Top Curr Chem (2006) 266: 1–47
DOI 10.1007/128_051

Published online: 8 July 2006

Microwave-Assisted Natural Product Chemistry

Prasad Appukkuttan[1] · Erik Van der Eycken[2] (✉)

[1]Department of Medicinal Chemistry, Organic Pharmaceutical Chemistry, BMC, Uppsala University, P.O. Box. 574, SE 751 23 Uppsala, Sweden

[2]Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium
erik.vandereycken@chem.kuleuven.be

Abstract An overview of the application of microwave irradiation in natural product synthesis is presented, focusing on the developments in the last 5–10 years. This contribution covers the literature concerning the total synthesis of natural products and their analogues, the synthesis of alkaloids and the construction of building blocks of interest for natural product synthesis. As microwave irradiation appeared on the scene only recently, we are at an early stage of its application in natural product chemistry, even though some nice examples have been communicated recently. The application of dedicated microwave instruments as well as domestic microwave ovens is discussed, giving emphasis to the microwave-enhanced transformations.

Keywords Alkaloids · Microwave irradiation · Natural products · Steroids · Total synthesis

Abbreviations

Boc	*tert*-butoxycarbonyl
CNS	central nervous system
m-CPBA	*m*-chloroperbenzoic acid
CTH	catalytic transfer hydrogenation
o-DCB	*o*-dichlorobenzene

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
HIV	human immunodeficiency virus
IEDDA	inverse electron-demand Diels–Alder
PEA	phenethylamine
PMB	*p*-methoxybenzyl
PTSA	*p*-toluene sulfonic acid
RCAM	ring-closing alkyne metathesis
RCM	ring-closing metathesis
TBAF	*N*,*N*,*N*,*N*-tetrabutylammonium fluoride
TBDMS	*tert*-butyl dimethyl silyl
THF	tetrahydrofuran

1 Introduction

For many years the (total) synthesis of natural products has inspired many chemists to develop synthetic approaches that many times are conceptually real beauties. Nature is an inexhaustible source of diverse chemical compounds and many of them possess interesting biological activities. That is exactly what makes natural products so important for mankind: they represent a nearly unlimited reservoir of precious starting compounds for the development of new medicines by combinatorial chemistry, high throughput screening and medicinal chemistry. Taxol and penicillin are two of the striking examples of what nature is offering us.

In contrast with the enormous effort directed at natural product synthesis, the application of microwave irradiation in this field is rather scarcely investigated, and a systematic use of this technique for most of the conversions in a (total) synthesis sequence is still a challenging target. We have just reached dawn in the development of microwave-assisted natural product synthesis, although unquestionably, some beautiful examples have already been described.

We attempted to give an overview of the last 5–10 years and via different searches we tried to retrieve the relevant literature, which was not an obvious task. Nevertheless, we hope that we have covered as much as possible of the published research, although obviously some work will be missing. For the sake of clarity we divided the collected literature into five subsections: (1) Total synthesis of various classes of natural products; (2) Synthesis of alkaloids, as this is a clear and well-defined subcategory of natural products; (3) Modifications of natural products (i.e. synthesis starting from natural products); (4) Synthesis of unnatural analogues of natural products (i.e. synthesis not starting from natural products) and finally; (5) Synthesis of interesting building blocks for natural product synthesis. We decided not to

incorporate peptide chemistry and related topics in this work, as we judged that this belongs to a separate field from natural product chemistry. Moreover, the literature dealing with the application of microwave irradiation in peptide synthesis is, to date, relatively scarce.

As dedicated microwave instruments appeared rather recently on the market and several interesting applications of microwave irradiation for natural product synthesis were described applying domestic microwave ovens, we decided to include also research performed with domestic ovens, although one could argue that some of these experiments lack reproducibility. On the other hand, the development of safe and reproducible synthetic routes for domestic instruments, which are cheap and at the disposal of every research lab all over the world, is a challenge worth the task as this should tremendously speed up the introduction of microwave irradiation in organic synthesis in general.

2 Total Synthesis of Various Classes of Natural Products

Natural products are undoubtedly the most challenging class of compounds for total synthesis, due to their structural diversity and complexity as well as the interesting biological activity inherent in many of them. During the last decades many examples of beautifully designed synthetic approaches have been published, using the plethora of available reagents and methods of the time. However, as microwave irradiation appeared on the scene only recently, its application has not been used in full strength for natural product synthesis, although some attractive examples have appeared in the recent literature.

Turrianes [1] are naturally occurring cyclophane derivatives (Fig. 1). These compounds are of particular interest as they are proven to be potent DNA cleaving agents under oxidative conditions [2–4] when administered in the presence of copper ions. An ingenious total synthesis has been elaborated by A. Fürstner et al. [5], applying a Ring Closing Metathesis (RCM) [6–10] or a Ring Closing Alkyne Metathesis (RCAM) [11–14].

The sequence starts with the synthesis of the sterically hindered biaryl entity, formed by the Grignard reaction, followed by further conversions

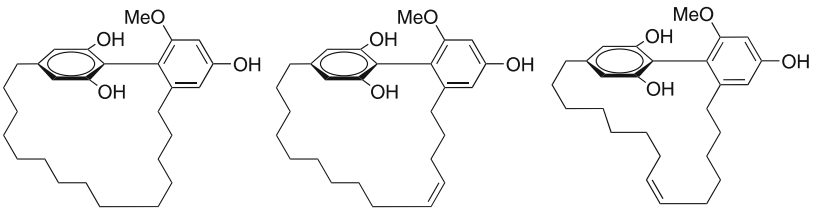
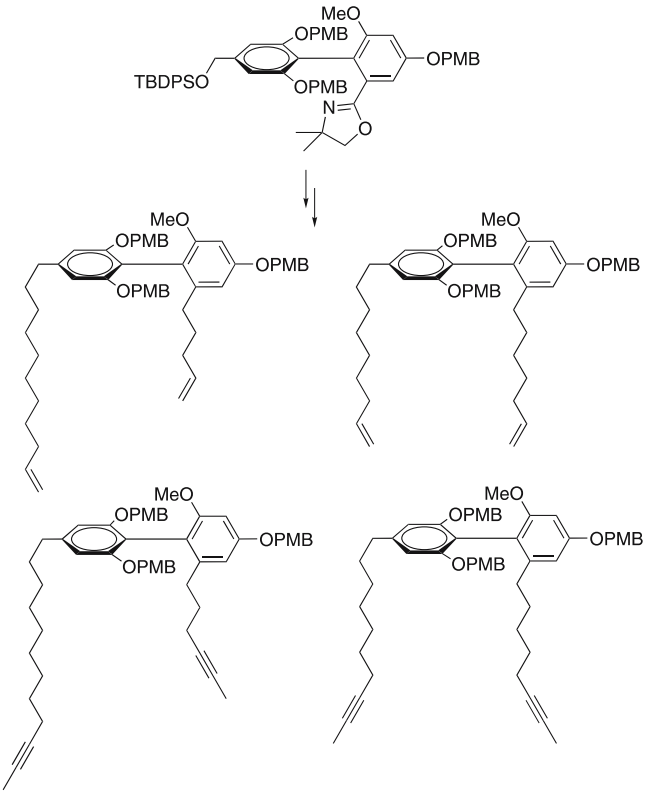


Fig. 1 Naturally occurring cyclophane derivatives belonging to the Turriane family

allowing the introduction of two different unsaturated tethers for macrocyclization (Scheme 1). PMB-ethers (PMB = *p*-methoxybenzyl) were found to be compatible protective groups with the diverse reaction conditions *en route* to the final natural compounds. Macrocyclization was investigated via RCM starting from the alkene-tethered substrates applying the Grubbs catalyst or a phenylindenylidene analogue in refluxing CH_2Cl_2. As expected, these compounds cyclize smoothly to the corresponding 20-membered rings, although unfortunately in a mixture of both stereoisomers with the undesired (*E*)-alkene prevailing (Fig. 2).

This problem could be circumvented when RCAM was applied starting from the acetylene-tethered compounds, as the initially formed cycloalkynes could be stereoselectively reduced to the *Z*-alkenes using Lindlar hydrogenation (Fig. 2). For the RCAM two different catalyst systems were evaluated: *t*-$(BuO)_3W \equiv CCMe_3$ in toluene at 80 °C for 16 h and $Mo(CO)_6/F_3CC_6H_4OH$ in chlorobenzene at 135 °C for 4–6 h, resulting in good yields of the cyclized products. However, the reaction times were rather long and, as in the



Scheme 1 Synthesis of the biaryl precursors for RCM and RCAM

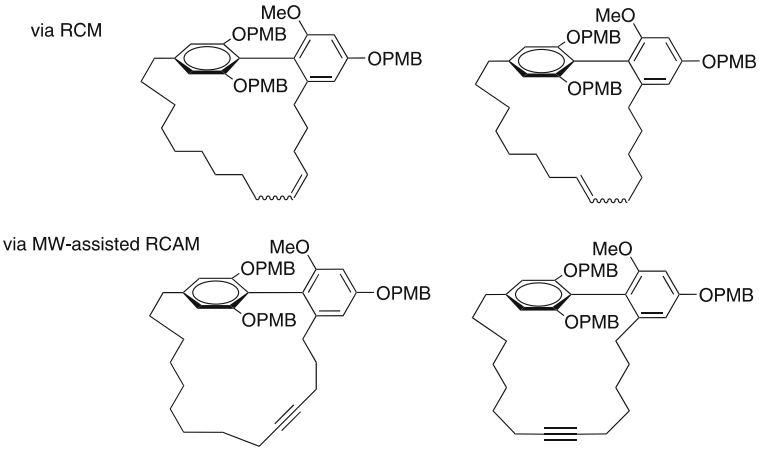
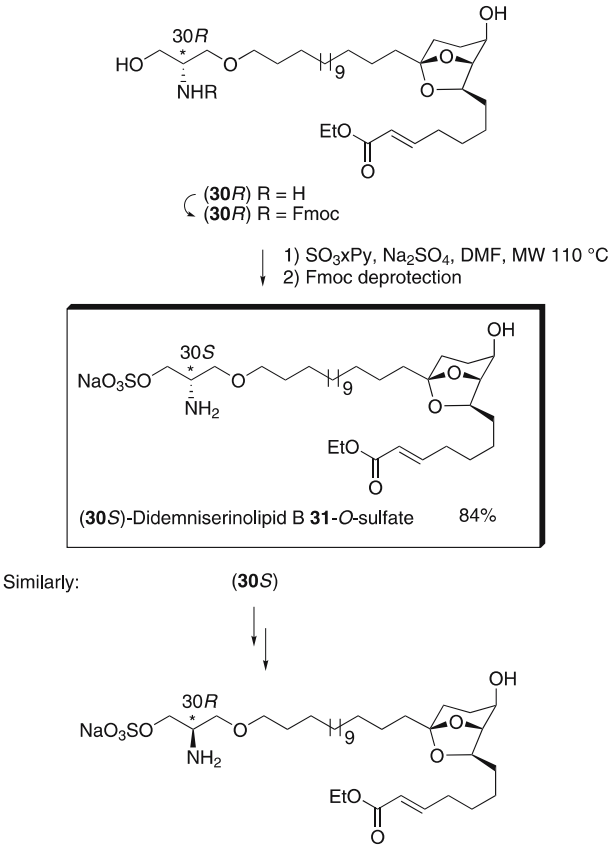


Fig. 2 Macrocycles formed via RCM or microwave-assisted RCAM

latter case a high temperature was required, the authors tried out focused microwave irradiation in chlorobenzene at 150 °C.

This resulted in a dramatic decrease of the reaction time to a mere 5 min with comparable yields. The sequence was accomplished upon full (H_2/Pd – C) or partial and stereoselective reduction (Lindlar catalyst) of the double bond and cleavage of the PMB-ethers.

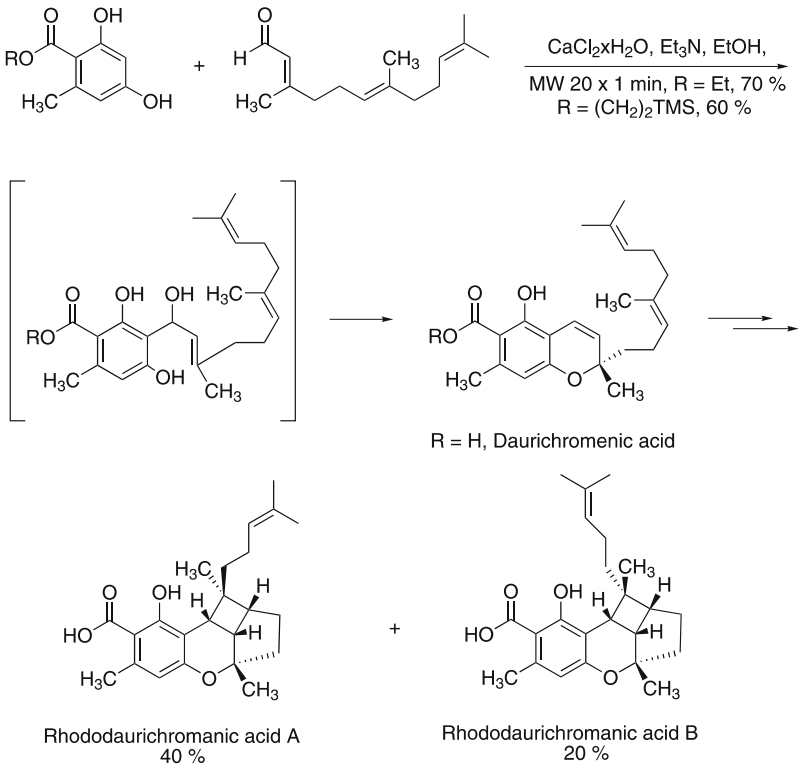
Another interesting class of natural products is the Serinol marine compounds isolated from Tunicate *Didemnum* sp. (Scheme 2). These structures shows promising biological activity as for example HIV-1 integrase inhibitors [15]. All these Serinolipids possess a unique serinol component and a 6,8-dioxabicyclo[3.2.1]octane core structure, which make them attractive targets for synthesis. S.V. Ley et al. [16] developed a multistep sequence starting from D-(or L-) serinol and a known butanediacetal (BDA)-protected chiral building block [17] to prove by synthesis the absolute and relative stereochemistry of (+)-Didemniserinolipid B [18]. After the accomplishment of the sequence, comparison of the ^{1}H NMR spectra of the synthesized compound with that of the natural product revealed that the peaks associated with the Serinol unit of the molecule were shifted significantly up field. In view of the fact that related natural products were sulfated on the Serinol unit, the authors believed that the structure should be reassigned as the monosulfated one. This was supported by re-measurements of the HR-FAB-MS spectrum. Therefore, the authors started to synthesize the monosulfate derivative (Scheme 2). To achieve monosulfation, the amino group was protected as the fluorenylmethoxycarbonyl (Fmoc) group. However, standard sulfation conditions (SO_3 × Py or SO_3 × NMe_3 in DMF, 1,4-dioxane and/or pyridine at 20–100 °C) failed to derivatize the diol and only starting material was obtained. On the contrary, when the reaction was performed with the aid



Scheme 2 Microwave-assisted synthesis of (30*R*)- and (30*S*)-Didemniserinolipid B 31-*O*-sulfate

of a dedicated microwave instrument, treatment of the diol (30*R*) with 1 equiv $SO_3 \times$ Py at 110 °C for 1 h provided the desired 31-*O*-sulfate as the major product. Deprotection of the Fmoc group under mild conditions (piperidine in DMF, rt) furnished 31-*O*-sulfate (30*S*). Similarly the (30*R*) diastereomer was synthesized for spectral comparison. It was shown that the spectroscopic data as well as the specific rotation of the (30*S*) diastereomer were in full agreement with those of the natural product, establishing a final proof for the structure of the natural product.

The two novel chromane derivatives rhododaurichromanic acids A and B [19] as well as the known Daurichromenic acid [20] are members of a new interesting class of anti-HIV agents and are therefore attractive synthetic targets (Scheme 3). These compounds were successfully synthesized by Z. Jin et al. [21] in good overall yields, applying a microwave-assisted tandem condensation and intramolecular S_N2'-type cyclization to form the



Scheme 3 Microwave-assisted synthesis of Daurichromenic Acid and Rhododaurichromanic Acids A and B

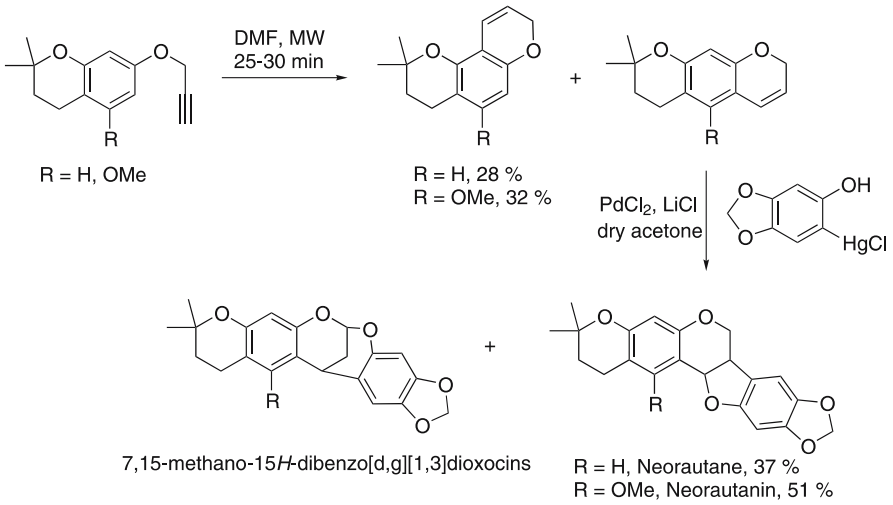
2*H*-benzopyran core structure. This approach for the construction of the 2*H*-benzopyran scaffold was developed by Shigemasa [22]. However, the authors found that the reaction of the ethyl ester with the aldehyde was extremely slow under Shigemasa's conditions.

The mixture gave only a 15% yield of the desired product after refluxing for 4 days. The yield was improved to 32% when the mixture was heated at 90 °C in a sealed tube for 1 day. As the intramolecular S_N2'-type cyclization is believed to be fast, the overall slow reaction is presumably due to the high activation energy in the condensation step. Therefore, the authors tried microwave irradiation, applying a domestic microwave oven. This resulted in a dramatic increase of the rate and the yield (70%) of the reaction. Optimized conditions were found to be microwave irradiation of a mixture of the ethyl ester (1 equiv) with the aldehyde (2.0 equiv) for 20×1 min, after which time an additional 1.0 equiv of the aldehyde was added and the mixture was irradiated again for 20 min. As the hydrolysis of the ethyl ester moiety to Daurichromenic acid proved to be extremely difficult, the authors switched to the application of a β-trimethylsilyl ethyl ester, which

could be easily converted to the carboxylic acid upon treatment with TBAF. The microwave-assisted condensation reaction using the optimized conditions, yielded the β-trimethylsilyl ethyl ester of Daurichromenic acid in 60% yield upon irradiation in a Teflon pressure vessel for 20×1 min. After deprotection of the carboxylic acid functionality, resulting in the formation of Daurichromenic acid, the compound was converted into the rhododaurichromanic acids A and B upon irradiation with a low-pressure mercury lamp for about 5 days, to afford a mixture of the desired compounds in 40 and 20% respectively, calculated on recovered starting material. The physical data of the synthesized material were identical with those reported for the natural products.

Two other natural products, Neorautane and Neorautanin [23], belonging to the class of pterocarpans [24], were also synthesized via the formation of intermediate chromenes (Scheme 4). G.K. Trivedi et al. reported an approach applying the microwave-assisted cyclization of propargyl phenyl ethers [25]. Thus, heating of these starting materials to reflux (170 °C) in dry xylene resulted in the formation of the angular chromene as the sole product in good yield (76–83%). Microwave irradiation (domestic microwave, sealed tube) sped up these reactions tremendously (25–30 min) and a mixture of the desired linear chromene was formed, together with the angular chromene, albeit in low yield (22–32%).

These chromenes were further converted into the natural products Neorautane (37%) and Neorautanin (51%), upon Heck reaction with the appropriate phenol derivative in the presence of LiCl and $PdCl_2$ in dry acetone. The 7,15-methano-15*H*-dibenzo[*d*,*g*][1,3]dioxocins were isolated as undesired side compounds (R = OMe, 15%; R = H, 26%).

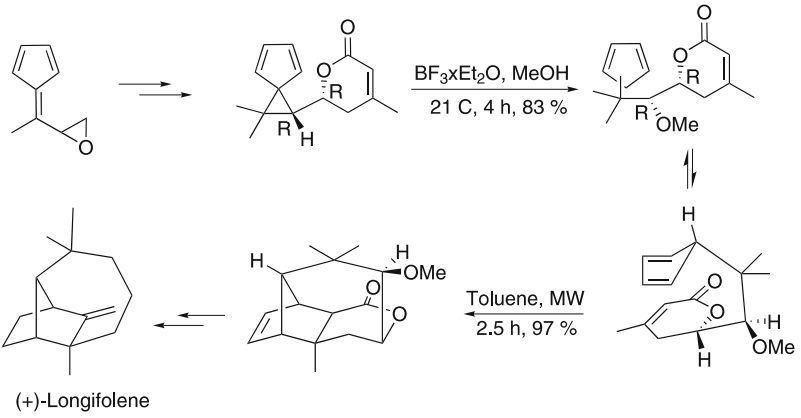


Scheme 4 Microwave-assisted synthesis of Neorautane, Neorautanin

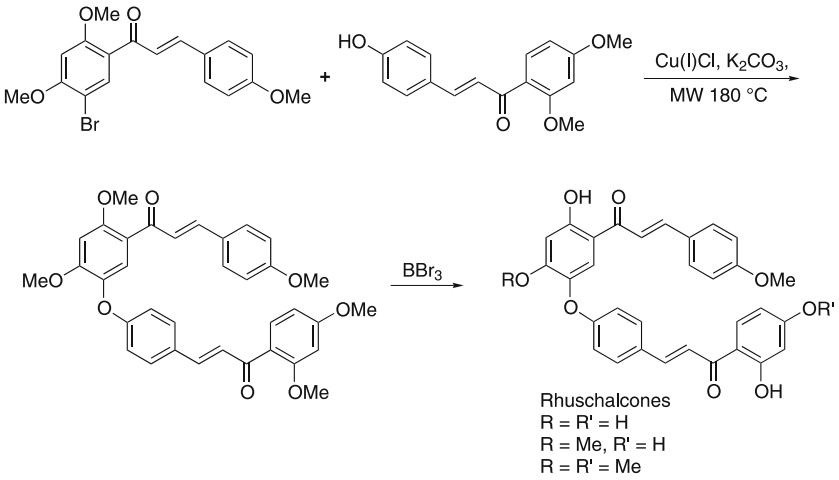
An interesting application of microwave irradiation, although with a domestic oven, is found in the total synthesis of (+)-Longifolene [26, 27], a bridged-ring sesquiterpene (Scheme 5). Its unusual topology inspired many organic chemists and several superb total syntheses have been published. The approach of A.G. Fallis et al. [28] starts from an epoxyfulvene that was converted into an unsaturated lactone via a four-step sequence including a resolution with (–)-menthol chloroformate and a condensation with the anion derived from methyl 3-methylcrotonate. The cyclopropane ring was regioselectively cleaved applying $BF_3 \times Et_2O$ in methanol, affording a rapidly equilibrating mixture of substituted cyclopentadiene lactone isomers, due to the facile 1,5-sigmatropic rearrangement. Surprisingly, one single adduct was formed in 97% yield upon microwave irradiation (domestic oven) of a toluene solution of this triene mixture in a sealed tube for 2.5 h. This compound was further transformed into the desired natural product.

As part of the proof of the identity of three newly isolated chalcones, B.M. Abegaz et al. developed a synthetic route which involves a microwave irradiation promoted Ullmann coupling [29]. A mixture of the dimethylated phenolic chalcone and the bromochalcone in the presence of potassium carbonate and copper(I)chloride was microwave irradiated (domestic oven) at 180 °C, giving 19% yield of the resulting bichalcone (Scheme 6). This bichalcone was converted into a mixture of the desired Rhuschalcones, upon treatment with BBr_3, followed by chromatographic separation.

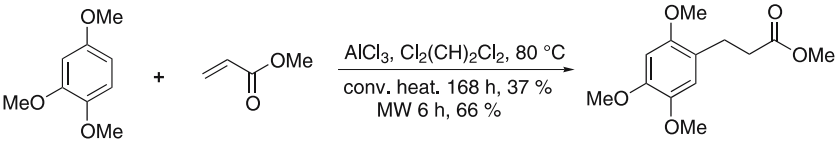
A one-step synthesis of the antifungal and larvicidal natural product methyl 3-(2,4,5-trimethoxyphenyl)propionate was described by J. Tamariz et al. [30] (Scheme 7). Reaction of methyl acrylate with 1,2,4-trimethoxybenzene catalyzed by $AlCl_3$ in 1,1,2,2-tetrachloroethane took 168 h (7 days) at 80 °C, yielding the compound in the low yield of 37%. However, when the reaction was run under microwave irradiation (domestic oven) in a Teflon



Scheme 5 Total synthesis of (+)-Longifolene



Scheme 6 Microwave-assisted synthesis of Rhuschalcones

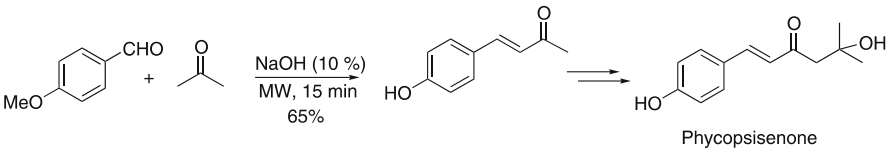


Scheme 7 Microwave-assisted synthesis of methyl 3-(2,4,5-trimethoxyphenyl)propionate

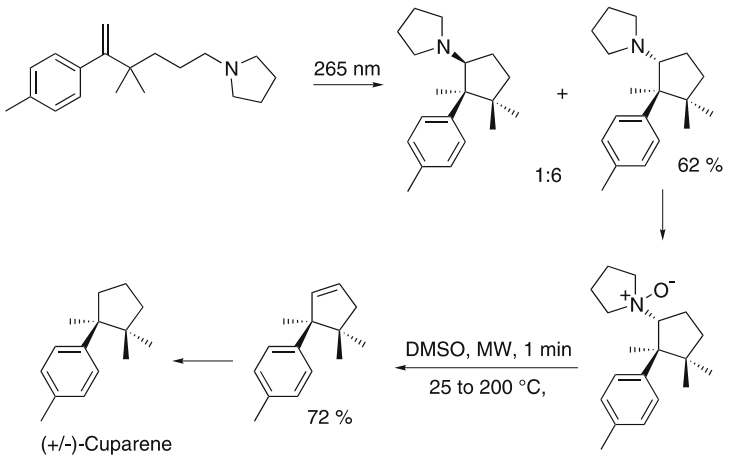
screw-capped glass tube at 80 °C, the reaction time was drastically shortened to 8 h and the yield was increased to 66%.

A short total synthesis of Phycopsisenone, a new phenolic secondary metabolite from the sponge *Phycopsis* sp, was performed by G.L. Kad et al. [31]. A microwave irradiation-induced (domestic oven) aldol condensation of 4-hydroxy-benzaldehyde and acetone in aqueous NaOH solution afforded the α,β-unsaturated ketone in 65% yield (Scheme 8). This was further converted in Phycopsisenone applying a two-step sequence.

Several members of the Cuparene class of sesquiterpenoids show interesting biological activity, including potent antifungal, neurotrophic and lipid peroxidation inhibition activity. Moreover, the presence of a hindered, quaternary



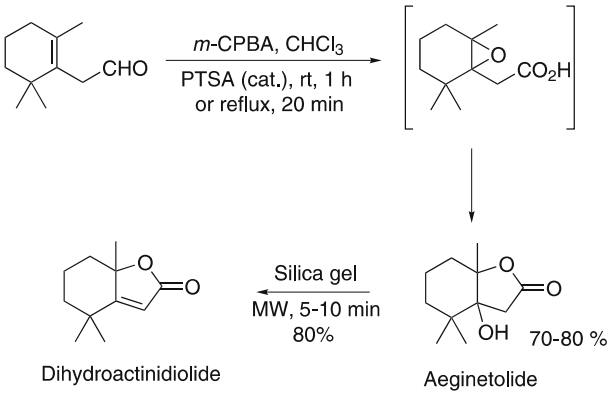
Scheme 8 Microwave-assisted synthesis of Phycopsisenone



Scheme 9 Photomediated and microwave-assisted synthesis of Cuparene

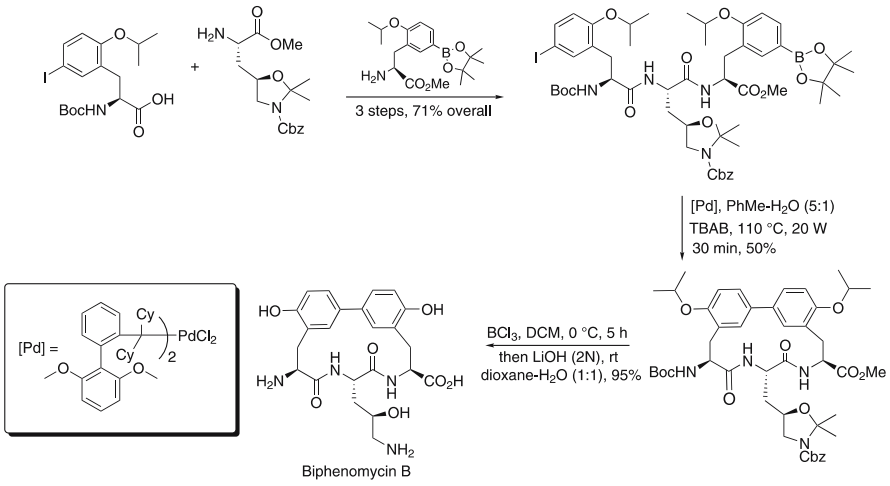
stereocenter on a five-membered ring has made these sesquiterpenoids popular synthetic targets. A photomediated asymmetric synthesis of (–)-Cuparene is described by R.S. Grainger et al. [32] (Scheme 9). The key step of the sequence is the photomediated ring closure of an aminostyrene to cyclopentane according to the procedure of Lewis et al. [33, 34]. Irradiation of this aminostyrene at 265 nm under high dilution conditions (0.005 M) resulted in the quantitative formation of a mixture of two cycloadducts in a 6 : 1 ratio. The major diastereomer could be isolated in 62% yield. For the further conversion to Cuparene the authors used the thermally induced Cope elimination (THF, 60 °C, 8 h), after oxidation of the cycloadduct with *m*-CPBA. This proved to be troublesome and yielded the desired alkene in only 40% yield. However, applying focused microwave irradiation on a solution of the *N*-oxide in DMSO for 1 min going from 25–200 °C in temperature, afforded the product in 72% yield. Finally, hydrogenation of the double bond completed a racemic synthesis of Cuparene. An asymmetric variant was elaborated applying (*S*)-(+)-2-(methoxymethyl)pyrrolidine, rendering (*S*)-Cuparene with an optical rotation identical to that reported for the natural product.

An improved synthesis of the C_{11}-terpenic lactone Dihydroactinidiolide was described by A.K. Bose et al. [35]. The synthesis started from a commercially available aldehyde that was subjected to treatment with *m*-CPBA and a catalytic amount of PTSA (Scheme 10). The intermediate epoxy acid underwent cyclization resulting in the formation of Aeginetolide. Dehydration has been reported earlier by heating of this compound with aqueous NaOH, at 60 °C for 24 h, or with $SOCl_2$ and pyridine at room temperature for 5 h. The authors observed expeditious and convenient dehydration of this compound supported on silica gel, under microwave irradiation for 5–10 min (domestic oven), yielding Dihydroactinidiolide in 80% yield.



Scheme 10 Improved synthesis of Dihydroactinidiolide

The natural cyclic tripeptide Biphenomycin B [36–39], structurally belonging to the still expanding family of macrocyclic natural products with an endo aryl-aryl bond, displays potent activities against Gram-positive, β-lactam-resistant bacteria. The combination of structural novelty and biological activity motivated J. Zhu et al. to develop a concise asymmetric total synthesis for this compound [40] (Scheme 11). The key step is a microwave-assisted intramolecular Suzuki–Miyaura reaction of a linear tripeptide, for the formation of a 15-membered *meta,meta*-cyclophane. This tripeptide could be prepared from three non-proteinogenic amino acids, by standard peptide chemistry. However, even after extensive optimization of the reaction parameters for macrocyclization via the Suzuki–Miyaura coupling, the



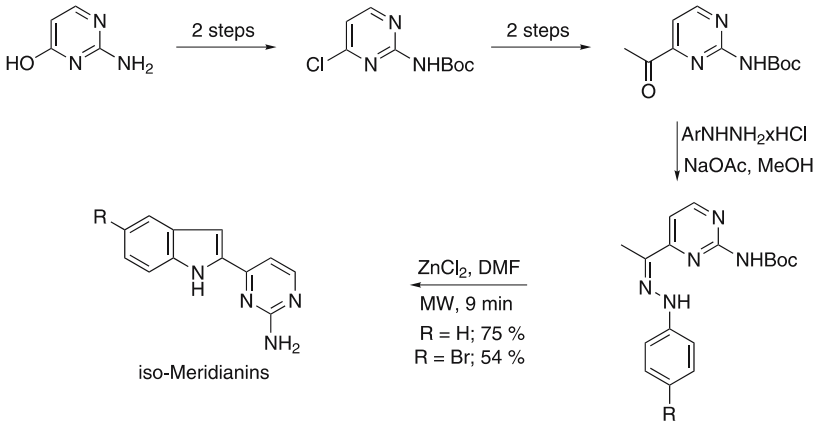
Scheme 11 Synthesis of Biphenomycin B

yield of the desired compound did not exceed 20%. On the contrary, upon microwave irradiation, the yield was increased and the reaction rate was dramatically raised. Under optimized conditions the intramolecular Suzuki–Miyaura coupling afforded the desired macrocycle in 50% yield. After final deprotection of all functional groups, the total synthesis of Biphenomycin B was accomplished.

3 Synthesis of Alkaloids

Among the various classes of natural products that have stimulated extensive research in the fields of both synthetic and pharmaceutical chemistry, alkaloids can arguably be described as the most important class. While their structural complexity has invited the attention of synthetic organic chemistry, their diverse biological activities and somewhat limited abundance has demanded the interest of pharmaceutical and medicinal research. With the ever-increasing demand for novel lead- and drug-like substrates for the purpose of biological screening, a plethora of literature has been published in recent years related to the synthesis, structural modification and biological studies of alkaloids and alkaloid-like structures. Consequently, research related to the total and partial syntheses of alkaloids has stimulated extensive research in the fields of methodology development. Automated synthesis and related high throughput technologies have been investigated to achieve fast and efficient generation of natural product related libraries. The use of microwave-assisted methods in the synthesis of alkaloids and alkaloid-related structures has therefore attracted an enormous current interest in both academia and industry [41–46], owing to the potential of microwave-assisted methods in rapid, easy and efficient synthesis of target libraries.

Because of the large number of biologically interesting natural products bearing highly functionalized indole skeletons [47–49], Fischer indole synthesis has received considerable synthetic interest. As a consequence, microwave-assisted Fischer indole synthesis has recently been investigated as a key step in the synthesis of a large number of indole alkaloids and their structural analogues. As a typical example, the microwave-assisted synthesis of iso-meridianins was explored by J.A. Palermo et al. [50], using a $ZnCl_2$ promoted microwave-assisted Fischer indole synthesis as the key step (Scheme 12). Iso-Meridianins are close structural analogues of the naturally occurring indole alkaloids Meridianins and Psammopemmins which exhibit high antitumor activity [51–53]. Iso-meridianins bear a pyrimidine ring at the C-2 position of the indole skeleton, in comparison with the parent compounds containing a pyrimidine ring at the C-3 position. As the corresponding 2-amino pyrimidines and phenylhydrazines are considerably

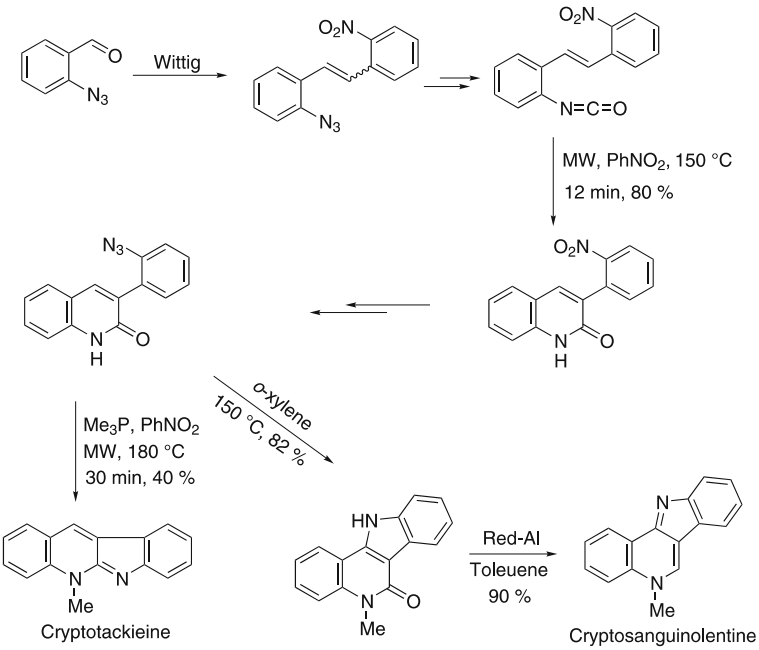


Scheme 12 Microwave-assisted synthesis of iso-Meridianins

cheaper and more easily available than the corresponding functionalized indoles, the authors reasoned that a diversity oriented and flexible synthesis could be achieved (Scheme 12). They started the synthesis from the commercially available isocytosine, which was converted to the corresponding *N*-Boc-4-chloro analogue by known transformations. The methyl ketone functionality was introduced at the C-4 position via Pd-catalyzed cross-coupling of the chloro derivative with tri-*n*-butyl(1-ethoxyvinyl)tin followed by an acidic hydrolysis of the intermediate. The phenylhydrazones of the compounds were then generated following standard protocols.

However, the Fischer indole synthesis met with failure under classical heating conditions, using a variety of solvents and catalysts. The authors then explored $ZnCl_2$-mediated microwave-assisted cyclization in a domestic microwave oven using the full irradiation power of c.a. 1500 W. The cyclization was found to proceed smoothly in DMF in a mere 9 min and the iso-Meridianins were isolated in good yields.

Another interesting example of the influence of microwave irradiation is illustrated in the total synthesis of the indoloquinoline alkaloids Cryptotackieine and Cryptosanguinolentine, isolated from *Cryptolepis sanguinolenta*, a shrub indigenous to West Africa. These alkaloids exhibit various interesting biological activities such as antimuscarinic, antibacterial, antiviral, antimycotic and antihyperglycemic activities, considerable *in vitro* antitumor activity, and strong antiplasmodial activity of Cryptotackieine against chloroquine-resistant strains of *P. falciparum* [54–57]. P.M. Fresneda et al. reported an elegant microwave-assisted synthesis of Cryptotackieine and Cryptosanguinolentine [58], based on a divergent approach for the generation of the key 1-methyl-(*o*-azidophenyl)-quinoline-2-one followed by its selective indolization (Scheme 13). 2-Azidobenzaldehyde was converted into the key isocyanate intermediate following known synthetic manipulations and the

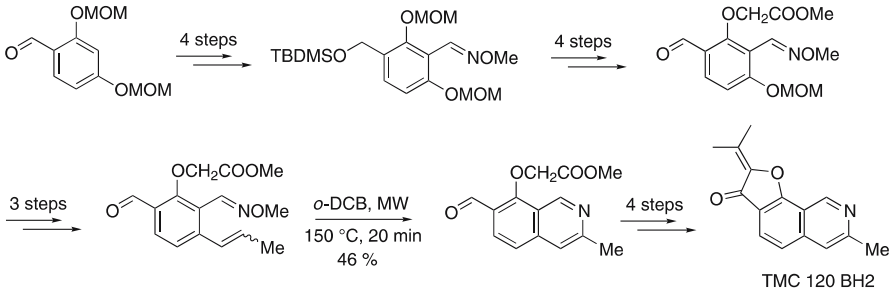


Scheme 13 Microwave-assisted synthesis of Cryptotackieine and Cryptosanguinolentine

quinolin-2-one skeleton was generated via the microwave-assisted cyclization of the corresponding isocyanate intermediate at 150 °C, using a dedicated microwave reactor (Scheme 13).

The quinoline-2-one was then converted into the required 1-methyl-(*o*-azidophenyl)-quinoline-2-one via known synthetic manipulations. Cyclization of this intermediate to the target Cryptotackieine was performed under microwave irradiation at 180 °C for 30 min, in the presence of trimethyl phosphine. It is noteworthy that the same aza-Wittig reaction, when carried out under classical heating for 24 h, furnished inferior yields. The quinolin-2-one intermediate, when heated at 150 °C in *o*-xylene under conventional heating conditions, underwent a nitrene insertion at the C-4 position of the pyridinone ring. Subsequent Red-Al reduction of the carbonyl group furnished the Cryptosanguinolentine.

S. Hibino et al. have recently reported an interesting total synthesis of a new furo[3,2-*h*]isoquinoline alkaloid TMC 120B [59], starting from 2,4-bismethoxymethyloxybenzaldehyde (Scheme 14). TMC 120A, B and C were isolated in 1999 by J. Kohno et al. from a fermentation broth of *Aspergillus ustus* TC 1118. TMC 120B shows moderate inhibitory activity against the interleukin-5 mediated prolongation of eosinophil survival with an IC_{50} value of 2.0 μM [60–62]. The key 3,7,8-trisubstituted isoquinoline intermediate was obtained starting from the *o*-alkenylbenzaldoxime methyl ester,



Scheme 14 Microwave-assisted synthesis of alkaloid TMC 120B

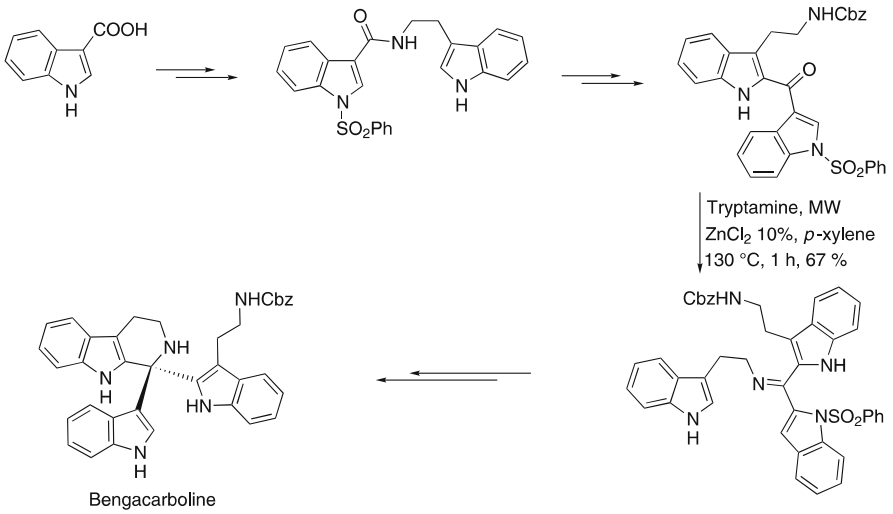
which was synthesized from 2,4-bismethoxymethyloxybenzaldehyde in 11 steps via known synthetic manipulations.

The electrocyclic cyclization was investigated by heating the sample in *o*-dichlorobenzene (*o*-DCB), both under conventional heating conditions and under microwave irradiation in a dedicated monomode apparatus. It was found that the microwave-assisted cyclization provided slightly elevated yields at the lower reaction temperature of 150 °C, in comparison with the conventional heating experiment conducted at 180 °C (Scheme 14). The intermediate isoquinoline was then converted to the final alkaloid using known synthetic manipulations to complete the synthesis.

Y. Langlois et al. have recently reported the total synthesis of the marine alkaloid Bengacarboline [63], using a microwave-assisted imination and subsequent Pictet–Spengler cyclization [64]. Bengacarboline, extracted from the Fijian ascidian *Didemnum* sp. exhibits interesting inhibitory activity of topoisomerase II and significant in vitro activity against tumor cell lines [65].

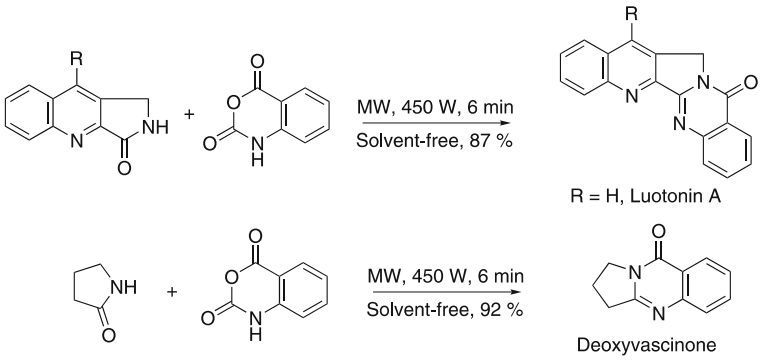
The authors started their explorations from indole-3-carboxylic acid, which was easily converted into the corresponding amide using known synthetic manipulations. The di-indolyl ketone intermediate was then developed in two steps via a Bischler–Napieralski reaction with $POCl_3$ followed by nucleophilic attack of a hydroxyl anion and spontaneous ring opening (Scheme 15). The imination was then explored under a variety of conventional heating conditions, albeit without favorable results. Microwave-assisted conditions in the presence of $ZnCl_2$ in *p*-xylene at 130 °C for 1 h solved this problem. The imine intermediate was then converted into the target Bengacarboline structure in two steps.

The pyrroloquinazolinoquinoline alkaloids Luotonin A and B were isolated recently from the aerial parts of *Peganum nigellastrum*, a plant that has been used against rheumatism, abscesses and inflammation in Chinese traditional medicine. The alkaloid Luotonin A was found to possess a pentacyclic skeleton closely resembling Camptothecin, derivatives of which are clinically useful anticancer agents [66, 67]. The compound was proven to be cytotoxic against the P-388 cell line of murine leukemia. J.S. Yadav et al. elab-



Scheme 15 Microwave-assisted total synthesis of Bengacarboline

orated a rapid microwave-assisted synthesis of these cytotoxic alkaloids [68], albeit using a domestic microwave oven (Scheme 16). The authors devised a two-component condensation reaction for the generation of the pentacyclic system of the target molecule. Thus, 3-oxo-1*H*-pyrrolo[3,4-*b*]quinoline, easily generated in three steps following known procedures, was condensed with isatoic anhydride under solvent-free microwave-assisted conditions. Condensation proceeded smoothly in 6 min at an irradiation power of 450 W, and Luotonin A was isolated in the high yield of 87% (Scheme 16). Furthermore, the antitumor active alkaloid deoxyvascinone, also isolated from *Peganum nigellastrum*, was obtained in a similar fashion in an excellent yield of 92%. It is noteworthy that this condensation furnished a much lower yield of 60%

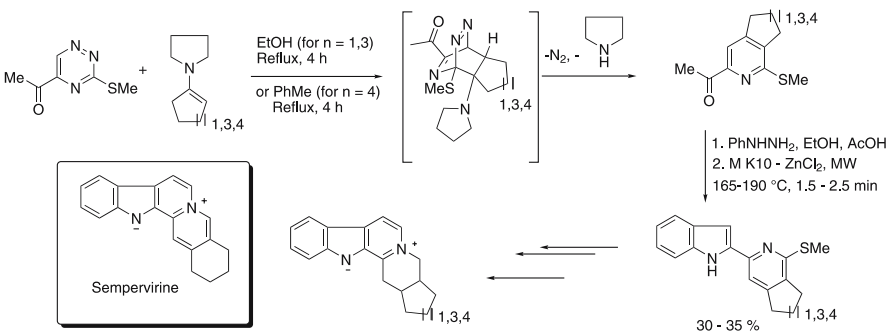


Scheme 16 Microwave-assisted synthesis of Luotonin A and Deoxyvascinone

in a considerably longer reaction time of 5–8 h when carried out under conventional heating conditions at a maximum temperature of 120 °C.

T. Lipinska et al. have recently reported an ingenious microwave-assisted synthesis of E-ring modified Sempervirine analogues [69] (Scheme 17). Since the first isolation from *Gelsenium sempervirens* in 1916, Sempervine and its structural analogues have gained considerable synthetic interest due to their impressive range of biological potential [70, 71]. Some of the known members of this family such as Flavopereirine, Serpentine and Alstonine exhibit a variety of biological activities, for example anti-HIV, antipsychotic, sedative and immunostimulant activities together with notable cytostatic effects [72]. Even though the synthesis of these molecules has been targeted in the past, a major issue to be addressed was to find synthetic routes towards Sempervirine analogues with a modified core structure. An Inverse Electron-Demand Diels–Alder reaction (IEDDA) [73] between a suitably functionalized 1,2,4-triazene and a 1-pyrrolidino-1-cycloalkene was initially explored to generate the cyclic intermediate, which upon loss of nitrogen furnished the required bicyclic intermediate for the synthesis of the target molecules (Scheme 17). After converting the intermediate to the corresponding phenylhydrazone quantitatively in refluxing ethanol with traces of acetic acid, the authors carried out a microwave-assisted, solvent-free Fischer indole synthesis with morillonite K10 modified with $ZnCl_2$ at the very high temperatures of 165–190 °C for 1.5–2.5 min (Scheme 17). The thus formed 2-substituted indole-analogues were then converted into the final targets by a three-step protocol based on known synthetic manipulations, furnishing the Sempervirine analogues in high yields.

T. Lipinska further used this methodology to generate a series of 9-methoxy analogues of Sempervirines [74, 75], by simply choosing 4-methoxyphenylhydrazine as the starting material. This case study is particularly interesting due to the fact that a variety of methoxy analogues of indole alkaloids are known to be more effective on the nervous system than the parent compounds. The Fischer indolizations were performed under con-

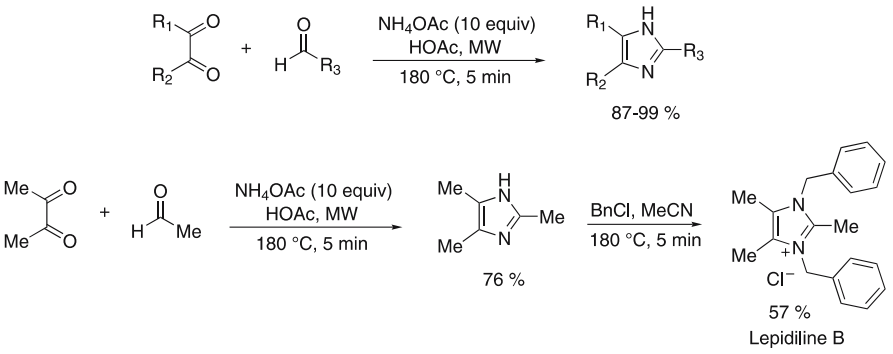


Scheme 17 Microwave-assisted synthesis of Sempervirine analogues

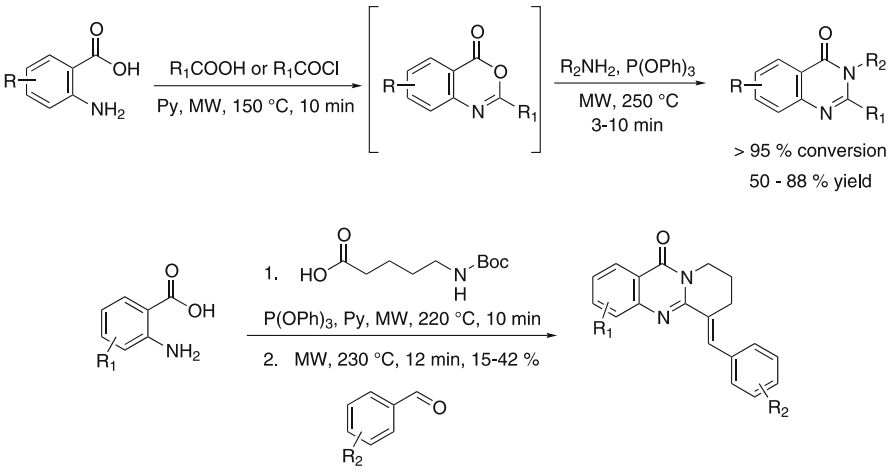
trolled microwave-assisted conditions in an open vial, applying the optimized MK10/$ZnCl_2$ system at 150 °C for 2 min.

S.E. Wolkenberg et al. have recently investigated the microwave-assisted synthesis of richly decorated imidazoles from 1,2-diketones [76] in the presence of ammonium acetate as the nitrogen source (Scheme 18). The reactions were carried out at 180 °C for 5 min in a dedicated microwave apparatus using acetic acid as the solvent, and the corresponding imidazoles were isolated in very high yields and purities. Furthermore, the authors extended the strategy for the synthesis of Lepidiline B [77], an alkaloid isolated from the root extracts of *Lepidium meyenii* of Peruvian origin, which exhibits potent micromolar cytotoxicity against several human cancer cell lines.

An interesting investigation regarding the microwave-assisted synthesis of biologically potent alkaloids has recently been reported by J.-F. Liu et al. [78]. The authors initially explored a microwave-assisted one-pot synthesis of the 2,3-disubstituted 3*H*-quinazolin-4-one skeleton, a privileged structure present in many biologically interesting alkaloids such as the sedative-hypnotic Methaqualone, antitussive Chloroqualone and anticonvulsant Piriqualone [79–81]. The quinazolinone core is found in a variety of natural products possessing interesting bioactivity, such as anti-inflammatory, cardiovascular, CNS, antimalarial and antiviral effects [82]. The authors developed a highly efficient, microwave-assisted three-component procedure in view of circumventing the known drawback that most of the conventional methodologies were only applicable to the *N*-aryl analogues (Scheme 19). This strategy involved the one-pot reaction between a suitably substituted anthranilic acid, a functionalized acid chloride, carboxylic acid or aldehyde and a suitable aryl or alkyl amine in the presence of $P(OPh)_3$ as the coupling agent. The synthesis was performed using a monomode microwave station integrated in the solution-phase high-throughput automated platform, with the aim of combining the rapid microwave-assisted synthesis and the novel high-throughput methods for library design. It is noteworthy that the same



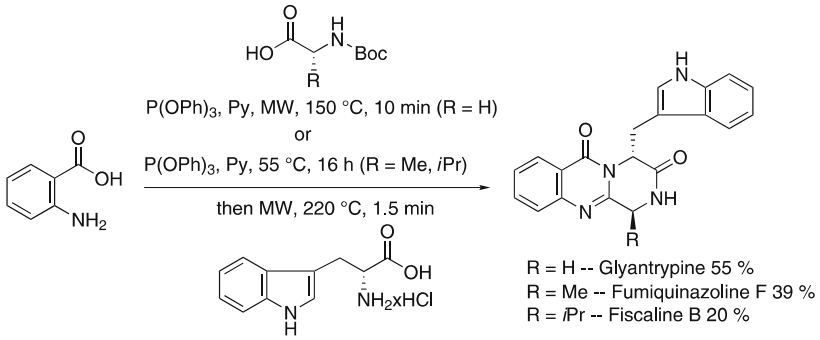
Scheme 18 Microwave-assisted synthesis of Lepidiline B



Scheme 19 Microwave-assisted one-pot synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones

protocol, under conventional heating conditions, provided inferior conversions of $\leq 50\%$ (Scheme 19).

J.-F. Liu et al. further explored this novel three-component one-pot strategy to generate a variety of alkaloids bearing a pyrazino[2,1-*b*]quinazoline-3,6-dione skeleton. The synthesis and post-synthetic manipulations of these natural products had been previously explored owing to the large variety of biological and pharmacological activities they exhibit. Some notable members of these families are Fumiquinazolines F and G, and Glyantrypine [83–85]. J.-F. Liu et al. applied their previously developed microwave-assisted one-pot protocol for the synthesis of Glyantrypine, Fumiquinazoline F and Fiscaline B (Scheme 20) [86]. The cleavage of the Boc protecting group was found to be strongly temperature dependent. When the temperature was raised from 180 °C to 220 °C, the deprotection of the *N*-Boc to NH was found



Scheme 20 Synthesis of Glyantrypine, Fumiquinazolines F and Fiscaline B

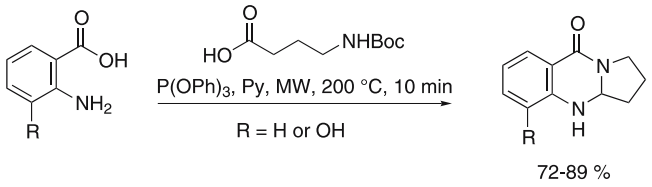
to increase from 0 to 100%. The strategy was successfully applied for the synthesis of these alkaloids.

J.-F. Liu et al. have explored a highly efficient, microwave-assisted, domino reaction protocol [87, 88] for the synthesis of a variety of 2,3-disubstituted-quinazolin-4-ones starting from readily available compounds (Scheme 21) [89]. A one-pot procedure was applied using $P(OPh)_3$ as the coupling reagent in pyridine at 200 °C for 10 min, using a monomode microwave apparatus. The target alkaloids Deoxyvasicinone, Mackinazolinone and 8-Hydroxydeoxyvasicinone were isolated in high yields of 72–89% in a mere 10 min irradiation time. The authors used the thus optimized procedure to generate a small library of structurally similar alkaloid analogues with high yields and purity.

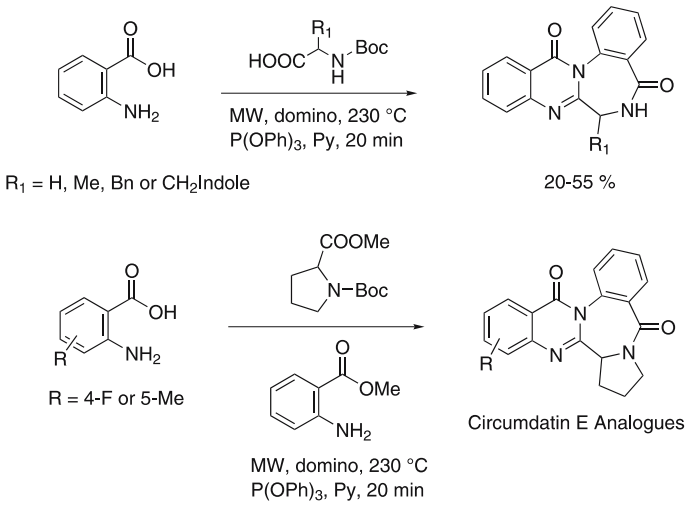
This optimized, microwave-assisted, domino protocol was used for the synthesis of a variety of quinazolinobenzadiazepine alkaloid natural products [90]. The members of this broad family of naturally occurring alkaloids feature a broad spectrum of very intriguing biological potential: Sclerotigenin exhibits high anti-insectant activity, Aspercilin C and E show high Cholecystokinin (CCK) antagonist activity and Benzomalvin A features inhibitory activity against substance P at the neurokinin NK1 receptor [91, 92]. The microwave-assisted domino reaction between anthranilic acid and a suitable *N*-Boc amino acid in the presence of $P(OPh)_3$ was explored, as in the previous cases, to generate the target natural products (Scheme 22).

However, the reaction was found to proceed slowly, taking 20 min under microwave irradiation, resulting in comparatively lower yields, probably owing to the seven-membered ring in the target compounds. In a similar fashion, the authors generated the chemotaxonomic marker analogues for the quinazolinobenzadiazepine alkaloids (Circumdatin E derivatives) by employing *N*-Boc-proline as the amino acid coupling partner.

Another interesting investigation of the use of microwave irradiation for the synthesis of alkaloids was recently reported by M. Álvarez et al., where the authors investigated a modular total synthesis of Lamellarin D [93]. After 20 years of the first isolation of this compound from the marine prosobranch mollusk *Lamellaria* sp, this family currently comprises more than 30 members, isolated from various natural sources. With its recent identification as

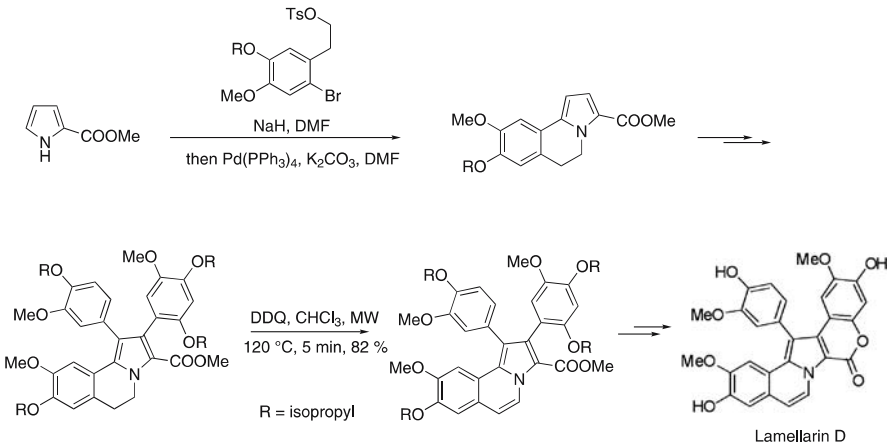


Scheme 21 Microwave-assisted domino reaction protocol for the synthesis of 2,3-disubstituted-quinazolin-4-ones



Scheme 22 Synthesis of the quinazolinobenzadiazepine alkaloids

a potent topoisomerase I inhibitor as well as its candidature for in vivo preclinical development as an antitumor agent, there has been a lot of current interest in the synthesis and structural manipulation of Lamellarin D [94, 95]. The authors started the synthesis with the *N*-alkylation of methyl pyrrole-2-carboxylate applying a suitable tosylate under conventional heating conditions, followed by an intramolecular Heck-type cyclization to access the basic pyrroloisoquinoline skeleton (Scheme 23). Then a regioselective bromination and subsequent Suzuki–Miyaura reaction was performed to generate the intermediate 3-aryl pyrrole and the sequence was repeated to furnish the 3,4-diarylpyrrole intermediate.



Scheme 23 Total synthesis of Lamellarin D

The aromatization of the dihydroisoquinoline was achieved under microwave-assisted conditions, irradiating the intermediate in $CHCl_3$ at 120 °C for 5 min with DDQ as the oxidizing agent (Scheme 23). It is noteworthy that the use of DDQ, MnO_2 or Pd – C in various solvents under conventional heating conditions was not successful. The authors completed the total synthesis by an $AlCl_3$-mediated lactonization to furnish lamellarin D in a total of eight steps with 18% overall yield.

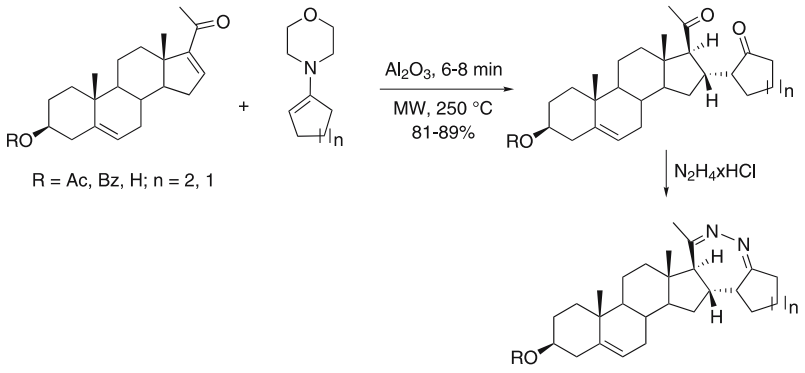
4
Modifications of Natural Products

Boosted by the demand for novel molecules for the purpose of biological screening, recent research in both organic synthesis and medicinal chemistry have resulted in a plethora of recent literature related to the modification of natural products. Altering the structures of existing natural products for the purpose of increasing their biological potential has therefore received widespread current interest. Consequently, microwave irradiation has been investigated for the fast and easy modifications of biologically interesting molecules.

4.1
Modifications of Steroids

An efficient preparation of 1,5-diketones as precursors to D-ring annulated heterosteroids was elaborated by R.C. Boruah et al. [96] (Scheme 24). Readily available 16-dehydropregnenolone acetate (16-DPA) was used in a Michael reaction with enamines.

Thus, freshly prepared 1-morpholino-1-cyclohexene was mixed thoroughly with 16-DPA and basic alumina and this was irradiated in a dedicated

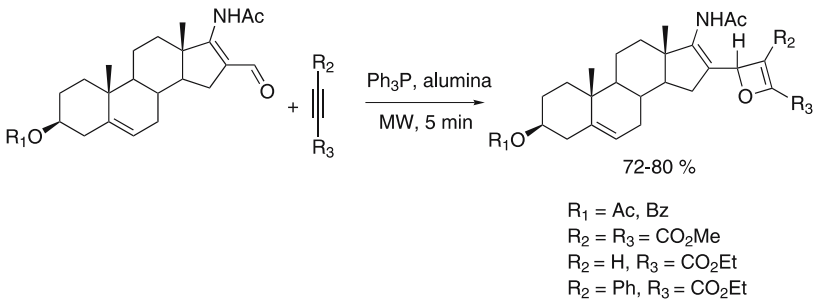


Scheme 24 Synthesis of a novel class of 1′,2′-diazepino(17,16-*d*′) steroids

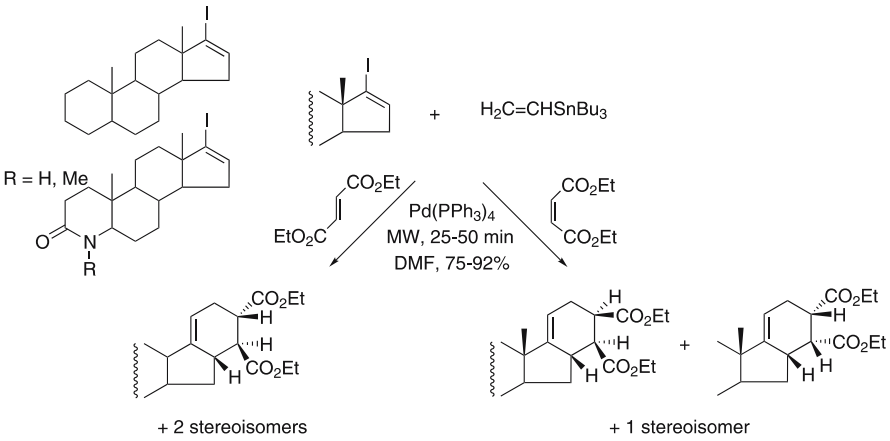
microwave instrument for 6 min. The 3β-acetoxy-16-(2′-cyclohexanoyl)pregnenolone was isolated in 79% yield. In a similar manner, related Michael adducts were obtained in high yields. It was observed that the reactions were sluggish in the absence of basic alumina, which indicated the catalytic role of alumina in this solid-phase reaction. Interestingly, the reactions did not work under conventional heating conditions, even with prolonged heating. The obtained compounds were then cyclized upon reaction with hydrazine hydrochloride, affording the 1′,2′-diazepino(17,16-*d*′) steroids.

R.C. Boruah et al. described the microwave-mediated [2 + 2] cycloaddition of steroidal formyl enamides and alkynes under solvent-free conditions [97] (Scheme 25). Although much attention has been paid to the development of synthetic methodologies for oxetanes, the corresponding unsaturated analogue oxetene has received only limited interest. In the course of a program directed towards the synthesis of D-ring annulated heterosteroids, the authors investigated the reaction of a mixture of 3β-acetoxy-16-formyl-17-acetamido-androst-5,16-diene, triphenylphosphine and various acetylenes, which were thoroughly mixed with basic alumina. This mixture was irradiated using a microwave reactor for 5 min. Steroidal oxetane derivatives were obtained in good yields (72–80%). Interestingly, in the absence of alumina, the reaction was found to be sluggish. Also, the conventional thermal heating of formyl enamides with alkynes in the presence of PPh_3 in a protic solvent under prolonged heating (72 h) led to very poor yields of oxetenes (15–23%).

R. Skoda-Földes et al. synthesized steroidal dienes and investigated them as starting materials for further functionalization of the steroidal skeleton via cycloaddition reactions [98] (Scheme 26). In a previous work the authors described the synthesis of these dienes via Stille coupling of steroidal alkenyl halides with vinyltributyltin [99, 100]. However, under conventional heating conditions, these reactions were rather slow, requiring a reaction time of many hours. Rapid reactions could here be achieved under microwave irradiation using a domestic oven. 17-Iodo-androst-16-ene, 17-iodo-4-aza-4-methyl-androst-16-en-3-one and 17-iodo-4-aza-androst-16-en-3-one were reacted with vinyltributyltin in the presence of $Pd(PPh_3)_4$. As toluene does



Scheme 25 [2 + 2] Cycloaddition of steroidal formyl enamides with various alkynes



Scheme 26 One-pot Stille coupling/Diels–Alder reaction of steroidal alkenyl halides

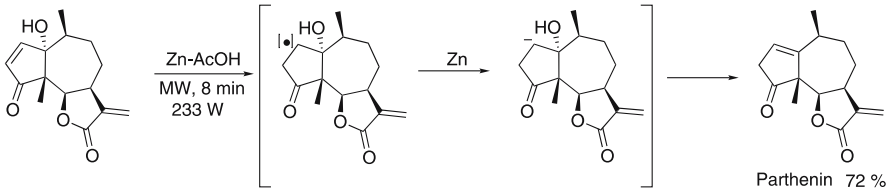
not couple efficiently with microwaves, DMF was chosen as the solvent. Reactions were complete in minutes rather than in hours. As it was possible to increase the substrate/catalyst ratio, the products precipitated on cooling and could be isolated by simple filtration. Moreover, the authors found that the subsequent Diels–Alder reaction with diethyl fumarate or diethyl maleate could be run as a one-pot reaction under microwave irradiation. In some cases the stereoselectivity of this reaction could be greatly improved.

4.2 Modifications of Non-Steroidal Compounds

B. Das et al. have demonstrated a microwave-assisted modification of Parthenin [101]. This compound is a major sesquiterpinoid content of the weed *Parthenium hysterophorus L* (compositae) showing a variety of potent biological effects such as anticancer, antibacterial, antiamoebic and antimalarial activities [102–106]. However, Parthenin is also known to be highly toxic and to cause allergy, which prevents its usage for any medical purposes. In view of increasing its biological potential and decreasing its toxicity, B. Das et al. carried out a microwave-assisted reduction protocol, applying Zn – AcOH as the reducing media (Scheme 27).

The reduction was carried out applying a household microwave oven. In contrast to the Zn – AcOH reduction of Parthenin, which was performed under conventional heating conditions, the microwave-assisted protocol was found to be useful in preventing the deoxygenation of the compound and the reduction of the exocyclic methylene group.

B. Das et al. have also elaborated the microwave-assisted synthesis of Mappicine ketone, a potent antiviral lead compound derived from the natural product Camptothecin. The naturally occurring pyrrolo[3,4-*b*]quinoline

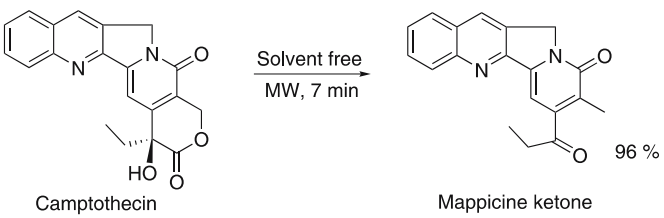


Scheme 27 Microwave-assisted modification of Parthenin

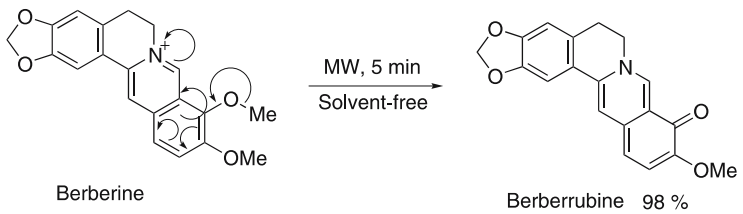
alkaloid Camptothecin, isolated from *Camptotheca acuminate* Decne (Nyssaceae), shows promising antineoplastic activity against animal tumor models [107–110]. The decarboxylated E-ring analogue of Camptothecin, known as Mappicine ketone, has been shown to exhibit potent activity against herpes viruses (HSV1 and HSV2) and human cytomegalovirus (HCMV) [107–110]. B. Das et al. have elaborated a successful conversion of Camptothecin into Mappicine ketone [111] using a commercial household microwave oven (Scheme 28).

Camptothecin was irradiated under solvent-free conditions for 7 min at the full power of the microwave oven (Scheme 28). The product, Mappicine ketone, was isolated in 96% yield without a trace of undesired side products, which clearly exhibits the potential of microwave-assisted chemistry. In comparison, when the reaction was run at rt in THF and in the presence of $BF_3 \times Et_2O$, Mappicine ketone was isolated in a mere 65% yield.

B. Das et al. have further demonstrated the use of microwave irradiation in the modification of natural products, by converting Berberine into Berberrubine (Scheme 29) [112]. Berberine, the quarternary alkaloid from *Tinospora*



Scheme 28 Microwave-assisted conversion of Camptothecin into Mappicine ketone

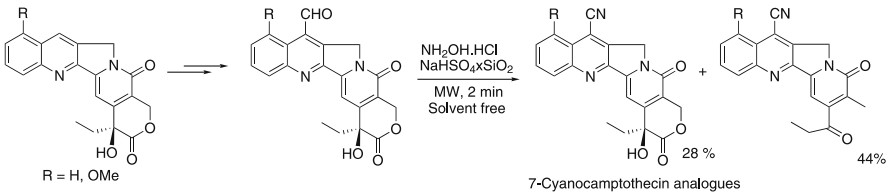


Scheme 29 Microwave-assisted conversion of Berberine to Berberrubine

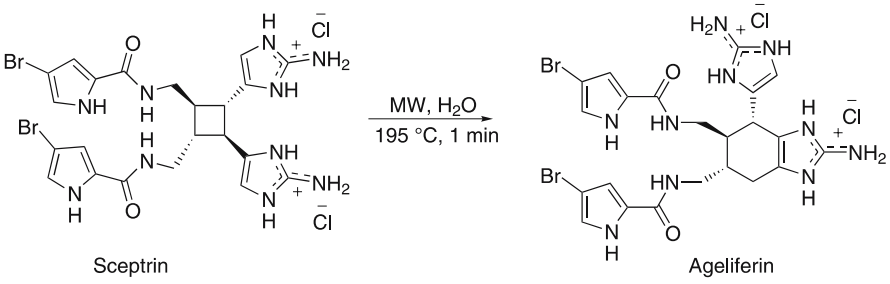
cardifolia, exhibits potent antianaemic and antineoplastic activities, besides featuring interesting pharmacological effects including respiratory stimulation, transient hypotension and convulsion [113, 114]. The authors converted the naturally occurring alkaloid Berberine into Berberrubine by irradiating the former under solvent-free conditions for 5 min, applying a domestic microwave oven.

B. Das et al. have also investigated the microwave-assisted generation of 7-cyano camptothecins and 7-cyanomappicine ketones [115], using a direct conversion of a formyl group into a nitrile functionality (Scheme 30). The 7-Cyanocamptothecin derivatives were irradiated with hydroxylamine hydrochloride using $NaHSO_4 \times SiO_2$ as a catalyst to perform the desired conversions. Microwave-irradiation experiments were carried out under solvent-free conditions for 2 min using a domestic microwave oven and the 7-cyano derivatives of Camptothecin and Mappicine ketone were isolated in good yields.

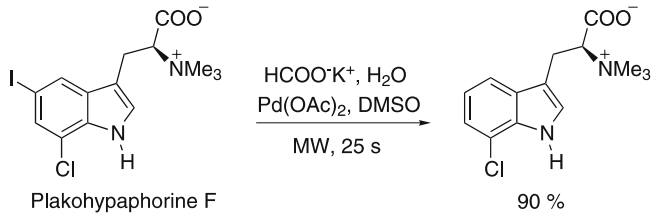
An interesting exploration related to the microwave-assisted modification of a naturally occurring bioactive molecule was recently demonstrated by P.S. Baran et al., where the authors converted the natural product Sceptrin into Ageliferin under microwave-assisted conditions [116]. While attempting to rationalize the presence of Sceptrin as the major product during the biosynthesis of Ageliferin, the authors managed an ingenious interconversion of Sceptrin to Ageliferin simply by shifting the thermodynamic equilibrium of the reaction (Scheme 31).



Scheme 30 Microwave-assisted synthesis of 7-Cyanocamptothecin analogues



Scheme 31 Microwave-assisted formation of Ageliferin from Sceptrin



Plakohypaphorine F 90 %

Scheme 32 Microwave-assisted selective dehalogenation of Plakohypaphorine F

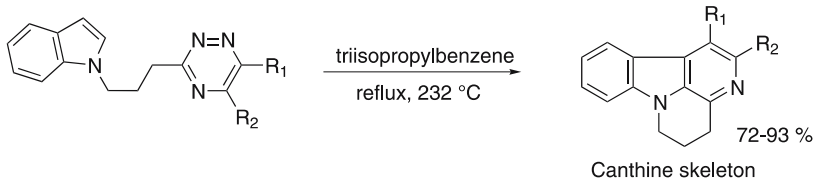
The authors irradiated a sample of Sceptrin in water at 195 °C for 1 min, using a dedicated monomode microwave apparatus. They investigated the process in detail and found that after a series of tandem tautomerizations and [1,2] shifts, Scerptin did indeed convert into the structural analogue Ageliferin. They further confirmed the reaction and mechanistic details by deuterium-labeling.

Another interesting application of microwave irradiation is found in the selective dehalogenation of the iodinated indole alkaloid Plakohypaphorine F, described by E. Fattorusso et al. [117, 118] (Scheme 32). The bis-halogenated compound was treated with potassium formate and palladium acetate under controlled microwave irradiation, resulting in selective deiodination. The choice of the solvent, in this case DMSO, was found to be crucial.

5
Synthesis of Unnatural Analogues of Natural Products

In parallel with the developments in microwave-assisted synthesis and modification of known natural products, there has been some progress in the use of microwave irradiation in the synthesis of unnatural analogues of known natural product skeletons. A typical example of such an attempt is the synthesis of unnatural β-carboline alkaloids by C.W. Lindsey et al. [119]. The authors devised a microwave-assisted one-pot procedure to easily access the basic Canthine skeleton [120]. Canthines represent a tetracyclic subclass of β-carboline alkaloids, bearing an additional D-ring. Almost forty members have been reported in the literature up to the present day from the first isolation in 1952 of the parent compound Canthine from *Pentaceras australis*. Several members of this family have been known to possess very intriguing anti-fungal, antiviral and antitumor activities [121–127]. The authors applied the ingenious Inverse Electron-Demand Diels–Alder (IEDDA) strategy developed by S. Snyder et al. [128] (Scheme 33), based on the formation of an indole derived triazine followed by intramolecular IEDDA at high temperature, while the indole was acting as the dienophile.

While trying to improve the yields and diversity of the reaction, the authors studied the reaction under microwave-assisted conditions. They ini-

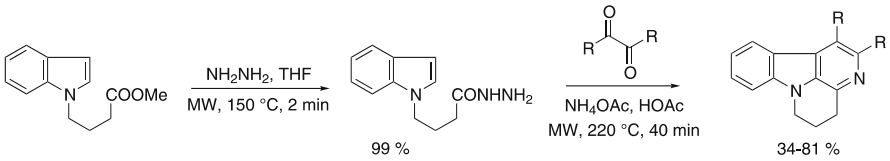


Scheme 33 Intramolecular IEDDA reaction in the synthesis of the Canthine core

tially explored the synthesis of the hydrazide intermediate needed for the formation of the triazine derivative, applying a dedicated microwave apparatus. The indole-derived ester (Scheme 34) was thus irradiated together with hydrazine in THF at 150 °C and the corresponding hydrazides were generated in high yields in a mere 2 min irradiation time. The authors further explored a microwave-assisted one-pot strategy for the formation of the triazine derivatives, followed by the IEDDA reaction to generate the corresponding Canthine analogues in high yields and purity. The condensation of the acyl hydrazide with the appropriate diketone was found to be temperature sensitive, and resulted in high yields at 220 °C in 40 min irradiation time (Scheme 34).

The authors further developed this strategy for the synthesis of unsymmetrically substituted canthine analogues, starting from the synthesis of an unsymmetrical benzil, followed by the synthesis of the corresponding acylhydrazide and subsequently the Canthine analogues [129]. This rapid microwave-assisted one-pot procedure was then utilized in the synthesis of more complex Canthine analogues (Fig. 3) featuring potent Akt (Protein Kinase B, a serine/threonine kinase) kinase inhibitory activity, equipotent against both Akt1- and Akt2-type kinases.

Another interesting exploration was recently published by J.P. Bazureau et al., where the authors investigated a microwave-assisted, solventless procedure for the synthesis of the 2-aminoimidazolone core [130] (Fig. 4). This cyclic guanidine skeleton represents an interesting pharmacophore that displays a wide range of pharmacological activities such as hypoglycemic and hypotensive activities, protein kinase C activity and inhibitory activity for the Nuclear Factor Kappa B (NF-κB) activation (Fig. 4). Among the interesting marine sponge-derived alkaloids comprising the guanidine moiety can Dispacamide, exhibiting potent antihistamine activity and Leucettamine B,



Scheme 34 Microwave-assisted synthesis of Canthine analogues

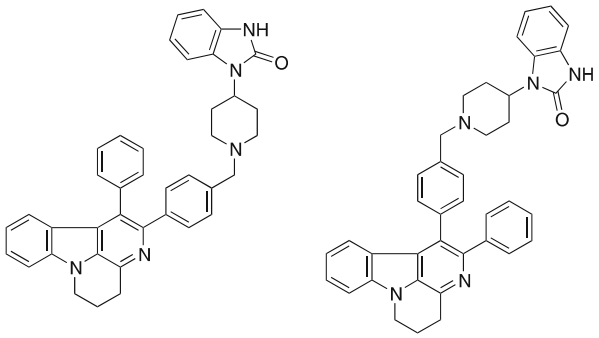


Fig. 3 Two Akt(PKB) kinase inhibitors

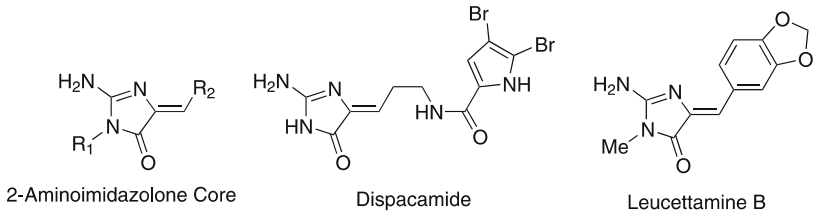
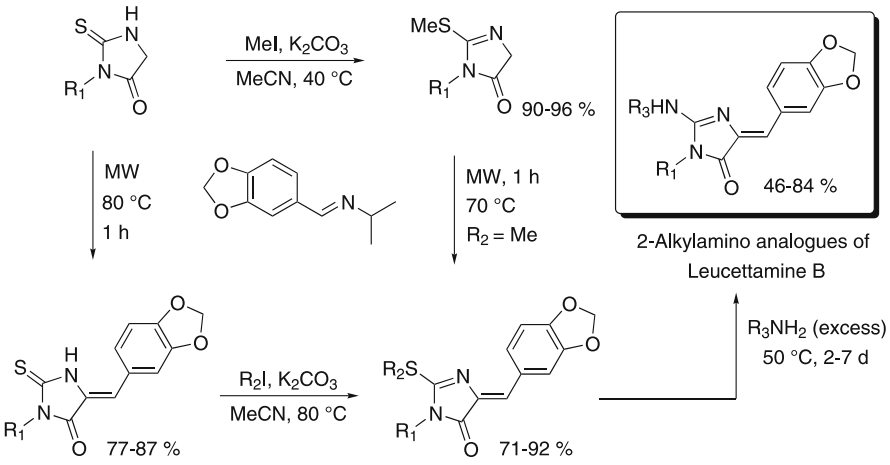


Fig. 4 The 2-aminoimidazolone core

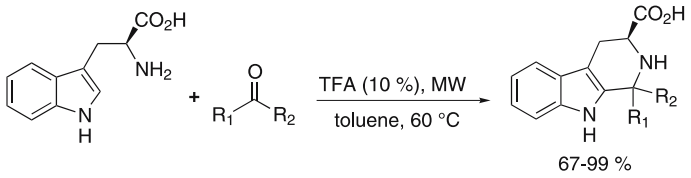
which acts as a mediator of inflammation, be mentioned [131, 132]. Even though there are a number of known methods for the synthesis of the basic skeleton, there are almost no literature precedents dealing with the construction of the 2-alkylamino derivatives of the 2-aminoimidazolones.

The authors explored two high yielding convergent approaches for the synthesis of the 2-alkylamino derivatives of Leucettamine B, applying microwave-assisted conditions using a dedicated reactor (Scheme 35). The 2-thiohydantoine intermediates were easily generated by the base-mediated condensation of the corresponding isothiocyanates with the required amino esters. These compounds were then converted to the corresponding 5-benzo-[1,3]-dioxo-5-ylmethylene-2-alkylsulfanyl-3,5-dihydroimidazol-4-ones under microwave-assisted conditions, as can be viewed in Scheme 35. It is noteworthy that the microwave irradiation provided the required intermediates in high yields and purity, while the reactions were performed under solvent-free conditions at 70–80 °C for 1 h. The compounds were then converted into the corresponding Leucettamine B analogues by reacting them with the corresponding alkylamines at 50 °C.

Y.-H. Chu et al. described the application of a microwave-accelerated Pictet–Spengler reaction for the preparation of 1,1-disubstituted indole alkaloids [133] (Scheme 36). Most of the synthetic pathways concerning the Pictet–Spengler cyclization were performed with aldehydes or activated ke-



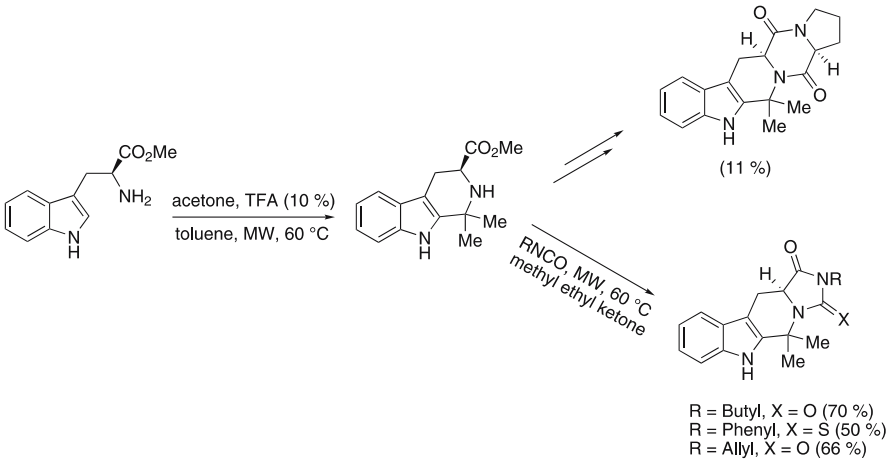
Scheme 35 Microwave-assisted synthesis of Leucettamine B analogues



Scheme 36 Pictet–Spengler reaction of tryptophan with various ketones

tones such as 1,2-dicarbonyl compounds. Reactions with ketones at room temperature mostly require days and are sluggish even under reflux conditions. Many arylketones are known to be unreactive and consequently these ketone reactions have never been addressed [134–138]. The authors found that at ambient temperature, Pictet–Spengler reactions of tryptophan with ketones could be sped up if a large excess (12 equiv) of ketone was used, although the average reaction time was in the order of days. However, upon the application of controlled microwave irradiation, the reactions proceeded remarkably faster and cleaner with both aliphatic and aromatic ketones, though the latter were much less reactive [139].

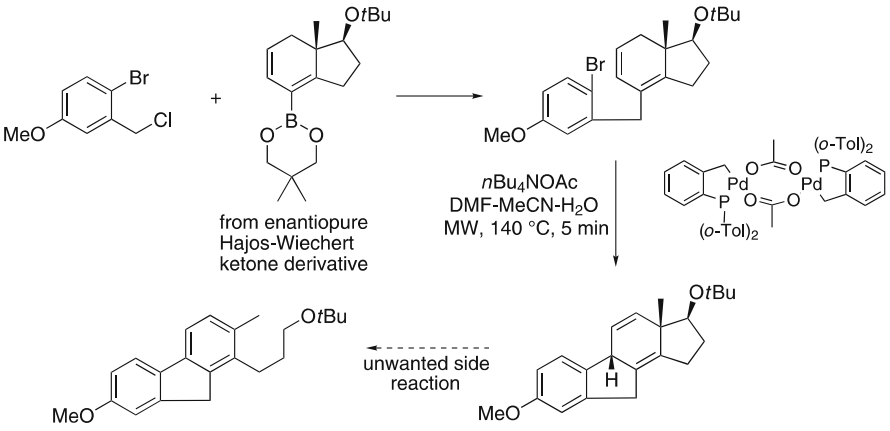
To demonstrate the usefulness of this microwave methodology the authors carried out a multistep synthesis of a new, ketone-derived Demethoxyfumitremorgin C analogue and tetrahydro-β-carbolinehydantoins [140] (Scheme 37). The former was synthesized starting from the L-tryptophan methyl ester, in an overall yield of 11%, via a three-step synthesis comprising a microwave assisted Pictet–Spengler reaction, a Schotten–Baumann acylation, deprotection and an intramolecular cyclization. In addition, good overall yields (5–70%) were achieved for the latter compound applying microwave ir-



Scheme 37 Microwave-assisted synthesis of a new, ketone-derived Demethoxyfumitremorgin C analogue and Tetrahydro-β-carbolinehydantoins

radiation on both the Pictet–Spengler cyclization and the following hydantoin formation.

In a route towards new estrogens which bind to the β-unit of the K^+-channel located on the surface of the endothelium, L.F. Tietze et al. described the synthesis of a novel enantiopure B-Nor-steroid, applying multiple Pd-catalyzed transformations [141] (Scheme 38). A combination of a Suzuki–Miyaura and a Heck reaction using a 2-bromobenzylchloride derivative and a boronic ester, derived from the enantiopure Hajos–Wiechert ketone [142–



Scheme 38 Synthesis of the B-Nor-estradiol analogue

144] was used. The Suzuki–Miyaura reaction was performed in refluxing THF using $Pd(PPh_3)_4$ as the catalyst and sodium hydroxide as the base yielding the *seco*-B-Nor-steroid in 72% with high regioselectivity. Ring B could be formed at 140 °C in an intramolecular Heck reaction using a suitable palladacycle as the catalyst, yielding the B-Nor-estradiol in 70% yield. As expected, reaction took place from below, *anti* to the angular methyl group, to form a single diastereomer. Under high-density microwave irradiation the reaction time could be shortened to 5 min and the aromatization of ring C with opening of ring D, which is an unwanted side reaction under standard conditions, could be suppressed.

E. Van der Eycken et al. have recently explored an interesting microwave-assisted synthesis of the 1,2,3-triazole-derived aza-analogues of the naturally occurring lignan lactones (–)-Steganacin and (–)-Steganone (Fig. 5). They were isolated from *Steganotaenia Araliacea* by the late S.M. Kupchan 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 [145–148]. In order to increase the biological potential and to solve the problems associated with stereoselection, K. Koga et al. proposed the synthesis of unnatural (–)-Steganacin 7-aza-analogues [149, 150]. Some of these compounds have been shown to exhibit anti-tumor activity even higher than the corresponding natural lignan lactones.

The authors explored a microwave-assisted nine-step protocol for the synthesis of the unnatural Steganacin and Steganone analogues [151], where the fused oxazolidinone ring was replaced by a 1,2,3-triazole ring system (Scheme 39). They used a microwave-assisted Suzuki–Miyaura cross-coupling reaction [152–157] to generate the key biaryl intermediates in high yields and purity. It is noteworthy that these cross-couplings, owing to the difficult oxidative addition of the transition-metal catalyst to the highly electron-rich aryl bromide and consequently the increase of competitive proto-deboronation of the boronic acid, often furnish inferior yields under conventional heating conditions. In this case, the authors observed a drop

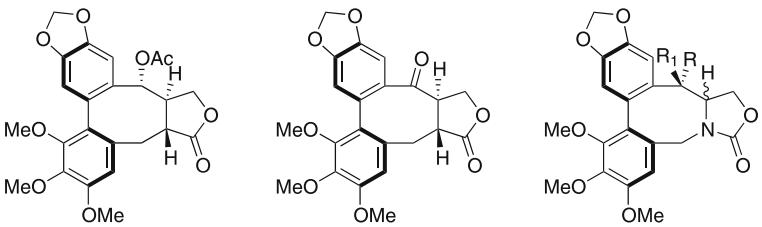
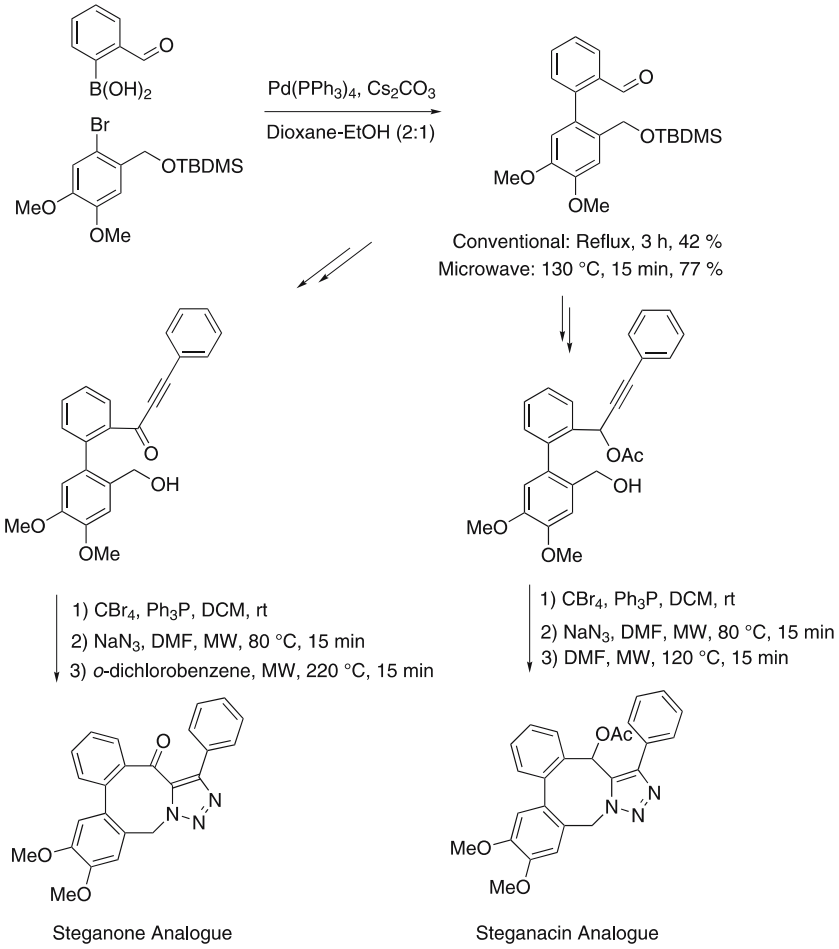


Fig. 5 Naturally occurring lignan lactones and their 7-aza-analogues



Scheme 39 Microwave-assisted synthesis of triazole-derived analogues

in yield from 77% when the microwave irradiation was used to a mere 42% under conventional heating conditions.

The required intermediate alcohols were generated by known synthetic manipulations. The intramolecular cyclization into the target molecules was then carried out following a three-step one-pot procedure, applying a microwave-assisted intramolecular Huisgen 1,3-dipolar cycloaddition as the key step. As expected, the ketone requires a much higher temperature for cyclization compared to the acetate precursor. It is also noteworthy that the intramolecular cycloaddition reaction, when carried out under conventional heating conditions, completely failed to promote the reaction.

E. Van der Eycken et al. explored a microwave-assisted Suzuki–Miyaura reaction to generate structural analogues of the apogalanthamine family

of *Amaryllidaceae alkaloids* [158]. The Apogalanthamine analogues (Fig. 6) represent an intriguing class of natural products, featuring a rare 5,6,7,8-tetrahydrobenzo[*c*,*e*]azocine skeleton. Buflavine, isolated from *Boophane flava*, an endemic *Amaryllidaceae* alkaloid species from South Africa, is a typical member of the family featuring potent biological activities such as alpha-adrenolytic and serotonin antagonistic activities [159–164].

In search of a suitable protocol for the selective generation of the biaryl axis of these compounds, the authors explored the Suzuki–Miyaura reaction of highly electron-rich phenethylamines (PEA) with a variety of boronic acids, including hindered boronic acids and acids bearing electron-withdrawing substituents, promoting proto-deboronations during cross-coupling. Despite the non-aqueous conditions advocated in the literature for conventional heating protocols, the authors were successful in developing a small library of 2-(hetero)aryl PEAs, performing the cross-coupling in a 1 : 1 mixture of DMF and water with $NaHCO_3$ or Cs_2CO_3 as the base, under focussed microwave irradiation at 150 °C for 15 min (Scheme 40). Furthermore, a microwave-assisted pseudo one-pot three-step procedure was developed for the construction of the medium-sized ring to generate a Buflavine analogue in high yield and purity.

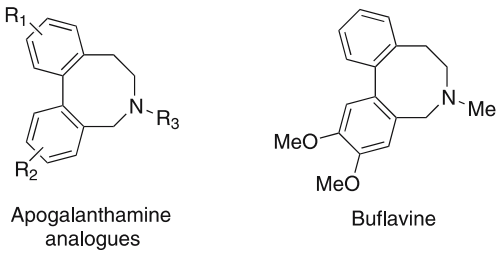
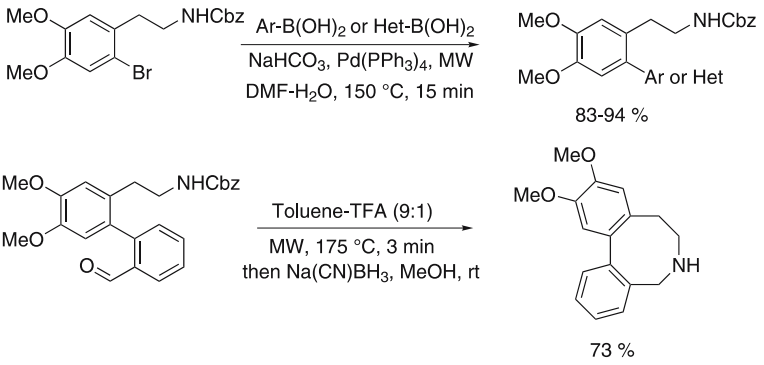


Fig. 6 Apogalanthamine analogues and Buflavine

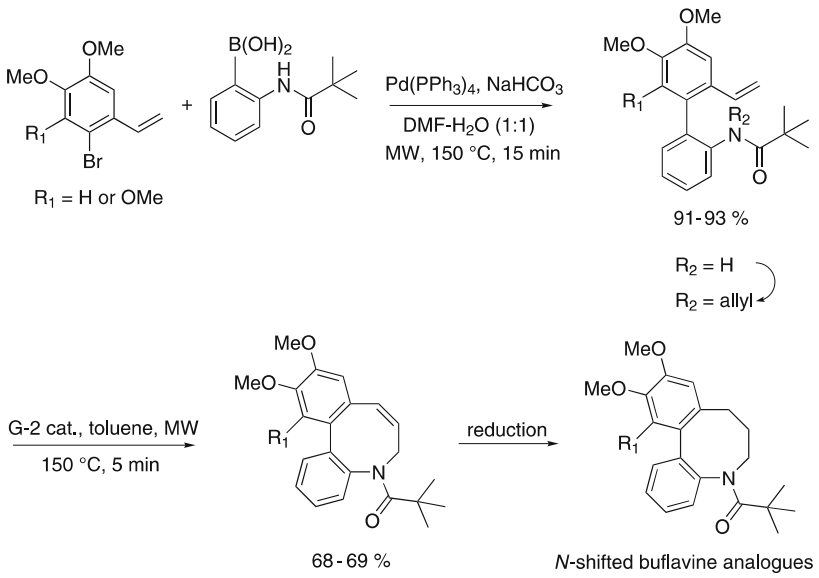


Scheme 40 Microwave-assisted biaryl coupling and synthesis of a Buflavine analogue

It is noteworthy that the microwave-assisted Suzuki–Miyaura reactions were found to be far superior to the reactions under conventional heating, as can be demonstrated by yield improvements from 22% to 84% in the case of cross-coupling of PEA derivatives. Microwave-irradiation also provided smooth conversions in water as the sole solvent.

E. Van der Eycken et al. further explored the microwave-assisted transition-metal catalyzed reactions [165–170] for the synthesis of structural analogues of Buflavine, using a combination of microwave-assisted Suzuki–Miyaura cross-coupling and Ring-Closing Metathesis (RCM). The authors developed a novel nine-step protocol for the synthesis of *N*-shifted Buflavine analogues [171], making use of their previously optimized cross-coupling conditions. Thus, highly electron-rich aryl bromides were cross-coupled with the hindered 2-pivaloylamino phenylboronic acid applying a monomode reactor to generate the required biaryl intermediates (Scheme 41).

The reactions were performed in a 1 : 1 mixture of DMF and water for 15 min at a temperature of 150 °C to furnish the biaryl intermediates in excellent yields. After installing the allyl-"handle" under standard conditions, the RCM reaction was investigated under microwave irradiation. The application of Grubbs' 2nd-generation catalyst (G-2 cat) was found to be highly beneficial, irradiating the samples for 5 min in toluene at a temperature of 150 °C (Scheme 41). It is worth mentioning that microwave-irradiation was found to be highly beneficial in generating the highly strained ring system of the target compounds, as the yields under conventional heating conditions were lower.



Scheme 41 Microwave-assisted synthesis of *N*-shifted Buflavine analogues

The newly generated double bond was then reduced under Pd-mediated hydrogenation conditions to successfully complete the synthesis.

6 Synthesis of Interesting Building Blocks for Natural Product Synthesis

Apart from valuable applications in the synthesis of natural products and analogues, microwave irradiation has been applied for the generation of generally applicable building blocks for natural product synthesis. A typical example was recently reported by J.C. Menéndez et al. [172]. The authors described the synthesis of a small library of molecules possessing the pyrazino[2,1-*b*]quinazoline-3,6-dione skeleton, which is the structural core of a number of biologically interesting natural products such as Glyantrypine, the Fiscalins and Fumiquinazolines (Fig. 7). More complex natural products bearing this skeleton have been demonstrated to possess important biological properties. As an example, Ardeemin is a very potent inhibitor of multi-drug resistance (MDR) to antitumor drugs, which is an important obstacle to antitumor chemotherapy, and it has been shown that the pharmacophore unit of *N*-acetylardeemin is the pyrazino[2,1-*b*]quinazoline-3,6-dione moiety. Additionally, Spiroquinazoline inhibits the binding of substance P to the human NK-1 receptor [173, 174].

The authors explored an ingenious synthesis involving the direct cyclocondensation of the lactim ethers of the corresponding diketopiperazine

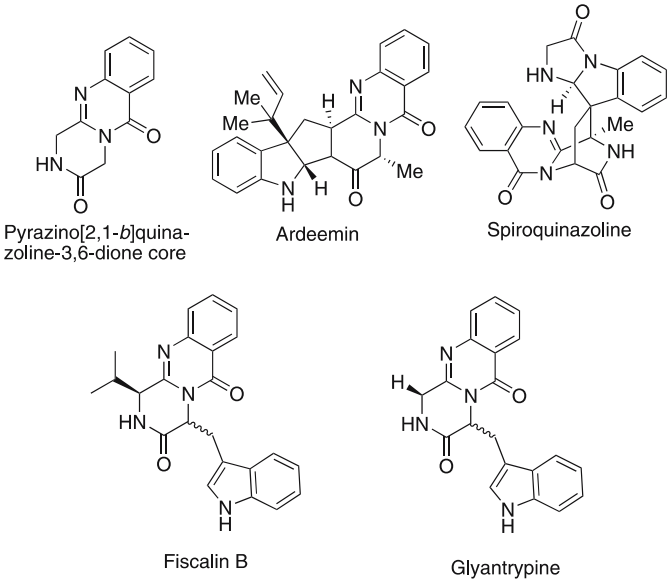
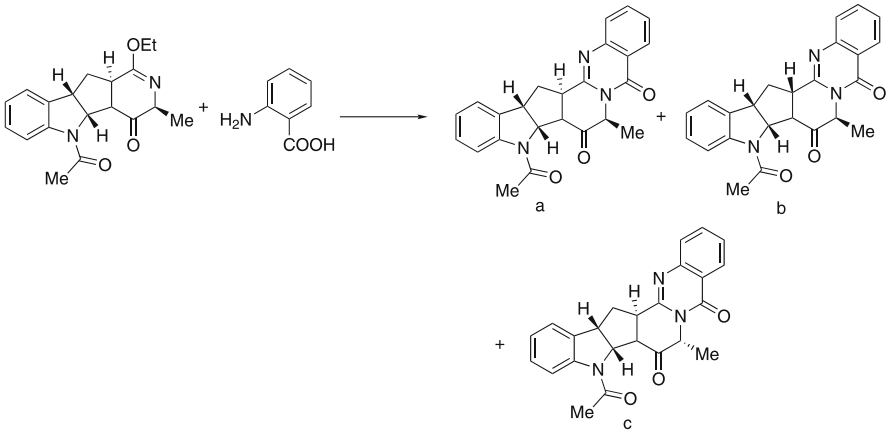


Fig. 7 Natural products with a pyrazino[2,1-*b*]quinazoline-3,6-dione skeleton

(DKP) building blocks with a suitable anthranilic acid derivative (Scheme 42). Even though this method has been explored previously under conventional heating conditions, it has been rather neglected owing to the long and harsh reaction conditions as well as inferior product yields. An additional problem observed during conventional heating was the epimerization of the stereocenters adjacent to the carbonyl groups. The authors carried out the reaction in a domestic microwave oven at 600 W maximum irradiation power with three 1 min heating-2 min cooling cycles with the reactants absorbed on alumina (Scheme 42). Reactions under microwave irradiation proved to be beneficial both in terms of rates and yields in comparison with the conventional heating conditions.

Another interesting example of the use of microwave irradiation in generating interesting building blocks for natural product synthesis, was reported by A.G. Falliset al. [175] regarding the synthesis of the functionalized tricycle[9,3,1,0]pentadecene system of Taxanes, the core skeleton that can be found in Taxol (Fig. 8). Taxol has elicited considerable interest [176–178] due



Scheme 42 Microwave-assisted synthesis of de-Prenylardeemins

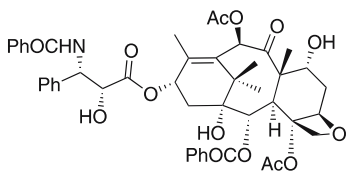


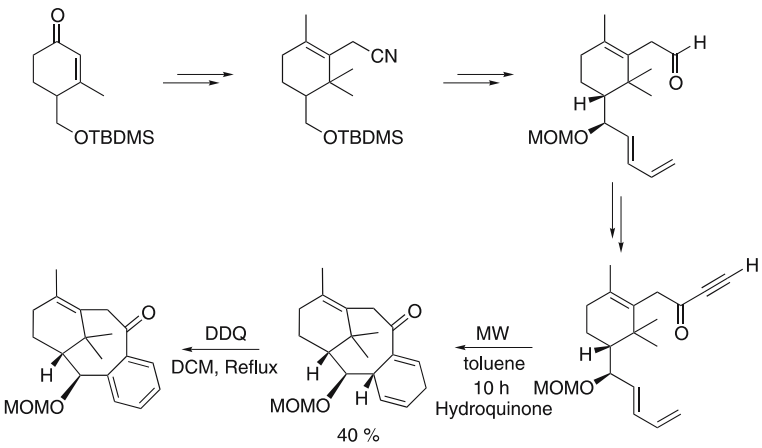
Fig. 8 Taxol skeleton

to its high biological potential as an antitumor agent and the tremendous synthetic challenges in generating this complex ring system (Fig. 8). Diversely functionalized synthetic Taxane cores could serve as building blocks for the synthesis of Taxol analogues for the purpose of drug discovery. As a consequence, a number of synthetic studies have been reported on the synthesis and manipulation of Taxol analogues under conventional heating conditions.

The authors elaborated an innovative synthesis of the Taxane core based on an intramolecular Diels–Alder reaction as the key step. The TBDMS-protected cylohexenone-derived alcohol was converted into the corresponding nitrile intermediate in five steps by known synthetic manipulations (Scheme 43), mainly based on transmetallation protocols. The diene handle for the Diels–Alder reaction was then introduced following a simple but highly efficient four-step procedure. The dienophile for the cycloaddition, the terminal acetylene moiety, was incorporated via lithiation chemistry to furnish the substrate for the intramolecular Diels–Alder cyclization (Scheme 43).

The reaction was carried out in a sealed glass tube applying a "modified" microwave oven. A 0.05 M solution of the substrate together with 1 mol equiv of hydroquinone in toluene was irradiated for 10 h to furnish the target Taxane core in 40% yield. When conventional heating conditions were used, the authors found that the double bond of the cyclohexene ring shifted into conjugation with the acetylenic ketone, preventing the cyclization from taking effect. This example clearly illustrates the advantage of microwave irradiation over conventional heating.

Another interesting investigation was reported by J.A. Prieto et al. describing the microwave-assisted $VO(acac)_2$-catalyzed epoxidation [179] of hindered homoallylic alcohols. From a synthetic point of view this is of particular interest as the literature abounds with examples of syntheses of 3,4-epoxy alcohols, owing to their potential in the generation of valuable intermedi-



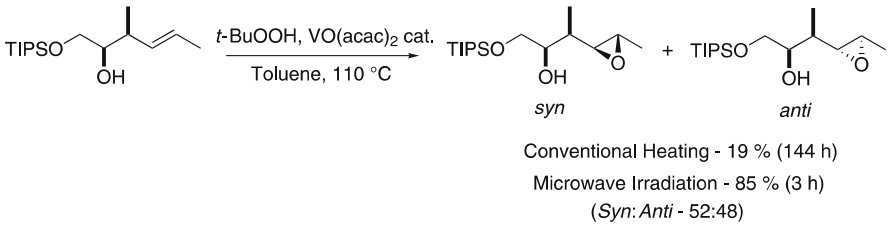
Scheme 43 Microwave-assisted synthesis of the Taxane core by Diels–Alder cyclization

ates such as 1,3-diols [180–186]. The 3,4-epoxy alcohols are usually generated via epoxidation of the corresponding homoallylic alcohols, albeit with minor control of the stereochemistry of the resultant epoxides. The most common method for this purpose is iodocyclization after carbonylation. However, this procedure has been shown to be rather slow and the application of very strong bases, such as *n*-BuLi, is required. Complex mixtures are mostly obtained when *trans* homoallylic alcohols are employed.

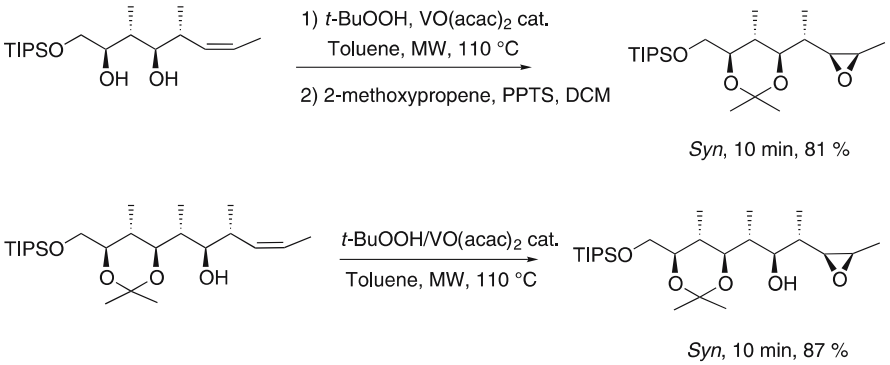
The reagent $VO(acac)_2$/*t*-butyl hydroperoxide has been extensively used for the epoxidation of homo-allylic alcohols. While the *cis*-homoallylic alcohols generally give high yields and stereoselectivity, the *trans*-analogues are known to furnish poor selectivities and sluggish reactions, particularly as the steric demand of the alkenol system increases. Therefore, the authors sought to increase the reaction rates by performing the epoxidation under microwave irradiation applying a multimode apparatus. Dramatic accelerations and yield enhancements were observed under these conditions. The authors demonstrated that the reaction times were shortened from 6–10 days, to only 45 min–3 h under microwave-assisted conditions (Scheme 44). In addition, the yields were improved considerably. Further attempts to improve the synthesis, such as the use of solvent-free conditions or doping with an ionic liquid failed to improve the outcome even under microwave irradiation. The diastereoselectivities remained unchanged in comparison with the reactions under conventional heating.

Furthermore, the authors explored the epoxidation of more complex homoallylic alcohols, in view of their application as precursors for the synthesis of the polypropionate chains of Streptovaricins D and U (Scheme 45) [187–189]. These complex alcohols were found to undergo the $VO(acac)_2$-catalyzed epoxidations smoothly under microwave-assisted conditions and the products were isolated in very high yields in only 10 min, after being protected as the corresponding acetonides (Scheme 45). Moreover, in this specific case, the authors were successful in obtaining exclusive diastereoselectivity, as only the *syn*-isomers were isolated as the products of epoxidation.

Another interesting investigation was reported by A.K. Bose et al. [190], where the authors successfully carried out Catalytic Transfer Hydrogena-



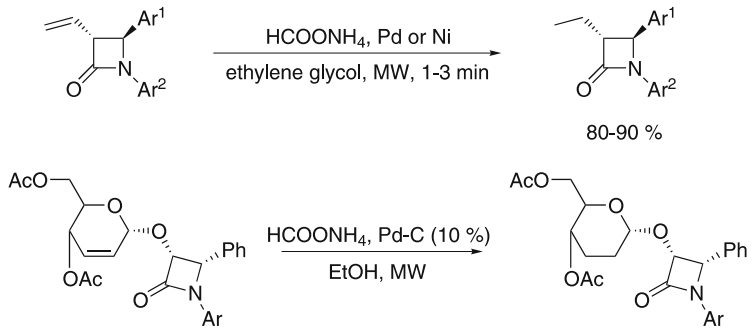
Scheme 44 $VO(acac)_2$-catalyzed epoxidation; conventional heating versus microwave irradiation



Scheme 45 Microwave-assisted $VO(acac)_2$-catalyzed diastereoselective epoxidations

tion (CTH) under microwave-irradiation [191–194] (Scheme 46). They investigated the reduction via CTH of ring substituents of diverse β-lactams, containing alkene or alkylidene groups or conjugated esters, applying an unmodified domestic microwave oven. A beaker or an Erlenmeyer flask was used as the reaction vessel, in the presence of a beaker containing water as the heat sink. The authors used this simple yet effective set-up for the CTH reactions of differently substituted β-lactams in ethylene glycol using an irradiation power of 600–1000 W. Ammonium formate or hydrazine hydrate were used as the hydrogen transfer sources, and the reactions were catalyzed either by Pd – C or Raney nickel. The reactions were found to proceed with the very high yields of 80–90% in only 2–3 min of irradiation times.

Curiously, the *N*-benzyl moiety on a variety of β-lactams was untouched by the microwave-assisted CTH reactions. The authors further elaborated this interesting strategy for the reduction of the double bond in an unsaturated sugar moiety, without inducing the ring fission of the attached β-lactam side chains (Scheme 46).



Scheme 46 Microwave-assisted CTH reactions of β-lactams

7 Summary and Overview

Natural product synthesis is undoubtedly one of the most challenging topics for synthetic organic chemists and has received much attention during the past decades. In contrast, the application of microwave irradiation in natural product synthesis has only been fragmentarily explored and has so far not been systematically applied for the majority of possible conversions in synthetic sequences. Nevertheless, its usefulness has already been demonstrated in the synthesis of complex systems such as the taxol skeleton. Among the advantages of microwave irradiation can the dramatic shortening of reaction time and in many cases also higher yields be mentioned. Sometimes a different outcome of the reaction can be observed, for example an induction of a more favorable reaction ratio. It is clear that shorter heating periods, caused by the application of microwave irradiation, might be advantageous for these complex and sometimes fragile and labile systems.

Concomitant with the tremendously increased application of microwave irradiation in synthesis during the last 5 years, we might expect a rise in interest in its application for natural product chemistry, as more and more natural product chemists are discovering the benefits of this powerful technique.

References

1. Ridley DD, Ritchie E, Taylor WC (1970) Aust J Chem 23:147
2. Lytollis W, Scannell RT, An H, Murty VS, Reddy KS, Barr JR, Hecht SM (1995) J Am Chem Soc 117:12683
3. Singh US, Scannell RT, An H, Carter BJ, Hecht SM (1995) J Am Chem Soc 117:12691
4. Scannell RT, Barr JR, Murty VS, Reddy KS, Hecht SM (1988) J Am Chem Soc 110:3650
5. Fürstner A (2002) Chem Eur J 8:1856
6. Agrofoglio LA, Nolan SP (2005) Topics Curr Med Chem 5:1541
7. Nicolaou KC, Bulger PG, Sarlah D (2005) Angew Chem Int Ed 44:4490
8. Grubbs RH (2004) Tetrahedron 60:7117
9. Schmidt B, Hermanns J (2004) Topics Organometallic Chem 13:223
10. Deiters A, Martin SF (2004) Chem Rev 104:2199 and references cited therein
11. Mulzer J, Oehler E (2004) Topics Organometallic Chem 13:269
12. Diver ST, Giessert AJ (2004) Chem Rev 104:1317
13. Furstner A, Davies PW (2005) Chem Commun, p 2307
14. Thiel OR (2004) In: Transition Metals for Organic Synthesis. 2nd Ed. Wiley-VCH, Weinheim 1:321
15. Michell SS, Rhodes D, Bushman FD, Faulkner D (2000) Org Lett 2:1605
16. Kiyota H, Dixon DJ, Luscombe CK, Hettstedt S, Ley SV (2002) Org Lett 4:3223
17. Dixon DJ, Ley SV, Reynolds DJ (2002) Chem Eur J 8:1621
18. Gonzalez N, Rodriguez J, Jiminez C (1999) J Org Chem 64:5705
19. Kashiwada Y, Yamazaki K, Ikeshiro Y, Yamasishi T, Fujioka T, Mihashi K, Mizuki K, Cosentino LM, Fowke K, Morris-Natschke SL, Lee K-H (2001) Tetrahedron 57:1559

20. Mamoru E, Hiroshi E (1982) Jpn Kokai Tokko Koho JP 82–28:080
21. Kang Y, Mei Y, Du Y, Jin Z (2003) Org Lett 5:4481
22. Saimoto H, Yoshida K, Murakami T, Morimoto M, Sashiwa H, Shigemasa Y (1996) J Org Chem 61:6768
23. Narkhede DD, Iyer PR, Iyer CSR (1989) J Nat Prod 52:502
24. Brink AJ, Rall GJH, Breytenbach JC (1977) Phytochemistry 16:273
25. Subburaj K, Katoch R, Murugesh MG, Trivedi GK (1997) Tetrahedron 53:12621
26. Volkmann RA, Andrews GC, Johnson WS (1975) J Am Chem Soc 97:4777
27. Corey EJ, Ohno M, Mitra RB, Vatakencherry PA (1964) J Am Chem Soc 86:478
28. Lei B, Fallis AG (1993) J Org Chem 58:2186
29. Abegaz BM (2002) Phytochem Rev 1:299
30. Aguilar R, Benavides A, Tamariz J (2004) Synthetic Commun 34:2719
31. Kad GL, Singh V, Khurana A, Singh J (1998) J Nat Prod 61:297
32. Grainger RS, Patel A (2003) Chem Commun, p 1072
33. Lewis FD, Reddy GD, Bassani DM (1993) J Am Chem Soc 115:6468
34. Lewis FD, Reddy GD, Bassani DM, Schneider S, Gahr M (1994) J Am Chem Soc 116:597
35. Subbaraju GV, Manhas MS, Bose AK (1991) Tetrahedron Lett 32:4871
36. Ezaki M, Iwami M, Yamashita M, Hashimoto S, Komori T, Umehara K, Mine Y, Kohsaka M, Aoiki H, Imanaka H (1985) J Antibiot 38:1453
37. Uchida I, Shigematsu N, Ezaki M, Hashimoto M, Hatsuo A, Hiroshi I (1985) J Antibiot 38:1462
38. Uchida I, Ezaki M, Shigematsu N, Hashimoto M (1985) J Org Chem 50:1341
39. Chang CC, Morton GO, James JC, Siegel MM, Kuck NA, Testa RT, Borders DB (1991) J Antibiot 44:674
40. Lépine R, Zhu J (2005) Org Lett 7:2981
41. Kappe CO (2004) Angew Chem Int Ed 43:6250
42. Kappe CO (2002) Curr Opin Chem Biol 6:314
43. Kappe CO, Dallinger D (2006) Drug Discov 5:51
44. Ersmark K, Larhed M, Wannberg J (2004) Curr Opin Drug Discov Dev 7:417
45. Mavandadi F, Lidstroem P (2004) Curr Top Med Chem 4:773
46. Alexandre F-R, Domon L, Frere S, Testard A, Thiery V, Besson T (2003) Mol Diver 7:273
47. Somei M, Yamada F (2005) Nat Prod Rep 22:73
48. Somei M, Yamada F (2004) Nat Prod Rep 21:278
49. Toyota M, Ihara M (1998) Nat Prod Rep 15:327, and references cited therein
50. Franco LH, Palermo JA (2003) Chem Pharm Bull 51:975
51. Hernández FL, Bal de Kier JE, Puricelli L, Tatian M, Seldes AM, Palermo JA (1998) J Nat Prod 61:1130
52. Butler MS, Capon RJ, Lu CC (1992) Aust J Chem 45:1871
53. Perry NB, Ettouati L, Litaudon M, Blunt JW, Munro MHG, Parkin S, Hope H (1994) Tetrahedron 50:3987
54. Rauwald HW, Kobar M, Mutschler E, Lambrecht G (1992) Planta Med 58:486
55. Sharaf MH M, Schiff PL Jr, Tackie AN, Phoebe CH Jr, Martin GE (1996) J Heterocycl Chem 33:239
56. Cimanga K, De Bruyne T, Pieters L, Claeys M, Vlietinck A (1996) Tetrahedron Lett 37:1703
57. Cimanga K, De Bruyne T, Pieters L, Claeys M, Vlietinck A (1997) J Nat Prod 60:688
58. Fresneda PM, Molina P, Delgado S (2001) Tetrahedron 51:6197
59. Kumemura T, Choshi T, Hirata A, Sera M, Takahashi Y, Nobuhiro J, Hibino S (2005) Chem Pharm Bull 53:393

60. Kohno J, Hiramatsu H, Nishio M, Sakurai M, Okuda T, Komatsubara S (1999) Tetrahedron 55:11247
61. Kohno J, Sakurai M, Kameda N, Nishio M, Kawano K, Kishi N, Okuda T, Komatsubara S (1999) J Antibiot 52:913
62. Kumemura T, Choshi T, Hirata A, Sera M, Takahashi Y, Nobuhiro J, Hibino S (2003) Heterocycles 61:13
63. Pouìlhes A, Langlois Y, Chiaroni A (2003) Synlett, p 1488
64. Cox ED, Cook JM (1995) Chem Rev 95:1797
65. Foderato TA, Barrows LR, Lassota P, Ireland CM (1997) J Org Chem 62:6064
66. Ma ZZ, Hano Y, Nomura T, Chen JJ (1997) Heterocycles 46:541
67. Slichenmyer WJ, Rowinsky EK, Donehower RC, Kaufmann SH (1993) J Nat Cancer Inst 85:271
68. Yadav JS, Reddy BVS (2002) Tetrahedron Lett 43:1905
69. Lipińska T (2002) Tetrahedron Lett 43:9565
70. Costa-Campos L, Lara DR, Nunes DS, Elisabetsky E (1998) Pharmacol Biochem Behav 60:133
71. Lipińska T, Guibe-Jampel E, Petit A, Loupy A (1999) Synth Commun 29:1349
72. Beljanski M, Crochet S (1996) Int J Oncol 8:1143 and references cited therein
73. Rykowski A, Lipińska T (1997) Pol J Chem 71:83
74. Lipińska T (2004) Tetrahedron Lett 45:8831
75. Lipińska T (2005) Tetrahedron 61:8148
76. Wolkenberg SE, Wisnoski DD, Leister WH, Wang Y, Zhao ZJ, Lindsley CW (2004) Org Lett 6:1453
77. Cui B, Zheng BL, He K, Zheng QY J (2003) Nat Prod 66:1101
78. Liu J-F, Lee J, Dalton AM, Bi G, Yu L, Baldino CM, McElory E, Brown M (2005) Tetrahedron Lett 46:1241
79. Wolfe JF, Rathman TL, Sleevi MC, Campbell JA, Greenwood TD (1990) J Med Chem 33:161
80. Buzas A, Hoffmann C (1959) Bull Soc Chim Fr, p 1889
81. Welch WM, Ewing FE, Huang J, Menniti FS, Pagnozzi MJ, Kelly K, Seymour PA, Guanowsky V, Guhan S, Guinn MR, Critchett D, Lazzaro J, Ganong AH, DeVries KM, Staigers TL, Chenard BL (2001) Bioorg Med Chem Lett, p 177
82. Liu J-F, Kaselj M, Isome Y, Ye P, Sargent K, Sprague K, Cherrak D, Wilson CJ, Si Y, Yohannes D, Ng S-C (2006) J Comb Chem 8:7
83. Penn J, Mantle PG, Bilton JN, Sheppard RN (1992) J Chem Soc, Perkin Trans 1, p 1495
84. Numata A, Takahashi C, Matsushita T, Miyamoto T, Kawai K, Usami Y, Matsumura E, Inoue M, Ohishi H, Shingu T (1992) Tetrahedron Lett 33:1621
85. Takahashi C, Matsushita T, Doi M, Minoura K, Shingu T, Kumeda Y, Numata A (1995) J Chem Soc, Perkin Trans 1, p 2345
86. Liu J-F, Ye P, Zhang B, Bi G, Sargent K, Yu L, Yohannes D, Baldino CM (2005) J Org Chem 70:6339
87. Tietze LF (1996) Chem Rev 96:115
88. Tietze LF, Haunert F (2000) In: Shibasaki M, Stoddart JF, Vögtle F (eds) Stimulating Concepts in Chemistry. Wiley, Weinheim, p 39
89. Liu J-F, Ye P, Sprague K, Sargent K, Yohannes D, Baldino CM, Wilson CJ, Ng S-C (2005) Org Lett 7:3363
90. Liu J-F, Kaselj M, Isome Y, Chapnick J, Zhang B, Bi G, Yohannes D, Yu L, Baldino CM (2005) J Org Chem 70:10488
91. Goetz MA, Monaghan RL, Chang RSL, Ondeyka J, Chen TB, Lotti VJ (1988) J Antibiot 41:875

92. Sun HH, Barrow CJ, Sedlock DM, Gillum AM, Cooper R (1994) J Antibiot 47:515
93. Pla D, Marchal A, Olsen CA, Albericio F, Alvarez M (2005) J Org Chem 70:8231
94. Cironi P, Albericio F, Alvarez M (2004) In: Gribble GW, Joule JA (eds) Progress in Heterocyclic Chemistry. Pergamon, Oxford, UK, vol 16, p 1
95. Facompré M, Tardy C, Bal-Mahieu C, Colson P, Pérez C, Manzanares I, Cuevas C, Bailly C (2003) Cancer Res 63:7392
96. Sharma U, Bora U, Boruah RC, Sandhu JS (2002) Tetrahedron Lett 43:143
97. Longchar M, Bora U, Boruah RC, Sandhu JS (2002) Synthetic Commun 32:3611
98. Skoda-Földes R, Pfeiffer P, Horváth J, Tuba Z, Kollár L (2002) Steroids 67:709
99. Skoda-Földes R, Kollár L, Heil B, Gálik G, Tuba Z, Arcadi A (1991) Tetrahedron Asymm 2:633
100. Skoda-Földes R, Csákai Z, Kollár L, Horváth J, Tuba Z (1995) Steroids 60:812
101. Das B, Venkataiah B, Kashinatham A (1999) Tetrahedron 55:6585
102. Kupchan SM, Eakin MA, Thomas AM (1971) J Med Chem 14:1147
103. Mew D, Baiza F, Towers GHN, Levy JG (1982) Planta Med 45:23
104. Picman AK, Towers GHN (1983) Biochem Syst Ecol 11:321
105. Sharma GL, Bhutani KK (1988) Planta Med 54:120
106. Hopper M, Kirby GC, Kulkarni MM, Kulkarni SN, Nagasampagi BA, O'Neill MJ, Philipson JD, Rojatkar SR, Warhurs DC (1990) Eur J Med Chem 25:717
107. Gallo ILC, Whang-peng J, Adamson ILK (1971) J Nat Cancer Inst 46:789
108. Wall ME, Wani MC (1977) Ann Rev Pharmacol Toxicol 17:117
109. Pendrak I, Wittrock R, Kingsbury WD (1995) J Org Chem 60:2912
110. Pendrark I, Berney S, Wittrock R, Lambert DM, Kingsbury WD (1994) J Org Chem 59:2623
111. Das B, Madhusudhan P, Kashinatham A (1998) Tetrahedron Lett 39:431
112. Das B, Srinivas KVNS (2002) Synth Commun 32:3027
113. Buckingham J (ed) (1994) Dictionary of Natural Products. 1st Ed. Chapman and Hall, London, vol 1, p 640
114. Gharbi SA, Beal JL, Doskotch RW, Mitscher LA (1973) Lloydia 36:349
115. Das B, Srinivas KVNS (2004) Synth Commun 34:199
116. Baran PS, O'Malley DP, Zografos AL (2004) Angew Chem Int Ed 43:2674
117. Borrelli F, Campagnuolo C, Capasso R, Fattorusso E, Taglialatela-Scafati O (2004) Eur J Org Chem 15:3227
118. Campagnuolo C, Fattorusso E, Taglialatela-Scafati O (2003) Eur J Org Chem 2:284
119. Lindsley CW, Wisnoski DD, Wang Y, Leister WH, Zhao Z (2003) Tetrahedron Lett 44:4495
120. Ohmoto T, Koike K (1989) In: Brossi A (ed) The Alkaloids. Academic Press, New York, vol 36, p 135
121. Haynes HF, Nelson ER, Price JR (1952) Aust J Sci Res Ser A 5:387
122. Nelson ER, Price JR (1952) Aust J Sci Res Ser A 5:563
123. Nelson ER, Price JR (1952) Aust J Sci Res Ser A 5:68
124. Anderson LA, Harris A, Phillipson JD (1983) J Nat Prod 46:374
125. Arisawa M, Kinghorn AD, Cordell GA, Farnsworth NR (1983) J Nat Prod 46:222
126. Ohmoto T, Nikaido T, Koide K, Kohda K, Sankawa U(1988) Chem Pharm Bull 36:4588
127. Ouyang Y, Koide K, Ohmoto T (1994) Phytochemistry 36:1543
128. Benson SC, Li J-H, Snyder JK (1992) J Org Chem 57:5285
129. Lindsley CW, Bogusky MJ, Leister WH, McClain RT, Robinson RG, Barnett SF, Defeo-Jones D, Ross CW, Hartman GD (2005) Tetrahedron Lett 46:2779
130. Chérouvrier J-R, Carreaux F, Bazureau JP (2002) Tetrahedron Lett 43:3581

131. Cafieri F, Fattorusso E, Mangani A, Tagliakatela-Scafati O (1996) Tetrahedron Lett 37:3587
132. Boehm JC, Gleason JG, Pendrak I, Sarau HM, Schmidt B, Foley JJ, Kingsbury WD (1993) J Med Chem 36:3333
133. Kuo F-M, Tseng M-C, Yen Y-H, Chu Y-H (2004) Tetrahedron 60:12075
134. Horiguchi Y, Nakamura M, Saitoh T, Sano T (2003) Chem Pharm Bull 51:1368
135. Horiguchi Y, Nakamura M, Kida A, Kodama H, Saitoh T, Sano T (2003) Heterocycles 59:691
136. Cheng CC, Chu Y-H (1999) J Comb Chem 1:461
137. Papadopoulou D, Spyros IP, Varvoglis A (1998) Tetrahedron Lett 39:2865
138. Mayer JP, Bankaitis-Davis D, Zhang J, Beaton G, Bjergarde K, Anderson CM, Goodman BA, Herrera CJ (1996) Tetrahedron Lett 37:5633
139. Horiguchi Y, Kodama H, Nakamura M, Yoshimura T, Hanezi K, Hamada H, Saitoh T, Sano T (2002) Chem Pharm Bull 50:253
140. Tseng M-C, Liang Y-M, Chu Y-H (2005) Tetrahedron Lett 46:6131
141. Tietze LF, Wiegand JM, Vock CA (2004) Eur J Org Chem, p 4107
142. Micheli RA, Hajos ZG, Cohen N, Parrish DR, Portland LA, Sciamanna W, Scott MA, Wehrli PA (1975) J Org Chem 40:675
143. Eder U, Sauer G, Wiechert R (1971) Angew Chem 83:492
144. Eder U, Sauer G, Wiechert R (1971) Angew Chem Int Ed Engl 10:496
145. Kupchan SM, Britton RW, Ziegler MF, Gilmore CJ, Restivo RJ, Bryan RF (1973) J Am Chem Soc 95:1335
146. Wang RW, Rebhum LI, Kupchan SM (1977) Cancer Res 37:3071
147. Sackett DL (1993) Pharmacol Ther 59:163
148. Zavala F, Guenard D, Robin J-P, Brown E (1980) J Med Chem 23:546
149. Tomioka K, Kubota Y, Kawasaki H, Koga K (1989) Tetrahedron Lett 30:2949
150. Kubota Y, Kawasaki H, Tomioka K, Koga K (1993) Tetrahedron 49:3081
151. Beryozkina T, Appukkuttan P, Mont N, Van der Eycken E (2006) Org Lett 8:487
152. Miyaura N, Suzuki A (1995) Chem Rev 95:2457
153. Diederich F, Stang PJ (eds) (1998) Metal-Catalyzed Cross-coupling Reactions. Wiley, Weinheim, p 517
154. Suzuki A (1999) J Organometallic Chem 576:147
155. Kotha S, Lahiri K, Kashinath D (2002) Tetrahedron 58:9633
156. Leadbeater NE (2005) Chem Commun 23:2881
157. Apukkuttan P, Van der Eycken E, Dehaen W (2005) Synlett, p 127
158. Appukkuttan P, Orts AB, Chandran RP, Goeman JL, Van der Eycken J, Dehaen W, Van der Eycken E (2004) Eur J Org Chem, p 3277
159. Ishida Y, Sasaki Y, Kimura Y, Watanabe K (1985) J Pharmacobiodyn 8:917
160. Ishida Y, Sadamune K, Kobayashi S, Kihara M (1983) J Pharmacobiodyn 6:391
161. Viladomat F, Bastida J, Codina C, Campbell WE, Mathee S (1995) Phytochemistry 40:307
162. Hoarau C, Couture A, Deniau E, Grandclaudon P (2002) J Org Chem 67:5846
163. Patil PA, Snieckus V (1998) Tetrahedron Lett 39:1325
164. Sahakitpichan P, Ruchiravat S (2003) Tetrahedron Lett 44:5239
165. Lidström P, Tierney J, Wathey B, Westman J (2001) Tetrahedron 57:9225
166. Lidström P, Westman J, Lewis A (2002) Comb Chem High Throughput Screening 6:441
167. Larhed M, Moberg C, Hallberg A (2002) Acc Chem Res 35:717
168. Loupy A (2002) Microwaves in Organic Synthesis. Wiley, Weinheim, Germany, and references therein

169. Kappe CO (2004) Angew Chem Int Ed 43:6250
170. Hayes BL (2004) Aldrichim Acta 37:66
171. Appukkuttan P, Dehaen W, Van der Eycken E (2005) Org Lett 7:2723
172. Cledera P, Sánchez JD, Caballero E, Avendaño C, Ramos MT, Menéndez JC (2004) Synlett, p 803
173. Hochlowski JE, Mullally MM, Spanton SG, Whittern DN, Hill P, McAlpine JB (1993) J Antibiotics 46:380
174. Barrow CJ, Sun HH (1994) J Nat Prod 57:471
175. Lu Y-F, Fallis AG (1993) Tetrahedron Lett 34:3367
176. Wani MC, Taylor HL, Wall ME, Coggan P, McPhail AT (1971) J Am Chem Soc 93:2325
177. Pamess J, Horwitz SB (1981) J Cell Biol 91:479
178. Chapin SJ, Bulinski JC, Gundersen GG (1991) Nature 349:24
179. Torres G, Torres W, Prieto JA (2004) Tetrahedron 60:10245
180. Corey EJ, Hase T (1979) Tetrahedron Lett 20:335
181. Lipshutz BH, Kozlowski J (1984) J Org Chem 49:1147
182. Lipshutz BH, Barton JC (1988) J Org Chem 53:4495
183. Mohr P (1992) Tetrahedron Lett 33:2455
184. Burova SA, McDonald FE (2002) J Am Chem Soc 124:8188
185. Martin HJ, Drescher M, Mulzer J (2000) Angew Chem Int Ed 39:581
186. Wang Z, Schreiber SL (1990) Tetrahedron Lett 31:312
187. Rinehart K, Maheshwari ML, Antosz FJ, Mathur HH, Sasaki K, Schacht RJ (1971) J Am Chem Soc 93:6273
188. Rinehart KL, Antosz FJ, Sasaki K, Martin PK, Maheshwari ML, Reussre F, Li HL, Moran D, Wiley PF (1974) Biochemistry 13:861
189. Miyashita M, Shiratani T, Kawamine K, Hatakeyama S, Miyazawa M, Irie H (1996) Chem Commun, p 1027
190. Banik BK, Barakat KJ, Wagle DR, Manhas MS, Bose AK (1999) J Org Chem 64:5746
191. Sharma A, Kumar V, Sinha AK (2006) Adv Synth Catal 348:354
192. Arefalk A, Larhed M, Hallberg A (2005) J Org Chem 70:938
193. Berthold H, Schotten T, Honig H (2002) Synthesis 11:1607
194. Daga MC, Taddei M, Varchi G (2001) Tetrahedron Lett 42:5191