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## Total synthesis of (–)-indolizidine 167B via an unusual Wolff rearrangement from an $\alpha,\beta$ -unsaturated diazoketone

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## ABSTRACT

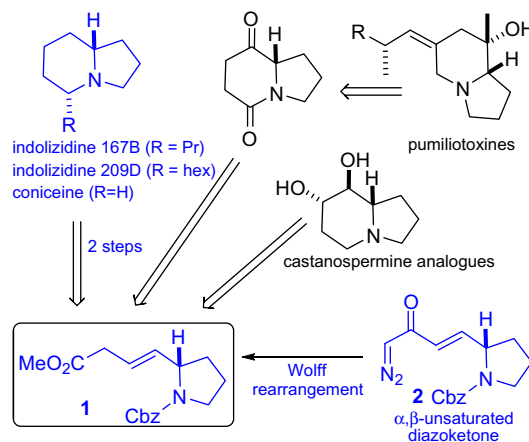
A concise synthesis of the (–)-indolizidine alkaloid 167B and two formal syntheses of (–)-indolizidine 209D and (–)-coniceine are described in just three steps from an  $\alpha,\beta$ -unsaturated diazoketone, via an unusual photochemical Wolff rearrangement. Preparation of the unsaturated diazoketone is straightforward from *N*-Cbz-prolinal and a 3-diazo-2-oxopropylphosphonate, employing a Horner–Wadsworth–Emmons reaction. The strategy should be feasible and easily adaptable to the synthesis of other indolizidine alkaloids and analogues.

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Indolizidine alkaloids are among the most important classes of nitrogen heterocycles. Possessing an azabicyclic unit, these compounds have become common targets in synthesis due to their unique structure and interesting pharmacological activities.<sup>1</sup> For example, non-natural<sup>2</sup> indolizidines 167B and 209D and the natural pumiliotoxins (Scheme 1), isolated from the skin secretions of certain neotropical amphibians, are noncompetitive blockers of neuromuscular transmission<sup>3</sup> and promising cardiotonics,<sup>4</sup> respectively. Despite many interesting total syntheses of these compounds, more general, short and diversity-oriented approaches are still desirable.

Recently, we described a new method<sup>5</sup> to prepare  $\alpha,\beta$ -unsaturated diazoketones from aldehydes, employing a new Horner–Wadsworth–Emmons (HWE) reagent, and its application in a short synthesis of pyrrolidines. Herein, in continuation with this chemistry, we would like to describe an expedient synthesis of (–)-indolizidine 167B in four steps from commercially available and easily prepared (*S*)-*N*-Cbz-prolinal.<sup>6</sup> It is worth of mentioning that the majority of examples in the literature<sup>1,7,8</sup> describes the asymmetric total synthesis of these indolizidines in lengthy paths (8–14 steps) from commercially available reagents, only a few being shorter than that. Shibasaki<sup>9</sup> and Rovis<sup>10</sup> reported the shortest syntheses known to date of (–)-indolizidine 209D (five steps from glutarimide and 5-hexenoic acid, respectively), whereas O'Brien<sup>11</sup> and Settambolo<sup>12</sup> reported the syntheses of (–)-indolizidine 167B in six steps from *N*-Boc-Pyrrolidine and *D*-norvaline, respectively.

As depicted in Scheme 1, we envisaged that the synthesis of indolizidines 167B and 209D, as well as other indolizidine alkaloids such as pumiliotoxins, coniceine, and castanospermine analogues, could be easily and concisely reached from  $\beta,\gamma$ -unsaturated ester **1**. In turn, key intermediate **1** could be prepared in a single step by an unusual Wolff rearrangement from an  $\alpha,\beta$ -unsaturated diazoketone such as **2**. In contrast to the enormous number of applications from common saturated diazoketones, few reports of applications of the rarer  $\alpha,\beta$ -unsaturated diazoketones are found in the literature. Despite that, we believe that  $\alpha,\beta$ -unsaturated

Scheme 1. Indolizidines alkaloids from  $\alpha,\beta$ -unsaturated diazoketones.

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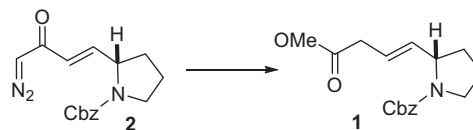
diazoketones are very promising multi-functional intermediates and can lead to short and diversity-oriented syntheses of many compounds, including alkaloids.

We started our work by preparing  $\alpha,\beta$ -unsaturated diazoketone **2** in a 70% yield as a single *E* isomer, employing our recently described methodology<sup>5</sup> (Scheme 2). No epimerization occurred at this critical step according to careful HPLC analysis<sup>13</sup> (>99% ee). Conversion of diazoketone **2** into key intermediate **1** proved to be difficult, affording only low yields under usual thermal conditions for the Wolff rearrangement (30 mol % AgOBz, Et<sub>3</sub>N, 25 °C). In view of that, a detailed study on the Wolff rearrangement was carried out, aiming the synthesis of the Arndt–Eistert homologated product **1** (Table 1).

Initially, silver benzoate was selected as the model catalyst to optimize the conditions. As described in entry 5, 50 mol % of the catalyst is necessary to obtain a moderate yield, together with its slow addition and a 50 °C reaction temperature. Sequential investigation employing different silver catalysts (entries 9–12) leads to practically similar results, CF<sub>3</sub>SO<sub>3</sub>Ag being the best catalyst. Although these conditions provided good yields for the Wolff rearrangement, high loadings of the expensive silver catalysts are needed, together with tedious experimental procedures such as the requirement of very slow addition of the catalyst for total substrate conversion. Fortunately, this problem was totally circumvented when photochemical conditions were applied, furnishing the desired ester **1** in almost quantitative yield with no need of purification.<sup>14</sup> Notwithstanding the wide range of applications known of the Arndt–Eistert homologation from saturated diazoketones,<sup>15</sup> the use of  $\alpha,\beta$ -unsaturated diazoketones as substrates for this transformation is scarcely described in the literature.<sup>16</sup> Moreover, unsaturated diazoketone **2** sets an even worse scenario due to the existence of an epimerizable stereocenter. Fortunately, comparison of the optical rotation value of the *N*-Boc derivative of compound **1** {[ $\alpha$ ]D –26.0 (c 1.0, MeOH)} with the one described in the literature<sup>17</sup> {[ $\alpha$ ]D –21.4 (c 1.0, MeOH)} demonstrated the integrity of the chiral center after the photochemical or thermal Wolff rearrangement.

After the synthesis of **1**, completion of the total synthesis of indolizidine 167B was straightforward. Removal of the Cbz protecting group in the presence of H<sub>2</sub>/Pd and TEA as base (with concomitant reduction of the double bond and cyclization) afforded known lactam **3** in a 92% yield and in a single step. Synthesis of lactam

**Table 1**  
Studies on the Arndt–Eistert homologation reaction



Entry	Catalyst (mol %)	Temp (°C)	Time (h)	Yield (%)
1 <sup>16,a,c</sup>	C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> Ag (30)	25	1	30
2 <sup>a,b</sup>	C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> Ag (50)	25	1	37
3 <sup>a,b</sup>	C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> Ag (40)	25–50	1	50
4 <sup>a,c</sup>	C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> Ag (50)	50	1	50
5 <sup>a,b</sup>	C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> Ag (50)	50	1	66
6 <sup>c</sup>	Ag <sub>2</sub> O (15)	25	1	16
7 <sup>a,b</sup>	CF <sub>3</sub> CO <sub>2</sub> Ag (30)	50	1	26
8 <sup>a,b</sup>	CF <sub>3</sub> SO <sub>3</sub> Ag (30)	50	1	28
9 <sup>a,b</sup>	AgNO <sub>3</sub> (50)	50	1	51
10 <sup>a,b</sup>	CF <sub>3</sub> CO <sub>2</sub> Ag (50)	50	1	71
11 <sup>a,b</sup>	CF <sub>3</sub> SO <sub>3</sub> Ag (50)	50	1	76
12 <sup>a,b</sup>	CH <sub>3</sub> CO <sub>2</sub> Ag (50)	50	1	66
13 <sup>d</sup>	None	25	4	97

<sup>a</sup> 5 equiv of Et<sub>3</sub>N and a 0.1 M solution of **2** in dry MeOH was used, except in entry 6 where no base was used.

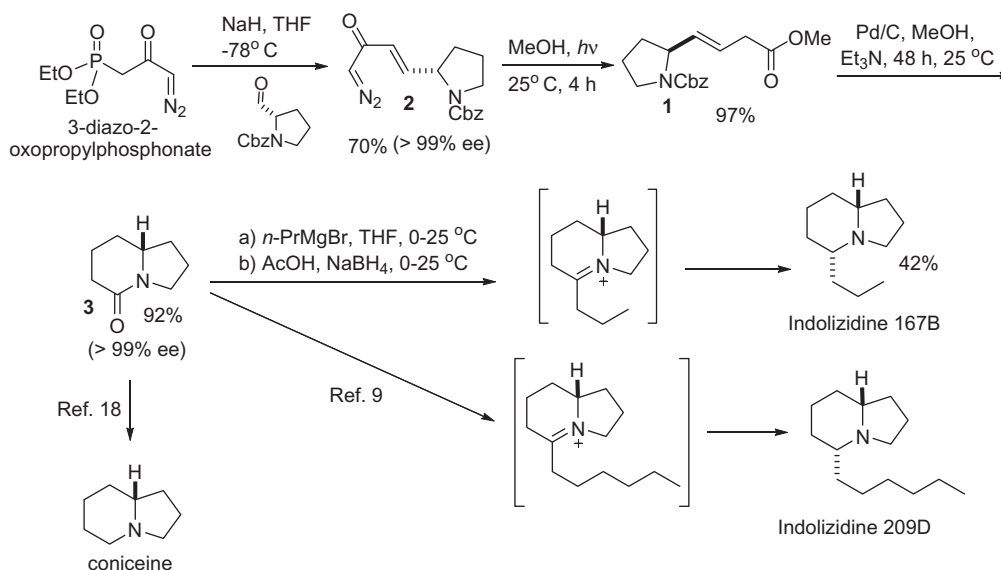
<sup>b</sup> Very slow addition of the catalyst as a solution in Et<sub>3</sub>N.

<sup>c</sup> Fast and direct addition of the catalyst as a solution in Et<sub>3</sub>N.

<sup>d</sup> The photochemical reactions (0.3 M solution of **2** in dry MeOH) were carried out using UV light generated by an Osram 150 Xenon lamp accommodated in an Oriol Model 8500 Universal arc lamp source with focusing quartz lens, a water-filled infrared filter, and a thermostated cell holder.

**3** {>99% ee from chiral HPLC;<sup>13</sup> [ $\alpha$ ]D –6.7 (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); Lit<sup>18</sup> [ $\alpha$ ]D –6.6 (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>)} also constitutes a very concise formal synthesis of the natural alkaloid concine<sup>18</sup> and of (–)-indolizidine 209D.<sup>9</sup> Addition of propylmagnesium bromide to lactam **3**, followed by AcOH/NaBH<sub>4</sub>, concluded the total synthesis of indolizidine (–)-167B as a single diastereomer<sup>19</sup> in a 42% yield (Scheme 2), being its spectroscopic data and optical rotation value in accordance with the literature.<sup>7,8</sup>

In conclusion, we have shown that  $\alpha,\beta$ -unsaturated diazoketones can be powerful substrates for the short and diversity-oriented synthesis of indolizidine alkaloids. This was demonstrated by preparing indolizidine 167B in four steps from *l*-Cbz-prolinal and with an overall yield of 26%. Success in this endeavor was possible after a



**Scheme 2.** Synthesis of (–)-indolizidine alkaloids 167B, 209D and concine.

high yielding unusual photochemical Arndt–Eistert homologation from an unsaturated diazoketone. This strategy should be feasible and can be easily adaptable to the concise synthesis of other indolizidine alkaloids. The total syntheses of some pumiliotoxins and castanospermine analogues using the present strategy will be reported in due course.

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### Supplementary data

Supplementary data (experimental procedures and copies of the NMR spectra of all compounds and chiral HPLC chromatograms of diazoketone **2** and lactam **3**.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.029.

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