



**HAL**  
open science

**An expeditious total synthesis of ( $\pm$ )-jamtine using condensation between imine and acid anhydride total synthesis of ( $\pm$ )-jamtine using condensation between imines and acid anhydride**

Joelle Pérard-Viret, Florence Souquet, Marie-Line Manisse, Jacques Royer

► **To cite this version:**

Joelle Pérard-Viret, Florence Souquet, Marie-Line Manisse, Jacques Royer. An expeditious total synthesis of ( $\pm$ )-jamtine using condensation between imine and acid anhydride total synthesis of ( $\pm$ )-jamtine using condensation between imines and acid anhydride. *Tetrahedron Letters*, 2010, 51 (1), pp.96-98. 10.1016/j.tetlet.2009.10.091 . hal-01904955

**HAL Id: hal-01904955**

**<https://hal.science/hal-01904955>**

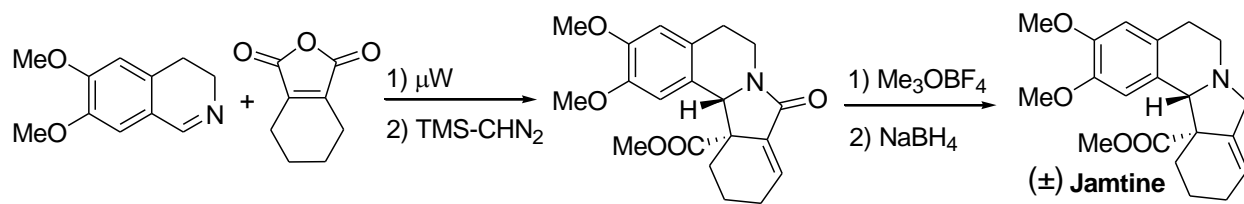
Submitted on 25 Oct 2018

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**An expeditious total synthesis of (±)-jamtine using condensation between imines and acid anhydride**

Joelle Pérard-Viret, Florence Souquet, Marie-Line Manisse, Jacques Royer\*



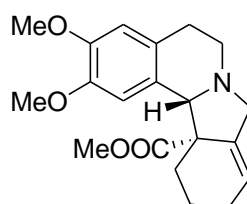
# An expeditious total synthesis of ( $\pm$ )-jamtine using condensation between imines and acid anhydride.

**Joelle Pérard-Viret, Florence Souquet, Marie-Line Manisse, Jacques Royer\***

Synthèse et structure de molécules d'intérêt pharmacologique, UMR 8638 CNRS-Université Paris Descartes, 4 avenue de l'Observatoire, 75270 Paris cedex 06, France  
jacques.royer@parisdescartes.fr

**Abstract:** A totally convergent and very short (3 steps) synthesis of ( $\pm$ )-jamtine was described. The key step of this sequence was the condensation of 6,7-dimethoxy-3,4-dihydroisoquinoline and tetrahydrophthalic anhydride under microwave activation which occurred in good yield and high diastereomeric excess.

Our general interest to the synthesis of diversely substituted pyrrolidine derivatives<sup>1</sup> led us to launch a study on the total synthesis of jamtine (**1**). This compound is one of the medicinal alkaloids isolated from the climbing shrub *coculus hirsutus* which originates from Pakistan and India.<sup>2</sup> This plant is renowned for its therapeutic properties and is used in folk medicine. Jamtine together with others extracted substances was found to have significant antihyperglycemic activity.<sup>3</sup>



jamtine **1**

Figure

Up to now, only two total syntheses have been reported: the first one was based on a thionium/N-acyliminium ion cascade by Padwa<sup>4</sup> and the second was an asymmetric synthesis using a chiral base desymmetrisation by Simpkins.<sup>5</sup>

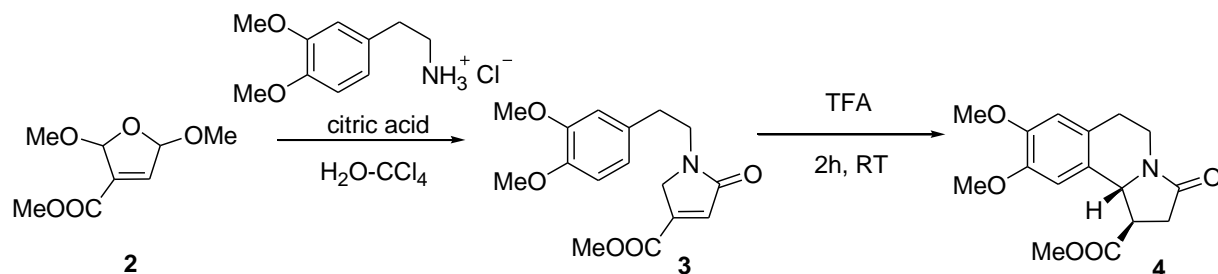
We want to report herein our own efforts towards the synthesis of jamtine which allowed us to achieve an expeditious synthesis of this alkaloid.<sup>6</sup> During the redaction of this manuscript we were aware from a recent paper of Shaw<sup>7</sup> which described the condensation reaction we used as a key step, with the same substrates and experimental conditions along a methodologic study.

## Results and discussion.

### 1- First synthetic plan: dimethoxydihydrofuran condensation.

We already reported on the condensation of a primary amine with dimethoxydihydrofuran to prepare pyrrolidones.<sup>1</sup> The reaction was applied to the preparation of several pyrrolidine derivatives but also to polycyclic compounds including pyrroloisoquinolines.<sup>1b</sup> We thought

that this condensation could be extended to adequately substituted dimethoxydihydrofuran to prepare pyrroloisoquinoline ester **4** as a precursor of jamtine (**1**) (Scheme 1). We thus prepared dimethoxydihydrofuran methyl ester **2** according to the literature<sup>8</sup> and engaged this compound in the condensation with 2-(3,4-dimethoxyphenyl)ethylamine.HCl in a water/CCl<sub>4</sub> biphasic system. The reaction provided pyrrolidone **3** (50% yield) which was treated with TFA at rt for 2h to give the pyrroloisoquinoline **4** in 76% yield as a single diastereomer.

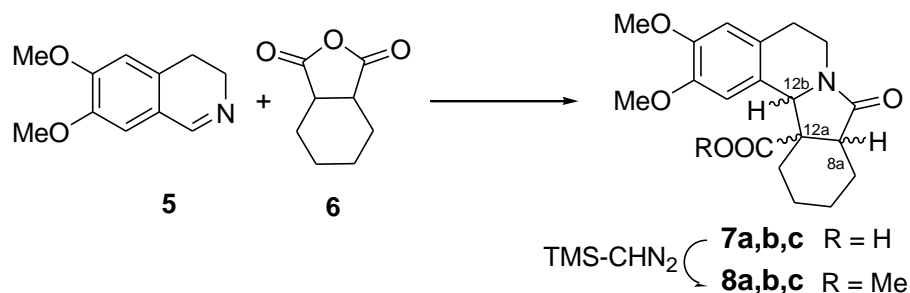


Though this condensation gave a rapid access to the tricyclic intermediate **4**,<sup>9</sup> the rest of the synthesis to jamtine (**1**) would consist in the introduction of the cyclohexene D-ring which would probably hamper the overall sequence by the use of some tedious further steps. We then looked for a more convergent approach and turned our attention to the Castagnoli<sup>10</sup> reaction which should offer a better solution to our synthetic task.

#### 2-second synthetic plan: Castagnoli condensation

Forty years ago, Castagnoli described a reaction between imines and cyclic anhydrides to form lactams. This process could be used to achieve convergent syntheses of natural or biological active products.<sup>11</sup> We thought that this cycloaddition could be the exact answer to the synthesis of jamtine (**1**) allowing the installation in a single step of the four rings of the natural product as well as the carboxylic acid function.

The reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline (**5**)<sup>12</sup> with 1,2-cyclohexanedicarboxylic anhydride (**6**) was first investigated in refluxing toluene (scheme 2, table 1, entry 1). After 3 days, 29% of diastereomeric mixture of the expected carboxylic acid **7** was isolated.



It was rapidly found that the condensation could be dramatically improved by the use of microwaves activation<sup>13</sup> since 70% yield was obtained after a 45 minutes irradiation at 150° C in toluene (table 1, entry 2).<sup>14</sup>

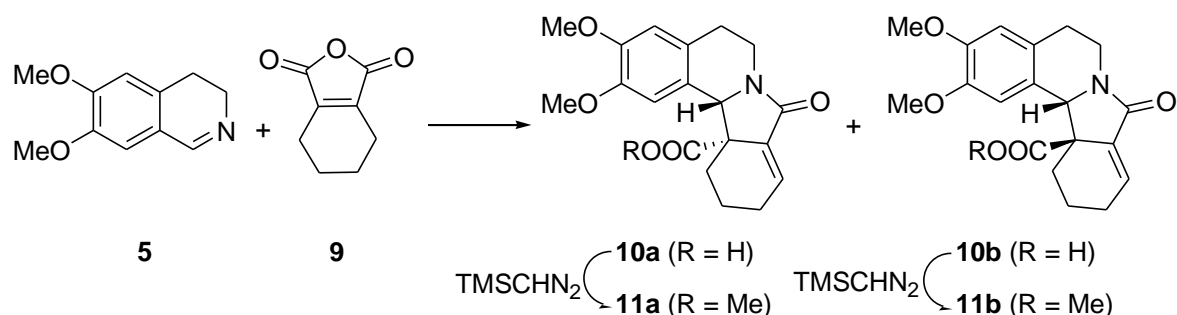
**Table 1. Condensation of imine 5 with anhydride 6:**

entry	solvent	Experimental conditions	<b>7</b> Yield (%)	diastereomeric ratio <sup>(a)</sup> a / b / c (%)
1	toluene	Reflux, 3 days	29	68 / 5 / 27
2	toluene	$\mu$ W, <sup>(b)</sup> 45 min, 150° C	70	53 / 30 / 17
3	ClCH <sub>2</sub> CH <sub>2</sub> Cl	$\mu$ W, 45 min, 150° C	20	61 / 36 / 3
4	DMF	$\mu$ W, 45 min, 150° C	33	50 / 50 / -
5	CH <sub>3</sub> CN	$\mu$ W, 45 min, 150° C	75	60 / 32 / 8

<sup>(a)</sup> estimated by NMR on the crude reaction mixture <sup>(b)</sup>microwaves reactor

Nevertheless, this better yield was accompanied by a lower diastereoselectivity. Then the effect of the solvent on the reaction was briefly examined. Toluene or acetonitrile were found to give the best yields while with similar and poor diastereoselectivity (table 1, entries 2 and 5). In any cases, three isomers were detected among the four theoretically possible. The major isomer **8a**<sup>15</sup> could be easily isolated after esterification (TMSCHN<sub>2</sub>,<sup>16</sup> 88-100% yield). This compound was not identical with that one described by Simpkins (epimeric at C<sub>8a</sub>), but it possessed the required *syn* (C<sub>12a</sub>-C<sub>12b</sub>) configuration<sup>17</sup> and thus could be transformed to jamine through the already described synthesis. Ester **8b** exhibited a reverse *anti* (C<sub>12a</sub>-C<sub>12b</sub>) stereochemistry.<sup>18</sup>

Despite this success, we anticipated that the use of unsaturated anhydride **9** instead of **6**, should provide a more convergent approach giving an intermediate possessing the required double bond. Indeed, under similar experimental conditions (CH<sub>3</sub>CN,  $\mu$ W reactor, 150° C for 45min.) it was our delight to find that isoindoloisoquinoline acid **10**<sup>14</sup> was formed in a nice 78% yield and a 1:1 mixture of two diastereomers (scheme 3, table 2):



Scheme 3

**Table 2. Condensation of imine 5 with anhydride 9:**

entry	solvent	Experimental <sup>(a)</sup> conditions	<b>10</b> Yield (%)	diastereomeric ratio <sup>(b)</sup> <b>a</b> ( <i>syn</i> ) / <b>b</b> ( <i>anti</i> ) (%)
1	CH <sub>3</sub> CN	45 min, 150° C	78	43/57
2	toluene	45 min, 150° C	62	25/75
<b>3</b>	<b>THF</b>	<b>45 min, 150° C</b>	<b>84</b>	<b>20/80</b>
4	CHCl <sub>3</sub>	45 min, 150° C	62	36/64
5	CH <sub>3</sub> CN	90 min, 150° C	84	62/38
<b>6</b>	<b>CH<sub>3</sub>CN</b>	<b>90 min, 160° C</b>	<b>76</b>	<b>83/17</b>
7	CH <sub>3</sub> CN	45 min, 180° C	48	95/ 5

<sup>(a)</sup>All the reactions were performed under microwave activation. <sup>(b)</sup> estimated by NMR.

By analogy with the previous study, we reasoned that the diastereomeric ratio should be modified by varying the experimental conditions (Table 2). We then investigated the reaction of **9** in different solvents (Table 2, entries 1-4). Using the same irradiation time and temperature, it appeared that when acetonitrile or tetrahydrofuran were employed, highest yields were observed, but variable diastereoselectivity ratio was found. With THF (Table 2, entry 3), a clean and high yielding reaction was observed but unfortunately the *anti* diastereoisomer **10b** was the major isomer.

In order, to reverse the diastereomeric ratio, we focussed on the reaction in acetonitrile and changed the irradiation time and the temperature (table 2, entries 1, 5-7)). It was then found that a longer reaction time led predominantly to **10a**. In the same way, a slight increase of the temperature (Table 2, entry 6) led to a 76% yield and a good 83/17 ratio in favour of the *syn* diastereomer. Eventually higher temperature (Table 2, entry 7) gave a 95 / 5 ratio albeit in lower yield (some degradation occurred).

The supposed thermodynamic control of the reaction was checked. On heating ( $\mu$ W reactor, 150°C, 90 min.), the 20 / 80 mixture of *syn* / *anti* diastereomers **10** (arising from THF experiment) was converted into a 50 / 50 mixture in 80% yield. The reaction was thus reversible and an acyliminium intermediate could be invoked. This clearly suggested that the *syn* isomer should be the thermodynamic product of this condensation as proposed by Shaw,<sup>7</sup> on the basis of theoretical calculations. Nevertheless, this author did not experimentally verify his proposal and suggested an inverse diastereomeric ratio according to the presence, or not, of Et<sub>3</sub>N, Et<sub>3</sub>N-HCl.

The *syn* methyl ester **11a** was obtained in 56% from **5** after treatment of the crude mixture (83 / 17) of acids **10** with trimethylsilyl diazomethane and separation. The reduction of the amide function following the published method (Et<sub>3</sub>OBf<sub>4</sub> then NaBH<sub>4</sub>, 64%) gave jamtine (**1**).

In summary, we described an efficient and highly convergent synthesis of ( $\pm$ )-jamtine (**1**)<sup>19</sup> in 3 steps and 36% overall yield.

## References and notes

- 1 (a) Baussanne, I. ; Dudot, B. ; Pérard-Viret, J. ; Planas, L. ; Royer, J. *Arkivoc*, **2006**, 7, 57-66 and references cited herein. (b) Fontaine, H. ; Baussanne, I. ; Royer, J. *Synthetic Commun.* **1997**, 27, 2817-2824. (c) Halie, D.; Pérard-Viret, J.; Dufour, S.; Royer, J. *Tetrahedron* **2009**, 65, 1402-1414.
- 2 (a) Ahmad, V. U.; Rahman, A.; Rasheed, T.; Rehman, H. *Heterocycles* **1987**, 26, 1251-1255. (b) Rasheed, T.; Khan, M. N. I.; Zhadi, S. S. A.; Durrani, S. J. *J. Nat. Prod.* **1991**, 54, 582-584.
- 3 Badole, S.; Patel, N.; Bodhankar, S.; Jain, B.; Bhardwaj, S. *Indian. J. Pharmacol.* **2006**, 38, 49-53.
- 4 (a) Padwa, A.; Danca, M. D. *Org. Lett.* **2002**, 4, 715-717. (b) Padwa, A.; Danca, M. D.; Hardcastle, K. I.; McClure, M. S. *J. Org. Chem.* **2003**, 68, 929-941.
- 5 (a) Simpkins, N. S.; Gill, C. D. *Org. Lett.* **2003**, 5, 535-537. (b) Gill, C. D.; Greenhalgh, D. A.; Simpkins, N. S. *Tetrahedron* **2003**, 59, 9213-9230.
- 6 Preliminary communication at the XIIth ICSN Symposium: "from organic chemistry to chemical biology", July, 11-12<sup>th</sup>, 2009. Gif-sur-Yvette, France.
- 7 Tang, Y.; Fettinger, J. C.; Shaw, J. T. *Org. Lett.* **2009**, 11, 3802-3805.
- 8 Stibor, I.; Srogl, J.; Janda, M.; Piricova, N.; Vlazny, K. *Coll. Czech. Chem. Commun.* **1982** 47, 3261-3267.

- 
- 9 analytical data for **4**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  (ppm) : 2.35-2.62 (4H, m); 2.68-2.86 (2H, m); 3.53 (3H, s,  $\text{OCH}_3$ ); 3.55 (3H, s,  $\text{OCH}_3$ ); 3.59 (3H, s,  $\text{OCH}_3$ ); 3.89 (1H, m); 4.68 (1H, d,  $J = 7.5$  Hz, CHN); 6.34 (1H, s,  $\text{H}_{\text{ar}}$ ); 6.49 (1H, s,  $\text{H}_{\text{ar}}$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) : 27.7 ( $\text{CH}_2$ ); 35.1 ( $\text{CH}_2$ ); 36.9 ( $\text{CH}_2$ ); 45.4 (CH); 52.3 ( $\text{COOMe}$ ); 55.4 (OMe); 55.5 (OMe); 58.4 (CH); 107.6 ( $\text{CH}_{\text{ar}}$ ); 111.5 ( $\text{CH}_{\text{ar}}$ ); 125.6 ( $\text{C}_{\text{ar}}$ ); 127.7 ( $\text{C}_{\text{ar}}$ ); 147.8 ( $\text{C}_{\text{ar}}$ ); 147.9 ( $\text{C}_{\text{ar}}$ ); 169.7 (CO); 173.4 (CO)
- 10 Castagnoli, N. *J. Org. Chem.* **1969**, *34*, 3187-3189.
- 11 (a) Cushman, M.; Castagnoli, N. *J. Org. Chem.* **1971**, *36*, 3404-3406. (b) Cushman, M.; Gentry, J.; Dekow, F. W. *J. Org. Chem.* **1977**, *42*, 1111-1116. (c) Gonzalez-Lopez, M.; Shaw, J. T. *Chem. Rev.* **2009**, *109*, 164-189.
- 12 Warrenner, R. N.; Liu, L.; Russel, R. A. *Tetrahedron* **1998**, *54*, 7485-7496.
- 13 Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles* **1990**, *30*, 741-744.
- 14 General procedure : Imine **5** (96 mg; 0.5 mmol) and anhydride **6** or **9** (0.5 mmol) in 2 mL of solvent was heated in microwave reactor under stirring. The solution was concentrated *in vacuo* and extracted with NaOH 1M, washed twice with  $\text{CH}_2\text{Cl}_2$ . The aqueous layer was acidified by concentrated HCl, extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 15mL). The organic layers were dried with anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo*.
- 15 Analytical data for **8a**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  (ppm) : 1.15-1.35 (3H, m); 1.60-1.85 (3H, m); 2.06 (1H, m); 2.35 (1H, m); 2.47 (1H, m); 2.65-2.76 (3H, m); 3.16 (3H, s,  $\text{COOMe}$ ); 3.80 (3H, s,  $\text{OCH}_3$ ); 3.84 (3H, s,  $\text{OCH}_3$ ); 4.33 (1H, m); 4.62 (1H, s, CHN); 6.53 (1H, s,  $\text{H}_{\text{ar}}$ ); 6.59 (1H, s,  $\text{H}_{\text{ar}}$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) : 21.9 ( $\text{CH}_2$ ); 23.0 ( $\text{CH}_2$ ); 25.1 ( $\text{CH}_2$ ); 28.1 ( $\text{CH}_2$ ); 32.4 ( $\text{CH}_2$ ); 36.5 ( $\text{CH}_2$ ); 51.1 (CH); 51.2 ( $\text{COOMe}$ ); 55.8 (OMe); 56.0 (OMe); 58.8 ( $\text{C}_q$ ); 64.4 (CHN); 111.4 ( $\text{CH}_{\text{ar}}$ ); 109.5 ( $\text{CH}_{\text{ar}}$ ); 123.5 ( $\text{C}_{\text{ar}}$ ); 127.2 ( $\text{C}_{\text{ar}}$ ); 147.6 ( $\text{C}_{\text{ar}}$ ); 148.1 ( $\text{C}_{\text{ar}}$ ); 171.3 (CO); 173.4 (CO)
- 16 Presser, A.; Hüfner, A. *Monatsh. Chem.* **2004**, *135*, 1015-1022.
- 17 The *syn* isomer is characterized by a strong upfield shift of the methyl group of the ester; see ref. 2a.
- 18 Compound **8c** has not been obtained in pure form, its configuration was tentatively assigned as *anti* ( $\text{C}_{12a}$ - $\text{C}_{12b}$ ) after examination of the NMR spectra of the mixture **8a-c**.
- 19 The analytical data of our synthetic material were identical with those described by Padwa<sup>4</sup> and Simpkins<sup>5</sup> who mentioned some doubt on the structure of the natural product.