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Synthetic studies of quinolizidine 195C and derivatives

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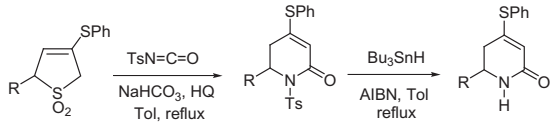
ABSTRACT

Sulfur-substituted dihydropyridones prepared by aza-Diels–Alder reactions were converted to the *cis*-2,6-disubstituted derivatives, which could then proceed through ring-closing metathesis (RCM) and cross metathesis (CM) reactions to give many quinolizidine derivatives, including two epimers of (±)-195C.

1. Introduction

Many quinolizidine alkaloids have been isolated from amphibian skin,[1] some of which show interesting biological activities.[2] Many methods have been developed for the synthesis of these novel compounds.[3,4] We have previously developed a new aza-Diels–Alder reaction of thio-substituted 3-sulfolenes with *p*-toluenesulfonyl isocyanate (PTSI) to synthesize tetrahydropyridones **2** and **3** (Scheme 1),[5] and have used this method to prepare some indolizidines and quinolizidines.[6] We now report the use of ring-closing metathesis (RCM)[7,8] and cross-metathesis (CM)[9] as key steps for the synthesis of many quinolizidine derivatives, including two epimers of quinolizidine 195C. Quinolizidine 195C was first isolated from a Panamanian poison frog, *Dendrobates speciosus*.[10] It was also detected in an extract of a Brazilian myrmicine ant (*Solenopsis picea*), and its structure was determined by chemical synthesis.[11]



1 2 3

Scheme 1.

2. Results and discussion

Treatment of a solution of compounds **3a**–**c**[5] in CH_2Cl_2 sequentially with Et_3N, DMAP, and Boc_2O at room temperature gave the Boc-protected amides **4a**–**c**. Hydrogenation of the allyl group in compound **4c** provided the propyl-substituted product **4d**. Further oxidation of sulfides **4a**,**b** and **4d** with *m*CPBA afforded the corresponding sulfones **5a**–**c**, which were then reduced with $LiEt_3BH$ in CH_2Cl_2 at −78 °C to give the aminals **6a**–**c** in excellent yields. Compounds **6b** and **6c** were obtained as a diastereomeric mixture of isomers (10.5:1, and 4.4:1, respectively, as judged from the ^1H NMR integrations). Without separation, this mixture of compounds **6a**–**c** was treated sequentially with boron trifluoride etherate and allyltrimethylsilane[12] to give products **7a**–**c**. The Boc group was conveniently removed during the workup. The stereochemistry of the 2,6-disubstituted compounds **7b** and **7c** was established to be *cis* from the X-ray crystal structures of compound **7b** and the Cbz-protected derivative **8b**, respectively. Presumably, the allyl nucleophile preferentially approaches the iminium ion intermediate from the axial direction due to the stereoelectronic effect. It is interesting to note that the X-ray crystal structure of compound **7b** (Fig. 1)[13] shows that the 2,6-disubstituents are at the equatorial position whereas the X-ray crystal structure of compound **8b** (Fig. 2)[13] shows that the 2,6-disubstituents are both at the axial position. Apparently, the Cbz group of compound **8b** would suffer serious A[1,3] strains with the 2,6-disubstituents if they were both in the equatorial position (Scheme 2).

Heating compounds **7a**,**b** with allyl bromide or 3-bromo-2-methylpropene in the presence of Et_3N gave the *N*-allylated products **9a**–**c**. Ring-closing metathesis (RCM) of compounds **9a**–**c** with

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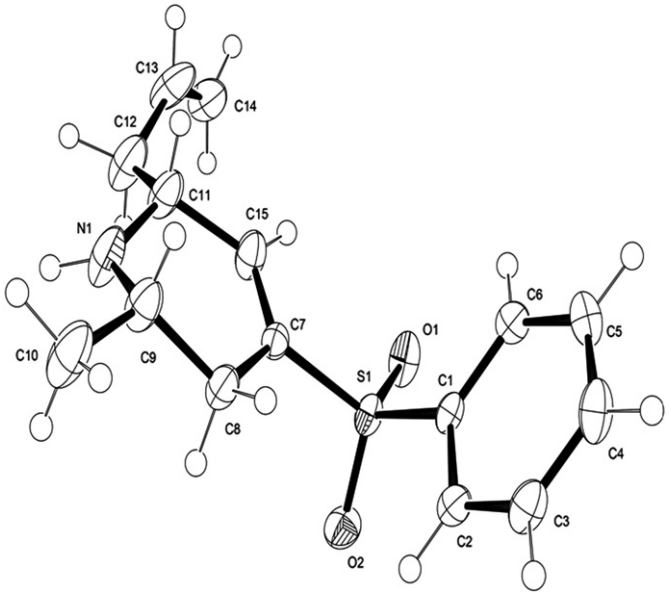


Fig. 1. X-ray crystal structure of compound **7b**.

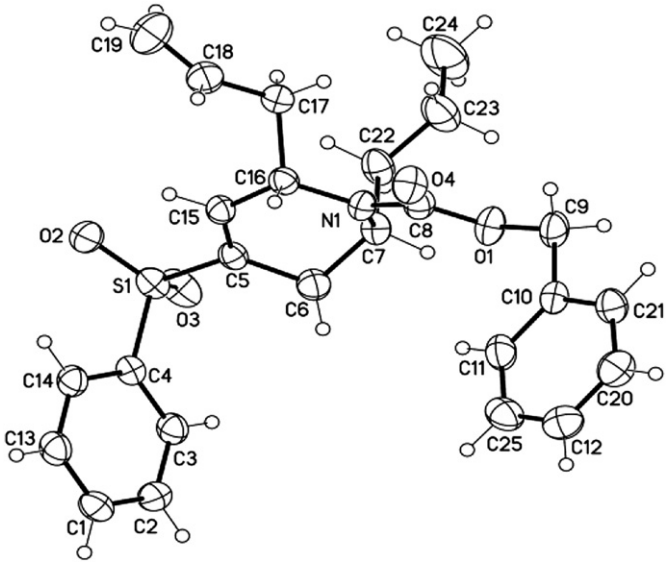
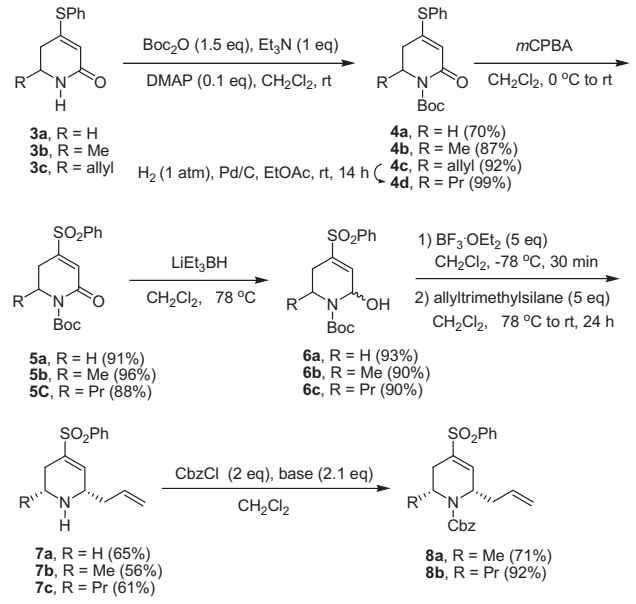
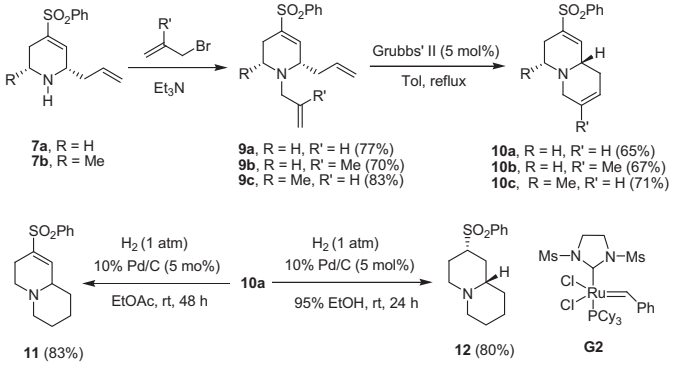


Fig. 2. X-ray crystal structure of compound **8b**.



Scheme 2.



Scheme 3.

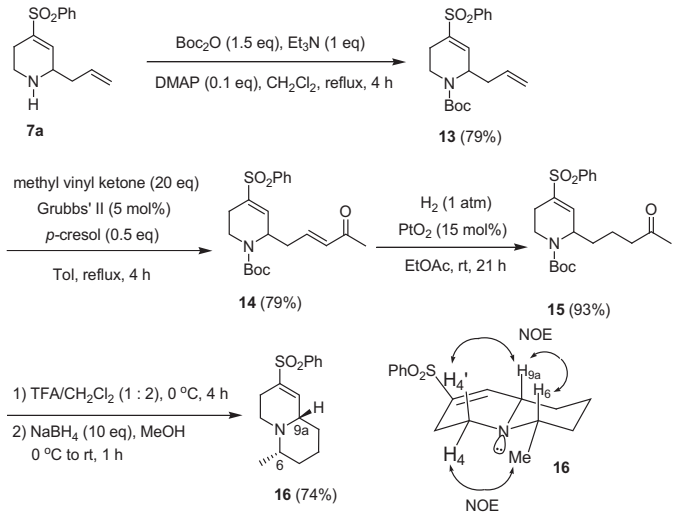
5 mol % of Grubbs' II catalyst (**G2**) in refluxing toluene provided the *cis*-4,9a-quinolizidines **10a**–**c**.

Atmospheric pressure hydrogenation of compound **10a** with 10% Pd/C in EtOAc reduced only the disubstituted C=C double bond to give product **11**, whereas similar reaction using 95% EtOH as the solvent reduced both C=C double bonds to give the *cis*-2,9a-quinolizidine **12**. The IR spectra of compounds **11** and **12** show a Bohlmann band at 2757 cm^{-1} and 2765 cm^{-1}, respectively, indicating the presence of one or more α-hydrogens oriented *trans*-biaxially to the nitrogen lone pair.[14] The ^1H NMR of compound **12** shows a resonance for the H-2 at δ 2.99 (tt, J=3.3, 12.3 Hz). Thus, the H-2 must be at the axial position of the ring. This means that hydrogenation occurs from the less hindered side of compound **10a** (*cis* to H-9a) to give product **12** (Scheme 3).

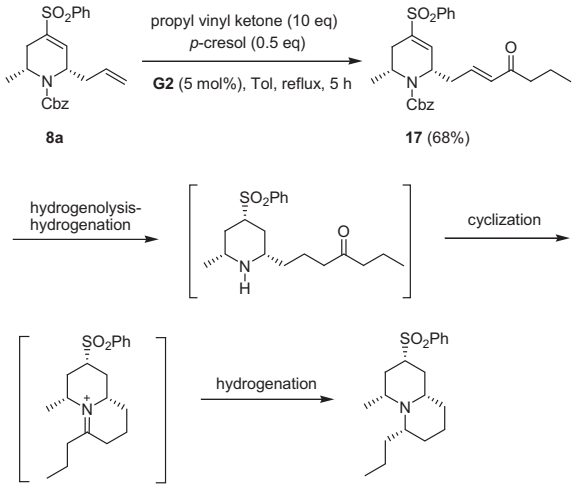
Compound **7a** was protected as the Boc derivative **13**. Cross metathesis (CM) was successfully achieved by treatment of methyl vinyl ketone (20 equiv) in the presence of Grubbs' II catalyst (**G2**) and *p*-cresol[15] in refluxing toluene to give the α,β-unsaturated ketone **14**, the ^1H and ^{13}C NMR spectra of which showed that only the *trans* isomer was obtained. Atmospheric hydrogenation of compound **14** gave the ketone **15**, which was treated sequentially with trifluoroacetic acid to remove the Boc group and then with sodium borohydride in methanol to afford the *cis*-6,9a-quinolizidine **16**. The stereochemistry of compound **16** was established by NOESY. There are cross signals between H_{9a} and H_6 and $H_{4'}$, as well as between H_4 and the methyl group (Scheme 4).

Compound **8a** underwent cross metathesis (CM) with propyl vinyl ketone (10 equiv) in the presence of Grubbs' II catalyst (**G2**) and *p*-cresol in refluxing toluene to give the *E*-α,β-unsaturated ketone **17**. We intended to synthesize a quinolizidine structure from compound **17** through a one-pot hydrogenolysis/hydrogenation–cyclization–hydrogenation sequence[16] (Scheme 5). However, we tried many reaction conditions without success (Table 1).

With the most commonly used catalyst Pd/C for the atmospheric pressure hydrogenation (entry 1), only the exocyclic C=C double bond of compound **17** was reduced to give product **18**. Using PtO_2 as the catalyst (entry 2), product **18** was obtained in quantitative yield. The use of $Pd(OH)_2$ as the catalyst in methanol (entry 3) cleaved the Cbz group as well as reduced both the endocyclic and exocyclic C=C double bonds to give product **19** in excellent yield. In

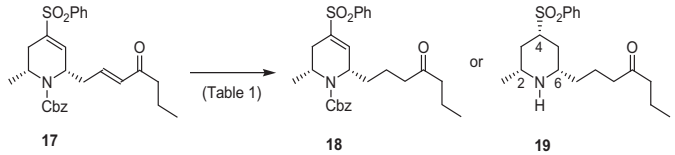


Scheme 4.



Scheme 5.

Table 1
Hydrogenation of compound **17**



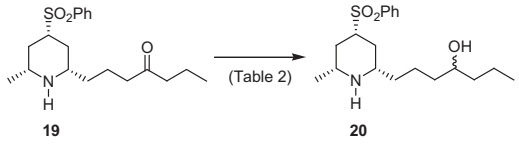
Entry	Catalyst (mol %)	H_2	Conditions	Yield (%)
1	Pd/C (10)	1 atm	MeOH, rt, 24 h	**18** (90)
2	PtO_2 (15)	1 atm	EA, rt, 20 h	**18** (99)
3	$Pd(OH)_2$ (10)	1 atm	MeOH, rt, 24 h	**19** (90)
4	$Pd(OH)_2$ (10)	1 atm	TFA/MeOH (1:5), rt, 24 h	**19** (95)
5	$Pd(OH)_2$ (10)	1 atm	Et_3N (5 equiv), MeOH, rt, 48 h	**19** (90)
6	$Pd(OH)_2$ (10)	100 psi	MeOH, rt, 24 h	**19** (80)
7	$Pd(OH)_2$ (10)	5 bar	1 M $HCl_{(aq)}$/MeOH (1:5), rt, 48 h	**19** (84)
8	Raney-Ni (20 equiv)[a]	None	95% EtOH, reflux, 22 h	ND[b]
9	Raney-Ni (20 equiv)[a]	1 atm	95% EtOH, reflux, 60 h	ND[c]

[a] Catalyst (20 equiv) was used.
[b] A complex mixture of products together with recovered compound **17** (22%) was obtained.
[c] A complex mixture of products was obtained.

order to promote further cyclization of compound **19**, trifluoroacetic acid (entry 4) or Et_3N (entry 5) was added, but with no success. Increasing the pressure of hydrogen (entry 6) or addition of 1 M HCl under high pressure of hydrogen (entry 7) did not result in the formation of the expected quinolizidine product. We also used Raney nickel as the catalyst (entries 8–9) in refluxing 95% EtOH, with or without external hydrogen, but a complex mixture of products was obtained. The ^1H NMR of compound **19** shows a resonance for the H-4 at δ 3.05 (tt, J=3.6, 12.6 Hz). Thus, the H-4 must be at the axial position of the ring, and the phenylsulfonyl group is at the more stable equatorial position. It seems reasonable that hydrogenation occurs from the less hindered side of compound **17** to give product **19**.

We then tried to carry out the reductive amination of compound **19** to give the quinolizidine product, but again without success (Table 2). If compound **19** was first dissolved in a mixture of CF_3CO_2H and CH_2Cl_2, followed by treatment with $NaBH_4$ in methanol, only the carbonyl group was reduced to give the alcohol **20** as a 1:1 diastereomeric mixture (entry 1). The same result was obtained when $NaCNBH_3$ was used (entry 2), or with further control of the pH (entry 3). We also added $CeCl_3\cdot 7H_2O$ to activate the carbonyl group (entry 4), but the product **20** was obtained in even lower yield. The use of $NaBH(OAc)_3$ in HOAc/MeOH at room temperature (entry 5) or at reflux (entry 6) only gave the recovered starting material.

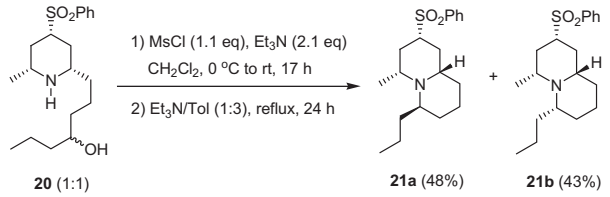
Table 2
Reduction of compound **19**



Entry	Reaction conditions	Yield (%)
1	TFA/CH_2Cl_2 (1:2), 0 °C; $NaBH_4$, MeOH, 0 °C to rt, 2 h	**20** (87)
2	$NaCNBH_3$, TFA/MeOH (1:10), 0 °C to rt, 4 h	**20** (92)
3	$NaCNBH_3$, TFA/MeOH, pH 6, 0 °C to rt, 4 h	**20** (90)
4	$CeCl_3\cdot 7H_2O$, THF, reflux, 2 h; HOAc, 0 °C; $NaBH_4$, MeOH, 0 °C to rt, 5 h	**20** (59)
5	$NaBH(OAc)_3$ (10 equiv), HOAc/MeOH (1:40), 0 °C to rt, 24 h	NR[b]
6	$NaBH(OAc)_3$, HOAc/MeOH (1:40), reflux, 24 h	NR[b]

[a] An inseparable 1:1 diastereomeric mixture of product **20** was obtained.
[b] No reaction was observed.

Alcohol **20** was first converted to its mesylate by standard procedure, and the crude product was then directly heated with Et_3N in toluene to give two diastereomeric quinolizidines **21a** and **21b** (Scheme 6), which were separated by flash column chromatography. The structure of crystalline compound **21a** was determined by X-ray crystallography (Fig. 3).[13] The stereochemistry of liquid compound **21b** was established by NOESY (Fig. 4). There are cross signals between H_{9a} and H_2, H_4 and $H_{6'}$, but there is no cross signal between H_{9a} and the methyl group.



Scheme 6.

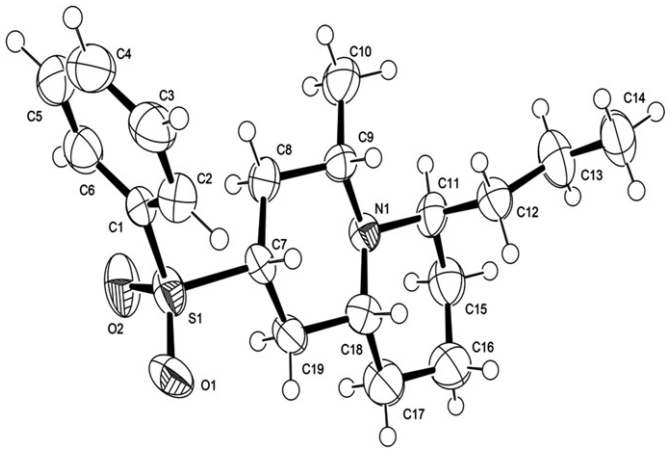


Fig. 3. X-ray crystal structure of compound **21a**.

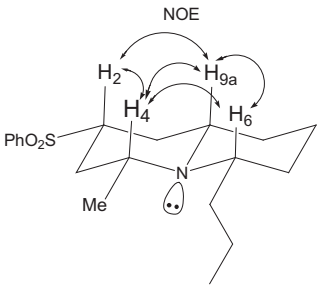
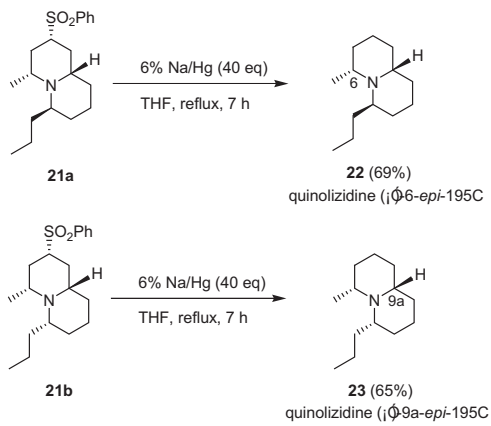


Fig. 4. NOESY correlations of compound **21b**.

We can convert compounds **21a** and **21b** to two epimers of quinolizidine (±)-195C (Scheme 7). Treatment of compounds **21a** and **21b** individually with 6% Na/Hg in refluxing THF gave the corresponding products **22** and **23**. The spectral data of compound **23** were the same as the literature report, which used NOESY technique to determine its structure.[16d] Although the IR and MS data of compound **22** have been reported and used to elucidate its stereochemistry,[11] we have now fully characterized it by ^{1}H and ^{13}C NMR spectroscopy. Furthermore, since the structure of crystalline compound **21a** has been established by X-ray crystallography (Fig. 3), its conversion by reductive cleavage of the phenylsulfonyl group to compound **22** would confirm the relative stereochemistry of compound **22**. It should be noted that compounds **22** and **23** differ from the stereochemistry of natural product quinolizidine 195C at C_6 and C_{9a}, respectively.



Scheme 7.

3. Conclusions

Starting from simple 6-substuted 5,6-dihydro-2-pyridones **3**, the *cis*-2,6-disubstituted derivatives **7**–**8** were readily prepared. Further elaboration through ring-closing metathesis (RCM) and other reactions provided the quinolizidines **10**–**12** with complete stereocontrol. Cross metathesis (CM) of compounds **8a** and **13** with a suitable enone afforded the α,β-unsaturated ketones **17** and **14**, respectively. *cis*-6,9a-Quinolizidine **16** was then obtained from compound **14**, whereas synthetic transformations of compound **17** led to quinolizidine 6-*epi*-195C (**22**) and quinolizidine 9a-*epi*-195C (**23**).

4. Experimental section

4.1. General

Melting points were determined with a SMP3 melting apparatus. ^{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) from the internal reference standard tetramethylsilane (TMS), and the coupling constants (J) are given in Hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN–O–S-Rapid Analyzer, or Elementar Vario EL III. Flash column chromatographic purifications were performed using Merck 60H silica gel. The microwave reactions were carried out with a CEM Focused™ Discover-S system.

4.2. General procedure for protection of compounds 3

To a solution of amide **3** (4.88 mmol) and 4-dimethylaminopyridine (0.49 mmol) in CH_2Cl_2 (20 mL) under nitrogen were added sequentially Et_3N (0.68 mL) and di-*tert*-butyl dicarbonate (7.32 mmol). After stirring at room temperature for 3 h, the reaction mixture was quenched with saturated sodium bicarbonate (20 mL). The aqueous solution was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:9) containing 5% Et_3N as eluent to give product **4**.

*4.2.1. 1-(tert-Butoxycarbonyl)-4-(phenylthio)-1,2,5,6-tetrahydro-2-pyridinone (**4a**).* Yield (70%); colorless liquid; IR (neat) ν 3059, 2981, 2935, 2891, 1761, 1711, 1598, 1475, 1388, 1318, 1155, 1101, 968, 939, 750, 705, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52–7.36 (5H, m), 5.32 (1H, s), 3.87 (2H, t, J=6.3 Hz), 2.53 (2H, t, J=6.3 Hz), 1.51 (9H, s); ^{13}C NMR ($CDCl_3$) δ 162.0, 158.4, 151.9, 134.9, 129.9, 129.6, 127.5, 115.4, 82.2, 43.1, 28.9, 27.7; EI-MS (rel intensity) m/z 305 (M^+, 7), 244 (52), 205 (38), 172 (22), 86 (64), 84 (100); EI-HRMS m/z calcd for $C_{16}H_{19}NO_3S$ 305.1086, found 305.1092.

*4.2.2. 1-(tert-Butoxycarbonyl)-6-methyl-4-(phenylthio)-1,2,5,6-tetrahydro-2-pyridinone (**4b**).* Yield (87%); white solid mp 83.1–84.1 °C; IR (ATR, film) ν 3060, 2979, 2933, 1760, 1683, 1456, 1391, 1225, 1156, 1114, 1075, 1024, 822, 751, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55–7.48 (5H, m), 5.34 (1H, d, J=2.4 Hz), 4.59 (1H, qdd, J=6.9, 6.0, 1.5 Hz), 2.97 (1H, ddd, J=17.4, 6.0, 2.4 Hz), 2.20 (1H, dd, J=17.4, 1.5 Hz), 1.52 (9H, s), 1.31 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 161.8, 155.9, 152.4, 135.4, 130.3, 130.0, 128.0, 115.3, 82.7, 49.9, 35.0, 28.1, 18.7; EI-MS (rel intensity) m/z 319 (M^+, 36), 246 (26), 219 (100), 204 (74), 177 (24), 86 (39), 84 (59), 57 (45); EI-HRMS m/z calcd for $C_{17}H_{21}NO_3S$ 319.1242, found 319.1249.

*4.2.3. 6-Allyl-1-(tert-butoxycarbonyl)-4-(phenylthio)-1,2,5,6-tetrahydro-2-pyridinone (**4c**).* Yield (92%); light yellow oil; IR (neat) ν 3076, 3062, 2979, 2931, 1760, 1710, 1601, 1583, 1441, 1224, 1156,

1117, 1075, 835, 751, 705, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58–7.47 (5H, m), 5.84–5.66 (1H, m), 5.35 (1H, d, J=2.4 Hz), 5.19–5.06 (2H, m), 4.54–4.46 (1H, m), 2.83 (1H, ddd, J=17.4, 6.0, 2.4 Hz), 2.53–2.30 (3H, m), 1.52 (9H, s); ^{13}C NMR ($CDCl_3$) δ 161.4, 155.8, 152.0, 135.1, 133.6, 130.0, 129.7, 127.6, 118.6, 115.2, 82.4, 53.0, 36.7, 31.3, 27.8; EI-MS (rel intensity) m/z 345 (M^+, 0.18), 205 (15), 204 (100); EI-HRMS m/z calcd for $C_{19}H_{23}NO_3S$ 345.1399, found 345.1406.

*4.2.4. 1-(tert-Butoxycarbonyl)-4-(phenylthio)-6-propyl-1,2,5,6-tetrahydro-2-pyridinonoe (**4d**).* To a solution of compound **4c** (110 mg, 0.32 mmol) in ethyl acetate (5 mL) was added 10% Pd/C (16.9 mg). Then the reaction mixture was stirred vigorously under a balloon of hydrogen at room temperature for 22 h, filtered with Celite, washed with ethyl acetate, dried ($MgSO_4$), and evaporated under vacuum to give pure product **4d** (111 mg, 99%). Colorless liquid; IR (neat) ν 3060, 2962, 2933, 2873, 1760, 1710, 1602, 1457, 1392, 1157, 1119, 1089, 1075, 827, 751, 706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55–7.46 (5H, m), 5.33 (1H, d, J=2.4 Hz), 4.54–4.42 (1H, m), 2.89 (1H, ddd, J=17.4, 6.0, 2.4 Hz), 2.32 (1H, dd, J=17.4, 1.5 Hz), 1.76–1.56 (2H, m), 1.52 (9H, s), 1.44–1.21 (2H, m), 0.93 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 161.8, 156.0, 152.2, 135.2, 130.1, 129.8, 127.8, 115.3, 82.4, 53.5, 34.5, 32.4, 27.9, 19.5, 13.8; EI-MS (rel intensity) m/z 347 (M^+, 4), 205 (14), 204 (100), 86 (14), 84 (22); EI-HRMS m/z calcd for $C_{19}H_{25}NO_3S$ 347.1555, found 347.1560.

4.3. General procedure of oxidation of sulfides 4

To a solution of compound **4** (3.28 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added *m*CPBA (70–75% in H_2O, 8.19 mmol) in small portions. The reaction mixture was stirred at room temperature for 2 h, and was washed sequentially with 5% aqueous $Na_2S_2O_3$ and saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure to give pure product. If necessary, the solid crude product could be purified by recrystallization from CH_2Cl_2/hexane.

*4.3.1. 1-(tert-Butoxycarbonyl)-4-(phenylsulfonyl)-1,2,5,6-tetrahydro-2-pyridinone (**5a**).* Yield (91%); white solid mp 151.6–152.9 °C; IR (ATR, film) ν 2985, 2934, 1764, 1706, 1476, 1388, 1219, 1155, 1078, 968, 899, 751, 724, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01–7.81 (2H, m), 7.75–7.51 (3H, m), 6.63 (1H, t, J=1.3 Hz), 3.87 (2H, t, J=6.3 Hz), 2.59–2.54 (2H, m), 1.52 (9H, s); ^{13}C NMR ($CDCl_3$) δ 161.4, 153.2, 151.5, 137.0, 134.6, 129.7, 128.5, 128.4, 83.9, 43.3, 27.8, 23.0; EI-MS (rel intensity) m/z 338 (M^++1, 1), 283 (22), 282 (95), 264 (20), 238 (80), 208 (28), 125 (43), 96 (24), 86 (23), 77 (24), 67 (30), 57 (100); EI-HRMS m/z calcd for $C_{16}H_{19}NO_5S$ 337.0984, found 337.0982.

*4.3.2. 1-(tert-Butoxycarbonyl)-6-methyl-4-(phenylsulfonyl)-1,2,5,6-tetrahydro-2-pyridinone (**5b**).* Yield (96%); white solid mp 123.5–124.5 °C; IR (ATR, film) ν 2972, 2941, 1757, 1687, 1368, 1324, 1229, 1115, 1070, 817, 765, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (2H, d, J=7.5 Hz), 7.78–7.56 (3H, m), 6.73–6.65 (1H, m), 4.66 (1H, qd, J=6.6, 6.6 Hz), 2.77 (1H, ddd, J=17.7, 6.0, 2.7 Hz), 2.47 (1H, d, J=17.7 Hz), 1.52 (9H, s), 1.14 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 161.0, 151.5, 150.6, 136.8, 134.6, 134.6, 129.7, 128.6, 127.8, 83.9, 49.9, 28.9, 27.9, 18.7; FAB-MS (rel intensity) m/z 352 (M+H, 3), 297 (17), 296 (100), 252 (17), 57 (46); FAB-HRMS m/z calcd for $C_{17}H_{21}NO_5S$ 351.1140, found 351.1143.

*4.3.3. 1-(tert-Butoxycarbonyl)-4-(phenylsulfonyl)-6-propyl-1,2,5,6-tetrahydro-2-pyridinone (**5c**).* Yield (88%); colorless liquid; IR (neat) ν 3067, 2964, 2934, 2875, 1766, 1718, 1369, 1292, 1120, 1095, 1079, 817, 759, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91–7.82 (2H, m), 7.73–7.51 (3H, m), 6.69–6.64 (1H, m), 4.52–4.39 (1H, m), 2.66 (1H, ddd, J=18.0, 6.0, 3.0 Hz), 2.51 (1H, dd, J=18.0, 1.5 Hz), 1.51–1.39 (10H, m), 1.34–1.19 (1H, m), 1.12–0.83 (2H, m), 0.71 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 161.0, 151.5, 150.5, 136.7, 134.6, 129.6, 128.6, 128.1, 83.7, 53.6, 34.4, 27.8, 25.9, 19.1, 13.5; FAB-MS (rel intensity) m/z 380 (M+H, 1), 325 (19), 324 (100), 280 (19); FAB-HRMS m/z calcd for $C_{19}H_{25}NO_5S$ 379.1453, found 379.1448.

4.4. General procedure for reduction of amides 5

To a solution of compound **5** (0.3 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise $LiEt_3BH$ (1 M in THF, 0.33 mmol). The reaction mixture was stirred at −78 °C for another 1 h, and was quenched with saturated $NaHCO_3$ solution. The aqueous solution was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:2) containing 5% Et_3N as eluent to give pure product. If necessary, the solid crude product could be purified by recrystallization from CH_2Cl_2/hexane.

*4.4.1. 1-(tert-Butoxycarbonyl)-2-hydroxy-4-(phenylsulfonyl)-1,2,5,6-tetrahydro-2-pyridinone (**6a**).* Yield (93%); white solid mp 103–104 °C; IR (film) ν 3415, 3068, 2978, 1685, 1447, 1419, 1394, 1367, 1306, 1286, 1212, 1151, 1123, 1092, 1062, 1046, 1021, 986, 948, 913, 855, 827, 755, 727, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90–7.87 (2H, m), 7.69–7.54 (3H, m), 6.93–6.91 (1H, m), 5.91 (1H, br s), 4.13–4.03 (2H, m), 3.02 (1H, br s), 2.36–2.23 (2H, m), 1.46 (9H, s); ^{13}C NMR ($CDCl_3$) δ 154.7, 142.8, 138.3, 133.9, 133.3, 129.4, 128.4, 81.6, 72.4, 36.5, 28.4, 23.5; ESI-MS (rel intensity) m/z 339 (M^--H, 62), 338 (15), 274 (31), 272 (100); ESI-HRMS m/z calcd for $C_{16}H_{21}NO_5S$ 339.1140, found 339.1131.

*4.4.2. cis- and trans-1-(tert-Butoxycarbonyl)-2-hydroxy-6-methyl-4-(phenylsulfonyl)-1,2,5,6-tetrahydro-2-pyridinone (**6b**).* Yield (90%); yellow liquid; IR (neat) ν 3455, 3057, 2982, 2934, 1686, 1447, 1393, 1341, 1308, 1156, 1116, 1054, 851, 737, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98–7.85 (2H, m), 7.72–7.52 (3H, m), 7.03–6.88 (1H, m), 5.92–5.72 (1H, m), 4.65–4.22 (1H, m), 2.51–2.34 (1H, m), 2.30–2.13 (1H, m), 2.00 (1H, br s), 1.48 (9H, s), 0.97 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 154.7, 139.5, 138.5, 137.9, 133.8, 133.6, 132.9, 129.3, 129.0, 128.7, 128.4, 81.5, 81.3, 72.5, 43.5, 29.7, 28.9, 28.6, 28.3, 19.1, 18.8; ESI-MS (rel intensity) m/z 376 (M^++Na, 58), 280 (39), 258 (18), 236 (100); ESI-HRMS m/z calcd for $C_{17}H_{23}NO_5S$ 353.1297, found 353.1294.

*4.4.3. cis- and trans-1-(tert-Butoxycarbonyl)-2-hydroxy-4-(phenylsulfonyl)-6-propyl-1,2,5,6-tetrahydro-2-pyridinone (**6c**).* Yield (90%); yellow liquid; IR (neat) ν 3446, 3064, 2962, 2933, 2873, 1695, 1368, 1320, 1125, 1092, 1064, 1042, 813, 759, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95–7.87 (2H, m), 7.72–7.51 (3H, m), 7.01–6.89 (1H, m), 5.93–5.68 (1H, m), 4.42–4.05 (1H, m), 2.47–2.31 (1H, m), 2.30–2.19 (1H, m), 1.47 (9H, s), 1.23–0.82 (4H, m), 0.81–0.63 (3H, m); ^{13}C NMR ($CDCl_3$) δ 156.0, 155.1, 140.9, 139.3, 137.8, 137.7, 133.8, 133.7, 133.2, 132.3, 129.3, 129.2, 128.3, 128.2, 81.5, 81.3, 73.3, 72.2, 51.8, 47.5, 46.4, 35.0, 34.8, 28.2, 27.2, 25.6, 19.4, 13.6; ESI-MS (rel intensity) m/z 364 (M^+-H_2O+H, 12), 308 (100), 265 (13), 264 (80); ESI-HRMS m/z calcd for $C_{19}H_{25}NO_4S$ 363.1504, found 363.1517.

4.5. General procedure for the reaction of aminals 6 with allyltrimethylsilane

To a solution of compound **6** (0.3 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (1.5 mmol). After stirring at −78 °C for 30 min, allyltrimethylsilane (1.5 mmol) was then added dropwise. The reaction mixture was slowly warmed to room temperature, and was quenched with saturated $NaHCO_3$. The aqueous solution was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash

chromatography using ethyl acetate/hexane (1:1–1:3) containing 5% Et_3N as eluent to give pure product.

*4.5.1. 2-Allyl-4-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine (**7a**).* Yield (65%); yellow liquid; IR (film) ν 3058, 2931, 1641, 1446, 1303, 1149, 1124, 1091, 1033, 1016, 997, 924, 755, 729, 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86–7.83 (2H, m), 7.64–7.51 (3H, m), 6.96 (1H, d, J=1.8 Hz), 5.81–5.70 (1H, m), 5.18–5.13 (2H, m), 3.59–3.54 (1H, m), 3.13 (1H, dt, J=12.3, 4.4 Hz), 2.83–2.75 (1H, m), 2.39–2.19 (5H, m); ^{13}C NMR ($CDCl_3$) δ 139.4, 139.1, 138.8, 133.7, 133.2, 129.0, 127.9, 118.5, 53.5, 41.2, 38.9, 23.5; FAB-MS (rel intensity) m/z 264 (M^++H, 100), 262 (28), 222 (38), 125 (33), 122 (25), 80 (22), 30 (53); FAB-HRMS m/z calcd for $C_{14}H_{17}NO_2S$ m/z 263.0980, found 263.0980.

*4.5.2. cis-2-Allyl-6-methyl-4-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine (**7b**).* Yield (56%); yellow solid mp 71.7–73.3 °C; IR (ATR, film) ν 3055, 2988, 1645, 1443, 1422, 1265, 1127, 896, 739, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92–7.79 (2H, m), 7.68–7.58 (1H, m), 7.58–7.48 (2H, m), 6.93 (1H, s), 5.78 (1H, ddt, J=17.1, 9.9, 7.2 Hz), 5.26–5.09 (2H, m), 3.69–3.57 (1H, m), 2.94–2.77 (1H, m), 2.44–2.21 (3H, m), 1.85–1.67 (1H, m), 1.13 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 139.2, 138.9, 138.6, 133.4 (×2), 129.2, 128.0, 119.1, 54.8, 48.7, 39.0, 31.1, 21.4; FAB-MS (rel intensity) m/z 278 (M^++H, 55), 228 (33), 147 (37), 137 (48), 136 (87), 107 (33), 95 (31), 89 (34), 77 (36), 73 (100), 51 (61), 30 (35); FAB-HRMS m/z calcd for $C_{15}H_{19}NO_2S$ 277.1136, found 277.1139.

*4.5.3. cis-2-Allyl-4-(phenylsulfonyl)-6-propyl-1,2,5,6-tetrahydropyridine (**7c**).* Yield (61%); yellow liquid; IR (neat) ν 3062, 2957, 2931, 2874, 1686, 1369, 1307, 1155, 1094, 1073, 758, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99–7.78 (2H, m), 7.73–7.59 (1H, m), 7.58–7.42 (2H, m), 6.93 (1H, s), 5.78 (1H, ddt, J=17.1, 10.2, 7.2 Hz), 5.27–5.11 (2H, m), 3.73–3.52 (1H, m), 2.81–2.66 (1H, m), 2.47–2.21 (3H, m), 1.85–1.60 (2H, m), 1.49–1.24 (4H, m), 0.89 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 139.7, 139.4, 139.2, 133.8, 133.4, 129.2, 128.1, 118.9, 54.9, 52.9, 39.5, 38.5, 30.0, 19.0, 14.1; FAB-MS (rel intensity) m/z 306 (M^++H, 100), 304 (40), 264 (34), 162 (17); FAB-HRMS m/z calcd for $C_{17}H_{23}NO_2S$ 305.1449, found 305.1460.

4.6. General procedure for the conversion of compounds 7 to compounds 8

To a mixture of compound **7** (0.50 mmol) and K_2CO_3 (1.05 mmol) in CH_2Cl_2 (10 mL) under nitrogen was added CbzCl (0.142 mL, 1.0 mmol) in one portion. The reaction mixture was refluxed for 4 h, and was then quenched with water (10 mL). The aqueous solution was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:3) containing 5% Et_3N as eluent to give pure product.

*4.6.1. cis-2-Allyl-1-(benzyloxycarbonyl)-6-methyl-4-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine (**8a**).* Yield (71%); colorless liquid; IR (neat) ν 3065, 3034, 2977, 2934, 1693, 1656, 1447, 1383, 1358, 1328, 1308, 1071, 1055, 890, 758, 729, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92–7.88 (2H, m), 7.67–7.58 (1H, m), 7.58–7.48 (2H, m), 7.41–7.22 (5H, m), 7.05 (1H, s), 5.93–5.71 (1H, m), 5.22–5.03 (4H, m), 4.76 (1H, br s), 4.60 (1H, br s), 2.56 (1H, br s), 2.49–2.17 (3H, m), 1.00 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 154.3 (×2), 138.3, 136.1, 134.7, 133.4 (×2), 129.1, 128.3, 127.9, 127.8, 127.7, 118.6, 67.2, 51.8, 43.5, 39.5, 28.4, 19.7; FAB-MS (rel intensity) m/z 412 (M^++H, 4), 370 (6), 326 (7), 124 (6), 79 (100), 69 (5), 66 (7); FAB-HRMS m/z calcd for $C_{23}H_{25}NO_4S$ 411.1504, found 411.1501.

*4.6.2. cis-2-Allyl-1-(benzyloxycarbonyl)-4-(phenylsulfonyl)-6-propyl-1,2,5,6-tetrahydropyridine (**8b**).* Yield (90%); white solid mp 101.1–102.8 °C; IR (ATR, film) ν 3059, 2950, 2915, 2863, 1698, 1343, 1303, 1149, 1118, 1093, 1068, 884, 840, 767, 728, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95–7.78 (2H, m), 7.72–7.49 (3H, m), 7.44–7.25 (5H, m), 7.02 (1H, br s), 5.84 (1H, br s), 5.29–4.99 (4H, m), 4.79–4.38 (2H, m), 2.78–2.45 (1H, m), 2.41–2.11 (3H, m), 1.41–1.22 (1H, m), 1.22–0.98 (3H, m), 0.77 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 155.0, 138.7, 136.3 (×2), 135.0, 133.6 (×3), 129.3, 128.6, 128.2, 128.1, 119.0, 67.6, 52.3, 48.2, 40.0, 35.5, 27.0, 19.8, 13.8; FAB-MS (rel intensity) m/z 440 (M^++H, 91), 438 (24), 399 (25), 398 (91), 355 (23), 354 (89), 348 (69), 332 (27), 308 (90), 140 (62), 105 (59), 88 (43), 67 (54), 51 (100); FAB-HRMS m/z calcd for $C_{25}H_{29}NO_4S$ 439.1817, found 439.1812.

4.7. 1,2-Bis(allyl)-4-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine (9a)

To a solution of compound **7a** (100 mg, 0.38 mmol) in THF (10 mL) was added sequentially Et_3N (0.16 mL, 1.14 mmol) and allyl bromide (0.1 mL, 1.14 mmol). The reaction mixture was then refluxed for 4 h. The solvent was evaporated under vacuum, and the residue was purified by flash chromatography using ethyl acetate/hexane (1:6) containing 5% Et_3N as eluent to give product **9a** (88.7 mg, 77%). Red-brown liquid; IR (film) ν 3071, 2937, 2810, 1641, 1555, 1446, 1381, 1354, 1304, 1208, 1150, 1091, 1063, 997, 958, 918, 802, 755, 723, 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86–7.84 (2H, m), 7.59–7.50 (3H, m), 6.94 (1H, t, J=1.2 Hz), 5.85–5.70 (2H, m), 5.20–5.07 (4H, m), 3.32–3.25 (2H, m), 3.03–2.90 (2H, m), 2.55–2.12 (5H, m); ^{13}C NMR ($CDCl_3$) δ 139.4, 139.1, 138.5, 134.6, 134.0, 133.2, 129.1, 127.9, 118.0, 117.6, 58.3, 56.2, 45.7, 36.2, 22.2; FAB-MS (rel intensity) m/z 304 (M^++H, 31), 302 (39), 262 (100); FAB-HRMS m/z calcd for $C_{17}H_{21}NO_2S$ 303.1293, found 303.1288.

4.8. 2-Allyl-1-(2-methyl-2-propenyl)-4-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine (9b)

To a solution of compound **7a** (100 mg, 0.38 mmol) in toluene (10 mL) was added sequentially Et_3N (0.16 mL, 1.14 mmol) and 3-bromo-2-methylpropene (0.12 mL, 1.14 mmol). The reaction mixture was then refluxed for 4 h. The solvent was evaporated under vacuum, and the residue was purified by flash chromatography using ethyl acetate/hexane (1:6) containing 5% Et_3N as eluent to give product **9b** (84.4 mg, 70%). Red-brown liquid; IR (film) ν 3074, 2939, 2806, 1642, 1446, 1355, 1304, 1207, 1150, 1092, 1063, 1024, 998, 908, 802, 755, 726, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87–7.84 (2H, m), 7.64–7.51 (3H, m), 6.95 (1H, t, J=1.2 Hz), 5.84–5.71 (1H, m), 5.12–5.04 (2H, m), 4.83 (2H, br s), 3.22–3.17 (2H, m), 2.93–2.85 (1H, m), 2.75 (1H, d, J=13.5 Hz), 2.39–2.09 (5H, m), 1.67 (3H, s); ^{13}C NMR ($CDCl_3$) δ 142.6, 139.6, 139.0, 138.3, 134.1, 133.2, 129.0, 127.8, 117.2, 112.9, 59.9, 58.9, 45.1, 36.5, 21.9, 20.4; FAB-MS (rel intensity) m/z 318 (M^++H, 22), 316 (39), 276 (100), 55 (27); FAB-HRMS m/z calcd for $C_{18}H_{23}NO_2S$ 317.1449, found 317.1449.

4.9. *cis*-1,2-Bis(allyl)-6-methyl-4-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine (9c)

To a solution of compound **7b** (22 mg, 0.08 mmol) in toluene (5 mL) was added sequentially Et_3N (0.03 mL, 0.24 mmol) and allyl bromide (0.04 mL, 0.48 mmol). The reaction mixture was heated in a sealed tube at 150 °C for 3 d. The solvent was evaporated under vacuum, and the residue was purified by flash chromatography using ethyl acetate/hexane (1:6) containing 5% Et_3N as eluent to give product **9c** (21 mg, 83%). Yellow-brown liquid; IR (neat) ν 3060, 2975, 2930, 1627, 1546, 1479, 1378, 1306, 1216, 1018, 894, 846, 737, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93–7.79 (2H, m), 7.65–7.59 (1H, m), 7.59–7.48 (2H, m), 6.92 (1H, s), 5.53–5.68 (2H, m), 5.28–5.05 (4H, m), 3.52–3.25 (3H, m), 2.92–2.75 (1H, m), 2.55–2.41 (1H, m),

2.39–2.25 (2H, m), 1.98–1.83 (1H, m), 1.16 (3H, d, J=6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 139.4, 139.3, 137.4, 134.2, 133.5, 133.3, 129.2, 128.1, 118.2, 117.8, 58.1, 51.8, 51.2, 37.4, 30.9, 20.1; FAB-MS (rel intensity) m/z 318 (M^++H, 47), 316 (35), 276 (76), 145 (34), 137 (38), 135 (32), 133 (37), 131 (31), 123 (38), 121 (46), 119 (60), 109 (50), 107 (47), 105 (57), 95 (76), 93 (54), 91 (54), 83 (38), 81 (100), 79 (35); FAB-HRMS m/z calcd for $C_{18}H_{23}NO_2S$ 317.1449, found 317.1441.

4.10. General procedure for RCM of compounds 9

A mixture of compound **9** (0.33 mmol) and **G2** (14 mg, 0.0165 mmol) in toluene (10 mL) was refluxed for 3–4 h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:5–1:4) containing 5% Et_3N as eluent to give pure product.

*4.10.1. 2-(Phenylsulfonyl)-4,6,9,9a-tetrahydro-3H-quinolizine (**10a**).* Yield (65%); yellow-brown solid mp 83–84 °C; IR (film) ν 3053, 2913, 2756, 1651, 1446, 1304, 1288, 1148, 1085, 1067, 999, 880, 859, 794, 732, 715, 688, 663 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.87–7.84 (2H, m), 7.64–7.50 (3H, m), 6.83 (1H, s), 5.79–5.68 (2H, m), 3.28 (1H, d, J=16.8 Hz), 3.05–2.89 (3H, m), 2.45–2.11 (5H, m); ^{13}C NMR ($CDCl_3$) δ 139.0, 138.4, 138.3, 133.4, 129.2, 128.1, 125.4, 124.8, 56.5, 53.9, 50.1, 31.4, 23.9; FAB-MS (rel intensity) m/z 276 (M^++H, 100), 275 (21), 274 (64), 134 (43), 132 (24), 130 (23); FAB-HRMS m/z calcd for $C_{15}H_{17}NO_2S$ 275.0980, found 275.0977.

*4.10.2. 7-Methyl-2-(phenylsulfonyl)-4,6,9,9a-tetrahydro-3H-quinolizine (**10b**).* Yield (67%); yellow-brown solid mp 87–88 °C; IR (film) ν 3058, 2913, 2761, 1734, 1652, 1446, 1369, 1303, 1263, 1218, 1151, 1098, 1080, 1019, 997, 968, 883, 805, 784, 732, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.88–7.84 (2H, m), 7.64–7.49 (3H, m), 6.84 (1H, s), 5.45 (1H, d, J=1.8 Hz), 3.11 (1H, d, J=15.6 Hz), 2.99–2.82 (3H, m), 2.44–2.33 (3H, m), 2.25–1.99 (2H, m), 1.65 (3H, s); ^{13}C NMR ($CDCl_3$) δ 139.1, 138.5, 138.1, 133.4, 132.6, 129.2, 128.0, 118.9, 58.0, 56.4, 50.0, 31.3, 24.0, 20.6; FAB-MS (rel intensity) m/z 290 (M^++H, 100), 289 (23), 288 (73), 148 (51), 146 (28), 144 (34); FAB-HRMS m/z calcd for $C_{16}H_{19}NO_2S$ 289.1136, found 289.1131.

4.10.3. (4R,9aS*)-4-Methyl-2-(phenylsulfonyl)-4,6,9,9a-tetrahydro-3H-quinolizine (**10c**).* Yield (71%); yellow-brown liquid; IR (neat) ν 3038, 2966, 2929, 1651, 1447, 1351, 1305, 1155, 1125, 1086, 829, 737, 718, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.05–7.78 (2H, m), 7.75–7.48 (3H, m), 6.81 (1H, s), 5.90–5.65 (2H, m), 3.53 (1H, br d, J=15.0 Hz), 3.12 (1H, br s), 2.75 (1H, br d, J=15.0 Hz), 2.58–1.92 (5H, m), 1.16 (3H, d, J=6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 139.2, 138.5, 137.6, 133.4, 129.3, 128.1, 125.6, 124.6, 57.6, 54.1, 50.0, 32.3, 32.2, 19.4; FAB-MS (rel intensity) m/z 290 (M^++H, 40), 288 (33), 148 (25), 147 (41), 144 (74), 73 (100); FAB-HRMS m/z calcd for $C_{16}H_{19}NO_2S$ 289.1136, found 289.1132.

4.11. 2-(Phenylsulfonyl)-4,6,7,8,9,9a-hexahydro-3*H*-quinolizine (11)

A mixture of compound **10a** (100 mg, 0.33 mmol) and 10% palladium on carbon (17.6 mg) in ethyl acetate (10 mL) was stirred vigorously under a balloon of hydrogen at room temperature for 48 h. The reaction mixture was then filtered with Celite, washed with ethyl acetate, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:4) containing 5% Et_3N as eluent to give product **11** (84 mg, 83%). Light yellow liquid; IR (film) ν 3061, 2937, 2757, 1650, 1554, 1446, 1359, 1303, 1292, 1216, 1179, 1132, 1098, 1016, 997, 885, 789, 734, 717, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.87–7.84 (2H, m), 7.63–7.50 (3H, m), 6.75 (1H, s), 2.91–2.81 (2H, m), 2.66–2.63 (1H, m), 2.42–2.28 (3H, m), 2.19 (1H, dt, J=3.6, 11.0 Hz), 1.85–1.78 (2H, m), 1.64–1.56 (2H, m), 1.46–1.26 (2H, m); ^{13}C NMR ($CDCl_3$) δ 139.6, 139.2, 138.0, 133.4, 129.2, 128.2, 61.4, 55.5, 51.5, 31.1, 25.6, 25.0, 24.1; FAB-MS (rel intensity) m/z 278 (M^++H, 17), 147 (33), 136 (17), 73 (100), 41 (20); FAB-HRMS m/z calcd for $C_{15}H_{19}NO_2S$ 277.1136, found 277.1141.

4.12. (2*S**,9a*S**)-2-(Phenylsulfonyl)-2,3,4,6,7,8,9,9a-octahydro-1*H*-quinolizine (12)

A mixture of compound **10a** (100 mg, 0.33 mmol) and 10% palladium on carbon (17.5 mg) in 95% EtOH (10 mL) was stirred vigorously under a balloon of hydrogen at room temperature for 24 h. The reaction mixture was then filtered with Celite, washed with ethyl acetate, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:4) containing 5% Et_3N as eluent to give product **12** (79 mg, 80%). Light yellow liquid; IR (film) ν 3060, 2935, 2805, 2765, 1586, 1447, 1353, 1304, 1277, 1224, 1178, 1146, 1126, 1084, 999, 895, 809, 794, 722, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.88–7.85 (2H, m), 7.69–7.54 (3H, m), 2.99 (1H, tt, J=3.3, 12.3 Hz), 2.91–2.86 (1H, m), 2.78 (1H, br d, J=11.7 Hz), 2.05–1.91 (4H, m), 1.76–1.51 (6H, m), 1.43–1.20 (3H, m); ^{13}C NMR ($CDCl_3$) δ 136.6, 133.8, 129.3, 129.2, 62.1, 61.2, 55.8, 54.7, 33.0, 32.3, 25.6 (×2), 24.2; FAB-MS (rel intensity) m/z 280 (M^++H, 100), 278 (42), 138 (69), 136 (58); FAB-HRMS m/z calcd for $C_{15}H_{21}NO_2S$ 279.1293, found 279.1291.

4.13. 2-Allyl-1-(*tert*-butoxycarbonyl)-4-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine (13)

To a solution of **7a** (412 mg, 1.57 mmol) and 4-dimethylaminopyridine (19 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) under nitrogen were added sequentially Et_3N (0.218 mL, 1.57 mmol) and di-*tert*-butyl dicarbonate (0.554 mL, 2.35 mmol). After refluxing for 4 h, the reaction mixture was quenched with saturated sodium bicarbonate (10 mL). The aqueous solution was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:2) as eluent to give product **13** (449 mg, 79%). Yellow-brown liquid; IR (neat) ν 3067, 2977, 2933, 1690, 1413, 1318, 1154, 1123, 1092, 1057, 953, 925, 758, 727, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.93–7.82 (2H, m), 7.72–7.49 (3H, m), 7.00 (1H, s), 5.91–5.72 (1H, m), 5.21–5.07 (2H, m), 4.69 (1H, br s), 4.26 (1H, br s), 2.79 (1H, br s), 2.49–2.28 (3H, m), 2.16 (1H, br s), 1.44 (9H, s); ^{13}C NMR ($CDCl_3$) δ 153.7, 139.0, 138.6, 137.2, 133.5, 133.2, 129.2, 128.0, 118.4, 80.2, 52.0, 37.6, 35.9, 28.2, 23.2; ESI-MS (rel intensity) m/z 364 (M^++H, 6), 266 (25), 264 (10), 221 (16), 125 (100), 122 (19); ESI-HRMS m/z calcd for $C_{19}H_{25}NO_4S$ m/z 363.1504, found 363.1501.

4.14. 1-(*tert*-Butoxycarbonyl)-2-[(*E*)-4-oxopent-2-enyl]-4-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine (14)

A mixture of compound **13** (250 mg, 0.69 mmol), **G2** (29 mg, 0.034 mmol), *p*-cresol (0.036 mL, 0.34 mmol), and methyl vinyl ketone (1.13 mL, 13.77 mmol) in toluene (10 mL) was refluxed for 7 h. The solvent was evaporated under vacuum, and the residue was purified by flash chromatography using ethyl acetate/hexane (1:4) containing 5% Et_3N as eluent to give product **14** (214 mg, 77%). Red-brown liquid; IR (neat) ν 3062, 2978, 2932, 1691, 1629, 1478, 1366, 1317, 1307, 1154, 1119, 981, 953, 760, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.91–7.83 (2H, m), 7.71–7.61 (1H, m), 7.61–7.52 (2H, m), 6.96 (1H, s), 6.82–6.71 (1H, m), 6.11 (1H, br s), 4.90 (1H, br s), 4.44–4.02 (1H, m), 2.76 (1H, br s), 2.67–2.42 (2H, m), 2.39–2.28 (1H, m), 2.24 (3H, s), 2.19–2.10 (1H, m), 1.42 (9H, s); ^{13}C NMR ($CDCl_3$) δ 198.2, 153.7, 142.6, 140.0, 138.4, 136.4, 133.7 (×2), 129.4, 128.1, 80.8, 51.8, 36.2 (×2), 28.2, 27.1, 23.3; ESI-MS (rel intensity) m/z 406 (M^++H, 5), 361

(29), 306 (100), 222 (45); ESI-HRMS m/z calcd for $C_{21}H_{27}NO_5S$ 405.1610, found 405.1617.

4.15. 1-(*tert*-Butoxycarbonyl)-2-(4-oxopentyl)-4-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine (15)

A mixture of compound **14** (160 mg, 0.39 mmol) and PtO_2 (13 mg, 0.06 mmol) in EtOAc (4 mL) was stirred vigorously under a balloon of hydrogen at room temperature for 21 h. The reaction mixture was then filtered with Celite, washed with ethyl acetate, dried ($MgSO_4$), and evaporated under vacuum to give product **15** (150 mg, 93%). Yellow liquid; IR (neat) ν 3061, 2977, 2935, 1712, 1683, 1478, 1447, 1367, 1307, 1152, 1118, 1058, 758, 735, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86 (2H, d, J=7.8 Hz), 7.70–7.50 (3H, m), 6.98 (1H, s), 4.62 (1H, br s), 4.40–3.99 (1H, m), 2.76 (1H, br s), 2.63–2.39 (2H, m), 2.34–2.22 (1H, m), 2.21–2.02 (4H, m), 1.74–1.49 (4H, m), 1.44 (9H, s); ^{13}C NMR ($CDCl_3$) δ 208.0, 154.0, 138.6, 137.6, 133.6 (×2), 129.3, 128.0, 80.4, 51.3, 42.9, 35.5, 32.2, 29.9, 28.3, 23.2, 20.1; FAB-MS (rel intensity) m/z 408 (M^++H, 38), 308 (48), 271 (30), 159 (30), 147 (32), 145 (39), 143 (31), 137 (35), 133 (38), 131 (34), 123 (36), 121 (44), 119 (70), 109 (50), 107 (47) 105 (64), 95 (77), 93 (53), 91 (62), 83 (43), 81 (97), 79 (41), 77 (33), 69 (95), 67 (47), 57 (74), 55 (100), 43 (69), 41 (70); FAB-HRMS m/z calcd for $C_{21}H_{29}NO_5S$ 407.1766, found 407.1773.

4.16. (6*S**,9a*S**)-6-Methyl-2-(phenylsulfonyl)-4,6,7,8,9,9a-hexahydro-3*H*-quinolizine (16)

A solution of compound **15** (13 mg, 0.032 mmol) in CF_3CO_2H/CH_2Cl_2 (1:2, 1 mL) was stirred in an ice bathe for 4 h. Then $NaBH_4$ (13 mg, 0.32 mmol) was added, followed by dropwise addition of MeOH (2 mL). The reaction mixture was further stirred at room temperature for 1 h. The solvent was evaporated under vacuum, and then CH_2Cl_2 (5 mL) and saturated $NaHCO_3$ (5 mL) were added. The aqueous solution was extracted with CH_2Cl_2 (5 mL×3), and the combined organic solution was evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:6) containing 5% Et_3N as eluent to give product **16** (7 mg, 75%). Red-brown liquid; IR (neat) ν 3066, 2967, 2931, 2851, 2795, 1655, 1468, 1331, 1305, 1151, 1125, 1070, 1034, 749, 716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95–7.80 (2H, m), 7.70–7.59 (1H, m), 7.59–7.47 (2H, m), 6.72 (1H, d, J=0.9 Hz), 3.42–3.25 (1H, m), 2.84–2.72 (1H, m), 2.42–2.27 (2H, m), 2.27–2.13 (1H, m), 2.13–2.01 (1H, m), 1.87–1.72 (2H, m), 1.69–1.58 (1H, m), 1.52–1.24 (3H, m), 1.09 (3H, d, J=6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 139.9, 139.2, 138.0, 133.4, 129.2, 128.2, 61.7, 57.6, 45.7, 34.7, 31.4, 24.8, 24.5, 20.5; FAB-MS (rel intensity) m/z 292 (M^++H, 63), 271 (41), 165 (42), 157 (41), 155 (40), 143 (49), 141 (41), 133 (40), 129 (48), 128 (52), 119 (77), 115 (50), 109 (43), 107 (46), 105 (79), 95 (63), 93 (54), 91 (100), 81 (76), 79 (47), 77 (60), 73 (57), 69 (75), 67 (44), 57 (40), 55 (89), 43 (51), 41 (67); FAB-HRMS m/z calcd for $C_{16}H_{21}NO_2S$ 291.1293, found 291.1297.

4.17. *cis*-1-(Benzyloxycarbonyl)-6-methyl-2-[(*E*)-4-oxohept-2-enyl]-4-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine (17)

A mixture of compound **8a** (50 mg, 0.12 mmol), **G2** (5 mg, 0.006 mmol), *p*-cresol (0.006 mL, 0.06 mmol) and 1-hexen-3-one (0.142 mL, 1.20 mmol) in toluene (5 mL) was refluxed for 5 h. The solvent was evaporated under vacuum, and the residue was purified by flash chromatography using ethyl acetate/hexane (1:2) as eluent to give product **17** (40 mg, 68%). Red-brown liquid; IR (neat, film) ν 3061, 2965, 2935, 1695, 1631, 1360, 1306, 1155, 1110, 982, 736, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.89–7.78 (2H, m), 7.71–7.61 (1H, m), 7.61–7.49 (2H, m), 7.42–7.22 (5H, m), 6.96 (1H, s), 6.91–6.72 (1H, m), 6.12 (1H, d, J=15.9 Hz), 5.12 (2H, s), 4.75 (2H, br s), 2.75–2.60 (1H, m), 2.59–2.41 (3H, m), 2.35–2.19 (2H, m), 1.72–1.43 (2H, m), 1.02 (3H, d, J=7.2 Hz), 0.93 (3H, t, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 199.9, 154.5, 140.8, 138.2, 137.0, 136.0, 134.1, 133.7, 133.0, 129.3, 128.5, 128.2, 128.1, 128.0, 67.6, 51.4, 43.6, 42.2, 38.4, 28.6, 20.0, 17.4, 13.7; ESI-MS (rel intensity) m/z 480 (M^--H, 40), 370 (100), 326 (64), 297 (37), 150 (17); ESI-HRMS m/z calcd for $C_{27}H_{31}NO_5S$ 481.1923, found 481.1931.

4.18. *cis*-1-(Benzyloxycarbonyl)-6-methyl-2-(4-oxoheptyl)-4-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine (18)

A mixture of compound **17** (119 mg, 0.25 mmol) and PtO_2 (8 mg) in EtOAc (5 mL) was stirred vigorously under a balloon of hydrogen at room temperature for 24 h. The reaction mixture was then filtered with Celite, washed with ethyl acetate, dried ($MgSO_4$), and evaporated under vacuum to give product **18** (119 mg, 99%). Light yellow liquid; IR (film) ν 3064, 3034, 2962, 2934, 2875, 1700, 1655, 1447, 1380, 1334, 1306, 1154, 1111, 1072, 752, 725, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98–7.79 (2H, m), 7.74–7.49 (3H, m), 7.48–7.23 (5H, m), 7.07 (1H, s), 5.26–5.02 (2H, m), 4.76 (1H, br s), 4.54 (1H, br s), 2.71–2.12 (6H, m), 1.89–1.45 (6H, m), 0.99 (3H, d, J=6.9 Hz), 0.90 (3H, t, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 210.2, 154.6, 138.4, 136.2, 135.9, 135.1, 133.5 (×2), 129.2, 128.4, 128.1, 128.0, 67.4, 52.0, 44.5, 43.6, 41.8, 34.8, 28.5, 20.4, 19.8, 17.1, 13.6; ESI-MS (rel intensity) m/z 482 (M^-−H, 34), 402 (21), 325 (26), 311 (13), 283 (100); ESI-HRMS m/z calcd for $C_{27}H_{33}NO_5S$ 483.2079, found 483.2093.

4.19. (2*R**,4*S**,6*S**)-2-Methyl-6-(4-oxoheptyl)-4-(phenylsulfonyl)piperidine (19)

A mixture of compound **17** (23 mg, 0.05 mmol) and $Pd(OH)_2$ (3 mg) in CF_3CO_2H/MeOH (1:5, 2 mL) was stirred vigorously under a balloon of hydrogen at room temperature for 24 h. The reaction mixture was then filtered with Celite and washed with ethyl acetate. To this was added 5% NaOH (10 mL), and the aqueous solution was extracted with CH_2Cl_2. The combined organic solution was dried ($MgSO_4$), and evaporated under vacuum to give product **19** (16 mg, 95%) as a light yellow liquid. IR (film) ν 3313, 3064, 2960, 2929, 2873, 1708, 1447, 1378, 1303, 1146, 1085, 755, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95–7.82 (2H, m), 7.72–7.62 (1H, m), 7.62–7.51 (2H, m), 3.05 (1H, tt, J=12.3, 3.6 Hz), 2.72–2.58 (1H, m), 2.58–2.45 (1H, m), 2.45–2.32 (4H, m), 2.08–1.92 (2H, m), 1.81–1.51 (5H, m), 1.42–1.28 (3H, m), 1.21–1.14 (1H, m), 1.09 (3H, d, J=6.3 Hz), 0.90 (3H, t, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 210.5, 136.5, 133.6, 128.9, 128.8, 62.1, 55.1, 50.7, 44.5, 42.2, 36.0, 32.9, 30.8, 22.2, 19.6, 17.0, 13.5; FAB-MS (rel intensity) m/z 352 (M^++H, 100), 210 (31), 126 (23), 52 (22), 51 (26); FAB-HRMS m/z calcd for $C_{19}H_{29}NO_3S$ 351.1868, found 351.1863.

4.20. *cis*- and *trans*-(2*S**,4*S**,6*R**)-6-Methyl-2-(4-hydroxyheptyl)-4-(phenylsulfonyl)piperidine (20)

To a solution of compound **19** (85 mg, 0.24 mmol) in CF_3CO_2H/MeOH (1:10, 11 mL) at 0 °C was added $NaCNBH_3$ (152 mg, 2.42 mmol). The reaction mixture was stirred at room temperature for 4 h, and the solvent was evaporated under vacuum. To this were added CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ (10 mL). The aqueous solution was extracted with CH_2Cl_2 (5 mL×3). The combined organic solution was dried ($MgSO_4$), evaporated under vacuum, and the crude product was purified by flash chromatography using ethyl acetate containing 5% Et_3N as eluent to give product **20** (79 mg, 92%). Light yellow liquid (1:1 diastereomeric mixture as judged from ^{13}C NMR); IR (neat) ν 3401, 3065, 2957, 2931, 2870, 1447, 1379, 1303, 1085, 894, 753, 719, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93–7.83 (2H, m), 7.73–7.51 (3H, m), 3.59 (1H, br s), 3.06 (1H, tt, J=12.5, 3.6 Hz), 2.73–2.61 (1H, m), 2.61–2.49 (1H, m), 2.13–1.92 (2H, m), 1.65–1.28 (11H, m), 1.23–1.13 (1H, m), 1.11 (3H, d, J=6.0 Hz), 0.92 (3H, t, J=6.0 Hz); ^1H NMR (DMSO-d_6)

δ 7.32–7.10 (5H, m), 3.71 (1H, br s), 2.92–2.68 (2H, m), 2.10–1.81 (2H, m), 1.42–1.05 (2H, m), 0.98–0.55 (10H, m), 0.53–0.38 (5H, m), 0.31 (3H, t, *J*=6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 136.9, 133.8, 129.3, 129.2, 71.5, 62.6, 55.8, 55.6, 51.2, 39.8, 37.5, 37.3, 36.9, 36.8, 33.4, 31.3, 22.5, 22.0, 21.9, 18.9, 14.2; ^{13}C NMR (DMSO-d_6) δ 136.9, 133.8, 129.3, 128.6, 69.2, 60.8, 54.6, 50.1, 37.4, 36.4, 32.8, 30.4, 22.1, 21.5, 21.4, 18.4, 14.1; ESI-MS (rel intensity) *m*/*z* 354 (M^++H, 100), 336 (5); ESI-HRMS *m*/*z* calcd for $C_{19}H_{31}NO_3S$ 353.2025, found 353.2015.

4.21. (2*S**,4*R**,6*R**,9a*S**)-4-Methyl-2-(phenylsulfonyl)-6-propyl-2,3,4,6,7,8,9,9a-octahydro-1*H*-quinolizine (21a) and (2*S**,4*R**,6*S**,9a*S**)-4-methyl-2-(phenylsulfonyl)-6-propyl-2,3,4,6,7,8,9,9a-octahydro-1*H*-quinolizine (21b)

To a solution of compound **20** (110 mg, 0.31 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added sequentially Et_3N (0.091 mL, 0.65 mmol) and MsCl (0.027 mL, 0.34 mmol). The reaction mixture was then stirred at room temperature for 17 h, and saturated $NaHCO_3$ (5 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (5 mL×3). The combined organic solution was dried ($MgSO_4$) and evaporated under vacuum. The residue was dissolved in Et_3N/toluene (1:3, 20 mL), and refluxed under nitrogen for 1 d. The solvent was removed under vacuum, and the residue was purified by flash chromatography using ethyl acetate/hexane (1:4) containing 5% Et_3N as eluent to give compound **21a** (50 mg, 48%) and compound **21b** (45 mg, 43%). Compound **21a**: yellow solid mp 108.1–109.5 °C; IR (ATR, film) ν 3054, 2936, 2863, 2796, 1445, 1377, 1297, 1279, 1144, 1083, 1024, 755, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.91–7.80 (2H, m), 7.72–7.61 (1H, m), 7.61–7.50 (2H, m), 3.09 (1H, d, *J*=8.7 Hz), 2.98 (1H, tt, *J*=12.6, 3.3 Hz), 2.61–2.45 (1H, m), 2.44–2.31 (1H, m), 2.70–1.90 (2H, m), 1.83–1.67 (2H, m), 1.67–1.56 (1H, m), 1.53–1.16 (9H, m), 1.07 (3H, d, *J*=6.3 Hz), 0.91 (3H, t, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 136.7, 133.7, 129.3, 129.1, 61.8, 53.0, 52.8, 52.2, 34.3 (×2), 33.9, 27.7, 22.5, 20.3, 19.9, 18.3, 14.4; EI-MS (rel intensity) *m*/*z* 336 (M^++1, 1), 293 (22), 292 (100), 150 (25); EI-HRMS *m*/*z* calcd for $C_{19}H_{29}NO_2S$ 335.1919, found 335.1916. Compound **21b**: yellow liquid; IR (neat) ν 3065, 2951, 2935, 2870, 2791, 1638, 1447, 1378, 1306, 1147, 1086, 1021, 750, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.92–7.81 (2H, m), 7.72–7.62 (1H, m), 7.61–7.50 (2H, m), 3.03 (1H, tt, *J*=12.6, 3.6 Hz), 2.77–2.64 (1H, m), 2.53–2.38 (2H, m), 1.93 (1H, dq, *J*=12.6, 3.0 Hz), 1.88–1.77 (1H, m), 1.73–1.54 (4H, m), 1.51–1.36 (4H, m), 1.35–1.20 (4H, m), 1.12 (3H, d, *J*=6.0 Hz), 0.87 (3H, t, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 137.0, 133.7, 129.3, 129.2, 62.2, 57.2, 55.5, 54.7, 40.4, 34.5, 33.1, 29.5, 21.6, 21.4, 20.1, 15.3, 14.3; ESI-MS (rel intensity) *m*/*z* 336 (M^++H, 100), 190 (12); ESI-HRMS *m*/*z* calcd for $C_{19}H_{29}NO_2S$ 335.1919, found 335.1916.

4.22. General procedure for reductive cleavage of sulfones 21

A mixture of compound **21** (0.10 mmol) and 6% Na/Hg (2.09 mmol) in dried THF (5 mL) was refluxed for 3.5 h. Additional 6% Na/Hg (2.09 mmol) was added, and refluxed for another 3.5 h. The reaction mixture was then filtered through Celite, washed with ethyl acetate, and evaporated under vacuum. The residue was purified by flash chromatography using hexane containing 5% Et_3N as eluent to give pure product.

4.22.1. (4R,6R*,9aS*)-4-Methyl-6-propyl-2,3,4,6,7,8,9,9a-octahydro-1H-quinolizine (**22**).* Yield (69%); light yellow liquid; IR (neat) ν 2929, 2861, 2792, 2709, 1455, 1375, 1319, 1262, 1104, 1052, 880, 750, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.19–3.06 (1H, m), 2.54–2.40 (1H, m), 2.37–2.25 (1H, m), 1.99 (1H, s), 1.81–1.69 (1H, m), 1.66–1.50 (5H, m), 1.49–1.37 (4H, m), 1.34–1.17 (5H, m), 1.05 (3H, d, *J*=6.3 Hz), 0.93 (3H, t, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 54.1, 53.1, 53.0, 35.7, 35.4, 34.7, 28.0, 24.6, 22.5, 20.5, 20.1, 18.7, 14.6; EI-MS (rel intensity) *m*/*z* 196 (M^++1, 1), 152 (9), 77 (100), 69 (8), 57 (11); EI-HRMS *m*/*z* calcd for $C_{13}H_{25}N$ 195.1987, found 195.1987.

4.22.2. (4R,6S*,9aS*)-4-Methyl-6-propyl-2,3,4,6,7,8,9,9a-octahydro-1H-quinolizine (**23**).* Yield (65%); light yellow liquid; IR (neat, film) ν 3059, 2929, 2859, 2789, 2708, 1456, 1376, 1274, 1160, 1105, 876, 755, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.65–2.55 (1H, m), 2.54–2.47 (2H, m), 1.84–1.72 (1H, m), 1.72–1.59 (3H, m), 1.55–1.42 (5H, m), 1.38–1.18 (7H, m), 1.11 (3H, d, *J*=6.3 Hz), 0.90 (3H, t, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 58.1, 57.1, 55.8, 39.8, 34.4, 33.5, 30.6, 23.6, 22.7, 22.5, 20.2, 17.6, 14.4; ESI-MS (rel intensity) *m*/*z* 196 (M^++H, 100); ESI-HRMS *m*/*z* calcd for $C_{13}H_{25}N$ 195.1987, found 195.1981.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.12.017.

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