Generation of a Small Library of Highly Electron-Rich 2-(Hetero)Aryl-Substituted Phenethylamines by the Suzuki−Miyaura Reaction: A Short Synthesis of an Apogalanthamine Analogue

Prasad Appukkuttan,[a] Amparo Baiget Orts,[a] R. Prakash Chandran,[a][‡] Jan. L. Goeman,[b] Johan Van der Eycken,[b] Wim Dehaen,[a] and Erik Van der Eycken*[a]

Keywords: Apogalanthamine / Biaryls / Cross coupling / Microwave irradiation / Palladium

The Suzuki–Miyaura reaction is presented as a versatile procedure for the synthesis of a small library of highly electron-rich 2-[4,5-dimethoxy-2-(hetero)arylphenyl]ethylamines. Microwave-irradiation accelerates the reaction tremendously and furnishes superior yields. The difficult oxidative addition of the catalyst to a highly electron-rich and *ortho*-substituted system could be performed easily, and the proto-deboronation during cross-coupling reactions involving the highly electron-withdrawing (2-formylphenyl)boronic acid could be minimized. Enhanced yields and complete compatibility with aqueous conditions were found. This strategy was developed en route towards the synthesis of an apogalanthamine analogue.

Introduction

Phenethylamines (PEAs) and their structural analogues are of great importance in modern chemistry, due to their potential for application in molecular recognition processes and targeted drug discovery. Vast numbers of recently synthesized biologically active molecules and natural products feature a substituted (hetero)arylethylamine unit in their core structure.[1] Introduction of bulky substituents and aryl moieties often enhances the biological activity of phenethylamines and phenylalanines, by altering the conformational features of the molecules and thereby promoting their selective binding to the active site. 2-Aryldopamines are interesting examples belonging to this class, as they are weak stimulators of dopamine-sensitive adanylate cyclase (D_1-dopamine receptor activity)[2] and potent inhibitors of the dopaminergic D_2 agonists in the brain striatum.[3] Introduction of aryl moieties to enhance the binding features is further supported by the fact that 2-aryl-or (2-naphthyl)-phenylalanines and tryptophans show stronger binding properties than their 2-H counterparts in molecular recognition studies.[4] The presence of electron-rich substituents on the aryl rings of PEAs is often regarded as a factor in their interesting physiological and biological activities. The creation of a small library of highly electron-rich PEAs is therefore an interesting task.

Despite their potential biological activities, there has been scarcely any effort done to develop a high-yielding and general pathway for the synthesis of electron-rich arylethylamines featuring a 2-aryl or 2-heteroaryl substitution pattern. The available literature is almost exclusively based either on modification of a pre-selected biaryl core or the use of Grignard-type reagents.[5] Ladd and co-workers[6] used the ingenious Meyers procedure,[7] based on the site-specific cross-coupling of a Grignard reagent with suitably substituted isoxazolines, for the generation of the biaryl skeleton. However, most of these methods demand sensitive reaction conditions and long reaction times, delivering the products in low yields. This makes them unsuited for the generation of small libraries of analogues for screening for possible biological activity.

Transition-metal catalyzed Suzuki,[8] Stille,[9] or Negishi[10] reactions are powerful tools for the synthesis of aryl−aryl- and aryl−heteroaryl-containing molecules; there has been a plethora of recent literature about their application for the synthesis of biologically active natural product analogues.[11] To the best of our knowledge, however, these coupling reactions have hardly been investigated for the synthesis of 2-aryldopamines or 2-aryl PEAs bearing highly electron-donating substituents.[12] Presumably this is attributable to the difficult oxidative addition of the tran-

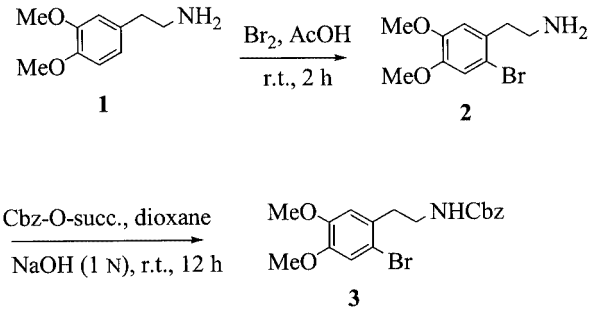
[a] Laboratory for Organic Synthesis, University of Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium
Fax: (internat.) +32-16-327990
E-mail: Erik.VanderEycken@chem.kuleuven.ac.be
[b] Laboratory for Organic and Bio-organic Synthesis, Ghent University, Krijgslaan 281(S4), 9000 Gent, Belgium
[‡] Present address: Center for Super Functional Materials, Department of Chemistry, Pohang University for Science & Technology, San 31, Hyojadong, Namgu, Pohang 790−784, Korea (Sotuh)

sition metal to the C−X bond of the electron-rich aromatic ring, the complexation of the amine nitrogen with the catalyst, and also the unfavorable steric factors imposed by the substrate.[13] Even though these problems could possibly be minimized by the use of palladacycles or bulky phosphane ligands, long synthetic manipulations and sensitive reaction conditions are often required.[14] The application of focused microwave irradiation has been demonstrated as a valuable tool in accelerating the rate and yield of organic reactions in general, as is evident from the enormous amount of literature published in recent years.[15] It is also apparent that the transition metal-catalyzed cross-coupling reactions greatly benefit from microwave irradiation, with many reactions being performed under mild conditions, and in some cases even in water.[16]

From our expertise in transition metal C−C and C−B bond-forming reactions, we became interested in the synthesis of a small library of 2-aryl- and 2-heteroaryl-4,5-dialkoxy PEAs as part of a program to develop novel receptor ligands for binding studies. We chose the Suzuki−Miyaura cross-coupling for the generation of the biaryl axis, due to its milder reaction conditions, increased yields, and lack of toxic by-products. Although the reactions were less satisfactory under conventional heating conditions, owing to the extremely electron-rich nature of the aryl ring, microwave-irradiation was found to improve the cross-coupling remarkably. We also chose to extend our methodology en route towards a short total synthesis of analogues of the apogalanthamine family. Several members of these Amaryllidaceae alkaloids feature a unique 5,6,7,8-tetrahydrobenzo-[*c*,*e*]azocine skeleton,[17] and show very promising alpha-adrenergic, antiserotonin, and antihepatitic activities. In this contribution we report the elaboration of a total synthesis of 10,11-dimethoxy-5,6,7,8-tetrahydro-dibenzo[*c*,*e*]azocine. The superiority of microwave irradiation over experiments under conventional heating conditions is also discussed in this case.

Results and Discussion

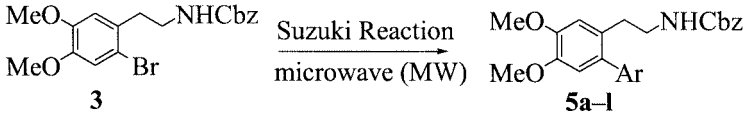
We started our synthesis from the commercially available 2-(3,4-dimethoxyphenyl)ethylamine (Scheme 1). The regioselective bromination of the amine was carried out with bromine in acetic acid at room temperature, providing **2** in 89% yield. In order to avoid problems involving complex formation between the amine-nitrogen and palladium(0) during the biaryl coupling, the free amine was protected as the carbamate by treatment with Cbz−O-succinimide in dioxane, in the presence of 1 N NaOH solution. After 12 h of stirring at ambient temperature, the desired compound **3** was isolated in 93% yield.



Scheme 1. Synthesis of benzyl [2-(2-bromo-4,5-dimethoxyphenyl)-ethyl]carbamate (**3**)

Our next goal was to carry out Suzuki−Miyaura cross-coupling reactions between the phenethylamine **3** and various boronic acids, aiming at the generation of a small library of the target PEAs. We started our experiments with phenylboronic acid (**4a**) as the coupling partner. A mixture of the boronic acid **4a**, the phenethylamine **3**, $NaHCO_3$ as the base, and tetrakis(triphenylphosphane)palladium(0) as the catalyst in a mixture (1:1) of *N*,*N*-dimethylformamide (DMF) and water was sealed in a vial (aluminium/Teflon crimp) and was irradiated in the cavity of a monomode CEM-Discover apparatus[18] at 120 °C, with an irradiation power of 100 W (Scheme 2, Table 1).

The reaction was found to proceed smoothly, and the expected biaryl compound **5a** was isolated in good yield (83%, Table 1, Entry 1), together with traces of unchanged starting material. Increasing the reaction temperature to 140 °C was found to drive the reaction to completion, and the product **5a** was isolated in excellent yield (94%, Table 1, Entry 2). Sodium hydrogencarbonate (3 equiv.) and tetrakis-(triphenylphosphane)palladium(0) (5 mol %) were found to be the base and catalyst of choice, though cesium carbonate also gave equivalent results (90%, Table 1, Entry 3). Lower amounts of catalyst and base were found to diminish the yield considerably (Table 1, Entries 8−11). Although a mixture of ethylene glycol dimethyl ether (DME) and water (1:1) was found to furnish compatible yields, the reaction turned out to be slow (20 min, Table 1, Entries 12−13). Experiments without the use of any transition metal catalyst met with failure, and the starting amine **3** was reisolated untouched. On the basis of these initial results, we decided



Ar-B(OH)$_2$ [**4a–l**], $NaHCO_3$, $Pd(Ph_3P)_4$, (1:1) DMF/H_2O, MW, 100 W

Scheme 2. Suzuki−Miyaura cross-coupling of the phenethylamine **3** with various boronic acids **4a**−**l**

Table 1. Optimization experiments for cross-coupling of the phenylethylamine **3** and boronic acid **4a**

Entry	Base (equiv.)	Catalyst (mol %)	Solvent	Time (min)	*T* (°C)	Yield (%)
1	$NaHCO_3$ (3)	$Pd(Ph_3P)_4$ (5)	DMF/H_2O	10	120	83
2	$NaHCO_3$ (3)	$Pd(Ph_3P)_4$ (5)	DMF/H_2O	10	140	94
3	Cs_2CO_3 (3)	$Pd(Ph_3P)_4$ (5)	DMF/H_2O	10	140	90
4	Na_2CO_3 (3)	$Pd(Ph_3P)_4$ (5)	DMF/H_2O	10	140	82
5	$NaHCO_3$ (3)	$Pd(dppf)Cl_2$ (5)	DMF/H_2O	10	140	78
6	$NaHCO_3$ (3)	$Pd_2(dba)_3$ (5)	DMF/H_2O	10	140	61
7	$NaHCO_3$ (3)	$Pd(Ph_3P)_2Cl_2$ (5)	DMF/H_2O	10	140	87
8	$NaHCO_3$ (2)	$Pd(Ph_3P)_4$ (5)	DMF/H_2O	10	140	81
9	$NaHCO_3$ (1)	$Pd(Ph_3P)_4$ (5)	DMF/H_2O	10	140	69
10	$NaHCO_3$ (3)	$Pd(Ph_3P)_4$ (4)	DMF/H_2O	10	140	80
11	$NaHCO_3$ (3)	$Pd(Ph_3P)_4$ (2.5)	DMF/H_2O	10	140	73
12	$NaHCO_3$ (3)	$Pd(Ph_3P)_4$ (5)	DME/H_2O	10	140	79
13	$NaHCO_3$ (3)	$Pd(Ph_3P)_4$ (5)	DME/H_2O	20	140	91

to extend the scope of our study by including a series of commercially available boronic acids (Table 2).

Naphthylboronic acid (**4b**, Table 2, Entry 2) gave an excellent yield of 89% in 10 min at 140 °C. When electron-withdrawing groups were present (Table 2, Entries 3 and 4) the reactions required slightly more time (15 min) and the products **5c** and **5d** were isolated in good yields (86% and 84%, respectively). The proto-deboronation of **4c** and **4d** caused by the electron-withdrawing groups could be successfully diminished upon microwave irradiation. The (4-bromophenyl)boronic acid (**4e**) was found to be unsuitable for cross-coupling reaction (Table 2, Entry 5), as it resulted in homocoupling and polymerization of the boronic acid, as was evident from CI-MS. The electron-rich boronic acids **4f**−**i** gave satisfactory yields (Table 2, Entries 6−9), though the free hydroxy group of **4i** was seen to diminish the yield slightly (Table 2, Entry 9, 79%). Heterocyclic compounds were successfully introduced at the 2-position with good to excellent yields (Table 2, Entries 10−12). The corresponding furan **5j** and pyridine **5k** analogues were isolated in good to excellent yields (Table 2, Entries 10−11, 85%, and 90%, respectively). However, the reaction with (5-methylthiophen-2-yl)boronic acid (**4l**) met with failure (Table 2, Entry 12), as the compound was too unstable under the reaction conditions and exclusive formation of 2-methylthiophene was found.

At this point we decided to expand the scope of our investigation towards the use of boronic acids bearing highly electron-withdrawing substituents in the sterically unfavorable *ortho*-position. We envisaged that the use of (2-formylphenyl)boronic acid (**6**) in the Suzuki−Miyaura cross-coupling with the phenethylamine **3** might afford a useful intermediate for the synthesis of apogalanthamine analogues, an intriguing class of natural products endowed with interesting biological activity. As a typical member, the natural Amaryllidaceae alkaloid buflavine (**10**) shows α-adrenolytic, antiserotonin, and antihepatitic activities[19] (Figure 1).

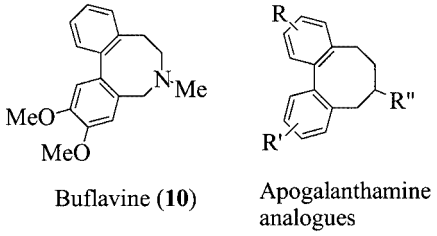


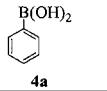
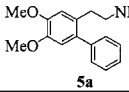
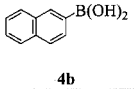
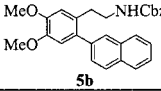
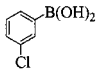
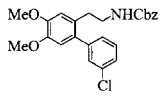
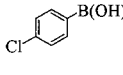
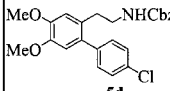
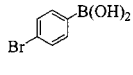
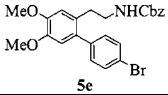
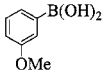
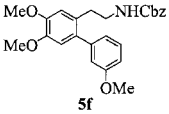
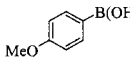
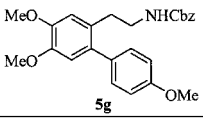
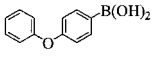
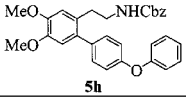
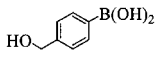
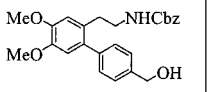
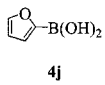
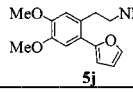
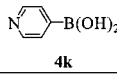
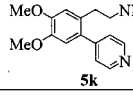
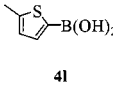
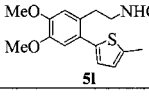
Figure 1. Apogalanthamine analogues and Buflavine (**10**)

These compounds possess a rare 5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine skeleton composed of a biaryl ring system linked through an eight-membered N-heterocyclic ring. Only minor efforts towards the synthetic elaboration of the apogalanthamine skeleton have been made, and only three total syntheses of buflavine (**10**) have appeared in the literature.

The first synthetic sequences of the apogalanthamine analogues were reported by Kobayashi et al.,[20] who constructed the biaryl axis by applying a copper(I)- or nickel(0)-mediated Ullmann-type coupling or a photochemical coupling, yielding the compounds in rather low yields. Snieckus et al.[21] proposed a synthesis of buflavine (**10**) based on the selective generation of a dialkoxy phenylboronic acid by "directed *ortho* metallation" (D.O.M.) of the corresponding brominated compound and subsequent cross-coupling with a suitable aldehyde as the key steps. Ruchirawat et al.[22] explored cross-coupling reactions between dialkoxy phenylboronic acid and suitable *ortho*-halogenated benzonitriles, followed by a Pictet−Spengler-type reaction. Both strategies were based on cross-coupling between an electron-rich boronic acid, avoiding the chance for proto-deboronation, and an electron-withdrawing aryl halide, making the transmetallation step easier.

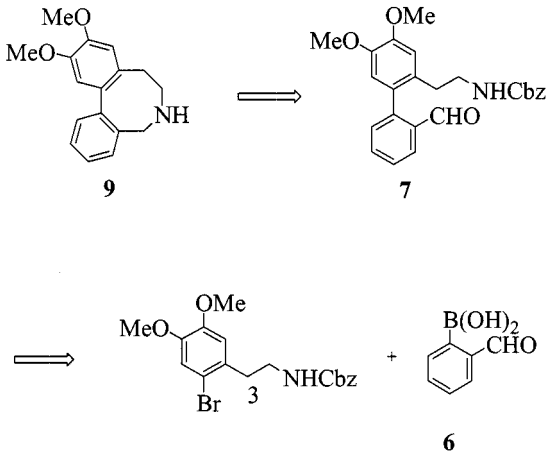
In order to demonstrate the usefulness of our strategy in promoting cross-coupling between highly electron-rich and

Table 2. Suzuki−Miyaura cross-coupling between the phenylethylamine **3** and various boronic acids **4a**−**l**

Entry	Ar-B(OH)$_2$	Product[a]	Time [min]	Temp. [°C]	Yield [%]
1a 1b	 **4a**	 **5a**	10 10	120 140	83 94
2	 **4b**	 **5b**	10	140	89
3	 **4c**	 **5c**	15	150	86
4	 **4d**	 **5d**	15	150	84
5	 **4e**	 **5e**	15	150	0[b]
6	 **4f**	 **5f**	10	140	89
7	 **4g**	 **5g**	10	140	88
8	 **4h**	 **5h**	10	140	87
9	 **4i**	 **5i**	15	140	79
10	 **4j**	 **5j**	10	140	85
11	 **4k**	 **5k**	15	150	90
12	 **4l**	 **5l**	10	140	0[c]

[a] All reactions were carried out with 5 mol % of [Pd(Ph$_3$P)$_4$], 1.3 equiv. of boronic acid, and 3.0 equiv. of NaHCO$_3$ in 1.5 mL each of DMF and water, under microwave irradiation conditions at a power level of 100 W. [b] Homocoupling and polymerization of the boronic acid. [c] Decomposition of the boronic acid; the starting amine was recovered completely.

hindered (aryl)ethylamines and boronic acids bearing highly electron-withdrawing substituents in the sterically unfavorable *ortho* position, we chose to synthesize 10,11-dimethoxy-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine (**9**); its specific substitution pattern in the aromatic rings should present severe challenges to our strategy. Indeed, retrosynthetic analysis shows that the success of the synthesis is mainly predicated on the selective generation of the benzyl [2-(2′-formyl-4,5-dimethoxybiphenyl-2-yl)ethyl]carbamate (**7**). The eight-membered ring can be constructed through a simple reductive amination of **7** (Scheme 3).



Scheme 3. Retrosynthetic analysis for the generation of **9**

A careful literature survey, however, revealed that the presence of electron-withdrawing groups, especially in the *ortho*-position of the boronic acid, tend to destabilize the compound during the Suzuki reaction, by making the C−B bond weaker and thereby promoting the proto-deboronation.[23] When an electron-rich aryl halide is used in combination, the slow oxidative addition of the palladium further enhances the proto-deboronation process. The available literature suggests the use of milder bases, nonaqueous and therefore slower reaction conditions, and protection of the boronic acid as the ester.[24] The Suzuki coupling between (2-formylphenyl)boronic acid[25] (**6**) and benzyl [2-(3,4-dimethoxyphenyl)ethyl]carbamate (**3**) was therefore a challenge to our methodology, and we carried out a number of experiments to optimize the reaction parameters (Table 3).

In a typical procedure, a mixture of the aryl bromide **3** and (2-formylphenyl)boronic acid (**6**, 1.3 equiv.) was irradiated at 100 W maximum power for 15 min at 150 °C. A variety of solvents was used (Table 3, Entries 1−8), as well as different bases (Entries 8−12) and catalysts (Entries 12−16). The best conditions were found to be cesium carbonate or sodium hydrogencarbonate as bases (Entries 6 and 9) and tetrakis(triphenylphosphane)palladium(0) as catalyst (Entry 6) in a 1:1 mixture of DMF or DME with water (Entries 6 and 9, respectively). We were able to perform the reaction successfully in water as the sole solvent, with a good yield of 72% (Entry 8). All the experiments were also carried out under conventional heating conditions, as can be seen in the table, but failed to furnish good yields, benzaldehyde and the phenethylamine **3** being

Table 3. Suzuki−Miyaura biaryl coupling between the phenethylamine **3** and (2-formylphenyl)boronic acid (**6**); a comparative study between conventional heating and microwave (MW) irradiation

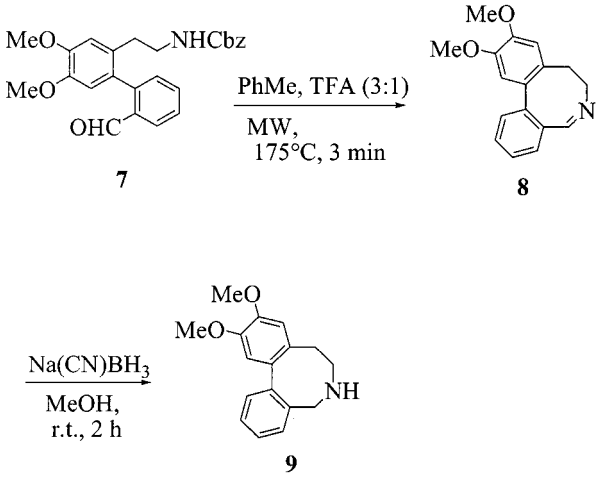
Entry[a]	Base	Catatalyst	Solvent	Temperature (°C) Oil bath	MW	Yield (%) Oil bath	MW
1	1	A	PhMe	110	125	13	61
2	1	A	DME	100	125	21	74
3	1	A	DMF	150	150	25	78
4	1	A	EtOH	87	125	16	73
5	1	A	PhMe + water	150	150	12	51
6	1	A	DMF + water	150	150	22	84
7	1	A	DME + water	100	150	14	79
8	1	A	water	100	150	10	72
9	2	A	DMF + water	150	150	14	79
10	3	A	DMF + water	150	150	11	61
11	4	A	DMF + water	150	150	15	71
12	5	A	DMF + water	150	150	14	68
13	1	B	DMF + water	150	150	12	51
14	1	C	DMF + water	150	150	19	72
15	1	D	DMF + water	150	150	14	64
16	1	E	DMF + water	150	150	17	41

[a] All reactions were carried out at 1 mmol scales with 1.3 equiv. of boronic acid, 3 equiv. of base and 5 mol % of catalyst, under conventional heating conditions for 14 h and under microwave irradiation conditions for 15 min, at a power level of 100 W. 1 = Cs_2CO_3, 2 = $NaHCO_3$, 3 = Na_2CO_3, 4 = K_3PO_4, 5 = $Ba(OH)_2$; A = $[Pd(Ph_3P)_4]$, B = $Pd(OAc)_2$, C = $[Pd_2(dba)_3]$, D = $[Pd(Ph_3P)_2Cl_2]$, E = $[Pd(dppf)Cl_2]$. The ratio between water and organic solvent was always 1:1.

isolated as the side products. Immersion of a sealed tube containing the same mixture as described in Entry 6 in a pre-heated oil-bath (200 °C), gave only a slightly elevated yield of 37%. This, together with the highly accelerated reaction times, clearly underlines the power of microwave irradiation for performing the biaryl coupling between **3** and **6**. We are currently expanding the scope of this reaction towards the introduction of a series of aryl- and (heteroaryl)boronic acids bearing the destabilizing *ortho*-formyl group.

At this stage, we faced the final ring-closure to generate the eight-membered ring. However, several attempts at the deprotection and consecutive reductive amination of the biaryl compound **7** were unsuccessful. Standard deprotection methods for the Cbz group, such as Pd−C/H_2 in methanol or transfer hydrogenation methods in the presence of cyclohexene, ammonium acetate or formic acid, were found to reduce the aldehyde to the corresponding alcohol and other highly polar compounds. However, we found out that an acid-mediated microwave-enhanced deprotection procedure, followed by a one-pot reductive amination, gave satisfactory results (Scheme 4).

Microwave irradiation of a sample of the biaryl **7** in a mixture of toluene and trifluoroacetic acid (3:1) for 3 min at a ceiling temperature of 175 °C, at a maximum power of 100 W, yielded the imine **8**. The reduction of **8** to the desired apogalanthamine analogue **9** was effected by addition of the crude mixture to a methanolic solution of an excess of sodium cyanoborohydride at room temperature. Purification by reversed-phase HPLC, by gradient elution with acetonitrile and water containing $NH_4(OAc)$, yielded the desired compound **9** in 73% overall yield



Scheme 4. Ring closure of the biaryl **7** to the Apogalanthamine analogue **9**

Conclusion

We describe the synthesis of a small library of highly electron-rich 2-aryl and 2-heteroaryl PEAs through Suzuki−Miyaura cross-coupling, in view of their presumably interesting biological activities. A variety of electron-rich, neutral, and electron-poor rings were successfully introduced at the 2-position of the highly electron-rich 2-(3,4-dimethoxyphenyl)ethylamine through microwave-enhanced Suzuki−Miyaura cross-coupling reaction. Excellent yields and high reaction rates were observed, without any real

need for special catalysts or bulky ligands. A small library of 2-aryl and 2-heteroaryl PEAs was obtained and will be investigated for possible biological activity.

Next, the "near-impossible" cross-coupling between the electron-rich and hindered bromo-phenethylamine **3** and the electron-deficient and hindered (2-formylphenyl)boronic acid (**6**) was investigated. While this cross-coupling reaction gave very poor results under conventional heating conditions, excellent yields were obtained with microwave irradiation and a dramatic acceleration of the reaction was observed. Moreover, this reaction could be performed in aqueous medium, even in water as the sole solvent. The proto-deboronation could be avoided, clearly demonstrating the benefit of microwave irradiation. The strategy has successfully been extended towards the synthesis of 10,11-dimethoxy-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine (**9**), an interesting member of the Amaryllidaceae family; several members of this alkaloid family show interesting biological activity. This approach opens an easy route for the synthesis of a library of highly substituted and heteroaryl-bearing apogalanthamine analogues. This work is currently under investigation.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded with Bruker AMX 400 or Bruker 300 Avance instruments. The ^{1}H chemical shifts are reported in ppm relative to tetramethylsilane, with the residual solvent signal as an internal reference and ^{13}C with $CDCl_3$ as internal standard. The low-resolution mass spectra were obtained with a HP5989A MS instrument. High-resolution mass spectra were recorded by use of a Kratos MS50TC and a Kratos Mach III data system. The ion source temperature was 150−250 °C as required. High-resolution EI-mass spectra were performed with a resolution of 10000. For thin layer chromatography, analytical TLC plates (Alugram SIL G/UV_{254} and 70−230 mesh silica gel (E. M. Merck)) were used. All compounds have been characterized by ^{1}H and ^{13}C NMR/EI-MS. All commercially available compounds were used without any further purification.

Microwave Irradiation Experiments: All microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 300 W maximum power. The reactions were carried out in 10-mL glass tubes, sealed with aluminium/Teflon crimp tops, which can be exposed 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 cooled rapidly (60−120 s) to ambient temperature by gas jet cooling.

Synthesis of Benzyl [2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]carbamate (3): Bromine (1.1 mL, 22 mmol) in acetic acid (10 mL) was slowly added to a vigorously stirred solution of 2-(3,4-dimethoxyphenyl)ethylamine (**1**, 3.4 mL, 20 mmol) in acetic acid (50 mL) in a 250 mL round-bottomed flask. After 15 minutes, the brominated amine started precipitating out. Stirring was continued for an additional 105 minutes and the mixture was filtered, washed with dichloromethane (×3) and with petroleum ether (×3), and dried under vacuum to yield **2** (4.63 g, 89%), which was used without further purification. NaOH solution (1 M, 11 mL) was added at room temperature to a vigorously stirred solution of **2** (2.60 g, 10 mmol) in dioxane (25 mL). Benzyloxy-*N*-carbonyloxy succinimide (2.74 g, 11 mmol) in dioxane (25 mL) was added to this solution, and the resultant mixture was stirred at room temperature for 12 h, when TLC and CI-MS indicated the completion of the reaction. Dioxane was removed under vacuum, the mixture was extracted with ethyl acetate (25 mL × 3), and the combined organic layers were washed successively with saturated $NaHCO_3$ solution, 5% citric acid solution, and finally with water. After drying over $MgSO_4$ and removal of the solvent under vacuum, analytically pure product **3** was obtained as yellowish white crystals (3.664 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.88 (t, *J* = 7.3 Hz, 2 H), 3.42 (q, *J* = 7.0 Hz, 2 H), 3.82 (s, 3 H), 3.77 (s, 3 H), 4.98 (br. s, NH), 5.01 (s, 2 H), 6.69 (s, 1 H), 6.98 (s, 1 H), 7.32 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.3, 41.4, 56.4, 56.6, 67.0, 113.9, 116.0, 127.4, 127.9, 128.5, 128.9, 129.0, 129.2, 129.8, 130.2, 130.5 ppm. DEPT (75 MHz, $CDCl_3$): δ = −36.3, −41.4, 56.4, 56.5, −67.0, 113.9, 116.0, 127.4, 128.5, 129.0, 129.2 ppm. LR-MS (EI) [M^+]: 394, 91 (100%). HR (EI) − MS: $C_{18}H_{20}BrNO_4$ found 393.05749, calcd. 393.05757.

General Procedure for the Synthesis of Biarylamines 5a−d and 5f-k by Suzuki−Miyaura Cross-Coupling: Synthesis of Benzyl [2-(4,5-Dimethoxybiphenyl-2-yl)ethyl]carbamate (5a): Bromoamine **3** (197 mg, 0.5 mmol), phenylboronic acid **4a** (79 mg, 0.65 mmol, 1.3 equiv.), and tetrakis(triphenylphosphane)palladium(0) (29 mg, 5 mol %) were suspended in DMF (1.5 mL) in a 10 mL reaction glass vial containing a tiny stirring magnet. To this were added Cs_2CO_3 (490 mg, 1.5 mmol, 3 equiv.) and water (1.5 mL), and the vial was sealed tightly with an aluminium-Teflon® crimp top. The mixture was irradiated for 10 min at a pre-selected temperature of 140 °C, with an irradiation power of 100 W. After the reaction, the vial was cooled to 60 °C by gas 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 × 25 mL). The combined organic layers were dried on magnesium sulfate and solvents were removed under reduced pressure to yield the crude product **5a** as a yellow oil. Column chromatography [silica gel, diethyl ether/hexane (1:1)] afforded analytically pure **5a** (184 mg, 94%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73 (t, *J* = 6.9 Hz, 2 H), 3.23 (q, *J* = 6.9 Hz, 2 H), 3.81 (s, 3 H), 3.84 (s, 3 H), 4.84 (t, NH), 5.02 (s, 2 H), 6.73 (s, 1 H), 6.78 (s, 1 H), 7.33 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.5, 42.0, 52.9, 56.0, 66.5, 112.7, 113.6, 126.9, 127.7, 128.0, 128.3, 128.5, 129.4, 133.8, 134.7, 136.7, 141.4, 147.2, 148.3, 156.3 ppm. DEPT (100 MHz, $CDCl_3$): δ = −35.9, −42.0, 55.9, 56.0, −66.5, 112.7, 113.6, 126.9, 127.9, 128.0, 128.3, 128.5, 129.4 ppm. LR-MS (EI) [M^+]: 391, 91(100%).

Synthesis of Benzyl [2-(4,5-Dimethoxy-2-naphthalen-2-ylphenyl)-ethyl]carbamate (5b): Compound **5b** was synthesized from amine **3** (197 mg) and 2-naphthylboronic acid (**4b**, 112 mg, 0.65 mmol, 1.3 equiv.). Column chromatography [silica gel, diethyl ether/hexane (1:1)] afforded analytically pure product (196 mg, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.83 (t, *J* = 8.0 Hz, 2 H), 3.30 (q, *J* = 6.6 Hz, 2 H), 3.89 (s, 3 H), 3.92 (s, 3 H), 4.66 (t, NH), 5.04 (s, 2 H), 6.68 (s, 1 H), 6.89 (s, 1 H), 7.39 (m, 3 H), 7.53 (m, 3 H), 7.88 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.4, 42.5, 56.4, 56.5, 67.0, 113.0, 114.1, 126.4, 126.8, 127.4, 128.1, 128.2, 128.3, 128.4, 128.5, 128.9, 129.0, 132.7, 133.7, 134.6, 136.7, 138.2, 139.4, 147.7, 148.8, 156.7 ppm. DEPT (100 MHz, $CDCl_3$): δ = −33.6, −412.5, 56.4, 56.5, −67.0, 113.0, 114.0, 126.4, 126.8, 128.1, 128.2, 128.3, 128.4, 128.4, 128.5, 128.9, 129.0 ppm.

Synthesis of Benzyl [2-(3′-Chloro-4,5-dimethoxybiphenyl-2-yl)ethyl]-carbamate (5c): Compound **5c** was synthesized from amine **3** (197 mg) and (3-chlorophenyl)boronic acid (**4c**, 101 mg, 0.65 mmol, 1.3 equiv.). Column chromatography [silica gel, diethyl ether/hexane (1:1)] afforded analytically pure product (183 mg, 86%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73 (t, *J* = 6.4 Hz, 2 H), 3.26 (q, *J* = 6.4 Hz, 2 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 4.84 (br. s, NH), 5.05 (s, 2 H), 6.69 (s, 1 H), 6.78 (s, 1 H), 7.23 (m, 5 H), 7.42 (d, *J* = 8.7 Hz, 1 H), 7.55 (d, *J* = 8.7 Hz, 1 H), 7.83 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.8, 42.0, 55.8, 56.1, 66.7, 112.7, 113.4, 119.8, 127.1, 127.7, 128.0, 128.1, 128.5, 129.4, 129.5, 133.6, 134.1, 143.2, 147.3, 148.7, 156.5, 157.8, ppm. DEPT (100 MHz, $CDCl_3$): δ = −32.9, −42.1, 55.9, 56.0, −66.5, 113.6, 126.9, 127.9, 128.0, 128.3, 128.5, 129.4 ppm. LR-MS (EI) [M^+]: 425, 91 (100%).

Synthesis of Benzyl [2-(4′-Chloro-4,5-dimethoxybiphenyl-2-yl)ethyl]-carbamate (5d): Compound **5d** was synthesized from amine **3** (197 mg) and (4-chlorophenyl)boronic acid (**4d**, 101 mg, 0.65 mmol, 1.3 equiv.). Column chromatography [silica gel, diethyl ether/hexane (1:1)] afforded analytically pure product (179 mg, 84%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74 (t, *J* = 6.6 Hz, 1 H), 3.27 (dd, *J* = 6.6 Hz, 2 H), 3.86 (s, 3 H), 3.88 (s, 3 H), 4.73 (br. s, NH), 5.05 (s, 2 H), 6.69 (s, 1 H), 6.79 (s, 1 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.35 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.8, 41.9, 55.8, 55.9, 65.2, 112.5, 113.2, 126.9, 127.5, 128.0, 128.5, 130.6, 132.0, 132.9, 133.3, 136.4, 139.7, 148.4, 156.1 ppm. DEPT (100 MHz, $CDCl_3$): δ = −33.3, −42.4, 56.3, 56.4, −65.7, 113.0, 113.7, 127.4, 128.5, 129.1, 131.1, 132.4 ppm. LR-MS (EI) [M^+]: 425, 390, 91 (100%).

Synthesis of Benzyl [2-(4,5,3′-Trimethoxybiphenyl-2-yl)ethyl]carbamate (5f): Compound **5f** was synthesized from amine **3** (197 mg) and (3-methoxyphenyl)boronic acid (**4f**, 99 mg, 0.65 mmol, 1.3 equiv.). Column chromatography [silica gel, diethyl ether/hexane (1:1)] afforded analytically pure product (187 mg, 89%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.96 (t, *J* = 7.0 Hz, 2 H), 3.43 (dd, *J* = 6.7 Hz, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 3.88 (s, 3 H), 4.87 (br. s, NH), 5.08 (s, 2 H), 6.48 (s, 1 H), 6.73 (s, 1 H), 7307 (s, 1 H), 7.40 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.8, 41.8, 55.8, 55.9, 56.0, 65.2, 107.3, 112.2, 112.4, 111.3, 111.6, 111.9, 120.6, 123.0, 127.5, 128.0, 128.5, 136.5, 141.6, 147.4, 148.7, 153.4, 156.3 ppm. DEPT (100 MHz, $CDCl_3$): δ = −34.3, −42.3, 56.2, 56.3, 56.4, −66.9, 112.1, 112.4, 113.8, 121.1, 127.4, 128.4, 128.9, 130.8, 142.0 ppm. LR-MS (EI) [M^+]: 421, 91 (100%).

Synthesis of Benzyl [2-(4,5,4′-Trimethoxybiphenyl-2-yl)ethyl]carbamate (5g): Compound **5g** was synthesized from amine **3** (197 mg, 0.5 mmol) and (4-methoxyphenyl)boronic acid (**4g**, 99 mg, 0.65 mmol, 1.3 equiv.). Column chromatography [silica gel, diethyl ether/hexane (1:1)] afforded analytically pure product (183 mg, 87%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74 (t, *J* = 7.3 Hz, 1 H), 3.25 (dd, *J* = 6.6 Hz, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 4.66 (br. s, 1 H), 5.04 (s, 2 H), 6.71 (s, 1 H), 6.76 (s, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 7.20 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.8, 41.9, 55.2, 55.8, 55.9, 65.2, 112.5, 113.6, 114.7, 126.9, 127.5, 127.9, 128.0, 128.2, 128.5, 131.7, 134.3, 136.5, 140.8, 147.1, 148.0 ppm. DEPT (100 MHz, $CDCl_3$): δ = −33.2, −42.4, 55.7, 56.3, 56.4, −65.7, 112.9, 114.0, 127.4, 128.0, 128.5, 128.9, 130.8 ppm. LR-MS (EI) [M^+]: 421, 91 (100%).

Synthesis of Benzyl [2-(4,5-Dimethoxy-4′-phenoxybiphenyl-2-yl)-ethyl]carbamate (5h): Compound **5h** was synthesized from amine **3** (197 mg) and (4-phenoxyphenyl)boronic acid (**4h**, 139 mg, 0.65 mmol, 1.3 equiv.). Column chromatography [silica gel, diethyl ether/hexane (1:1)] afforded analytically pure product (210 mg, 87%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.78 (t, *J* = 7.0 Hz, 2 H), 3.29 (dd, *J* = 7.0 Hz, 2 H), 3.86 (s, 3 H), 3.88 (s, 3 H), 4.78 (br. s, NH), 5.05 (s, 2 H), 6.75 (s, 1 H), 6.79 (s, 1 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 7.09 (d, *J* = 7.7 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.36 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.0, 41.9, 55.8, 55.9, 65.0, 112.4, 113.4, 118.3, 119.0, 123.3, 126.8, 127.9, 128.0, 128.4, 129.7, 130.6, 132.0, 133.9, 136.1, 141.0, 147.1, 148.1, 156.3, 156.9 ppm. DEPT (100 MHz, $CDCl_3$): δ = −33.3, −42.4, 56.3, 56.4, −65.6, 113.0, 113.9, 119.5, 123.9, 127.4, 128.5, 128.9, 130.2, 131.1, 132.4 ppm. LR-MS (EI): [M^+]: 483, 91 (100%).

Synthesis of Benzyl [2-(4′-Hydroxymethyl-4,5-dimethoxybiphenyl-2-yl)ethyl]carbamate (5i): Compound **5i** was synthesized from amine **3** (197 mg) and [(4-hydroxymethyl)phenyl]boronic acid (**4i**, 99 mg, 0.65 mmol, 1.3 equiv.). Column chromatography [silica gel, diethyl ether/hexane (1:1)] afforded analytically pure product (166 mg, 79%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73 (t, *J* = 7.0 Hz, 2 H), 3.22 (dd, *J* = 7.0 Hz, 2 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.2 (br. s, OH), 4.69 (s, 2 H), 4.76 (br. s, NH), 5.01 (s, 2 H), 6.70 (s, 1 H), 6.77 (s, 1 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.35 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.8, 41.9, 55.8, 55.9, 64.8, 65.0, 112.6, 113.5, 126.8, 127.4, 128.0, 128.4, 129.4, 131.9, 134.4, 139.7, 140.6, 141.0, 147.2, 148.2, 156.2 ppm. DEPT (100 MHz, $CDCl_3$): δ = −32.9, −42.0, 55.9, 56.0, −64.9, −65.1, 112.7, 113.5, 126.9, 127.5, 128.4, 129.5, 132.0 ppm. LR-MS (EI) [M^+]: 421, 91 (100%).

Synthesis of Benzyl [2-(2-Furan-2-yl-4,5-dimethoxyphenyl)ethyl]carbamate (5j): Compound **5j** was synthesized from amine **3** (197 mg) and 2-furylboronic acid (**4j**, 73 mg, 0.65 mmol, 1.3 equiv.). Column chromatography [silica gel, diethyl ether/hexane (1:1)] afforded analytically pure product (162 mg, 79%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74 (t, *J* = 6.7 Hz, 2 H), 3.25 (dd, *J* = 6.7 Hz, 2 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.75 (br. s, NH), 5.02 (s, 2 H), 6.70 (s, 1 H), 6.76 (s, 1 H), 6.85 (m, 3 H), 7.30 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.8, 42.0, 55.9, 56.0, 66.6, 112.7, 113.5, 115.2, 121.9, 126.9, 128.2, 128.5, 129.3, 134.6, 136.6, 142.9, 147.3, 148.4, 156.4, 159.5 ppm. DEPT (100 MHz, $CDCl_3$): δ = −32.8, −42.1, 55.9, 56.0, −66.6, 112.4, 112.7, 113.5, 115.2, 121.9, 128.0, 128.5, 129.3 ppm. LR-MS (EI) [M^+]: 381, 91 (100%). HR-MS (EI) : $C_{22}H_{23}NO_5$ found 381.15768, calcd. 381.15762.

Synthesis of Benzyl [2-(4,5-Dimethoxy-2-pyridin-4-ylphenyl)ethyl]-carbamate (5k): Compound **5k** was synthesized from amine **3** (197 mg, 0.5 mmol) and (benzofuran-2-yl)boronic acid (**4k**, 80 mg, 0.65 mmol, 1.3 equiv.). Column chromatography [silica gel, dichloromethane − methanol (19:1)] afforded analytically pure product (176 mg, 90%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.75 (t, *J* = 7.3 Hz, 2 H), 3.28 (q, *J* = 7.3 Hz, 2 H), 3.86 (s, 3 H), 3.88 (s, 3 H), 4.81 (br. s, 1 H), 5.00 (s, 2 H), 6.68 (s, 1 H), 6.80 (s, 1 H), 7.33 (m, 6 H), 7.46 (dt, ^1J = 7.32, ^2J = 2.93 Hz, 1 H), 7.55 (dt, ^1J = 7.32, ^2J = 1.47 Hz, 1 H), 7.67 (dd, *J* = 7.32, 6.59 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.7, 42.0, 55.9, 56.0, 66.6, 112.6, 113.7, 128.0, 128.1, 128.4, 128.5, 128.5, 131.2, 131.3, 131.9, 131.9, 132.0, 132.1, 147.5, 149.33, 156.1 ppm. DEPT (75 MHz, $CDCl_3$): δ = −33.2, −42.4, 56.4, 56.4, −67.0, 113.1, 113.1, 128.5, 128.8, 129.0, 132.6, 149.8 ppm. LR-MS (EI) [M^+]: 392, 91 (100%).

Synthesis of Benzyl [2-(2′-Formyl-4,5-dimethoxybiphenyl-2-yl)ethyl]-carbamate (7): Compound **3** (197 mg, 0.5 mmol), (2-formylphenyl)boronic acid (**6**, 97.5 mg, 0.65 mmol, 1.3 equiv.), and tetrakis-(triphenylphosphane)palladium(0) (29 mg, 5 mol %) were sus-

pended in DMF (1.5 mL) in a 10 mL reaction glass vial. Water (1.5 mL) and Cs_2CO_3 (490 mg, 1.5 mmol, 3 equiv.) were added, and the vial was sealed tightly with an aluminium-Teflon® crimp top. The mixture was irradiated for 15 min at a pre-selected temperature of 150 °C, with an irradiation power of 100 W. After the reaction, the vial was cooled to 60 °C by gas jet cooling. The crude mixture was partitioned between diethyl ether and brine, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried on magnesium sulfate, and solvents were removed under vacuum to yield the crude product as a yellow oil. Column chromatography [silica gel, diethyl ether/hexane (2:1)] afforded **7** (177 mg, 84%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.58 (m, 2 H), 3.21 (q, 2 H), 3.82 (s, 3 H), 3.88 (s, 3 H), 3.88 (s, 3 H), 4.75 (br. s, NH), 5.00 (s, 2 H), 6.68 (s, 1 H), 6.82 (s, 1 H), 7.32 (m, 6 H), 7.48 (t, 1 H), 7.60 (t, 1 H), 7.98 (d, 1 H), 9.77 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.9, 41.5, 55.8, 66.4, 112.2, 113.5, 127.3, 127.8, 127.9, 127.9, 128.3, 129.2, 129.5, 131.2, 133.5, 134.1, 136.4, 144.6, 147.0, 148.8, 156.0, 192.1 ppm. DEPT (100 MHz, $CDCl_3$): δ = −33.5, −42.0, 56.4, −66.9, 112.7, 114.0, 127.8, 128.4, 128.4, 128.5, 128.9, 131.7, 134.1. LR-MS (EI) [M^+]: 419. HR-MS (EI): $C_{25}H_{25}NO_5$ found 419.17320, calcd. 419.17327.

Synthesis of 10,11-Dimethoxy-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine (9): Compound **7** (84 mg, 0.2 mmol) was dissolved in dry toluene (2.25 mL) and the solution was placed in a 10 mL reaction vial containing a magnetic stirring bar. TFA (0.75 mL) was added, and the vial was sealed tightly with an aluminium-Teflon® crimp top. The mixture was irradiated for 3 min at a pre-selected temperature of 175 °C, with a power level of 100 W. After cooling down to 60 °C, the vial was opened and the contents were injected into a solution of sodium cyanoborohydride (61 mg, 1 mmol, 5 equiv.) in dry, degassed methanol (5 mL), under argon. The resultant mixture was stirred for an additional 2 h at room temperature. Excess K_2CO_3 was added to the mixture to neutralize the TFA, and after filtration it was washed with MeOH (10 mL × 5). Solvents were removed under vacuum, and the resultant yellowish white slurry was extracted with ethyl acetate (25 mL × 3). Removal of the solvent under reduced pressure furnished the crude product, which was further purified by reversed-phase HPLC (gradient elusion with 40% MeCN and 60% water containing 0.5% of NH_4(OAc) to 100% MeCN in 25 min, Retention time = 10 min) to furnish 39 mg of **9** (73% from **7**) as a pale yellow oil. ^{1}H NMR (400 MHz, MeOD): δ = 2.67 (m, 2 H), 2.89 (m, 2 H), 3.78 (s, 3 H), 3.89 (s, 3 H), 4.36 (s, 2 H), 6.74 (s, 1 H), 6.95 (s, 1 H), 7.19 (d, J = 7.3 Hz, 2 H), 7.38 (dd, J^2 = 7.3, J^1 = 1.5 Hz, 2 H), 7.41 (dd, J^2 = 7.3, J^1 = 1.5 Hz, 2 H), 7.60 (d, J = 7.3 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 30.9, 40.3, 55.5, 55.6, 61.7, 113.1, 114.0, 127.0, 127.4, 128.0, 128.5, 130.1, 133.3, 139.4, 139.6, 148.2, 149.1 ppm. DEPT (100 MHz, MeOD): δ = −31.0, −40.3, 55.5, 55.6, −61.7, 113.1, 114.0, 127.4, 128.0, 128.5, 130.1 ppm. LR(EI)-MS [M^+]: 269 (100%). HR(EI)-MS: $C_{17}H_{19}NO_2$ found 269.14169, calcd. 269.14160.

Acknowledgments

The authors wish to thank the F.W.O. [Fund for Scientific Research − Flanders (Belgium)] and the Research Funds of the Universities of Leuven and of Ghent for financial support to the laboratory. P. A. is grateful to the University of Leuven for a scholarship. We also wish to thank Mr. K. Deurinckx for his valuable help with NMR experiments, and Drs. S. Depraetere and W. De Borggraeve for providing some of the boronic acids.

[1] Y. Kubota, H. Kawasaki, K. Tomioka, K. Koga, *Tetrahedron* **1993**, *49*, 3081−3090. R. Suau, R. Rico, J. M.-R. Lopez, F. Najera, A. Cuevas, *Phytochemistry* **1998**, *49*, 2545−2549. Y. Kosio, Y. Li, S. Iwasaki, *J. Antibiot.* **1994**, *47*, 765−773. Z. W.-D. Li, Y.-Q. Wang, *Org. Lett.* **2003**, *5*, 2931−2934.
[2] H. Sheppard, C. R. Burghart, *Mol. Pharmacol.* **1971**, *7*, 1−7.
[3] P. Seeman, *Pharmacol. Rev.* **1980**, *32*, 229−313.
[4] V. J. Hruby, G. Li, C.-L. Haskell, M. Schenderovich, *Bioploymers (Pept. Sci.)* **1997**, *43*, 219−266. V. J. Hruby, *Life Sci* **1982**, *31*, 189−199; S. Liao, J. Lin, M. D. Schenderovich, Y. Han, K. Hosohata, P. Davis, W. Qiu, F. Porreca, H. I. Yamamura, V. J. Hruby, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3049−3052.
[5] J. M. Bruce, F. K. Sutcliffe, *J. Chem. Soc.* **1955**, *79*, 4435−4440.
[6] D. Ladd, J. Weinstock, M. Wise, G. W. Gessner, J. L. Sawyer, K. S. Flaim, *J. Med. Chem.* **1986**, *29*, 1904−1912.
[7] A. I. Meyers, E. D. Mihelich, *J. Am. Chem. Soc.* **1975**, *97*, 7383−7385.
[8] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457−2483. A. Suzuki, *J. Organometallic Chem.* **1999**, *576*, 147−168. S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633−9695, and references cited therein.
[9] J. K. Stille, *Angew. Chem.* **1986**, *98*, 483−502, *Angew. Chem. Int. Edit.* **1986**, *25*, 508−524. T. N. Mitchell, *Synthesis* **1992**, 803−815. R. B. Bedford, S. L. Hazelwood, M. E. Limmert, D. A. Albisson, S. M. Draper, P. N. Scully, S. J. Coles, M. B. Hursthouse, *Chem. Eur. J.* **2003**, *9*, 3216−3227, and references cited therein.
[10] E. Neghishi, in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, New York, **1998**, 1−47. S. Ribe, R. K. Kondru, D. N. Beratan, P. Wipf, *J. Am. Chem. Soc.* **2000**, *122*, 4608−4617, and references cited therein.
[11] See for example: J.-G. E. Anctil, V. Snieckus, *J. Organomet. Chem.* **2002**, *653*, 150−160. M. C. Pirrung, Z. Li, K. Park, J. Zhu, *J. Org. Chem.* **2002**, *67*, 7919−7926. R. Benhida, F. Lecubin, J.-L. Fourrey, L. R. Castellanos, L. Quintero, *Tetrahedron Lett.* **1999**, *40*, 5701−5703. M. G. Banwell, B. L. Flynn, E. Hamel, D. C. R. Hockless, *Chem. Commun. (Cambridge, U. K.)* **1997**, *2*, 207−208.
[12] T. R. Hoye, M. Chen, *Tetrahedron Lett.* **1996**, *37*, 3099−3100. V. Upender, D. J. Pollart, J. Liu, P. D. Hobbs, C. Olsen, W.-R. Chao, B. Bowden, J. L. Crase, D. W. Thomas, A. Pandey, J. A. Lawson, M. I. Dawson, *J. Heterocyclic Chem.* **1996**, *33*, 1371−1384. W. Wang, J. Zhang, C. Xiong, V. J. Hruby, *Tetrahedron Lett.* **2002**, *43*, 2137−2140, *Tetrahedron* **2002**, *58*, 3101−3110.
[13] A. Suzuki, in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, New York, **1998**, 49−97.
[14] T. Ishiyama, K. Ishida, N. Miyaura, *Tetrahedron* **2001**, *57*, 9813−9816. G. R. Rosa, G. Ebeling, J. Dupont, A. L. Monteiro, *Synthesis* **2003**, *18*, 2894−2897. A. D. Alonso, C. Najera, M. C. Pacheco, *Org. Lett.* **2000**, *2*, 1823−1826. *Adv. Synth. Catal.* **2002**, *344*, 172−183. **2003**, *345*, 1146−1158.
[15] D. Adam, *Nature* **2003**, *421*, 571−572. A. Lew, P. O. Krutzik, M. E. Hart, A. R. Chamberlin, *J. Comb. Chem.* **2002**, *2*, 95−105. C. O. Kappe, *Curr. Opin. Chem. Biol.* **2002**, *6*, 314−320. Lidstrom, J. Westman, A. Lewis, *Comb. Chem. High Throughput Screen.* **2002**, *5*, 441−458, and references cited therein.
[16] A. Loupy, *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, **2002** and the references cited therein, N. E. Leadbeater, M. Marco, *J. Org. Chem.* **2003**, *68*, 888−892. *Angew. Chem.* **2003**, *115*, 1445−1447; *Angew. Chem. Int. Edit.* **2003**, *42*, 1407−1409; N. E. Leadbeater, M. Marco, *J. Org. Chem.* **2003**, *68*, 5660−5667. N. Kaval, K. Bisztray, W. Dehaen, C. O. Kappe, E. Van der Eycken, *Mol. Diversity* **2003**, *7*, 125−133.
[17] Y. Ishida, Y. Sasaki, Y. Kimura, K. Watanabe, *J. Pharmacobiodyn.* **1985**, *8*, 917−923. Y. Ishida, K. Sadamune, S. Kobayashi, M. Kihara, *J. Pharmacobiodyn.* **1983**, *6*, 391−396. Y. Ishida,

K. Watanabe, S. Kobayashi, M. Kihara, *Chem. Pharm. Bull.* **1977**, *25*, 1851−1855.
[18] CEM−Discover, CEM Corporation P. O. Box 200 Matthews, NC 28106.
[19] F. Viladomat, J. Bastida, C. Codina, W. E. Campbell, S. Mathee, *Phytochemistry* **1995**, *40*, 307−311. C. Hoarau, A. Couture, E. Deniau, P. Grandclaudon, *J. Org. Chem.* **2002**, *67*, 5846−5849, and the references cited therein.
[20] S. Kobayashi, M. Kihara, S. Shizu, S. Katayama, H. Ikeda, K. Kitahiro, H. Matsumoto, *Chem. Pharm. Bull.* **1977**, *25*, 3312−3323. M. Kihara, S. Vangveravong, K. Ohnishi, Y. Imakura, S. Kobayashi, *Chem. Pharm. Bull.* **1989**, *37*, 1744−1747. S. Kobayashi, M. Kihara, Y. Nakauchi, *Yakugaku Zasshi.* **1978**, *98*, 161−164.
[21] P. A. Patil, V. Snieckus, *Tetrahedron Lett.* **1998**, *39*, 1325−1326.
[22] P. Sahakitpichan, S. Ruchiravat, *Tetrahedron Lett.* **2003**, *44*, 5239−5241.
[23] L. G. Monovich, Y. Le Huérou, M. Rönn, G. A. Molander, *J. Am. Chem. Soc.* **2000**, *122*, 52−57, and references cited therein.
[24] S. W. Wright, D. L. Hageman, L. D. McClure, *J. Org. Chem.* **1994**, *59*, 6095−6097. S. Gronowitz, A.-B. Hörnfledt, Y.-H. Yang, *Chem. Scr.* **1986**, *26*, 383−386. T. Watanabe, N. Miyaura, A. Suzuki, *Synlett* **1992**, 207−210.
[25] D. F. O′Shea, J. T. Sharp, *J. Chem. Soc., Perk. Trans. 1* **1996**, *6*, 515−518. J. A. Wytko, J. Weiss, *J. Org. Chem.* **1990**, *55*, 5200−5202. G. M. Keserü, G.-V. Mezey, M. Nógrádi, B. Vermes, M..-P.Kajtár, *Tetrahedron* **1992**, *48*, 913−922.

Received March 30, 2004

