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An Overview of Syntheses of Apogalanthamine Analogues and 7-Aza Derivatives of Steganacin and Steganone

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A concise and critical overview of the developments in the synthesis of apogalanthamine analogues and steganacin and steganone 7-aza analogues over the last four decades is presented. These amaryllidaceae alkaloid analogues bear a 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine skeleton, and are well known for their diverse and potent biological activities. This microreview will briefly glance over the history and early developments in the field at the beginning, and will, in the latter parts, concentrate on the recent synthetic developments in the synthesis of the title molecules.

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1. Introduction

During the last two decades, amaryllidaceae alkaloids[1] have been a highly interesting area of research in organic, bio-organic and pharmaceutical chemistry, as the amazing structural diversity of these natural products presents an ample challenge to the creativity of the synthetic chemist.[2] The name amaryllidaceae originated from the word *Amaryllis*, the name of a Greek shepherdess.

In South Africa, plant extracts containing these alkaloids have been used in male adolescent initiation rites, to induce visual hallucinations by diviners as well as for treating a variety of ailments.[3] However, many species in the family have bulbs that contain toxic alkaloids, most of them being fatal to humans and animals if consumed in the slightest overdose.

There has been a plethora of available literature regarding the isolation, structural determination, synthesis and SAR studies of these alkaloids,[4] not to mention the countless attempts to develop structurally similar unnatural analogues to screen them for interesting biological activities such as anticholinergic, antitumor, immunosuppressive, analgesic as well as anti-Alzheimer.[5] For instance, galanthamine[6] is known for its anti-Alzheimer activity, hippadine[7] inhibits the fertility in male rats and narciclasine[8] exhibits potent antimitotic acitivity as well as inhibiting the growth of the pathogenic yeast *Cryptococcus neofroms* while certain derivatives act against the pathogenic bacterium *Neisseris gonorrhoeae* (Figure 1).

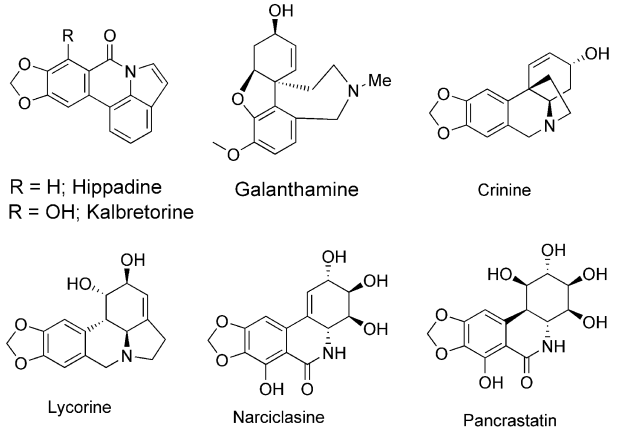


Figure 1. Some biologically active amaryllidaceae alkaloids.

In this contribution, our aim is to present an overview of the developments in the synthesis of amaryllidaceae alkaloids bearing a 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine skeleton. For the clarity of presentation, the subject is treated by roughly dividing the molecules into two groups as apogalanthamine analogues and steganacin/steganone 7-aza analogues. We will attempt to present a critical and concise account on the synthetic developments in the chemistry of 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines over the last four decades.

2. Apogalanthamine and Its Structural Analogues

2.1. The Early History of Apogalanthamine Analogues

Apogalanthamines are a scarcely-studied sub-family of the amaryllidaceae alkaloids comprising natural products of intriguing biological potential.[9] Apogalanthamine analogues feature a unique 5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine skeleton, a biaryl subunit with a fused eight-membered ring-system bearing a nitrogen atom on the benzylic position with respect to the lower a biaryl subunit with a fused eight-membered ring system bearing a nitrogen atom on the benzylic position with respect to the lower aromatic ring (Figure 2).

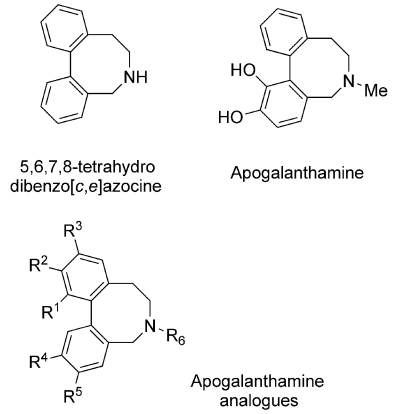
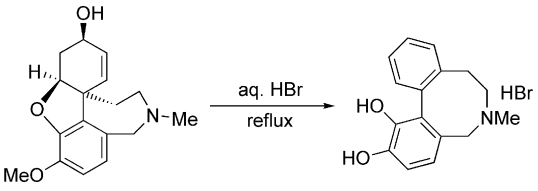


Figure 2. Apogalanthamine analogues.

They are well known for their antihypotensive as well as antiserotonin activities. Furthermore, apogalanthamine analogues are found to act as α-adrenergic blocking agents.[10] Like phentolamine, they are proved to be active against both α_1- and α_2-type adrenergic receptors. It is also well-demonstrated that the substitution pattern on the upper and lower rings of these molecules has a regulatory effect on their biological activities, and therefore can be viewed as a tuning factor whether the molecule shows antiserotonin activity or α-adrenergic activity.[11] Apogalanthamine analogues show also high activity against the *Herpes simplex* virus,[12] and therefore are indeed interesting from the view-point of anti-HIV and antihepatitis studies.

The history of the 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines began in the 1950s with the synthesis of the parent compound apogalanthamine, i.e. 6-methyl-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine-11,12-diol (Scheme 1).[13] Proskurnina and Yakoleva have first reported[14] a transformation of galanthamine (Lycoremine), an alkaloid of the amaryllidaceae family, into a dihydric phenolic base which was later named as apogalanthamine. The authors investigated an acid-mediated transformation of galanthamine, which causes demethylation and cleavage of the oxide ring, accompanied by aromatisation of the cyclohexene ring with concomitant loss of an alcoholic hydroxy group. While searching for more active hypotensive agents, Kobayashi and coworkers have synthesized apogalanthamine as the corresponding hy-

drobromide by refluxing galanthamine in aqeous HBr (Scheme 1).[15] Later, the same group has proposed the synthesis of the corresponding N–H analogue and a small number of *N*-alkylated analogues, starting from galanthamine analogues.



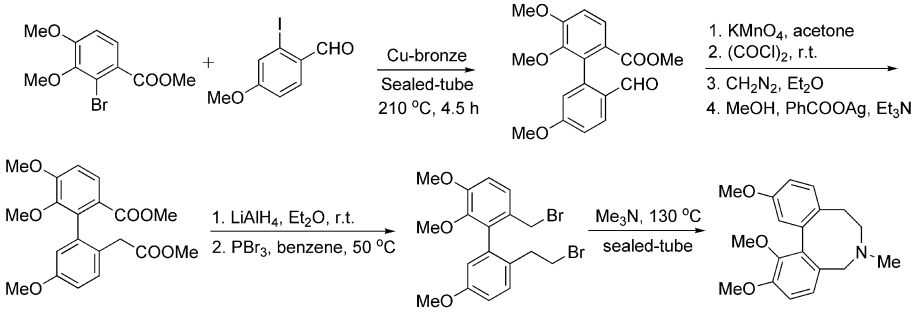
Scheme 1. First synthesis of apogalanthamine from galanthamine.

Very soon, it was found that apogalanthamine has interesting biological properties and this triggered further research to develop a number of structural analogues bearing the dibenzo[*c*,*e*]azocine skeleton. Most of the attempts to synthesize apogalanthamine and its structural analogues came from the pioneering work of the Kobayashi group in the 1970s.

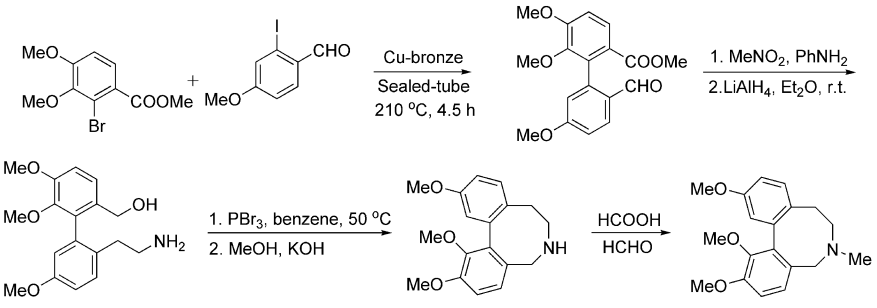
The initial attempts to generate the structural analogues of apogalanthamine were mainly based on Cu-mediated Ullmann-type reactions[16] to generate the biaryl skeleton, followed by various protocols for the ring closure of the thus formed biaryl intermediates to generate the target molecules. However, most of the early attempts were featuring the drawbacks of low yields, harsh conditions and long synthetic sequences. As a typical example, Kobayashi and coworkers has described the first attempt to generate an apogalanthamine analogue,[17] based on Ullmann reaction as the key step (Schemes 2 and 3), where the authors explored two somewhat lengthy sequences for the preparation of the target apogalanthamine analogue.

The first attempt was based on the biaryl intermediate methyl 2′-formyl-5,6,5′-trimethoxy-biphenyl-2-carboxylate, generated in a moderate 32% yield by the Ullmann reaction between 2-iodo-4-methoxybenzaldehyde and methyl 2-bromoveretrate in presence of copper bronze in a sealed tube (Scheme 2). Lengthening of the formyl chain by one carbon was explored by the Arndt–Eistert protocol.[18] Thus, the aldehyde was first oxidized to the corresponding ester by $KMnO_4$ which was converted into the corresponding acid chloride by reacting with oxallyl chloride. The corresponding diazo ketone was then generated using a diazomethane reaction and this diazo ketone was further converted into the corresponding methyl ester by reacting it with methanol in the presence of a catalytic amount of silver benzoate and triethylamine in a good 53% overall yield (Scheme 2). Double reduction of the esters with $LiAlH_4$ followed by the conversion of the resultant alcohols to the corresponding bromides using PBr_3 and a final treatment with methylamine in a sealed tube furnished the target apogalanthamine analogue.

The authors explored an alternative approach in the same report, choosing the same biphenyl ester aldehyde as the key intermediate (Scheme 3). The aldehyde group was converted into the corresponding nitrostyrene by a Henry reaction[19] with nitromethane in the presence of aniline the base. After $LiAlH_4$-mediated reduction to the corresponding amino alcohol,[20] the alcohol function was converted into the corresponding bromide using PBr_3



Scheme 2. Synthesis of apogalanthamine analogues using an Ullmann-type reaction.



Scheme 3. Alternative approach based on an Ullmann-type reaction.

(Scheme 3). The target molecule was obtained by a base-mediated ring closure using methanolic KOH solution, followed by the *N*-methylation of the thus generated secondary amine using a mixture of formic acid and formaldehyde.

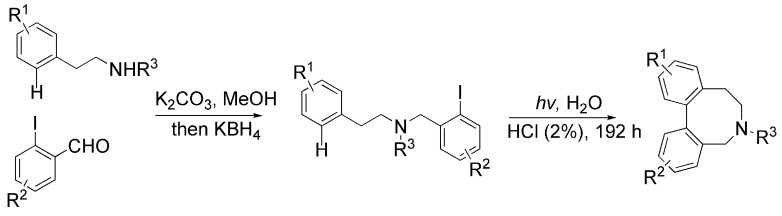
Jeffs and coworkers demonstrated[21] a photochemical synthesis for the synthesis of 6,7-dihydro-5*H*-dibenz[*c*,*e*]-azepine and 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine derivatives in 1975. The authors developed the outer skeleton needed for the photochemical ring closure by the reductive amination of a 2-iodobenzaldehyde derivative with the same amine in presence of a borohydride (Scheme 4). The photochemical ring closures were effected by irradiating the sample in water with 2% HCl at a wavelength of >280 nm with a type L 450 W medium-pressure mercury-vapour lamp. The target molecules were isolated in moderate yields of 30–50% together with some dehalogenated and chlorinated materials.

The Kobayashi group has reported the synthesis of another interesting apogalanthamine analogue, featuring a 2-bromoethyl group as the alkyl chain on the nitrogen atom.[22] This particular compound was targeted due to the observation that it had a more specific α-adrenergic blocking action than phenoxy benzamine on the responses of isolated strips of rat aorta.[23] The selectivity was more towards adrenaline than towards 5-hydroxy-tryptamine (5-HT) and it was more specific and selective in the biological activity. The authors began the synthesis by generating the biaryl axis using an Ullmann reaction between 2-bromopiperonal and methyl 2-bromobenzoate, and the biaryl was isolated in a moderate yield of 21% (Scheme 5).

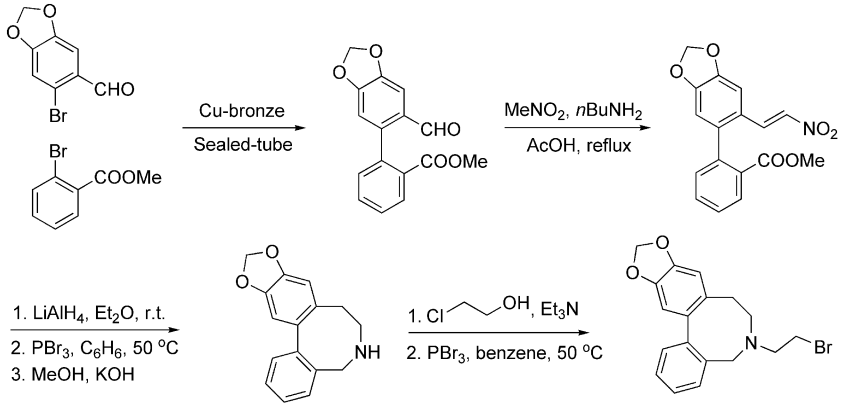
The formyl group was then converted into the corresponding nitroalkene by reacting the biphenyl with nitromethane in acetic acid in presence of *n*-butylamine in a remarkable 93% yield.

The cyclization was effected in three standard steps; reduction of the nitrostyrene to the corresponding amino alcohol using $LiAlH_4$, conversion of the alcohol to the corresponding bromide by reaction with PBr_3 and a based mediated ring closure induced by methanolic KOH. This cyclized form was then reacted with ethylene chlorohydrin in the presence of triethylamine to generate the corresponding aminoethanol which was converted into the target molecule by the reaction of the aminoethanol with PBr_3 (Scheme 5). The same synthetic procedure, based on the Ullmann coupling and base-mediated ring closure through the formation of nitrostyrenes using Henry reaction, was used later on multiple occasions by the Kobayashi group in order to generate a number of diversely functionalized apogalanthamine analogues. Later, an alternative methodology was proposed by the same group for the generation of the key biaryl intermediates (Scheme 6).[24]

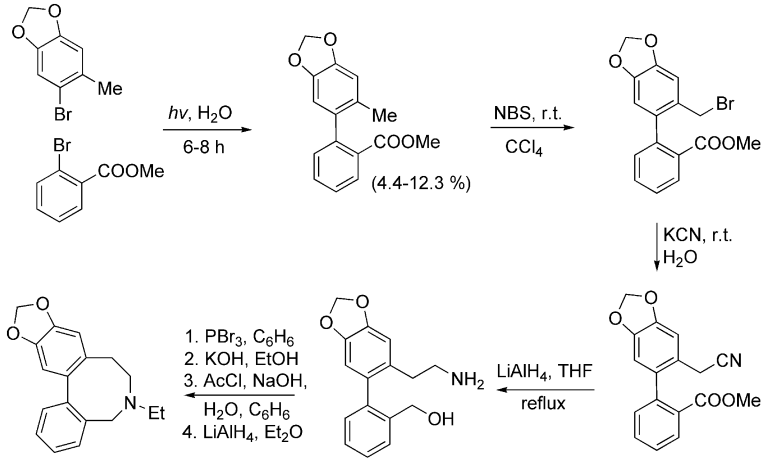
In the modified procedure, the cross-coupling was carried out under UV irradiation, but again yielding the biaryl compound in very poor yield of 4.4–12.3%. The biaryl intermediate was then converted into the corresponding amino alcohol (Scheme 6) by an NBS-mediated bromination followed by a cyanation and subsequent reduction of the cyano-ester by $LiAH_4$. Conversion of the alcohol to the corresponding bromide followed by a base-mediated ring closure yielded the corresponding apogalanthamine analogue (Scheme 6).



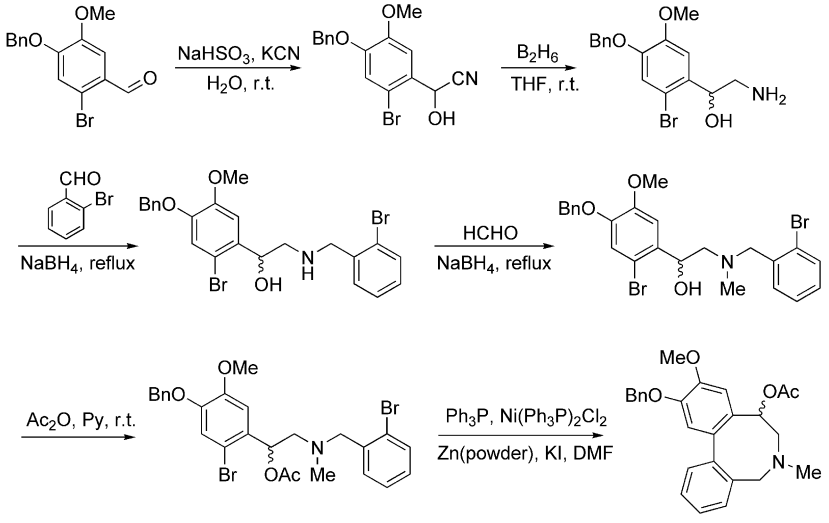
Scheme 4. Synthesis of apogalanthamine analogue using photochemical ring closure.



Scheme 5. Ullmann-reaction in the synthesis of a dibenzo[*c*,*e*]azocine analogue.



Scheme 6. Synthesis of dibenzo[*c*,*e*]azocines using photochemical conditions.



Scheme 7. Synthesis of dibenzo[*c*,*e*]azocines using a Ni^0-mediated Ullmann-type reaction.

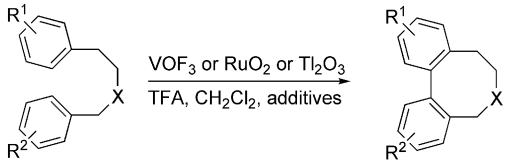
The nitrogen atom was then subjected to *N*-acylation using acetyl chloride and a subsequent $LiAlH_4$-mediated reduction, in view to introduce structural diversity. Another methodology for the synthesis of apogalanthamine analogues was proposed by Kobayashi and coworkers[25] using an intramolecular Ni^0-mediated Ullmann-type coupling reaction as the key step for generation of the biaryl axis (Scheme 7).[26] This procedure utilized Ni^0 species as the catalyst, which can be conveniently generated in situ from $Ni(Ph_3P)_2Cl_2$ in combination with a reducing agent like zinc powder. As can be viewed from Scheme 7, the aldehyde was converted into the corresponding cyanohydrin by the treatment with aqueous KCN.[27] A subsequent borane-mediated reduction generated the required β-hydroxy phenethylamine intermediate. Reductive amination with a suitable *ortho*-bromobenzaldehyde followed by *N*-methylation and *O*-acylation furnished the "open" structure needed for the biaryl-coupling step (Scheme 7).

The final ring closure was effected by the use of $Ni(Ph_3P)_2Cl_2$ and Zn powder in combination with Ph_3P and KI in DMF at 55 °C and the target dibenzo[*c*,*e*]azocine was isolated in a moderate cross-coupling yield of 48%.

2.2. Synthesis of Apogalanthamine Analogues via Metal-Mediated, Non-Phenolic, Oxidative Cyclizations

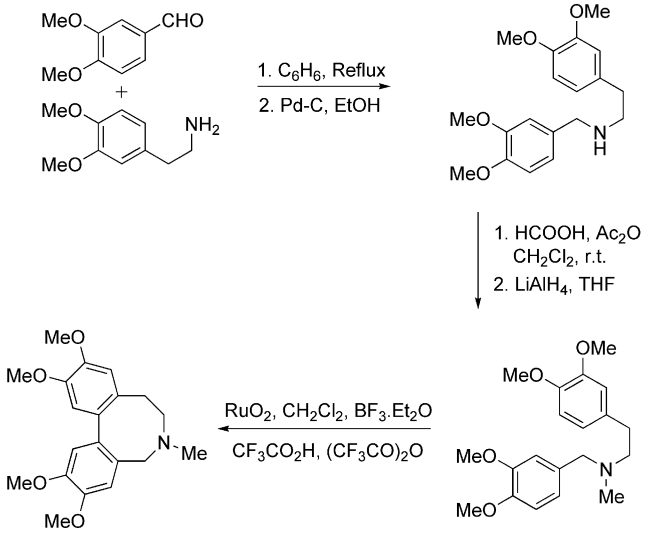
Even though the Ullmann-type cross-couplings and photochemical methods to generate the biaryl skeleton were moderately successful in generating the apogalanthamine analogues, they featured severe drawbacks of low yields and long reaction times. The search for an alternative methodology led to the invention of non-phenolic oxidative biaryl-coupling protocols in the early 1990s,[28] where the apogalanthamine analogues could be prepared in high yields. A number of biogenetic type biaryl coupling reactions has been investigated, often using mercury(II), thallium(III), vanadium(V), iron(III), manganese(IV), or ruthenium(IV) salts such as VOF_3, RuO_2 or Tl_2O_3 etc., in combination

with a strong acid like trifluoroacetic acid (TFA) (Scheme 8).[29] This combination generally provides the catalyst, the metal trifluoroacetate, in an in-situ fashion.



Scheme 8. Metal-mediated, non-phenolic, oxidative cyclizations.

Robin and coworkers demonstrated a general and easy approach to the dibenzazocine skeleton of the apogalanthamines (Scheme 9).[30] The authors used metal-mediated non-phenolic oxidative cyclization to generate the key biaryl axis. The "open" precursors needed for the biaryl coupling reaction were prepared from the commercially available veratraldehyde through a reductive amination with a suitable amine, and the *N*-formylation was effected by the reaction with formic acid/acetic anhydride (FAA) in CH_2Cl_2, affording the formamide in an excellent 89% yield. Standard $LiAlH_4$-mediated reduction of these formamides furnished the required *N*-methyl analogue in good yields (Scheme 9). The authors then investigated a variety of different metal salts to effect the oxidative cyclization. Although they noticed that the use of Tl_2O_3, VOF_3 and $VOCl_3$ in combination with CH_2Cl_2/TFA/TFAA resulted in a complex mixture, RuO_2 together with a CH_2Cl_2/TFA/TFAA mixture in the presence of $BF_3{\cdot}Et_2O$ was found to be satisfactory for the purpose and the resultant apogalanthamine analogue was isolated in moderate yield.



Scheme 9. Ru-mediated oxidative ring closure.

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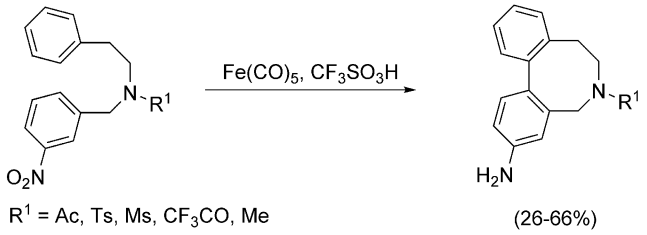
Shudo and coworkers proposed another interesting synthesis of an apogalanthamine analogue[31] using a metal-catalyzed, non-phenolic, intramolecular reductive cyclization strategy, instead of the usually practiced oxidative cyclization protocol (Scheme 10). The advantageous nature of the synthesis was that the biaryl units needed no highly electron-rich substituents for the biaryl formations. This imparted the possibility of a higher versatility for the biaryl skeleton, as the need of highly electron-rich functional groups on the aromatic rings is often a mandatory parameter in the oxidative cyclizations.

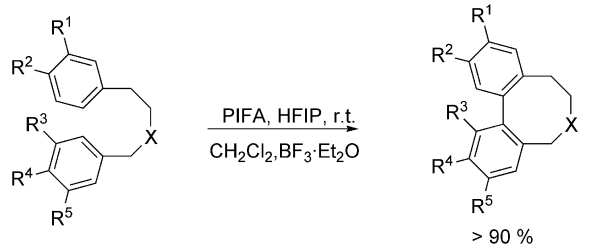


Scheme 10. Reductive cyclization in the synthesis of apogalanthamine analogues.

The authors demonstrated that the direct addition of 2 equiv. of ironpentacarbonyl to the required *N*-substituted benzyl-β-phenyl ethylamines with large excess of trifluoromethanesulfonic acid (up to 100 equiv.) provided the required apogalanthamine analogues (Scheme 10), where the nitro group was also reduced to an amino group, in moderate to good yields. The authors used the same procedure to generate a number of cyclized analogues where the ring size varied from 7–10.

2.3. Synthesis of Apogalanthamine Analogues via Non-Phenolic, Oxidative Cyclizations Using Polyvalent Iodine Reagents

Even though the metal-mediated oxidative cyclizations were successful in generating the apogalanthamine analogues, the corrosive nature of the strong acids together with the lack of regiocontrol during the cyclization and the use of often toxic metals soon demanded the invention of a milder and more environmentally benign protocol. Thus, polyvalent iodine reagents like phenyliodonium(III) bis(trifluoroacetate) [PIFA] were used in the non-phenolic, oxidative biaryl coupling reactions as a milder alternative.[32] The added advantage was the fact that these reagents tolerated a wide variety of functional groups, which was often a problem in the case of metal-based methods, due to the presence of strong reagents like TFA. The pioneering works of Kita and coworkers was crucial in the development of novel protocols for the generation of apogalanthamine analogues. The Kita group demonstrated the use of PIFA in combination with poorly nucleophillic polar solvents[33] like 2 ,2,2-trifluoroethanol (TFE) or 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as a milder and high yielding route to perform the biaryl coupling reactions (Scheme 11).[34]



X = CH_2, O, $NCOCF_3$ etc.; R^1 = OMe or OAlk; R^2 = H, OMe or OAlk; R^3 = OMe or OAlk; R^4 = OMe, OAc, OTBS or OAlk; R^5 = H, OMe etc.

Scheme 11. PIFA-mediated synthesis of apogalanthamine analogues.

Initially, the authors investigated the biaryl coupling of 1,3-diarylpropanes using PIFA together with HFIP as a solvent at room temperature. They found that the reactions proceeded with moderate to good yields, where the use of HFIP was a prerequisite for success. Reactions in other solvents like CF_3CH_2OH, MeCN and CH_2C1_2 furnished the target molecule, albeit in lower yields (Scheme 11).

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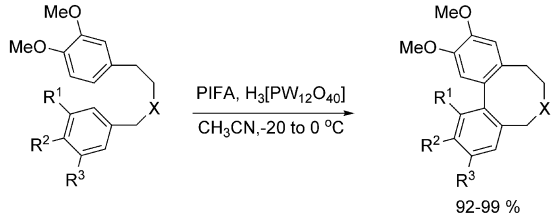
The authors extended the methodology by synthesizing a diverse variety of amaryllidaceae alkaloids as well as interesting spirodienone compounds, which are useful intermediates for the synthesis of some amaryllidaceae alkaloids. In addition the authors proposed a mechanism for the use of PIFA for both phenolic and non-phenolic oxidative coupling reactions (Scheme 12).

The authors concluded that in the case of *p*-substituted phenols, the presence of a free OH group in the molecule likely causes the reaction to proceed via an ionic mechanism in a standard polar solvent, where the major product was a cross-conjugated spirodienone. On the other hand, *p*-substituted phenol ethers where the presence of strong electron-donating groups and the absence of an OH group tended to generate a radical cation intermediate via a single-electron transfer process generate biaryl compounds as the major products (Scheme 12). The Kita group also demonstrated that the yields were enhanced when the couplings were carried out in the presence of $BF_3{\cdot}Et_2O$[35] which activates PIFA, as indicated by the increase in yield up to 91%.

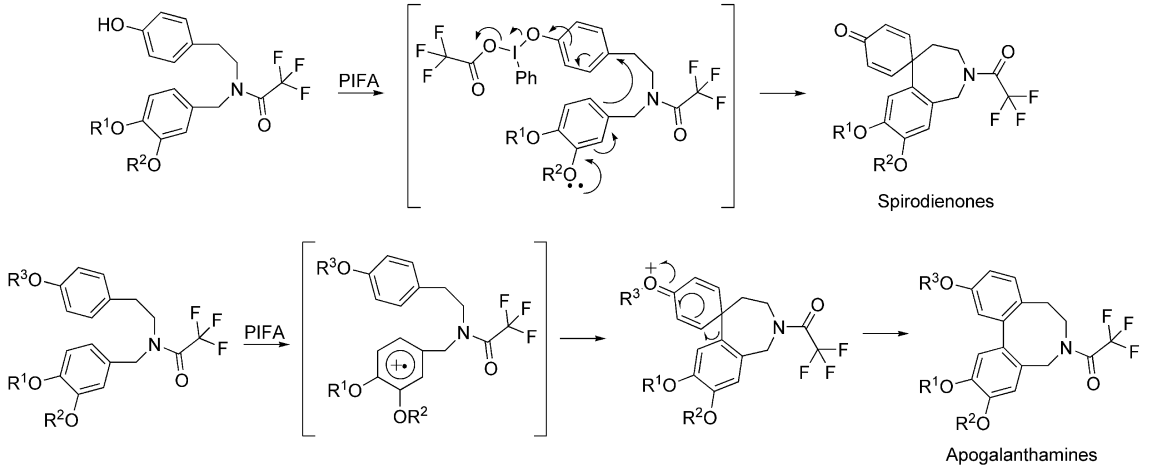
Owing to the demand for more environmentally benign and greener protocols with increased safety, organic reactions using the expensive fluorinated solvents or excessive amounts of $BF_3{\cdot}Et_2O$ are not deemed as viable and cheap protocols. In view of circumventing this problem, the Kita group has investigated the use of heteropoly acids (HPAs) in combination with PIFA for the generation of novel biaryl systems.[36] HPAs are readily available, inexpensive, easy to handle, noncorrosive, nonvolatile, and odorless solid acids.[37] They effectively activate polyvalent iodine reagents like PIFA, and the authors demonstrated that the PIFA-HPA reagent system facilitates the oxidative biaryl coupling of phenol ethers in a remarkably friendlier and efficient manner (Scheme 13).



X = CH_2, O, $NCOCF_3$ etc.; R^1 = R^2 = OMe or CH_2-O-CH_2; R^3 = H or OMe

Scheme 13. Oxidative cyclizations mediated by PIFA in combination with HPAs.

The authors explored the conversion of the *N*-benzyl-*N*-phenethylamine derivatives into the dibenzazocine derivatives, using four HPAs – $H_3[PW_{12}O_{40}]$, $H_3[PMo_{12}O_{40}]$,



Scheme 12. The proposed mechanism for the oxidative, non-phenolic ring closure.

$H_4[SiW_{12}O_{40}]$, and $H_4[SiMo_{12}O_{40}]$ – for the activation of PIFA in the biaryl coupling reaction. All four of the HPAs were found to furnish excellent yields of the required apogalanthamine analogues, often in > 90% yields, where the reactions conducted with the absence of HPAs furnished a mere 4% yield of the target apogalanthamine analogues, and the absence of PIFA leads to unreactive mixtures.

2.4. Recent Work on Apogalanthamine Analogues

Even though a number of suitable protocols for the synthesis of apogalanthamine analogues could be found in the literature, as exemplified above, it is clear that these methods could hardly be considered as general and robust synthetic protocols. The initial work based on Cu- or Ni-mediated Ullmann-type couplings or photochemical ring closures were using harsh conditions and provide low yields. Metal-mediated oxidative cyclization protocols had the hazard of handling toxic and often sensitive reagents, while strict constraints on the nature of the participating aryl moieties were imposed. While the polyvalent iodine reagents were successful in eliminating the need of toxic metal-based reagents up to a good extent, they almost always needed the presence of highly electron-rich substituents on the aromatic rings, which dampened the usefulness of the protocol to great extends. Owing to this reason, there were a limited number of attempts in the recent literature to develop relatively softer transition-metal mediated protocols for the efficient synthesis of apogalanthamine analogues.

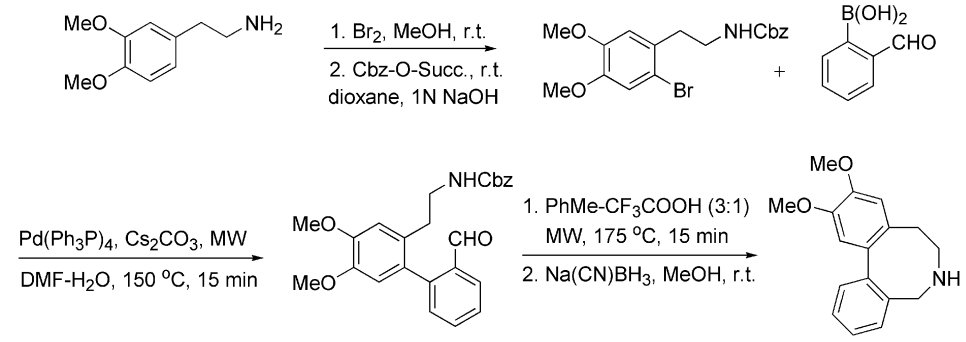
Van der Eycken and coworkers has proposed a novel protocol for the synthesis of the apogalanthamine analogues,[38] based on the mild, robust and well-investigated Suzuki–Miyaura reaction (Scheme 14). While attempting to synthesize a small library of 2-aryldopamines or 2-aryl phenyl ethylamines bearing highly electron-donating substituents, the authors demonstrated a short and efficient synthesis of an apogalanthamine analogue using microwave-assisted Suzuki–Miyaura[39] reaction as the key step. The authors started their synthesis from the commercially available 3,4-dimethoxy phenylethylamine, which was converted into the corresponding *o*-bromo-carbamate analogue in two high yielding steps, using standard protocols (Scheme 14).

This carbamate analogue was then cross-coupled with 2-formylphenylboronic acid in presence of $Pd(Ph_3P)_4$ and Cs_2CO_3 in a 1:1 mixture of DMF and H_2O. The reaction proceeded smoothly under microwave-assisted conditions at 150 °C for 15 min, furnishing an excellent 84% of the required biaryl intermediate (Scheme 14). It is noteworthy that this reaction, when carried out under the same conditions using classical heating, provided a mere 22% of the required biaryl intermediate. An intramolecular reductive amination was then carried out by the authors to affect the ring closure and thus complete the synthetic sequence. The imination was also facilitated by microwave-irradiation, where the sample was irradiated at 175 °C for 3 min in a 3:1 mixture of toluene and CF_3COOH. Subsequent reduction of the cyclic imine with sodium cyanoborohydride at room temperature furnished the apogalanthamine analogue in good yield (Scheme 14).

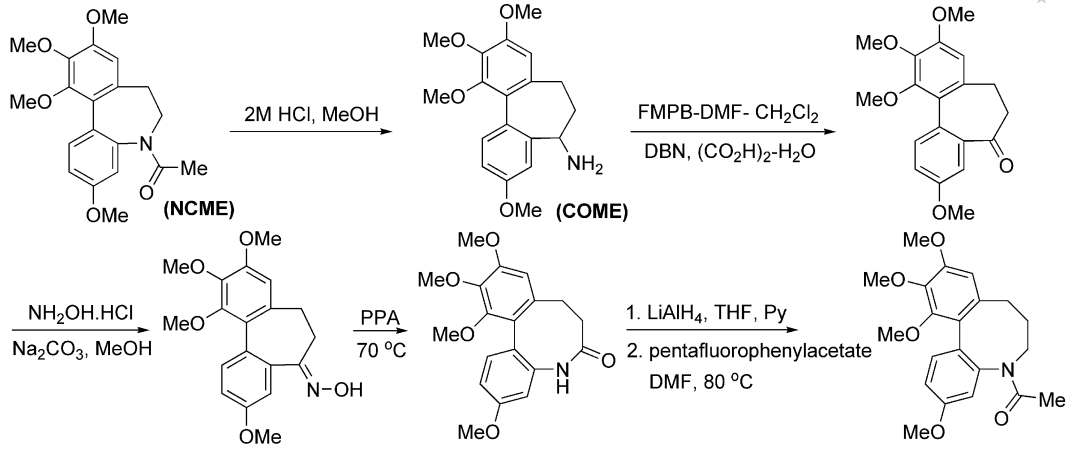
In view of developing *hitherto* unknown B-ring-modified allocolchicinoids, Seitz and coworkers[40] have elaborated the syntheses of novel variants of the highly potent (–)-*N*-acetylcolchinol *O*-methyl ether (NCME), which included novel eight-membered B-ring (*N*-shifted) apogalanthamine analogues (see also Figure 4 and the approach of Van der Eycken and coworkers in Scheme 22). The authors generated the target molecules by extending the seven-membered B-ring to novel semisynthetic variations which are the eight-membered ring analogues.

In order to access novel B-ring variations of NCME, the authors employed the transformation of the allocolchicinoid into the well known ketone (Scheme 15). The acetamido group was first reacted with methanolic hydrochloric acid to form the deacetylated product, colchinol *O*-methyl ether (COME). Biomimetic transamination of COME using 4-formyl-*N*-methylpyridinium benzenesulfonate (FMPB) furnished the required ketone in the racemic form. Reaction of this ketone with hydroxylamine hydrochloride in the presence of sodium carbonate afforded the corresponding (*E*)-oxime as the only isolated product (Scheme 15).

The oxime was then converted into a mixture of the two lactams using Berg's methodology for the Beckmann rearrangement and a seperable mixture of lactams was isolated in a 10:1 ratio, due to the preferential migration of the group *anti* to the oxime hydroxy group (Scheme 15).



Scheme 14. Synthesis of apogalanthamine analogue using microwave-assisted Suzuki–Miyaura reaction.

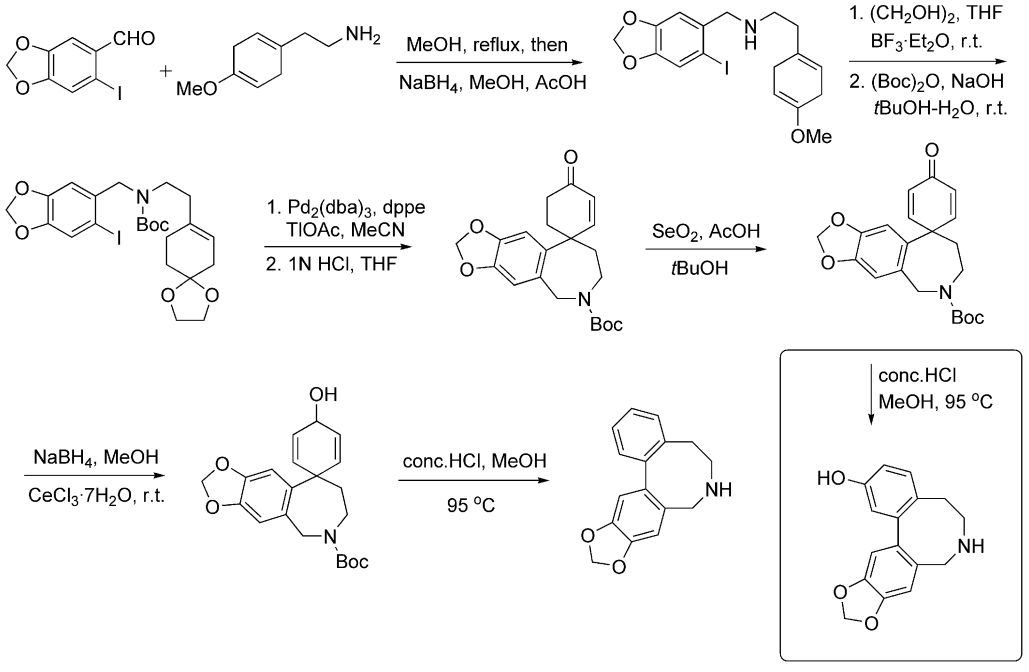


Scheme 15. Synthesis of an *N*-shifted apogalanthamine analogue.

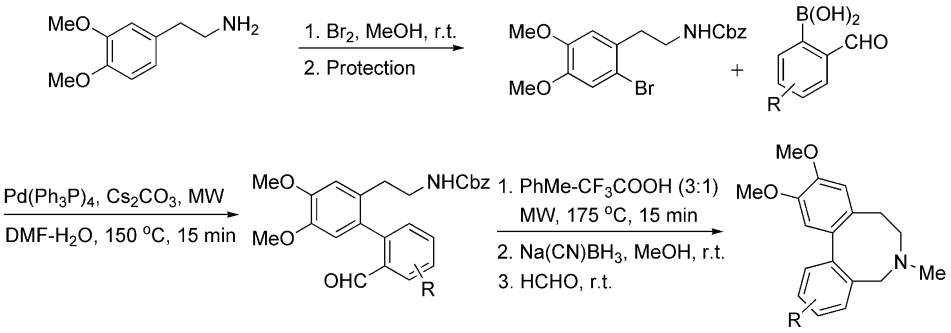
Reduction of the lactam with $LiAlH_4$ led to the unstable apogalanthamine analogue, which was rapidly converted into the corresponding acetamide by reaction with pentafluoro-phenylacetate.

Guillou and coworkers has recently demonstrated[41] a novel Pd-catalyzed protocol for the synthesis of Crinine and related alkaloids belonging to the amaryllidaceae alkaloid family where the authors synthesized two apogalanthamine analogues using a very robust and effective strategy. The Guillou group started their synthetic protocol from 2-iodopiperonal and a known ethylamine derivative. Reductive amination of these two components using $NaBH_4$ followed by a protection as the dioxolane derivative furnished the amine intermediate in good yield (Scheme 16). This was converted into the corresponding *tert*-butyl carbamate analogue, in view of protecting the amine nitrogen for the Pd-catalyzed coupling reaction.

The key carbon bond-forming reaction was achieved by an intramolecular Heck-coupling protocol (Scheme 16), using the catalytic combination of $Pd_2(dba)_3$ in presence of diphenylphosphanylethane (dppe) and thallium acetate. After HCl-mediated removal of the dioxolane group, oxidation of the unsaturated ketone function to the corresponding spirodienone was carried out using selenium dioxide and acetic acid in *tert*-BuOH. Finally, the apogalanthamine analogue was generated from the spirodienone via an HCl-mediated spirodienone-phenol rearrangement. In another sequence, the spirodienone was reduced to the corresponding dienol



Scheme 16. Intramolecular Heck-coupling in the synthesis of crinine alkaloids and apogalanthamine analogues.



Scheme 17. Microwave-assisted synthesis of apogalanthamine analogues.

using $NaBH_4$ and an HCl-mediated dienol-benzene rearrangement furnished the target apogalanthamine analogue.

In view of solving the purification problems associated with the apogalanthamine analogues as well as to generate a small library of the title molecules, Van der Eycken and coworkers[42] have recently investigated the microwave-assisted synthesis of apogalanthamine analogues in great detail (Scheme 17). The authors used their previously optimized methodology based on microwave-assisted Suzuki–Miyaura reactions of highly electron-rich aryl bromides for the generation of apogalanthamine analogues.

After successful cross-coupling of the suitably functionalized phenyl ethylamine analogues with 2-formylphenylboronic acids followed by a microwave-assisted intramolecular ring closure to the apogalanthamine analogues (Scheme 17), the authors performed an in situ methylation of the thus formed apogalanthamine analogues by adding formaldehyde to the reaction medium, thus avoiding the problem of excessive polarity of the target molecules. A small number of structurally diverse apogalanthamine analogues was generated, even with successful incorporation of heterocyclic moieties into the apogalanthamine skeleton.

Among the various apogalanthamine analogues, only two compounds bearing the 5,6,7,8-tetrahydrodibenzo[*c*,*e*]-azocine skeleton were found to be naturally occurring. They are called buflavine and 8-*O*-demethylbuflavine (Figure 3), and were isolated in 1995 from *Boophane flava*,[43] an endemic amaryllidaceae alkaloid species from South Africa. Being a typical member of the family, buflavine exhibits potent biological activities such as alpha-adrenolytic and anti-serotonin activities.[44] Five total syntheses of buflavine have been reported in the literature so far, and minor efforts have been made to elaborate a strategy for the synthesis of a small library of the unnatural structural analogues of these molecules for the purpose of biological screening.

The first pioneering total synthesis of buflavine was reported by Snieckus and coworkers (Scheme 18).[45] The authors proposed a convergent route to buflavine and 8-*O*-demethylbuflavine, making use of the Directed *ortho* Metallation (D*o*M)[46] reactivity and intramolecular Peterson olefination[47] reactivity of the α′,α′-disilylated tertiary amide, which was used as both the dual *ortho*- and the α′-carbanion synthon. The amide was regiospecifically metalated using *tert*-BuLi in combination with TMEDA to generate

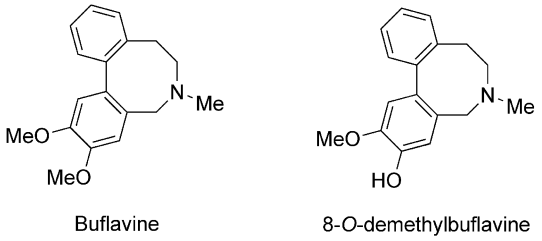


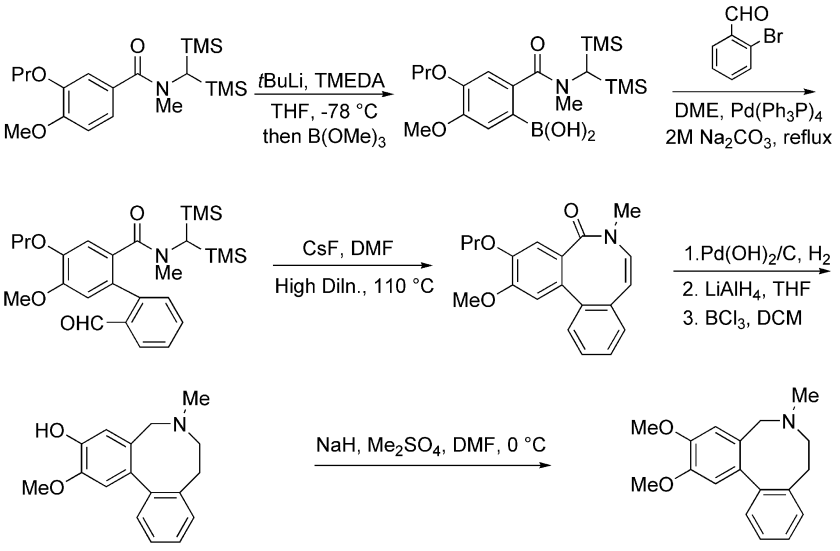
Figure 3. Naturally occurring dibenzo[*c*,*e*]azocines.

the boronic acid (Scheme 18). Suzuki–Miyaura cross coupling of the boronic acid with 2-bromobenzaldehyde furnished the biaryl intermediate in good yield. The Peterson olefination was carried out by reacting the biaryl aldehyde with CsF in DMF under high dilution conditions at 110 °C. Subsequent catalytic hydrogenation, reduction, and chemoselective deisopropylation with $BC1_3$ gave 8-*O*-demethylbuflavine, which was then converted to buflavine by a standard alkylation protocol (Scheme 18).

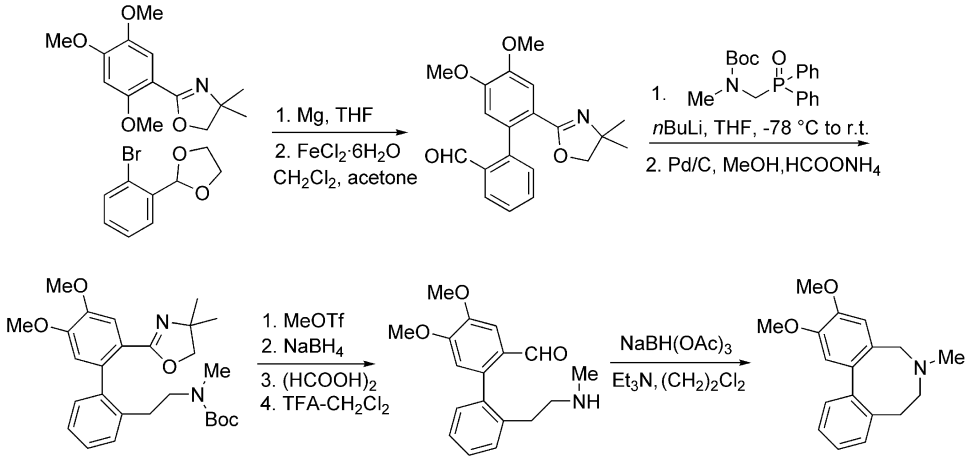
Couture and coworkers have demonstrated a tactically new six-step sequence for the synthesis of buflavine,[48] based on the ingenious Meyers' biaryl coupling protocol.[49] The key biaryl formation was carried out via a Mg-mediated Grignard-type coupling (Scheme 19) between a 2-aryl-4,4-dimethyl-2-oxazoline, easily derived from the corresponding benzoic acid, and the acetal of 2-bromobenzaldehyde in an excellent yield of 76%.

After the regeneration of the aldehyde, the Horner reaction to generate the corresponding ene-carbamates was explored in great success, and the targets were isolated as a mixture of the *E* and *Z* isomers, where the *E* isomer was found to be the predominant product. The synthesis of the corresponding biphenyl ethylamine was performed by a Pd-mediated hydrogenation of the enecarbamates (Scheme 19). After the reductive cleavage of the oxazoline ring under Meyer's conditions, the thus generated amino aldehyde was subjected to an intramolecular reductive amination to complete the sequence and buflavine was isolated in a good yield of 66% from the biphenyl-oxazoline.

Ruchirawat and coworkers have recently published a more flexible and high-yielding route[50] based on a combination of the Suzuki–Miyaura cross-coupling reaction and



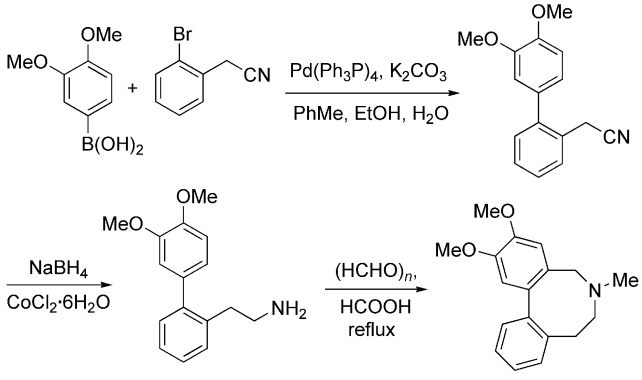
Scheme 18. First total sSynthesis of buflavine and 8-*O*-demethylbuflavine.



Scheme 19. Synthesis of buflavine using Meyer's biaryl coupling protocol.

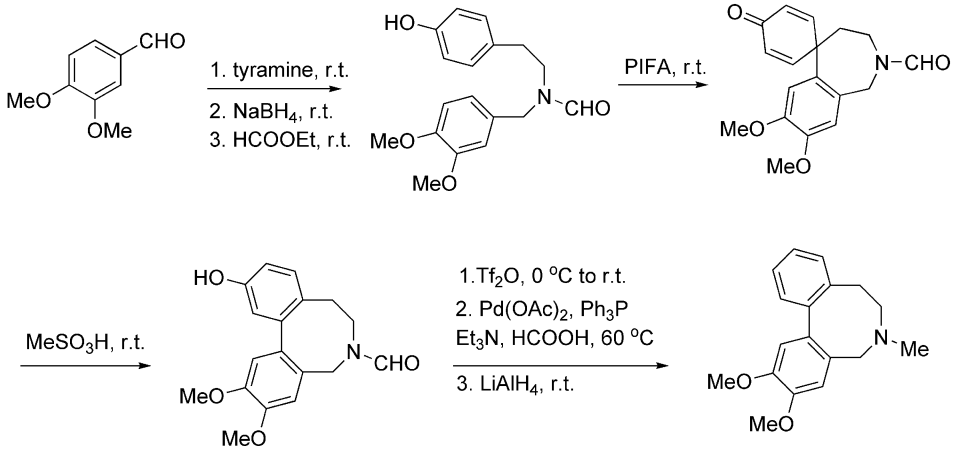
a modified Pictet-Spengler cyclization (Scheme 20).[51] They explored the cross-coupling reaction of 3,4-dimethoxyphenylboronic acid with (*ortho*-bromophenyl)acetonitrile to generate the key biaryl intermediate. Subsequent Co-assisted reduction of the nitrile group to the corresponding amine and a Pictet-Spengler reaction with paraformaldehyde in HCOOH generated buflavine in effectively three steps and an excellent overall yield of 54%. It is noteworthy that the target molecule was synthesized in a mere three non-complicated steps.

Node and coworkers explored another ingenious synthesis of buflavine, making use of a spirodienone-phenol rearrangement (Scheme 21).[52] Reductive amination of 3,4-dimethoxybenzaldehyde with tyramine using sodium borohydride generated the required intermediate which was successfully converted into the corresponding *N*-formyl analogue using ethyl formate. The authors found that the attempts to generate the biaryl intermediate were unsuccessful, as the oxidative coupling generated the spirodienone intermediate. The ring-



Scheme 20. Pictet-Spengler reaction in the synthesis of buflavine.

expansion of this spirodienone to the target molecule was achieved by a spirodienone-phenol rearrangement with methanesulfonic acid (Scheme 21). The phenolic hydroxy group was then converted into the corresponding triflate fol-



Scheme 21. PIFA-mediated synthesis of buflavine.

lowed by a palladium-catalyzed reduction and $LiAlH_4$-mediated reduction of the *N*-formyl group furnishing buflavine in an excellent overall yield of 64%.

Van der Eycken and coworkers have recently proposed a novel strategy for the synthesis of the *N*-shifted buflavine analogues[53] which are the structural analogues of Apogalanthamine (Figure 4, see also the approach of Seitz and coworkers in Scheme 15). The approach comprises a combination of a microwave-assisted Suzuki cross-coupling reaction followed by a microwave-induced ring-closing metathesis (RCM) reaction (Scheme 22).[54]

The authors started the synthesis with the generation of the required styrene intermediates which were synthesized in high yields and purity from the corresponding commercially available benzaldehydes in two steps, using a standard bromination followed by a Wittig reaction. They then explored the Suzuki cross-coupling reaction of the styrene intermediates with 2-pivaloylaminophenylboronic acid, generated from the protected aniline via Directed *ortho* Metallation (D*o*M) (Scheme 22).

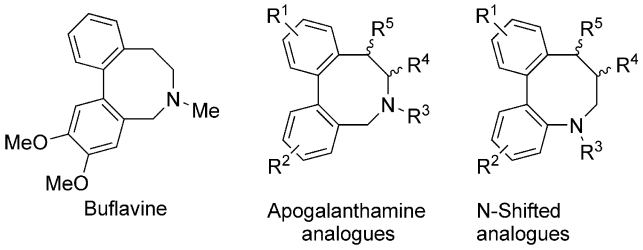
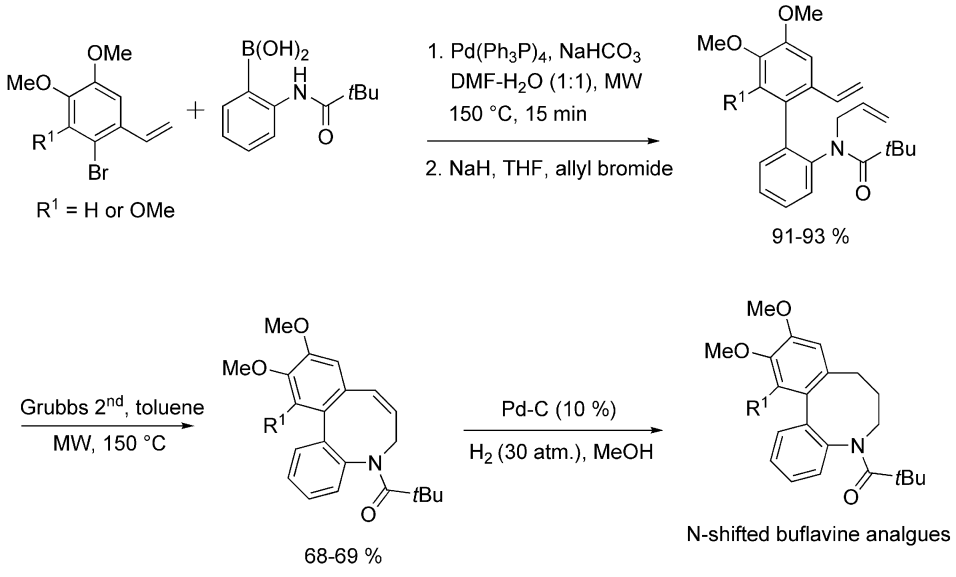
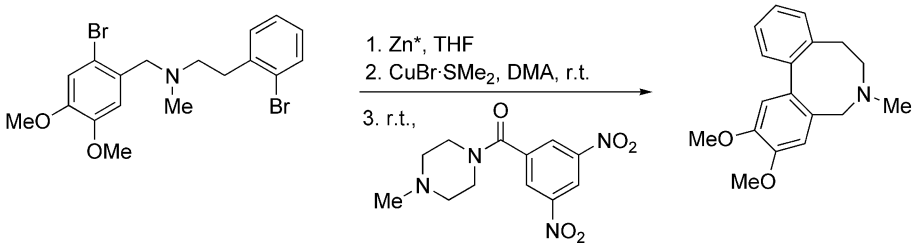


Figure 4. *N*-shifted buflavine analogues.

The Suzuki cross-coupling reaction was investigated under microwave irradiation, using $Pd(Ph_3P)_4$ as the catalyst in a 1:1 mixture of DMF and H_2O (3 mL) at 150 °C for 15 min and the biaryl intermediates were isolated in excellent yields of 91–93%. Following the allylation of the aniline nitrogen under standard NaH-mediated conditions to generate the "handle" needed for the RCM reaction, the authors explored the key RCM reaction under microwave-



Scheme 22. Microwave-assisted synthesis of *N*-shifted buflavine analogues.



Scheme 23. Intramolecular Ullmann-type coupling in the synthesis of buflavine.

assisted conditions (Scheme 22). The best results were obtained using Grubbs' 2nd-generation catalyst (Grubbs II) in toluene at 150 °C for 5 min, delivering the products in good yields. To complete the sequence, the dihydrodibenzo[*b*,*d*]-azocines were converted into the corresponding buflavine analogues via a simple palladium-catalyzed hydrogenation protocol.

Spring and coworkers delineated a straightforward synthesis of buflavine,[55] with the most direct strategy for generating both the medium ring and the key biaryl axis in one step (Scheme 23). Treatment of the acyclic aryl bromide with Rieke zinc under the standard conditions, followed by a transmetallation to the intramolecular cuprate and subsequent oxidation provided buflavine in an excellent yield of 80%.

The Van der Eycken group has also proposed an elegant pathway towards the synthesis of *hitherto* unknown ring-expanded buflavine analogues (Figure 5).[56] Once again, their strategy relied on the combination of a microwave-assisted Suzuki cross-coupling reaction of highly electron-rich aryl halides to generate the biaryl axes, followed by a microwave-assisted RCM reaction to construct the medium-sized ring (Scheme 24).

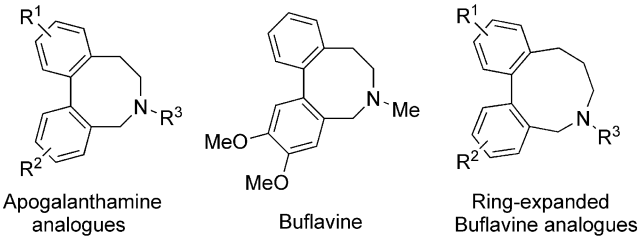
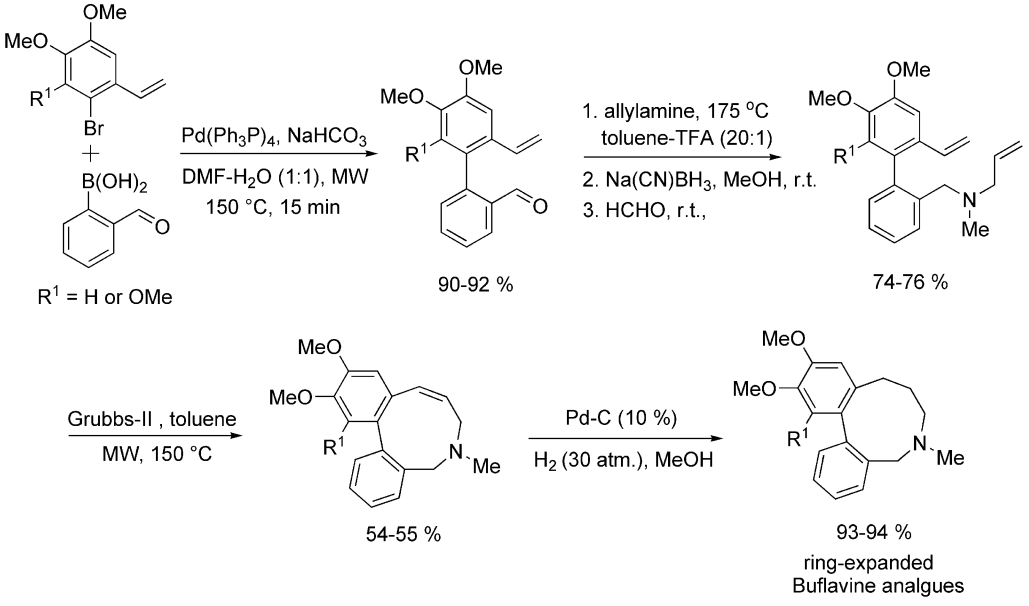


Figure 5. Ring-expanded buflavine analogues.

It is particularly noteworthy that, as the application of the RCM for the generation of nine-membered ring systems is only scarcely documented in the literature, the proposed strategy represents a real challenge in generating the difficultly obtainable medium-sized ring system of the target molecules.

The authors, once again, investigated the microwave-assisted Suzuki cross-coupling reaction of 2-formylphenylboronic acid with the electron-rich *ortho*-bromostyrenes (Scheme 24) as the starting point of their explorations. The Suzuki cross-coupling reaction was investigated under microwave irradiation conditions using $Pd(Ph_3P)_4$ as the cata-



Scheme 24. Synthesis of ring-expanded buflavine analogues.

lyst in a 1:1 mixture of DMF and H_2O at 150 °C for 15 min, to generate the required biaryl intermediates in excellent yields. In order to generate the key biaryl intermediates for RCM (Scheme 24), the authors first performed an imination of the biaryl aldehyde with allylamine. Subsequent reduction of the crude imine in MeOH with an excess of $Na(CN)BH_3$ at room temp. followed by a one-pot reductive amination with an excess of formaldehyde generated the *N*-methylated biarylamines in 74–76% overall yield starting from the biaryl aldehyde (Scheme 24).

The RCM reaction was carried out in toluene and once again best results were obtained using Grubb's second generation catalyst under microwave-assisted conditions at 150 °C for 15 min, delivering the products in moderate yields of 54–55%. In order to complete the sequence, the dihydrodibenzo[*c*,*e*]azonines were converted into the corresponding ring-expanded buflavine analogues via a palladium-catalyzed hydrogenation protocol (Scheme 24) in excellent yields.

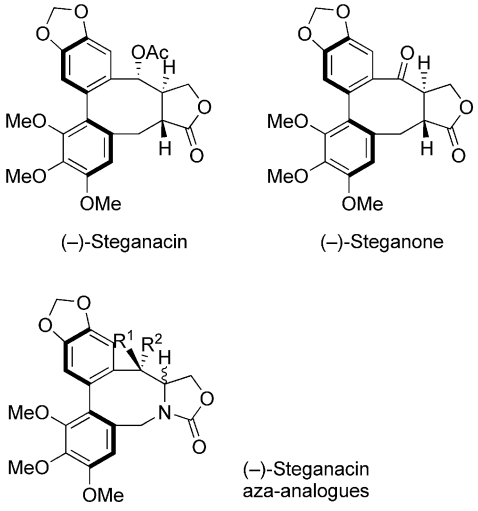


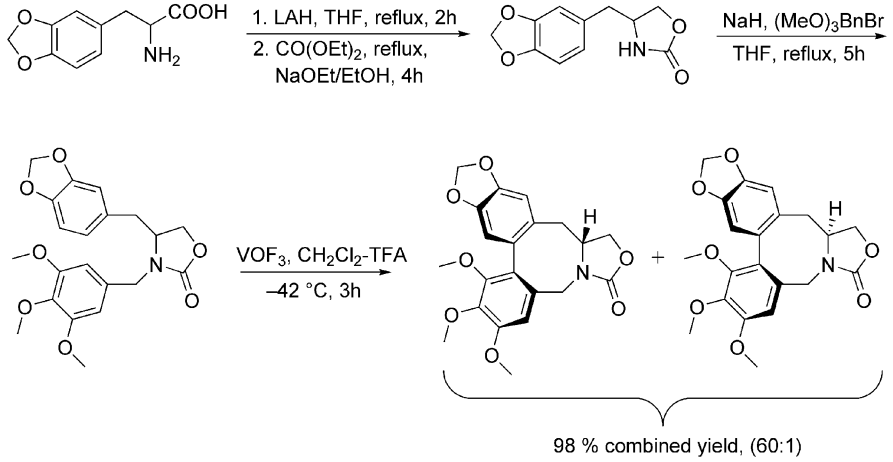
Figure 6. Naturally occurring lignan lactones and their 7-aza analogues.

3. Synthesis of Steganacin and Steganone Aza Analogues

Naturally occurring lignan lactones (–)-steganacin and (–)-steganone (Figure 6) were isolated from *Steganotaenia araliacea* by the late S. M. Kupchan[57] and have been demonstrated to possess significant in vivo activity against *P*-388 leukemia in mice and in vitro activity against cells derived from human carcinoma of the nasopharynx.[58]

These compounds inhibit the assembly of tubulin into microtubules by interacting with the colchicine binding site and have been shown to possess cytotoxic activity against several cancer cell lines.[59] While not featuring a direct benzazocine skeleton, these molecules are comprised of the basic skeleton together with an additional, fused, five-membered ring system. A detailed SAR study is now available[58,60] for the steganacin-type lignan lactones which exhibits some critical structural features for the potency; the dioxolane moiety is fundamental for the cytotoxic activity; (ii) the lactone ring is not essential, although it contributes to potency; (iii) the acetate is not essential as stegane is equally active; and (iv) the trimethoxyphenyl ring is essential in both compounds for cytotoxic and antitubulic activities.

In a program aimed at the creation of new antitumor agents related to these lignans as well as to solve the stereochemical issues related to their synthesis, Koga and coworkers investigated the synthesis and biological activity of isopicrostegane aza analogues.[61] The authors conclude that these novel nitrogen analogues exhibit antitumor activity even higher than the corresponding natural lignan lactones, where the mode of action was through inhibiting the microtubule assembly. The aza analogue exhibits promising in vitro cytotoxicity ($ED_{50} < 0.3$ μg/mL) against KB cell as well as in vivo activity (T/C 137) against experimental tumor in P388 mouse. The Koga group achieved the synthesis of an aza analogue of isopicrostegane using the metal-mediated, non-phenolic, oxidative ring closure as the key biaryl-form-

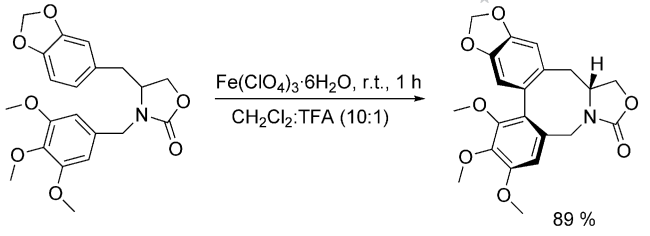


Scheme 25. Synthesis of 7-aza-isopicrostegane using oxidative cyclization method.

ing step (Scheme 25). The authors began their synthesis with the generation of the racemic amino acid from piperonyl chloride and acetyl aminomalonate by standard protocols. The key intermediate, oxazolidinone was then generated by the $LiAlH_4$ reduction of the racemic amino acid, followed by the reaction with diethyl carbonate (Scheme 25).

The needed outer skeleton for the biaryl formation was then generated by the alkylation of the oxazolidinone with trimethoxybenzyl bromide. Finally, the key biaryl formation and thus the total synthesis was achieved via an intramolecular non-phenolic oxidative-coupling using VOF_3 in CH_2Cl_2/CF_3COOH at –42 °C to furnish the target molecule as a mixture of two separable diastereoisomers in a ratio of 60:1 in an amazing combined yield of 98%.

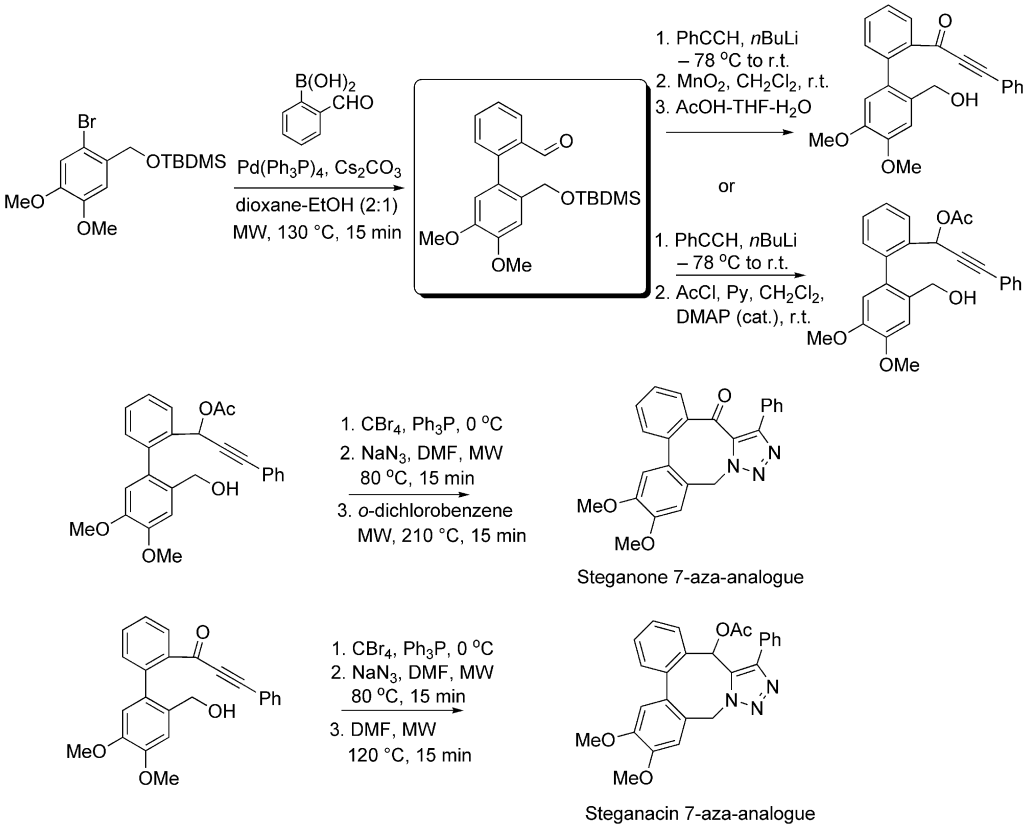
The Koga group has further explored the synthesis of steganone and isopicrostegane aza analogues[62] by investigating the use of a variety of reagents for the purpose of oxidative coupling of non phenolic and phenolic compounds (Scheme 26). In the course of their investigations, the authors found that, in the presence of trifluoroacetic acid, iron(III)perchlorate can act as an efficient reagent for the oxidative coupling reaction of aromatic compounds (Scheme 26). The reactions were carried out using 2.4 equiv. of iron(III) perchlorate at room temperature in CH_2Cl_2/CF_3COOH, on a number of structurally diverse alkoxybenzene intermediates.



Scheme 26. Fe-mediated oxidative cyclization in the synthesis of 7-aza analogues.

Albeit the moderate yields, this method afforded high selectivities and tolerated the presence of the methylene dioxy group, which is often a problem during the V- or Th-mediated biaryl formation protocols under very acidic conditions due to the incompatibility of the alkoxy groups with the highly acidic conditions.

Van der Eycken and coworkers have recently demonstrated a microwave-assisted synthesis of the 1,2,3-triazole-derived steganacin and steganone aza analogues (Scheme 27).[63] They investigated a novel microwave-assisted multi-step protocol for the generation of these unnatural steganacin and steganone analogues, where the fused urethane ring was replaced by a 1,2,3-triazole moiety (Scheme 27). Considering the fact that the lactone ring might be vulnerable to metabolic cleavage, it was reasoned that the 1,5-disubstituted 1,2,3-triazole ring would be meta-



Scheme 27. Synthesis of 1,2,3-triazole aza analogues of steganone and steganacine using click chemistry.

bolically stable and able to participate as a hydrogen-bond acceptor. The authors used a microwave-assisted Suzuki–Miyaura cross-coupling reaction as one of the key steps to generate the required biaryl intermediates in high yields and purity. The synthesis starts from 3,4-dimethoxybenzyl alcohol, which was converted into the corresponding brominated silyl ether derivative in two steps, following a standard bromination protocol using NBS in CCl_4 followed by protection of the alcohol (Scheme 27) into the TBDMS-derivative. The required biaryl intermediate was then generated following a microwave-assisted Suzuki–Miyaura reaction using $Pd(Ph_3P)_4$ and Cs_2CO_3 in a 2:1 mixture of dioxane and ethanol. It is to be noted that these cross-couplings seldom furnish good yields under conventional heating conditions. This is due to the highly electron-rich nature of the aryl halide, which makes the oxidative addition rather slow and sluggish which, in turn, facilitates the proto-deboronation of the boronic acid enhanced by the electron withdrawing formyl group at the 2-position.

Indeed the authors noticed an inferior yield of 42% under conventional heating conditions. However, the same reaction run under focused microwave irradiation furnished a good yield of 77%. The thus obtained biaryl aldehyde was then transformed into the corresponding propargylic alcohol via nucleophillic addition of phenylacetylene in the presence of *n*-BuLi, followed by a MnO_2-mediated oxidation of the alcohol to the corresponding ketone intermediate (Scheme 27). The silyl ether was then transformed to the primary alcohol under mildly acidic conditions. This intermediate was then converted into the target molecule by a three-step, pseudo one-pot procedure. The alcohol was first brominated using CBr_4 and Ph_3P, followed by the reaction of the thus formed bromide with sodium azide. A microwave-assisted intramolecular Huisgen 1,3-dipolar cycloaddition was then carried out at 210 °C to generate the target molecule in very good overall yield of 43% (Scheme 27).

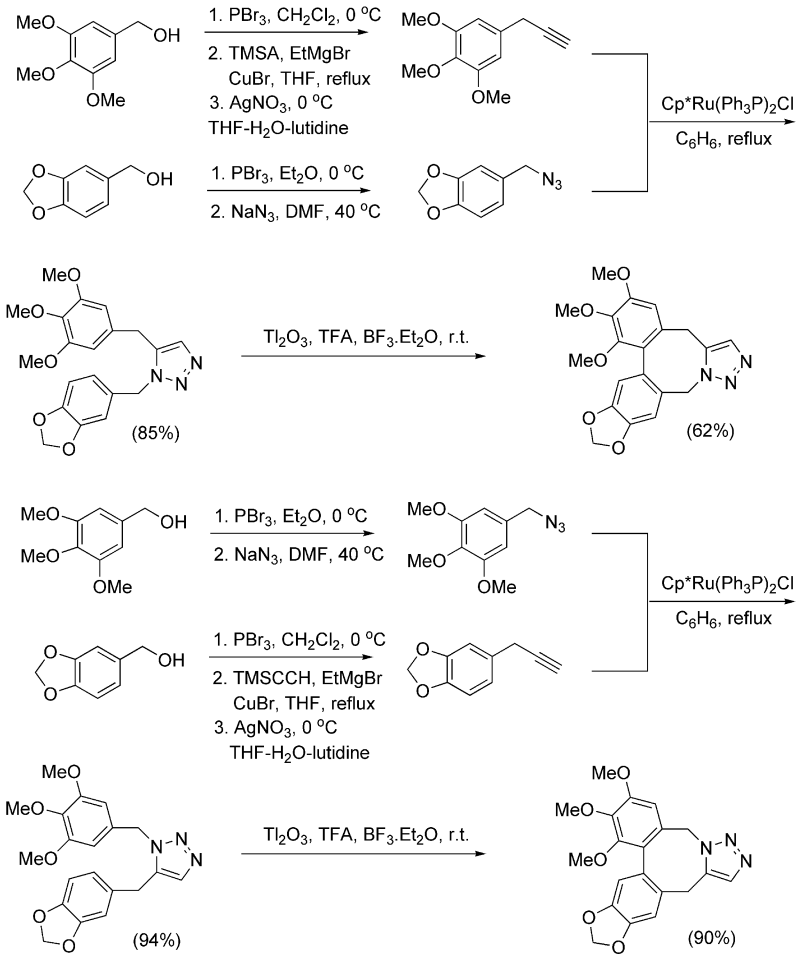
The authors also explored the synthesis of a steganacin analogue, following the same protocol (Scheme 27). Thus the alcohol generated by the addition of phenylacetylene to the aldehyde was converted into the acetate, and the corresponding intermediate was then subjected to ring closure according to same protocol to generate the target steganacin 7-aza analogue in good yield. In contrast to the ketone analogue which needed an elevated temperature of 210 °C for the intramolecular ring closure, the cyclization of the acetate analogue could be carried out at a much lower temperature of 120 °C under microwave irradiation, owing to the considerably lower conformational rigidity of the target molecule. It is noteworthy that the intramolecular cycloaddition reaction, when carried out under conventional heating conditions, completely failed to promote the ring closure (Scheme 27).

Tron and coworkers have very recently demonstrated an ingenious synthesis of steganacin and podophyllotoxin aza analogues[64] by the replacement of the lactone moiety on these lignan lactones with a 1,5-disubstituted 1,2,3-triazole ring via ruthenium-catalyzed click chemistry (Scheme 28). The authors began their synthesis by generating piperonyl azide from the commercially available piperonyl alcohol in two steps, following a standard PBr_3-mediated-bromination and consecutive an azidation using sodium azide in DMF/H_2O. Trimethoxybenzyl azide was synthesized using similar conditions starting from 3,4,5-trimethoxybenzyl alcohol via the bromide derivative.

The required alkynes were generated from the corresponding bromide derivatives, by inserting the acetylenic group using ethynyltrimethylsilane in the presence of ethylmagnesium bromide and freshly purified copper(I) bromide (Scheme 28). Here the authors noted that the reaction times and the reagent amounts (ethynyltrimethylsilane/ethylmagnesium bromide/bromide derivatives in ratio 4:4:1) were crucial to obtain reproducible results in high yields. These alkynes were deprotected using silver nitrate to give the desired alkynes free of any alkyne–allene isomerisation. It is to be noted that the normal TBAF-mediated deprotection resulted in the formation of the corresponding allenic derivatives. The key synthesis of the 1,5-disubstituted 1,2,3-triazole and thus the outer skeleton of the target molecules was generated via a click-chemistry protocol,[65] using $Cp^*Ru(PPh_3)_2Cl$ as catalyst in refluxing benzene (Scheme 28). The final ring closure to the target steganacin aza analogue was achieved via an intramolecular, non-phenolic, oxidative biaryl-coupling reaction using thallium(III) oxide in trifluoro-acetic acid in the presence of boron trifluoride, and the racemic azasteganacin derivatives were obtained in excellent yields (Scheme 28).

Hilt and coworkers have recently proposed a modular approach[66] for the synthesis of dibenzoazepine derivatives, wherein the authors demonstrated the synthesis of an interesting tetrahydrodibenzo[3,4,5,6]azocino[2,1-*a*]isoindolone, which can be viewed as a ring-shifted aza analogue of steganacins (Scheme 29). The authors investigated in detail the use of protected propargylic amine building blocks in the Cobalt-catalyzed Diels–Alder reactions with 1,3-dienes such as 2,3-dimethyl-1,3-butadiene. These propargylic amines are easily accessible from three components like phthalimides, propargylic halides and functionalised iodoarene derivatives.

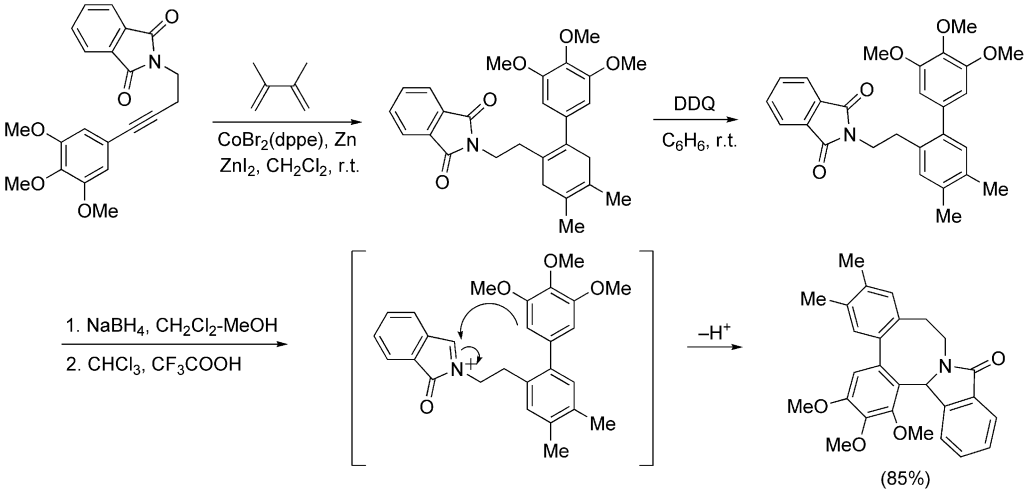
The Diels–Alder reactions were carried out using $CoBr_2$(dppe) as the catalyst of choice in the presence of metallic Zinc and ZnI_2 in CH_2Cl_2 at room temp. The authors then demonstrated that the thus generated dihydroaromatic cycloaddition products could easily be converted into the corresponding biaryl derivatives through a DDQ oxidation (Scheme 29). The Hilt group has then carried out a nice two step sequence comprising of a chemoselective reduction of the phthalimide functionality of the biaryl derivatives using $NaBH_4$ and an acid-catalysed Friedel–Crafts-type alkylation by the acyliminium ion in the presence of trifluoroacetic acid to generate the corresponding tetrahydrodibenzo[3,4,5,6]azocino[2,1-*a*]isoind-olone in very high yield of 85%, together with a number of functionalized dibenzoazepine derivatives (Scheme 29). It is noteworthy that the cyclization proceeds via the attack of the more electron rich aromatic ring on the acyliminium ion, and the authors noted that the cyclization leads to a six membered ring compound when the trimethoxy aryl ring



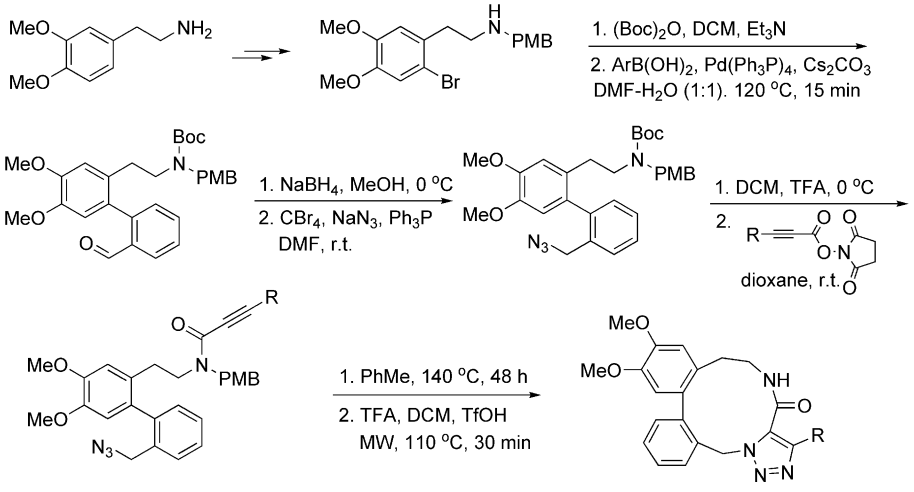
Scheme 28. Synthesis of 1,2,3-triazole analogues of steganacin.

was made unsubstituted, in which the more electron-rich aryl ring with the methyl groups participated in the cyclization process.

Van der Eycken and coworkers have proposed an alternative, microwave-assisted synthesis of a 1,2,3-triazole-derived, ring-expanded (–)-isopicrostegane aza analogue (Scheme 30).[67] They investigated an elegant, microwave-assisted multi-step protocol for the development of the ring-expanded lignan lactone analogues, where the eight-membered ring of the parent compound was replaced by an 11-membered ring system, featuring an amide group as a part of the fused ring system (Scheme 30). The authors started



Scheme 29. Synthesis of *N*-shifted steganacin 7-aza analogue.



Scheme 30. Synthesis of ring-expanded steganone aza analogues.

the synthesis by generating the required brominated phenylethylamine intermediate in two steps from the commercially available 4,5-dimethoxyphenylethylamine through a standard bromination protocol followed by a subsequent protection. The amine nitrogen was further protected with a Boc-group to avoid complications during the cross-coupling stage. Upon Suzuki–Miyaura reaction with 2-formylphenylboronic acid under microwave-assisted conditions this intermediate furnished the required biaryl intermediate in an excellent 94% yield in a mere 15 min at 120 °C (Scheme 30). Subsequent reduction of the formyl group with $NaBH_4$ lead to the corresponding alcohol, which was then converted into the azide using a one-pot bromination/azidation procedure, by adding a solution PPh_3 in dry DMF to the mixture of the benzylic alcohol containing CBr_4 and sodium azide.

After TFA-mediated removal of the BOC group, the free amine was coupled with *N*-hydroxysuccinimide (NHS)-derivatives of three-substituted propiolic acids needed for the 1,3-dipolar cycloadditions in very good yields. The final ring closure to obtain the target molecules was effected by heating the biaryl intermediates in toluene in sealed vessel at 140 °C for 48 h using high-dilution conditions (Scheme 30), and the target steganone analogues were isolated in good yields. It is noteworthy that the microwave-assisted conditions had an adverse effect in the cyclization step, where an increased by-product formation was noted by the authors.

4. Summary and Outlook

In this brief contribution, we have tried to present an overview of the synthesis of alkaloids and alkaloid analogues bearing a 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine skeleton. Despite the intriguing biological potentials inherent on these molecules like antiserotonin, antitumor and α-adrenolytic acitivities, minor effort has been spent for developing novel synthetic protocols. A number of issues still remain unexplored, like the incorporation of heterocyclic moieties into the biaryl skeleton, the development of more structurally diverse synthetic and semi-synthetic analogues for the purpose of detailed biological investigations, the generation of small libraries of these molecules for biological screening, as well as a more focused investigation of the generation of positional analogues as well as ring-altered analogues. We have tried to present a critical and concise overview of the synthetic work done in the last three decades, while omitting a few repetitive examples due the lack of novelty to deserve separate treatment. In view of clarity, the apogalanthamines and steganacin analogues are treated in separate chapters, for better emphasizing the development in each of these fields. We hope this account will interest the synthetic community and will result in more focused research delivering new developments in the chemistry of 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines.

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[1] For some general literature on amaryllidaceae alkaloids, please see: a) A. Kornienko, A. Evidente, *Chem. Rev.* **2008**, *108*, 1982; b) Y. Chapleur, F. Chretien, S. I. Ahmed, M. Khaldi, *Curr. Org. Synth.* **2006**, *3*, 341; c) R. Uwe, T. Hudlicky, *Synlett* **2005**, 365; d) E. E. Elgorashi, S. Zschocke, J. Van Staden, *S. Afr. J. Bot.* **2003**, *69*, 448; e) Z. Jin, *Nat. Prod. Rep.* **2003**, *20*, 606; f) T. S. Pohl, N. R. Crouch, D. A. Mulholland, *Curr. Org. Chem.* **2000**, *4*, 1287; g) J. Bastida, C. Codina, C. L. Porras, L. Paiz, *Planta Med.* **1996**, *62*, 74; h) S. F. Martin, *Alkaloids* **1987**, *30*, 251; i) J. L. Hartwell, *Lloydia* **1967**, *30*, 379.

[2] For a selected literature on the isolation and synthesis of some amaryllidaceae alkaloids, please see: a) Z. Jin, *Nat. Prod. Rep.* **2007**, *24*, 886; b) M. Matveenko, O. J. Kokas, M. G. Banwell, A. C. Willis, *Org. Lett.* **2007**, *9*, 3683; c) M. Bohno, K. Sugie, H. Imase, Y. B. Yusof, T. Oishi, N. Chida, *Tetrahedron* **2007**, *63*, 6977; d) A. Padwa, H. Zhang, *J. Org. Chem.* **2007**, *72*, 2570; e) A. S. Kireev, O. N. Nadein, V. J. Agustin, N. E. Bush, A. Evidente, M. Manpadi, M. A. Ogasawara, S. K. Rastogi, S. Rogelj, S. T. Shors, A. Kornienko, *J. Org. Chem.* **2006**, *71*, 5694;

f) M. Moser, X. Sun, T. Hudlicky, *Org. Lett.* **2005**, *7*, 5669; g) U. Rinner, T. Hudlicky, H. Gordon, G. R. Pettit, *Angew. Chem. Int. Ed.* **2004**, *43*, 5342; h) J. Jin, S. M. Weinreb, *J. Am. Chem. Soc.* **1997**, *119*, 2050; i) J. Jin, S. M. Weinreb, *J. Am. Chem. Soc.* **1997**, *119*, 5773; j) W. H. Pearson, F. E. Lovering, *J. Am. Chem. Soc.* **1995**, *117*, 12336; k) L. E. Overman, L. T. Mendelson, E. J. Jacobsen, *J. Am. Chem. Soc.* **1983**, *105*, 6629.

[3] a) C.-J. Paterson, D. Snijman, *Africa Environment & Wildlife* **1996**, *4*, 25; b) J. Loubser, P. C. Zietsman, *S. Afr. J. Sci.* **1994**, *90*, 611.

[4] a) P. J. Houghton, J. M. Agbedahunsi, A. Adegbulugbe, *Phytochemistry* **2004**, *65*, 2893; b) A. Evidente, A. Andolfi, A. H. Abou-Donia, S. M. Touema, H. M. Hammoda, E. Shawky, A. Motta, *Phytochemistry* **2004**, *65*, 2113; c) N. K. Unver, G. I. Kaya, C. Werner, R. Verpoorte, B. Gozler, *Planta Med.* **2003**, *69*, 869; d) J. Hohmann, P. Forgo, J. Molnar, K. Wolfard, A. Molnar, T. Thalhammer, I. Mathe, D. Sharples, *Planta Med.* **2002**, *68*, 54; e) G. R. Pettit, R. A. Backhaus, F. E. Boettner, *J. Nat. Prod.* **1995**, *58*, 37; f) B. Weniger, L. Italiano, J. P. Beck, J. Bastida, S. Berganon, C. Codina, A. Lobstein, R. Anton, *Planta Med.* **1995**, *61*, 77.

[5] a) G. Eamanza, J. M. Fernandez, E. W. Wakori, F. Viladomat, C. Codina, J. Bastida, *Phytochemistry* **1996**, *43*, 1375; b) J. Chen, K. Chen, H. Jiang, M. Lin, R. Ji, *Prog. Nat. Sci.* **1997**, *7*, 323; c) B. Gabrielsen, T. P. Monath, J. W. Huggins, D. F. Kefauver, G. R. Pettit, G. Groszek, M. Hollingshead, J. J. Kirsi, W. M. Shannon, E. M. Schubert, J. Dare, B. Ugrakar, M. A. Ussery, M. J. Phealn, *J. Nat. Prod.* **1992**, *52*, 1569.

[6] a) V. Satcharoen, N. J. McLean, S. C. Kemp, N. P. Camp, R. C. D. Brown, *Org. Lett.* **2007**, *9*, 1867; b) X.-D. Hu, Y. Q. Tu, E. Zhang, S. Gao, S. Wang, A. Wang, C.-A. Fan, M. Wang, *Org. Lett.* **2006**, *8*, 1823; c) J. Marco-Contelles, M. C. Carreiras, C. Rodriguez, M. Villarroya, A. G. Garcia, *Chem. Rev.* **2006**, *106*, 116; d) M. Rrainer, *Drugs Today* **1997**, *33*, 273; e) H. A. M. Mucke, *Drugs Today* **1997**, *33*, 251; f) K. Unni, *CNS Drugs* **1998**, *10*, 447.

[7] a) U. V. Mentzel, D. Tanner, J. E. Tonder, *J. Org. Chem.* **2006**, *71*, 5807; b) M. D. Ganton, M. A. Kerr, *Org. Lett.* **2005**, *7*, 4777; c) J. C. Torres, A. C. Pinto, S. J. Garden, *Tetrahedron* **2004**, *60*, 9889; d) C. G. Hartung, A. Fecher, B. Chapell, V. Snieckus, *Org. Lett.* **2003**, *5*, 1899; e) D. L. Boger, S. E. Wolkenberg, *J. Org. Chem.* **2000**, *65*, 9120; f) S. Ghosal, P. H. Rao, D. K. Jaiswal, Y. Kumar, A. W. Frahm, *Phytochemistry* **1981**, *20*, 2003.

[8] a) M. Matveenko, M. G. Banwell, A. C. Willis, *Tetrahedron* **2008**, *64*, 4817; b) I.-J. Shin, E.-S. Choi, C.-G. Cho, *Angew. Chem. Int. Ed.* **2007**, *46*, 2303; c) T. Hudlicky, U. Rinner, D. Gonzalez, H. Akgun, S. Schilling, P. Siengalewicz, T. A. Martinot, G. R. Pettit, *J. Org. Chem.* **2002**, *67*, 8726; d) G. R. Pettit, N. Melody, D. L. Herald, *J. Org. Chem.* **2001**, *66*, 2583; e) J. H. Rigby, U. S. M. Maharoof, M. E. Mateo, *J. Am. Chem. Soc.* **2000**, *122*, 6624; f) G. E. Keck, T. T. Wager, J. F. D. Rodriquez, *J. Am. Chem. Soc.* **1999**, *121*, 5176; g) J. H. Rigby, M. E. Mateo, E. Mary, *J. Am. Chem. Soc.* **1997**, *119*, 12655.

[9] Y. Ishida, K. Sadamune, S. Kobayashi, M. Kihara, *J. Pharmacobiodyn.* **1983**, *6*, 391.

[10] a) S. Kobayashi, M. Kihara, K. Yamasaki, Y. Ishida, K. Watanabe, *Chem. Pharm. Bull.* **1975**, *23*, 3036; b) S. Kobayashi, M. Kihara, S. Shizu, S. Katayama, H. Ikeda, K. Kitahiro, H. Matsumoto, *Chem. Pharm. Bull.* **1977**, *25*, 3312; c) M. Kihara, S. Kobayashi, *Chem. Pharm. Bull.* **1978**, *26*, 155.

[11] M. Kihara, Y. Miyake, M. Iitomi, S. Kobayashi, *Chem. Pharm. Bull.* **1985**, *33*, 1260.

[12] J. Renard-Nozaki, T. Kim, Y. Imakura, M. Kihara, S. Kobayashi, *Res. Virol.* **1989**, *140*, 115.

[13] S. Ueyo, S. Kobayashi, *Chem. Pharm. Bull.* **1953**, *1*, 139.

[14] N. F. Proskurnina, A. P. Yakovleva, *Zhur. Obshchei Khim.* **1956**, *26*, 172.

[15] S. Kobayashi, S. Uyeo, *J. Chem. Soc.* **1957**, 638.

[16] See a) G. Bringmann, R. Walter, R. Weirich, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977; b) P. E. Fanta, *Chem. Rev.* **1946**, *38*, 139; c) P. E. Fanta, *Chem. Rev.* **1964**, *64*, 613; d) P. E. Fanta, *Synthesis* **1974**, 9; e) G. H. Posner, *An Introduction to Synthesis using Organocopper Reagents*, John Wiley, New York, **1980**.

[17] J. Koizumi, S. Kobayashi, S. Uyeo, *Chem. Pharm. Bull.* **1964**, *12*, 696.

[18] For a detailed report on Arndt–Eistert reaction, please see: a) J. Podlech, in: *Enantioselective Synthesis of β-Amino Acids*, 2nd ed. (Eds.: E. Juaristi, V. A. Soloshonok), Wiley-VCH, New York, **2004**, p. 93; b) A. B. Hughes, B. E. Sleebs, *Aust. J. Chem.* **2008**, *61*, 131; c) A. B. Hughes, B. E. Sleebs, *Aust. J. Chem.* **2005**, *58*, 778; d) R. Magnus, Y. R. Mahajuan, J. Bernhard, D. Seebach, *Chem. Eur. J.* **2004**, *10*, 1607; e) J. L. Matthews, C. Braun, C. Guibourdenche, M. Overhand, D. Seebach in: *Enantioselective Synthesis of β-Amino Acids* (Ed.: E. Juaristi), Wiley-VCH, New York, **1997**, p. 105.

[19] a) N. Rono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**, 30; b) G. Rosini, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, C. H. Heathcock), Pergamon, Oxford, **1991**, Vol. 2, 321; c) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290; M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236.

[20] For a detailed syntheis of phenethylamines, please see: A. Shulgin, A. Shulgin, *PIHKAL: A Chemical Love Story*, Transform Press, **1991**.

[21] P. W. Jeffs, J. F. Hansen, G. A. Brine, *J. Org. Chem.* **1975**, *40*, 2883.

[22] S. Kobayashi, M. Kihara, S. Shizu, S. Katayama, H. Ikeda, K. Kitahiro, H. Matsumoto, *Chem. Pharm. Bull.* **1977**, *25*, 3312.

[23] Y. Ishida, K. Watanabe, S. Kobayashi, M. Kihara, *Jpn. J. Pharmacol.* **1976**, *26*, 607.

[24] a) S. Kobayashi, M. Kihara, T. Shingu, *Yakugaku Zasshi.* **1980**, *100*, 302; b) S. Kobayashi, M. Kihara, Y. Miyake, *Heterocycles* **1985**, *23*, 159; c) M. Kihara, Y. Miyake, M. Iitomi, S. Kobayashi, *Chem. Pharm. Bull.* **1985**, *33*, 1260; d) F. Szemes, A. Rybár, E. Solčániová, *Collect. Czech. Chem. Commun.* **1991**, *56*, 2986.

[25] M. Kihara, J. Itoh, S. Iguchi, S. Kobayashi, *J. Chem. Res. Synop.* **1988**, *1*, 8.

[26] a) K. Takagi, N. Hayama, K. Sasaki, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1997; b) G. Meyer, Y. Rollin, J. Perichon, *J. Organomet. Chem.* **1987**, *333*, 263.

[27] a) K. Harda, *Nature* **1963**, *200*, 1201; b) K. Pfister, W. J. Leanza, J. P. Conbere, H. J. Becker, A. R. Matzuk, E. F. Rogers, *J. Am. Chem. Soc.* **1955**, *77*, 697; c) T. Takenishi, O. Simamura, *Bull. Chem. Soc. Jpn.* **1954**, *27*, 207; d) For a recent review, see: R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539.

[28] R. Dahl, Y. Landias, A. Lebrun, V. Lenanin, J. P. Robin, *Tetrahedron* **1994**, *50*, 1153.

[29] a) P. P. Reddy, C.-Y. Chu, D.-R. Hwang, S.-K. Wang, B.-J. Uang, *Coord. Chem. Rev.* **2003**, *237*, 257; b) Y. Landais, J.-P. Robin, A. Lebrun, *Tetrahedron* **1991**, *47*, 3787; c) Y. Landais, A. Lebrun, J.-P. Robin, *Tetrahedron Lett.* **1986**, *27*, 5377; d) D. Planchenault, R. Dhal, J.-P. Robin, *Tetrahedron* **1993**, *49*, 5823; e) D. Planchenault, R. Dhal, J.-P. Robin, *Tetrahedron* **1995**, *51*, 1395.

[30] Y. Landais, J.-P. Robin, *Tetrahedron* **1992**, *48*, 7185.

[31] S. Miyake, A. Sasaki, T. Ohta, K. Shudo, *Tetrahedron Lett.* **1985**, *26*, 5815.

[32] a) H. Tohma, Y. Kita, *Adv. Synth. Catal.* **2004**, *346*, 111; b) D. Mirk, A. Willner, R. Frohlich, S. R. Waldvogel, *Adv. Synth. Catal.* **2004**, *346*, 675; c) V. V. Zhdankin, *Top. Curr. Chem.* **2003**, *224*, 99; d) H. Tohma, Y. Kita, *Top. Curr. Chem.* **2003**, *224*, 209; e) I. Moreno, I. Tellitu, M. T. Herrero, R. SanMartin, E. Dominguez, *Curr. Org. Chem.* **2002**, *6*, 1433; f) I. Moreno, I. Tellitu, J. Etayo, R. SanMartin, E. Dominguez, *Tetrahedron* **2001**, *57*, 5403; g) P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123; h) Y. Kita, T. Takada, H. Tohma, *Pure Appl. Chem.* **1996**, *68*, 627; i) A. Varvoglis, *Hypervalent Iodine in Organic Synthesis*, Academic, San Diego, **1997**.

[33] a) S. Kodama, H. Takita, T. Kajimoto, K. Nishide, M. Node, *Tetrahedron* **2004**, *60*, 4901; b) Y. Kita, T. Takada, S. Mihara, H. Tohma, *Synlett* **1995**, 211; c) Y. Kita, H. Tohma, K. Hatanaka, T. Takada, S. Fujita, S. Mitoh, H. Sakurai, S. Oka, *J. Am. Chem. Soc.* **1994**, *116*, 3684; d) Y. Kita, T. Takada, S. Mihara, B. A. Whelan, H. Tohma, *J. Org. Chem.* **1995**, *60*, 7144.

[34] Y. Kita, T. Takada, M. Gyoten, H. Tohma, M. H. Zenk, J. Eichorn, *J. Org. Chem.* **1996**, *61*, 5857.

[35] a) Y. Kita, M. Gyoten, M. Ohtsubo, H. Tohma, T. Takada, *Chem. Commun.* **1996**, 1481; b) H. Tohma, H. Morioka, S. Takizawa, M. Arisawa, Y. Kita, *Tetrahedron* **2001**, *57*, 345.

[36] a) H. Hamamoto, G. Anilkumar, H. Tohma, Y. Kita, *Chem. Eur. J.* **2002**, *8*, 5377; b) H. Hamamoto, G. Anilkumar, H. Tohma, Y. Kita, *Chem. Commun.* **2002**, 450.

[37] For some reviews on heteropoly acids, see: a) I. V. Kozhevnikov, *Chem. Rev.* **1998**, *98*, 171; b) N. Mizuno, M. Misono, *Chem. Rev.* **1998**, *98*, 199.

[38] P. Appukkuttan, A. B. Orts, R. P. Chandran, J. L. Goeman, J. Van der Eycken, W. Dehaen, E. Van der Eycken, *Eur. J. Org. Chem.* **2004**, 3277.

[39] For a selected reading on microwave-assisted Suzuki–Miyaura reactions, see: a) M. Larhed, G. Lindeberg, A. Hallberg, *Tetrahedron Lett.* **1996**, *37*, 8219; b) N. E. Leadbeater, M. Marco, *Angew. Chem. Int. Ed.* **2003**, *42*, 1407; c) C. O. Kappe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6250; d) N. E. Leadbeater, *Chem. Commun.* **2005**, 2881; e) C. O. Kappe, D. Dallinger, *Nat. Rev. Drug Discovery* **2006**, *5*, 51; f) P. Appukkuttan, E. Van der Eycken, *Eur. J. Org. Chem.* **2008**, 1133.

[40] S. Bergemann, R. Brecht, F. Büttner, D. Guénard, R. Gust, G. Seitz, M. T. Stubbsa, S. Thoret, *Bioorg. Med. Chem.* **2003**, *11*, 1269.

[41] C. Bru, C. Guillou, *Tetrahedron* **2006**, *62*, 9043.

[42] P. Appukkuttan, W. Dehaen, E. Van der Eycken, *Comb. Chem. High Throughput Screening* **2007**, *10*, 790.

[43] F. Viladomat, J. Bastida, C. Codina, W. E. Campbell, S. Mathee, *Phytochemistry* **1995**, *40*, 307.

[44] a) S. Ishida, Y. Sasaki, Y. Kimura, K. Watanabe, *J. Pharmacobiodyn.* **1985**, *8*, 917; b) K. Ishida, K. Watanabe, S. Kobayashi, M. Kihara, *Chem. Pharm. Bull.* **1977**, *25*, 1851.

[45] P. A. Patil, V. Snieckus, *Tetrahedron Lett.* **1998**, *39*, 1325.

[46] For a detailed account, see: a) C. G. Hartung, V. Snieckus, *Mod. Arene Chem.* **2002**, 330; b) E.-F. G. Anctil, V. Snieckus, *J. Organomet. Chem.* **2002**, *653*, 150; c) B. Chauder, L. Green, V. Snieckus, *Pure Appl. Chem.* **1999**, *71*, 1521; d) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; e) V. Snieckus, *Pure Appl. Chem.* **1990**, *62*, 671.

[47] For recent riviews, see: a) L. F. Van Staden, D. Gravestock, D. J. Ager, *Chem. Soc. Rev.* **2002**, *31*, 195; b) D. J. Ager, *Org. React.* **1990**, *42*, 1–223; c) D. J. Ager, *Synthesis* **1984**, 384.

[48] C. Hoarau, A. Couture, E. Deniau, P. Grandclaudon, *J. Org. Chem.* **2002**, *67*, 5846.

[49] a) R. H. Hutchings, A. I. Meyers, *J. Org. Chem.* **1996**, *61*, 1004; b) A. I. Meyers, R. Gabel, E. D. Mihelich, *J. Org. Chem.* **1978**, *43*, 1372.

[50] P. Sahakitpichan, S. Ruchirawat, *Tetrahedron Lett.* **2003**, *44*, 5239.

[51] a) T. E. Nielsen, F. Diness, M. Meldal, *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 801; b) E. D. Cox, J. M. Cook, *Chem. Rev.* **1995**, *95*, 1797.

[52] a) S. Kodama, H. Takita, T. Kajimoto, K. Nishide, M. Node, *Tetrahedron* **2004**, *60*, 4901.

[53] P. Appukkuttan, W. Dehaen, E. Van der Eycken, *Org. Lett.* **2005**, *7*, 2723.

[54] a) M. Schuster, S. Blechert, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036; b) R. H. Grubbs, H. E. Blackwell, *Angew. Chem. Int. Ed.* **1998**, *37*, 3281; c) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413; d) A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 3812; e) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18; f) R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117; g) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199; h) A. Fürstner, K. Radkowski, C. Wirtz, R. Goddard, C. W. Lehmann, R. Mynott, *J. Am. Chem. Soc.* **2002**, *124*, 7061; i) L. Banfi, A. Basso, G. Guanti, R. Riva, *Tetrahedron Lett.* **2003**, *44*, 7655; j) C. Rodriguez, J. L. Ravelo, V. S. Martin, *Org. Lett.* **2004**, *6*, 4787; k) Y. J. Kim, D. Lee, *Org. Lett.* **2004**, *6*, 4351; l) G. Vassilikogiannakis, I. Margaros, M. Tofi, *Org. Lett.* **2004**, *6*, 205; m) M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. J. P. White, K. K. Hii, P. N. Horton, M. B. Hursthouse, *J. Org. Chem.* **2005**, *70*, 1545; n) M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. J. P. White, K. K. Hii, P. N. Horton, M. B. Hursthouse, *J. Org. Chem.* **2005**, *70*, 1552.

[55] X. Su, D. J. Fox, D. T. Blackwell, K. Tanaka, D. R. Spring, *Chem. Commun.* **2006**, 3883.

[56] P. Appukkuttan, W. Dehaen, E. Van der Eycken, *Chem. Eur. J.* **2007**, *13*, 6452.

[57] S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, R. F. Bryan, *J. Am. Chem. Soc.* **1973**, *95*, 1335.

[58] F. Zavala, D. Guenard, L. Robin, E. Brown, *J. Med. Chem.* **1980**, *23*, 546.

[59] a) A. Jordan, J. A. Hadfield, N. J. Lawrence, A. T. McGown, *Med. Res. Rev.* **1998**, *18*, 259; b) D. L. Sackett, *Pharmacol. Ther.* **1993**, *59*, 163.

[60] a) K. Tomioka, T. Ishiguro, H. Mizuguchi, N. Komeshima, K. Koga, S. Tsukagoshi, T. Tsuruo, T. Tashiro, S. Tanida, T. Kishi, *J. Med. Chem.* **1991**, *34*, 54; b) K. Tomioka, H. Kawasaki, K. Koga, *Chem. Pharm. Bull.* **1990**, *38*, 1898.

[61] K. Tomioka, Y. Kubota, H. Kawasaki, K. Koga, *Tetrahedron Lett.* **1989**, *30*, 2949.

[62] Y. Kubota, H. Kawasaki, K. Tomioka, K. Koga, *Tetrahedron* **1993**, *49*, 3081.

[63] T. Beryozkina, P. Appukkuttan, N. Mont, E. Van der Eycken, *Org. Lett.* **2006**, *8*, 487.

[64] D. Imperio, T. Pirali, U. Galli, F. Pagliai, L. Cafici, P. L. Canonico, G. Sorba, A. A. Genazzani, G. C. Tron, *Bioorg. Med. Chem.* **2007**, *15*, 6748.

[65] For some recent reviews on "click chemistry", see: a) B. L. Wilkinson, L. F. Bornaghi, T. A. Houston, S.-A. Poulsen, *Drug Des. Res. Perspective* **2007**, 57; b) V. V. Fokin, *ACS Chem. Biol.* **2007**, *2*, 775; c) H. Nandivada, J. Xuwei, J. Lahann, *Adv. Mater.* **2007**, *19*, 2187; d) Y. L. Angell, K. Burgess, *Chem. Soc. Rev.* **2007**, *36*, 1369; e) I. Aprahamian, O. S. Miljanic, W. R. Dichtel, K. Isoda, T. Yasuda, T. Kato, J. F. Stoddart, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1856; f) M. V. Gil, M. J. Arevalo, O. Lopez, *Synthesis* **2007**, 1589; g) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249; h) J.-F. Lutz, *Angew. Chem. Int. Ed.* **2007**, *46*, 1018; i) S. Roper, H. C. Kolb, *Methods Principles Med. Chem.* **2006**, *34*, 313; j) K. B. Sharpless, R. Manetsch, *Expert Opin. Drug Discovery* **2006**, *1*, 525; k) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128; l) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004 and references cited thererin. Also see the special issue: E. Van der Eycken, K. B. Sharpless, *QSAR Comb. Sci.* **2007**, *26*, 212.

[66] G. Hilt, F. Galbiati, K. Harms, *Synthesis* **2006**, 3575.

[67] P. A. Donets, E. Van der Eycken, *QSAR Comb. Sci.* **2007**, *26*, 1239.

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