Article

Studies toward the First Stereoselective Total Synthesis of (±)-Quinolizidine 195C and Other Transformations

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Abstract: Starting from a thio-substituted 4-quinolizidinone, a series of C-6 alkylated derivatives with a *trans* C-6, C-9a relationship was synthesized. Further transformations led to the first stereoselective total synthesis of the structure proposed for (±)-quinolizidine 195C, the major alkaloid isolated from the skin extracts of the Madagascan frog *Mantella betsileo*. Since the spectral data of the synthetic and natural products differed significantly, the true structure of (±)-quinolizidine 195C remains uncertain.

Keywords: aza-Diels-Alder reaction; intramolecular aza-Michael reaction; quinolizidines; quinolizidine 195C

1. Introduction

The piperidine ring is one of the most abundant molecular fragments in both natural and synthetic compounds displaying various biological activities [1–4]. Among the piperidine natural products are the bicyclic indolizidines and quinolizidines [5–16]. Imino-Diels-Alder reactions are very useful for the synthesis of tetrahydropyridines [17–19]. We have previously developed a new imino-Diels-Alder reaction of thio-substituted 3-sulfolenes with *p*-toluenesulfonyl isocyanate (PTSI) to synthesize piperidine derivatives [20,21], and have used this method to prepare some indolizidines and quinolizidines [22–32]. We have recently reported the use of cross metathesis (CM) to transform the terminal alkenes **1a–c** into the α,β-unsaturated esters **2a–c**, and after detosylation the resulting amides **3a–c**

can undergo the intramolecular aza-Michael reaction to give sulfur-substituted bicyclic compounds **4a–c** (Scheme 1) [33].

Scheme 1. Cross-metathesis and aza-Michael reaction.
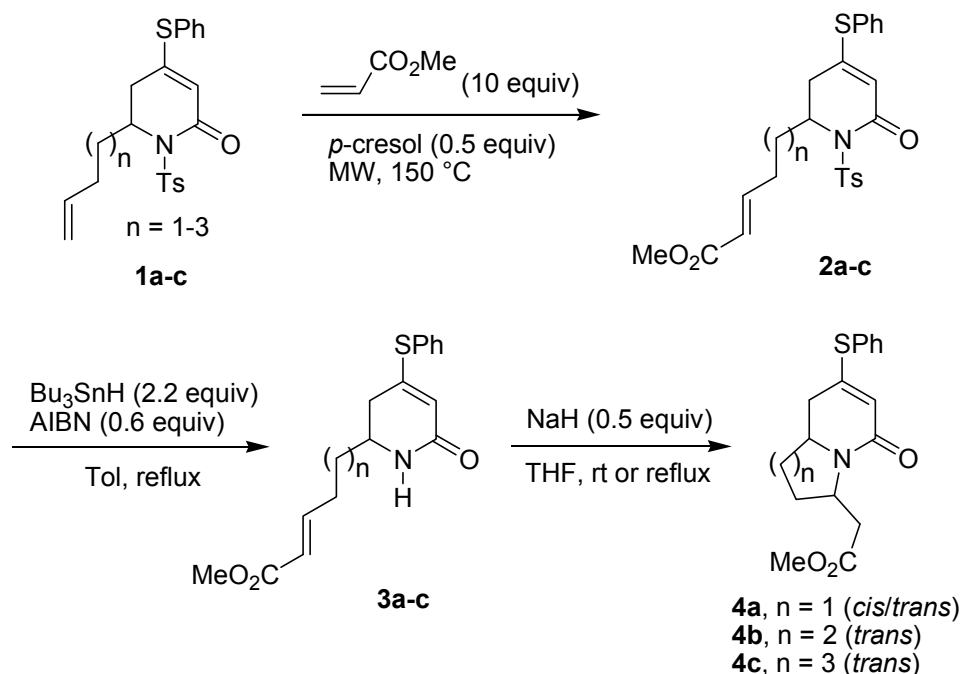
Herein a new method for the synthesis of C-6 alkylated quinolizidines with a *trans*-C-6, C-9a relationship is reported, and the *trans*-compound **4b** could be used for the preparation of quinolizidine 195C (Figure 1), which was isolated as a major alkaloid from the skin extracts of the Madagascan frog *Mantella betsileo* [34,35]. The proposed structure of quinolizidine 195C was based only on its mass spectral and FTIR data. There has been no synthesis of quinolizidine 195C itself, and only that of (±)-quinolizidine 9a-*epi*-195C was reported [36]. We also reported recently the synthesis of (±)-quinolizidine 4-*epi*-195C and (±)-quinolizidine 9a-*epi*-195C [37]. We hoped to achieve the synthesis of quinolizidine 195C and to confirm its structure by providing more spectral data.

**Figure 1.** Proposed structure of quinolizidine 195C.
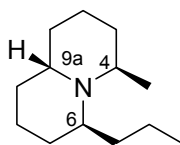
2. Results and Discussion

Reduction of compound **4b** [33] with LiAlH$_4$ in THF at low temperature gave the primary alcohol **5** (Scheme 2). Further treatment with PBr$_3$ provided the expected bromide, but since the bromide was rather unstable, we directly carried out the debromination with Bu$_3$SnH/AIBN to give the ethyl-substituted product **6**. If the bromide was treated with Me$_2$CuLi, the propyl-substituted product **7** was obtained. Further reactions of compounds **6** and **7** with Raney nickel cleaved the C-S bond and

also reduced the C=C bond to give the products **8** and **9**, respectively. Compounds **8** and **9** were then reduced with lithium aluminum hydride in THF at 0 °C to give the corresponding quinolizidines **10** and **11**. Since compound **4b** has been previously established to have a *trans*-C-6, C-9a relationship [33], the compounds **10** and **11** should retain the same configuration. The ^{1}H- and ^{13}C-NMR spectral data of compound **11** however were significantly different from those of the *cis* isomer reported in the literature [36].

Scheme 2. Synthesis of compounds **8–11**.
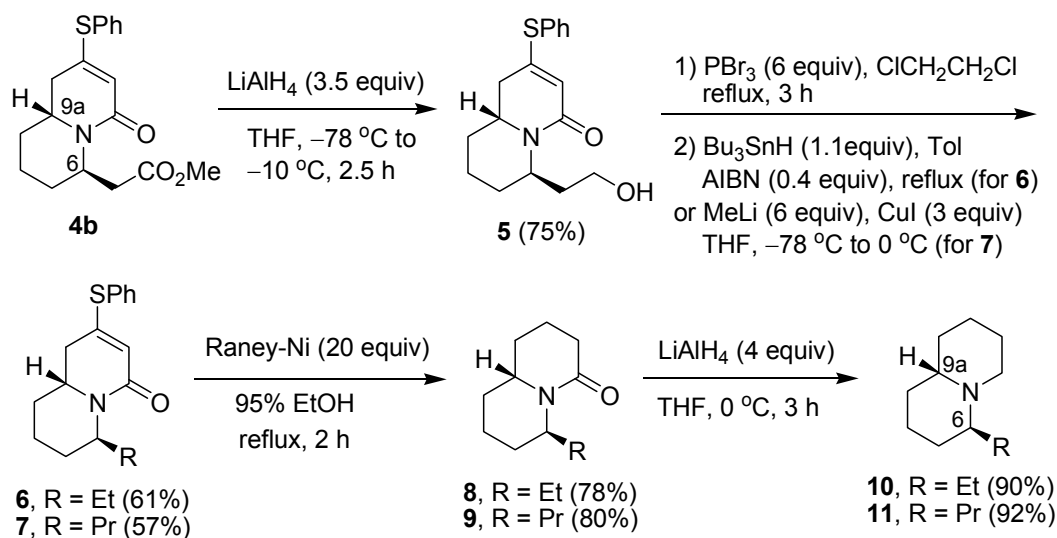
We then studied the conversion of compound **9** to quinolizidine 195C. Unfortunately, various reaction conditions of compound **9** with a methyl nucleophile, followed by treatment with acetic acid and NaBH$_4$/MeOH all failed, as shown in Table 1. Reaction of compound **9** with methylmagnesium bromide at 65 °C gave only the recovered starting material (entry 1). The reaction with methyllithium at room temperature gave the same result (entry 2). Increasing the reaction temperature to 50 °C, however, gave an unidentified mixture of products (entry 3). We suspect that the axial propyl group of compound **9** at C-6 hinders the reaction of the nucleophile with the C=O group.

**Table 1.** Reactions of compound **9** with a methyl nucleophile.

Entry	Reaction Conditions	Results
1	MeMgBr (4 equiv), 65 °C, 3 h	NR [a]
2	MeLi (5 equiv), rt, 5 h	NR [a]
3	MeLi (5 equiv), 50 °C, 5 h	ND [b]

[a] No reaction was observed; [b] An unidentified mixture of products was obtained.

We then decided to react compound **7** with the carbon nucleophile, because the more planar structure of compound **7** should offer less steric hindrance (Table 2). Treatment of compound **7** with

methylmagnesium bromide, followed by acidification with acetic acid and reduction with $NaBH_4$ at 0 °C (entry 1) gave the 1,2-addition products **12** and **13** (in a ratio of 2:1), and some undesired 1,4-substitution product **14**. Since compound **12** has the correct stereochemistry for the conversion to quinolizidine 195C, we tried to increase the **12/13** ratio. When a bulkier reducing agent, $NaB(OAc)_3H$, was used at 0 °C (entry 2), the ratio of **12/13** remained the same at 2:1. If the reduction with $NaB(OAc)_3H$ was carried out at room temperature (entry 3), the ratio of **12/13** was reduced to 1.5:1. In contrast, carrying out the reaction at −50 °C for 2 h and then slowly warming to 0 °C (entry 4) afforded the products **12** and **13** in a higher ratio of 4:1. From these results it seems that compound **12** is the kinetic product, which is more favored at lower temperature. However, use of a more bulky and less reactive reductant like $NaB(OAc)_3H$ or $NaBH_3CN$ at low temperature gave only the 1,4-substitution product **14** (entries 5 and 6). This could be attributed to a slower rate of reduction of the iminium ion intermediate at low temperature by the less reactive reductants. The unreacted iminium ion was then hydrolyzed during aqueous work-up, or was lost in the aqueous solution.
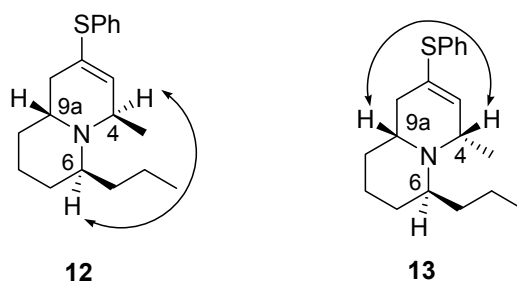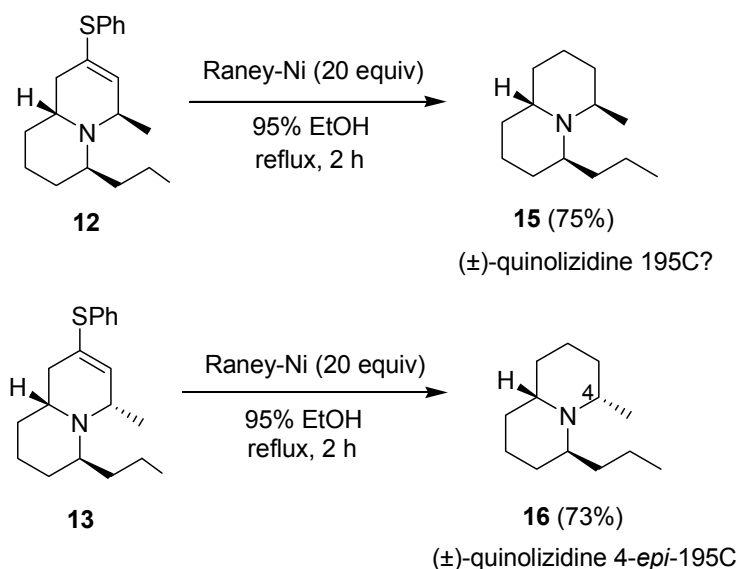
Table 2. Reactions of compound **7** with MeMgBr followed by reduction.
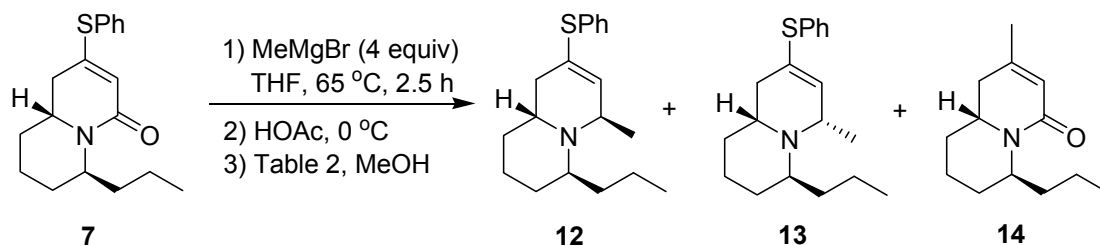

Entry	Reaction Conditions	Products (%Yield) [a]	Ratio of 12/13 [b]
1	$NaBH_4$, 0 °C, 2.5 h	**12** (27), **13** (13), **14** (31)	2:1
2	$NaB(OAc)_3H$, 0 °C, 2 h	**12** (29), **13** (14), **14** (27)	2:1
3	$NaB(OAc)_3H$, rt, 2 h	**12/13** (33%), [c] **14** (30)	1.5:1
4	$NaBH_4$, −50 °C, 2.5 h, then to 0 °C, 2 h	**12** (34), **13** (8), **14** (38)	4:1
5	$NaB(OAc)_3H$, −50 °C to 0 °C, 2 h	**14** (34)	-
6	$NaBH_3CN$, −50 °C to 0 °C, 2 h	**14** (36)	-

[a] Isolated yield of the purified products; [b] The ratio of **12/13** was determined from the ¹H-NMR of crude reactions mixtures; [c] The mixture of compounds **12** and **13** was not separated.

The stereochemistry of compounds **12** and **13** was determined from their NOESY spectra. Compound **12** shows cross signals between the hydrogens at C_4 and C_6, but no cross signals between the hydrogens at C_6 and C_{9a}. On the other hand, compound **13** shows cross signals between the hydrogens at C_4 and C_{9a}, but no cross signals between the hydrogens at C_4 and C_6 (Figure 2). Further treatment of compounds **12** and **13** with Raney nickel in refluxing 95% EtOH gave compounds **15** and **16**, respectively (Scheme 3). The spectral data of compound **16** were identical with what we had earlier reported for (±)-quinolizidine 4-*epi*-195C [37]. On the other hand, the three most downfield CHN protons of compound **15** at δ 3.0–3.2 are quite different from the partial ¹H-NMR data (δ 3.7–4.0) of (±)-quinolizidine 195C descried in the literature [34]. Compound **15** exhibits a weak Bohlmann band at 2795 cm⁻¹ whereas the literature data for (±)-quinolizidine 195C was at 2811 cm⁻¹ [34]. Thus, since we are quite confident about the structure of compound **15** based on all the spectral data and related chemical reactions, its identity with the true structure of (±)-quinolizidine 195C remains uncertain.

Figure 2. NOESY correlations of compounds **12** and **13**.

12   **13**

Scheme 3. Preparation of compounds **15** and **16**.

12

Raney-Ni (20 equiv)

95% EtOH
reflux, 2 h

15 (75%)

(±)-quinolizidine 195C?

13

Raney-Ni (20 equiv)

95% EtOH
reflux, 2 h

16 (73%)

(±)-quinolizidine 4-*epi*-195C

Since the reaction of compound **7** with MeMgBr under various conditions of Table 2 all gave significant amounts of the 1,4-substitution product **14**, we hoped that the conversion of the phenylthio group of compound **7** first to the sulfone **17** would disfavor the formation of the 1,4-substitution product **14** because of the greater steric hindrance of the phenylsulfonyl group. However, the reaction of compound **17** with methylmagnesium bromide, followed by HOAc and NaBH$_4$ gave only the 1,4-substitution product **14** (Scheme 4).

Scheme 4. Preparation of compound **17** and reaction with a nucleophile.

7

*m*CPBA (4 equiv)

CH$_2$Cl$_2$, 0 °C
to rt, 4h

17 (79%)

Table 2, entry 4

14 (82%)
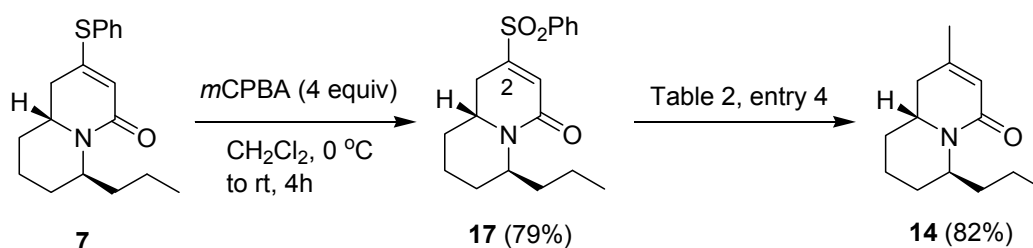
It seems that the strongly electron-withdrawing phenylsulfonyl group increases the partial positive charge at C-2 significantly and outweighs its steric effect so that only the 1,4-substitution was observed.

We are also interested in studying the biological effects of the quinilizidine derivatives, so we have carried out further synthetic transformations of some of these quinolizidines (Scheme 5). Reaction of compound **5** with Raney nickel in refluxing 95% EtOH gave the product **18**. Under catalytic hydrogenation conditions, compound **14** was converted to an inseparable 1:1 mixture of compounds **19**. Treatment of compound **17** with 6% sodium amalgam in the presence of a small amount of phosphoric acid [38,39] resulted in the selective cleavage of the phenylsulfonyl group to give product **20**. We also found that the reaction of compound **4b** with an excess of (trimethylsilyl)methylmagnesium chloride, followed by treatment with aqueous HCl solution gave the methyl ketone product **21**. Presumably, the reaction proceeds through the single addition/elimination intermediate **A**, which is sterically too hindered to react with another molecule of the Grignard reagent.

Scheme 5. Preparation of compounds **18**−**21**.
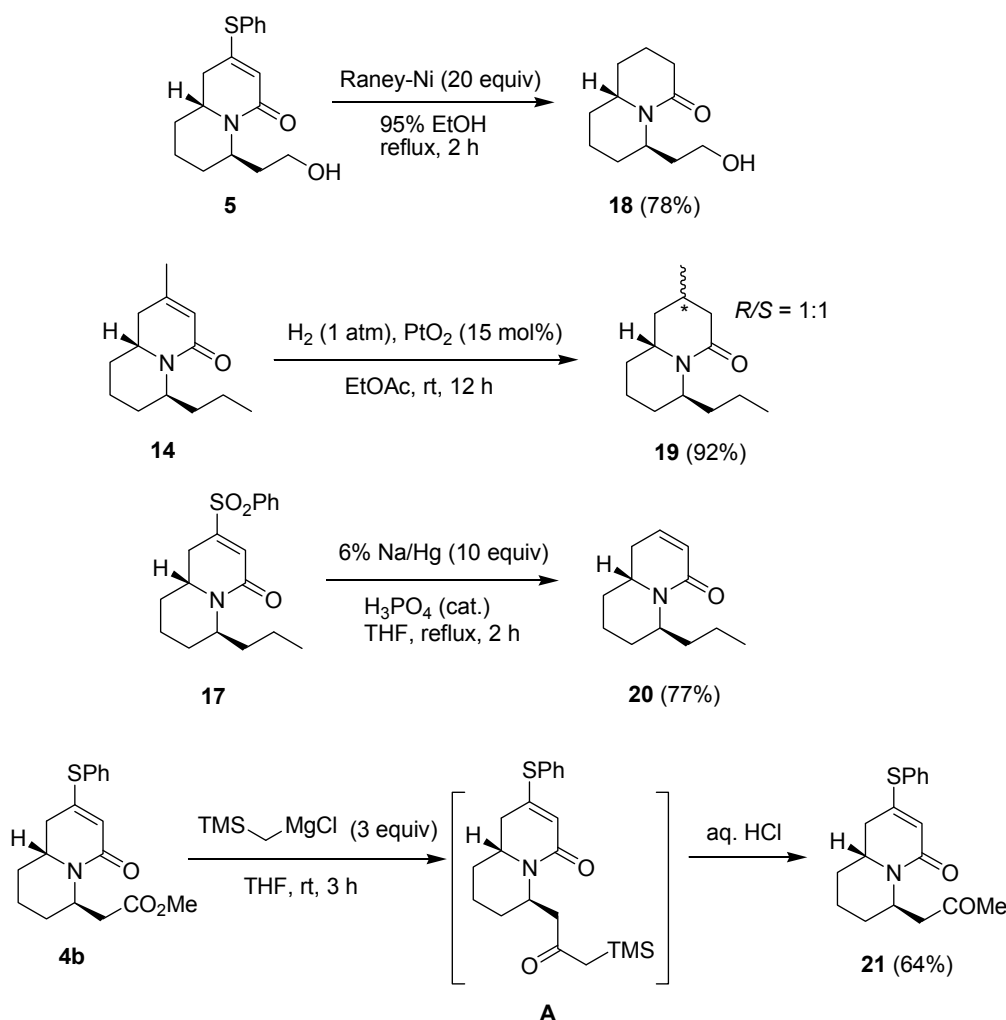
3. Experimental

General

Infrared spectra were recorded with a Perkin-Elmer 100 series FTIR spectrometer using the ATR (attenuated total reflectance) mode. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance 300 spectrometer operating at 300 and at 75 MHz, respectively. Chemical shifts (δ) are reported in

parts per million (ppm) and the coupling constants (*J*) are given in Hertz. High-resolution mass spectra (HRMS) were measured with a Finnigan/Thermo Quest MAT 95XL mass spectrometer, or a Shimadzu LCMS-IT-TOF mass spectrometer for electrospray ionization (ESI) measurements. Flash column chromatographic purifications were performed using Merck 60 H silica gel. The microwave reactions were carried out with a CEM Focused™ Discover-S system.

Trans-6-(2-hydroxyethyl)-2-(phenylthio)-1,6,7,8,9,9a-hexahydro-4-quinolizinone (**5**). To a solution of compound **4b** (510 mg, 1.54 mmol) in THF (50 mL) under nitrogen was added dropwise LiAlH$_4$ (2.4 M in THF, 2.6 mL, 6.16 mmol) at −78 °C. The mixture was slowly warmed to −10 °C in 2.5 h. The solvent was removed under reduced pressure. Saturated NaHCO$_3$ solution was then slowly added. The mixture was extracted three times with ethyl acetate. The organic solution was concentrated under reduced pressure and dried (MgSO$_4$) to give the crude product, which was purified by flash chromatography on silica gel prewashed with Et$_3$N using ethyl acetate/hexane (1:1) and 5% Et$_3$N as eluent to give product **5** (350 mg, 75%). Colorless oil; ^{1}H-NMR (CDCl$_3$) δ 7.51–7.40 (5H, m), 5.31 (1H, d, *J* = 1.8 Hz), 4.77–4.73 (1H, m), 3.96 (1H, OH), 3.60–3.49 (2H, m), 3.30–3.22 (1H, m), 2.57–2.38 (2H, m), 1.89–1.38 (8H, m); ^{13}C-NMR (CDCl$_3$) δ 164.8, 151.8, 135.1, 129.8, 129.7, 127.9, 114.5, 58.2, 49.0, 45.1, 35.3, 33.4, 33.2, 28.5, 18.1; IR (neat) 3404, 3054, 2943, 2873, 1675, 1596, 1436, 1335, 1266, 1068, 864, 705 cm^{-1}; EI-MS (rel. intensity) *m/z* 303 (M$^+$, 8), 272 (27), 259 (44), 258 (100), 231 (29), 229 (53), 119 (24), 55 (20); Exact mass calcd for C$_{17}$H$_{21}$NO$_2$S *m/z* 303.1293; EI-HRMS *m/z* 303.1295.

Trans-6-ethyl-2-(phenylthio)-1,6,7,8,9,9a-hexahydro-4-quinolizinone (**6**). To a solution of compound **5** (130 mg, 0.43 mmol) in 1,2-dichloroethane (2.5 mL) under nitrogen was added dropwise PBr$_3$ (0.24 mL, 2.57 mmol) at reflux for 3 h. The mixture was cooled in an ice bath, and saturated NaHCO$_3$ solution was then slowly added. The liquid layer was extracted three times with ethyl acetate. The organic solution was concentrated under reduced pressure and dried (MgSO$_4$) to give the crude product, to which were added AIBN (28 mg, 0.17 mmol), degassed toluene (2.5 mL) and Bu$_3$SnH (0.13 mL, 0.47 mmol). The mixture was then heated at reflux for 2 h, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel prewashed with Et$_3$N using ethyl acetate/hexane (1:4) and 5% Et$_3$N as eluent to give product **6** (75 mg, 61%). Colorless oil; ^{1}H-NMR (CDCl$_3$) δ 7.51–7.37 (5H, m), 5.35 (1H, s), 4.49–4.45 (1H, m), 3.63–3.53 (1H, m), 2.55 (1H, dd, *J* = 17.1, 6.3 Hz), 2.31 (1H, ddd, *J* = 17.1, 9.3, 1.2 Hz), 1.71–1.41 (8H, m), 0.86 (3H, t, *J* = 7.5 Hz); ^{13}C-NMR (CDCl$_3$) δ 164.3, 150.3, 135.2, 129.7 (×2), 128.4, 115.8, 50.4, 49.5, 35.2, 32.9, 26.0, 21.8, 18.4, 11.0; IR (neat) 3057, 2935, 2872, 1635, 1600, 1408, 1306, 1084, 856, 751, 692 cm^{-1}; EI-MS (rel. intensity) *m/z* 287 (M$^+$, 8), 259 (31), 258 (100); Exact mass calcd for C$_{17}$H$_{21}$NOS *m/z* 287.1344; EI-HRMS *m/z* 287.1345.

Trans-6-propyl-2-(phenylthio)-1,6,7,8,9,9a-hexahydro-4-quinolizinone (**7**). To a solution of compound **5** (112 mg, 0.37 mmol) in 1,2-dichloroethane (3 mL) under nitrogen was added dropwise PBr$_3$ (0.21 mL, 2.22 mmol) at reflux for 3 h. The mixture was cooled in an ice bath, and saturated NaHCO$_3$ solution was then slowly added. The liquid layer was extracted three times with ethyl acetate. The organic solution was concentrated under reduced pressure and dried (MgSO$_4$) to give the crude product, to which were added THF (1 mL). To a mixture of CuI (211 mg, 1.11 mmol) in THF (1 mL)

at 0 °C was added dropwise a solution of MeLi (1.5M in THF, 1.5 mL, 2.22 mmol). After stirring at 0 °C for 30 min, the mixture added to the prepared solution of crude product at −78 °C. The reaction mixture was slowly warmed to 0 °C in 2 h, and quenched with saturated ammonium chloride. The aqueous solution was extracted three times with ethyl acetate. The organic solution was removed under reduced pressure and dried (MgSO$_4$). The residue was purified by flash chromatography on silica gel prewashed with Et$_3$N using ethyl acetate/hexane (1:5) and 5% Et$_3$N as eluent to give product **7** (63 mg, 57%). Colorless oil; ^{1}H-NMR (CDCl$_3$) δ 7.51–7.38 (5H, m), 5.33 (1H, d, *J* = 0.9 Hz), 4.62–4.56 (1H, m), 3.65–3.55 (1H, m), 2.57 (1H, dd, *J* = 16.8, 6.0 Hz), 2.32 (1H, ddd, *J* = 16.8, 9.0, 1.5 Hz), 1.75–1.40 (8H, m), 1.34–1.22 (2H, m), 0.90 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR (CDCl$_3$) δ 164.3, 150.4, 135.4, 129.8 (×2), 128.6, 115.9, 49.7, 48.9, 35.3, 33.0, 31.3, 26.8, 19.8, 18.7, 14.1; IR (neat) 3052, 2938, 2870, 1637, 1598, 1411, 1319, 1266, 1086, 858, 738, 692 cm^{-1}; EI-MS (rel. intensity) *m/z* 301 (M$^+$, 7), 259 (30), 258 (100), 164 (22); Exact mass calcd for C$_{18}$H$_{23}$NOS *m/z* 301.1500; EI-HRMS *m/z* 301.1497.

Trans-6-ethyl-1,6,7,8,9,9a-hexahydro-4-quinolizinone (**8**). A mixture of compound **6** (140.2 mg, 0.49 mmol) and a W-2 Raney-Ni (1.1 g) in 95% EtOH (5 mL) was heated at reflux under nitrogen for 2 h. The solid was filtered off, and the residue was evaporated under vacuum. The crude product was purified by flash chromatography on silica gel prewashed with Et$_3$N using ethyl acetate/hexane (1:1) and 5% Et$_3$N as eluent to give product **8** (69.1 mg, 78%). Yellow oil; ^{1}H-NMR (CDCl$_3$) δ 4.86–4.79 (1H, m), 3.40–3.31 (1H, m), 2.46–2.27 (2H, m), 2.00–1.92 (1H, m), 1.82–1.75 (1H, m), 1.72–1.40 (9H, m), 1.32–1.23 (1H, m), 0.85 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR (CDCl$_3$) δ 169.4, 51.0, 48.9, 34.1, 33.2, 30.7, 27.2, 22.4, 18.9, 18.8, 10.6; IR (neat) 2937, 2871, 1634, 1463, 1347, 1268, 1050, 791 cm^{-1}; EI-MS (rel. intensity) *m/z* 181 (M$^+$, 3), 153 (29), 152 (100), 41 (30); Exact mass calcd for C$_{11}$H$_{19}$NO *m/z* 181.1467; EI-HRMS *m/z* 181.1474.

Trans-6-propyl-1,6,7,8,9,9a-hexahydro-4-quinolizinone (**9**). Using a procedure similar to that for the preparation of compound **8**, compound **7** (39.1 mg, 0.13 mmol) gave product **9** (20.3 mg, 80%). Yellow oil; ^{1}H-NMR (CDCl$_3$) δ 4.94–4.87 (1H, m), 3.42–3.33 (1H, m), 2.45–2.26 (2H, m), 1.97–1.91 (1H, m), 1.82–1.38 (10H, m), 1.32–1.18 (3H, m), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR (CDCl$_3$) δ 169.4, 51.1, 47.5, 34.3, 33.3, 32.0, 30.8, 27.8, 19.5, 19.1, 18.9, 14.2; IR (neat) 3054, 2944, 2872, 1621, 1450, 1265, 1092, 705 cm^{-1}; EI-MS (rel. intensity) *m/z* 195 (M$^+$, 7), 153 (14), 152 (100); Exact mass calcd for C$_{12}$H$_{21}$NO *m/z* 195.1623; EI-HRMS *m/z* 195.1620.

(4S/9aS,4R/9aR)-4-Ethyloctahedro-1H-quinolizine (**10**). To a solution of compound **8** (17.1 mg, 0.09 mmol) in THF (1 mL) under nitrogen was added dropwise LiAlH$_4$ (2.4 M in THF, 0.16 mL, 0.38 mmol) at 0 °C. After stirring at 0 °C for 3 h, the solvent was removed under reduced pressure. Saturated NaHCO$_3$ solution was then slowly added. The mixture was extracted three times with ethyl acetate. The organic solution was carefully concentrated under reduced pressure and dried (MgSO$_4$) to give the crude product, which was purified by flash chromatography on silica gel prewashed with Et$_3$N using ethyl acetate/hexane (1:10) and 5% Et$_3$N as eluent to give product **10** (14.2 mg, 90%). Yellow liquid; ^{1}H-NMR (CDCl$_3$) δ 2.67–2.48 (2H, m), 2.30–2.26 (1H, m), 1.73–1.14 (15H, m), 0.84 (3H, t, *J* = 7.5 Hz); ^{13}C-NMR (CDCl$_3$) δ 61.5, 54.1, 52.1, 34.3, 34.0, 27.7, 26.2, 24.7, 18.7, 15.0, 12.0; IR

(neat) 2931, 2865, 2800, 1445, 1096 cm^{-1}; ESI-MS (rel. intensity) *m/z* 168 (M$^+$+H, 100); Exact mass calcd for C$_{11}$H$_{21}$N *m/z* 167.1674; ESI-HRMS *m/z* 167.1664.

(4S/9aS,4R/9aR)-4-Propyloctahedro-1H-quinolizine (**11**). Using a procedure similar to that for the preparation of compound **10**, compound **9** (26.3 mg, 0.13 mmol) gave product **11** (22.2 mg, 92%). Yellow liquid; ^{1}H-NMR (CDCl$_3$) δ 2.77–2.71 (1H, m), 2.62–2.47 (2H, m), 2.33–2.26 (1H, m), 1.70–1.11 (16H, m), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR (CDCl$_3$) δ 59.7, 54.1, 52.0, 34.3, 34.0, 28.5, 26.2, 24.8, 24.7, 21.0, 18.8, 14.5; IR (neat) 2933, 2866, 2808, 1449, 1096 cm^{-1}; FAB-MS (rel. intensity) *m/z* 182 (M$^+$+H, 14), 127 (27), 92 (32), 82 (55), 73 (51), 71 (62), 63 (87), 54 (69), 53 (100); Exact mass calcd for C$_{12}$H$_{23}$N *m/z* 181.1830; FAB-HRMS *m/z* 181.1833.

(4R/6S/9aR,4S/6R/9aS)-4-Methyl-2-(phenylthio)-6-propyl-1,6,7,8,9,9a-hexahydroquinolizine (**12**), *(4S/6S/9aR,4R/6R/9aS)-4-methyl-2-(phenylthio)-6-propyl-1,6,7,8,9,9a-hexahydroquinolizine* (**13**) *and trans-2-Methyl-6-propyl-1,6,7,8,9,9a-hexahydro-4-quinolizinone* (**14**). To a stirred solution of compound **7** (108.1 mg, 0.36 mmol) in THF (9.5 mL) was added MeMgBr (3M in THF, 0.48 mL, 1.43 mmol) dropwise at room temperature under nitrogen, followed by heating at 65 °C for 2.5 h. The reaction was then quenched with AcOH (0.1 mL) at 0 °C with stirring for about 10 min, then cooled to −50 °C. NaBH$_4$ (78 mg, 2.06 mmol) and MeOH (2 mL) were then added sequentially with stirring at −50 °C for 2.5 h. The mixture was slowly warmed to 0 °C in 2 h. The solvent was removed under reduced pressure. Saturated NaHCO$_3$ solution was then added. The mixture was extracted three times with CH$_2$Cl$_2$. The organic solution was carefully concentrated under reduced pressure and dried (MgSO$_4$) to give the crude product, which was purified by flash chromatography on silica gel prewashed with hexane using ethyl acetate/hexane (1:10) and 5% Et$_3$N as eluent to give compound **12** (37.2 mg, 34%), compound **13** (8.4 mg, 8%) and compound **14** (28.2 mg, 38%). Compound **12**: yellow liquid; ^{1}H-NMR (CDCl$_3$) δ 7.35–7.27 (4H, m), 7.24–7.21 (1H, m), 5.97–5.95 (1H, m), 3.65–3.62 (1H, m), 3.36–3.29 (1H, m), 2.74–2.66 (1H, m), 2.25 (1H, dd, *J* = 17.4, 7.8 Hz), 1.96 (1H, dd, *J* = 17.4, 5.1 Hz), 1.74–1.22 (10H, m), 1.19 (3H, d, *J* = 6.6 Hz), 0.90 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR (CDCl$_3$) δ 135.1, 134.7, 130.5, 129.0, 128.2, 126.6, 53.0, 50.5, 48.6, 35.6, 31.0, 27.9, 27.7, 21.2, 20.1, 19.2, 14.6; IR (neat) 2954, 2930, 2867, 1439, 1378, 1161, 1067, 1024, 744, 692 cm^{-1}; ESI-MS (rel. intensity) *m/z* 302 (M$^+$+H, 50), 300 (100), 298 (12); Exact mass calcd for C$_{19}$H$_{27}$NS *m/z* 301.1864; ESI-HRMS *m/z* 301.1872. Compound **13**: yellow liquid; ^{1}H-NMR (CDCl$_3$) δ 7.33–7.27 (4H, m), 7.23–7.18 (1H, m), 5.83 (1H, d, *J* = 1.2 Hz), 3.47–3.42 (1H, m), 3.14–3.11 (1H, m), 2.76–2.66 (1H, m), 2.06–2.00 (2H, m), 1.79–1.21 (10H, m), 1.17 (3H, d, *J* = 6.6 Hz), 0.94 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR (CDCl$_3$) δ 135.8, 134.6, 130.6, 129.0, 127.5, 126.6, 53.3, 52.2, 50.7, 38.8, 34.4, 28.6, 24.2, 21.0, 20.0, 18.2, 14.5; IR (neat) 2955, 2929, 2867, 1439, 1371, 1133, 1068, 1025, 740, 691 cm^{-1}; ESI-MS (rel. intensity) *m/z* 302 (M$^+$+H, 96), 300 (100), 298 (11); Exact mass calcd for C$_{19}$H$_{27}$NS *m/z* 301.1864; ESI-HRMS *m/z* 301.1881. Compound **14**: yellow oil; ^{1}H-NMR (CDCl$_3$) δ 5.69 (1H, q, *J* = 1.2 Hz), 4.68–4.62 (1H, m), 3.63–3.53 (1H, m), 2.39 (1H, dd, *J* = 17.7, 6.9 Hz), 2.08 (1H, dd, *J* = 17.7, 8.4 Hz), 1.85 (3H, s), 1.70–1.23 (10H, m), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR (CDCl$_3$) δ 165.4, 147.7, 120.4, 49.1, 48.6, 36.0, 33.5, 31.2, 26.8, 22.6, 19.7, 18.8, 14.1; IR (neat) 2934, 2869, 1677, 1424, 1327, 1040 cm^{-1}; EI-MS (rel. intensity) *m/z* 207 (M$^+$, 7), 165 (17), 164 (100), 82 (6); Exact mass calcd for C$_{13}$H$_{21}$NO *m/z* 207.1623; EI-HRMS *m/z* 207.1623.

(4R/6S/9aS,4S/6R/9aR)-4-Methyl-6-propyl-2,3,4,6,7,8,9,9a-octahydro-1H-quinolizine (**15**). A mixture of compound **12** (23.4 mg, 0.08 mmol) and a W-2 Raney-Ni (175 mg) in 95% EtOH (3 mL) was heated at reflux under nitrogen for 2 h. The solid was filtered off, and the residue was evaporated under vacuum. The crude product was purified by flash chromatography on silica gel prewashed with hexane using hexane and 5% Et_3N as eluent to give product **15** (11.4 mg, 75%). Yellow liquid; ^{1}H-NMR ($CDCl_3$) δ 3.22–3.18 (1H, m), 3.14–3.00 (2H, m), 1.90–1.81 (2H, m), 1.70–1.54 (9H, m), 1.34–1.24 (4H, m), 1.16–1.12 (1H, m), 1.06 (3H, d, *J* = 6.0 Hz), 0.91 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$) δ 52.4, 49.4, 47.1, 34.4, 33.7, 30.2, 24.6, 22.5, 21.0, 20.3 (×2), 20.0, 14.5; IR (neat) 2931, 2864, 2795, 1457, 1365 cm^{-1}; ESI-MS (rel. intensity) *m/z* 196 (M$^+$+H, 100); Exact mass calcd for $C_{13}H_{25}N$ *m/z* 195.1987; ESI-HRMS *m/z* 195.1968.

(4S/6S/9aS,4R/6R/9aR)-4-Methyl-6-propyl-2,3,4,6,7,8,9,9a-octahydro-1H-quinolizine (**16**). A mixture of compound **13** (34.4 mg, 0.11 mmol) and a W-2 Raney-Ni (258 mg) in 95% EtOH (5 mL) was heated at reflux under nitrogen for 2 h. The solid was filtered off, and the residue was evaporated under vacuum. The crude product was purified by flash chromatography on silica gel prewashed with hexane using hexane and 5% Et_3N as eluent to give product **16** (16.3 mg, 73%) as a yellow liquid. The spectral data of compound **16** were identical with the literature data [37].

Trans-6-propyl-2-(phenylsulfonyl)-1,6,7,8,9,9a-hexahydro-4-quinolizinone (**17**). To a solution of compound **7** (69.5 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added dropwise another solution of mCPBA (60% in H_2O, 264 mg, 0.92 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was slowly warmed to room temperature and stirred for another 4 h, then diluted with more CH_2Cl_2. The solution was washed with saturated aqueous sodium thiosulfate and saturated sodium bicarbonate solution. The organic solution was removed under reduced pressure and dried ($MgSO_4$). The residue was purified by flash chromatography on silica gel prewashed with Et_3N using ethyl acetate/hexane (1:3) and 5% Et_3N as eluent to give product **17** (60.4 mg, 79%). Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.90 (2H, d, *J* = 7.2 Hz), 7.73–7.68 (1H, m), 7.60 (2H, t, *J* = 7.2 Hz), 6.62 (1H, s), 4.65–4.59 (1H, m), 3.71–3.61 (1H, m), 2.73 (1H, dd, *J* = 17.4, 6.6 Hz), 2.26 (1H, ddd, *J* = 17.4, 8.7, 1.8 Hz), 1.70–1.43 (7H, m), 1.38–1.20 (3H, m), 0.90 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$) δ 162.1, 147.2, 137.3, 134.4, 129.6, 128.5, 127.8, 49.7, 49.6, 33.0, 31.3, 28.3, 26.6, 19.6, 18.3, 13.9; IR (neat) 3064, 2936, 2870, 1665, 1623, 1428, 1322, 1155, 1081, 858, 759, 689 cm^{-1}; FAB-MS (rel. intensity) *m/z* 334 (M$^+$+H, 100), 332 (14), 290 (17), 126 (16), 105 (20); Exact mass calcd for $C_{18}H_{23}NO_3S$ *m/z* 333.1399; FAB-HRMS *m/z* 333.1400.

Trans-6-(2-hydroxyethyl)-1,6,7,8,9,9a-hexahydro-4-quinolizinone (**18**). Using a procedure similar to that for the preparation of compound **8**, compound **5** (309 mg, 1.02 mmol) gave product **18** (157 mg, 78%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ 5.00–4.96 (1H, m), 3.86 (1H, OH), 3.64–3.57 (1H, m), 3.32–3.23 (2H, m), 2.51–2.32 (2H, m), 2.05–1.46 (11H, m), 1.38–1.26 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 171.4, 58.0, 51.7, 44.4, 34.0, 33.1, 32.5, 30.8, 29.2, 19.2, 19.0; IR (neat) 3400, 2938, 2867, 1610, 1449, 1064 cm^{-1}; EI-MS (rel. intensity) *m/z* 197 (M$^+$, 10), 153 (26), 152 (100); Exact mass calcd for $C_{11}H_{19}NO_2$ *m/z* 197.1416; EI-HRMS *m/z* 197.1416.

(2R/4S/9aS,2S/4R/9aR)- and (2S/4S/9aS,2R/4R9aR)-2-Methyl-6-propyl-1,2,3,6,7,8,9,9a-octa-hydro-4-quinolizinone (**19**). A mixture of compound **14** (22.3 mg, 0.11 mmol) and PtO_2 (4 mg) in EtOAc (3 mL)

was stirred vigorously under a balloon of hydrogen at room temperature for 12 h. The reaction mixture was then filtered with Celite, washed with ethyl acetate, dried (MgSO$_4$), and evaporated under vacuum to give product **19** (20.6 mg, 92%). Yellow liquid; ^{1}H-NMR (CDCl$_3$) δ 4.94–4.84 (m), 3.53–3.45 (m), 3.40–3.31 (m), 2.50–2.42 (m), 2.06–1.87 (m), 1.81–1.03 (m), 0.99–0.88 (m); ^{13}C-NMR (CDCl$_3$,) δ 169.5, 168.9, 51.4, 49.0, 48.0, 47.5, 41.6, 40.8, 39.9, 37.1, 34.9, 33.8, 32.2, 31.9, 27.9, 27.8, 26.3, 23.9, 21.2, 20.3, 19.8, 19.7, 19.6, 18.8, 14.2 (×2); IR (neat) 3052, 2936, 2872, 1623, 1452, 1266, 1088, 738 cm^{-1}; EI-MS (rel. intensity) *m/z* 209 (M$^+$, 14), 167 (38), 166 (100); Exact mass calcd for C$_{13}$H$_{23}$NO *m/z* 209.1780; EI-HRMS *m/z* 209.1784.

Trans-6-propyl-1,6,7,8,9,9a-hexahydro-4-quinolizinone (**20**). To a solution of compound **17** (56.2 mg, 0.17 mmol) in dried THF (4 mL) was added 6% sodium amalgam (1.68 mmol) and two drops of concentrated phosphoric acid. The mixture was heated at reflux for 2 h. Upon cooling the mixture was filtered through Celite, rinsed with ethyl acetate, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel prewashed with Et$_3$N using ethyl acetate/hexane (1:2) and 5% Et$_3$N as eluent to give product **20** (25.1 mg, 77%). Yellow oil; ^{1}H-NMR (CDCl$_3$) δ 6.43–6.37 (1H, m), 5.88 (1H, dt, *J* = 9.6 1.8 Hz), 4.71–4.64 (1H, m), 3.65–3.56 (1H, m), 2.51 (1H, dddd, *J* = 18.0, 7.2, 5.1, 1.8 Hz), 2.15 (1H, dddd, *J* = 18.0, 8.4, 3.6, 2.4 Hz), 1.72–1.43 (8H, m), 1.37–1.25 (2H, m), 0.93 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR (CDCl$_3$) δ 164.6, 136.8, 125.1, 49.2, 48.8, 33.4, 31.2, 30.8, 26.8, 19.7, 18.8, 14.1; IR (neat) 2934, 2870, 1667, 1614, 1424, 1307, 1157 cm^{-1}; ESI-MS (rel. intensity) *m/z* 194 (M$^+$+H, 100); Exact mass calcd for C$_{12}$H$_{19}$NO *m/z* 193.1467; ESI-HRMS *m/z* 193.1459.

Trans-6-[2-oxoproyl]-2-(phenylthio)-1,6,7,8,9,9a-hexahydro-4-quinolizinone (**21**). To a stirred solution of compound **4b** (22.2 mg, 0.07 mmol) in THF (1.5 mL) was added (trimethylsilyl)methylmagnesium chloride (1.3 M in THF, 0.15 mL, 0.20 mmol) at room temperature under nitrogen for 3 h. The reaction solution was washed with 1N HCl solution. The aqueous layer was extracted three times with ethyl acetate. The organic solution was concentrated under reduced pressure and dried (MgSO$_4$) to give the crude product, which was purified by flash chromatography on silica gel prewashed with hexane using ethyl acetate/hexane (1:4) and 5% Et$_3$N as eluent to give compound **21** (13.4 mg, 64%). Colorless oil; ^{1}H-NMR (CDCl$_3$) δ 7.50–7.38 (5H, m), 5.28 (1H, d, *J* = 1.8 Hz), 5.02–4.96 (1H, m), 3.62–3.52 (1H, m), 2.60 (2H, d, *J* = 7.2 Hz), 2.50 (1H, dd, *J* = 17.1, 6.0 Hz), 2.38 (1H, ddd, *J* = 17.1, 10.2, 1.8 Hz), 2.18 (3H, s), 1.80–1.76 (1H, m), 1.71–1.55 (4H, m), 1.47–1.38 (1H, m); ^{13}C-NMR (CDCl$_3$) δ 207.4, 164.7, 152.0, 135.3, 129.9, 129.8, 128.2, 115.2, 50.3, 45.7, 43.8, 35.6, 32.7, 29.8, 27.3, 18.2; IR (neat) 3057, 2938, 2864, 1712, 1639, 1599, 1408, 1303, 1168, 1023, 856, 752 cm^{-1}; EI-MS (rel. intensity) *m/z* 315 (M$^+$, 24), 314 (17), 272 (39), 258 (67), 56 (100); Exact mass calcd for C$_{18}$H$_{21}$NO$_2$S *m/z* 315.1293; EI-HRMS *m/z* 315.1291.

4. Conclusions

In summary, we have converted *trans*-quinolizidinone **4b** into the C-6 alkylated derivatives **6–11**. Treatment of compound **7** with methylmagnesium bromide, followed by acidification with acetic acid and reduction with NaBH$_4$ at low temperature gave selectively the C-6,9a *trans*-compound **12**, which was reacted with Raney nickel in refluxing 95% EtOH to achieve the synthesis of compound **15** which was the proposed structure of the natural product (±)-quinolizidine 195C. However, the spectral data of

compound **15** differed significantly from that reported in the literature, so the true structure of (±)-quinolizidine 195C remains uncertain. We have also prepared some other functionalized quinolizidines **17–21** for further biological studies.

Supplementary Material

¹H- and ¹³C-NMR spectra of compounds **5–21** can be found in the online Supplementary Data. Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/18/7/8243/s1.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

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Sample Availability: Not available.