Total synthesis of tubastrine and 3-dehydroxy tubastrine by microwave-assisted cross-coupling reactions

Marianne Lorentzen,[a] Annette Bayer,[b] Magne O. Sydnes[a]* and Kåre B. Jørgensen[a]*

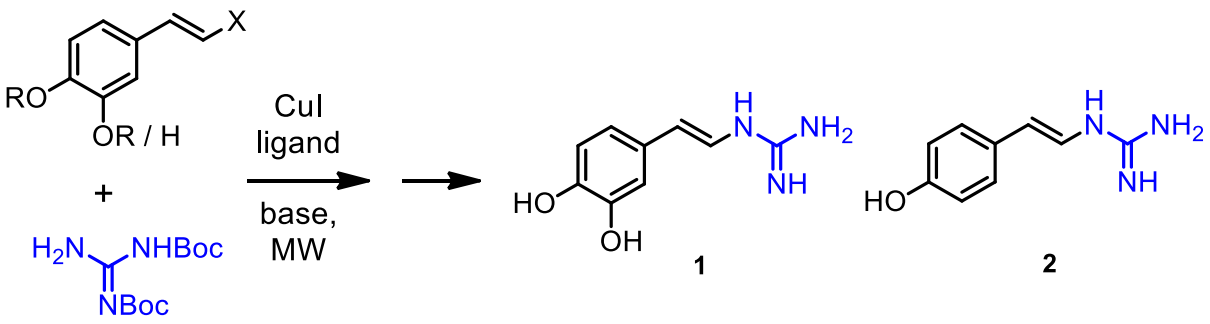
[a] Department of Mathematics and Natural Science, Faculty of Science and Technology, University of Stavanger, NO-4036 Stavanger, Norway

[b] Department of Chemistry, Faculty of Science and Technology, UiT The Arctic University of Norway, NO-9037 Tromsø, Norway

Email: kare.b.jorgensen@uis.no; magne.o.sydnes@uis.no

Corresponding author contact information: Kåre B. Jørgensen, Faculty of Science and technology, University of Stavanger, NO-4036 Stavanger, Norway. Phone: +47 51832306, Fax: +47 51831750, E-mail: kare.b.jorgensen@uis.no

Graphical abstract:



ABSTRACT: The first syntheses of tubastrine and 3-dehydroxy tubastrine are described. The target compounds were prepared in four consecutive steps from commercially available starting materials. The central scaffold was formed by a microwave-assisted C-N cross-coupling reaction between 1,3-bis(*tert*-butoxycarbonyl)-guanidine and (*E*)-((4-(2-iodovinyl)-

1,2-phenylene)bis(oxy))bis(*tert*-butyldimethylsilane) and (*E*)-*tert*-butyl(4-(2-iodovinyl)phenoxy)–dimethylsilane, respectively. The aryl vinyl iodides were obtained by a Hunsdiecker-Borodin-type reaction of aryl acrylic acids, which were easily available from *trans*-caffeic acid or *trans*-*p*-coumaric acid.

Keywords:

Natural product synthesis

C-N cross-coupling

Hunsdiecker-Borodin reaction

Tubastrine

Microwave-assisted reaction

1. Introduction

Tubastrine (**1**), and 3-dehydroxy tubastrine (**2**), shown in Figure 1, are two guanidine containing natural products. The former was first isolated from the coral *Tubastrea aurea* by Sakai *et al*. in 1987.[1] In recent years tubastrine has also been found in a *Dendrodoa* specie, *Dendrodoa grossularia*, and the ascidian *Ascidiella scabra*, both collected from the Orkney Islands,[2] as well as in a New Zealand ascidian, *Aplidium orthium*.[3] Tubastrine showed antiviral,[1] anticancer, antimicrobial[2] and anti-inflammatory activity,[3] making it an interesting starting point for further SAR studies. 3-Dehydroxy tubastrine, in turn, has been isolated from an Australian marine sponge, *Spongosorites sp*.,[4] as well as in the sub-arctic ascidian, *Dendrodoa aggregate*[5] and displayed antimicrobial activity against several bacteria such as *Staphylococcus aureus*, *Serratia sp.*, *Escherichia coli*[4] and *Corynebacterium glutamicum*.[5]

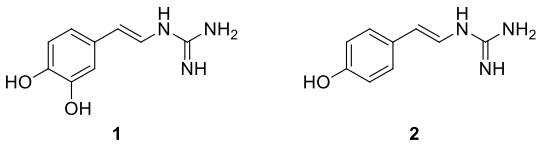
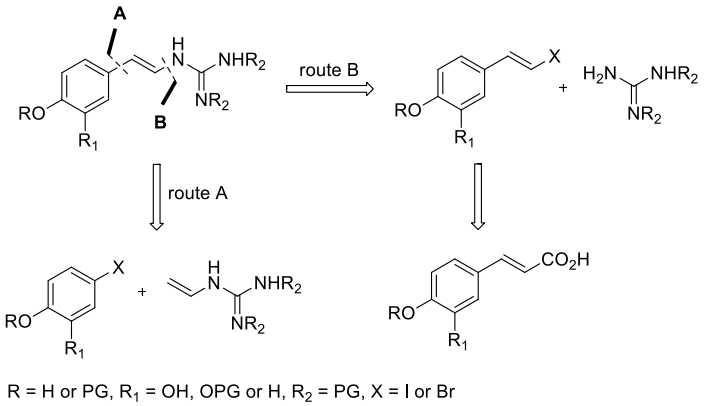


Figure 1. Tubastrine **(1)**, and 3-dehydroxy tubastrine **(2)**

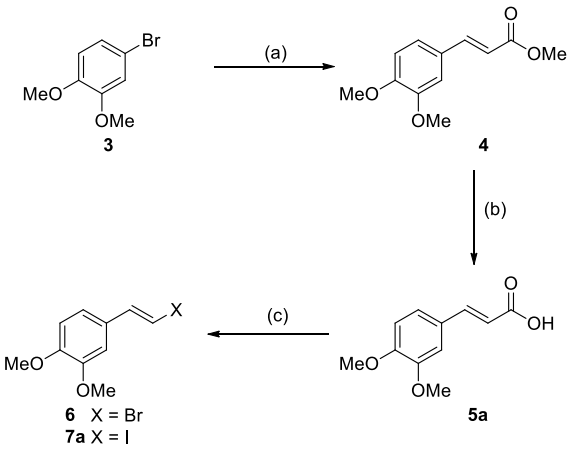
To the best of our knowledge, tubastrines **1** and **2** have not yet been synthesized. One attempt to prepare compound **2** has been reported in the literature, however, the synthesis failed in the final step.[6] Our endeavor into the tubastrines, motivated by their biological activity, required a convergent approach that could easily generate analogous compounds. Two obvious disconnections could be envisioned (Scheme 1). Disconnection A corresponds to a Heck cross-coupling reaction[7] between the respective aryl halides and protected vinylguanidines, while disconnection B corresponds to a C-N cross-coupling reaction[8] between the respective aryl vinyl halides and protected guanidines. In the following, we present the first synthesis of tubastrine (**1**) and 3-dehydroxy tubastrine (**2**) following the above outlined strategy.



Scheme 1. Retrosynthetic analysis of tubastrine (**1**) and 3-dehydroxy tubastrine (**2**).

2. Results and discussion

Initial studies concentrated on the approach corresponding to disconnection A (Scheme 1). To begin with, methyl acrylate was used as a model for vinylguanidine (route A) in a Heck cross-coupling reaction[7] with 4-bromoveratrol **3** to provide ester **4** (Scheme 2) similar to previously reported couplings.[9] Later it became evident that vinylguanidine was not available to us in spite of several attempts from different starting points.[*] We therefore turned our attention to the alternative approach employing the C-N cross-coupling reaction[8] of the respective aryl vinyl halides and protected guanidines (Scheme 1, route B).



Scheme 2. Reagent and conditions: (a) Methyl acrylate (1 equiv.), $Pd(OAc)_2$ (5 mol%), P(*o*-tolyl)$_3$ (10 mol%), Et_3N (2 equiv.), MeCN, MW (100W), 110 °C, 45 min, 81% (b) NaOH (2 equiv.), MeOH : H_2O (10:1), 60 °C, 18 h, 77%; (c) NBS / NIS (1 equiv.), LiOAc (0.2 equiv.), MeCN : H_2O (19:1), rt, 1 h, 83% (**6**) / 80% (**7a**).

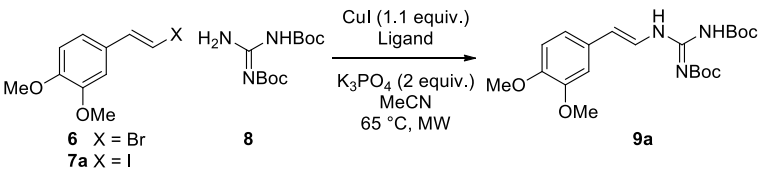
The aryl vinyl halides were obtained by a Hunsdiecker-Borodin-type decarboxylation/halogenation reaction[10] of aryl acrylic acids (Scheme 2). Treatment of acid **5a** with *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) gave the corresponding aryl

[*] In the early stages of this project, vinylguanidine was listed as commercially available in Scifinder®, but the source turned out to be a custom synthesis company that did not have the compound in stock. No straightforward synthesis of this compound was found.

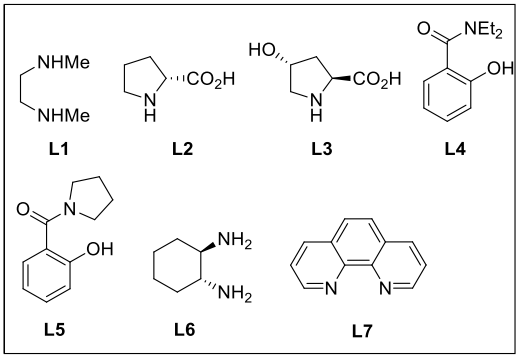
vinyl bromide **6** and -iodide **7a** in 83% and 80% yields, respectively. Acid **5a** was either obtained by hydrolysis of ester **4** with NaOH in methanol/water in 77% isolated yield (Scheme 2) or from commercial sources.

Next, a C-N cross-coupling reaction[11] between 1,3-bis(*tert*-butoxycarbonyl)guanidine (**8**) and either aryl vinyl bromide **6** or aryl vinyl iodide **7a** forming the protected tubastrine precursor **9a** was investigated. Using different conditions (ligands, catalyst, heating source, solvents, base and reaction time), product **9a** was formed in yields as shown in Table 1 and Table 2. Microwave-assisted reactions gave improved yields of **9a** (49%; Entry 6, Table 1) compared to traditional heating using an oil bath at 65 °C (22%; Entry 1, Table 1). The aryl vinyl iodide **7a** performed better in the cross-coupling reaction (Entries 6 and 7, Table 1) than the aryl vinyl bromide **6** (Entries 2, 3 and 5, Table 1). A stoichiometric amount of CuI was necessary for the reaction to occur (Entries 1-3 and 5-7, Table 1). Catalytic amounts of CuI gave no trace of product as observed by TLC analysis. A number of ligands were tested (see Table 1). *N*,*N*′-Dimethylethylenediamine (DMEDA, **L1**) (Entries 1,3 and 5-7, Table 1) and (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (**L6**) (Entry 12, Table 1) promoted the cross-coupling reaction, while *L*-proline (**L2**), *trans*-4-hydroxy-*L*-proline (**L3**), *N*,*N*-diethylsalicylamide (**L4**), *N*-(2-hydroxybenzoyl)pyrrolidine (**L5**) and 1,10-phenanthroline (**L7**) gave no trace of product (Entries 8-11, Table 1). No product was observed when CuI was used as catalyst without ligands (Entry 14, Table 1). The ideal reaction time was found to be 35 min (Entries 2, 5-7 and 12, Table 1), since longer reaction time decreased the yield of product **9a** (Entry 3, Table 1).

Table 1. C-N cross-coupling of aryl vinyl halide **6 or 7a** and guanidine **8**



6 X = Br
7a X = I
8
9a



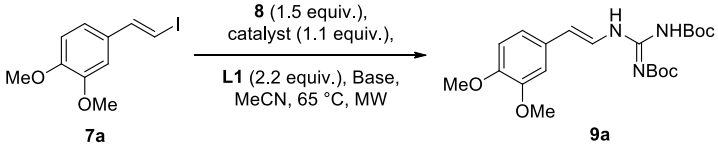
Entry	6 / 7a	8 (equiv.)	Ligand (equiv.)	Time (min)	Yield (%) of 9a[a]
1	**7a**	1.5	**L1** (2.2)	18 (h)[b]	22
2	**6**	1	**L1** (2.2)	35	34
3	**6**	1	**L1** (2.2)	60	24
4	**6**	1	**L1** (0.2)	35	nr
5	**6**	1.5	**L1** (2.2)	35	29
6	**7a**	1.5	**L1** (2.2)	35	49
7	**7a**	2	**L1** (2.2)	35	53
8	**7a**	1.5	**L2** (2.2)	35	nr
9	**7a**	1.5	**L3** (2.2)	35	nr
10	**7a**	1.5	**L4** (2.2)	35	nr
11	**7a**	1.5	**L5** (2.2)	35	nr
12	**7a**	1.5	**L6** (2.2)	35	30
13	**7a**	1.5	**L7** (2.2)	35	nr
14	**7a**	1.5	-	35	nr

[a]Isolated yield. [b]Traditional heating (oil bath).

The cross-coupling reaction was also tested with different solvents (THF, toluene, CH_2Cl_2 or MeCN), copper sources (CuI, CuOAc, $Cu(OAc)_2$ or CuCl) and bases (K_3PO_4, Cs_2CO_3, K_2CO_3 or Et_3N). The amount of base was important for the yield. Two equivalents of K_3PO_4 gave higher yield of product **9a** (Entries 1 and 3, Table 2) than one equivalent (Entry 2, Table 2), while four equivalents gave a significant decrease in the yield of product **9a** (Entry 4, Table 2). With K_2CO_3 or Et_3N as base lower yield of compound **9a** was obtained (Entries 5 and 7, Table 2), while Cs_2CO_3 gave approximately the same yield as with K_3PO_4 (Entry 6,

Table 2). Changing solvent from MeCN to THF, toluene or CH_2Cl_2 was not beneficial for the cross-coupling reaction. Only trace amounts of product were observed using toluene or CH_2Cl_2 as solvent (Entries 9 and 10, Table 2), while a 19% yield of product **9a** was obtained with THF (Entry 8, Table 2). With CuOAc or CuCl only trace amounts of product were observed by TLC analysis (Entries 11 and 13, Table 2), while $Cu(OAc)_2$ did not promote the reaction in any way (Entry 12, Table 2).

Table 2. C-N cross-coupling of arylvinyliodide **7a** and guanidine **8**



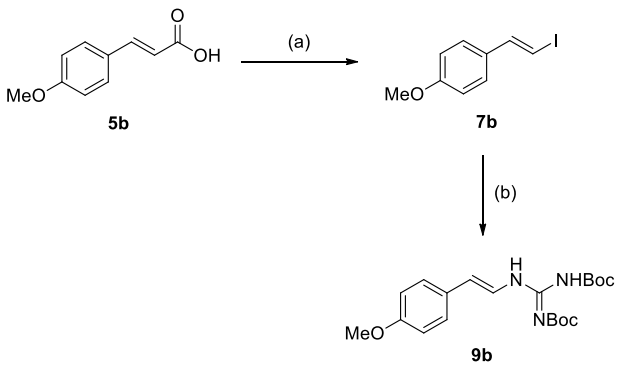
7a **9a**

Entry	Copper source	Base (equiv.)	Solvent	Yield (%) of 9a[a]
1	CuI	K_3PO_4 (2)	MeCN	34[b]
2	CuI	K_3PO_4 (1)	MeCN	26[b]
3	CuI	K_3PO_4 (2)	MeCN	49
4	CuI	K_3PO_4 (4)	MeCN	29
5	CuI	K_2CO_3 (2)	MeCN	39
6	CuI	Cs_2CO_3 (2)	MeCN	45
7	CuI	Et_3N (2)	MeCN	29
8	CuI	K_3PO_4 (2)	THF	19
9	CuI	K_3PO_4 (2)	Toluene	trace
10	CuI	K_3PO_4 (2)	CH_2Cl_2	trace
11	CuOAc	K_3PO_4 (2)	MeCN	trace
12	$Cu(OAc)_2$[c]	K_3PO_4 (2)	MeCN	nr
13	CuCl	K_3PO_4 (2)	MeCN	trace

[a]Isolated yield. [b]Bromostyrene. [c]Ascorbinic acid (1.1 equiv.) as reducing agent was added.

Typical side products observed in the cross-couplings were 1,2-dimethoxy-4-vinylbenzene and (*E*)-*tert*-butyl 3,4-dimethoxystyrylcarbamate, which accounted for approximately 20-25% of the starting material **7a**. Under most of the reaction conditions tested, the reaction did not go to completion. However, longer reaction time only resulted in a decreased yield of product **9a** and an increased yield of (*E*)-*tert*-butyl 3,4-dimethoxystyrylcarbamate. Less (*E*)-*tert*-butyl 3,4-dimethoxystyrylcarbamate was isolated when using K_3PO_4 as base compared to Cs_2CO_3. In addition, trace amounts of several other side products were observed by TLC and ^{1}H NMR analysis of the crude reaction mixture, but these products were difficult to isolate.

Next, the 3-dehydroxy tubastrine precursor **9b** was prepared employing the optimized conditions for the formation of **9a** (Scheme 3). (*E*)-1-(2-Iodovinyl)-4-methoxybenzene (**7b**) was obtained from commercially available (*E*)-3-(4-methoxyphenyl)acrylic acid (**5b**) after treatment with NIS at room temperature for 1 h to yield product **7b** in 74% yield. The cross-coupling of substrate **7b** with guanidine **8** using either K_3PO_4, or Cs_2CO_3 as base, resulted in the formation of product **9b**. For the reaction using K_3PO_4 as base substrate **9b** was formed in 45% yield. In addition, the corresponding product with a Boc group on the internal *N* atom instead of one of the terminal *N* atoms was isolated in 13% yield, thus giving in total 58% yield of isomers relevant for the synthesis of target compound **2**. Utilizing Cs_2CO_3 as base resulted only in the formation of product **9b** in 50% yield.

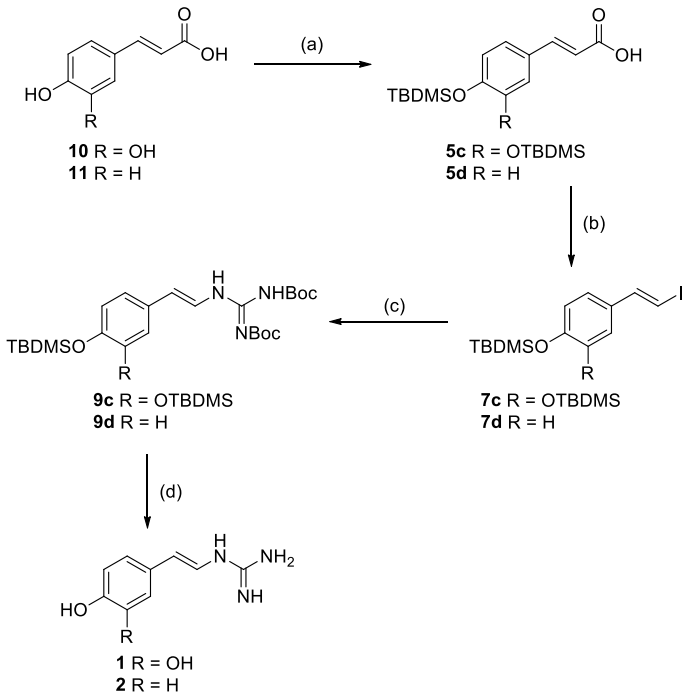


Scheme 3. Reagent and conditions: (a) NIS (1 equiv.), LiOAc (0.2 equiv.), MeCN : H_2O (19:1), rt, 1 h, 74%; (b) **8** (1.5 equiv.), CuI (1.1 equiv.), DMEDA (2.2 equiv.), base (2 equiv), MeCN, MW (50 W), 65 °C, 35 min, with K_3PO_4, 45%, or with Cs_2CO_3, 50%.

The Boc groups in compound **9a** and **9b** were easily removed using TFA at 100 °C (microwave) for 20 min. The removal of the methoxy groups in substrate **9a** and **9b** was more difficult than first anticipated. Treatment with BBr_3 gave an intractable mixture of products, while a premixture of NaI and TMSCl[12] was inefficient in the removal of the methoxy groups. Due to the difficulties with the final deprotection of substrate **9a** and **9b,** the corresponding *tert*-butyldimethylsilyl (TBDMS) protected analogues were envisioned to be better precursors for target compounds **1** and **2**.

The TBDMS protected analogues **9c** and **9d** were prepared by the established strategy (Scheme 4). Commercially available *trans*-caffeic acid (**10**) and *p*-coumaric acid (**11**) were silylated with TBDMSCl / Et_3N in CH_2Cl_2, followed by hydrolysis of the silyl ester with K_2CO_3 in methanol/water to afford the protected aryl acrylic acids **5c** and **5d** in 76% and 44% yields.[10b,13] The Hunsdiecker-Borodin-type reaction[10] of **5c** and **5d** with NIS gave aryl vinyl iodides **7c** and **7d** in 71% and 74% yield, respectively. In the microwave-assisted C-N cross-coupling reaction with guanidine **8** products **9c** and **9d** were formed in 45% or 37% yield, respectively. The synthesis was completed by desilylation with tetrabutylammonium fluoride

(TBAF), followed by a Boc deprotection using TFA, providing target compounds **1** and **2** in 64% and 61% yield, respectively.



Scheme 4. Reagent and conditions: (a) (i) Et_3N, TBDMSCl, CH_2Cl_2, rt, 18 h. (ii) K_2CO_3 (1 equiv.), MeOH : H_2O (1:1), rt, 1 h, 76% (**5c**) / 44% (**5d**); (b) NIS (1 equiv.), LiOAc (0.2 equiv.), MeCN : H_2O (19:1), rt, 1 h,71% (**6c**) / 74% (**6d**); (c) **8** (1.5 equiv.), CuI (1.1 equiv.), DMEDA (2.2 equiv.), K_3PO_4 (2 equiv), MeCN, MW (50 W), 65 °C, 35 min, 45% (**9c**) / 37% (**9d**); (d) (i) TBAF, THF, rt, 18 h. (ii) TFA (4.4 equiv.), MeCN, MW, 100 °C, 15 min, 64%. (**1**) / 61% (**2**).

3. Conclusion

The first total synthesis of tubastrine (**1**) and 3-dehydroxy tubastrine (**2**) were completed utilizing a microwave-assisted C-N cross-coupling reaction between 1,3-bis(*tert*-butoxycarbonyl)guanidine (**8**) and (*E*)-((4-(2-iodovinyl)-1,2-phenylene)bis(oxy))bis(*tert*-butyldimethylsilane) (**7c**) or (*E*)-*tert*-butyl(4-(2-iodovinyl)phenoxy)dimethylsilane, respectively (**7d**). Target compounds **1** and **2** were prepared in four steps from commercial

available starting materials with overall yields of 15.5% and 7.3%, respectively. The total synthesis opens up for further biological evaluation of the two natural products and analogues thereof.

4. Experimental

4.1 General

Acetonitrile (MeCN) was dried over molecular sieves (oven dried) three times, and stored over molecular sieves under nitrogen atmosphere. Anhydrous Toluene, THF and CH_2Cl_2 were purchased from VWR and used as received. *N*,*N*'-Dimethylethylenediamine (DMEDA) was distilled and stored over KOH, the same was Et_3N. Copper(I)iodide was recrystallized from potassium iodide solution (concentrated) and water, and dried in an oven prior to use. All reactions were carried out under argon atmosphere if not otherwise specified. The microwave reactions were performed in 10 mL pressure vials with caps using Discover SP from CEM. TLC was performed on Merck silica gel 60 F_{254} plates, using UV light at 254 nm and 5% alcoholic molybdophosphoric acid for detection. Normalsil 60, 40-63 μm silica gel was used for flash chromatography. Reverse phase purification of compound **1** and **2** were performed on g C18 prepacked Isolute® SPE columns. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz, all at room temperature. Chemical shifts were reported in ppm compared to TMS (δ 0, singlet, for ^{1}H NMR), or for ^{13}C resonance signal to $CDCl_3$ (δ 77.0, triplet). The splitting pattern was recorded as a singlet, s; doublet, d; triplet, t; double doublet, dd; double triplet, dt; quartet, q; multiplet, m; broad, br. IR was recorded on a Perkin Elmer FT-IR spectrometer, version 3.02.01. Melting points were determined on a Stuart Scientific melting point apparatus SMP3. High-resolution mass spectra (HRMS) were recorded from MeOH solutions on a LTQ Orbitrap XL (Thermo Scientific) in positive or negative electrospray ionization (ESI) mode.

4.2. (*E*)-Methyl 3-(3,4-dimethoxyphenyl)acrylate (4)

4-Bromoveratrol (**3**) (90 μL, 0.713 mmol), methyl acrylate (130 μL, 1.43 mmol) and Et_3N (0.2 mL, 1.43 mmol) were added to a pre-stirred solution of $Pd(OAc)_2$ (8 mg, 0.035 mmol) and P(*o*-tolyl)$_3$ (22 mg, 0.070 mmol) in MeCN (2 mL). The mixture was microwave heated (150 W, 110 °C) for 45 min, cooled to room temperature and concentrated *in vacuo* on silica gel. The crude product was purified by flash column chromatography (petroleum ether: EtOAc 5:1) to afford 133 mg (84%) of product **4** as a white solid. mp 67.9-69.4 °C (hexane), lit.[14a] 68-69 °C. Published data[14] were in accordance with ours: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 16.0 Hz, 1H), 7.11 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 3.92 (s, 6H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6 (**C**O), 151.1 (**C**), 149.1 (**C**), 144.8 (**C**H), 127.3 (**C**), 122.6 (**C**H), 115.4 (**C**H), 110.9 (**C**H), 109.5 (**C**H), 55.9 (**C**H_3), 55.8 (**C**H_3), 51.6 (**C**H_3); IR (KBr) 2945 (w), 2840 (w), 1697 (s), 1626 (m), 1596 (m), 1511 (m), 1465 (m), 1440 (m), 1422 (m), 1348 (w), 1254 (s), 1232 (m), 1162 (m), 1145 (m), 1040 (m), 1022 (m), 984 (m), 870 (w), 857 (w), 815 (w)757 (w); Mass spectrum *m/z* (relative intensity %) 245.2 $[M+Na]^+$ (100); HRMS (ESI) Calc. for $C_{12}H_{14}O_4Na$: 245.0784, Found 245.0787.

4.3. (*E*)-3-(3,4-Dimethoxyphenyl)acrylic acid (5a)

To a solution of acrylate **4** (1.997 g, 8.98 mmol) in MeOH (50 mL) and water (5 mL) was added KOH (715 mg, 17.88 mmol). The reaction mixture was heated to 60 °C for 18 h, before concentrated *in vacuo*. The residue was dissolved in water (50 mL), added 2 M aqueous NaOH solution (1 mL) and extracted with Et_2O (2 x 60 mL). The water layer was adjusted to pH 0 by the addition of 6 M HCl (4 mL) and extracted a second time with CH_2Cl_2 (5 x 50 mL). The latter organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether: EtOAc 1:2) to afford 1.443 g (77%) of product **5a** as a white solid. mp 180.7-181.8 °C (hexane), lit.[15] 181-

182 °C. Published data[15] were in accordance with ours: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, *J* = 15.9 Hz, 1H), 7.14 (dd, *J* = 8.4, 1.96 Hz, 1H), 7.08 (d, *J* = 1.92 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 3.93 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4 (**C**O), 151.5 (**C**), 149.2 (**C**), 147.0 (**C**H), 127.0 (**C**), 123.2 (**C**H), 114.8 (**C**H), 111.0 (**C**H), 109.7 (**C**H), 56.0 (**C**H_3), 55.9 (**C**H_3); IR (KBr) 2840 (w), 1683 (s), 1625 (m), 1597 (m), 1517 (s), 1459 (m), 1427 (m), 1341 (m), 1299 (m), 1265 (s), 1211 (m), 1169 (w), 1142 (s), 1025 (m), 976 (w), 841 (m), 770 (w); Mass spectrum *m/z* (relative intensity %) 207.2 $[M]^-$ (100); HRMS (ESI) Calc. for $C_{11}H_{11}O_4$: 207.0663, Found 207.0663.

4.4. (*E*)-3-(3,4-Bis((*tert*-butyldimethylsilyl)oxy)phenyl)acrylic acid (5c)

tert-Butyldimethylsilyl chloride (3.396 g, 22.53 mmol) in anhydrous CH_2Cl_2 (15 mL) was added slowly to a precooled solution of *trans*-caffeic acid (1.196 g, 6.66 mmol) in anhydrous CH_2Cl_2 (15 mL) and Et_3N (6.1 mL, 43.74 mmol) at 0 °C. The mixture was warmed to room temperature and stirred overnight (18 h), washed with 1 M HCl (2 x 30 mL) and water (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The brown oil was dissolved in MeOH (30 mL) and water (30 mL) before K_2CO_3 (949 mg, 6.87 mmol) was added. The mixture was stirred for 4 h and concentrated *in vacuo* to half of the volume. EtOAc (50 mL) and concentrated HCl (4 mL, pH 0) were added, the phases were separated and the water layer was extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether: EtOAc 3:1) to afford 1.979 g (73%) of product **5c** as a white solid. mp 157.8-158.8 °C (hexane), lit.[13] 152-155 °C. Published data[13] were in accordance with ours: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, *J* = 15.9 Hz, 1H), 7.05-7.04 (m, 2H), 6.84 (d, *J* = 8.8 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 1.00 (s, 9H), 0.99 (s, 1H), 0.23 (s, 6H), 0.22 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3 (**C**O), 149.9 (**C**), 147.2 (**C**), 147.0 (**C**H), 127.6 (**C**), 122.7 (**C**H), 121.2 (**C**H), 120.6 (**C**H), 114.7

(**C**H), 125.9 (3x**C**H_3), 25.8 (3x**C**H_3), 18.5 (**C**), 18.4 (**C**), ÷4.1(0) (2x**C**H_3), ÷4.1(1) (2x**C**H_3); IR (KBr) 2929 (m), 2857 (m), 1679 (m), 1629 (m), 1596 (m), 1507 (s), 1472 (w), 1426 (m), 1292 (s), 1253 (m), 1202 (m), 1165 (w), 1126 (w), 993 (w), 916 (m), 860 (m), 836 (m), 812 (w), 781 (m), 679 (w); Mass spectrum *m/z* (relative intensity %) 431.2 $[M+Na]^+$ (100); HRMS (ESI) Calc. for $C_{21}H_{36}O_4NaSi_2$: 431.2044, Found 431.2046.

4.5. (*E*)-3-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)acrylic acid (5d)

tert-Butyldimethylsilyl chloride (2.452 g, 16.27 mmol) in anhydrous CH_2Cl_2 (15 mL) was added slowly to a precooled solution of *trans-p*-coumaric acid (1.205 g, 7.31 mmol) in anhydrous CH_2Cl_2 (15 mL) and Et_3N (4.5 mL, 32.27 mmol) at 0 °C. The mixture was warmed to room temperature and stirred overnight (18 h), washed with 1 M HCl (2 x 30 mL) and water (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The brown oil was solved in MeOH (30 mL) and water (30 mL) before K_3CO_3 (1.050 g, 7.60 mmol) was added. The mixture was stirred for 4 h and concentrated *in vacuo* to half of the volume. EtOAc (50 mL) and concentrated HCl (4 mL, pH 0) was added. The two phases were separated and the water layer was extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether: EtOAc 3:1) to afford 887 mg (44%) of product **5d** as a white solid. mp 129.4-130.4 °C (hexane), lit.[13c] 128.5-130 °C. Published data[10b,13c] were in accordance with ours: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, *J* = 15.9 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.32 (d, *J* = 15.9 Hz, 1H), 0.99 (s, 9H), ÷0.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.8 (**C**O), 158.3 (**C**), 146.8 (**C**H), 130.1 (2x**C**H), 127.4 (**C**), 120.6 (2x**C**H), 114.9 (**C**H), 25.6 (3x**C**H_3), 18.3 (**C**), ÷4.4 (2x**C**H_3); IR (KBr) 2928 (m), 2857 (m), 2606 (w), 1682 (s), 1623 (m), 1599 (s), 1573 (m), 1508 (s), 1471 (m), 1426 (m), 1361 (w), 1334 (m), 1311 (m), 1286 (m), 1258 (s), 1223 (m), 1168 (m), 1101 (w), 1005 (w), 985 (m), 912 (m), 837 (m), 802 (w), 778 (m), 685 (w),

633 (w); Mass spectrum *m/z* (relative intensity %) 301.1 $[M+ Na]^+$ (100); HRMS (ESI) Calc. for $C_{15}H_{22}O_3NaSi$: 301.1230, Found 301.1228.

4.6. (*E*)-4-(2-Iodovinyl)-1,2-dimethoxybenzene (7a)

To a solution of acrylic acid **5a** (1.088 g, 5.23 mmol) in MeCN : H_2O (19:1, 60 mL) were added LiOAc (69 mg, 1.05 mmol) and NIS (1.178 g, 5.23 mmol) at room temperature. The orange mixture was stirred at room temperature for 1 h before being concentrated *in vacuo* on silica gel. The crude product was purified by flash column chromatography (petroleum ether: EtOAc 5:1) to afford 1.206 g (80%) of product **7a** as a white solid. mp 76.6-77.7 °C (hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (d, *J* = 14.9 Hz, 1H), 6.86-6.80 (m, 3H), 6.65 (d, *J* = 14.9 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.4 (**C**), 149.0 (**C**), 144.5 (**C**H), 130.9 (**C**), 119.3 (**C**H), 110.9 (**C**H), 108.2 (**C**H), 73.9 (**C**H), 55.9 (**C**H_3), 55.8 (**C**H_3); IR (KBr) 2925 (w), 2833 (w), 1601 (m), 1573 (w), 1514 (s), 1460 (m), 1336 (w), 1305 (m), 1264 (s), 1180 (m), 1154 (m), 1136 (s), 1024 (m), 949 (s), 855 (w), 811 (w), 764 (m); Mass spectrum *m/z* (relative intensity %) 312.9 $[M+Na]^+$ (100); HRMS (ESI) Calc. for $C_{10}H_{11}O_2INa$: 312.9696, Found 312.9699.

4.7. (*E*)-1-(2-Iodovinyl)-4-methoxybenzene (7b)

To a solution of 4-methoxycinnamic acid (1.028 g, 5.77 mmol) in MeCN : H_2O (19:1, 60 mL) was added LiOAc (77 mg, 1.17 mmol) and NIS (1.291 g, 5.74 mmol) at room temperature. The orange mixture was stirred at room temperature for 1 h before concentrated *in vacuo* on silica gel. The crude product was purified by flash column chromatography (petroleum ether: EtOAc 19:1) to afford 1.111 g (74%) of product **7b** as a beige solid (turned black after 2 days in fridge). Published data[16] were in accordance with ours: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 (d, *J* = 14.8 Hz, 1H), 7.23 (d, *J* = 6.8 Hz, 2H), 6.88 (d, *J* = 6.8 Hz, 2H), 6.63 (d, *J* = 14.8 Hz,

1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.7 (**C**), 144.3 (**C**H), 130.7 (**C**), 127.3 (2x**C**H), 114.1 (2x**C**H), 73.6 (**C**H), 55.3 (**C**H_3)

4.8. (*E*)-((4-(2-Iodovinyl)-1,2-phenylene)bis(oxy))bis(*tert*-butyldimethylsilane) (7c)

To a solution of acrylic acid **5c** (693 mg, 1.70 mmol) in MeCN : H_2O (19:1, 20 mL) was added LiOAc (26 mg, 0.36 mmol) and NIS (385 mg, 1.71 mmol) at room temperature. The orange mixture was stirred at room temperature for 3 h, added sodium thiosulphate (concentrated, 2-3 drops) and silica gel and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2% EtOAc in petroleum ether) to afford 594 mg (71%) of product **7c** as a pale pink oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 (d, J = 14.6 Hz, 1H), 6.77-6.76 (m, 3H), 6.56 (d, J = 14.8 Hz, 1H), 0.99 (s, 9H), 0.98 (s, 9H), 0.20 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.6 (**C**), 147.0 (**C**), 144.5 (**C**H), 131.5 (**C**), 121.1 (**C**H), 119.6 (**C**H), 118.6 (**C**H), 73.7 (**C**H), 25.9 (6x**C**H_3), 18.5 (**C**), 18.4 (**C**), ÷4.0(8) (2x**C**H_3), ÷4.0(7) (2x**C**H_3); IR (KBr) 2956 (m), 2930 (m), 2895 (w), 2858 (m), 1596 (w), 1561 (m), 1508 (s), 1472 (m), 1419 (w), 1405 (w), 1362 (w), 1295 (s), 1254 (m), 1234 (m), 1175 (m), 1124 (w), 983 (w), 906 (m), 839 (s), 781 (m), 685 (w); Mass spectrum *m/z* (relative intensity %) 513.1 $[M+Na]^+$ (100); HRMS (ESI) Calc. for $C_{20}H_{35}O_2INaSi_2$: 513.1112, Found 513.1116.

4.9. (*E*)-*tert*-Butyl(4-(2-iodovinyl)phenoxy)dimethylsilane (7d)

To a solution of acrylic acid **5d** (415 mg, 1.49 mmol) in MeCN : H_2O (19:1, 20 mL) was added LiOAc (20 mg, 0.30 mmol) and NIS (335 mg, 1.49 mmol) at room temperature. The orange mixture was stirred at room temperature for 18 h, added sodium thiosulphate (concentrated, 2-3 drops) and silica gel and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2% EtOAc in petroleum ether) to afford 396 mg (74%) of product **7d** as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (d, J = 14.8 Hz, 1H), 7.17 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 6.62 (d, J = 14.8 Hz, 1H), 0.98 (s, 9H),

÷0.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0 (**C**), 144.4 (**C**H), 131.3 (**C**), 127.2 (2x**C**H), 120.3 (2x**C**H), 73.8 (**C**H), 25.7 (3x**C**H_3), 18.2 (**C**), ÷4.4 (2x**C**H_3); IR (KBr) 2956 (m), 2929 (m), 2858 (m), 1601 (m), 1508 (s), 1472 (m), 1362 (w), 1266 (br. s), 1175 (m), 949 (w), 914 (s), 839 (m), 800 (w), 781 (m), 682 (w); Mass spectrum *m/z* (relative intensity %) 264.9 $[M]^+$ (100); HRMS (ESI) Calc. for $C_{10}H_{11}O_2BrNa$: 264.9835, Found 264.9839.

4.10. (*E*)-4-(2-Bromovinyl)-1,2-dimethoxybenzene (6)

To a solution of acrylic acid **5a** (400 mg, 1.92 mmol) in MeCN : H_2O (19:1, mL) was added LiOAc (25 mg, 0.38 mmol) and NIS (343 mg, 1.92 mmol) at room temperature. The yellow mixture was stirred at room temperature for 1 h before concentrated *in vacuo* on silica gel. The crude product was purified by flash column chromatography (petroleum ether: EtOAc 5:1) to afford 387 mg (83%) of product **6** as a white solid. mp 61.8-63.2 °C (hexane), lit.[17] 66 °C. Published data[17] were in accordance with ours: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.03 (d, *J* = 14.0 Hz, 1H), 6.86-6.80 (m, 3H), 6.62 (d, *J* = 13.9 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.2 (**C**), 149.0 (**C**), 136.7 (**C**H), 128.9 (**C**), 119.3 (**C**H), 111.1 (**C**H), 108.4 (**C**H), 104.2 (**C**H), 55.9 (**C**H_3), 55.8 (**C**H_3); IR (KBr) 3081 (w), 2953 (w), 2835 (m), 1602 (m), 1577 (w), 1512 (s), 1461 (m), 1438 (m), 1418 (m), 1328 (w), 1304 (w), 1263 (s), 1249 (m), 1208 (m), 1193 (m), 1155 (m), 1139 (s), 1037 (m), 1024 (m), 943 (m), 854 (w), 813 (w), 773 (m), 712 (w); Mass spectrum *m/z* (relative intensity %) 312.9 $[M+Na]^+$ (100); HRMS (ESI) Calc. for $C_{10}H_{11}O_2INa$: 312.9696, Found 312.9699.

4.11. (*Z*)-1-((*E*)-3,4-Dimethoxystyryl)-2,3-bis(*tert*-butoxycarbonyl)guanidine (9a)

A vial loaded with compound **8** (80 mg, 0.309 mmol), **6** (51 mg, 0.209 mmol) or **7a** (58 mg, 0.200 mmol), K_3PO_4 (87 mg, mmol) and CuI (43 mg, mmol) were evacuated and backfilled with argon three times. DMEDA (50 µL, 0.46 mmol) and MeCN (1.5 mL) was added and the turkish-blue mixture was microwave heated (50 W, 65 °C) for 35 min, cooled and

concentrated *in vacuo* on silica gel. Purification by flash column chromatography (petroleum ether: EtOAc 5:1) afforded 41 mg (49%) from **7a**, or 26 mg (29%) from **6**, of product **9a** as a fluffy white foamy oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.61 (br s, 1H), 10.26 (d, *J* = 10.3 Hz, 1H), 7.52 (dd, *J* = 14.6, 10.4 Hz, 1H), 6.92 (d, *J* = 1.9 Hz, 1H), 6.83 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.78 (d, *J* = 8.3 Hz), 6.12 (d, *J* = 14.6 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 1.54 (s, 9H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0 (**C**O), 153.1 (**C**=N), 152.8 (**C**), 149.0 (**C**), 148.3 (**C**), 128.7 (**C**), 120.6 (**C**H), 119.4 (**C**H), 115.1 (**C**H), 111.1 (**C**H), 108.0 (**C**H), 83.9 (**C**), 80.0 (**C**), 56.0 (O**C**H_3), 55.9 (O**C**H_3), 28.2 (3x**C**H_3), 28.0 (3x**C**H_3); IR (KBr) 3263 (w), 2977 (m), 2932 (m), 1720 (m), 1638 (br. s), 1614 (br. s), 1513 (m), 1454 (m), 1407 (br. m), 1368 (m), 1310 (s), 1265 (m), 1233 (m), 1206 (m), 1153 (br. s), 1104 (s), 1057 (m), 1027 (m), 943 (br. w), 854 (w), 803 (w), 771 (w); Mass spectrum *m/z* (relative intensity %) 444.2 $[M+Na]^+$ (100); HRMS (ESI) Calc. for $C_{21}H_{31}O_6N_3Na$: 444.2105, Found 444.2101.

4.12. (*Z*)-1-((*E*)-4-Methoxystyryl)-2,3-bis(*tert*-butoxycarbonyl)guanidine (9b)

A vial loaded with compound **8** (80 mg, 0.309 mmol), **7b** (53 mg, 0.204 mmol), K_3PO_4 (87 mg, 0.410 mmol) and CuI (43 mg, 0.226 mmol) were evacuated and backfilled with argon three times. DMEDA (50 µL, 0.46 mmol) and MeCN (1.5 mL) was added and the turkish-blue mixture was microwave heated (50 W, 65 °C) for 35 min, cooled and concentrated *in vacuo* on silica gel. Purification by flash column chromatography (petroleum ether: EtOAc 5:1) afforded 36 mg (45%) of product **9b** as a fluffy white foamy oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.57 (s, 1H), 10.20 (d, *J* = 10.4 Hz, 1H), 7.52 (dd, *J* = 14.6, 10.4 Hz, 1H), 7.27 (dd, *J* = 8.8 Hz, 2H), 6.82 (dd, *J* = 8.8 Hz, 2H), 6.12 (d, *J* = 14.6 Hz, 1H), 3.79 (s, 3H), 1.53 (s, 9H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0 (**C**), 158.6 (**C**=N), 153.1 (**C**), 153.1 (**C**), 152.7 (**C**), 128.4 (**C**), 127.0 (2x**C**H), 120.6 (**C**H), 114.6 (**C**H), 114.0 (2x**C**H), 83.8 (**C**), 79.8 (**C**), 55.2 (O**C**H_3), 28.2 (3x**C**H_3), 28.0 (3x**C**H_3); IR (KBr) 3267 (w), 3093 (w), 2978 (m), 2932 (w), 1722 (m), 1639 (br. s), 1615 (br. s), 1509 (w), 1408 (br. m), 1368 (m), 1319 (s),

1293 (m), 1247 (s), 1155 (s), 1112 (s), 1057 (m), 1030 (m), 945 (w), 843 (w), 805 (w); Mass spectrum *m/z* (relative intensity %) 392.2 $[M]^+$ (100); HRMS (ESI) Calc. for $C_{20}H_{30}O_5N_3$: 392.2176, Found 392.2176.

4.13. (*Z*)-1-((*E*)-3,4-Bis((*tert*-butyldimethylsilyl)oxy)styryl)-2,3-bis(*tert*-butoxycarbonyl)guanidine (9c)

A vial loaded with compound **8** (102 mg, 0.393 mmol), **7c** (129 mg, 0.263 mmol), K_3PO_4 (112 mg, 0.528 mmol) and CuI (55 mg, 0.289 mmol) were evacuated and backfilled with argon three times. DMEDA (60 µL, 0.55 mmol) and MeCN (1.5 mL) was added and the turkish-blue mixture was microwave heated (50 W, 65 °C) for 35 min, cooled and concentrated *in vacuo* on silica gel. Purification by flash column chromatography (petroleum ether: EtOAc 5:1) afforded 74 mg (45%) of product **9c** as a fluffy white foamy oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.6 (s, 1H), 10.18 (d, *J* = 10.3 Hz, 1H), 7.45 (dd, *J* = 14.6, 10.4 Hz, 1H), 6.87 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.73 (dd, *J* = 5.4, 3.2 Hz, 2H), 6.05 (d, *J* = 14.6 Hz, 1H), 1.53 (s, 9H), 1.52 (s, 9H), 0.98 (s, 9H), 0.97 (s, 9H), 0.19 (s, 6H), 0.18 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0 (**C**), 153.1 (**C**O), 152.7 (**C**O), 146.7 (**C**), 146.1 (**C**), 129.4 (**C**), 121.2 (**C**H), 120.8 (**C**H), 119.5 (**C**H), 118.7 (**C**H), 115.0 (**C**H), 83.8 (**C**), 79.8 (**C**), 28.2 (3x**C**H_3), 28.0 (3x**C**H_2), 25.9 (6x**C**H_3), 18.5 (**C**), 18.4 (**C**), ÷4.1(0) (2x**C**H_3), ÷4.1(1) (2x**C**H_3); IR (KBr) 3264 (w), 2958 (m), 2931 (m), 2859 (m), 1721 (m), 1642 (s), 1617 (s), 1563 (m), 1509 (s), 1473 (m), 1412 (s), 1369 (m), 1316 (s), 1275 (s), 1253 (s), 1232 (m), 1154 (s), 1124 (m), 1105 (m), 1058 (m), 1029 (w), 983 (w), 940 (w), 908 (m), 840 (m), 806 (m), 781 (m), 733 (w), 695 (w); Mass spectrum *m/z* (relative intensity %) 644.4 $[M+Na]^+$ (100); HRMS (ESI) Calc. for $C_{31}H_{55}O_6N_3NaSi_2$: 644.3522, Found 644.3522.

4.14. (*Z*)-1-((*E*)-4-((*tert*-Butyldimethylsilyl)oxy)styryl)-2,3-bis(*tert*-butoxycarbonyl)guanidine (9d)

A vial loaded with compound **8** (135 mg, 0.521 mmol), **6d** (125 mg, 0.347 mmol), Cs_2CO_3 (226 mg, 0.693 mmol) and CuI (73 mg, 0.383 mmol) were evacuated and backfilled with argon three times. DMEDA (80 μL, 0.73 mmol) and MeCN (1.5 mL) was added and the turkish-blue mixture was microwave heated (50 W, 65 °C) for 35 min, cooled and concentrated *in vacuo* on silica gel. Purification by flash column chromatography (petroleum ether: EtOAc 5:1) afforded 63 mg (37%) of product **9d** as a fluffy white foamy oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.56 (s, 1H), 10.19 (d, *J* = 10.4 Hz, 1H), 7.51 (dd, *J* = 14.6, 10.4 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.11 (d, *J* = 14.6 Hz, 1H), 1.52 (s, 9H), 1.52 (s, 9H), 0.97 (s, 9H), ÷0.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1 (**C**), 154.8 (**C**), 153.1 (**C**O), 152.8 (**C**O), 129.0 (**C**), 127.0 (2x**C**H), 120.8 (**C**H), 120.2 (2x**C**H), 114.8 (**C**H), 83.9 (**C**), 80.1 (**C**), 28.2 (3x**C**H_3), 28.1 (3x**C**H_3), 25.7 (3x**C**H_3), 18.2 (**C**), ÷4.4 (2x**C**H_3); IR (KBr) 2929 (m), 1720 (m), 1639 (s), 1615 (s), 1407 (m), 1368 (m), 1316 (s), 1252 (s), 1154 (s), 1108 (s), 1057 (m), 912 (w), 839 (w), 805 (w), 780 (w); Mass spectrum *m/z* (relative intensity %) 492.7 $[M+Na]^+$ (100); HRMS (ESI) Calc. for $C_{25}H_{42}O_5N_3Si$: 492.2888, Found 492.2897.

4.15. Tubastrine (1)

To a solution of compound **9c** (53 mg, 0.085 mmol) in THF (3 mL) was added TBAF (1 M in THF 0.18 mL, 0.18 mmol) dropwise at ÷10 °C (brine/ice). The green solution was stirred for 5 min, quenched with NH_4Cl (sat., 10 mL) and extracted with Et_2O (3 x 15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether: EtOAc 2:1) to afford 32 mg (97%) of product as a fluffy white foamy oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.56 (s, 1H), 10.19 (d, *J* = 10.4 Hz, 1H), 7.35 (dd, *J* = 14.4, 10.4 Hz, 1H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.60 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.99 (d, *J* = 14.5 Hz, 1H), 1.52 (s, 9H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6 (**C**), 153.0 (**C**), 152.9 (**C**), 143.7 (**C**), 143.5

(**C**), 128.6 (**C**), 120.2 (**C**H), 119.7 (**C**H), 115.6 (**C**H), 115.3 (**C**H), 111.5 (**C**H), 84.1 (**C**), 80.5 (**C**), 28.2 (3x**C**H_3), 28.0 (3x**C**H_3). A solution of the tubastrine precursor (26 mg, 0.066 mmol) and TFA (0.02 mL, 0.27 mmol) in MeCN (2 mL) was microwave heated (100 W, 100 °C) for 20 min, cooled to room temperature and concentrated *in vacuo*. The crude product was purified by a C18-column using water : MeCN gradient to obtain 14 mg (67% (64% from **9c**)) as a fluffy pale yellow foamy oil. Published data[1-3] were in accordance with ours: ^{1}H NMR (CD_3OD, 400 MHz): δ 6.93 (d, *J* = 13.9 Hz, 1H), 6.82 (s, 1H), 6.70 (s, 2H), 6.16 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz): δ 156.1 (C), 146.6 (C), 146.2 (C), 128.7 (C), 120.0 (C), 119.0 (CH), 118.3 (CH), 116.5 (CH), 113.8 (CH); Mass spectrum *m/z* (relative intensity %) 194.2 $[M]^+$ (100); HRMS (ESI) Calc. for $C_9H_{11}O_2N_3$: 194.0924, Found 194.0924.

4.16. 3-Dehydroxy-tubastrine (2)

To a solution of compound **9d** (47 mg, 0.096 mmol) in THF (3 mL) was added TBAF (1 M in THF, 0.12 mL, 0.12 mmol) dropwise at room temperature. The yellow solution was stirred for 30 min, quenched with water (10 mL) and extracted with Et_2O (3 x 15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether: EtOAc 2:1) to afford 33 mg (92%) of product as a fluffy white foamy oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.55 (s, 1H), 10.22 (d, *J* = 10.3 Hz, 1H), 7.40 (dd, *J* = 14.4, 10.3 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.82 (br.s, 1H), 6.75 (d, *J* = 7.9 Hz, 2H), 6.08 (d, *J* = 14.5 Hz, 1H), 1.52 (s, 9H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8 (**C**), 155.4 (**C**), 153.1 (**C**), 152.8 (**C**), 127.8 (**C**), 127.2 (2x**C**H), 120.2 (**C**H), 115.7 (2x**C**H), 115.4 (**C**H), 84.0 (**C**), 80.2 (**C**), 28.2 (3x**C**H_3), 28.1 (3x**C**H_3). A solution of the 3-dehydroxy tubastrine precursor (27 mg, 0.072 mmol) and TFA (0.02 mL, 0.27 mmol) in MeCN (2 mL) was microwave heated (100 W, 100 °C) for 20 min, cooled to room temperature and concentrated *in vacuo*. The crude product was purified by a C18-column

using water : MeCN gradient to obtain 15 mg (68% (61% from **9d**)) as a fluffy pale yellow foamy oil. Published data[4,5] were in accordance with ours: ^{1}H NMR (CD_3OD, 400 MHz): δ 7.20 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 14 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.22 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz): δ 158.1 (**C**), 156.0 (**C**), 128.1(1) (**C**H), 128.1(0) (**C**), 120.0 (2x**C**H), 118.0 (**C**H), 116.6 (**C**H); Mass spectrum *m/z* (relative intensity %) 178.2 $[M]^+$ (100); HRMS (ESI) Calc. for $C_9H_{11}ON_3$: 178.0975, Found 178.0972 which is in accordance with literature.[4,5]

Acknowledgment

This work has received support from the University of Stavanger and the Research Council of Norway through a project grant (224790/O30).

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of all new and known compounds are provided.

Supplementary data related to this article is available on …

References

1) (a) Sakai, R.; Higa, T. *Chem. Lett*. **1987**, 127-128. (b) Higa, T. Sakai, R. *PCT Int. Appl.* **1988**, WO8800181 (A1) 19880114.
2) Barenbrock, J. S.; Köck, M. *J. Biotechnol.* **2005**, *117*, 225-232.
3) Pearce, A. N.; Chia, E. W.; Berridge, M. W.; Maas, E.; Page, M J.; Harper, J. L.; Webb, V. L.; Copp, B. R. *Tetrahedron* **2008**, *64*, 5748-5755.
4) Urban, S.; Capon, R. J.; Hooper, J. N. A. *Aust. J. Chem*. **1994**, *47*, 2279 – 2282.
5) Tadesse, M.; Tørfoss, V.; Strøm, M. B.; Hansen, E.; Andersen, J. H.; Stensvåg, K.; Haug, T. *Biochem. Syst. Ecol.* **2010**, *38*, 827-829.
6) Santos, K. O.; Craveiro, M. V.; Berlinck, R. G. S. *Quim. Nova* **2007**, *30*, 1892-1895.

7) (a) Heck, R. F.; Nolley, J. P. *J. Org. Chem*. **1972**, *37*, 2320–2322. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*. **2000**, *100*, 3009-3066.

8) (a) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett*. **2003**, *5*, 3667-3669. (b) Pan, X.; Cai, Q.; Ma. D. *Org. Lett*. **2004**, *6*, 1809-1812. (c) Martin, R.; Cuenca, A.; Buchwald, S. L. *Org. Lett*. **2007**, *9*, 5521-5524. (d) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. *J. Am. Chem. Soc*. **2003**, *125*, 7889-7901. (e) Cesati, R. R.; Dwyer, G.; Jones, R. C.; Hayes, M. P.; Yalamanchili, P.; Casebier, D. S. *Org. Lett*. **2007**, *9*, 5617-5620. (f) Cheung, C. W.; Buchwald, S. L. *J. Org. Chem*. **2012**, *77*, 7526-7537. (g) Pandey, A. K.; Sharma, R.; Shivahare, R.; Arora, A.; Rastogi, N.; Gupta, S.; Chauhan, P. M. S. *J. Org. Chem*. **2013**, *78*, 1534-1546.

9) (a) Larhed, M.; Hallberg, A. *J. Org. Chem*. **1996**, *61*, 9582-9584. (b) Vallin, K. S. A.; Emilsson, P.; Larhed, M.; Hallberg, A. *J. Org. Chem*. **2002**, *67*, 6243-6246. (c) Sadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; Van der Eycken, E.; Kaval, N.; Kappe, C. O. *Org. Process Res. Dev*, **2003**, *7*, 707-716. (d) Hajipour, A. R.; Rafiee, F. *Appl. Organometal. Chem*. **2011**, *25*, 542-551.

10) (a) Borodin, A. *Ann*. **1861**, *119*, 121-123. (b) Hunsdiecker, H.; Hunsdiecker, C. *Ber.* **1942**, *75*, 291-297. (c) Chowdhury, S.; Roy, S. *J. Org. Chem*. **1997**, *62*, 199-200. (d) Georgiades, S. N.; Clardy, J. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 3117-3121 (e) Zhang, W.; Su, C.; Kuang, C.; Yang, Q. *Russ. Chem. Bull., Int. Ed*. **2010**, *59*, 452-456. (f) Xu, R. S.; Yue, L.; Pan, Y. J. *Tetrahedron* **2012**, *68*, 5046-5052. (e) Kuang, C.; Senboku, H.; Tokuda, M. *Synlett* **2000**, *10*, 1439-1442.

11) (a) Gao, X.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. *J. Org. Chem*. **2008**, *73*, 6864-6866. (b) Cortes-Salva, M.; Nguyen, B. L.; Cuevas, J.; Pennypacker, K. R. *Org. Lett*. **2010**, *12*, 1316-1319. (c) Xing, H.; Zhang, Y.; Lai, Y.; Jiang, Y.; Ma, D. *J. Org. Chem*. **2012**, *77*, 5449-5453. (d) Rauws, T. R. M.; Maes, B. U. W. *Chem. Soc. Rev*. **2012**, *41*,

2463-2497. (e) Hammound, H.; Schmitt, M.; Bihel, F.; Antheaume, C.; Bourguignon, J. J. *J. Org. Chem*. **2012**, *77*, 417-423.

12) (a) Jung, M. E.; Lyster, M. A.; *J. Org. Chem*. **1977**, *42*, 3761-3764 (b) Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem*. **2008**, *73*, 4895-4902.

13) (a) Bogucki, D. E.; Charlton, J. L. *Can. J. Chem*. **1997**, *75*, 1783-1794. (b) Capone, D. L.; Black, C. A.; Jeffery, D. W. *J. Agric. Food. Chem*. **2012**, *60*, 3515-3523. (c) Brandt, D. R.; Pannone, K. M.; Romano, J. J.; Casillas, E. G. *Tetrahedron* **2013**, *69*, 9994-10002.

14) (a) Adler, E.; Björkqvist, K. J. *Acta Chem. Scand.* **1951**, *5*, 541-525. (b) Sharma, A.; Sharma, N.; Shard, A.; Kumar, R., D.; Sinha, A. K.; Sahal, D. *Org. Biomol. Chem.* **2011**, *9*, 5211-5219.

15) (a) Ohta, G.; Shimizu, M. *Pharm. Bull*. **1957**, *5*, 36, 40-44. (b) Brittelo, D. R. *J. Org. Chem*. **1981**, *46*, 2414-2520. (c) Peterson, J. R.; Russell, M. E.; Surjasasmita, I B. *J. Chem. Eng. Data* **1988**, *33*, 534-537. (d) Mogilaiah, K.; Reddy, G. R. *Synth. Commun*. **2004**, *34*, 205-210. (e) Li, X.; Wang, Y.; Wu, J.; Li, Y.; Wang, Q.; Xu, W. *Bioorg. Med. Chem*. **2009**, *17*, 3061-3071. (f) Kumar, D.; Sandhu, J. S. *Synth. Commun*. **2010**, *13*, 1915-1919.

16) (a) Bull, J. A.; Mousseau, J. J.; Charette, A. B. *Org. Lett*. **2008**, *10*, 5485-5488. (b) Lee, G. C. M.; Tobias, B.; Holmes, J. M.; Harcourt, D. A.; Garst, M. E. *J. Am. Chem. Soc*. **1990**, *112*, 9330-9336.

17) (a) Nikishin, G. I.; Sokora, L. L.; Makhaev, V. D.; Kapustina, N. I. *Russ. Chem. Bull., Int. Ed.* **2008**, *57*, 118-123. (b) O'Byrne, A.; Evans, P. *Tetrahedron*, **2008**, *64*, 8067-8072. (c) Williams, D. R.; Fultz, M. W.; Christos, T. E.; Carter, J. S. *Tetrahedron Lett.* **2010**, *51*, 121-124.