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.

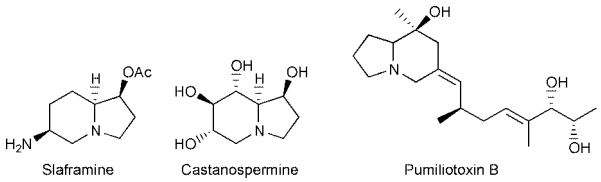


Fig. 1

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

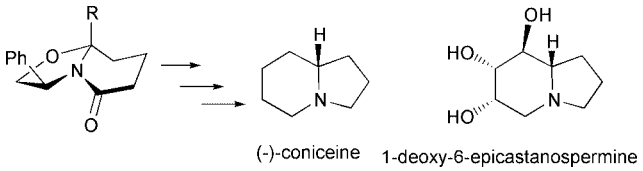
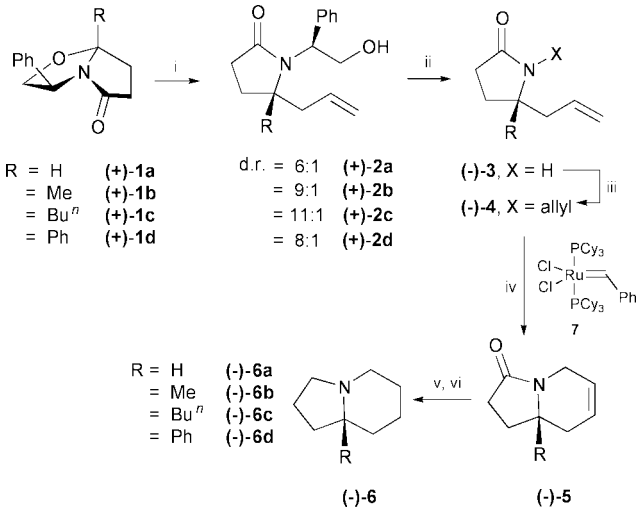


Fig. 2

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 **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_3, −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 *N*-benzyl 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.[4] 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

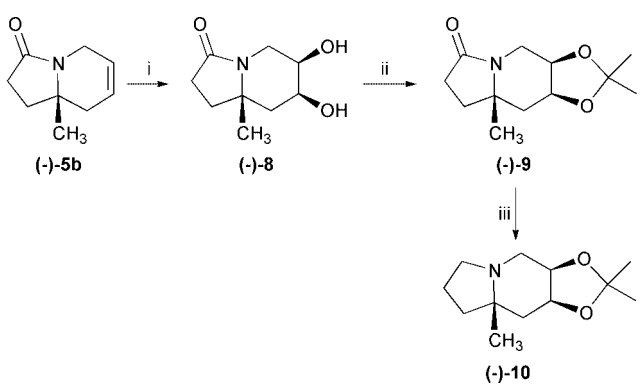


Scheme 1 *Reagents and conditions*: i, allyltrimethylsilane, $TiCl_4$, 68–79% 6:1–11:1 dr; ii, Ca/NH_3, 73–89%; iii, NaH/allylbromide, 81–92%; iv, cat. **7** (10 mol%), 89–93%; v, H_2, $Pd(OH)_2$, 92–96%; vi, $LiAlH_4$, 83–89%.

was identical with a sample previously reported from these laboratories.[3a]

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 ring-closing metathesis has been illustrated. The utility of this method is exemplified by the synthesis of (−)-coniceine with excellent stereocontrol and overall yield.[5]



Scheme 2 *Reagents and conditions*: i, OsO_4/NMO, 73% 4:1 dr; ii, 2,2-dimethoxypropane, TsOH, 94%; iii, $LiAlH_4$, 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 ring-closing 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 $TiCl_4$ (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_4Cl (50 mL) was added in one portion and the layers were separated. The aqueous layer was washed with dichloromethane (3 × 50 mL), the combined organic layers were dried over Na_2SO_4 and concentrated to an oil. ^1H NMR analysis of the crude material was used to analyze the diastereomeric ratio. Column chromatography (SiO_2, EtOAc) provided 1.25 g of **2c** (76%) as a colorless solid: mp 98 °C; $[\alpha]_D$ −177 (*c* 1.9, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 0.97 (t, *J* 7 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_C (75 MHz, $CDCl_3$) 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) ν/cm^{-1} 1658, 3351. Anal. Calc. for $C_{18}H_{27}NO_2$: 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_2, EtOAc) to provide **5c** (179 mg, 92%) as a colorless solid: mp 63 °C; $[\alpha]_D$ −58 (*c* 1.0, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 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); δ_C (75 MHz, $CDCl_3$) 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) ν/cm^{-1} 1692.