CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200700177

Microwave-Assisted Transition-Metal-Catalyzed Synthesis of N-Shifted and Ring-Expanded Buflavine Analogues

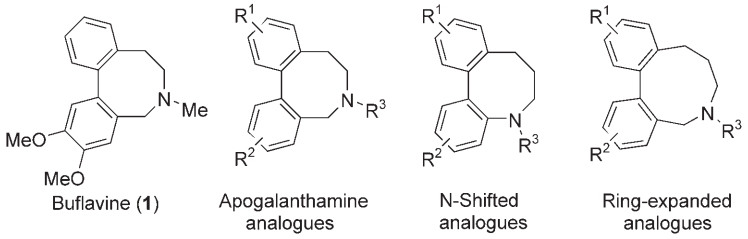
Prasad Appukkuttan,[a, b] Wim Dehaen,[a] and Erik Van der Eycken*[a]

Abstract: Two novel and efficient strategies for the synthesis of hitherto unknown N-shifted and ring-expanded buflavine analogues are presented. Construction of the medium-sized ring system of the title molecules, a difficult task due to the high activation energy needed for the ring-closure with the additional rigidity imposed by the biaryl skeleton, was achieved by using Suzuki–Miyaura biaryl coupling and a ring-closing metathesis reaction as the key steps. The combination of a second-generation Grubbs catalyst and microwave irradiation proved to be highly useful in generating the otherwise difficult to obtain medium-sized ring system of the buflavine analogues.

Keywords: buflavine · cross-coupling · medium-sized rings · metathesis · microwave irradiation

Introduction

The apogalanthamine analogues[1] feature a unique 5,6,7,8-tetrahydrodibenzo-[*c*,*e*]azocine skeleton composed of a biaryl-fused eight-membered N-heterocyclic ring system. Isolated from an endemic *amaryllidaceae* alkaloid species *Boophane flava*, buflavine[2] (**1**), a typical member of this family, exhibits interesting α-adrenolytic and anti-serotonin activities (Scheme 1).[3] Despite the intriguing biological potential of this class of natural products, few efforts have been made towards the synthesis of analogues since the pioneering work of Kobayashi et al.[4] Their approaches were mainly based on Ullmann-type[5] or photochemical[6] coupling reactions for the key biaryl-forming step. However, as these protocols are associated with rather low yields, long reaction times, and a strong dependence on the nature of the substituents on the aryl components, they are not efficient for the generation of structurally diverse libraries for screening purposes. To date, only four total syntheses of buflavine (**1**) have been reported,[7] based on various biaryl formation strategies, while little effort has been made towards an efficient and general protocol for the generation of structurally diverse analogues.



Scheme 1. The 5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocines and buflavine (**1**).

We have previously demonstrated[8] the usefulness of microwave irradiation in promoting difficult Suzuki–Miyaura cross-coupling reactions of highly electron-rich aryl halides, en route to the synthesis of apogalanthamine analogues. As part of our ongoing research on the synthesis of difficult to obtain natural product analogues possessing a biaryl-fused medium-sized ring, we have devised a novel and efficient strategy for the generation of N-shifted and ring-expanded buflavine (**1**) analogues.[9] This strategy relies on the combination of a Suzuki–Miyaura reaction[10] of highly electron-rich aryl halides, to generate the biaryl axes, followed by ring-closing metathesis (RCM)[11] to construct the medium-sized ring. The formation of the medium-sized ring systems by RCM is rather difficult due to the high activation energy needed for the ring-closure, and the additional rigidity im-

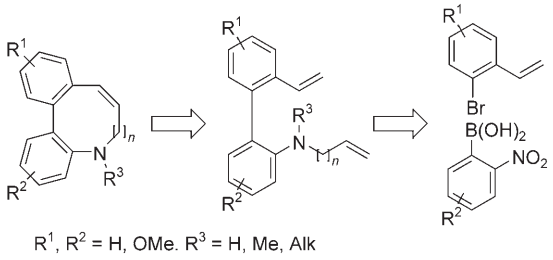
[a] Dr. P. Appukkuttan, Prof. W. Dehaen, Prof. Dr. E. Van der Eycken
Department of Chemistry, University of Leuven
Celestijnenlaan 200F, 3001 Leuven (Belgium)
Fax: (+32) 16-327990
E-mail: Erik.Vandereycken@chem.kuleuven.be

[b] Dr. P. Appukkuttan
Current Address: Department of Medicinal Chemistry
Uppsala Biomedical Centre (BMC), Uppsala University
P.O. Box 574, 75123 Uppsala (Sweden)

posed by the stiff biaryl backbone presented a considerable challenge to our methodology. We have previously demonstrated that both reactions benefit greatly from microwave irradiation.[9] Herein, we discuss the application of our methodology in full detail.

Results and Discussion

Synthesis of N-shifted buflavine analogues: As is apparent from the retrosynthetic scheme (Scheme 2), the success of

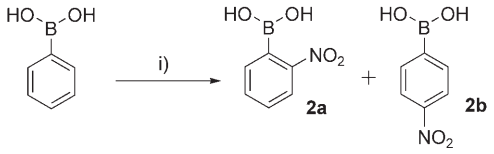


Scheme 2. Retrosynthetic analysis for N-shifted buflavine analogues.

our strategy depends on two key steps: a Suzuki–Miyaura coupling to generate the required biaryl intermediates and an RCM reaction to generate the medium-sized ring system of the title molecules.

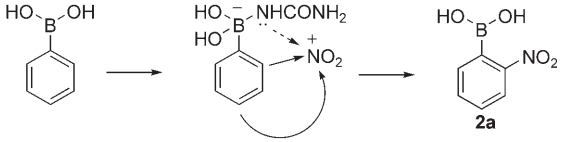
The required intermediates for the cross-coupling, a suitably functionalized *o*-bromostyrene and *o*-nitrophenylboronic acid, could be easily generated from inexpensive and commercially available starting materials. We chose to incorporate electron-rich substituents in the biaryl skeleton, with a view to keeping semblance with buflavine (**1**). Furthermore, the combination of a highly electron-rich aryl bromide with a boronic acid bearing an electron-withdrawing group at the *ortho* position poses an interesting challenge to the Suzuki–Miyaura cross-coupling, owing to the slow oxidative addition of the catalyst to the C–Br bond as well as the possibility of proto-deboronation of the boronic acid. We envisaged that our microwave-assisted cross-coupling protocol could be highly beneficial in circumventing these problems.[8,9,12] We also envisaged that the possibility of a competing Heck reaction,[13] promoted by complexation of the π-electrons of the double bond to the transition-metal catalyst, would make it an interesting challenge to our previously established cross-coupling strategy.

To evaluate our strategy, we decided to investigate the biaryl coupling by applying the unsubstituted 2-nitrophenylboronic acid (**2a**). This could be generated by regioselective nitration of the inexpensive and commercially available phenylboronic acid using 100% nitric acid in the presence of a catalytic amount of urea at −15°C for 3 h.[14] The desired product **2a** was obtained in a good yield of 63% with excellent regioselectivity (*ortho*:*para* 96:4) (Scheme 3).



Scheme 3. Synthesis of 2-nitrophenylboronic acid (**2a**): i) HNO_3 (100%), Ac_2O, urea (cat.), −15°C, 3 h, 63% combined yield (*ortho*:*para* 96:4).

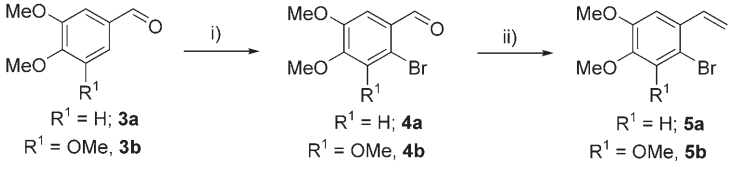
A detailed study aimed at tuning the selectivity of the nitration revealed that the temperature was critical. When the reaction was performed at −25°C, a period of 7 h was required to reach completion. However, at 0°C, the reaction was found to proceed too vigorously, resulting in decomposition of the boronic acid to a dark and tarry mass. The addition of a catalytic amount of urea seemed to be essential for obtaining high regioselectivity, as, in the absence of urea, a lower yield of 58% with predominant *para*-selectivity (*ortho*:*para* 36:64) was obtained. Although we are unaware of any literature precedent for this kind of ate-formation of urea and boronic acids, the experimental results lead us to believe that the mechanism of nitration most likely involves the attachment of one of the urea nitrogen atoms to the boron, such that it might act as a handle capable of directing the reactive nitronium ion to the *ortho* position (Scheme 4).



Scheme 4. Regioselective nitration of phenylboronic acid.

The methoxylated *ortho*-bromostyrenes **5a**,**b**, needed for the Suzuki–Miyaura cross-coupling, were generated in yields of 89 and 86%, respectively, starting from commercially available 3,4-dimethoxybenzaldehyde (**3a**) and 3,4,5-trimethoxybenzaldehyde (**3b**), by way of regioselective bromination using bromine in methanol (Scheme 5).[15]

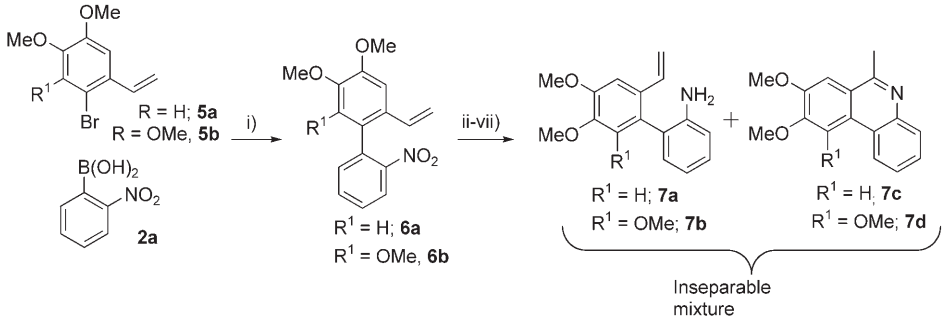
To achieve Wittig olefination,[16] aldehydes **4a**,**b** were treated with methyl(triphenyl)phosphonium bromide in THF, using *n*BuLi as the base at room temperature. The reactions proceeded smoothly, furnishing the corresponding



Scheme 5. Synthesis of bromostyrenes **5a**,**b**: i) Br_2, MeOH, RT, 1–3 h, 89% (**4a**), 86% (**4b**); ii) $MePPh_3Br$, *n*BuLi, THF, RT, 3 h, 89% (**5a**), 93% (**5b**).

styrenes **5a**,**b** in good yields of 89 and 93%, respectively.[17]

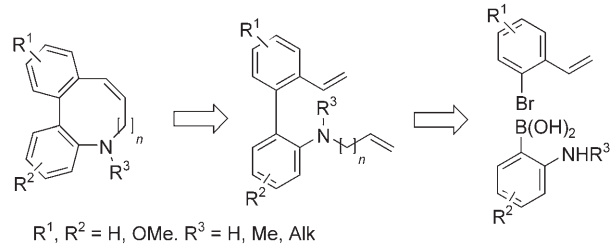
Having the required Suzuki counterparts at hand, we envisaged the cross-coupling reaction to generate the required biaryl intermediates **6a**,**b** (Scheme 6). From previous research,[8,18] we knew already that this coupling of electron-rich aryl bromides with a boronic acid, which is prone to proto-deboronation, would be difficult to achieve by applying conventional heating conditions. We therefore decided to directly investigate this cross-coupling reaction under microwave irradiation conditions. According to our optimized protocol,[17] boronic acid **2a** and styrene **5a** were reacted with $NaHCO_3$ as base and $[Pd(PPh_3)_4]$ as catalyst in a 1:1 mixture of DMF and water, using a pre-selected maximum temperature of 150°C and a maximum irradiation power of 150 W. To our satisfaction, the reaction was completed in 15 min and biaryl compound **6a** was isolated in an excellent yield of 84% with a negligible degree of proto-deboronation, and no homo-coupling products were observed. Following the same procedure, the trimethoxy analogue **6b** was synthesized in 82% yield, starting from boronic acid **2a** and styrene **5b**.



Scheme 6. Attempts to generate the biaryl anilines **7a**,**b**: i) $NaHCO_3$ (3.0 equiv), $[Pd(PPh_3)_4]$ (5 mol%), DMF/H_2O (1:1), 150 W, 150°C, 15 min, 84% (**6a**), 82% (**6b**); ii) $SnCl_2$, HCl (aq.), reflux, 12 h; iii) Sn, HCl (aq.), EtOH, reflux, 12 h; iv) Sn, NH_4OH (aq.), EtOH, reflux, 12 h; v) Fe, HCl (aq.), EtOH, reflux, 3 h; vi) Fe, NH_4OH (aq.), EtOH, reflux, 3 h; vii) Pd/C (10%), H_2, MeOH, RT, 2 h.

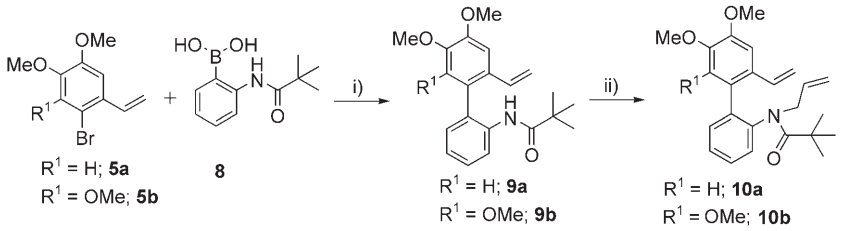
However, the subsequent reduction of the nitro group of **6a**,**b** turned out to be problematic as all attempted common reduction protocols,[19] using either $SnCl_2$ or granular tin, failed, even after prolonged heating (Scheme 6). Invariably, the starting compounds **6a**,**b** were recovered. Although the use of iron in refluxing EtOH with either 6N HCl or with NH_4OH was found to reduce the nitro group, a complex mixture was obtained, containing, for example, the phenanthridines **7c**,**d**. Attempts to perform catalytic hydrogenation, using Pd/C (10%) in MeOH, failed to furnish any substantial amount of the target anilines **7a**,**b**.

We therefore decided to redesign our retrosynthetic scheme, starting directly from a suitably protected aniline, thereby avoiding the problematic reduction of the nitro compound (Scheme 7). We envisaged that the required biaryl skeleton could be reached by way of a cross-coupling reaction between an *o*-bromostyrene and a suitable aniline-derived boronic acid, which might be generated in two steps from a commercially available aniline according to a directed *ortho*-metalation protocol (D*o*M).[20]



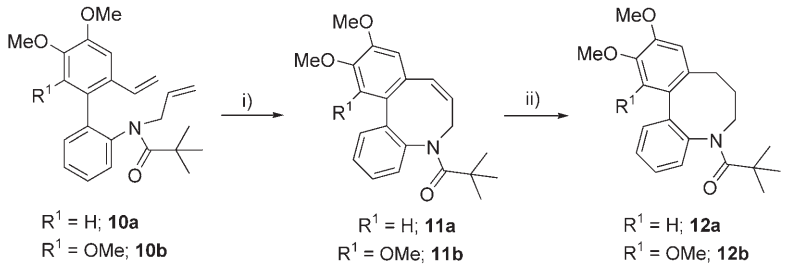
Scheme 7. Alternative retrosynthetic analysis for the synthesis of N-shifted analogues.

2-Pivaloylaminophenylboronic acid (**8**) was generated from the corresponding pivalamide, following the procedure reported by Rocca et al.[21] Subsequently, this boronic acid **8** was cross-coupled with the bromostyrenes **5a**,**b** to generate the required biaryl intermediates **9a**,**b** in excellent yields of 93 and 91%, respectively (Scheme 8). These microwave-assisted Suzuki couplings were run in a DMF/water (1:1) mixture at a ceiling temperature of 150°C in 15 min, using $NaHCO_3$ as base and $[Pd(PPh_3)_4]$ as catalyst. Finally, the second allyl handle, required for the subsequent RCM, was introduced by allylation of the aniline nitrogen by refluxing **9a**,**b** with allyl bromide in THF using NaH as base. The products **10a**,**b** were isolated in very high yields of 96 and 94%, respectively (Scheme 8).



Scheme 8. Synthesis of biaryl anilines **10a**,**b**: i) $NaHCO_3$, $[Pd(PPh_3)_4]$, DMF/H_2O (1:1), MW, 150 W, 150°C, 15 min, 93% (**9a**), 91% (**9b**); ii) NaH (80% in mineral oil), allyl bromide, THF, reflux, 6 h, 96% (**10a**), 94% (**10b**).

Having the required intermediates **10a**,**b** at hand, our next goal was to evaluate the RCM reaction for the generation of the required biaryl-fused medium-sized rings in compounds **11a**,**b** (Scheme 9). As expected, this conversion was rather troublesome. In a first run, **10a** (0.25 mmol) was



Scheme 9. Synthesis of N-shifted buflavine analogues **12a**,**b**: i) see Table 1; ii) Pd/C (10%), H_2 (30 atm), MeOH, 8 h, 94% (**12a**), 91% (**12b**).

stirred with a Grubbs first-generation (G-1) catalyst (3 mol%) in dry, degassed CH_2Cl_2 at room temperature. Unfortunately, no reaction took place even after 24 h and the starting material **10a** was fully recovered.[9] On the contrary, when the reaction was carried out at reflux temperature in CH_2Cl_2 for 3 h with G-1 (3 mol%) as the catalyst, the product **11a** was isolated in 17% yield, together with unreacted starting material **10a** (Table 1, entry 1). Increasing the reaction time to 12 h failed to improve the outcome. We

Table 1. Ring-closing metathesis to generate targets **11a**,**b**.[a]

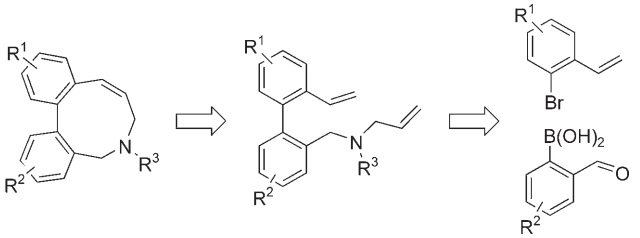
Entry	Alkene	Product	Catalyst	*t* [h]	Solvent	*T* [°C]	Yield [%][b]
1	**10a**	**11a**	G-1	3	CH_2Cl_2	reflux	17
2	**10a**	**11a**	G-2	3	$CHCl_3$	reflux	22
3	**10a**	**11a**	G-2	3	PhMe	reflux	28
4	**10a**	**11a**	G-2	3	CH_2Cl_2	reflux	32
5	**10a**	**11a**	G-2	3	$CHCl_3$	reflux	42
6	**10a**	**11a**	G-1	3	PhMe	reflux	58
7	**10a**	**11a**	G-1	5 min[c]	PhMe	150	69
8	**10b**	**11b**	G-2	3	PhMe	reflux	55
9	**10b**	**11b**	G-2	5 min[c]	PhMe	150	68

[a] All reactions were carried out on a 0.25 mmol scale with 3.0 mol% of catalyst in 5.0 mL of solvent. [b] Yield of isolated product. [c] Reactions were carried out under microwave irradiation in 3.0 mL of solvent at a maximum power level of 150 W.

therefore decided to perform the reaction at higher temperature in refluxing $CHCl_3$. This resulted in a slightly higher yield of 22%. Carrying out the reaction in refluxing toluene, a moderate 28% yield was obtained (Table 1, entries 2 and 3).

However, the use of catalyst G-2 was found to increase the yield substantially, and compound **11a** was isolated in an improved yield of 32% when the reaction was run in refluxing CH_2Cl_2. Switching to $CHCl_3$ or toluene raised the yield to 42 and 58%, respectively (Table 1, entries 4–6). As higher temperature seemed to be advantageous for the RCM, we decided to investigate the reaction upon microwave irradiation. When a sample of **10a** was irradiated in toluene, at 150°C, applying a maximum power level of 150 W, the yield of **11a** increased to 69% in a mere 5 min of irradiation time (Table 1, entry 7). As expected, only the *cis* isomer was generated in this RCM, owing to the high conformational rigidity of the ring system. Applying the same conditions, the trimethoxy analogue **11b** was synthesized in 55% yield under conventional heating conditions (Table 1, entry 8), but in a much better yield of 68% under microwave irradiation (Table 1, entry 9). To generate the target molecules **12a**,**b** and complete the synthesis, the ring-closed compounds **11a**,**b** were subjected to palladium-catalyzed hydrogenation (Scheme 9). Thereby, the N-shifted buflavine analogues **12a**,**b** were isolated in excellent yields of 94 and 91%, respectively.

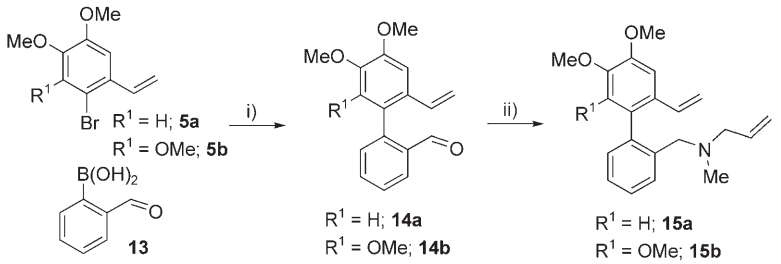
Synthesis of ring-expanded buflavine analogues: After the successful synthesis of N-shifted buflavine analogues **12a**,**b** by applying Suzuki biaryl coupling followed by an RCM reaction, we turned our attention to the synthesis of ring-expanded buflavine analogues possessing a nine-membered medium-sized ring (Scheme 10). It was envisaged that the



Scheme 10. Retrosynthetic analysis for ring-expanded buflavine analogues.

desired biaryl skeleton could be generated from the corresponding suitably functionalized styrene derivatives and *ortho*-formyl-phenylboronic acid by means of a Suzuki–Miyaura cross-coupling reaction. After introduction of the required double bond, the targeted nine-membered ring might then be constructed by an RCM reaction. It has to be stressed that, as the application of RCM for the generation of nine-membered ring systems has been scarcely documented in the literature,[22] the proposed strategy represents a real challenge.

To evaluate the usefulness of our previously optimized microwave-assisted Suzuki–Miyaura cross-coupling,[8] we chose to investigate the reaction of 2-formylphenylboronic acid (**13**) with the electron-rich *ortho*-bromostyrenes **5a**,**b** (Scheme 11). In a typical run, a mixture of **5a** (1.0 mmol),

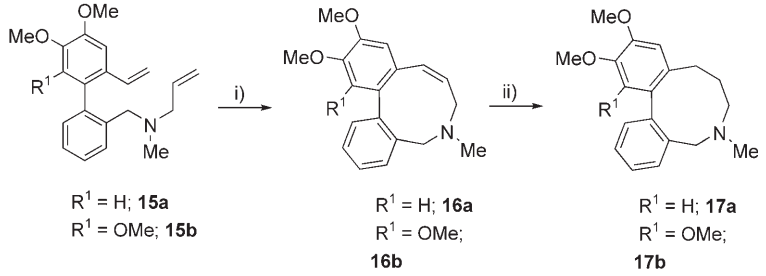


Scheme 11. Microwave-assisted Suzuki–Miyaura reaction: i) $NaHCO_3$ (3.0 equiv), $[Pd(PPh_3)_4]$ (5 mol%), DMF/H_2O (1:1), MW, 150 W, 150°C, 15 min, 92% (**14a**), 90% (**14b**); ii) a) allylamine, toluene/TFA (20:1), MW, 175°C, 3 min; b) $Na(CN)BH_3$ (5.0 mmol), MeOH, RT, 1.5 h; iii) HCHO (37% solution), RT, 1.5 h, 76% (**15a**), 74% (**15b**).

boronic acid **13** (1.3 mmol), $NaHCO_3$ (3.0 equiv), and $[Pd(PPh_3)_4]$ (5.0 mol%) in DMF/H_2O (1:1; 1.5 mL each) was sealed in a 10 mL glass vial. The mixture was then irradiated at a pre-selected ceiling temperature of 150°C for 15 min. The reaction was found to proceed smoothly, and compound **14a** was isolated in an excellent yield of 92% (Scheme 11). Applying the same conditions, we succeeded in synthesizing the trimethoxy analogue **14b** in 90% yield (Scheme 11).

Our next aim was to perform reductive aminations of the respective biaryl aldehydes **14a**,**b** with allylamine, followed by *N*-alkylations of the thus formed amines, to generate the key biaryl intermediates for RCM (Scheme 11). These conversions were tested with the least substituted aldehyde **14a**. Imination was carried out in refluxing toluene in the presence of 5% trifluoroacetic acid. When a Dean–Stark trap was used for the azeotropic removal of water, the reaction was found to be complete in 3 h. The imine, which was not isolated, was identified as the sole product of the reaction when the crude mixture was analyzed by CI-MS. Microwave irradiation was found to be extremely valuable in this regard, and the reaction was completed in a mere 3 min when the mixture was irradiated in a sealed reaction vessel at a ceiling temperature of 175°C. The presence of highly microwave-absorbing trifluoroacetic acid in the reaction mixture was useful not only for the condensation process, but also for enabling attainment of the high ceiling temperature in the reaction medium when using an almost microwave-transparent solvent such as toluene. The crude imine was reduced with an excess of $Na(CN)BH_3$ in MeOH at room temperature for 1.5 h under an inert atmosphere. Once the conversion to the corresponding amine was complete, an excess of formaldehyde was added to effect *N*-methylation. The reaction was completed after stirring for a further 1.5 h at room temperature, and the *N*-methylated amine **15a** was isolated in 76% overall yield starting from the aldehyde **14a**. Following the same procedure, the trimethoxy analogue **15b** was synthesized in 74% yield (Scheme 11).

Having obtained the necessary biaryl-amine intermediates **15a**,**b**, we proceeded to the crucial RCM reaction to generate the nine-membered ring system (Scheme 12). Although the use of Grubbs and Hoveyda first-generation catalysts (G-1 and H-1) was found to be inadequate for effecting the conversion, both under conventional heating conditions as well as under microwave irradiation (Table 2, entries 1–4), a Grubbs second-generation catalyst (G-2) was found to promote the reaction under conventional heating conditions, albeit in a low yield of 15% (Table 2, entry 5).



Scheme 12. Synthesis of ring-expanded buflavine analogues **17a**,**b**: i) RCM, see Table 1; ii) Pd/C (10%), MeOH, H_2 (30 atm.), 8 h, 94% (**17a**), 93% (**17b**).

The situation improved dramatically upon microwave irradiation of the reaction mixture. Thus, irradiating a sample of the biaryl-amine **15a** with G-2 (3 mol%) in toluene at a

Table 2. Ring-closing metathesis to generate the nine-membered ring in **16a**,**b**.[a]

Entry	Starting material	Product	Catalyst	*t* [min]	*T* [°C]	Yield [%][b]
1	**15a**	**16a**	G-1	720[c]	110[c]	0
2	**15a**	**16a**	G-1	15	125	0
3	**15a**	**16a**	H-1	720[c]	110[c]	0
4	**15a**	**16a**	H-1	15	125	0
5	**15a**	**16a**	G-2	720[c]	110[c]	15
6	**15a**	**16a**	G-2	5	125	38
7	**15a**	**16a**	G-2	10	125	44
8	**15a**	**16a**	G-2	15	125	49
9	**15a**	**16a**	G-2	15	150	55
10	**15a**	**16a**	H-2	15	150	41
11	**15b**	**16b**	G-2	15	125	42
12	**15b**	**16b**	G-2	15	150	54
13	**15b**	**16b**	H-2	15	150	39

[a] All reactions were carried out on a 0.2 mmol scale with 3.0 mol% of the catalyst in 3 mL of PhMe under microwave irradiation. [b] Yield of isolated product. [c] Experiments were carried out under conventional heating conditions in 5 mL of PhMe.

pre-selected temperature of 125 °C for 5 min was found to effect the conversion and the desired product **16a** was isolated in a moderate yield of 38 % (Table 2, entry 6). Increasing the reaction time to 10 and 15 min was found to furnish better yields of 44 and 49 %, respectively (Table 2, entries 7 and 8). The yield was further improved to 55 % when the reaction temperature was elevated to 150 °C (Table 2, entry 9). As expected, the *cis*-isomer was the only product generated by the RCM, owing to the high conformational rigidity of the ring system. Further increase of the reaction time and/or temperature was found to be ineffective. Changing the catalyst from G-2 to H-2 resulted in a decrease in the yield to 41 % (Table 2, entry 10). The trimethoxy analogue **16b** was likewise synthesized in a good yield of 54 % under the same microwave-assisted conditions (Table 2, entry 12).

To complete the sequence, the dihydrodibenzo[*c*,*e*]azonines **16a**,**b** were converted to the corresponding tetrahydrodibenzo[*c*,*e*]azonines **17a**,**b** by way of a palladium-catalyzed hydrogenation protocol (Scheme 12) using a high-pressure Parr hydrogenation apparatus. The reactions were run in MeOH at a hydrogen pressure of 30 atm for 8 h. The products **17a**,**b** were isolated in yields of 94 and 93 %, respectively.

Conclusion

We have developed two novel, flexible, and efficient strategies for the synthesis of N-shifted and ring-expanded buflavine analogues based on a Suzuki–Miyaura biaryl coupling followed by a ring-closing metathesis reaction for the construction of the medium-sized ring. The Suzuki–Miyaura reaction, which is often problematic in instances of cross-coupling between an electron-rich aryl halide and an electron-poor boronic acid, has been successfully applied under conditions of microwave irradiation. The combination of a second-generation Grubbs catalyst and microwave irradiation has proved to be highly useful in generating the otherwise difficult to synthesize eight- and nine-membered ring systems.

Experimental Section

General remarks: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 or Bruker 300 Avance instrument. The ^{1}H chemical shifts are reported in ppm relative to tetramethylsilane, using the residual solvent signal as an internal reference. ^{13}C chemical shifts are referenced to $CDCl_3$ as an internal standard, unless otherwise stated. Low-resolution mass spectra were obtained with a Hewlett–Packard MS Engine 5989 A instrument. High-resolution mass spectra were recorded by using a Kratos MS50 TC (ionization energy 70 eV) and a Kratos Mach III data system. The ion source temperature was 150–300 °C as required. High-resolution EI-mass spectra were measured with a resolution of 10000. For thin-layer chromatography, Alugram SIL G/UV_{254} analytical TLC plates (E. M. Merck) were used. Column chromatography was carried out using 70–230 mesh silica gel 60 (E. M. Merck). All compounds were characterized by ^{1}H, ^{13}C, and DEPT NMR, as well as by EI-MS. All commercially available compounds were purchased from Aldrich and were used without further purification.

Microwave irradiation experiments: All microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W, utilizing the standard absorbance level of 300 W maximum power. The reactions were carried out in 10 mL sealed glass tubes capable of withstanding exposure to 250 °C and 20 bar internal pressure. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was rapidly cooled (60–120 s) to ambient temperature by air-jet cooling.

Representative procedure for the bromination of aldehydes 3a,b

2-Bromo-4,5-dimethoxybenzaldehyde[23] **(4a)**: 3,4-Dimethoxybenzaldehyde **3a** (1.66 g, 10.0 mmol) was dissolved in dry, degassed MeOH (50 mL) and the resulting solution was stirred under argon. Bromine (0.52 mL, 10.5 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, as evidenced by TLC and CI-MS analyses, the solvent was evaporated and the residual mixture was partitioned between DCM (50 mL) and saturated aqueous $Na_2S_2O_3$ solution (50 mL). The aqueous layer was extracted once with DCM (50 mL), and the combined organic layers were washed sequentially with brine (25 mL) and water (25 mL). The solvent was removed under reduced pressure to furnish the bromoaldehyde **4a**, which was used without further purification.

Representative procedure: Wittig reaction in the synthesis of alkenes 5a,b

1-Bromo-4,5-dimethoxy-2-vinylbenzene[24] **(5a)**: *n*BuLi (2.5 M in hexanes, 1 mL) was slowly added to a stirred solution of methyl(triphenyl)phosphonium bromide (0.89 g, 2.5 mmol) in dry, degassed THF (20 mL) at room temperature under an argon atmosphere. The resultant yellowish solution was stirred for an additional 15 min until the deep yellow color of the ylide developed. A solution of 2-bromo-4,5-dimethoxybenzaldehyde (**4a**, 0.61 g, 2.5 mmol) in dry THF (10 mL) was then added by means of a hypodermic syringe, whereupon the color of the reaction mixture soon started to fade. The resultant off-white solution was stirred at room temperature for an additional 3 h, whereupon TLC and CI-MS analyses indicated completion of the reaction. After NH_4Cl work-up, the organic components were extracted with DCM (3×25 mL) and the combined organic layers were washed with brine (25 mL) and water (25 mL) and finally dried over $MgSO_4$. Removal of the solvents under reduced pressure left the styrene **5a** as a thick yellow oil, which was further purified by column chromatography (silica gel; heptane/diethyl ether 3:2) to furnish the pure product (0.54 g, 89 %).

General procedure: microwave-assisted Suzuki–Miyaura reaction for the synthesis of 2-nitro-biaryls 6a,b: Aryl bromide **5a**,**b** (0.25 mmol), boronic acid **2a** (0.325 mmol, 1.30 equiv), $NaHCO_3$ (0.75 mmol, 3.0 equiv), and $[Pd(PPh_3)_4]$ (5 mol %) were suspended in DMF (1.5 mL) and water (1.5 mL) and the vial was tightly sealed. The mixture was irradiated for 15 min at a pre-selected temperature of 150 °C, using a maximum irradiation power of 100 W. After the reaction, the vial was cooled to 60 °C by air-jet cooling. The crude mixture was partitioned between diethyl ether (25 mL) and water (25 mL) and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure to yield the crude product as a yellow oil. Column chromatography (silica gel; heptane/diethyl ether 3:2) afforded the 2-nitro-biaryls **6a**,**b** as yellowish oily materials.

Synthesis of biaryl 6a by Suzuki–Miyaura reaction: Biaryl **6a** was synthesized according to the general procedure for a microwave-assisted Suzuki–Miyaura reaction from styrene **5a** (0.48 g, 2.0 mmol), boronic acid **2a** (0.43 g, 2.6 mmol), $NaHCO_3$ (0.5 g, 6.0 mmol), and $[Pd(PPh_3)_4]$ (0.12 g, 5 mol %), using a maximum irradiation power of 150 W. After chromatographic purification (silica gel; heptane/diethyl ether 3:2), analytically pure product **6a** was isolated as a yellow oily material (0.48 g, 84 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.81$ (d, $J = 8.2$ Hz, 1H), 7.38 (dd, $J = 7.8$, 0.4 Hz, 1H), 7.34 (s, 1H), 7.33 (d, $J = 7.1$ Hz, 1H), 7.01 (s, 1H), 7.00 (dd, $J = 7.0$, 0.4 Hz, 1H), 6.85 (dd, $J = 11.1$, 17.3 Hz, 1H), 5.60 (dd,

J=17.3, 1.7 Hz, 1H), 5.20 (dd, J=11.1, 1.7 Hz, 1H), 3.87 (s, 3H), 3.81 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.1, 147.7, 147.3, 137.0, 136.8, 136.1, 134.5, 134.5, 133.6, 131.4, 129.0, 127.5, 115.6, 112.7, 56.0, 55.9 ppm; DEPT (100 MHz, $CDCl_3$): δ=137.0, 133.6, 129.0, 127.5, 115.6, 115.2, 112.7, 56.0, 55.9 ppm; MS (EI): m/z (%): 285 (100), 244, 239, 198.

Synthesis of biaryl 6b by a Suzuki–Miyaura reaction: Biaryl **6b** was synthesized according to the general procedure for a microwave-assisted Suzuki–Miyaura reaction from styrene **5b** (0.54 g, 2.0 mmol), boronic acid **2a** (0.43 g, 2.6 mmol), $NaHCO_3$ (0.5 g, 6.0 mmol), and $[Pd(Ph_3P)_4]$ (0.12 g, 5 mol%), using a maximum irradiation power of 150 W. After chromatographic purification (silica gel; heptane/diethyl ether 3:2), analytically pure product **6b** was isolated as a yellow oily material (0.52 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.89 (d, J=8.2 Hz, 1H), 7.39 (dd, J=7.5, 0.3 Hz, 1H), 7.11 (d, J=7.8 Hz, 1H), 6.96 (dd, J=7.5, 0.7 Hz, 1H), 6.85 (s, 1H), 6.83 (dd, J=11.0, 17.3 Hz, 1H), 5.56 (dd, J=17.3, 1.7 Hz, 1H), 5.24 (dd, J=11.0, 1.7 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.79 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.9, 149.6, 143.3, 140.1, 136.4, 136.1, 134.7, 133.6, 132.6, 129.6, 128.9, 124.6, 115.1, 103.2, 61.1, 60.9, 56.2 ppm; DEPT (100 MHz, $CDCl_3$): δ=136.4, 134.7, 132.6, 129.6, 128.9, 115.1, 103.2, 61.1, 60.9, 56.2 ppm; MS (EI): m/z (%): 315 (100%), 274, 269, 228.

Synthesis of 4′,5′-dimethoxy-2′-vinyl-1,1′-biphenyl-2-carbaldehyde (14a): The biphenyl carbaldehyde **14a** was synthesized from bromostyrene **5a** (0.24 g, 1 mmol), boronic acid **13** (0.20 g, 1.3 mmol), $NaHCO_3$ (0.25 g, 3.0 mmol), and $[Pd(PPh_3)_4]$ (0.6 g, 5 mol%) according to the general procedure for a microwave-assisted Suzuki–Miyaura reaction, using a maximum power level of 100 W. Column chromatography (silica gel; heptane/diethyl ether 3:2) afforded the analytically pure product **14a** (0.25 g, 92%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.21 (s, 1H), 8.53 (d, J=8.1 Hz, 1H), 7.47 (d, J=8.1 Hz, 1H), 7.42 (s, 1H), 7.12 (s, 1H), 6.86 (dd, J=17.3, 11.0 Hz, 1H), 6.76 (t, J=8.1 Hz, 1H), 6.50 (t, J=8.1 Hz, 1H), 5.56 (dd, J=17.3, 1.7 Hz, 1H), 5.20 (dd, J=11.0, 1.7 Hz, 1H), 3.87 (s, 3H), 3.81 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.9, 149.3, 148.7, 148.3, 141.9, 136.8, 133.6, 131.6, 130.4, 127.9, 127.1, 122.9, 121.4, 115.2, 111.9, 56.0, 55.9 ppm; DEPT (75 MHz, $CDCl_3$): δ=190.9, 136.8, 133.6, 130.4, 127.9, 122.9, 121.4, 115.2, 111.9, 56.0, 55.9 ppm; MS (EI): m/z (%): 268 (100%), 239, 198; HRMS (EI): m/z (%): calcd for $C_{17}H_{16}O_3$: 268.10994; found: 268.10991.

Synthesis of 2′,3′,4′-trimethoxy-6′-vinyl-1,1′-biphenyl-2-carbaldehyde (14b): The biphenyl carbaldehyde **14b** was synthesized from bromostyrene **5b** (0.27 g, 1.0 mmol), boronic acid **13a** (0.20 g, 1.3 mmol), $NaHCO_3$ (0.25 g, 3.0 mmol), and $[Pd(PPh_3)_4]$ (0.6 g, 5 mol%) according to the general procedure for a microwave-assisted Suzuki–Miyaura reaction, using a maximum power level of 100 W. Column chromatography (silica gel; heptane/diethyl ether 3:2) afforded the analytically pure product **14b** (0.27 g, 90%) as a yellowish oily material. ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.97 (s, 1H), 8.57 (dd, J=17.8, 11.3 Hz, 1H), 8.30 (d, J=7.7 Hz, 1H), 7.95 (s, 1H), 7.66 (t, J=7.7 Hz, 1H), 7.23 (d, J=8.1 Hz, 1H), 6.54 (t, J=8.1 Hz, 1H), 5.48 (dd, J=17.8, 1.7 Hz, 1H), 5.21 (dd, J=11.3, 1.7 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.77 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=191.0, 154.3, 154.1, 144.5, 139.3, 138.8, 135.2, 134.7, 129.0, 128.9, 127.2, 121.2, 115.8, 115.1, 102.4, 61.1, 60.9, 56.2 ppm; DEPT (75 MHz, $CDCl_3$): δ=191.0, 138.8, 134.7, 129.0, 127.2, 121.2, 115.1, 102.4, 61.1, 60.9, 56.2 ppm; MS (EI): m/z (%): 298 (100%), 269, 228; HRMS (EI): m/z (%): calcd for $C_{18}H_{18}O_4$: 298.12051; found: 298.12055.

Synthesis of *N*-[{4′,5′-dimethoxy-2′-vinyl-(1,1′-biphenyl)-2-yl}methyl]-*N*-methyl-2-propen-1-amine (15a) under microwave irradiation: Biaryl aldehyde **14a** (0.13 g, 0.5 mmol) was dissolved in PhMe (2.85 mL) and the solution was transferred to a 10 mL glass vial equipped with a small stirring magnet. TFA (0.15 mL) was then added, which led to an immediate darkening of the golden-yellow solution. The vial was tightly sealed and irradiated at a pre-selected temperature of 175 °C for 3 min, using a maximum power level of 150 W. It was then returned to room temperature by air-jet cooling and the contents were transferred to a 50 mL round-bottomed flask by rinsing with dry, degassed MeOH (3×5 mL). The resulting methanolic solution was thoroughly flushed with argon, and then $Na(CN)BH_3$ (0.32 g, 5.0 mmol) was added in a portionwise manner. Vigorous evolution of H_2 gas was observed and the solution took on a pale-yellow hue. Stirring was continued for a further 1.5 h, whereupon TLC and CI-MS analyses indicated completion of the reaction. HCHO (37% aqueous solution, 0.15 mL) was then added by means of a hypodermic syringe and stirring was continued for a further 1.5 h, whereupon the reaction was found to be complete. The solvents were then removed under reduced pressure and the residue was redissolved in EtOAc (50 mL). The resulting solution was stirred at room temperature for 30 min with an excess of K_2CO_3 (2.5 g). The mixture was then filtered through a small pad of silica and the pad was repeatedly washed with EtOAc (3×10 mL) and DCM (2×10 mL). The organic layers were combined and the solvents were removed under reduced pressure. The crude residue was purified by column chromatography (silica gel; DCM/MeOH 9:1) to afford the analytically pure product **15a** (0.12 g, 76% from **14a**) as a deep yellow oil. ^{1}H NMR (400 MHz, MeOD): δ=8.52 (dd, J=17.8, 11.3 Hz, 1H), 7.59 (s, 1H), 7.58 (d, J=7.9 Hz, 1H), 7.24 (t, J=8.0 Hz, 1H), 7.21 (t, J=7.5 Hz, 1H), 7.09 (s, 1H), 6.69 (d, J=7.5 Hz, 1H), 5.71–5.83 (m, 1H), 5.56 (dd, J=17.8, 1.7 Hz, 1H), 5.20 (dd, J=11.3, 1.3 Hz, 1H), 5.05 (dd, J=16.4, 1.3 Hz, 1H), 5.00 (dd, J=10.3, 1.3 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 2H), 3.81 (s, 3H), 3.11 (d, J=5.3 Hz, 1H), 2.28 ppm (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ=151.6, 144.9, 142.3, 134.7, 133.9, 133.6, 131.6, 131.3, 131.0, 129.2, 127.8, 126.4, 117.4, 116.5, 115.2, 115.1, 57.7, 56.5, 56.0, 55.9, 43.8 ppm; DEPT (100 MHz, MeOD): δ=133.9, 133.6, 131.6, 129.2, 126.4, 117.4, 116.5, 115.2, 115.1, 57.7, 56.5, 56.0, 55.9, 43.8 ppm; MS (EI): m/z (%): 323 (100%), 282, 267, 253, 226; HRMS (EI): m/z (%): calcd for $C_{21}H_{25}NO_2$: 323.18853; found: 323.18856.

Synthesis of *N*-methyl-*N*-[{2′,3′,4′-trimethoxy-6′-vinyl-(1,1′-biphenyl)-2-yl}methyl]-2-propen-1-amine (15b) under microwave irradiation: Amine **15b** was synthesized from the biaryl aldehyde **14b** (0.15 g, 0.5 mmol) following the procedure for the synthesis of **15a**. Column chromatography (silica gel; DCM/MeOH 9:1) afforded the analytically pure product **15b** (0.13 g, 76% from **14b**) as a deep yellow oil. ^{1}H NMR (400 MHz, MeOD): δ=7.23 (d, J=8.1 Hz, 1H), 6.94 (d, J=8.1 Hz, 1H), 6.83 (dd, J=17.3, 11.30 Hz, 1H), 6.69 (d, J=7.5 Hz, 1H), 6.64 (s, 1H), 6.58 (t, J=7.5 Hz, 1H), 6.28 (t, J=8.1 Hz, 1H), 5.80–5.92 (m, 1H), 5.56 (dd, J=17.3, 1.6 Hz, 1H), 5.09–5.22 (m, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.80 (s, 2H), 3.79 (s, 3H), 3.10 (d, J=4.95 Hz, 1H), 2.29 ppm (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ=150.5, 148.8, 142.6, 136.9, 134.7, 134.3, 133.3, 131.8, 131.0, 129.3, 127.4, 126.3, 117.4, 116.2, 115.1, 105.7, 61.1, 60.9, 60.5, 58.5, 56.2, 46.0 ppm; DEPT (100 MHz, MeOD): δ=134.7, 134.3, 133.3, 131.0, 127.4, 126.3, 117.4, 115.1, 105.7, 61.1, 60.9, 60.5, 58.5, 56.2, 46.0 ppm; MS (EI): m/z (%): 353 (100%), 312, 297, 283, 256; HRMS (EI): m/z (%): calcd for $C_{22}H_{27}NO_3$: 353.19909; found: 353.19916.

General procedure for the synthesis of dihydrodibenzo[*c*,*e*]azonines 16a,b by ring-closing metathesis under microwave irradiation: The *N*-allyl derivative **15a**,**b** (0.25 mmol) was dissolved in dry, degassed solvent (Table 1, 3 mL) and then the catalyst (Table 1, 3 mol%) was added to this solution. The vial was tightly sealed and the mixture was irradiated at a maximum power level of 150 W, for the time and at the temperature indicated in Table 1. The mixture was then diluted with DCM (25 mL) and washed with brine (10 mL), saturated $NaHCO_3$ solution (10 mL), and H_2O (10 mL), and dried over $MgSO_4$. After removal of the solvent, the crude mixture was purified by column chromatography (silica gel; DCM/MeOH 9:1) to furnish pure products **16a**,**b** in the yields noted in Table 1.

11,12-Dimethoxy-6-methyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azonine (16a): ^{1}H NMR (400 MHz, MeOD): δ=7.52 (d, J=8.1 Hz, 1H), 7.41 (s, 1H), 7.30–7.38 (m, 3H), 6.85 (s, 1H), 6.53–6.60 (m, 1H), 6.56 (d, J=11.4 Hz, 1H), 5.79 (dt, J=11.4, 1.9 Hz, 1H), 4.71 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.29 (d, J=1.9 Hz, 1H), 2.28 ppm (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ=154.8, 150.3, 142.6, 142.1, 139.8, 134.2, 131.8, 131.7, 129.8, 129.2, 127.5, 124.9, 115.8, 114.7, 61.4, 56.0, 55.9, 55.9, 55.4, 42.2 ppm; DEPT (100 MHz, MeOD): δ=131.8, 131.7, 129.8, 129.2, 127.5, 124.9, 115.8, 114.7, 61.4, 56.0, 55.9, 55.4, 42.2 ppm; MS (EI): m/z (%): 295 (100%), 280, 214; HRMS (EI): m/z (%): calcd for $C_{19}H_{21}NO_2$: 295.15723; found: 295.15724.

11,12,13-Trimethoxy-6-methyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azonine (16b): ^{1}H NMR (400 MHz, MeOD): δ=8.00 (d, J=8.0 Hz, 1H), 7.65 (t, J=8.0 Hz, 1H), 7.41 (t, J=8.0 Hz, 1H), 7.09 (d, J=8.0 Hz, 1H), 6.99 (s,

1H), 6.52 (d, $J=11.4$ Hz, 1H), 5.82 (dt, $J=11.4$, 1.9 Hz, 1H), 4.61 (s, 2H), 3.88 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.27 (d, $J=1.9$ Hz, 1H), 2.29 ppm (s, 3H); ^{13}C NMR (100 MHz, MeOD): $\delta=152.1$, 150.6, 142.9, 139.1, 134.2, 133.7, 131.8, 131.7, 131.0, 127.4, 127.3, 125.9, 118.1, 104.4, 60.9, 60.4, 59.5, 56.0, 55.4, 42.2 ppm; DEPT (100 MHz, MeOD): $\delta=$ 131.8, 131.7, 131.0, 127.4, 127.3, 125.9, 104.4, 60.9, 60.4, 59.5, 55.4, 42.2 ppm; MS (EI): *m*/*z* (%): 325 (100%), 310, 244; HRMS (EI): *m*/*z* (%): calcd for $C_{20}H_{23}NO_3$: 325.16779; found: 325.16781.

General procedure: synthesis of dihydrodibenzo[*c*,*e*]azonines 17a,b: The cyclized compound **16a**,**b** (0.25 mmol) was dissolved in dry, degassed MeOH (25 mL) and the solution was transferred to a high-pressure Parr hydrogenation bottle. 10% Pd/C (10 mol%) was added and the vessel was repeatedly evacuated and flushed with hydrogen (4×). The mixture was then kept under hydrogen pressure (30 atm) for 8 h, whereupon TLC and CI-MS analyses showed completion of the reaction. The contents of the vessel were then filtered though a small pad of Celite and the pad was repeatedly washed with DCM (3×25 mL). The solvents were removed under reduced pressure to furnish the crude products **17a**,**b**, which were further purified by column chromatography (silica gel; DCM/MeOH 9:1) to furnish the pure products as pale-yellow oils.

11,12-Dimethoxy-6-methyl-6,7,8,9-tetrahydro-5*H*-dibenzo[*c*,*e*]azonine (17a): Compound **17a** was synthesized from the cyclized compound **16a** (0.25 mmol) according to the general procedure. Column chromatography (silica gel; DCM/MeOH 9:1) afforded the pure product **17a** (0.07 g, 94%) as a pale yellow oil. ^{1}H NMR (400 MHz, MeOD): $\delta=7.84$ (s, 1H), 7.40 (d, $J=8.3$ Hz, 1H), 7.29–7.36 (m, 2H), 6.61 (d, $J=8.5$ Hz, 1H), 6.34 (s, 1H), 4.31 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.79 (t, $J=7.0$ Hz, 2H), 2.32 (s, 3H), 2.26 (dt, $J=7.0$, 0.8 Hz, 2H), 1.46 ppm (m, 2H); ^{13}C NMR (100 MHz, MeOD): $\delta=153.9$, 151.4, 141.9, 140.3, 138.2, 135.7, 129.0, 127.9, 127.5, 126.0, 117.7, 112.8, 60.4, 60.3, 56.0, 55.8, 47.1, 34.3, 29.7 ppm; DEPT (100 MHz, MeOD): $\delta=129.0$, 127.9, 127.5, 126.0, 117.7, 112.8, 60.4, 60.3, 56.0, 55.8, 47.1, 34.3, 29.7 ppm; MS (EI): *m*/*z* (%): 297 (100%), 282, 214; HRMS (EI): *m*/*z* (%): calcd for $C_{19}H_{23}NO_2$: 297.17288; found: 297.17294.

11,12,13-Trimethoxy-6-methyl-6,7,8,9-tetrahydro-5*H*-dibenzo[*c*,*e*]azonine (17b): Compound **17b** was synthesized from the cyclized compound **16b** (0.25 mmol) according to the general procedure. Column chromatography (silica gel; DCM/MeOH 9:1) afforded the pure product **17b** (0.08 g, 93%) as a pale yellow oil. ^{1}H NMR (400 MHz, MeOD): $\delta=7.72$ (d, $J=$ 8.0 Hz, 1H), 7.07 (d, $J=8.0$ Hz, 1H), 6.79 (t, $J=8.1$ Hz, 1H), 6.58 (t, $J=$ 8.1 Hz, 1H), 6.54 (s, 1H), 4.35 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.44 (t, $J=7.0$ Hz, 2H), 3.42 (s, 3H), 2.31 (s, 3H), 2.28 (dt, $J=7.0$, 0.8 Hz, 2H), 1.49 ppm (m, 2H); ^{13}C NMR (100 MHz, MeOD): $\delta=154.0$, 151.6, 144.0, 138.4, 134.3, 129.8, 128.2, 127.8, 127.4, 124.0, 108.0, 61.1, 60.9, 60.4, 60.3, 56.1, 47.1, 34.7, 29.7 ppm; DEPT (100 MHz, MeOD): $\delta=129.8$, 127.8, 127.4, 124.0, 108.0, 61.1, 60.9, 60.4, 60.3, 56.1, 47.1, 34.7, 29.7 ppm; MS (EI): *m*/*z* (%): 327 (100%), 312, 244; HRMS (EI): *m*/*z* (%): calcd for $C_{20}H_{25}NO_3$: 327.18344; found: 327.18340.

Acknowledgements

The authors wish to thank the F.W.O. [Fund for Scientific Research - Flanders (Belgium)] and the Research Fund of the University of Leuven for financial support. P.A. is grateful to the University of Leuven for granting a postdoctoral fellowship. We also wish to thank Prof. Dr. S. Toppet for her valuable help with the NMR experiments.

[1] a) J. L. Hartwell, *Lloydia* **1967**, *30*, 379; b) L. E. Overman, L. T. Mendelson, E. J. Jacobsen, *J. Am. Chem. Soc.* **1983**, *105*, 6629; c) W. H. Pearson, F. E. Lovering, *J. Am. Chem. Soc.* **1995**, *117*, 12336; d) G. R. Pettit, R. A. Backhaus, F. E. Boettner, *J. Nat. Prod.* **1995**, *58*, 37; e) G. Eamanza, J. M. Fernandez, E. W. Wakori, F. Viladomat, C. Codina, J. Bastida, *Phytochemistry* **1996**, *43*, 1375; f) J. Bastida, C. Codina, C. L. Porras, L. Paiz, *Palanta Med.* **1996**, *62*, 74; g) J. Jin, S. M. Weinreb, *J. Am. Chem. Soc.* **1997**, *119*, 2050; h) J. Jin, S. M. Weinreb, *J. Am. Chem. Soc.* **1997**, *119*, 5773; i) E. E. Elgorashi, S. Zschocke, J. S. Van Staden, *S. Afr. J. Bot.* **2003**, *69*, 448; j) Z. Jin, *Nat. Prod. Rep.* **2003**, *20*, 606; k) T. S. Pohl, N. R. Crouch, D. A. Mulholland, *Curr. Org. Chem.* **2000**, *4*, 1287; l) P. J. Houghton, J. M. Agbedahunsi, A. Adegbulugbe, *Phytochemistry* **2004**, *65*, 2893.

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

[3] a) K. Ishida, K. Watanabe, S. Kobayashi, M. Kihara, *Chem. Pharm. Bull.* **1977**, *25*, 1851; b) S. Ishida, Y. Sasaki, Y. Kimura, K. Watanabe, *J. Pharmacobio-Dyn.* **1985**, *8*, 917; c) J. Renard-Nozaki, T. Kim, Y. Imakura, M. Kihara, S. Kobayashi, *Res. Virol.* **1989**, *140*, 115.

[4] M. Kihara, K. Ohnishi, S. Kobayashi, *J. Heterocycl. Chem.* **1988**, *25*, 161.

[5] See: a) P. E. Fanta, *Chem. Rev.* **1946**, *46*, 139; b) P. E. Fanta, *Chem. Rev.* **1964**, *64*, 613; c) P. E. Fanta, *Synthesis* **1974**, 9; d) G. H. Posner, *An Introduction to Synthesis using Organocopper Reagents*, Wiley, New York, **1980**; e) G. Bringmann, R. Walter, R. Weirich, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977.

[6] a) S. Kobayashi, M. Kihara, T. Shingu, *Yakugaku Zasshi* **1980**, *100*, 302; b) S. Kobayashi, M. Kihara, Y. Miyake, *Heterocycles* **1985**, *23*, 159.

[7] a) P. A. Patil, V. Snieckus, *Tetrahedron Lett.* **1998**, *39*, 1325; b) C. Hoarau, A. Couture, E. C. Deniau, P. Grandclaudon, *J. Org. Chem.* **2002**, *67*, 5846; c) P. Sahakitpichan, S. Ruchirawat, *Tetrahedron Lett.* **2003**, *44*, 5239; d) S. Kodama, H. Takita, T. Kajimoto, K. Nishide, M. Node, *Tetrahedron* **2004**, *60*, 4901.

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

[9] For our preliminary communication on microwave-assisted synthesis of N-shifted buflavine analogues, see: P. Appukkuttan, W. Dehaen, E. van der Eycken, *Org. Lett.* **2005**, *7*, 2723.

[10] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) A. Suzuki, in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, New York, **1998**, pp. 49; c) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; d) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633, and references therein. For microwave-assisted Suzuki–Miyaura reactions, see: e) M. Larhed, G. Lindeberg, A. Hallberg, *Tetrahedron Lett.* **1996**, *37*, 8219; f) N. E. Leadbeater, M. Marco, *Angew. Chem. Int. Ed.* **2003**, *42*, 1407; g) C. O. Kappe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6250; h) N. E. Leadbeater, *Chem. Commun.* **2005**, 2881; i) R. Lepine, J. Zhu, *Org. Lett.* **2005**, *7*, 2981; j) J. Hashim, T. N. Glasnov, J. M. Kremsner, C. O. Kappe, *J. Org. Chem.* **2006**, *71*, 1707; k) E. F. DiMauro, J. R. Vitullo, *J. Org. Chem.* **2006**, *71*, 3959; l) C. O. Kappe, D. Dallinger, *Nature Rev. Drug. Discov.* **2006**, *5*, 51, and references therein; m) R. L. Harker, R. D. Crouch, *Synthesis* **2007**, 25.

[11] a) M. Schuster, S. Blechert, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036; b) R. H. Grubbs, H. E. Blackwell, *Angew. Chem. Int. Ed.* **1998**, *37*, 3281; c) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413; d) A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 3812; e) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18; f) R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117; g) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199; h) M. Arisawa, A. Nishida, M. Nakagawa, *J. Organomet. Chem.* **2006**, *691*, 5109; i) S. K. Collins, *J. Organomet. Chem.* **2006**, *691*, 5122; j) B. Schmidt, J. Hermanns, *Curr. Org. Chem.* **2006**, *10*, 1363; k) B. Schmidt, *Pure Appl. Chem.* **2006**, *78*, 469. For examples of microwave-assisted metathesis reactions, see: l) G. V. Thanh, A. Loupy, *Tetrahedron Lett.* **2003**, *44*, 9091; m) S. Garbacia, B. Desai, O. Lavastre, C. O. Kappe, *J. Org. Chem.* **2003**, *68*, 9136; n) D. Balan, H. Adolfsson, *Tetrahedron Lett.* **2004**, *45*, 3089; o) S. G. Aitken, A. D. Abell, *Aus. J. Chem.* **2005**, *58*, 3; p) S. K. Collins, A. Grandbois, M. P. Vachon, J. Cote, *Angew. Chem. Int. Ed.* **2006**, *45*, 2923; q) Q. Yang, X.-Y. Li, H. Wu, W.-J. Xiao, *Tetrahedron Lett.* **2006**, *47*, 3893.

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

[13] a) R. F. Heck, *Acc. Chem. Res.* **1979**, *12*, 146; b) G. D. Daves Jr. , A. Hallberg, *Chem. Rev.* **1989**, *89*, 1433; c) A. De Meijere, F. E. Meyer,

Angew. Chem. Int. Ed. Engl. **1994**, *33*, 2379; d) W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 27; e) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009; f) M. Larhed, A. Hallberg, in *Handbook of Organopalladium Chemistry for Organic Synthesis, Vol. 1* (Ed.: E.-i. Negishi), Wiley, New York, **2002**, pp. 1133; g) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945.

[14] a) W. J. Seaman, *J. Am. Chem. Soc.* **1931**, *53*, 711; b) J. W. J. Kennedy, D. G. Hall, *Synlett* **2002**, 477.

[15] a) S. D. Saraf, *Synth. Commun.* **1983**, *13*, 7; b) D. C. Harrowven, M. Bradley, J. L. Castro, S. R. Flanagan, *Tetrahedron Lett.* **2001**, *42*, 6973; c) C.-H. Lai, Y.-L. Shen, M.-N. Wang, N. S. K. Rao, C.-C. Liao, *J. Org. Chem.* **2002**, *67*, 6493; d) G. A. Molander, K. M. George, L. G. Monovich, *J. Org. Chem.* **2003**, *68*, 9533; e) S. P. Khanapure, D. S. Garvey, D. V. Young, M. Ezawa, R. A. Earl, R. D. Gaston, X. Fang, M. Murty, A. Martino, M. Shumway, M. Trocha, P. Marek, S. W. Tam, D. R. Janero, L. G. Letts, *J. Med. Chem.* **2003**, *46*, 5484.

[16] a) T. Rein, T. M. Pedersen, *Synthesis* **2002**, 579; b) D. Li, B. Sun, B. Li, *Daxue Huaxue* **2003**, *18*, 59.

[17] a) A. Padwa, W. F. Rieker, R. J. Rosenthal, *J. Am. Chem. Soc.* **1985**, *107*, 1710; b) M. E. Jung, P. Y. S. Lam, M. M. Mansuri, L. M. Speltz, *J. Org. Chem.* **1985**, *50*, 1087; c) R. D. Clark, Jahangir, *J. Org. Chem.* **1989**, *54*, 1174; d) S. V. Gagnier, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 4804; e) M. Harmata, X. Hong, *J. Am. Chem. Soc.* **2003**, *125*, 5754.

[18] P. Appukkuttan, E. van der Eycken, W. Dehaen, *Synlett* **2005**, 127.

[19] R. C. Larock, in *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, VCH, Weinheim, **1996**, pp. 411–417.

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

[21] a) P. Rocca, F. Marsais, A. Godard, G. Queguiner, *Tetrahedron* **1993**, *49*, 49; b) F. Guillier, F. Nivoliers, A. Godard, F. Marsais, G. Queguiner, M. A. Siddiqui, V. Snieckus, *J. Org. Chem.* **1995**, *60*, 292.

[22] a) A. Fürstner, K. Radkowski, C. Wirtz, R. Goddard, C. W. Lehmann, R. Mynott, *J. Am. Chem. Soc.* **2002**, *124*, 7061; b) L. Banfi, A. Basso, G. Guanti, R. Riva, *Tetrahedron Lett.* **2003**, *44*, 7655; c) C. Rodriguez, J. L. Ravelo, V. S. Martin, *Org. Lett.* **2004**, *6*, 4787; d) Y. J. Kim, D. Lee, *Org. Lett.* **2004**, *6*, 4351; e) M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. J. P. White, K. K. Hii, P. N. Horton, M. B. Hursthouse, *J. Org. Chem.* **2005**, *70*, 1552.

[23] C.-L. Kao, J.-W. Chern, *J. Org. Chem.* **2002**, *67*, 6772.

[24] a) A. J. Stern, J. S. Swenton, *J. Org. Chem.* **1988**, *53*, 2465; b) S. Hibino, E. Sugino, Y. Adachi, K. Nomi, K. Sato, K. Fukumoto, *Heterocycles* **1989**, *28*, 275.

Received: February 1, 2007
Published online: May 16, 2007

