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Synthesis of psudoheliotridane via formal [3+2] annulation and ring-closing metathesis☆,☆☆

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Abstract—Base-induced coupling/cyclization stepwise [3+2] annulation of α-sulfonylacetamide with (*Z*)-2-bromoacrylates yielded polysubstituted pyroglutamates with three contiguous chiral centers with *trans–trans* orientation in a one-pot synthesis. The pyrrolizidine skeleton was obtained via the ring-closing metathesis (RCM) method. This facile strategy was used to synthesize psudoheliotridane.

1. Introduction

Recently, we introduced a new and general methodology for the syntheses of pyroglutamates via [3+2] annulation reactions between different α-sulfonylacetamide derivatives and various ethyl (*Z*)-2-bromo-2-propenoates.[1–4] To demonstrate the synthetic utility of our methodology and continuing our investigation on the application of this methodology to the synthesis of alkaloids, the synthesis of pyrrolizidine alkaloids psudoheliotridane (**1a**) was investigated.[5] Pyrrolizidines and related compounds have attracted considerable attention due to their chemical and pharmacological properties (Fig. 1).

Psudoheliotridane (**1a**) Heliotridane (**1b**)

Figure 1. Structure of psudoheliotridane (**1a**) and heliotridane (**1b**).

2. Results and discussion

2.1. Retrosynthetic approach to psudoheliotridane

Our approach to psudoheliotridane (**1a**) was shown in Scheme 1. We envisioned that the pyrrolizidine skeleton could be achieved via the facile intermolecular [3+2] annulation to pyroglutamate skeleton followed by intramolecular ring-closing metathesis (RCM) with Grubbs' catalyst.

2.2. Synthesis of psudoheliotridane

Allylamine was treated with chloroacetyl chloride and triethylamine to produce α-chloroacetamide, which was then treated with *p*-toluenesulfinic acid sodium salt; the two-step reaction gave α-sulfonylacetamide **3** in 85% yield. Treatment of acetaldehyde with $Ph_3P{=}C(Br)CO_2Et$ gave ethyl (*Z*)-2-bromo-2-butenoate **4** in 98% yield.[6] Compounds **3** and **4** were the reasonable starting materials for the synthesis of pyroglutamate skeleton.

The [3+2] reaction of **3** with **4** (NaH/THF)[1] proceeded smoothly, the cyclized pyroglutamate **5** was obtained as a single isomer in 52% yield in which the substitutents at C_2 and C_3 and C_3 and C_4 are *trans* to each other (Scheme 2). The reaction mechanism for the outstanding stereoselectivity of the annulation reaction has been reported by us.[1–4] The structure of **5** was determined by single-crystal X-ray analysis.[7] With the requisite pyroglutamate **5** in hand, we then examined the reduction of **5**. When **5** was treated with lithium aluminum hydride, **6a** and **6b** were yielded in the ratio of 7:1 with 86% overall yield. However, reaction of **5** with alane reagent [$LiAlH_4/AlCl_3$], only **6b** was produced. Under a milder condition, the reduction of **5** with sodium borohydride gave the desired **6a** as the sole product in 90%

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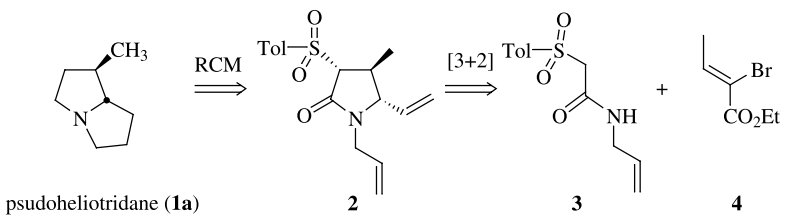
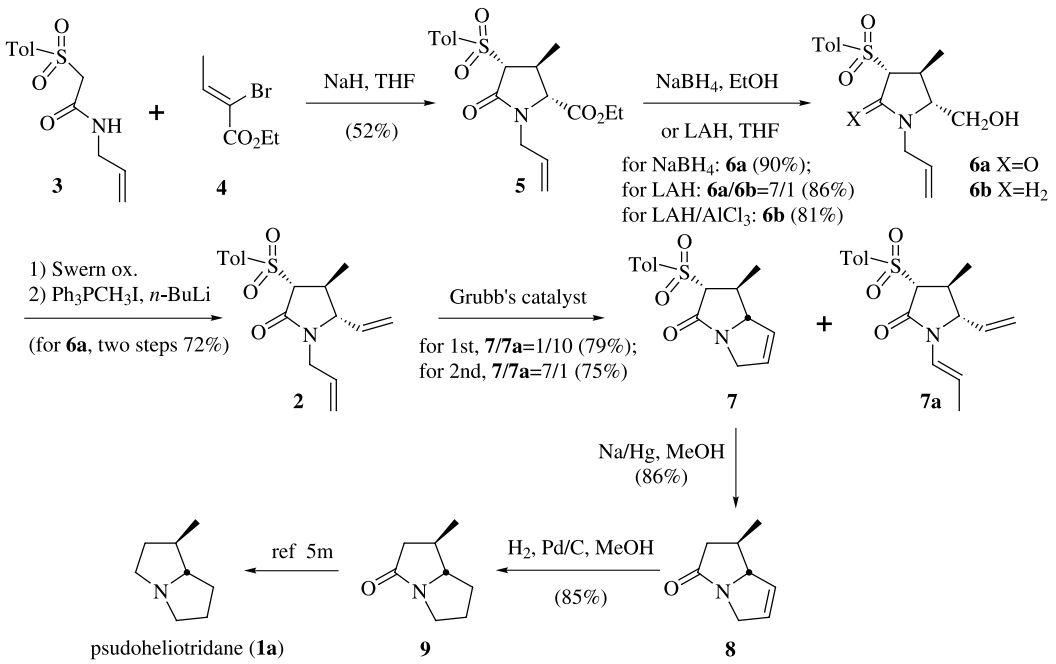


Scheme 1.



Scheme 2.

yield. Preparation of diene **2** was achieved by Swern oxidation of alcohol **6a** followed by Wittig olefination of the resulting aldehyde with methyl triphenylphosphonium iodide. Diene **2** is a reasonable intermediate for the synthesis of psudoheliotridane (**1a**) (Diagram 1).

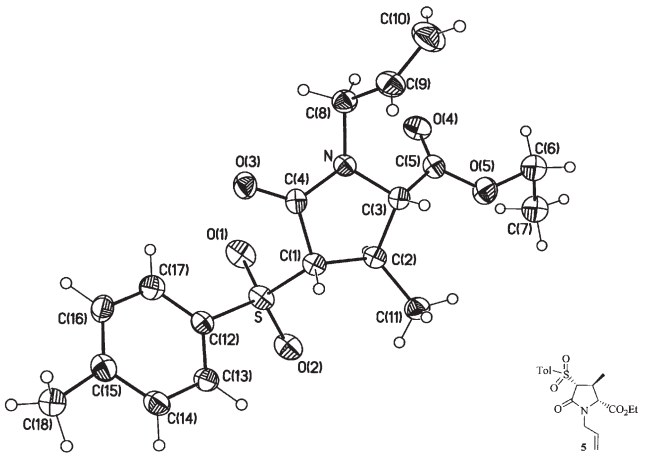


Diagram 1. X-ray crystallography of **5**.

To build up the pyrrolizidine skeleton, diene **2** was subjected to RCM reaction. Ring-closing metathesis (RCM) has been established as a powerful method for the elaboration of medium-sized rings, including carbohydrates, heterocycles and alkaloids.[8,9] In our case, the pivotal issues were the ring strain in the [3.3.0] bicyclic product and the amino group in the pyrrolidine ring that could potentially chelate the metal center of the Grubbs' metathesis catalyst and thus form unproductive complex. When **2** was subjected to a RCM reaction employing first generation Grubbs' catalyst **A** [$Cl_2(PCy_3)_2Ru{=}CHPh$], the expected bicyclic lactam **7** was generated in low yield (Fig. 2).

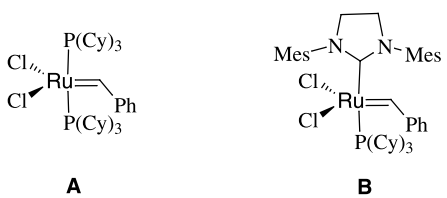


Figure 2. Commercially available Grubbs catalyst **A** and **B**.

During the ring closure process, bis(olefin)-pyroglutamate **2** was affected by catalyst **A**, isomerization of double bond occurred and enamine-olefin **7a** was the major product under a number of conditions (prolonged reaction time, elevated temperature, different solvents). This result was rather surprising because catalyst **A** has been shown tolerant a variety of functional groups, although there have been scattered reports of double bond migration problems with this catalyst.[8,9] The ring strain existed in the desired

5,5-fused product **7** might retard the normally facile cyclization.[8]

We next turn our attention to examine the second generation Grubbs' catalyst **B**, which has higher thermal stability and lower sensitivity to double bond migration. Using similar reaction conditions, compound **7** was obtained as the major product in 65% yield. Finally, desulfonation of **7** was accomplished by treatment of **7** with 6% sodium amalgam (Na/Hg) to give compound **8**. To accomplish the synthesis of psudoheliotridane (**la**), hydrogenation of double bond in **8** was conducted with 10% palladium on carbon.

3. Conclusion

We explored one-pot reaction, using facile intermolecular cycloaddition strategy, to form the pyroglutamate skeleton. Efficient intramolecular ring-closing metathesis (RCM), using the second Grubbs' catalyst **B**, generated pyrrolizidine skeleton. This consecutive cyclization strategy is synthetically useful for constructing pyrrolizidine alkaloids. The formal synthesis of psudoheliotridane (**la**) was accomplished. We are currently studying the scope of this process as well as additional applications of this approach to the synthesis of various pyrrolizidines and indolizidines.

4. Experimental

4.1. General

Dichloromethane (DCM) and tetrahydrofuran (THF) were distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. All reported melting temperatures are uncorrected.

4.1.1. 1-Allyl-2-(4-methylphenylsulfonyl)acetamide (3). Chloroacetyl chloride (1.2 g, 10.6 mmol) in THF (20 mL) was added to a solution of allylamine (0.57 g, 10.0 mmol) and triethylamine (1.06 g, 10.5 mmol) in THF (30 mL) in an ice bath for 30 min, then stirred at rt for 4 h. The mixture was concentrated under reduced pressure. Water (30 mL) was added to the crude product and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (2×20 mL), dried, filtered and evaporated. Without purification, the crude product with *p*-toluenesulfinic acid sodium salt (3.2 g, 16.5 mmol) was refluxed in dioxane (70 mL) and water (70 mL) for 15 h. The mixture was concentrated under reduced pressure and the residue was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (2×20 mL), dried, filtered and evaporated. Recrystallization on hexane (60 mL) and ethyl acetate (30 mL) yielded **3** (2.15 g, 85%): mp 136–137 °C (hexane/ethyl acetate); EI-MS: $C_{12}H_{15}NO_3S$ *m/z* (%)=98 (100), 253 (M^+, 1); HRMS (EI, M^+) Calcd for $C_{12}H_{15}NO_3S$ 253.0773, found 253.0770; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J*=8.1 Hz, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 6.90 (br s, 1H), 5.82–5.73 (m, 1H), 5.24–5.12 (m, 2H), 4.00 (s, 2H), 3.86–3.83 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.60, 145.64, 135.29, 133.10, 130.05 (2×), 128.18 (2×), 117.00, 62.06, 42.34, 21.66. Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.72; H, 6.04; N, 5.58.

4.1.2. Ethyl 2-bromo-2-buteoate (4).[6] A solution of acetaldehyde (1.32 g, 30.0 mmol) in DCM (10 mL) was added to a rapidly stirred solution of $Ph_3P{=}C(Br)CO_2Et$ (13.2 g, 3.1 mmol) in DCM (40 mL), then stirred at rt for 7 h. The resulting mixture was concentrated under reduced pressure. Water (20 mL) was added to the residue, and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification of the crude product by column chromatography on silica gel with hexane/ethyl acetate (40/1–20/1) produced **4** (585 mg, 98%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (q, *J*=6.0 Hz, 1H), 4.27 (q, *J*=6.0 Hz, 2H), 1.94 (d, *J*=6.0 Hz, 3H), 1.32 (t, *J*=6.0 Hz, 3H).

4.1.3. Ethyl 1-allyl-3-methyl-4-(4-methylphenylsulfonyl)pyroglutamate (5). A solution of **3** (253 mg, 1.0 mmol) in THF (30 mL) was carefully added to a rapidly stirred suspension of sodium hydride (1.24 g, 3.1 mmol, 60%) in THF (30 mL). After the reaction mixture was stirred at rt for 15 min, a solution of **4** (212 mg, 1.1 mmol) in THF (30 mL) was added. The resulting mixture was stirred for 6 h at refluxed temperature, quenched with saturated ammonium chloride solution (2 mL) in an ice bath, and concentrated under reduced pressure. Water (20 mL) was added to the crude product, and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification of the crude product by column chromatography on silica gel with hexane/ethyl acetate (4/1–2/1–1/1) produced **5** (190 mg, 52%): mp 101–103 °C; FAB-MS: $C_{18}H_{23}NO_5S$ *m/z* (%)=136 (100), 154 (28), 210 (10), 366 (M^++1, 45); HRMS (FAB, M^++1) Calcd for $C_{18}H_{24}NO_5S$ 366.1375, found 366.1373; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J*=8.0 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 5.65–5.57 (m, 1H), 5.20–5.12 (m, 2H), 4.42 (dd, *J*=5.0, 15.0 Hz, 1H), 4.31–4.18 (m, 2H), 3.70 (d, *J*=4.5 Hz, 1H), 3.62 (dd, *J*=8.0, 15.0 Hz, 1H), 3.60 (d, *J*=5.5 Hz, 1H), 3.21–3.14 (m, 1H), 2.44 (s, 3H), 1.42 (d, *J*=7.5 Hz, 3H), 1.32 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.46, 164.94, 145.29, 134.37, 130.78, 129.54 (2×), 129.42 (2×) 119.72, 71.72, 63.69, 61.79, 44.92, 32.59, 21.67, 20.79, 14.07. Anal. Calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.83. Found: C, 59.41; H, 6.24; N, 3.80.

Single-crystal X-ray diagram:[7] crystal of **5** was grown by slow diffusion of ethyl acetate into a solution of **5** in DCM to yield colorless prism. The compound crystallizes in the orthorhombic crystal system, space group. *Pca*2(1), *a*=9.8102(11) Å, *b*=10.3120(12) Å, *c*=18.686(2) Å, *V*=1890.3(4) Å^3, *Z*=4, d_{Calcd}=1.284 mg/m^3, absorption coefficient 0.198 mm^{-1}, *F*(000)=776, 2θ range (1.97–26.04°).

4.1.4. 1-Allyl-5-hydroxymethyl-4-methyl-3-(4-methylphenylsulfonyl)pyrrolidin-2-one (6a) and 1-allyl-3-methyl-4-(4-methylphenylsulfonyl)prolinol (6b). For

$NaBH_4$ condition: a solution of **5** (310 mg, 0.85 mmol) in ethanol (10 mL) was stirred at rt, and sodium borohydride (150 mg, 4.0 mmol) and lithium chloride (170 mg, 4.0 mmol) was added. The mixture was stirred for 12 h at rt. Saturated sodium bicarbonate solution (1 mL) was added to the mixture and the mixture was concentrated under reduced pressure. Water (1 mL) was added to the residue, and the mixture was extracted with DCM (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification of the crude product by column chromatography on silica gel with hexane/ethyl acetate (2/1–1/1) produced **6a** (247 mg, 90%).

For LAH condition: a solution of **5** (310 mg, 0.85 mmol) in THF (20 mL) was added to a rapidly stirred suspension of lithium aluminum hydride (76 mg, 2.0 mmol) and the resulting reaction mixture was stirred for 2 h, then quenched with saturated ammonium chloride solution (1 mL) and extracted with ethyl acetate (3×20 mL). The organic layers were washed with brine, dried, filtered and evaporated. Purification of the crude product by column chromatography on silica gel with hexane/ethyl acetate (2/1–1/1) produced **6a** (206 mg, 75%) and **6b** (29 mg, 11%).

For alane condition: a solution of **5** (310 mg, 0.85 mmol in THF (10 mL) was added to a solution of lithium aluminum hydride (57 mg, 1.5 mmol) and aluminum chloride (214 mg, 1.6 mmol) in THF (10 mL) via syringe at 0 °C. The mixture was refluxed for 2 h at rt, quenched with saturated ammonium chloride solution (1 mL) under cooling, and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine and water, dried, filtered and concentrated to produce crude compound. Purification on silica gel (hexane/ethyl acetate=1/1–1/2) produced **6b**.

For **6a**: gum; FAB-MS: $C_{16}H_{21}NO_4S$ *m/z* (%)=136 (71), 154 (63), 324 (M^++1, 100); HRMS (FAB, M^++1) Calcd for $C_{16}H_{22}NO_4S$ 324.1269, found 324.1270; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J*=8.5 Hz, 2H), 7.37 (d, *J*=8.5 Hz, 2H), 5.75–5.67 (m, 1H), 5.22–5.18 (m, 2H), 4.12 (dd, *J*=5.5, 15.5 Hz, 1H), 3.84–3.73 (m, 3H), 3.62 (d, *J*=6.0 Hz, 1H), 3.23 (q, *J*=4.5 Hz, 1H), 2.97–2.90 (m, 1H), 2.45 (s, 3H), 2.18 (br s, 1H), 1.33 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.34, 145.32, 134.60, 131.91, 129.58 (2×), 129.47 (2×), 118.36, 72.29, 64.62, 61.85, 44.32, 30.16, 21.72, 20.70. Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33. Found: C, 59.66; H, 6.32; N, 4.40.

For **6b**: gum; FAB-MS: $C_{16}H_{23}NO_3S$ *m/z* (%)=122 (100), 154 (59), 278 (32), 310 (M^++1, 99); HRMS (FAB, M^++1) Calcd for $C_{16}H_{24}NO_3S$ 310.1477, found 310.1476; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.0 Hz, 2H), 7.37 (d, *J*=8.0 Hz, 2H), 5.79–5.71 (m, 1H), 5.21–5.14 (m, 2H), 3.69 (dd, *J*=3.0, 11.5 Hz, 1H), 3.60 (dd, *J*=3.0, 11.5 Hz, 1H), 3.42 (d, *J*=11.5 Hz, 1H), 3.37 (dd, *J*=4.5, 13.5 Hz, 1H), 3.20–3.16 (m, 1H), 2.72–2.60 (m, 3H), 2.48–2.44 (m, 1H), 2.46 (s, 3H), 2.17 (br s, 1H), 1.00 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.93, 134.68, 133.88, 129.80 (2×), 129.15 (2×), 118.21, 71.98, 68.21, 57.56, 55.18, 52.95, 35.91, 21.66, 18.04. Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53. Found: C, 61.91; H, 7.32; N, 4.55.

4.1.5. 1-Allyl-4-methyl-3-(4-methylphenylsulfonyl)-5-vinyl-pyrrolidin-2-one (2). A solution of oxalyl chloride (0.14 mL, 1.56 mmol) in DCM (10 mL) at −78 °C, and dimethyl sulfoxide (0.19 mL, 2.67 mmol) were added carefully. The solution was warmed to −40 °C for 5 min and recooled to −78 °C, and then a solution of alcohol **6a** (160 mg, 0.5 mmol) in DCM (5 mL) was added dropwise for 40 min followed by excess triethylamine (4 mL) for 30 min. The reaction mixture was warmed to rt and poured into saturated aqueous ammonium chloride solution (2 mL), and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine and water, dried, filtered and evaporated to give the crude aldehyde product: FAB-MS: $C_{17}H_{21}NO_3S$ *m/z* (%)=136 (100), 154 (41), 219 (11), 320 (M^+−1, 63), 322 (M^++1, 20); HRMS (FAB, M^++1) Calcd for $C_{16}H_{20}NO_4S$ 322.1113, found 322.1111; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (d, *J*=3.0 Hz, 1H), 7.78 (d, *J*=9.0 Hz, 2H), 7.35 (d, *J*=9.0 Hz, 2H), 5.74–5.66 (m, 1H), 5.25–5.15 (m, 2H), 4.20–4.05 (m, 1H), 3.93–3.83 (m, 1H), 3.58 (d, *J*=3.0 Hz, 1H), 3.50–3.40 (m, 1H), 3.06–2.93 (m, 1H), 2.43 (s, 3H), 1.35 (d, *J*=6.0 Hz, 3H). To a stirred solution of methyl triphenylphosphonium iodide (808 mg, 2.0 mmol) in THF (50 mL) was added *n*-butyllithium (1.0 mL, 1.6 M, 1.6 mmol) and hexamethylphosphoric triamide (HMPA, 0.4 mL) at −78 °C. The orange red colored mixture was stirred at −78 °C for 1 h. The resulting aldehyde product was added to the reaction mixture at −78 °C via a syringe and further stirred at −78 °C for 2 h. The reaction was quenched with aqueous saturated ammonium chloride (10 mL) and the mixture was extracted with diethyl ether (3×50 mL) and the combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=2/1) produced compound **2** (114 mg, 72%): gum; FAB-MS: $C_{17}H_{21}NO_3S$ *m/z* (%)=136 (36), 219 (13), 320 (M^++1, 100); HRMS (FAB, M^++1) Calcd for $C_{17}H_{22}NO_3S$ 320.1322, found 320.1320; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J*=8.0 Hz, 2H), 7.36 (d, *J*=8.0 Hz, 2H), 5.69–5.55 (m, 2H), 5.33–5.28 (m, 2H), 5.18–5.05 (m, 2H), 4.13 (dd, *J*=4.5, 15.0 Hz, 1H), 3.64 (d, *J*=8.0 Hz, 1H), 3.49–3.43 (m, 2H), 2.75–2.68 (m, 1H), 2.44 (s, 3H), 1.33 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.90, 145.11, 136.05, 134.98, 131.11, 129.54 (2×), 129.48 (2x), 120.70, 118.47, 71.60, 66.85, 43.64, 34.61, 21.69, 18.53. Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.68; H, 6.57; N, 4.47.

4.1.6. 1-Methyl-2-(4-methylphenylsulfonyl)-1,2,5,7a-tetrahydro-pyrrolizin-3-one (7) and 4-methyl-1-propenyl-3-(4-methylphenylsulfonyl)-5-vinyl-pyrrolidin-2-one (7a). 1st or 2nd Grubbs' catalyst (0.01 mmol) was added to a solution of **2** (32 mg, 0.1 mmol) in 1,2-dichloroethane (3 mL) and the reaction mixture was refluxed under nitrogen atmosphere for 36 h. The mixture was concentrated and purified by flash column chromatography (hexane/ethyl acetate=2/1–1/1) to yield **7** and **7a**. For Grubb's 1st generation catalyst, the yield: **7** (2 mg, 7%) and **7a** (23 mg, 72%); For Grubb's 2nd generation catalyst, the yield: **7** (21 mg, 66%) and **7a** (3 mg, 9%).

For **7**: gum; FAB-MS: $C_{15}H_{17}NO_3S$ *m/z* (%)=136 (100), 154 (94), 242 (3), 292 (M^++1, 78); HRMS (FAB, M^++1) Calcd for $C_{15}H_{18}NO_3S$ 292.1008, found 292.1007; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 (d, *J*=8.0 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H), 5.94–5.88 (m, 2H), 4.37–4.32 (m, 1H), 4.13–4.11 (m, 1H), 3.98 (d, *J*=11.5 Hz, 1H), 3.67–3.62 (m, 1H), 2,82–2.77 (m, 1H), 2.45 (s, 3H), 1.47 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.55, 145.01, 135.28, 129.84 (2×), 129.71 (2×), 120.11, 111.72, 72.95, 71.26, 50.58, 40.50, 21.69, 17.92.

For **7a**: mp 113–114 °C; EI-MS: $C_{17}H_{21}NO_3S$ *m/z* (%)=69 (77), 91 (100), 164 (78), 319 (M^+, 2); HRMS (EI, M^+) Calcd for $C_{17}H_{21}NO_3S$ 319.1237, found 319.1236; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J*=8.5 Hz, 2H), 7.35 (d, *J*=8.5 Hz, 2H), 6.59 (dd, *J*=1.5, 14.5 Hz, 1H), 5.79–5.72 (m, 1H), 5.30–5.23 (m, 3H), 3.74 (dd, *J*=4.6, 8.5 Hz, 1H), 3.64 (d, *J*=6.0 Hz, 1H), 2.75–2.69 (m, 1H), 2.44 (s, 3H), 1.64 (dd, *J*=1.5, 7.0 Hz, 3H), 1.32 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.99, 145.21, 137.62, 134.70, 129.53 (2x), 129.42 (2x), 123.26, 118.07, 111.83, 72.04, 66.58, 34.83, 21.65, 19.61, 15.50. Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.76; H, 6.54; N, 4.44.

4.1.7. 1-Methyl-1,2,5,7a-tetrahydro-pyrrolizin-3-one (8). 6% Sodium amalgam (Na/Hg, 0.5 g) and sodium phosphate (71 mg, 0.5 mmol) were added to a stirred solution of **7** (30 mg, 0.1 mmol) in methanol (5 mL), and vigorously stirred for 2 h at rt. The residue was filtered and washed with methanol (2×10 mL) and the combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=1/1–1/2) produced **8** (12 mg, 86%): oil; HRMS (EI, M^+) Calcd for $C_8H_{11}NO$ 137.0841, found 137.0841; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.92–5.83 (m, 2H), 4.41–4.32 (m, 1H), 4.22–4.14 (m, 1H), 3.70–3.61 (m, 1H), 2.32–2.15 (m, 2H), 1.82–1.72 (m, 1H), 1.22 (d, *J*=7.5 Hz, 3H).

4.1.8. 1-Methyl-hexahydro-pyrrolizin-3-one (9).[5e,g,m,p] 10% Palladium on activated carbon (10 mg) was added to the solution of **8** (7 mg, 0.05 mmol) in methanol (10 mL). Then hydrogen was bubbled into the mixture for 10 min, and the reaction mixture was continued to stir for 3 h at rt. The catalyst was filtered through a short plug of Celite and washing with methanol (2×5 mL). The combined organic layers were evaporated. Purification on silica gel (hexane/ethyl acetate=1/1–1/2) produced **9** (6 mg, 85%). The ^{1}H NMR data was in accordance with the reported in the literature.

5. Supplementary Material

Experimental procedures and photocopies of ^{1}H-NMR ($CDCl_3$) spectral data for **2**, **5**, **6a**, **6b**, **7**, **7a**, **8** were supported.

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