

# Synthesis of Venlafaxine from Azadiene via a Hetero-Diels–Alder Approach: New Microwave-Assisted Transketalization and Hydroxymethylation Reactions

Mauro Panunzio,<sup>\*a</sup> Elisa Bandini,<sup>b</sup> Antonio D'Aurizio,<sup>b</sup> Zhining Xia,<sup>c</sup> Xiaojing Mu<sup>c</sup>

<sup>a</sup> ISOF-CNR, Dipartimento di Chimica 'G. Ciamician', Via Selmi, 2, 40126 Bologna, Italy  
Fax +39(051)2099456; E-mail: mauro.panunzio@unibo.it

<sup>b</sup> ISOF-CNR, Area della Ricerca di Bologna, Via Gobetti 101, 40129 Bologna, Italy

<sup>c</sup> Institute of Chemistry and Chemical Engineering, Chongqing University, Chongqing 400044, P. R. of China  
E-mail: zhnxia@yahoo.cn

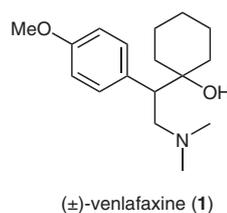
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**Abstract:** Hetero-Diels–Alder (HDA) methodology has been applied to the synthesis of Venlafaxine taking advantage of a novel MW-assisted transketalization and hydroxymethylation reaction.

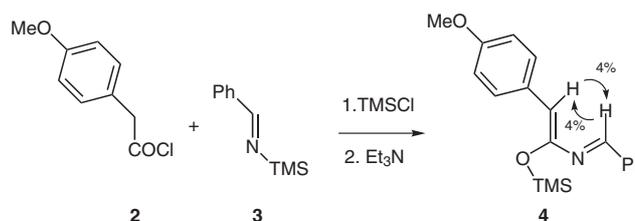
**Key words:** 1,3-aminol, hetero-Diels–Alder reaction, MAOS, Venlafaxine, transketalization

2-Azadienes<sup>1</sup> have been demonstrated to be versatile intermediates in hetero-Diels–Alder (HDA) reactions<sup>2</sup> with aldehydes to furnish perhydrooxazin-4-ones. The latter have been utilized for the production of the 1,3-hydroxyamino moiety, or skeleton, of different biologically active compounds and of important chiral auxiliaries/ligands in asymmetric organic synthesis.<sup>3</sup> In the course of our studies on these interesting intermediates, we have reported on the preparation of biologically active CNS-drugs, Prozac and Duloxetine, in racemic and optically pure form as well, presenting a scaffold of an 1,3-aminol *unsubstituted in the 2-position and a secondary hydroxy functionality*.<sup>4</sup> In this paper we report our attempts to apply this strategy to the synthesis of ( $\pm$ )-Venlafaxine (**1**)<sup>5</sup> characterized by the presence of a substituent (4-methoxyphenyl group) *in the 2-position* of the 1,3-aminol skeleton (Figure 1) and a *tertiary hydroxy functionality*. The importance of **1** resides in the fact that, among a large number of chemical structures found to exhibit antidepressant activity with diminished cardiovascular and anticholinergic liability, this compound has been proven to be the most potent antidepressant agent and has been approved by the drug agencies of many countries for the treatment of depression thanks to its faster onset of action and increased efficiency. From synthetic point of view, the choice of this particular target was dictated by our attempts of rendering the HDA protocol, developed in our laboratories, suitable for the preparation of a library of variably functionalized compounds presenting the 1-hydroxy-3-amino functionalities with or without further substitutions in the backbone chain identified by 1,3-aminol moiety and using as carbonyl-dienophile a ketone. Previous results showed that perhydrooxazin-2-ones may

be prepared from an 2-aza-1,3-diene variably substituted in the position 1 *but unsubstituted in position 4*, and a ketone as dienophile, including hindered ones such as menthone.<sup>6</sup> These results were very interesting since the poor reactivity of ketones compared to aldehydes in hetero-Diels–Alder reactions is well known, owing to both steric and electronic reasons. As a matter of fact, until recently, only a very few examples of HDA reactions of ketones have been reported.<sup>7</sup> Having in hand this information, we started our studies by preparing the intermediate azadiene **4** from (4-methoxyphenyl)acetyl chloride (**2**) and the trimethylsilylbenzaldimine **3** according to an existing protocol<sup>1a,8</sup> (Scheme 1).



**Figure 1** Venlafaxine (**1**)



**Scheme 1** Preparation of azadiene **4**

The necessary [4+2] HDA reaction was next attempted taking advantage of our recent procedure for the preparation of 1,3-perhydrooxazin-4-ones by EuFod [europium(III) tris(1,1,2,2,3,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate)-catalyzed microwave-assisted organic synthesis (MAOS)].<sup>8</sup> Accordingly, reaction of the azadiene **4** with dienophile cyclohexanone (**5**) was performed, using EuFod (0.05%) as catalyst and chlorobenzene as solvent under microwave irradiation (Scheme 2). Workup of the reaction mixture showed the formation of traces of the desired 1,3-perhydrooxazin-4-one **6** (Table 1, entry 1)

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**Table 1** Reaction of Azadiene **4** with Cyclohexanone (**5**) under Different Reaction Conditions

Entry	Diene <b>4</b> (equiv)	<b>5</b> (equiv)	Lewis acid (equiv)	Solvent	Temp (°C)/ Time	Yield of <b>6</b> (%)	Yield of <b>7</b> (%)
1	1	0.5	EuFOD (0.05)	PhCl <sup>a</sup>	135 (40 min) DH <sup>b</sup> 300 W	trace	55.0
2	1	1		PhCl	135 (2 h) DH 300 W	0	40.0
3	1	0.5	EuFOD (0.05)	PhCl	135 (10 h) CH <sup>c</sup>	trace	33.0
4	1	0.5	EuFOD (0.05)	toluene	110 (3 h) DH 300 W	0	32.0
5	1	0.5	EuFOD (0.05)	toluene	110 (20 h) CH	0	30.0
6	1	1	BF <sub>3</sub> ·OEt <sub>2</sub> (1)	CH <sub>2</sub> Cl <sub>2</sub>	-78 to r.t (12 h)	48.0	8.0
<b>7</b>	<b>1</b>	<b>1</b>	<b>BF<sub>3</sub>·OEt<sub>2</sub> (1)</b>	<b>CH<sub>2</sub>Cl<sub>2</sub></b>	<b>-78 (8 h)</b>	<b>62.0</b>	<b>trace</b>
8	1	1	BF <sub>3</sub> ·OEt <sub>2</sub> (1)	CH <sub>2</sub> Cl <sub>2</sub>	0 (8 h)	0	trace
9	1	1	BF <sub>3</sub> ·OEt <sub>2</sub> (1)	CH <sub>2</sub> Cl <sub>2</sub>	25 (72 h)	0	12.0
10	1	1	EuFOD (0.05)	CH <sub>2</sub> Cl <sub>2</sub>	-78 (8 h)	0	0
11	1	1		CHCl <sub>3</sub>	-78 (8 h)	0	0
12	1	1	BF <sub>3</sub> ·OEt <sub>2</sub> (1)	CHCl <sub>3</sub>	25 (12 h)	0	0
13	1	0.5	ZnCl <sub>2</sub> (0.05)	toluene	110 (1 h) DH 300 W	0	9.0
14	1	0.5	ZnCl <sub>2</sub> (0.05)	PhCl	135 (40 min) DH 300 W	0	14.0
15	1	0.5	TiCl <sub>4</sub> (0.05)	PhCl	135 (40 min) DH 300 W	0	11.0
16	1	0.5	AlCl <sub>3</sub> (0.05)	PhCl	135 (40 min) DH 300 W	0	17.0

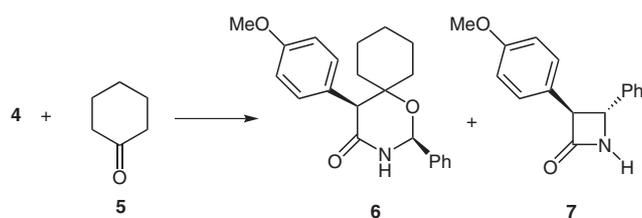
<sup>a</sup> PhCl = chlorobenzene.<sup>b</sup> DH = dielectric heating.<sup>c</sup> CH = convective heating.

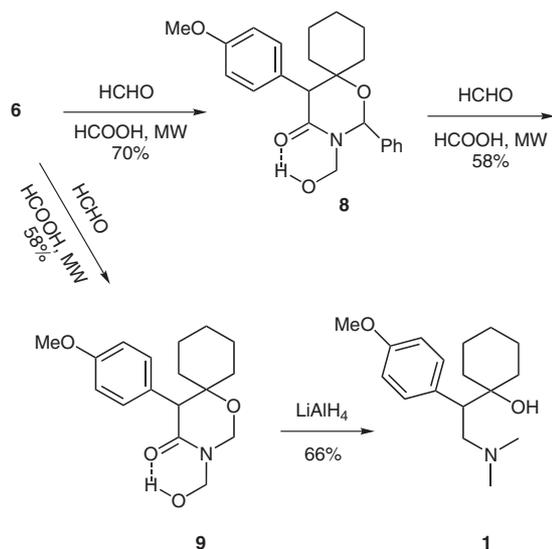
whereas the major product was constituted by the *trans*- $\beta$ -lactam ring **7**, arising from a [2+2] electrocyclozation (for the sake of easy reading only one enantiomer of the racemic mixtures has been depicted in Scheme 2) irrespective of the presence or not of the Lewis acid (Table 1, entry 2).<sup>9</sup> Use of chloroform as solvent, which is known to promote HDA via hydrogen bonding<sup>10</sup> was unsuccessful, even in the presence of BF<sub>3</sub> as Lewis acid (Table 1, entries 11 and 12).

Further experiments, changing different reaction parameters including the very nature of the Lewis acids (Table 1), showed that the preference for a [2+2] electrocyclozation versus a [4+2] HDA is strictly dependent on the reaction temperature used. The best results in the formation of the HDA adduct are obtained at very low temperature (-78 °C, 8 h) in the presence of BF<sub>3</sub> as Lewis acid and

dichloromethane as solvent (Table 1, entry 7).<sup>11</sup> Once obtained, the intermediate perhydroxazin-4-one **6** was used in the synthesis of racemic **1** in a straightforward manner (Scheme 3) by taking advantage of a new MW-mediated transketalization and hydroxymethylation methodologies. In detail, treatment of perhydroxazin-4-one **6** with a mixture of formic acid and formaldehyde under microwave irradiation furnished the *N*-hydroxymethyl derivative **8** in 70% yield. Further treatment of this product in the same reaction conditions gave the transketalized derivative **9** in 58% yield. Alternatively, exhaustive treatment of **6** reported as above (formic acid and formaldehyde, under microwave irradiation) furnished directly a stable intermediate **9** in 58% yield from **6**. Finally, reduction of **9** with LiAlH<sub>4</sub> in THF afforded the target racemic **1** in 66% yield.

In summary, the synthesis of **1** through a hetero-Diels-Alder approach has been achieved. This study has pointed out the high competition between a [2+2] and a [4+2] reactions probably due to stereoelectronic reasons. Notwithstanding, we have been able to address the formation of the sole [4+2] product arising from a HDA pathway by the right choice of the temperature and Lewis acid. Theoretical calculations and studies are currently in progress to fully clarify this important aspect. The results will be reported in due course.

**Scheme 2** For the Lewis acids and reaction conditions used, see Table 1 and the experimental section.



**Scheme 3** Synthesis of **1** from perhydrooxazinone **6**

All starting compounds, unless otherwise stated, were purchased. Reactions were run under an atmosphere of dry N<sub>2</sub> or argon. FT-IR spectra were recorded on a PerkinElmer IR spectrometer, mass spectra on Finnigan MAT instrument, and NMR spectra on a Varian Mercury 400 MHz spectrometer using the residual signal of the solvent as internal standard. Chemical shifts are reported on the  $\delta$  scale and coupling constants ( $J$ ) in Hertz. Microwave reactions were performed on a Prolabo Synthwave 402 microwave oven. Solvents were distilled and dried according to standard procedures.

**[(1Z,3E)-1-(4-Methoxyphenyl)-4-phenylbuta-1,3-dien-2-yloxy]trimethylsilane (**4**)**

An oven dried 100 mL three-necked, round-bottomed flask, equipped with a Teflon-coated magnetic stirring bar, a spirit thermometer, and a needle for nitrogen inlet was charged with anhydrous hexane (15 mL) and LiN(SiMe<sub>3</sub>)<sub>2</sub> (1 M soln in THF; 1 mL, 1 mmol) and placed in an ice bath. At 0 °C, benzaldehyde (0.101 mL, 1 mmol) in hexane (1 mL) was added from a dropping funnel and the mixture was stirred for 1 h at 0 °C. A solution of Me<sub>3</sub>SiCl (0.126 mL, 1 mmol) in hexane (1 mL) was added at 0 °C and the stirring was maintained for 1 h at r.t. A white precipitate was observed. At 0 °C were added Et<sub>3</sub>N (0.278 mL, 2 mmol) in hexane (1 mL) and (4-methoxyphenyl)acetyl chloride (184 mg, 1 mmol) in anhydrous Et<sub>2</sub>O (1 mL) and the mixture was stirred for 2 h at r.t. The mixture was filtered through a Celite pad and the solvent was evaporated, furnishing the azadiene **4**, which was identified by <sup>1</sup>H and <sup>13</sup>C NMR spectra and used as such in the following reactions; yield: 325 mg (100%); yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.45 (s, 1 H), 7.83 (m, 2 H), 7.57 (d,  $J$  = 8.8 Hz, 2 H), 7.45 (m, 3 H), 6.88 (d,  $J$  = 8.8 Hz, 2 H), 5.92 (s, 1 H), 3.82 (s, 3 H), 0.21 (s, 9 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 157.96, 154.45, 151.94, 136.04, 130.89, 129.84, 129.07, 128.65, 128.59, 113.58, 106.35, 55.06, 0.70.

**(2R\*,5R\*)-5-(4-Methoxyphenyl)-2-phenyl-1-oxa-3-azaspiro[5.5]undecan-4-one (**6**); Table 1, Entry 7**

Compound **4** (325 mg, 1 mmol) was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and added to a solution of cyclohexanone (**5**; 98 mg, 1 mmol) and BF<sub>3</sub>·OEt<sub>2</sub> (142 mg, 1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) previously cooled at -78 °C. The mixture was stirred at this temperature for 8 h and then poured into sat. aq NaHCO<sub>3</sub> (10 mL) and extracted

with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed under vacuum. The mixture was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 4:6) to give **6**; yield: 217 mg (62%); white solid; mp 186–188 °C.

IR (CHCl<sub>3</sub>): 1665 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.56 (m, 2 H), 7.46 (m, 3 H), 7.34 (d,  $J$  = 8.8 Hz, 2 H), 6.84 (d,  $J$  = 8.8 Hz, 2 H), 6.25 (br s, 1 H), 5.92 (s, 1 H), 3.78 (s, 3 H), 3.35 (s, 1 H), 2.27 (d,  $J$  = 9.2 Hz, 1 H), 1.62 (m, 5 H), 1.32 (m, 3 H), 1.13 (m, 1 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 171.12, 158.84, 138.30, 130.47, 129.61, 129.03, 126.63, 113.80, 79.52, 76.92, 56.65, 55.21, 34.92, 33.28, 25.45, 22.08, 21.27.

MS:  $m/z$  = 352 (M + 1), 306, 253, 201, 159, 148, 120, 105, 91, 77.

Anal. Calcd for C<sub>22</sub>H<sub>25</sub>NO<sub>3</sub>: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.38; H, 7.19; N, 3.95.

**(3S\*,4S\*)-3-(4-Methoxyphenyl)-4-phenylazetid-2-one (**7**)**

Table 1; Entry 1: Compound **4** (325 mg, 1 mmol) was dissolved in anhydrous chlorobenzene (5 mL). Cyclohexanone (**5**; 49 mg, 0.5 mmol) and EuFOD (50 mg, 0.05 mmol) were added. The resulting mixture was submitted to a microwave irradiation (40 min, 300 W). After the irradiation, the solvent was removed under vacuum. The crude mixture was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 7:3) to give the β-lactam **7**; yield: 139 mg (55%).

Table 1, Entries 13, 14, 15, and 16: These experiments were performed following the same procedure and using the Lewis acid shown in the table.

Table 1, Entry 5: Compound **4** (325 mg, 1 mmol) was dissolved in anhydrous toluene (10 mL), cyclohexanone (**5**; 49 mg, 0.5 mmol) and EuFOD (50 mg, 0.05 mmol) were added and the mixture was refluxed for 20 h. The solvent was removed under vacuum and the mixture was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 7:3) to give the β-lactam **7**; yield: 76 mg (30%); white solid; mp 135–138 °C.

IR (CHCl<sub>3</sub>): 1761 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.35 (m, 5 H), 7.24 (d,  $J$  = 8.8 Hz, 2 H), 6.90 (d,  $J$  = 8.8 Hz, 2 H), 6.80 (br s, 1 H), 4.61 (d,  $J$  = 2 Hz, 1 H), 4.14 (d,  $J$  = 2 Hz, 1 H), 3.80 (s, 3 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.77, 159.10, 139.50, 129.99, 128.51, 128.47, 126.75, 125.48, 114.31, 65.58, 60.48, 55.23.

MS:  $m/z$  = 254 (M + 1), 210, 194, 179, 165, 148, 120, 105, 91, 77.

Anal. Calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>2</sub>: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.60; H, 6.02; N, 5.48.

**(2R\*,5R\*)-3-Hydroxymethyl-5-(4-methoxyphenyl)-2-phenyl-1-oxa-3-azaspiro[5.5]undecan-4-one (**8**)**

Compound **6** (120 mg, 0.34 mmol) was dissolved in toluene (2 mL), and formic acid (0.1 mL) and formaldehyde (37% in H<sub>2</sub>O, 1 mL) were added. The mixture was irradiated in a microwave oven (6 min, 150 W). The formic acid was removed under vacuum and the mixture poured into sat. aq NaHCO<sub>3</sub> (5 mL) and then extracted with EtOAc (3 × 15 mL). The organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under vacuum. The crude mixture was purified by flash chromatography on silica gel to give **8**; yield: 90 mg (70%); colorless oil.

IR (CHCl<sub>3</sub>): 3350, 1641 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.56 (m, 2 H), 7.48 (m, 3 H), 7.44 (d,  $J$  = 8.8 Hz, 2 H), 6.87 (d,  $J$  = 8.8 Hz, 2 H), 6.04 (s, 1 H), 5.21 (d,  $J$  = 11.2 Hz, 1 H), 4.14 (d,  $J$  = 11.2 Hz, 1 H), 3.78 (s, 3 H), 3.42 (s, 1 H), 2.27 (d,  $J$  = 12.0 Hz, 1 H), 1.64 (m, 5 H + OH), 1.32 (m, 1 H), 1.14 (m, 1 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 172.18, 158.87, 137.12, 130.54, 129.78, 129.06, 128.64, 127.95, 113.83, 83.83, 76.61, 68.42, 56.88, 55.20, 34.58, 33.00, 25.39, 22.12, 21.14.

MS:  $m/z$  = 352, 253, 148, 120, 91, 77.

Anal. Calcd for  $\text{C}_{23}\text{H}_{27}\text{NO}_4$ : C, 72.42; H, 7.13; N, 3.67. Found: C, 72.18; H, 7.10; N, 3.58.

**( $\pm$ )-3-Hydroxymethyl-5-(4-methoxyphenyl)-1-oxa-3-aza-spiro[5.5]undecan-4-one (9) from 8**

Compound **8** (170 mg, 0.45 mmol) was dissolved in formic acid (2 mL) and formaldehyde (37% in  $\text{H}_2\text{O}$ , 1 mL). The mixture was irradiated in a microwave oven (1 min, 75 W). The formic acid was removed under vacuum and the mixture poured into sat. aq  $\text{NaHCO}_3$  (5 mL) and then extracted with  $\text{EtOAc}$  ( $3 \times 10$  mL). The organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under vacuum. The crude mixture was purified by flash chromatography on silica gel to give **9**; yield: 80 mg (58%); colorless oil.

IR ( $\text{CHCl}_3$ ): 1644, 3388  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.17 (d,  $J$  = 8.8 Hz, 2 H), 6.83 (d,  $J$  = 8.8 Hz, 2 H), 5.06 (dd,  $J$  = 7.6, 16.0 Hz, 2 H), 4.93 (d,  $J$  = 11.2 Hz, 1 H), 4.69 (d,  $J$  = 11.2 Hz, 1 H), 3.77 (s, 3 H), 3.31 (s, 1 H), 1.95 (d,  $J$  = 13.6 Hz, 1 H), 1.56–1.10 (m, 9 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 170.34, 158.86, 130.66, 128.47, 113.73, 76.54, 72.86, 68.37, 57.10, 55.21, 33.16, 32.77, 25.29, 21.68, 21.11.

MS:  $m/z$  = 306 ( $M + 1$ ), 276, 177, 148, 120, 105, 91.

Anal. Calcd for  $\text{C}_{17}\text{H}_{23}\text{NO}_4$ : C, 66.86; H, 7.59; N, 4.59. Found: C, 67.05; H, 7.61; N, 4.45.

**( $\pm$ )-3-Hydroxymethyl-5-(4-methoxyphenyl)-1-oxa-3-aza-spiro[5.5]undecan-4-one (9) from 6**

Compound **6** (100 mg, 0.28 mmol) was dissolved in formic acid (2 mL) and formaldehyde (37% in  $\text{H}_2\text{O}$ , 4 mL). The mixture was irradiated in a microwave oven (5 min, 150 W). The formic acid was removed under vacuum and the mixture poured into sat. aq  $\text{NaHCO}_3$  (5 mL) and then extracted with  $\text{EtOAc}$  ( $3 \times 10$  mL). The organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under vacuum. The crude mixture was purified by flash chromatography on silica gel to give **9**; yield: 50 mg (58%).

**( $\pm$ )-1-[2-Dimethylamino-1-(4-methoxyphenyl)ethyl]cyclohexanol (1) [( $\pm$ )-Venlafaxine]**

Compound **9** (92 mg, 0.3 mmol) was dissolved in anhyd THF (10 mL) at 0 °C.  $\text{LiAlH}_4$  (23 mg, 0.6 mmol) was added and the mixture was stirred for 30 min at 0 °C, and then heated at 40 °C for 2 h. Aq 1 M HCl (5 mL) was added at 0 °C and the THF was removed under vacuum. The aqueous phase was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL), basified (pH 10) with  $\text{NH}_4\text{OH}$  and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 15$  mL). The organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under vacuum to give **1**; yield: 182 mg (66%). An aliquot of the product was dissolved in *i*-PrOH (5 mL) saturated with HCl gas to prepare the hydrochloride salt of Venlafaxine-HCl, which presented spectral data identical with the literature data.<sup>5c</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.04 (d,  $J$  = 8.8 Hz, 2 H), 6.80 (d,  $J$  = 8.8 Hz, 2 H), 3.78 (s, 3 H), 3.27 (t,  $J_1$  = 12.4 Hz,  $J_2$  = 24.8 Hz, 1 H), 2.93 (dd,  $J$  = 3.6, 12.4 Hz, 1 H), 2.31 (s, 6 H), 2.28 (dd,  $J$  = 3.6, 24.8 Hz, 1 H), 1.50 (m, 8 H), 0.93 (m, 2 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 158.22, 132.70, 130.08, 113.27, 74.22, 61.17, 55.14, 51.60, 45.41, 38.01, 31.15, 25.95, 21.57, 21.30.

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