## Concise synthesis of indolizidines: total synthesis of (-)-coniceine

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The Ti-mediated allylsilane addition to bicyclic lactams occurs with high stereoselectivity and combined with a ring closure metathesis provides the title compounds in high ee.

Indolizidines represent an important class of biologically active compounds, including such alkaloids as slaframine, castanospermine (a potent glycosidase inhibitor) and a number of poisonous-frog alkaloids typified by pumiliotoxin  $B^1$  (Fig. 1). Development of a general method to access these 1-azabicyclo-[4.3.0]nonanes would provide a useful tool in studying a host of derivatives.



The construction of optically pure heterocycles using the bicyclic lactam template has been of great interest in our group,<sup>2</sup> and over the years we have published<sup>3</sup> applications of the [4.3.0] bicyclic lactam to access a variety of alkaloids (*e.g.* 1-deoxy-6-epicastanospermine and coniceine), Fig. 2.



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We now report a general protocol utilizing bicyclic lactams **1a–d** for the construction of a variety of enantiomerically pure indolizidines (Scheme 1) including the naturally occurring parent ring system, (–)-coniceine **6a**.

The synthetic route to the 1-azabicyclic systems  $\mathbf{6}$  began by the addition of allyltrimethylsilane to a dichloromethane solution of the enantiomerically pure bicyclic lactam and titanium tetrachloride to furnish the 5-substituted pyrrolidinone 2 with diastereomeric ratios ranging from 6:1 to 11:1. After the diastereomers in 2 were separated (silica gel column chromatography) the chiral auxiliary was removed by dissolving metal reduction using calcium metal (NH<sub>3</sub>, -78 to -30 °C over 4 h) affording **3**. It is noteworthy that for compound **2d** containing two possible benzylic cleavage sites only the exocyclic Nbenzyl bond was cleaved. Introduction of the N-allyl group to give 4 proceeded smoothly by addition of allyl bromide to the sodium salt of the pyrrolidinone. The bis-olefin 4 was subjected to a ring-closing metathesis (10 mol% 7 as catalyst, 25 °C, 1,2-dichloroethane) to afford the indolizidinones 5 in excellent yields.<sup>4</sup> Hydrogenation of the olefinic bond and reduction of the lactam carbonyl provided the target compounds 6a-d in 32–51% overall yield. In the case where R = H, the reaction sequence provided a 49% overall yield of (-)-coniceine, which



**Scheme 1** *Reagents and conditions*: i, allyltrimethylsilane, TiCl<sub>4</sub>, 68–79% 6:1–11:1 dr; ii, Ca/NH<sub>3</sub>, 73–89%; iii, NaH/allylbromide, 81–92%; iv, cat. **7** (10 mol%), 89–93%; v, H<sub>2</sub>, Pd(OH)<sub>2</sub>, 92–96%; vi, LiAlH<sub>4</sub>, 83–89%.

was identical with a sample previously reported from these laboratories.<sup>3a</sup>

To further illustrate the versatility of this methodology, the oxygenated derivatives of **6** were obtained by dihydroxylation of metathesis product **5b** providing the 3,4-dihydroxy indolizidinone **8** as a 4:1 mixture of diastereomers which were separable by column chromatography (Scheme 2). In order to simplify the purification and reduce water solubility of the diol **8**, it was protected as the acetonide **9** and reduced to the indolizidine **10** using lithium aluminium hydride. This route provides enantiomerically pure hydroxylated derivatives of 1-azabicyclo[4.3.0]nonanes.

In summary, a general method for the construction of a variety of optically pure indolizidines using the chiral non-racemic [3.3.0] bicyclic lactams **1a–d** in combination with ringclosing metathesis has been illustrated. The utility of this method is exemplified by the synthesis of (-)-coniceine with excellent stereocontrol and overall yield.<sup>5</sup>



Scheme 2 Reagents and conditions: i, OsO<sub>4</sub>/NMO, 73% 4:1 dr; ii, 2,2-dimethoxypropane, TsOH, 94%; iii, LiAlH<sub>4</sub>, 89%.

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## Notes and references

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- 4 For a review on olefin metathesis, see: R. H. Grubbs and S. Chang, *Tetrahedron* 1998, 54, 4413; for a review on applications of the ringclosing metathesis reaction to the construction of a wide variety of nitrogen containing ring systems, see: U. K. Pandit, H. S. Overkleeft, B. C. Borer and H. Bieraugel, *Eur. J. Org. Chem.*, 1999, 5, 959.
- 5 *Typical procedure*; the synthesis of **5c** from **1c**: A dichloromethane solution of the bicyclic lactam **1c** (1.4 g, 5.48 mmol) was cooled to -78

°C and TiCl<sub>4</sub> (9 ml of 1.0 M solution in dichloromethane, 1.6 equiv.) was slowly added via syringe followed by allyltrimethylsilane (1.3 mL, 1.5 equiv.). The solution was stirred under an argon atmosphere and allowed to warm to r.t. over a 4 h period. A solution of saturated NH<sub>4</sub>Cl (50 mL) was added in one portion and the layers were separated. The aqueous layer was washed with dichloromethane  $(3 \times 50 \text{ mL})$ , the combined organic layers were dried over Na2SO4 and concentrated to an oil. <sup>1</sup>H NMR analysis of the crude material was used to analyze the diastereomeric ratio. Column chromatography (SiO<sub>2</sub>, EtOAc) provided 1.25 g of 2c (76%) as a colorless solid: mp 98 °C;  $[\alpha]_{\rm D}$  -177 (c 1.9, CHCl<sub>3</sub>);  $\delta_{\rm H}$ (300 MHz, CDCl<sub>3</sub>) 0.97 (t, J7 Hz, 3H), 1.26–1.45 (m, 4H), 1.58–1.71 (m, 2H), 1.89–2.06 (m, 4H), 2.49 (t, J 9 Hz, 2H), 4.08–4.27 (m, 3H), 4.70–4.97 (m, 3H), 5.36 (dddd, J 17, 13, 10, 7 Hz, 1H), 7.24–7.43 (m, 5H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 14.0, 22.9, 25.5, 27.6, 30.4, 37.7, 44.7, 60. 3, 65.5, 68.2, 199.0, 127.2, 127.7, 128.2, 132.3, 139.1, 177.4; IR(film) v/cm<sup>-1</sup> 1658, 3351. Anal. Calc. for C<sub>18</sub>H<sub>27</sub>NO<sub>2</sub>: C, 75.71; H, 9.03. Found: C, 75.44; H, 9.03%. A dichloroethane solution of the bis-olefin 4c (200 mg, 0.9 mmol) was added to a solution of catalyst 7 (74 mg, 10 mol%). The purple solution slowly changed to brown. After 6 h the reaction was concentrated in vacuo to an oil and chromatographed (SiO<sub>2</sub>, EtOAc) to provide 5c (179 mg, 92%) as a colorless solid: mp 63 °C;  $[\alpha]_D$ -58 (c 1.0, CHCl<sub>3</sub>);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 0.91 (t, J 7 Hz, 3H), 1.12-1.39 (m, 4H), 1.48-1.82 (m, 3H), 2.01-2.21 (m, 3H), 2.38-2.53 (m, 2H), 3.40 (d, J 9 Hz, 1H), 4.38 (d, J 9 Hz, 1H), 5.71 (m, 2H);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 14.1, 23.1, 25.9, 27.8, 29.9, 30.3, 36.0, 38.4, 60.0, 122.8, 123.8, 173.5; IR(film) v/cm<sup>-1</sup> 1692.