

Total synthesis of biologically active alkaloids using transition metals^{*,**}

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Abstract: We have developed efficient synthetic routes to heterocyclic ring systems using transition metals (palladium, iron, and silver). Recent applications of this chemistry to the total synthesis of biologically active alkaloids include carbazole alkaloids (pityriazole, euchrestifoline, the antiostatins), crispine A, pentabromo- and pentachloropseudilin. The two latter alkaloids represent a novel class of myosin ATPase inhibitors that led to the discovery of a new allosteric binding site of the protein.

Keywords: alkaloids; iron; myosin; palladium; silver.

INTRODUCTION

Our research is focusing on the development of novel methodologies for the synthesis of biologically active compounds. In cooperation with groups from biochemistry, biology, and medicine, we are investigating the potential of these compounds as novel lead structures for drugs. One of our current projects is dealing with the stereoselective synthesis of steroids [1–13]. These studies have led to highly efficient total syntheses of the dafachronic acids (Fig. 1) [13].

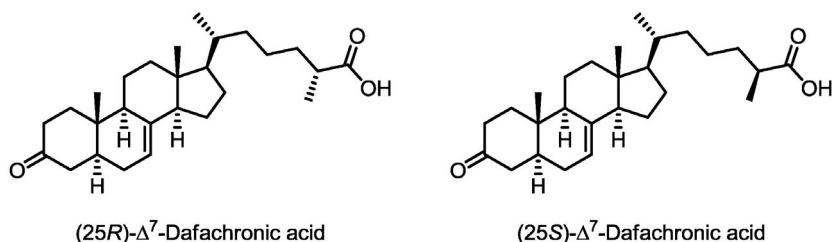


Fig. 1 Structures of the Δ^7 -dafachronic acids.

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Another topic of our research is the design and synthesis of membrane-anchored β -secretase inhibitors as potential novel agents for the treatment of Alzheimer's disease [14–16].

The present article describes our recent achievements in the total synthesis of biologically active alkaloids using transition-metal-catalyzed carbon–carbon and carbon–heteroatom bond formations as key steps. Among the different alkaloids being investigated in our group, a special emphasis is on carbazole alkaloids and pyrrole derivatives.

CARBAZOLE ALKALOIDS: OCCURRENCE AND SYNTHESSES

One of the major natural sources of carbazole alkaloids is the Indian curry-leaf tree (in Hindi: *kari patta*) with the botanical name *Murraya koenigii* Spreng. In 1964, Chakraborty et al. described the isolation of murrayanine and girinimbine from *Murraya koenigii* (Fig. 2) [17]. The extracts of this small tree have been used in traditional Indian folk medicine.

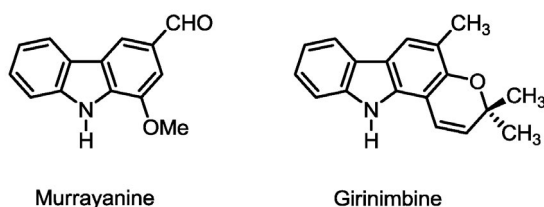
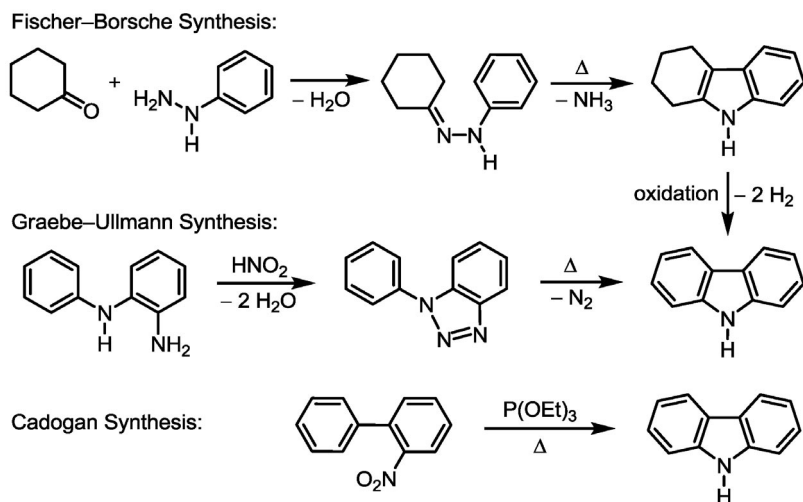


Fig. 2 Structures of murrayanine and girinimbine.

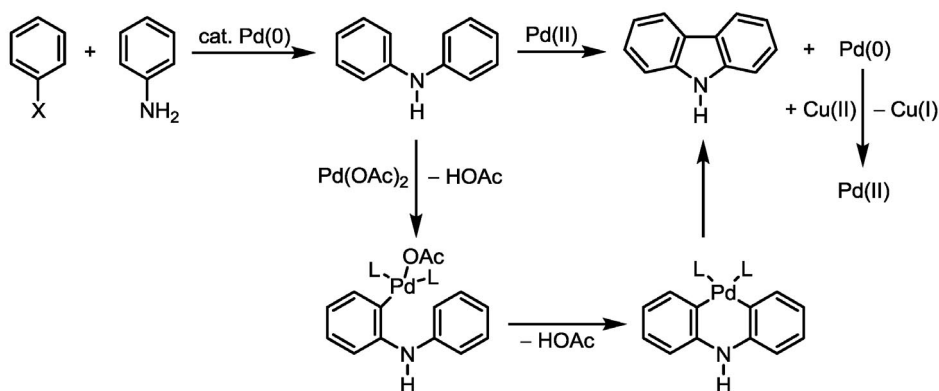
Over the past decades, the intriguing structural features and useful biological activities have led to a strong interest in the chemistry and biology of carbazole alkaloids [18–23]. Thus, many synthetic approaches for the construction of the carbazole framework have been developed.

Some classical syntheses of carbazoles are the Fischer–Borsche synthesis, which proceeds via a diaza-Cope rearrangement, the Graebe–Ullmann synthesis, involving a diradical intermediate, and the Cadogan synthesis, furnishing the skeleton by an aryl C–H insertion of a nitrene (Scheme 1).



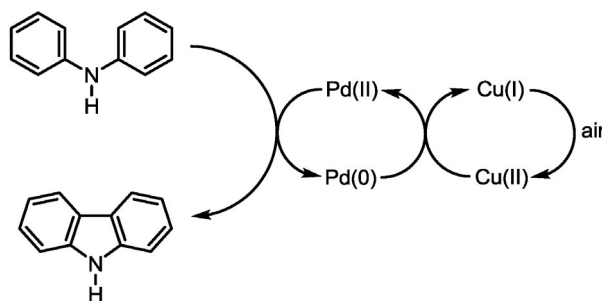
Scheme 1 Classical syntheses of carbazoles.

Based on the oxidative cyclization of *N,N*-diarylamines with stoichiometric amounts of Pd(II) acetate originally reported by Åkermarck et al. [24], we have developed an efficient Pd(II)-catalyzed synthesis of carbazoles (Scheme 2) [25–35]. Using catalytic amounts of Pd(0), the synthesis of *N,N*-diarylamines is readily achieved by Buchwald–Hartwig amination of aryl halides or triflates with arylamines [36,37]. We have found that the Pd(II)-mediated oxidative cyclization can be induced using catalytic amounts of Pd by reoxidation of Pd(0) to Pd(II) with Cu(II) salts [25]. Regeneration of a catalytically active Pd(II) species by oxidation with Cu(II) salts in the presence of air has also been used in the well-known Wacker process [38,39]. The oxidative cyclization proceeds via a double aryl C–H bond activation by electrophilic attack of Pd(II) generating a palladacycle. Reductive elimination of Pd generates the central C–C bond of the carbazole heterocycle.



Scheme 2 Pd(II)-catalyzed carbazole synthesis via double aryl C–H bond activation.

Optimization of this process over several years [25–35] led us to a highly efficient Pd(II)-catalyzed oxidative cyclization of *N,N*-diarylamines to carbazoles by double C–H bond activation. The reaction proceeds via a sequence of two catalytic cycles involving Pd(II)/Pd(0) and Cu(II)/Cu(I) with air as final oxidant for generation of the central C–C bond of carbazoles (Scheme 3).

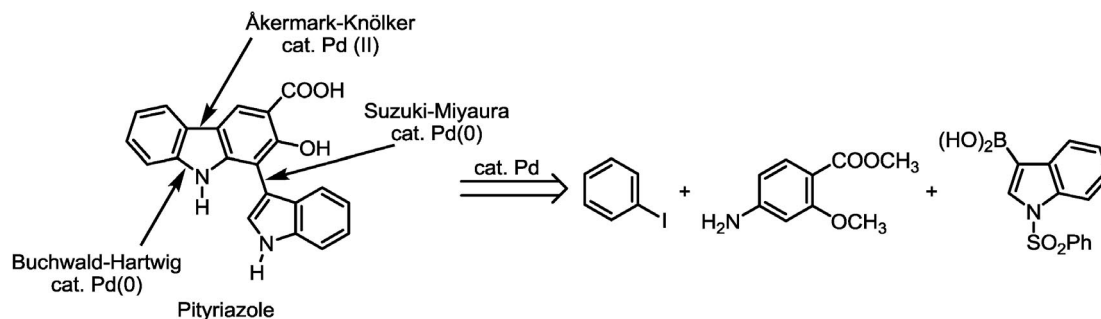


Scheme 3 Catalytic cycles of the Pd- and Cu-catalyzed oxidative cyclization to carbazoles.

Pd-catalyzed total synthesis of pityriazole

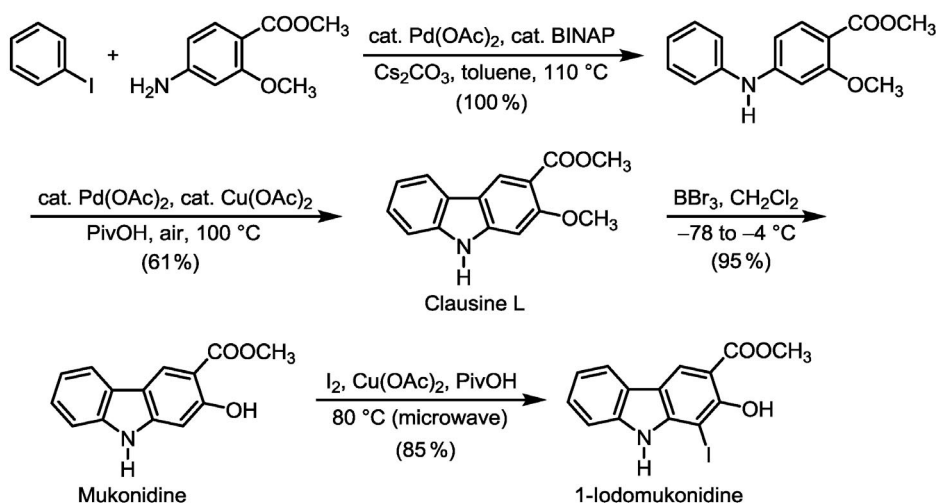
Steglich et al. isolated the structurally unprecedented 1-(indol-3-yl)carbazole alkaloid pityriazole from *Malassezia furfur*, a lipophilic yeast that is considered one of the pathogenic agents inducing the common skin disease pityriasis versicolor [40]. Based on our retrosynthetic analysis of pityriazole, we en-

visaged a convergent construction of the complete heterocyclic framework (Scheme 4). Three Pd-catalyzed coupling reactions of three cheap commercial building blocks open up the way to a concise synthesis of pityriazole [41].



Scheme 4 Retrosynthetic analysis of pityriazole.

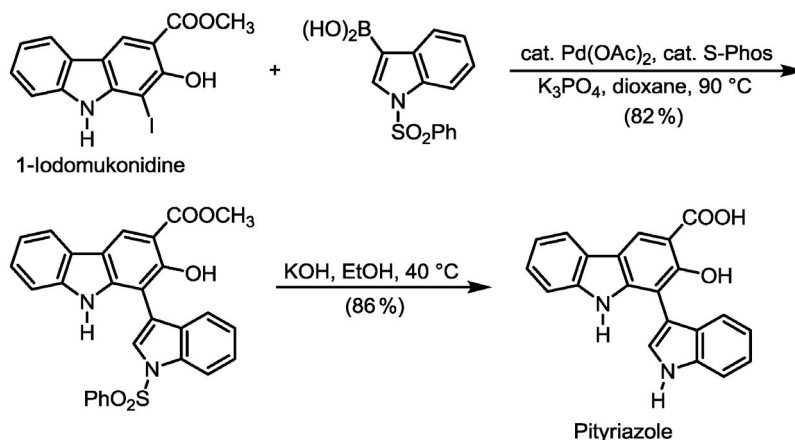
Pd(0)-catalyzed amination of iodobenzene with the appropriate arylamine followed by Pd(II)-catalyzed oxidative cyclization of the resulting *N,N*-diarylamine afforded clausine L (Scheme 5) [41]. Clausine L is a natural product, isolated first in 1993 by Wu et al. from the Chinese medicinal plant *Clausena excavata* [42], and one year later by Bhattacharyya et al. from the stem bark of *Murraya koenigii* [43]. Our route has also led to the first total synthesis of this natural product. Ether cleavage of clausine L provided mukonidine, which has been obtained by Wu et al. from the same natural source as clausine L [42]. This approach to mukonidine is superior in comparison to our Fe-mediated synthesis [44]. Electrophilic iodination of mukonidine afforded 1-iodomukonidine, which is used for the introduction of the indol-3-yl substituent by Suzuki–Miyaura coupling [45,46].



Scheme 5 Pd-catalyzed synthesis of 1-iodomukonidine.

Suzuki–Miyaura coupling of 1-iodomukonidine with *N*-(phenylsulfonyl)indol-3-ylboronic acid afforded *N*-phenylsulfonylpityriazole methyl ester (Scheme 6). Finally, hydrolysis using basic reaction

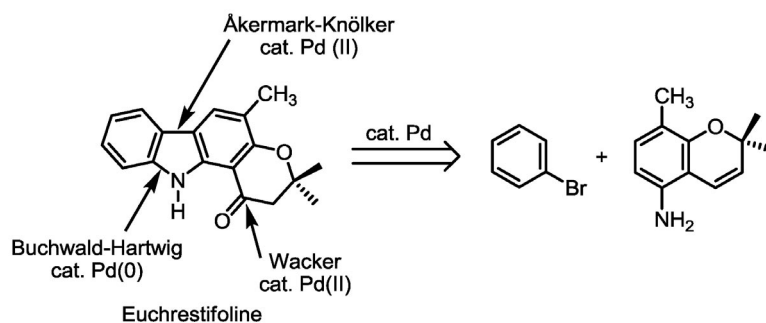
conditions provided pityriazole (6 steps and 35 % overall yield) [41]. Only 1 mg of pityriazole has been obtained by Steglich et al. from natural sources [40]. With the present synthesis, pityriazole becomes available in gram quantities and a program directed toward an investigation of its biological properties has been initiated.



Scheme 6 Total synthesis of pityriazole.

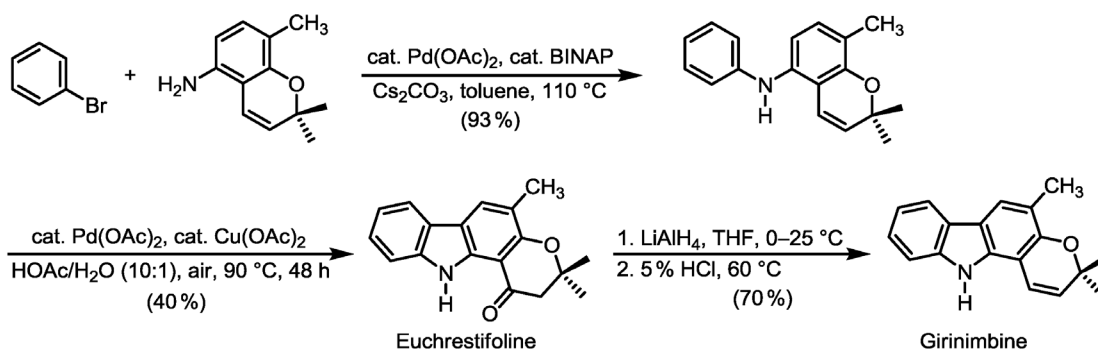
Pd-catalyzed total synthesis of euchrestifoline

Another interesting carbazole natural product is euchrestifoline, which was isolated in 1996 by Wu et al. from the leaves of the Chinese medicinal plant *Murraya euchrestifolia* [47]. The structurally related pyrano[3,2-*a*]carbazole alkaloid girinimbine was isolated earlier, in 1964, by Chakraborty from *Murraya koenigii* [17] and in 1970 by Joshi et al. from the root bark of *Clausena heptaphylla* [48]. We envisaged an efficient two-step synthesis of euchrestifoline based on a one-pot threefold C–H bond activation by combining the Pd(II)-catalyzed oxidative cyclization with the Wacker oxidation (Scheme 7).



Scheme 7 Retrosynthetic analysis of euchrestifoline.

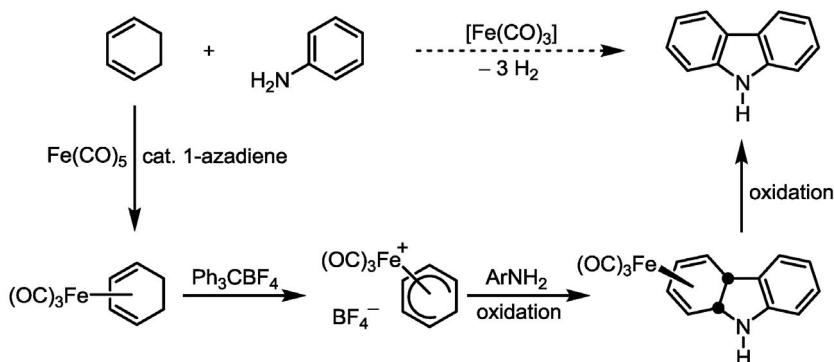
Buchwald–Hartwig amination of bromobenzene with the appropriate aminochromene led to a diarylamine which on reaction with catalytic amounts of Pd(II) and Cu(II) in the presence of air afforded directly euchrestifoline (Scheme 8) [49]. A detailed investigation showed that the vinylic C–H bond is activated more easily and thus, Wacker oxidation takes place first. Reduction of euchrestifoline followed by elimination provided an improved route to girinimbine [50].



Scheme 8 Pd-catalyzed synthesis of euchrestifoline and transformation into girinimbine.

Fe-mediated total synthesis of the antiostatins

The tricarbonyliron-mediated oxidative coupling of cyclohexadiene and arylamines represents an alternative efficient route to carbazoles (Scheme 9). Tricarbonyl(η^4 -cyclohexa-1,3-diene)iron complexes can be readily prepared on a large scale by the azadiene-catalyzed complexation of cyclohexadiene with pentacarbonyliron, which has been developed in our laboratories [51–54]. One of the most characteristic features of tricarbonyl(η^4 -cyclohexa-1,3-diene)iron complexes is the activation of the allylic C–H bonds. We have exploited this reactivity for a broad range of applications including the Fe-mediated carbazole synthesis [55–58].



Scheme 9 General principle of the Fe-mediated carbazole synthesis.

The Fe-mediated route to carbazoles has recently been used for the first total synthesis of the complete series of the antiostatins A and B (Fig. 3). These structurally unique carbazole alkaloids have been isolated by Seto et al. from *Streptomyces cyaneus* 2007-SV₁ and represent strong inhibitors of free radical-induced lipid peroxidation [59].

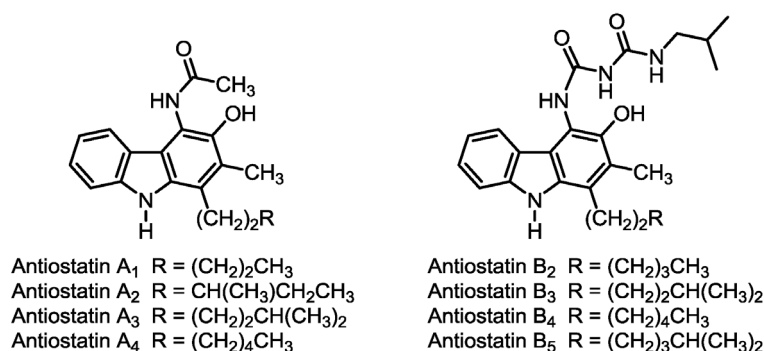
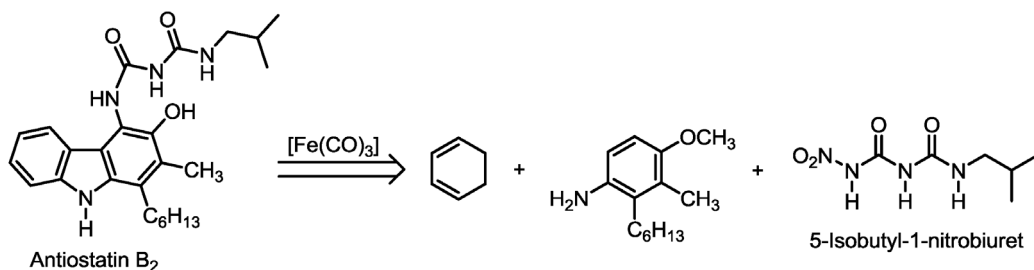


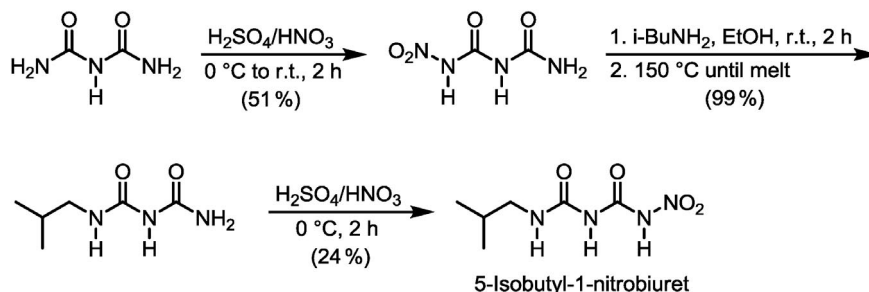
Fig. 3 Structures of the antiostatins A₁–A₄ and B₂–B₅.

Our synthetic strategy for this class of compounds is demonstrated for the total synthesis of antiostatin B₂, which requires cyclohexadiene, 2-hexyl-4-methoxy-3-methylaniline, and 5-isobutyl-1-nitrobiuret as precursors (Scheme 10) [60].



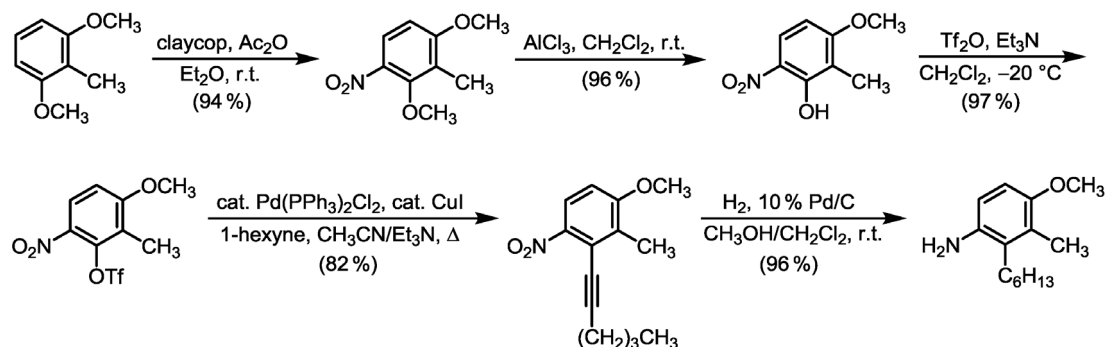
Scheme 10 Retrosynthetic analysis of antiostatin B₂.

We have prepared 5-isobutyl-1-nitrobiuret as reagent for the introduction of the antiostatin B side chain (Scheme 11) [60]. Nitration of biuret using the procedure of Thiele and Uhlfelder [61], followed by reaction with isobutylamine and a second nitration afforded 5-isobutyl-1-nitrobiuret.



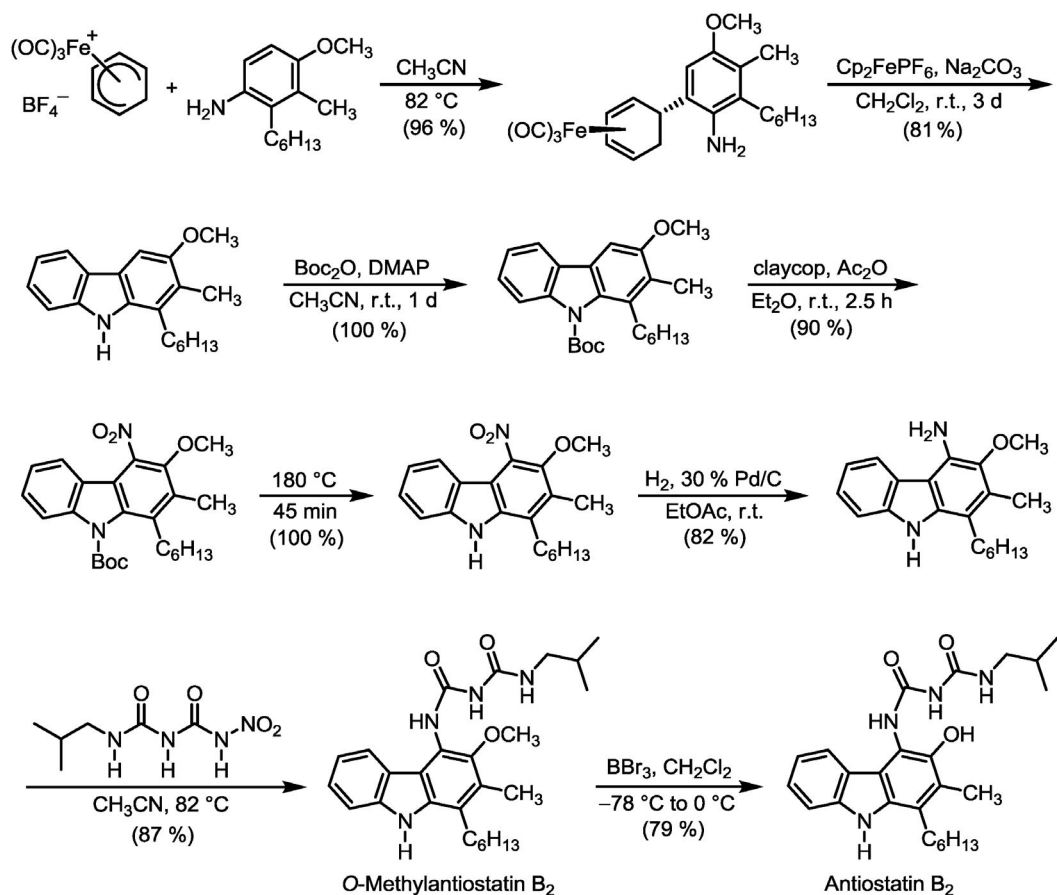
Scheme 11 Synthesis of 5-isobutyl-1-nitrobiuret.

The synthesis of 2-hexyl-4-methoxy-3-methylaniline has been achieved on a large scale starting from 2,6-dimethoxytoluene (Scheme 12). Nitration, followed by regioselective ether cleavage, transformation to the triflate, Sonogashira–Hagihara coupling with 1-hexyne [62,63] and catalytic hydrogenation provided the required arylamine in five steps and 69 % overall yield [60].



Scheme 12 Synthesis of the arylamine.

Electrophilic substitution of the arylamine by reaction with tricarbonyl(η^5 -cyclohexadienyl)iron tetrafluoroborate and subsequent Fe-mediated oxidative cyclization with concomitant aromatization led to 1-hexyl-3-methoxy-2-methylcarbazole (Scheme 13). Conversion to the *tert*-butyl carbamate, regioselective nitration at C-4, removal of the Boc group under thermal conditions, and catalytic hydrogenation provided a 4-aminocarbazole. Reaction of 5-isobutyl-1-nitrobiuret with the



Scheme 13 Fe-mediated total synthesis of antiostatin B₂.

4-aminocarbazole afforded *O*-methylantiostatin B₂, which on cleavage of the methyl ether provided antiostatin B₂. Using this methodology, the whole series of the antiostatins A and B has been prepared in excellent overall yields [60].

Recent total syntheses of carbazole alkaloids using Pd or Fe

We have an ongoing research program directed toward the total synthesis of carbazole alkaloids and the investigation of their biological activities. A special focus has been on the antibiotic properties and the inhibition of *Mycobacterium tuberculosis* exhibited by some carbazole derivatives [64–67]. In the course of our project, several total syntheses of carbazole alkaloids with a variety of structures have been completed over the last four years (Fig. 4).

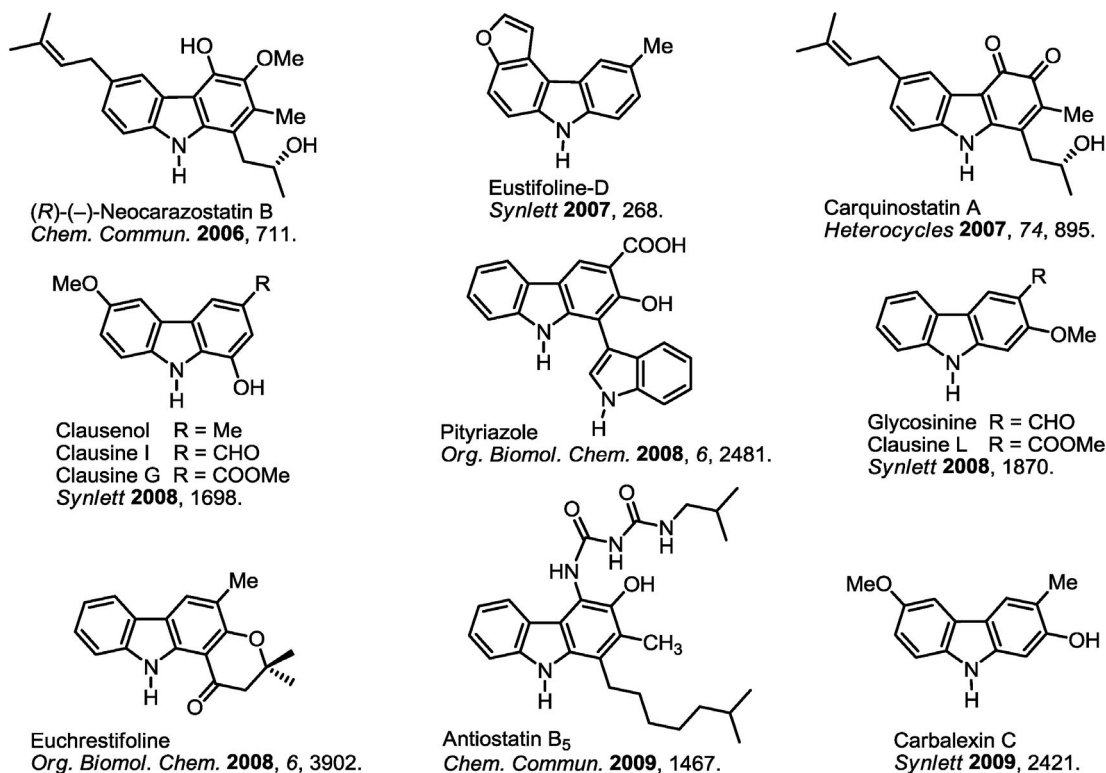


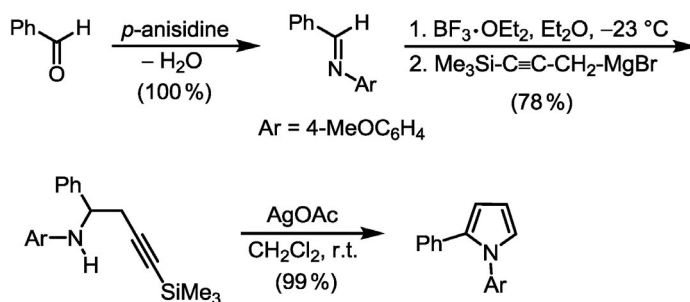
Fig. 4 Selection of carbazole alkaloids recently synthesized by our group.

PYRROLE DERIVATIVES

The pyrrole nucleus is a pivotal substructure of many natural products and pharmacologically active compounds [68]. Therefore, besides the classical Hantzsch, Knorr, and Paal–Knorr synthesis, many alternative routes to this heterocyclic framework have been described. Recently, we have developed a novel synthesis of pyrroles by a simple three-component coupling and subsequent Ag(I)-mediated cyclization [69].

Ag(I)-mediated synthesis of pyrroles

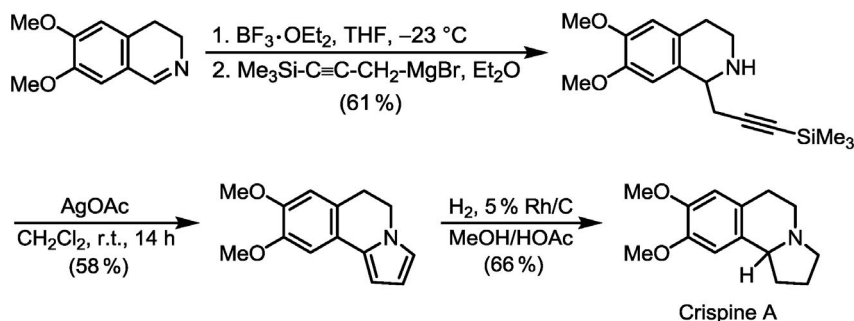
Condensation of benzaldehyde with *p*-anisidine followed by Lewis acid-promoted addition of trimethylsilylpropargylmagnesium bromide to the Schiff base afforded a homopropargylamine (Scheme 14). The Ag(I)-mediated oxidative cyclization of the homopropargylamine provides the corresponding 2-arylpyrrole in high yield [69]. This procedure has proven to be very useful for the construction of substituted pyrroles and has been applied to the total synthesis of the anti-leishmania active indolizino[8,7-*b*]indole alkaloid (±)-harmicine [70–73].



Scheme 14 Ag(I)-mediated oxidative cyclization to pyrroles.

Total synthesis of (±)-crispine A

The Ag-mediated synthesis of pyrroles has been applied to the first total synthesis of the antitumor active pyrrolo[2,1-*a*]isoquinoline alkaloid (±)-crispine A (Scheme 15). In 2002, crispine A was isolated by Zhao et al. from *Carduus crispus* L. [74]. Extracts of this plant have been used in Chinese folk medicine for the treatment of cold, stomach ache, and rheumatism. However, only a recent screening test revealed the antitumor activity of the extracts and led to the isolation of crispine A [74]. Our synthesis started from 3,4-dihydro-6,7-dimethoxyisoquinoline which is readily available via a Bischler–Napieralski cyclization. Lewis acid-promoted addition of trimethylsilylpropargylmagnesium bromide followed by Ag(I)-mediated oxidative cyclization led to 5,6-dihydro-8,9-dimethoxy-pyrrolo[2,1-*a*]isoquinoline [75]. Chemoselective hydrogenation of the pyrrole ring provided (±)-crispine A.



Scheme 15 Ag(I)-mediated total synthesis of (±)-crispine A.

Ag(I)-catalyzed synthesis of pseudilins

A wide range of biologically active halogenated natural products has been isolated from diverse natural sources [76–79]. Pentabromopseudilin and pentachloropseudilin are pentahalogenated 2-arylpyrrole derivatives which have been obtained from various microorganisms (Fig. 5) [80–83].

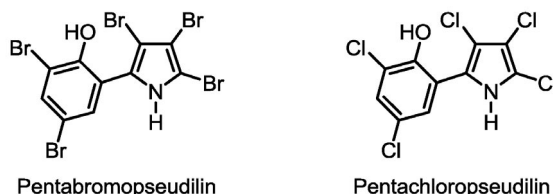
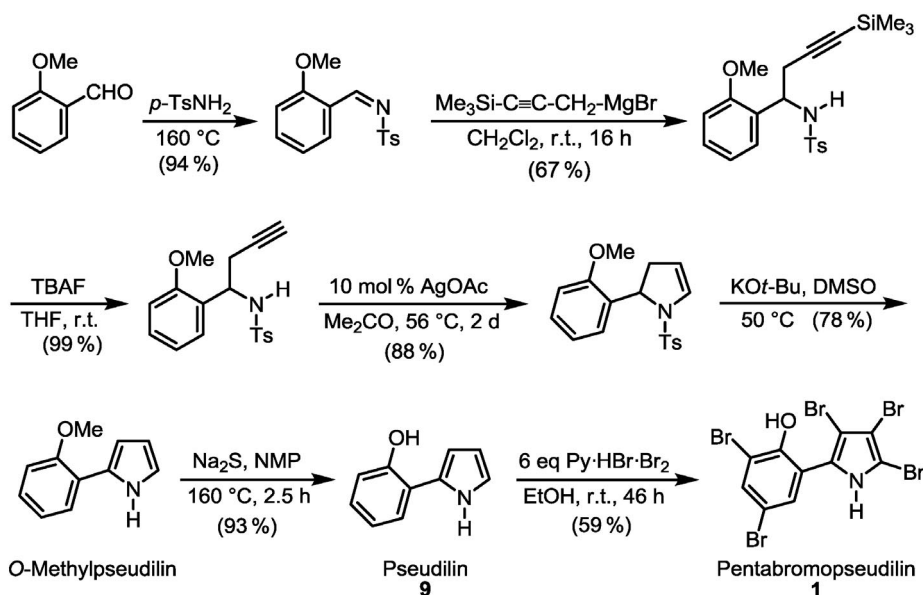


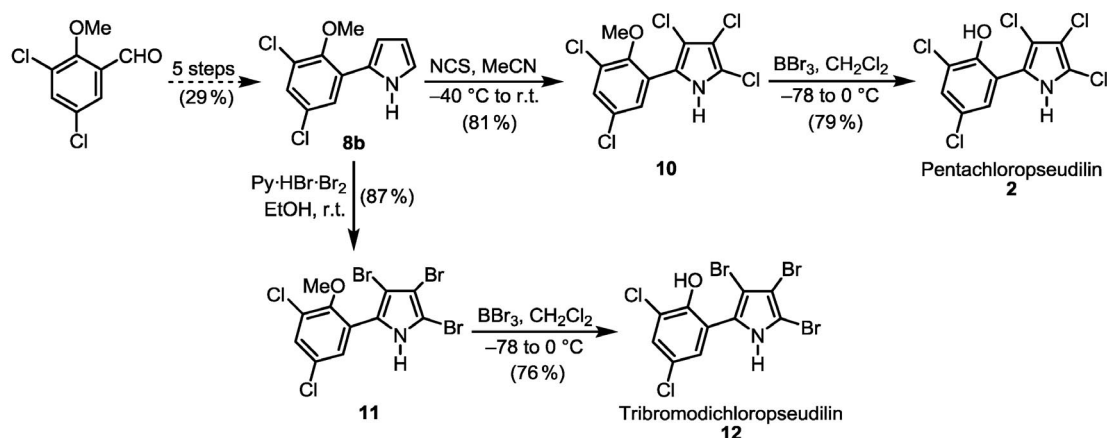
Fig. 5 Structures of pentabromopseudilin and pentachloropseudilin.

We have elaborated a concise synthesis of the pentahalogenated pseudilins and converted the cyclization of homopropargylamines to an efficient Ag(I)-catalyzed process (Scheme 16) [84]. Condensation of 2-methoxybenzaldehyde to the *N*-tosylaldimine and subsequent addition of trimethylsilylpropargylmagnesium bromide afforded the corresponding homopropargylamine. Protodesilylation followed by cyclization in the presence of 10 mol % of silver acetate provided the 2-aryl-2,3-dihydropyrrole. Aromatization by base-induced elimination of *p*-toluenesulfonic acid led to *O*-methylpseudilin. Cleavage of the ether to pseudilin followed by electrophilic bromination using an excess of pyridinium tribromide provided pentabromopseudilin [84].



Scheme 16 Ag(I)-catalyzed total synthesis of pentabromopseudilin.

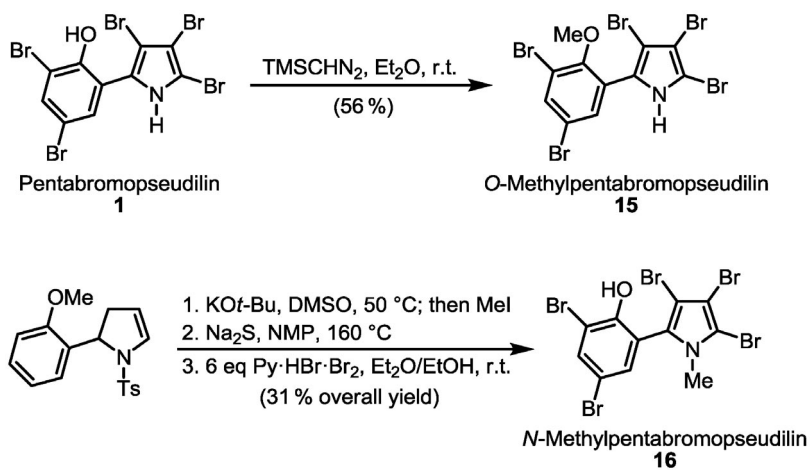
Since a pentachlorination of pseudilin could not be achieved, a different approach was developed for the synthesis of pentachloropseudilin. Using the same sequence of steps as described above, 3,5-dichloro-2-methoxybenzaldehyde was transformed in 29 % overall yield to dichloro-*O*-methylpseudilin (Scheme 17). Electrophilic chlorination using *N*-chlorosuccinimide to pentachloro-*O*-methyl-



Scheme 17 Ag(I)-catalyzed synthesis of pentachloropseudilin and tribromodichloropseudilin.

pseudilin and subsequent cleavage of the methyl ether afforded pentachloropseudilin. Bromination of dichloro-*O*-methylpseudilin followed by ether cleavage led to the non-natural tribromodichloropseudilin [84].

For a study of the structure–activity relationships, the corresponding *O*-methyl and *N*-methyl derivatives of pentabromopseudilin have been prepared (Scheme 18) [84]. *O*-Methylpentabromopseudilin was prepared by reaction of pentabromopseudilin with trimethylsilyldiazomethane. Treatment of the 2-aryl-2,3-dihydropyrrole with base, quenching with methyl iodide, and cleavage of the ether followed by electrophilic bromination using an excess of pyridinium tribromide, provided *N*-methylpentabromopseudilin.



Scheme 18 Syntheses of *O*-methylpentabromopseudilin and *N*-methylpentabromopseudilin.

Pseudilin derivatives as novel allosteric inhibitors of myosin ATPase

In a screening for the pharmacological activities of the heterocyclic compounds described above, we have found that pentabromopseudilin is a strong inhibitor of myosin ATPase [84–86]. This finding has attracted our interest since specific inhibitors of myosins represent potential agents for the treatment of

cancer, malaria, and a range of muscle malfunctions. In a subsequent study, the pseudilin derivatives were investigated for their inhibition of skeletal muscle myosin-2 ATPase activity (Fig. 6). The inhibitory activity of the pseudilins was compared with that of (*S*)-(-)-blebbistatin and *N*-benzyl-*p*-toluene sulfonamide (Fig. 7) [87–91]. The efficacy of pentabromopseudilin (**1**) is in the same range as that of (*S*)-(-)-blebbistatin (**17**) and pentachloropseudilin (**2**) is almost as efficient as *N*-benzyl-*p*-toluene sulfonamide (**18**) (Fig. 6).

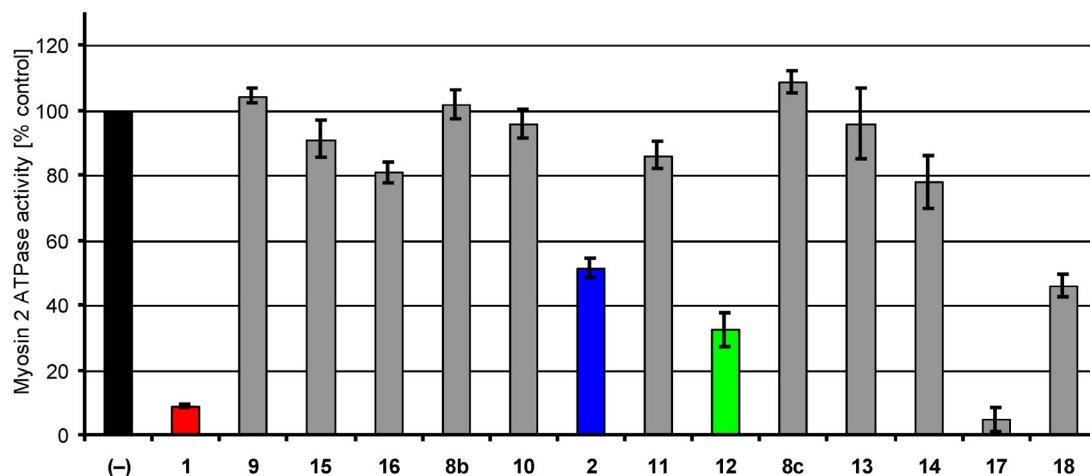


Fig. 6 Inhibition of skeletal muscle myosin-2 ATPase activity relative to control: (-) = 100 %.

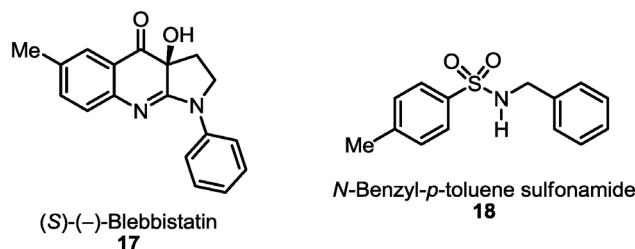


Fig. 7 Structures of (*S*)-(-)-blebbistatin (**17**) and *N*-benzyl-*p*-toluene sulfonamide (**18**).

The results obtained with the non-natural pseudilin derivatives indicated interesting structure–activity relationships. Tribromodichloropseudilin (**12**) is a more potent inhibitor than pentachloropseudilin (**2**) but not as efficient as pentabromopseudilin (**1**). The *O*-methyl and *N*-methyl derivatives **10**, **11**, **15**, and **16** exhibited significantly reduced inhibitory potencies with residual ATPase activities in the range of 80–90 %. Pseudilin (**9**) and dichloro-*O*-methylpseudilin (**8b**) showed no inhibition at all. Further studies showed that the pseudilins inhibit ATPase and motor activities for a range of different myosins. The inhibitory potency of pentabromopseudilin for vertebrate class-5 myosins is 25-fold higher than that observed for skeletal muscle myosin-2 isoforms [85,86].

An X-ray crystallographic analysis of the complex formed by *Dictyostelium* myosin-2 motor domain with Mg²⁺–ADP–*meta*-vanadate and pentabromopseudilin revealed a new allosteric binding site, located 16 Å away from the nucleotide binding site (Fig. 8) [86]. Superposition of the structure of the myosin-2 motor domain with Mg²⁺–ADP–*meta*-vanadate–pentabromopseudilin complex with the structure of the corresponding complex with (*S*)-(-)-blebbistatin (**17**) confirmed that the new allosteric binding site is 7.5 Å away from the allosteric binding site of blebbistatin (Fig. 9).

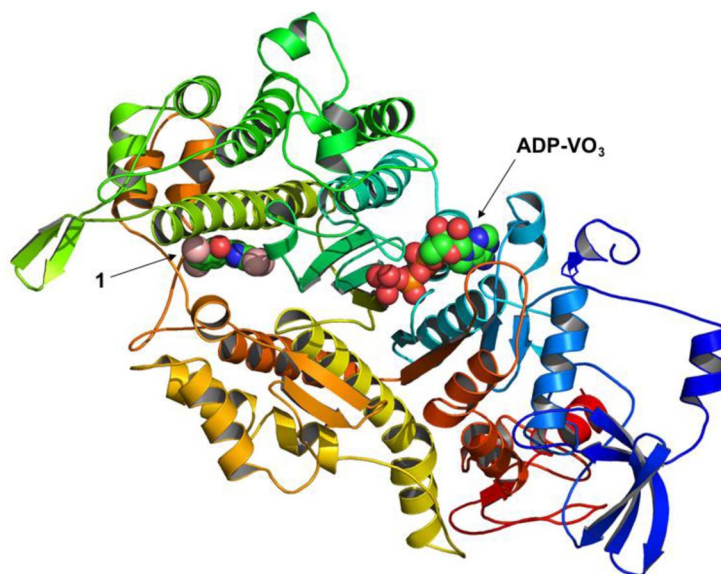


Fig. 8 Structure of the complex formed by the *Dictyostelium* myosin-2 motor domain with Mg^{2+} -ADP-*meta*-vanadate and pentabromopseudilin (**1**).

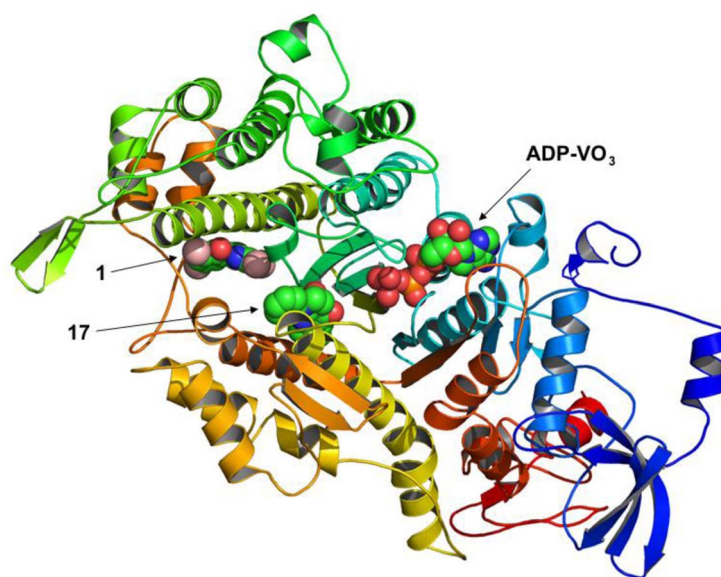


Fig. 9 Structure of the complex formed by the *Dictyostelium* myosin-2 motor domain with Mg^{2+} -ADP-*meta*-vanadate and pentabromopseudilin (**1**) in superposition with the structure of the corresponding complex with (S)-(-)-blebbistatin (**17**).

The discovery of a novel class of inhibitors for myosin ATPase activity and the identification of a new allosteric binding site paves the way for the development of more potent and isoform-specific myosin ATPase inhibitors by rational drug design. Such compounds represent potential candidates for the development of drugs for the treatment of cancer and malaria.

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