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

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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 *Asciidiella 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*.\(^5\)
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. 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\textsuperscript{7} with 4-bromoveratrol 3 to provide ester 4 (Scheme 2) similar to previously reported couplings.\textsuperscript{9} Later it became evident that vinylguanidine was not available to us in spite of several attempts from different starting points.\textsuperscript{*} We therefore turned our attention to the alternative approach employing the C-N cross-coupling reaction\textsuperscript{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$_3$N (2 equiv.), MeCN, MW (100W), 110 °C, 45 min, 81% (b) NaOH (2 equiv.), MeOH : H$_2$O (10:1), 60 °C, 18 h, 77%; (c) NBS / NIS (1 equiv.), LiOAc (0.2 equiv.), MeCN : H$_2$O (19:1), rt, 1 h, 83% (6) / 80% (7a).

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

\textsuperscript{*} 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\textsuperscript{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 (1R,2R)(−)-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
<table>
<thead>
<tr>
<th>Entry</th>
<th>6 / 8</th>
<th>Ligand</th>
<th>Time</th>
<th>Yield (%) of 9a</th>
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<tr>
<td>1</td>
<td>7a</td>
<td>1.5</td>
<td>L1 (2.2)</td>
<td>18 (h)</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>1</td>
<td>L1 (2.2)</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>1</td>
<td>L1 (2.2)</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>1</td>
<td>L1 (0.2)</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>1.5</td>
<td>L1 (2.2)</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>7a</td>
<td>1.5</td>
<td>L1 (2.2)</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>7a</td>
<td>2</td>
<td>L1 (2.2)</td>
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</tr>
<tr>
<td>8</td>
<td>7a</td>
<td>1.5</td>
<td>L2 (2.2)</td>
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</tr>
<tr>
<td>9</td>
<td>7a</td>
<td>1.5</td>
<td>L3 (2.2)</td>
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</tr>
<tr>
<td>10</td>
<td>7a</td>
<td>1.5</td>
<td>L4 (2.2)</td>
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</tr>
<tr>
<td>11</td>
<td>7a</td>
<td>1.5</td>
<td>L5 (2.2)</td>
<td>35</td>
</tr>
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<td>12</td>
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<tr>
<td>14</td>
<td>7a</td>
<td>1.5</td>
<td>-</td>
<td>35</td>
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</table>

*a* Isolated yield. *b* Traditional heating (oil bath).

The cross-coupling reaction was also tested with different solvents (THF, toluene, CH₂Cl₂ or MeCN), copper sources (CuI, CuOAc, Cu(OAc)₂ or CuCl) and bases (K₃PO₄, Cs₂CO₃, K₂CO₃ or Et₃N). The amount of base was important for the yield. Two equivalents of K₃PO₄ 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 K₂CO₃ or Et₃N as base lower yield of compound 9a was obtained (Entries 5 and 7, Table 2), while Cs₂CO₃ gave approximately the same yield as with K₃PO₄ (Entry 6,
Table 2. Changing solvent from MeCN to THF, toluene or CH$_2$Cl$_2$ was not beneficial for the cross-coupling reaction. Only trace amounts of product were observed using toluene or CH$_2$Cl$_2$ 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 arylvinyl iodide 7a and guanidine 8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Copper source</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>Yield (%) of 9a$^a$</th>
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<tr>
<td>1</td>
<td>CuI</td>
<td>K$_3$PO$_4$ (2)</td>
<td>MeCN</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>CuI</td>
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<td>MeCN</td>
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<td>3</td>
<td>CuI</td>
<td>K$_3$PO$_4$ (2)</td>
<td>MeCN</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>CuI</td>
<td>K$_3$PO$_4$ (4)</td>
<td>MeCN</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>CuI</td>
<td>K$_2$CO$_3$ (2)</td>
<td>MeCN</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>CuI</td>
<td>Cs$_2$CO$_3$ (2)</td>
<td>MeCN</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>CuI</td>
<td>Et$_3$N (2)</td>
<td>MeCN</td>
<td>19</td>
</tr>
<tr>
<td>8</td>
<td>CuI</td>
<td>K$_3$PO$_4$ (2)</td>
<td>THF</td>
<td>19</td>
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<td>9</td>
<td>CuI</td>
<td>K$_3$PO$_4$ (2)</td>
<td>Toluene</td>
<td>trace</td>
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<tr>
<td>10</td>
<td>CuI</td>
<td>K$_3$PO$_4$ (2)</td>
<td>CH$_2$Cl$_2$</td>
<td>trace</td>
</tr>
<tr>
<td>11</td>
<td>CuOAc</td>
<td>K$_3$PO$_4$ (2)</td>
<td>MeCN</td>
<td>trace</td>
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<tr>
<td>12</td>
<td>Cu(OAc)$_2$</td>
<td>K$_3$PO$_4$ (2)</td>
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<td>13</td>
<td>CuCl</td>
<td>K$_3$PO$_4$ (2)</td>
<td>MeCN</td>
<td>trace</td>
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</table>

$^a$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 K3PO4 as base compared to Cs2CO3. In addition, trace amounts of several other side products were observed by TLC and 1H 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 K3PO4, or Cs2CO3 as base, resulted in the formation of product 9b. For the reaction using K3PO4 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 Cs2CO3 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 : H₂O (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 K₃PO₄, 45%, or with Cs₂CO₃, 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 BBr₃ gave an intractable mixture of products, while a premixture of NaI and TMSCl 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-cafeic acid (10) and p-coumaric acid (11) were silylated with TBDMSCl / Et₃N in CH₂Cl₂, followed by hydrolysis of the silyl ester with K₂CO₃ in methanol/water to afford the protected aryl acrylic acids 5c and 5d in 76% and 44% yields. The Hunsdiecker-Borodin-type reaction 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) Et₃N, TBDMSCl, CH₂Cl₂, rt, 18 h. (ii) K₂CO₃ (1 equiv.), MeOH : H₂O (1:1), rt, 1 h, 76% (5c) / 44% (5d); (b) NIS (1 equiv.), LiOAc (0.2 equiv.), MeCN : H₂O (19:1), rt, 1 h, 71% (6c) / 74% (6d); (c) 8 (1.5 equiv.), Cul (1.1 equiv.), DMEDA (2.2 equiv.), K₃PO₄ (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 CH₂Cl₂ were purchased from VWR and used as received. N,N’-Dimethylethylenediamine (DMEDA) was distilled and stored over KOH, the same was Et₃N. 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 F₂₅₄ plates, using UV light at 254 nm and 5% alcoholic molybdophosphoric acid for detection. Normasil 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. ¹H NMR and ¹³C 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 ¹H NMR), or for ¹³C resonance signal to CDCl₃ (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 Et₃N (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 data¹⁴ were in accordance with ours: ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 100 MHz): δ 167.6 (C O), 151.1 (C), 149.1 (C), 144.8 (CH), 127.3 (C), 122.6 (CH), 115.4 (CH), 110.9 (CH), 109.5 (CH), 55.9 (CH₃), 55.8 (CH₃), 51.6 (CH₃); 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 C₁₂H₁₄O₄Na: 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 Et₂O (2 x 50 mL). The water layer was adjusted to pH 0 by the addition of 6 M HCl (4 mL) and extracted a second time with CH₂Cl₂ (5 x 50 mL). The latter organic layer was dried over MgSO₄, 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\textsuperscript{15} were in accordance with ours: $^1$H NMR (CDCl\textsubscript{3}, 400 MHz): $\delta$ 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\textsubscript{3}, 100 MHz): $\delta$ 172.4 (CO), 151.5 (C), 149.2 (C), 147.0 (CH), 127.0 (C), 123.2 (CH), 114.8 (CH), 111.0 (CH), 109.7 (CH), 56.0 (CH\textsubscript{3}), 55.9 (CH\textsubscript{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] \textsuperscript{-} (100); HRMS (ESI) Calc. for C\textsubscript{11}H\textsubscript{11}O\textsubscript{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\textsubscript{2}Cl\textsubscript{2} (15 mL) was added slowly to a precooled solution of trans-caffeic acid (1.196 g, 6.66 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (15 mL) and Et\textsubscript{3}N (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\textsubscript{4}, filtered and concentrated in vacuo. The brown oil was dissolved in MeOH (30 mL) and water (30 mL) before K\textsubscript{2}CO\textsubscript{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\textsubscript{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.\textsuperscript{13} 152-155 °C. Published data\textsuperscript{13} were in accordance with ours: $^1$H NMR (CDCl\textsubscript{3}, 400 MHz): $\delta$ 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\textsubscript{3}, 100 MHz): $\delta$ 172.3 (CO), 149.9 (C), 147.2 (C), 147.0 (CH), 127.6 (C), 122.7 (CH), 121.2 (CH), 120.6 (CH), 114.7
(CH), 125.9 (3xCH), 25.8 (3xCH), 18.5 (C), 18.4 (C), 4.1(0) (2xCH), 4.1(1) (2xCH);
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_{4}NaSi_{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_{2}Cl_{2} (15 mL) was added slowly to a precooled solution of trans-p-coumaric acid (1.205 g, 7.31 mmol) in anhydrous CH_{2}Cl_{2} (15 mL) and Et_{3}N (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_{3}CO_{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.\textsuperscript{13c} 128.5-130 °C. Published data\textsuperscript{10b,13c} were in accordance with ours: \textsuperscript{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); \textsuperscript{13}C NMR (CDCl_{3}, 100 MHz): δ 172.8 (CO), 158.3 (C), 146.8 (CH), 130.1 (2xCH), 127.4 (C), 120.6 (2xCH), 114.9 (CH), 25.6 (3xCH_{3}), 18.3 (C), 4.4 (2xCH_{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$_3$NaSi: 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$_2$O (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): $\delta$ 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): $\delta$ 149.4 (C), 149.0 (C), 144.5 (CH), 130.9 (C), 119.3 (CH), 110.9 (CH), 108.2 (CH), 73.9 (CH), 55.9 (CH$_3$), 55.8 (CH$_3$); 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$_2$INa: 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$_2$O (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): $\delta$ 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 (CH), 130.7 (C), 127.3 (2xCH), 114.1 (2xCH), 73.6 (CH), 55.3 (CH$_3$)

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$_2$O (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), 131.5 (C), 121.1 (CH), 119.6 (CH), 118.6 (CH), 73.7 (CH), 25.9 (6xCH$_3$), 18.5 (C), 18.4 (C), $^+$4.0(8) (2xCH$_3$), $^+$4.0(7) (2xCH$_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$_2$INaSi$_2$: 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$_2$O (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 (CH), 131.3 (C), 127.2 (2xCH), 120.3 (2xCH), 73.8 (CH), 25.7 (3xCH$_3$), 18.2 (C), +4.4 (2xCH$_3$); 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$_2$BrNa: 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$_2$O (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 (CH), 128.9 (C), 119.3 (CH), 111.1 (CH), 108.4 (CH), 104.2 (CH), 55.9 (CH$_3$), 55.8 (CH$_3$); IR (KBr) 3081 (w), 2953 (w), 2853 (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$_2$Na: 312.9696, Found 312.9699.

4.11. (Z)-1-((E)-3,4-Dimethoxystyril)-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$_3$PO$_4$ (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): \(\delta 11.61\) (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, 3H), 1.53 (s, 3H); \(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 163.0\) (C=O), 153.1 (C=N), 152.8 (C), 149.0 (C), 148.3 (C), 128.7 (C), 120.6 (CH), 119.4 (CH), 115.1 (CH), 111.1 (CH), 108.0 (CH), 83.9 (C), 80.0 (C), 56.0 (OCH\(_3\)), 55.9 (OCH\(_3\)), 28.2 (3xCH\(_3\)), 28.0 (3xCH\(_3\)); IR (KBr) 3263 (w), 2977 (m), 2932 (m), 1720 (m), 1638 (m), 1513 (m), 1454 (m), 1407 (br. m), 1368 (m), 1310 (s), 1265 (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\(_6\)N\(_3\)Na: 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\(_3\)PO\(_4\) (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): \(\delta 11.57\) (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, 3H), 1.52 (s, 3H); \(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 163.0\) (C), 158.6 (C=N), 153.1 (C), 153.1 (C), 152.7 (C), 128.4 (C), 127.0 (2xCH), 120.6 (CH), 114.6 (CH), 114.0 (2xCH), 83.8 (C), 79.8 (C), 55.2 (OCH\(_3\)), 28.2 (3xCH\(_3\)), 28.0 (3xCH\(_3\)); 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), 1234 (m), 1206 (m), 1153 (br. s), 1104 (s), 1057 (m), 1027 (m), 943 (br. w), 854 (w), 803 (w), 771 (w).
1293 (m), 1247 (s), 1152 (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 C20H30O5N3: 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), K3PO4 (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. 1H NMR (CDCl3, 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), 13C NMR (CDCl3, 100 MHz): δ 163.0 (C), 153.1 (CO), 152.7 (CO), 146.7 (C), 146.1 (C), 129.4 (C), 121.2 (CH), 120.8 (CH), 119.5 (CH), 118.7 (CH), 115.0 (CH), 83.8 (C), 79.8 (C), 28.2 (3xCH3), 28.0 (3xCH2), 25.9 (6xCH3), 18.5 (C), 18.4 (C), +4.1(0) (2xCH3), +4.1(1) (2xCH3); 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 C31H55O6N3NaSi2: 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$_2$CO$_3$ (226 mg, 0.693 mmol) and Cul (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 (CO), 152.8 (CO), 129.0 (C), 127.0 (2xCH), 120.8 (CH), 120.2 (2xCH), 114.8 (CH), 83.9 (C), 80.1 (C), 28.2 (3xCH$_3$), 28.1 (3xCH$_3$), 25.7 (3xCH$_3$), 18.2 (C), +4.4 (2xCH$_3$); IR (KBr) 2929 (m), 2860 (s), 1720 (m), 1639 (s), 1407 (m), 1368 (s), 1316 (s), 1297 (s), 1071 (m), 1057 (s), 912 (w), 889 (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$_3$N$_3$Si: 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$_4$Cl (sat., 10 mL) and extracted with Et$_2$O (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
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 data1-3 were in accordance with ours: 1H NMR (CD3OD, 400 MHz): \( \delta \) 6.93 (d, \( J = 13.9 \) Hz, 1H), 6.82 (s, 1H), 6.70 (s, 2H), 6.16 (d, \( J = 13.9 \) Hz, 1H); 13C NMR (CD3OD, 100 MHz): \( \delta \) 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 C9H11O2N3: 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 Et2O (3 x 15 mL). The organic layer was dried over MgSO4, 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. 1H NMR (CDCl3, 400 MHz): \( \delta \) 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); 13C NMR (CDCl3, 100 MHz): \( \delta \) 162.8 (C), 155.4 (C), 153.1 (C), 152.8 (C), 127.8 (C), 127.2 (2xCH), 120.2 (CH), 115.7 (2xCH), 115.4 (CH), 84.0 (C), 80.2 (C), 28.2 (3xCH3), 28.1 (3xCH3). 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\textsuperscript{4,5} were in accordance with ours: \textsuperscript{1}H NMR (CD\textsubscript{3}OD, 400 MHz): \(\delta\) 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); \textsuperscript{13}C NMR (CD\textsubscript{3}OD, 100 MHz): \(\delta\) 158.1 (C), 156.0 (C), 128.1(1) (CH), 128.1(0) (C), 120.0 (2xCH), 118.0 (CH), 116.6 (CH); Mass spectrum m/z (relative intensity %) 178.2 [M]\textsuperscript{+} (100); HRMS (ESI) Calc. for C\textsubscript{9}H\textsubscript{11}ON\textsubscript{3}: 178.0975, Found 178.0972 which is in accordance with literature.\textsuperscript{4,5}

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Supporting Information

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

Supplementary data related to this article is available on …

References


