(23E)	0.9800
C(23A)-H(23C)	0.9800	C(23B)-H(23F)	0.9800
C(24A)-H(24A)	0.9800	C(24B)-H(24D)	0.9800
C(24A)-H(24B)	0.9800	C(24B)-H(24E)	0.9800
C(24A)-H(24C)	0.9800	C(24B)-H(24F)	0.9800
N(25A)-C(26A)	1.415(3)	N(25B)-C(26B)	1.406(3)
C(26A)-C(27A)	1.379(3)	C(26B)-C(27B)	1.378(3)
C(26A)-C(31A)	1.385(3)	C(26B)-C(31B)	1.389(3)
C(27A)-C(28A)	1.383(4)	C(27B)-C(28B)	1.380(4)
C(27A)-H(27A)	0.9500	C(27B)-H(27B)	0.9500
C(28A)-C(29A)	1.371(4)	C(28B)-C(29B)	1.364(4)
C(28A)-H(28A)	0.9500	C(28B)-H(28B)	0.9500
C(29A)-C(30A)	1.373(4)	C(29B)-C(30B)	1.372(4)
C(29A)-H(29A)	0.9500	C(29B)-H(29B)	0.9500
C(30A)-C(31A)	1.384(4)	C(30B)-C(31B)	1.378(4)
C(30A)-H(30A)	0.9500	C(30B)-H(30B)	0.9500
C(31A)-H(31A)	0.9500	C(31B)-H(31B)	0.9500

Table VII-8: Bond angles [deg] for β -299ca

C(2A)-N(1A)-C(13A)	107.99(15)	C(2B)-N(1B)-C(13B)	107.83(17)
C(2A)-N(1A)-S(14A)	124.64(13)	C(2B)-N(1B)-S(14B)	124.10(15)
C(13A)-N(1A)-S(14A)	122.07(13)	C(13B)-N(1B)-S(14B)	121.76(14)
C(3A)-C(2A)-C(7A)	122.10(18)	C(3B)-C(2B)-C(7B)	122.3(2)
C(3A)-C(2A)-N(1A)	128.44(18)	C(3B)-C(2B)-N(1B)	128.3(2)
C(7A)-C(2A)-N(1A)	109.38(17)	C(7B)-C(2B)-N(1B)	109.39(19)
C(4A)-C(3A)-C(2A)	117.4(2)	C(2B)-C(3B)-C(4B)	117.4(3)
C(4A)-C(3A)-H(3A)	121.3	C(2B)-C(3B)-H(3B)	121.3
C(2A)-C(3A)-H(3A)	121.3	C(4B)-C(3B)-H(3B)	121.3
C(5A)-C(4A)-C(3A)	121.9(2)	C(5B)-C(4B)-C(3B)	121.6(3)
C(5A)-C(4A)-H(4A)	119.1	C(5B)-C(4B)-H(4B)	119.2
C(3A)-C(4A)-H(4A)	119.1	C(3B)-C(4B)-H(4B)	119.2
C(4A)-C(5A)-C(6A)	120.4(2)	C(4B)-C(5B)-C(6B)	120.9(2)
C(4A)-C(5A)-H(5A)	119.8	C(4B)-C(5B)-H(5B)	119.6
C(6A)-C(5A)-H(5A)	119.8	C(6B)-C(5B)-H(5B)	119.6
C(5A)-C(6A)-C(7A)	119.5(2)	C(5B)-C(6B)-C(7B)	119.3(2)
C(5A)-C(6A)-H(6A)	120.2	C(5B)-C(6B)-H(6B)	120.3
C(7A)-C(6A)-H(6A)	120.2	C(7B)-C(6B)-H(6B)	120.3
C(6A)-C(7A)-C(2A)	118.70(19)	C(2B)-C(7B)-C(6B)	118.5(2)
C(6A)-C(7A)-C(8A)	132.95(19)	C(2B)-C(7B)-C(8B)	108.67(18)
C(2A)-C(7A)-C(8A)	108.25(16)	C(6B)-C(7B)-C(8B)	132.8(2)
C(9A)-C(8A)-C(13A)	123.94(18)	C(9B)-C(8B)-C(13B)	123.72(19)
C(9A)-C(8A)-C(7A)	129.66(18)	C(9B)-C(8B)-C(7B)	129.98(18)
C(13A)-C(8A)-C(7A)	106.37(16)	C(13B)-C(8B)-C(7B)	106.28(18)
C(8A)-C(9A)-C(10A)	121.81(18)	C(8B)-C(9B)-C(10B)	122.24(18)
C(8A)-C(9A)-C(24A)	123.15(19)	C(8B)-C(9B)-C(24B)	122.7(2)
C(10A)-C(9A)-C(24A)	114.91(18)	C(10B)-C(9B)-C(24B)	114.99(19)
N(25A)-C(10A)-C(9A)	119.54(19)	N(25B)-C(10B)-C(9B)	119.01(18)
N(25A)-C(10A)-S(11A)	120.38(17)	N(25B)-C(10B)-S(11B)	121.17(17)
C(9A)-C(10A)-S(11A)	120.08(15)	C(9B)-C(10B)-S(11B)	119.82(15)
C(12A)-S(11A)-C(10A)	104.78(10)	C(12B)-S(11B)-C(10B)	104.57(10)
C(13A)-C(12A)-S(11A)	122.37(16)	C(13B)-C(12B)-S(11B)	122.56(16)
C(13A)-C(12A)-H(12A)	118.8	C(13B)-C(12B)-H(12B)	118.7
S(11A)-C(12A)-H(12A)	118.8	S(11B)-C(12B)-H(12B)	118.7
C(12A)-C(13A)-N(1A)	126.85(18)	C(12B)-C(13B)-N(1B)	127.04(18)
C(12A)-C(13A)-C(8A)	125.28(18)	C(12B)-C(13B)-C(8B)	125.2(2)
N(1A)-C(13A)-C(8A)	107.88(16)	N(1B)-C(13B)-C(8B)	107.74(17)
O(15A)-S(14A)-O(16A)	119.65(9)	O(15B)-S(14B)-O(16B)	119.76(10)
O(15A)-S(14A)-N(1A)	106.32(8)	O(15B)-S(14B)-N(1B)	106.28(10)
O(16A)-S(14A)-N(1A)	106.06(8)	O(16B)-S(14B)-N(1B)	106.09(9)
O(15A)-S(14A)-C(17A)	109.16(9)	O(15B)-S(14B)-C(17B)	109.44(10)
O(16A)-S(14A)-C(17A)	109.23(9)	O(16B)-S(14B)-C(17B)	108.75(10)
N(1A)-S(14A)-C(17A)	105.46(9)	N(1B)-S(14B)-C(17B)	105.57(9)
C(18A)-C(17A)-C(22A)	121.26(19)	C(22B)-C(17B)-C(18B)	120.9(2)
C(18A)-C(17A)-S(14A)	118.97(15)	C(22B)-C(17B)-S(14B)	119.69(17)
C(22A)-C(17A)-S(14A)	119.77(16)	C(18B)-C(17B)-S(14B)	119.41(17)
C(19A)-C(18A)-C(17A)	118.71(18)	C(19B)-C(18B)-C(17B)	118.5(2)
C(19A)-C(18A)-H(18A)	120.6	C(19B)-C(18B)-H(18B)	120.7
C(17A)-C(18A)-H(18A)	120.6	C(17B)-C(18B)-H(18B)	120.7
C(18A)-C(19A)-C(20A)	121.3(2)	C(18B)-C(19B)-C(20B)	121.7(2)
C(18A)-C(19A)-H(19A)	119.4	C(18B)-C(19B)-H(19B)	119.2
C(20A)-C(19A)-H(19A)	119.4	C(20B)-C(19B)-H(19B)	119.2
C(21A)-C(20A)-C(19A)	118.8(2)	C(21B)-C(20B)-C(19B)	118.5(2)
C(21A)-C(20A)-C(23A)	120.7(2)	C(21B)-C(20B)-C(23B)	120.9(3)

C(19A)-C(20A)-C(23A)	120.5(2)	C(19B)-C(20B)-C(23B)	120.6(3)
C(22A)-C(21A)-C(20A)	121.13(19)	C(20B)-C(21B)-C(22B)	121.2(2)
C(22A)-C(21A)-H(21A)	119.4	C(20B)-C(21B)-H(21B)	119.4
C(20A)-C(21A)-H(21A)	119.4	C(22B)-C(21B)-H(21B)	119.4
C(21A)-C(22A)-C(17A)	118.87(19)	C(17B)-C(22B)-C(21B)	119.2(2)
C(21A)-C(22A)-H(22A)	120.6	C(17B)-C(22B)-H(22B)	120.4
C(17A)-C(22A)-H(22A)	120.6	C(21B)-C(22B)-H(22B)	120.4
C(20A)-C(23A)-H(23A)	109.5	C(20B)-C(23B)-H(23D)	109.5
C(20A)-C(23A)-H(23B)	109.5	C(20B)-C(23B)-H(23E)	109.5
H(23A)-C(23A)-H(23B)	109.5	H(23D)-C(23B)-H(23E)	109.5
C(20A)-C(23A)-H(23C)	109.5	C(20B)-C(23B)-H(23F)	109.5
H(23A)-C(23A)-H(23C)	109.5	H(23D)-C(23B)-H(23F)	109.5
H(23B)-C(23A)-H(23C)	109.5	H(23E)-C(23B)-H(23F)	109.5
C(9A)-C(24A)-H(24A)	109.5	C(9B)-C(24B)-H(24D)	109.5
C(9A)-C(24A)-H(24B)	109.5	C(9B)-C(24B)-H(24E)	109.5
H(24A)-C(24A)-H(24B)	109.5	H(24D)-C(24B)-H(24E)	109.5
C(9A)-C(24A)-H(24C)	109.5	C(9B)-C(24B)-H(24F)	109.5
H(24A)-C(24A)-H(24C)	109.5	H(24D)-C(24B)-H(24F)	109.5
H(24B)-C(24A)-H(24C)	109.5	H(24E)-C(24B)-H(24F)	109.5
C(10A)-N(25A)-C(26A)	121.39(19)	C(10B)-N(25B)-C(26B)	123.26(18)
C(27A)-C(26A)-C(31A)	118.9(2)	C(27B)-C(26B)-C(31B)	119.0(2)
C(27A)-C(26A)-N(25A)	122.3(2)	C(27B)-C(26B)-N(25B)	122.9(2)
C(31A)-C(26A)-N(25A)	118.5(2)	C(31B)-C(26B)-N(25B)	117.7(2)
C(26A)-C(27A)-C(28A)	120.5(2)	C(26B)-C(27B)-C(28B)	120.2(3)
C(26A)-C(27A)-H(27A)	119.7	C(26B)-C(27B)-H(27B)	119.9
C(28A)-C(27A)-H(27A)	119.7	C(28B)-C(27B)-H(27B)	119.9
C(29A)-C(28A)-C(27A)	120.5(3)	C(29B)-C(28B)-C(27B)	120.8(3)
C(29A)-C(28A)-H(28A)	119.8	C(29B)-C(28B)-H(28B)	119.6
C(27A)-C(28A)-H(28A)	119.8	C(27B)-C(28B)-H(28B)	119.6
C(28A)-C(29A)-C(30A)	119.2(3)	C(28B)-C(29B)-C(30B)	119.3(3)
C(28A)-C(29A)-H(29A)	120.4	C(28B)-C(29B)-H(29B)	120.3
C(30A)-C(29A)-H(29A)	120.4	C(30B)-C(29B)-H(29B)	120.3
C(29A)-C(30A)-C(31A)	120.9(3)	C(29B)-C(30B)-C(31B)	120.8(3)
C(29A)-C(30A)-H(30A)	119.6	C(29B)-C(30B)-H(30B)	119.6
C(31A)-C(30A)-H(30A)	119.6	C(31B)-C(30B)-H(30B)	119.6
C(30A)-C(31A)-C(26A)	119.9(2)	C(30B)-C(31B)-C(26B)	119.9(3)
C(30A)-C(31A)-H(31A)	120.0	C(30B)-C(31B)-H(31B)	120.0
C(26A)-C(31A)-H(31A)	120.0	C(26B)-C(31B)-H(31B)	120.0

Table VII-9: Torsion angles [deg] for β -299ca

C(13A)-N(1A)-C(2A)-C(3A)	179.6(2)	C(13B)-N(1B)-C(2B)-C(3B)	-179.8(2)
S(14A)-N(1A)-C(2A)-C(3A)	25.1(3)	S(14B)-N(1B)-C(2B)-C(3B)	-27.5(3)
C(13A)-N(1A)-C(2A)-C(7A)	-3.8(2)	C(13B)-N(1B)-C(2B)-C(7B)	2.8(2)
S(14A)-N(1A)-C(2A)-C(7A)	-158.39(14)	S(14B)-N(1B)-C(2B)-C(7B)	155.11(15)
C(7A)-C(2A)-C(3A)-C(4A)	-0.5(3)	C(7B)-C(2B)-C(3B)-C(4B)	-1.5(4)
N(1A)-C(2A)-C(3A)-C(4A)	175.62(19)	N(1B)-C(2B)-C(3B)-C(4B)	-178.6(2)
C(2A)-C(3A)-C(4A)-C(5A)	-1.7(3)	C(2B)-C(3B)-C(4B)-C(5B)	2.1(4)
C(3A)-C(4A)-C(5A)-C(6A)	1.7(4)	C(3B)-C(4B)-C(5B)-C(6B)	-0.3(4)
C(4A)-C(5A)-C(6A)-C(7A)	0.4(3)	C(4B)-C(5B)-C(6B)-C(7B)	-2.1(4)
C(5A)-C(6A)-C(7A)-C(2A)	-2.5(3)	C(3B)-C(2B)-C(7B)-C(6B)	-0.8(3)
C(5A)-C(6A)-C(7A)-C(8A)	-178.3(2)	N(1B)-C(2B)-C(7B)-C(6B)	176.74(18)
C(3A)-C(2A)-C(7A)-C(6A)	2.6(3)	C(3B)-C(2B)-C(7B)-C(8B)	-179.1(2)
N(1A)-C(2A)-C(7A)-C(6A)	-174.23(17)	N(1B)-C(2B)-C(7B)-C(8B)	-1.5(2)
C(3A)-C(2A)-C(7A)-C(8A)	179.35(18)	C(5B)-C(6B)-C(7B)-C(2B)	2.6(3)
N(1A)-C(2A)-C(7A)-C(8A)	2.6(2)	C(5B)-C(6B)-C(7B)-C(8B)	-179.6(2)

C(6A)-C(7A)-C(8A)-C(9A)	-2.4(4)	C(2B)-C(7B)-C(8B)-C(9B)	178.5(2)
C(2A)-C(7A)-C(8A)-C(9A)	-178.5(2)	C(6B)-C(7B)-C(8B)-C(9B)	0.6(4)
C(6A)-C(7A)-C(8A)-C(13A)	175.8(2)	C(2B)-C(7B)-C(8B)-C(13B)	-0.3(2)
C(2A)-C(7A)-C(8A)-C(13A)	-0.3(2)	C(6B)-C(7B)-C(8B)-C(13B)	-178.2(2)
C(13A)-C(8A)-C(9A)-C(10A)	-5.6(3)	C(13B)-C(8B)-C(9B)-C(10B)	6.0(3)
C(7A)-C(8A)-C(9A)-C(10A)	172.34(19)	C(7B)-C(8B)-C(9B)-C(10B)	-172.7(2)
C(13A)-C(8A)-C(9A)-C(24A)	178.8(2)	C(13B)-C(8B)-C(9B)-C(24B)	-177.7(2)
C(7A)-C(8A)-C(9A)-C(24A)	-3.3(3)	C(7B)-C(8B)-C(9B)-C(24B)	3.6(4)
C(8A)-C(9A)-C(10A)-N(25A)	-164.4(2)	C(8B)-C(9B)-C(10B)-N(25B)	164.6(2)
C(24A)-C(9A)-C(10A)-N(25A)	11.6(3)	C(24B)-C(9B)-C(10B)-N(25B)	-12.0(3)
C(8A)-C(9A)-C(10A)-S(11A)	14.8(3)	C(8B)-C(9B)-C(10B)-S(11B)	-15.6(3)
C(24A)-C(9A)-C(10A)-S(11A)	-169.15(17)	C(24B)-C(9B)-C(10B)-S(11B)	+167.81(17)
N(25A)-C(10A)-S(11A)-C(12A)	164.98(18)	N(25B)-C(10B)-S(11B)-C(12B)	-165.89(19)
C(9A)-C(10A)-S(11A)-C(12A)	-14.2(2)	C(9B)-C(10B)-S(11B)-C(12B)	14.4(2)
C(10A)-S(11A)-C(12A)-C(13A)	6.6(2)	C(10B)-S(11B)-C(12B)-C(13B)	-5.8(2)
S(11A)-C(12A)-C(13A)-N(1A)	-178.19(16)	S(11B)-C(12B)-C(13B)-N(1B)	178.52(16)
S(11A)-C(12A)-C(13A)-C(8A)	1.4(3)	S(11B)-C(12B)-C(13B)-C(8B)	-2.8(3)
C(2A)-N(1A)-C(13A)-C(12A)	-176.75(19)	C(2B)-N(1B)-C(13B)-C(12B)	175.9(2)
S(14A)-N(1A)-C(13A)-C(12A)	-21.4(3)	S(14B)-N(1B)-C(13B)-C(12B)	22.9(3)
C(2A)-N(1A)-C(13A)-C(8A)	3.6(2)	C(2B)-N(1B)-C(13B)-C(8B)	-3.0(2)
S(14A)-N(1A)-C(13A)-C(8A)	158.90(13)	S(14B)-N(1B)-C(13B)-C(8B)	-156.04(14)
C(9A)-C(8A)-C(13A)-C(12A)	-3.4(3)	C(9B)-C(8B)-C(13B)-C(12B)	4.1(3)
C(7A)-C(8A)-C(13A)-C(12A)	178.32(19)	C(7B)-C(8B)-C(13B)-C(12B)	-176.9(2)
C(9A)-C(8A)-C(13A)-N(1A)	176.31(18)	C(9B)-C(8B)-C(13B)-N(1B)	-176.93(19)
C(7A)-C(8A)-C(13A)-N(1A)	-2.0(2)	C(7B)-C(8B)-C(13B)-N(1B)	2.0(2)
C(2A)-N(1A)-S(14A)-O(15A)	-32.36(18)	C(2B)-N(1B)-S(14B)-O(15B)	33.6(2)
C(13A)-N(1A)-S(14A)-O(15A)	176.49(15)	C(13B)-N(1B)-S(14B)-O(15B)	-177.74(16)
C(2A)-N(1A)-S(14A)-O(16A)	-160.73(15)	C(2B)-N(1B)-S(14B)-O(16B)	162.11(17)
C(13A)-N(1A)-S(14A)-O(16A)	48.12(17)	C(13B)-N(1B)-S(14B)-O(16B)	-49.25(18)
C(2A)-N(1A)-S(14A)-C(17A)	83.47(17)	C(2B)-N(1B)-S(14B)-C(17B)	-82.56(19)
C(13A)-N(1A)-S(14A)-C(17A)	-67.68(17)	C(13B)-N(1B)-S(14B)-C(17B)	66.08(18)
O(15A)-S(14A)-C(17A)-C(18A)	36.65(18)	O(15B)-S(14B)-C(17B)-C(22B)	128.49(17)
O(16A)-S(14A)-C(17A)-C(18A)	169.17(15)	O(16B)-S(14B)-C(17B)-C(22B)	-4.02(19)
N(1A)-S(14A)-C(17A)-C(18A)	-77.22(16)	N(1B)-S(14B)-C(17B)-C(22B)	-117.50(17)
O(15A)-S(14A)-C(17A)-C(22A)	-142.83(15)	O(15B)-S(14B)-C(17B)-C(18B)	-50.74(19)
O(16A)-S(14A)-C(17A)-C(22A)	-10.31(18)	O(16B)-S(14B)-C(17B)-C(18B)	176.76(16)
N(1A)-S(14A)-C(17A)-C(22A)	103.30(16)	N(1B)-S(14B)-C(17B)-C(18B)	63.27(18)
C(22A)-C(17A)-C(18A)-C(19A)	-1.1(3)	C(22B)-C(17B)-C(18B)-C(19B)	1.2(3)
S(14A)-C(17A)-C(18A)-C(19A)	179.45(15)	S(14B)-C(17B)-C(18B)-C(19B)	-179.61(17)
C(17A)-C(18A)-C(19A)-C(20A)	-0.1(3)	C(17B)-C(18B)-C(19B)-C(20B)	-0.6(3)
C(18A)-C(19A)-C(20A)-C(21A)	1.2(3)	C(18B)-C(19B)-C(20B)-C(21B)	-0.9(4)
C(18A)-C(19A)-C(20A)-C(23A)	-177.1(2)	C(18B)-C(19B)-C(20B)-C(23B)	178.6(2)
C(19A)-C(20A)-C(21A)-C(22A)	-1.2(3)	C(19B)-C(20B)-C(21B)-C(22B)	1.9(4)
C(23A)-C(20A)-C(21A)-C(22A)	177.2(2)	C(23B)-C(20B)-C(21B)-C(22B)	-177.6(2)
C(20A)-C(21A)-C(22A)-C(17A)	0.1(3)	C(18B)-C(17B)-C(22B)-C(21B)	-0.3(3)
C(18A)-C(17A)-C(22A)-C(21A)	1.1(3)	S(14B)-C(17B)-C(22B)-C(21B)	-179.47(17)
S(14A)-C(17A)-C(22A)-C(21A)	-179.45(15)	C(20B)-C(21B)-C(22B)-C(17B)	-1.3(3)
C(9A)-C(10A)-N(25A)-C(26A)	176.5(2)	C(9B)-C(10B)-N(25B)-C(26B)	-179.3(2)
S(11A)-C(10A)-N(25A)-C(26A)	-2.7(3)	S(11B)-C(10B)-N(25B)-C(26B)	1.0(3)
C(10A)-N(25A)-C(26A)-C(27A)	74.8(3)	C(10B)-N(25B)-C(26B)-C(27B)	-68.9(3)
C(10A)-N(25A)-C(26A)-C(31A)	-110.9(3)	C(10B)-N(25B)-C(26B)-C(31B)	118.7(2)
C(31A)-C(26A)-C(27A)-C(28A)	0.7(4)	C(31B)-C(26B)-C(27B)-C(28B)	-0.9(3)
N(25A)-C(26A)-C(27A)-C(28A)	174.9(2)	N(25B)-C(26B)-C(27B)-C(28B)	-173.2(2)
C(26A)-C(27A)-C(28A)-C(29A)	0.2(4)	C(26B)-C(27B)-C(28B)-C(29B)	0.2(4)
C(27A)-C(28A)-C(29A)-C(30A)	-0.3(5)	C(27B)-C(28B)-C(29B)-C(30B)	0.5(4)
C(28A)-C(29A)-C(30A)-C(31A)	-0.6(5)	C(28B)-C(29B)-C(30B)-C(31B)	-0.4(4)
C(29A)-C(30A)-C(31A)-C(26A)	1.5(4)	C(29B)-C(30B)-C(31B)-C(26B)	-0.4(4)
C(27A)-C(26A)-C(31A)-C(30A)	-1.5(4)	C(27B)-C(26B)-C(31B)-C(30B)	1.0(4)
N(25A)-C(26A)-C(31A)-C(30A)	-176.0(2)	N(25B)-C(26B)-C(31B)-C(30B)	173.7(2)

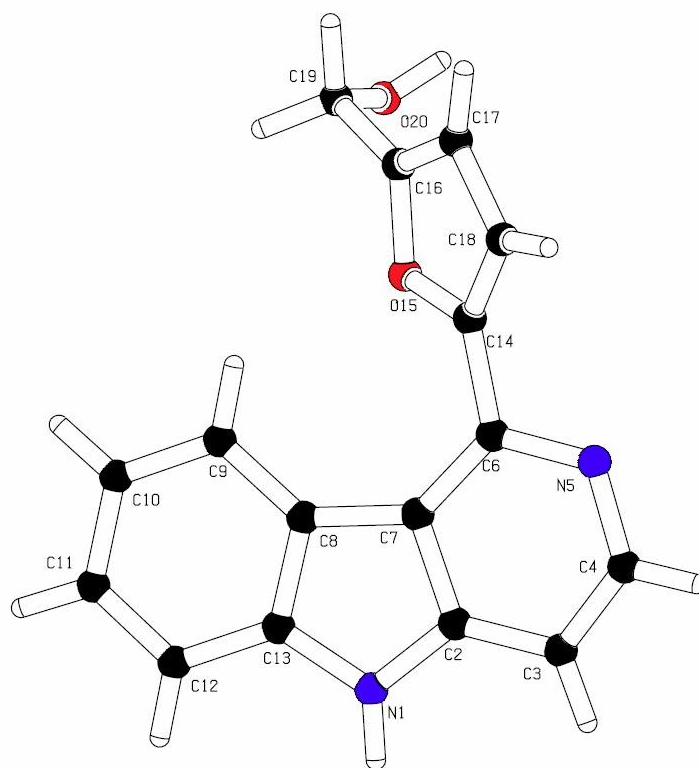
VII.3.4. X-Ray structure of *Isoperlolyrine*

Figure VII-29: X-Ray structure of *Isoperlolyrine*.

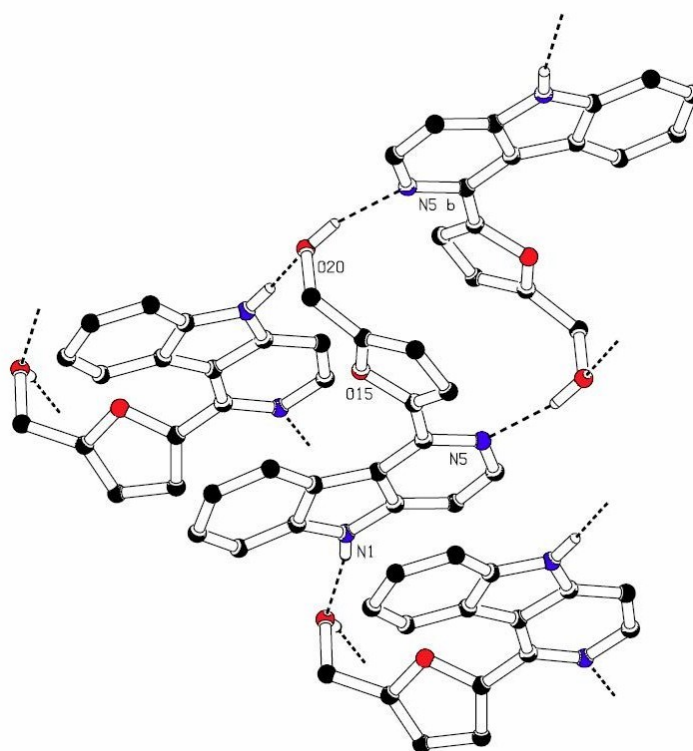


Figure VII-30: X-Ray structure of *Isoperlolyrine* with hydrogen bonds.

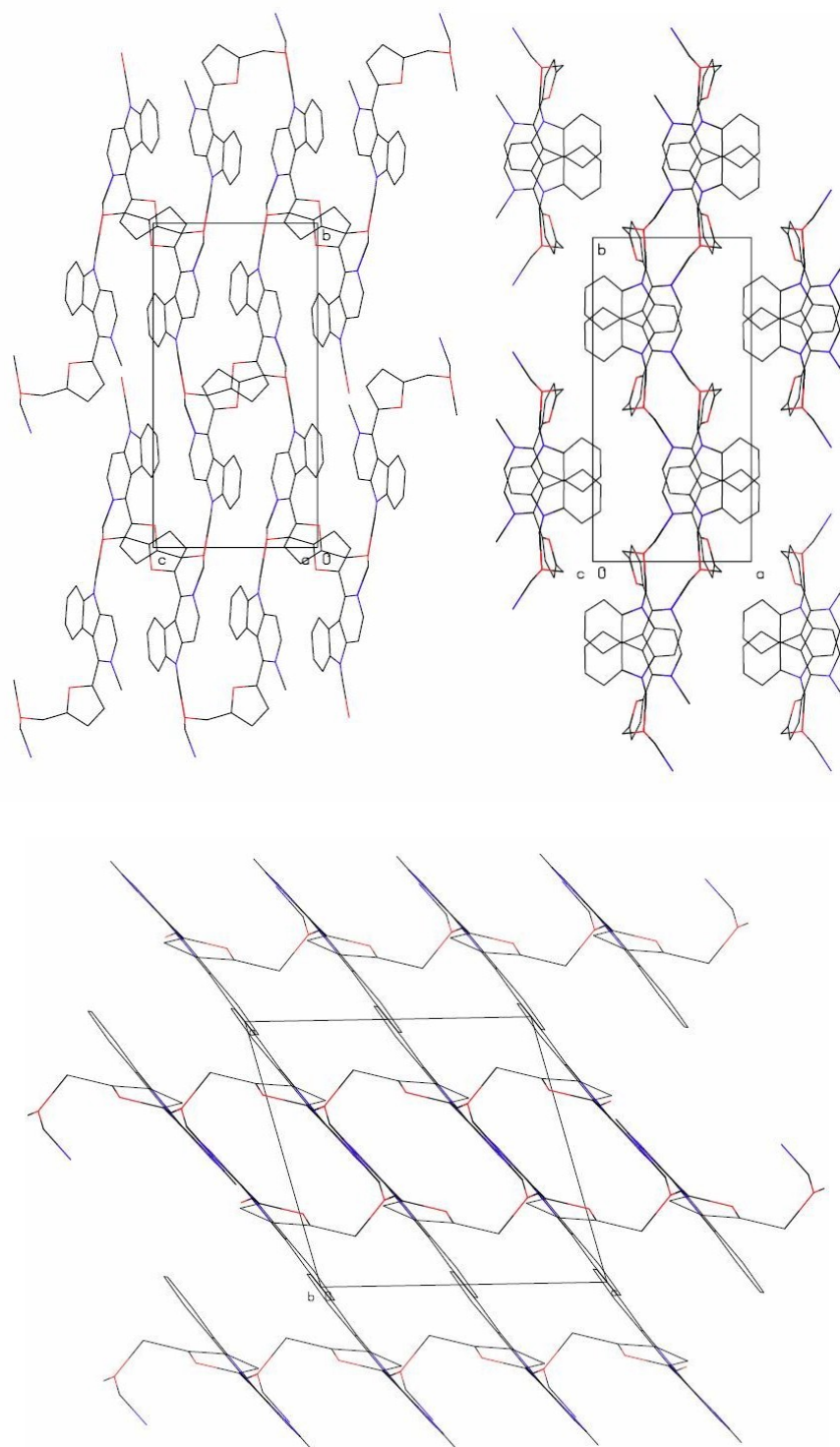


Figure VII-31: Crystalline packing of *Isoperlolyrine*.

Kristalldaten für Isoperlolyrine

Summenformel	C ₁₆ H ₁₂ N ₂ O ₂		
Molgewicht	264.3 g mol ⁻¹		
Absorption	$\mu = 0.79 \text{ mm}^{-1}$		
Kristallgröße	0.1 x 0.2 x 0.4 mm ³ farblose Platte		
Raumgruppe	P 2 ₁ /c (monoklin)		
Gitterkonstanten	a = 8.501(1) Å		
(berechnet aus	b = 16.858(2) Å	$\beta = 105.008(5)^\circ$	
25 Reflexen mit	c = 8.822(1) Å		
22° < θ < 29°)	V = 1221.1(2) Å ³	z = 4	F(000) = 552
Temperatur	-80°C		
Dichte	$d_{\text{rön}} = 1.438 \text{ g cm}^{-3}$		

Datensammlung

Diffraktometer	Turbo Cad4
Strahlung	Cu-K _{α} Graphitmonochromator
Scan – Typ	$\omega/2\theta$ -scans
Scan – Breite	1.0°+0.14*tan(θ)
Meßbereich	2° ≤ θ < 70°
	-10 ≤ h ≤ 10 0 ≤ k ≤ 20 0 ≤ l ≤ 10
Reflexzahl:	
gemessen	2572
unabhängige	2323 (R _{int} = 0.0602)
beobachtete	1510 (F /σ (F) > 4.0)

Datenkorrektur, Strukturlösung und -verfeinerung

Korrekturen	Lorentz- und Polarisationskorrektur.
Lösung	Intensitätsschwankungen mit kubischen Spline korrigiert
Verfeinerung	Programm: SIR-97 (Direkte Methoden)
	Programm: SHELXL-97 (Vollmatrixverfahren). 181
	verfeinerte Parameter, gewichtete Verfeinerung:
	$w=1/[\sigma^2(F_o^2) + (0.*P)^2+0.*P]$
	wobei $P=(\text{Max}(F_o^2,0)+2*F_o^2)/3$. Wasserstoffatome
	geometrisch eingefügt (NH,OH lokalisiert) und reitend
	verfeinert. Nichtwasserstoffatome anisotrop verfeinert.
Diskrepanzfaktor	wR2 = 0.1858 (R1=0.0648 für beobachtete Reflexe,
	0.1066 für alle Reflexe)
Fitgüte	S = 1.036
maximale Änderung	
der Parameter	0.001 * e.s.d
maximale Peakhöhe in	
diff. Fouriersynthese	0.28, -0.24 eÅ ⁻³

Table VII-10: Bond lengths [\AA] for *Isoperlolyrine*

N(1)-C(2)	1.361(4)	C(10)-H(10)	0.9500
N(1)-C(13)	1.382(4)	C(11)-C(12)	1.374(5)
N(1)-H(1)	0.8800	C(11)-H(11)	0.9500
C(2)-C(3)	1.390(5)	C(12)-C(13)	1.387(5)
C(2)-C(7)	1.418(4)	C(12)-H(12)	0.9500
C(3)-C(4)	1.358(5)	C(14)-C(18)	1.337(5)
C(3)-H(3)	0.9500	C(14)-O(15)	1.376(4)
C(4)-N(5)	1.339(4)	O(15)-C(16)	1.375(4)
C(4)-H(4)	0.9500	C(16)-C(17)	1.338(5)
N(5)-C(6)	1.351(4)	C(16)-C(19)	1.483(5)
C(6)-C(7)	1.408(4)	C(17)-C(18)	1.425(5)
C(6)-C(14)	1.463(4)	C(17)-H(17)	0.9500
C(7)-C(8)	1.454(4)	C(18)-H(18)	0.9500
C(8)-C(13)	1.402(5)	C(19)-O(20)	1.430(4)
C(8)-C(9)	1.402(4)	C(19)-H(19A)	0.9900
C(9)-C(10)	1.383(5)	C(19)-H(19B)	0.9900
C(9)-H(9)	0.9500	O(20)-H(20)	0.8400
C(10)-C(11)	1.386(5)		

Table VII-11: Bond angles [deg] for *Isoperlolyrine*

C(2)-N(1)-C(13)	109.4(3)	C(12)-C(11)-H(11)	119.7
C(2)-N(1)-H(1)	125.3	C(10)-C(11)-H(11)	119.7
C(13)-N(1)-H(1)	125.3	C(11)-C(12)-C(13)	118.0(3)
N(1)-C(2)-C(3)	129.7(3)	C(11)-C(12)-H(12)	121.0
N(1)-C(2)-C(7)	109.0(3)	C(13)-C(12)-H(12)	121.0
C(3)-C(2)-C(7)	121.3(3)	N(1)-C(13)-C(12)	128.2(3)
C(4)-C(3)-C(2)	116.0(3)	N(1)-C(13)-C(8)	109.2(3)
C(4)-C(3)-H(3)	122.0	C(12)-C(13)-C(8)	122.5(3)
C(2)-C(3)-H(3)	122.0	C(18)-C(14)-O(15)	109.8(3)
N(5)-C(4)-C(3)	125.9(3)	C(18)-C(14)-C(6)	133.2(3)
N(5)-C(4)-H(4)	117.1	O(15)-C(14)-C(6)	117.0(3)
C(3)-C(4)-H(4)	117.1	C(16)-O(15)-C(14)	106.7(3)
C(4)-N(5)-C(6)	118.4(3)	C(17)-C(16)-O(15)	109.5(3)
N(5)-C(6)-C(7)	121.5(3)	C(17)-C(16)-C(19)	133.9(3)
N(5)-C(6)-C(14)	113.8(3)	O(15)-C(16)-C(19)	116.5(3)
C(7)-C(6)-C(14)	124.7(3)	C(16)-C(17)-C(18)	107.2(3)
C(6)-C(7)-C(2)	116.9(3)	C(16)-C(17)-H(17)	126.4
C(6)-C(7)-C(8)	136.8(3)	C(18)-C(17)-H(17)	126.4
C(2)-C(7)-C(8)	106.2(3)	C(14)-C(18)-C(17)	106.8(3)
C(13)-C(8)-C(9)	118.4(3)	C(14)-C(18)-H(18)	126.6
C(13)-C(8)-C(7)	106.2(3)	C(17)-C(18)-H(18)	126.6
C(9)-C(8)-C(7)	135.5(3)	O(20)-C(19)-C(16)	113.1(3)
C(10)-C(9)-C(8)	118.6(3)	O(20)-C(19)-H(19A)	109.0
C(10)-C(9)-H(9)	120.7	C(16)-C(19)-H(19A)	109.0
C(8)-C(9)-H(9)	120.7	O(20)-C(19)-H(19B)	109.0
C(9)-C(10)-C(11)	121.9(3)	C(16)-C(19)-H(19B)	109.0
C(9)-C(10)-H(10)	119.1	H(19A)-C(19)-H(19B)	107.8
C(11)-C(10)-H(10)	119.1	C(19)-O(20)-H(20)	109.5
C(12)-C(11)-C(10)	120.6(3)		

Table VII-12: Torsion angles [deg] for *Isoperlolyrine*

C(13)-N(1)-C(2)-C(3)	175.9(4)	C(10)-C(11)-C(12)-C(13)	1.2(6)
C(13)-N(1)-C(2)-C(7)	-1.8(4)	C(2)-N(1)-C(13)-C(12)	-176.6(3)
N(1)-C(2)-C(3)-C(4)	-175.7(4)	C(2)-N(1)-C(13)-C(8)	2.1(4)
C(7)-C(2)-C(3)-C(4)	1.7(5)	C(11)-C(12)-C(13)-N(1)	178.5(3)
C(2)-C(3)-C(4)-N(5)	-1.7(6)	C(11)-C(12)-C(13)-C(8)	0.0(5)
C(3)-C(4)-N(5)-C(6)	-0.4(5)	C(9)-C(8)-C(13)-N(1)	179.7(3)
C(4)-N(5)-C(6)-C(7)	2.4(5)	C(7)-C(8)-C(13)-N(1)	-1.6(4)
C(4)-N(5)-C(6)-C(14)	-178.1(3)	C(9)-C(8)-C(13)-C(12)	-1.6(5)
N(5)-C(6)-C(7)-C(2)	-2.3(5)	C(7)-C(8)-C(13)-C(12)	177.2(3)
C(14)-C(6)-C(7)-C(2)	178.3(3)	N(5)-C(6)-C(14)-C(18)	-33.6(5)
N(5)-C(6)-C(7)-C(8)	173.9(4)	C(7)-C(6)-C(14)-C(18)	145.8(4)
C(14)-C(6)-C(7)-C(8)	-5.5(6)	N(5)-C(6)-C(14)-O(15)	143.3(3)
N(1)-C(2)-C(7)-C(6)	178.1(3)	C(7)-C(6)-C(14)-O(15)	-37.2(5)
C(3)-C(2)-C(7)-C(6)	0.2(5)	C(18)-C(14)-O(15)-C(16)	0.0(4)
N(1)-C(2)-C(7)-C(8)	0.8(4)	C(6)-C(14)-O(15)-C(16)	-177.6(3)
C(3)-C(2)-C(7)-C(8)	-177.1(3)	C(14)-O(15)-C(16)-C(17)	-0.6(4)
C(6)-C(7)-C(8)-C(13)	-176.0(4)	C(14)-O(15)-C(16)-C(19)	177.7(3)
C(2)-C(7)-C(8)-C(13)	0.5(4)	O(15)-C(16)-C(17)-C(18)	0.8(4)
C(6)-C(7)-C(8)-C(9)	2.5(7)	C(19)-C(16)-C(17)-C(18)	-177.0(4)
C(2)-C(7)-C(8)-C(9)	179.0(4)	O(15)-C(16)-C(17)-C(18)	0.5(4)
C(13)-C(8)-C(9)-C(10)	2.0(5)	C(6)-C(14)-C(18)-C(17)	177.6(3)
C(7)-C(8)-C(9)-C(10)	-176.3(4)	C(16)-C(17)-C(18)-C(14)	-0.8(4)
C(8)-C(9)-C(10)-C(11)	-0.9(6)	C(17)-C(16)-C(19)-O(20)	113.0(4)
C(9)-C(10)-C(11)-C(12)	-0.7(6)	O(15)-C(16)-C(19)-O(20)	-64.7(4)

Table VII-13: Hydrogen bonds for *Isoperlolyrine* [Å and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(20)#1	0.88	1.99	2.838(3)	162.0
O(20)-H(20)...N(5)#2	0.84	1.92	2.730(3)	162.8

Symmetry transformations used to generate equivalent atoms:

#1 $x, -y+3/2, z-1/2$ #2 $-x+1, -y+1, -z+1$

