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A short and concise synthetic route to (−)-coniceine

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Abstract—(−)-Coniceine, the simplest framework of indolizidine alkaloids, has been successfully accessed using a route in which ruthenium-catalyzed ring-closing olefin metathesis (RCM) was the key reaction to establish the unsaturated bicyclic lactam system.

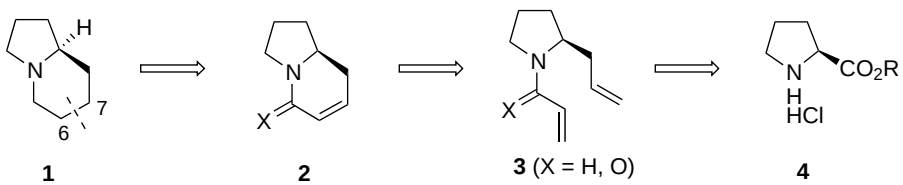
1. Introduction

Indolizidine alkaloids, isolated from the skin secretions of certain neotropical frogs, represent a class of pharmacologically important compounds.[1] For example, polyhydroxylated derivatives such as castanospermine, swainsonine, and lentiginosine have been known to inhibit glycosidase and cardiotonic activity.[2] Even structurally simpler members of this class of natural products such as indolizidine 167B and 209D act as non-competitive blockers of neuromuscular transmission.[3] Coniceine **1** (Scheme 1), containing the simplest indolizidine skeleton, has attracted great attention from synthetic chemists to establish a general route for the preparation of more complex derivatives and this has resulted in several successful approaches to the compound both in racemic[4] and optically active form.[5] In continuation of our program directed toward the development of general synthetic methods for the construction of certain natural products,[6] we describe herein a short and highly efficient synthetic pathway to (−)-coniceine as well as to a potentially useful synthetic intermediate for the synthesis of more complex indolizidine derivatives.

2. Results and discussion

As depicted in Scheme 1, we envisaged that ring-closing metathesis (RCM) of a diolefinic pyrrolidine **3** could provide a bicyclic alkaloid skeleton of **2** which is a direct precursor of **1**. In our approach, the C(6) and C(7) bond was chosen as the ring-forming position not only for the synthesis of (−)-coniceine itself but also to allow further manipulation of the resulting conjugated lactam in order to synthesize other indolizidine derivatives. It was also projected that the required diolefinic compound **3** might be readily accessed starting from proline derivatives **4**. It should be noted that we have now a flexibility in the choice of substrates for RCM reaction being either the simple diolefin (**3**, X = H) or α,β-unsaturated carbonyl compound (**3**, X = O) mainly due to the recent development of metathesis catalysts (vide infra).

As depicted in Scheme 2, our initial efforts were focused on the preparation of a simple diolefinic pyrrolidine **9** for the metathesis-based approach. *N*-Allylation of L-proline methyl ester hydrochloride **5** was readily carried out under standard conditions to afford



Scheme 1.

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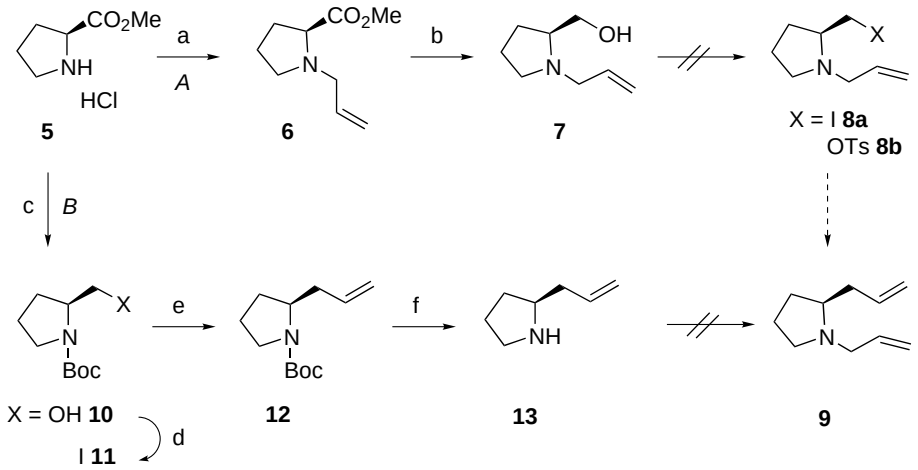
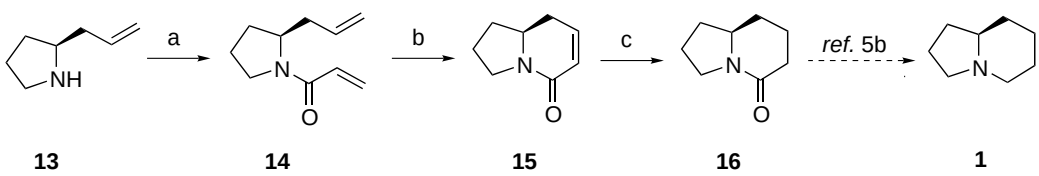


Scheme 2. *Reagents and conditions*: (a) allyl bromide (2 equiv.), Et_3N (4 equiv.), DMF, rt, 12 h, 92%; (b) LAH (3 equiv.), ether, reflux, 6 h, 99%; (c) (i) LAH (2.0 equiv.), THF, reflux, 2 h, (ii) $(Boc)_2O$ (1.2 equiv.), CH_2Cl_2, 60°C, 12 h, 90% (two steps); (d) imidazole (2.0 equiv.), I_2 (1.5 equiv.), PPh_3 (1.5 equiv.), ether, rt, 12 h, 89%; (e) CuI (3 equiv.), vinylmagnesium bromide (6 equiv.), THF, −40°C to rt, 3 h, 87%; (f) TFA/CH_2Cl_2 (1:1, excess), 0°C, 1 h, 99%.

N-allylated proline ester **6** in high yield (pathway *A*). The methyl ester **6** was then reduced with LAH to afford the corresponding alcohol **7** in quantitative yield. Direct conversion of the hydroxyl group in **7** to iodide **8a** turned out to be a low yielding reaction under the usual conditions.[6a] The fact that other substrates having a leaving group such as tosylate **8b** were also unexpectedly unstable led us to turn our attention to an alternative route (pathway *B*) for the formation of the same target compound **9** which requires an additional *N*-protection and deprotection sequence. Reduction of L-proline methyl ester hydrochloride **5** and subsequent *N*-Boc protection could be carried out in one pot in excellent yields to provide *N*-Boc prolinol **10**. Transformation of the hydroxyl group of **10** to provide iodide **11** was effected in 89% yield using imidazole/I_2/PPh_3 in ether. Vinyl group substitution on *N*-Boc-protected iodide **11** could be successfully achieved by a Grignard/CuI procedure in 87% yield. Cleavage of the *N*-Boc group of 2-allylpyrrolidine **12** was readily conducted under standard conditions (TFA) to afford deprotected 2-allylpyrrolidine **13** in quantitative yield. Subsequent *N*-monoallylation of **13** turned out to be problematic in pathway *B* in our hands. Instead of a clean *N*-monoallylation, a diallylated quaternary ammonium salt formed as the major product under a variety of reaction conditions such as using allyl halide (bromide, iodide, and chloride) in combination with a base (triethylamine, pyridine, and inorganic salts). Use of less equivalents of allyl halide compared to **13** still afforded the bis-allylated compound as the major product.

RCM now stands as one of the most powerful catalytic procedures for the preparation of medium- to large-ring skeletons via C–C bond formation.[7] Recent development of a new type of Ru-carbene catalysts has substantially widened substrate scopes in the metathesis-based approach, and it has now become possible to employ an acryloyl double bond as a connecting unit with the advent of dihydroimidazolylidene ruthenium catalyst.[8] Being faced with the difficulty of the synthesis of the simple diolefinic pyrrolidine **9** in Scheme 2, we envisaged that a diolefinic adduct having an acryloyl group could serve as an alternative substrate for the RCM reaction (Scheme 3). Coupling of the secondary amine **13** with acryloyl chloride was readily carried out to give an unsaturated amide **14** in good yield. We were then pleased to observe that metathesis of **14** was indeed effected with 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene (Im) substituted ruthenium-based catalyst, (Im)$Cl_2PCy_3RuCHPh$,[9] (**17**, 5 mol%) under mild conditions (CH_2Cl_2, rt, 3 h) to generate the unsaturated bicyclic lactam **15** in high yield. Subsequent selective hydrogenation of **15** with the use of platinum oxide catalyst gave a saturated lactam **16** in excellent yield. Hydride reduction of **16** to give **1** has already been reported in the literature.[5b] It should be noted that the unsaturated lactam **15** could also serve as a potentially valuable synthetic intermediate both for the formation of more complex indolizidine derivatives and for synthesis of certain natural products containing an azabicyclic system.[10]



Scheme 3. *Reagents and conditions*: (a) acryloyl chloride (5 equiv.), Et_3N (4 equiv.), CH_2Cl_2, 0°C to rt, 3 h, 65%; (b) (Im)$Cl_2PCy_3RuCHPh$ (**17**, 5 mol%), CH_2Cl_2 (0.05 M), rt, 3 h, 74%; (c) H_2/PtO_2 (10 mol%), EtOAc, rt, 3 h, 95%.

3. Conclusions

In summary, a concise formal synthesis of (−)-coniceine has been successfully achieved by the use of ruthenium-catalyzed RCM to construct the required bicyclic alkaloid skeleton. The present synthetic approach is highly efficient and convenient and it has the flexibility for further synthetic manipulation based on the unsaturated lactam **15**.

4. Experimental

4.1. General methods

All reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Anhydrous solvents were obtained by distillation from sodium/benzophenone ketyl (THF, Et_2O) or calcium hydride (CH_2Cl_2, $CHCl_3$, EtOAc) immediately prior to use. Chemical shifts (δ) are reported in ppm downfield from TMS with reference to an internal solvent. High-resolution mass spectra (HRMS) were provided by the Inter-University Center of Natural Science Research Facilities (Seoul National University). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated plates (0.25 mm thickness) with fluorescent indicator. Column chromatography was carried out on silica gel 60 (230–400 mesh, Merck).

4.2. (2*S*)-Methyl *N*-(2-propenyl)pyrrolidine carboxylate 6

To a solution of L-proline methyl ester hydrochloride **5** (3.32 g, 20.0 mmol) in DMF (40 mL) was added Et_3N (11.2 mL, 80.4 mmol) and allyl bromide (4.9 g, 40.5 mmol) at 0°C. After stirring for 12 h at rt, the reaction mixture was extracted with ethyl acetate (3×30 mL), washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography on silica gel (EtOAc/hexane = 1:3) gave **6** as a colorless liquid (3.1 g, 92%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.90 (m, 1H), 5.12 (m, 2H), 3.69 (s, 3H), 3.27 (m, 1H), 3.10 (m, 3H), 2.33 (m, 1H), 2.11 (m, 1H), 1.94–1.78 (m, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 175.1, 135.6, 117.9, 65.7, 58.2, 53.9, 52.2, 29.9, 23.5; IR (CH_2Cl_2): 1740 cm^{-1}; HRMS (EI) calcd for $C_9H_{15}NO_2$: 169.1104; found: 169.1104; $[\alpha]_D^{25}$ −11.4 (*c* 1.60, CH_2Cl_2).

4.3. (2*S*)-*N*-(2-Propenyl)prolinol 7

To a suspension of LAH (1.14, 30.0 mmol) in ether (45 mL) was added dropwise a solution of **6** (1.69 g, 10.0 mmol) in ether (10 mL) over 30 min at 0°C. After stirring under reflux for 6 h, the reaction mixture was quenched with water (10 mL) at 0°C, extracted with ether, dried over $MgSO_4$, and chromatographed on silica gel (EtOAc/hexane = 1:1) to afford **7** as a colorless liquid (1.4 g, 99%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.84 (m, 1H), 5.08 (m, 2H), 3.54 (m, 2H), 3.37 (m, 2H), 2.98 (m. 1H), 2.86 (m, 1H), 2.55 (m, 1H), 2.20 (m, 1H), 1.70 (m, 1H), 1.62 (m, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 136.3, 117.3, 64.7, 62.9, 57.9, 54.7, 26.0, 23.7; IR (CH_2Cl_2): 3393 (broad) cm^{-1}; HRMS (EI) calcd for $C_8H_{15}NO$: 141.1155; found: 141.1154; $[\alpha]_D^{25}$ −33.6 (*c* 1.60, CH_2Cl_2).

4.4. (2*S*)-*N*-(*tert*-Butyloxycarbonyl)prolinol 10

To a solution of LAH (2.28 g, 60.0 mmol) in THF (30 mL) was added L-proline methyl ester hydrochloride **5** (4.97 g, 30.0 mmol) at 0°C in three portions. After stirring under reflux for 2 h, the reaction mixture was quenched with water (15 mL) in an ice bath and most of the THF was removed under reduced pressure. To the residue was added CH_2Cl_2 (20 mL) followed by a solution of $(Boc)_2O$ (7.86 g, 36.0 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 12 h at 60°C and extracted with CH_2Cl_2 (2×30 mL) washing with brine. Column chromatography on silica gel (EtOAc/hexane = 1:1) provided **10** as a colorless liquid (5.4 g, 90%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.72 (bs, 1H), 3.90 (bs, 1H), 3.56 (bs, 2H), 3.40 (m, 1H), 3.32 (m, 1H), 1.97 (m, 1H), 1.89 (m, 3H), 1.31 (s, 9H); IR (CH_2Cl_2): 3429 (broad), 1695 cm^{-1}; ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 157.3, 80.4, 67.5, 60.4, 59.2, 47.8, 28.9, 24.3; HRMS (EI) calcd for $C_{10}H_{19}NO_3$: 201.1366; found: 201.1367; $[\alpha]_D^{25}$ −48.5 (*c* 1.68, CH_2Cl_2).

4.5. (2*S*)-2-Iodomethyl-*N*-(*tert*-butyloxycarbonyl)-pyrrolidine 11

To a solution of imidazole (1.78 g, 26.1 mmol) and triphenylphosphine (5.14 g, 19.6 mmol) in diethyl ether (30 mL) was added iodine (4.98 g, 19.6 mmol) in three portions over 30 min at 0°C. After stirring for an additional 10 min at rt, a solution of **10** (2.63 g, 13.1 mmol) in Et_2O (15 mL) was added and the resulting mixture was stirred for 12 h at rt. Column chromatography on silica gel (EtOAc/hexane = 1:6) gave **11** as a pale yellow solid (3.63 g, 89%); mp 102–104°C (dec.); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.85 (bs, 1H), 3.37–3.28 (m, 3H), 3.14 (m, 1H), 2.05 (m, 1H), 1.86 (m, 3H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 153.4, 78.8, 57.0, 46.5, 30.7, 27.9, 21.9, 10.1; HRMS (EI) calcd for $C_{10}H_{18}INO_2$: 311.0383; found: 311.0394; $[\alpha]_D^{25}$ −32.8 (*c* 1.46, $CHCl_3$).

4.6. (2*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-(2-propenyl)-pyrrolidine 12

To a suspension of CuI (3.68 g, 19.3 mL) in THF (15 mL) was added vinylmagnesium bromide (1.0 M in THF, 38 mL) at −40°C and the mixture was stirred for 30 min while allowing to warm up to −10°C. After recooling to −40°C, a solution of iodide **11** (2.00 g, 6.4 mmol) in THF (5 mL) was added and the reaction mixture was stirred for additional 3 h with slow warming to rt. Extraction with ether (2×30 mL) and chromatography on silica gel (EtOAc/hexane = 1:40) gave **12** as a colorless liquid (1.18 g, 87%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.84–5.68 (m, 1H), 5.10–5.03 (m, 2H), 3.79 (br, 1H), 3.34 (br, 2H), 2.54 (br, 1H), 2.10 (m, 1H), 1.92–1.72 (m, 4H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 154.9, 138.2, 117.3, 79.4, 57.2, 40.5, 31.4, 29.7, 28.9; HRMS (EI) calcd for $C_{12}H_{21}NO_2$: 211.1573; found: 211.1580; $[\alpha]_D^{25}$ −32.4 (*c* 1.56, $CHCl_3$).

4.7. (2*S*)-2-(2-Propenyl)pyrrolidine 13

A solution of **12** (0.50 g, 2.37 mmol) in CH_2Cl_2 (2 mL) was treated with trifluoroacetic acid (2 mL) at 0°C and the mixture was stirred for 1 h at the same temperature. After dilution with CH_2Cl_2 (15 mL), pH of the solution was adjusted to 7–8 using saturated aqueous $NaHCO_3$ solution. Crude product **13** was extracted with methylene chloride (10×20 mL) and used for the next step without further purification (0.26 g, 99%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.83–5.72 (m, 1H), 5.32–5.01 (m, 2H), 3.57 (m, 1H), 3.32–3.24 (m, 2H), 2.61–2.46 (m, 2H), 2.20–1.98 (m, 3H), 1.76–1.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 133.0, 119.4, 59.7, 45.2, 36.9, 30.4, 24.0; HRMS (EI) calcd for $C_7H_{13}N$: 111.1049; found: 111.1038.

4.8. (2*S*)-1-Acryloyl-2-(2-propenyl)pyrrolidine 14

To a solution of **13** (0.24 g, 2.16 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (1.2 mL, 8.6 mmol) and acryloyl chloride (0.88 mL, 10.8 mmol) at 0°C and the reaction mixture was stirred at rt for 3 h. After evaporation of volatile compounds, chromatography on silica gel (EtOAc/hexane = 1:5) of the residue afforded **14** as a grey liquid (0.23 g, 65%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 6.49–6.40 (m, 2H), 5.82–5.65 (m, 2H), 5.15–5.05 (m, 2H), 4.25 (br, 1H), 3.56 (m, 2H), 2.74 (m, 1H), 2.25 (m, 1H), 1.94 (m, 4H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 164.8, 135.4, 129.6, 126.4, 118.5, 57.3, 47.5, 37.7, 30.0, 24.3; HRMS (EI) calcd for $C_{10}H_{15}NO$: 165.1155; found: 165.1150; $[\alpha]_D^{25}$ −42.4 (*c* 1.54, CH_2Cl_2).

4.9. (*S*)-$\Delta^{6,7}$-Indolizidin-5-one 15

To a solution of **14** (165 mg, 1.0 mmol) in CH_2Cl_2 (20 mL, 0.05 M) was added ruthenium catalyst (Im)Cl_2PCy_3RuCHPh (**17**, 42.5 mg) and the reaction mixture was stirred for 3 h at rt. After removal of the solvent, analytically pure cyclized product **15** was obtained after column chromatography on silica gel (EtOAc/hexane = 3:1) in 74% yield as a yellowish liquid; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 6.50 (m, 1H), 5.95 (dd, 1H, J = 9.7, 2.8 Hz, 1H), 3.65 (m, 2H), 3.48 (m, 1H), 2.46 (m, 1H), 2.05 (m, 1H), 1.82–1.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 163.9, 138.4, 126.4, 56.9, 44.4, 33.9, 30.9, 23.2; IR (CH_2Cl_2): 1658 cm^{-1}; HRMS (EI) calcd for $C_8H_{11}NO$: 137.0841; found: 137.0838; $[\alpha]_D^{25}$ +129.2 (*c* 0.97, CH_2Cl_2).

4.10. (9*R*)-Indolizidin-5-one 16

To a solution of solution of **15** (82 mg, 0.6 mmol) in ethyl acetate (6 mL) was added PtO_2 (13.6 mg, 0.06 mmol), and the flask was evacuated and filled with H_2 gas three times. The reaction mixture was stirred for 3 h at rt and evaporated under reduced pressure. The residue was chromatographed on silica gel (EtOAc/hexane = 5:1) to give **16** (62 mg, 95%) as a colorless liquid; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.56 (m, 1H), 3.40 (m, 2H), 2.33 (m, 2H), 2.25–2.09 (m, 3H), 1.96 (m, 2H), 1.78 (m, 2H), 1.34 (m, 1H), 0.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 169.5, 59.7, 45.2, 33.9, 31.4, 29.5, 22.5, 21.5; IR (CH_2Cl_2): 1727 cm^{-1}; $[\alpha]_D^{25}$ −6.6 (*c* 0.40, CH_2Cl_2) [+3.0 (*c* 2.1, CH_2Cl_2) with the (*S*)-enantiomer **16** (86% ee)[5b]].

Acknowledgements

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