Stereospecific Synthesis of *trans*-5,6-Dihydropyridinones

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Abstract: An efficient synthesis of *trans*-5,6-dihydropyridinones bearing a heteroatom (Br, OH) at C-5 has been achieved. The formal synthesis of (±)-epiquinamide and (±)-homopumiliotoxin 223G has also been accomplished through the formation of (±)-*trans*-1-hydroxyquinolizidin-4-one.

Key words: aza-Diels–Alder reaction, *trans*-5,6-dihydropyridinones, *trans*-1-hydroxyquinolizidin-4-one, epiquinamide, homopumiliotoxin 223G

Many alkaloids have been isolated from amphibian skin.[1] Some of them have the indolizidine or quinolizidine structures, which often show interesting biological activities.[2] We have recently developed a new aza-Diels–Alder reaction of thio-substituted 3-sulfolenes with *p*-toluenesulfonyl isocyanate (PTSI) to synthesize piperidine derivatives.[3] This method was also used by us to prepare some indolizidines and quinolizidines,[4] and other heterocyclic compounds.[5] Some of these compounds showed novel biological activities.[6] Herein a new method for the synthesis of *trans*-5,6-dihydropyridinones bearing a heteroatom at C-5 is reported. There are only a few synthetic methods known in the literature for such structures.[7] In addition, we have also completed a formal synthesis of (±)-epiquinamide[8] and (±)-homopumiliotoxin 223G[9] through a common intermediate, (±)-*trans*-1-hydroxyquinolizidin-4-one[10] (Figure 1).

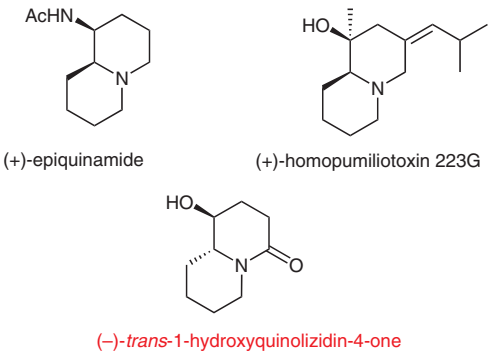
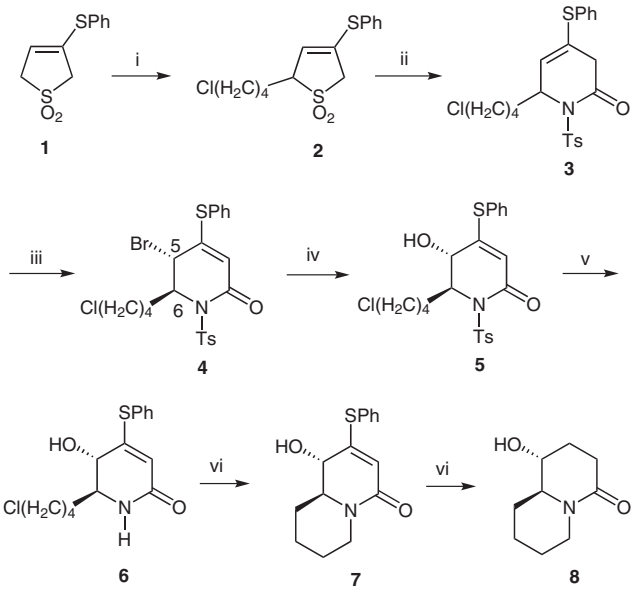


Figure 1

Deprotonation of 3-(phenylthio)-3-sulfolene (**1**)[11] in tetrahydrofuran with butyllithium at –78 °C in the presence of hexamethylphosphoric amide (HMPA), followed by reaction with 1-chloro-4-iodobutane gave the alkylated product **2**.[12] Treatment of compound **2** with *p*-toluenesulfonyl isocyanate (PTSI) in refluxing toluene in the presence of hydroquinone (HQ) and sodium bicarbonate afforded the cycloaddition product **3** in good yield. The reaction of compound **3** with 1.1 equivalents of *N*-bromosuccinimide (NBS) in refluxing acetonitrile provided the allylic bromide **4** in excellent yield (Scheme 1). The X-ray crystal structure of compound **4** (Figure 2)[13] shows that the bromo group and the alkyl side chain are *trans* to each other, and both are at the axial positions. We propose that NBS approaches compound **3** from the opposite side of the 4-chlorobutyl group, resulting in the formation of *trans*-product **4**. The diaxial conformations of the bromo and chlorobutyl groups are attributed mainly to the minimization of $A^{1,3}$-type strain of the *N*-tosyl group with the chlorobutyl side chain.[14] The coupling constant ($J_{5,6}$ = 1.8 Hz) of compound **4** agrees with the equatorial positions of H-5 and H-6.

Subsequent reaction of bromide **4** with sodium azide in tetrahydrofuran or *N*,*N*-dimethylformamide at room temperature or under heating did not lead to the expected S_N2



Scheme 1 Synthesis of 1-hydroxyquinolizidin-4-one (**8**). *Reagents and conditions*: (i) a) BuLi (1.1 equiv), HMPA (4 equiv), THF, –78 °C, b) $Cl(CH_2)_4I$ (4 equiv), –78 to –50 °C, 50%; (ii) PTSI (3 equiv), $NaHCO_3$ (1 equiv), HQ (cat.), toluene, reflux, 6 h, 77%; (iii) NBS (1.1 equiv), MeCN, reflux, 2 h, 96%; (iv) Et_3N–H_2O–MeCN (1:1.5:3.3), 70 °C, 24 h, 82%; (v) Bu_3SnH (1.2 equiv), AIBN (0.6 equiv), toluene, reflux, 1 h, 80%; (vi) BuLi (2 equiv), THF, –78 °C to r.t., then reflux, 7 h, 88%; (vii) Ra-Ni (10 equiv), 95% EtOH, reflux, 2 h, 83%.

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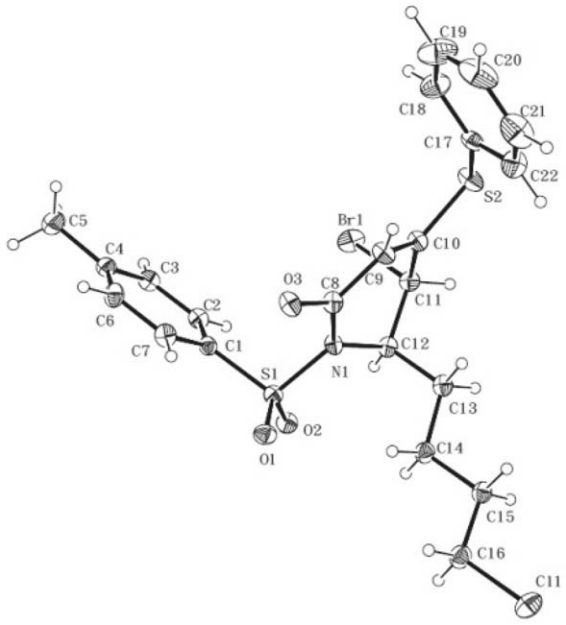


Figure 2 X-ray crystal structure of compound **4**

product. Instead, complex mixtures of elimination, S_N2' substitution and *N*- to *O*-tosyl migration products were obtained. It seems that the azido nucleophile is difficult to approach from the back side of compound **4** due to steric hindrance with the chlorobutyl group. Our attention was then turned to S_N1 reaction conditions. Indeed, treatment of compound **4** with 28% aqueous ammonia in acetonitrile[15] at 50 °C gave the substitution product **5** in 48% yield. The best reaction condition found was to heat compound **4** with triethylamine in aqueous acetonitrile to give the allylic alcohol **5** in 82% yield. The X-ray crystal structure of compound **5** (Figure 3)[13] shows that the hydroxy group and the alkyl side chain are *trans* to each other, and both are at the axial positions. The coupling constant ($J_{5,6}$ = 2.1 Hz) of compound **5** confirms that both H-5 and H-6 are at the equatorial positions. Since the conversion of compound **4** to compound **5** proceeds with retention of configuration, this reaction does not occur via an S_N2 mechanism. We propose that compound **4** undergoes an S_N1 reaction to generate an allylic carbocation, which is then attacked by water from the opposite side of the chlorobutyl group to give the *trans*-product **5**.

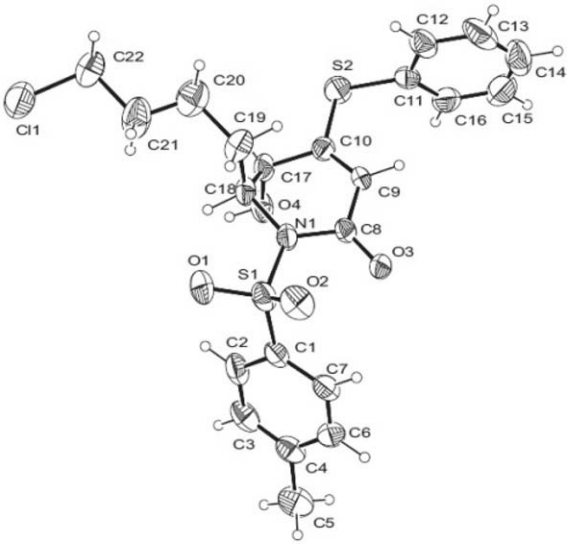


Figure 3 X-ray crystal structure of compound **5**

The tosyl group of compound **5** was effectively cleaved by Bu_3SnH/AIBN[16] to give the amide **6**. The X-ray crystal structure of compound **6** (Figure 4)[13] shows that the hydroxy group and the alkyl side chain are *trans* to each other, but both are now at the equatorial positions. The coupling constant ($J_{5,6}$ = 4.2 Hz) of compound **6** is considerably larger than those of compounds **4** (1.8 Hz) and **5** (2.1 Hz), confirming that H-5 and H-6 of compound **6** are both at the axial positions. This indicates that preference for the diequatorial conformations of the hydroxy group and the alkyl side chain of compound **6** outweighs the alternative $A^{1,3}$-type strain of the phenylthio group with the hydroxy group, since the bulky tosyl group has been cleaved from the nitrogen atom of compound **5**.

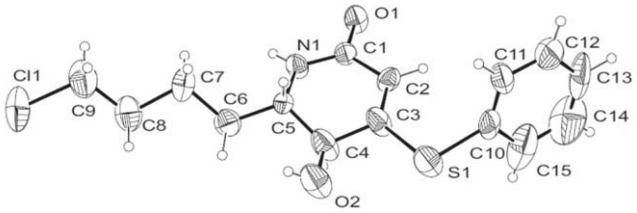
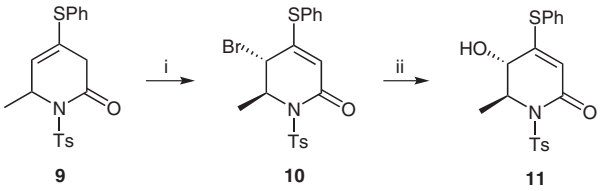


Figure 4 X-ray crystal structure of compound **6**

Treatment of compound **6** with butyllithium in refluxing tetrahydrofuran led to the quinolizidine **7** in good yield. It is important to note that the amount of base has significant influence on the yields of product **7**. The best yield (88%) was obtained with 2.0 equivalents of butyllithium, much higher than with 1.0 equivalent (53%) or 3.5 equivalents (45%) of butyllithium. Further reaction of compound **7** with the W-2 type Raney nickel resulted in both cleavage of the phenylthio group and reduction of the C=C bond to give (±)-*trans*-1-hydroxyquinolizidin-4-one (**8**).[10] It has recently been reported that (–)-*trans*-1-hydroxyquinolizidin-4-one is an efficient precursor to the synthesis of (–)-epiquinamide and (–)-homopumiliotoxin 223G.[17]

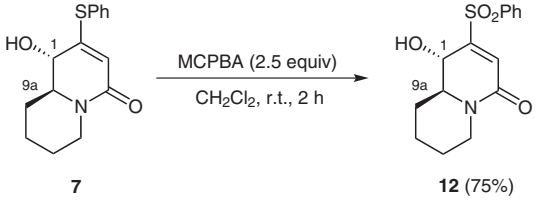
To further demonstrate that our method for stereospecific synthesis of *trans*-5,6-dihydropyridinones **4** and **5** is not restricted to structures bearing a long alkyl chain at C-6 of compound **3**, similar reactions were also carried out with 6-methyl derivatives **9** and **10** (Scheme 2). The X-ray crystal structure of compound **10** (Supporting Information)[13] not only shows that the bromo and methyl groups are *trans* to each other, but also that these two groups are both at the axial positions. The coupling constant ($J_{5,6}$ = 1.6 Hz) of compound **10** confirms that H-5 and H-6 are both at the equatorial positions. The *trans* diaxial transpositions of the methyl and hydroxy groups in compound **11** is proven by its X-ray structure (Supporting In-



Scheme 2 Synthesis of allylic alcohol **11**. *Reagents and conditions*: (i) NBS (1.1 equiv), MeCN, reflux, 1 h, 97%; (ii) Et_3N–H_2O–MeCN (1:1.2:4), 70 °C, 24 h, 74%.

formation),[13] and the coupling constant of $J_{5,6}$ (2.1 Hz) is identical with that of compound **5**.

Compound **7** was oxidized with MCPBA to produce the sulfone **12** (Scheme 3). The X-ray crystal structure of compound **12** (Supporting Information)[13] shows not only that the hydroxy group and the fused ring are *trans* to each other, but also that these two groups are both at the axial positions. The coupling constant ($J_{1,9a}$ = 2.1 Hz) of compound **12** confirms that H-1 and H-9a are at the equatorial positions. It is interesting to note that the corresponding coupling constant ($J_{1,9a}$ = 5.1 Hz) for compound **7** indicates that the hydroxy group and the fused ring are both at the equatorial positions. It seems that the bulkier phenylsulfonyl group in compound **12** has a more significant $A^{1,3}$-type strain with the hydroxy group than that between the phenylthio group and the hydroxy group in compound **7**.



Scheme 3 Synthesis of sulfone **12**

In summary, we have developed an efficient synthesis of *trans*-bromo compounds **4** and **10**, and used the steric effect of the C-6 substituent (methyl or 4-chlorobutyl) to control its stereospecific conversion to allylic alcohols **5** and **11** with retention of configuration. It was demonstrated that the axial/equatorial conformations of the 5,6-substituents are significantly affected by the $A^{1,3}$-type strain of the *N*-tosyl group with the C-6 substituent. We have also achieved a facile synthesis of (±)-1-hydroxyquinolizidin-4-one (**8**), which is known to be an efficient precursor for the synthesis of (±)-epiquinamide and (±)-homopumiliotoxin 223G.

Melting points were determined with a SMP3 melting apparatus. IR spectra were recorded with a PerkinElmer 100 series FTIR spectrometer. ^{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. 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 60 H silica gel.

6-(4-Chlorobutyl)-4-(phenylthio)-1-tosyl-1,6-dihydropyridin-2(3*H*)-one (3)

A mixture of compound **2**[12b] (820 mg, 2.59 mmol), $NaHCO_3$ (217.9 mg, 2.59 mmol), hydroquinone (28.5 mg, 0.26 mmol), and PTSI (1.2 mL, 7.78 mmol) in toluene (15 mL) was heated at reflux under N_2 for 6 h. After cooling in an ice bath, 5% aq NaOH (50 mL) was slowly added to decompose the excess PTSI. The mixture was then extracted with EtOAc (3 × 30 mL), the combined organic extracts dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexanes (1:6) as eluent; yield: 903 mg (77%); white solid; mp 121.6–122.0 °C.

IR (ATR, film): 2944, 1697, 1386, 1357, 1169, 1237, 1186, 1169, 1126, 1084, 840 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (2 H, d, *J* = 8.4 Hz), 7.40–7.29 (7 H, m), 5.85 (1 H, dd, *J* = 6.0, 2.8 Hz), 5.06–5.03 (1 H, m), 3.57–3.49 (2 H, m), 3.17 (1 H, dt, *J* = 21.0, 2.4 Hz), 2.92 (1 H, dd, *J* = 21.0, 0.9 Hz), 2.43 (3 H, s), 1.96–1.75 (4 H, m), 1.54–1.34 (2 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 145.1, 136.1, 133.3, 130.6, 130.3, 129.6, 129.3, 129.1, 128.8, 123.7, 58.1, 44.6, 38.3, 36.3, 32.0, 21.7 (2 ×).

EI-MS: *m*/*z* (%) = 449 (M^+, 0.5), 359 (21), 358 (100), 155 (24), 91 (47), 86 (45), 84 (71).

EI-HRMS: *m*/*z* calcd for $C_{22}H_{24}ClNO_3S_2$: 449.0886; found: 449.0889.

Anal. Calcd for $C_{22}H_{24}ClNO_3S_2$: C, 58.72; H, 5.38; N, 3.11. Found: C, 58.70; H, 5.36; N, 3.46.

***trans*-5-Bromo-6-(4-chlorobutyl)-4-(phenylthio)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (4)**

A mixture of compound **3** (1000 mg, 2.23 mmol) and NBS (372 mg, 2.45 mmol) in MeCN (15 mL) was heated at reflux under N_2 for 2 h. The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexanes (1:6) as eluent; yield: 1123 mg (96%); white solid; mp 156.7–157.2 °C.

IR (ATR, film): 3063, 2947, 2866, 1671, 1584, 1357, 1333, 1236, 1166, 1087, 910 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (2 H, d, *J* = 8.4 Hz), 7.51–7.42 (5 H, m), 7.27 (2 H, d, *J* = 8.4 Hz), 5.29 (1 H, d, *J* = 0.3 Hz), 4.92 (1 H, td, *J* = 6.6, 1.8 Hz), 4.56 (1 H, dd, *J* = 1.8, 0.3 Hz), 3.56 (2 H, t, *J* = 6.3 Hz), 2.41 (3 H, s), 1.88–1.74 (4 H, m), 1.65–1.52 (2 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 156.8, 145.1, 135.5, 135.1, 130.9, 130.2, 129.7, 129.0, 126.7, 116.1, 62.8, 44.4, 44.2, 33.7, 32.0, 23.7, 21.7.

FAB-MS: *m*/*z* (%) = 530 (M^+ + 3, 73), 528 (M^+ + 1, 55), 358 (32), 221 (38), 207 (36), 155 (53), 136 (62), 107 (42), 91 (100), 57 (58), 55 (53), 41 (42).

FAB-HRMS: *m*/*z* calcd for $C_{22}H_{23}BrClNO_3S_2$: 526.9991; found: 526.9998.

Anal. Calcd for $C_{22}H_{23}BrClNO_3S_2$: C, 49.96; H, 4.38; N, 2.65. Found: C, 49.92; H, 4.24; N, 2.91.

***trans*-6-(4-Chlorobutyl)-5-hydroxy-4-(phenylthio)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (5)**

To a solution of compound **4** (50 mg, 0.45 mmol) in MeCN (1 mL) was added Et_3N (0.3 mL) and H_2O (0.45 mL). The mixture was heated at 70 °C under N_2 for 24 h. After cooling, EtOAc (30 mL) was added and the mixture was washed with brine (2 × 30 mL),

dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexanes (1:4) as eluent; yield: 36 mg (82%); white solid; mp 160.2–160.6 °C.

IR (ATR, film): 3281, 3063, 2952, 2861, 1640, 1596, 1348, 1240, 1163, 900 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.94 (2 H, d, *J* = 8.4 Hz), 7.49–7.41 (5 H, m), 7.26 (2 H, d, *J* = 8.4 Hz), 5.18 (1 H, d, *J* = 0.6 Hz), 4.81 (1 H, td, *J* = 6.6, 2.1 Hz), 4.15 (1 H, ddd, *J* = 5.8, 2.1, 0.6 Hz), 3.57 (2 H, t, *J* = 6.6 Hz), 2.75 (1 H, d, *J* = 5.8 Hz), 2.39 (3 H, s), 1.87–1.82 (3 H, m), 1.66–1.62 (3 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 158.0, 144.8, 136.2, 135.3, 130.7, 130.2, 129.3, 129.1, 126.9, 115.0, 68.2, 61.8, 44.6, 32.3, 32.2, 23.6, 21.7.

EI-MS: *m*/*z* (%) = 465 (M^+, 0.1), 315 (23), 314 (100), 210 (21), 91 (43).

EI-HRMS: *m*/*z* calcd for $C_{22}H_{24}ClNO_4S_2$: 465.0835; found: 465.0845.

trans-6-(4-Chlorobutyl)-5-hydroxy-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (6)

To a refluxing solution of compound **5** (100 mg, 0.22 mmol) in degassed toluene (22 mL) was added slowly a solution of Bu_3SnH (0.07 mmol, 0.26 mmol) and AIBN (21.2 mg, 0.13 mmol) in toluene (4 mL) over 1 h. The solvent was then evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexanes (1:1) containing 5% Et_3N and 5% CH_2Cl_2 as eluent; yield: 53.2 mg (80%); white solid; mp 112.4–113.1 °C.

IR (ATR, film): 3269, 3214, 3055, 2951, 2870, 1631, 1571, 1439, 1412, 1266, 1096, 842 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.42 (5 H, m), 7.03 (1 H, br s), 5.29 (1 H, d, *J* = 1.5 Hz), 4.30 (1 H, d, *J* = 9.3 Hz), 3.95 (1 H, dd, *J* = 9.3, 4.2 Hz), 3.53–3.48 (3 H, m), 1.78–1.74 (2 H, m), 1.57–1.42 (4 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3, 157.8, 135.5, 130.2, 130.1, 128.1, 114.7, 69.2, 57.5, 44.6, 32.2 (2 ×), 23.0.

EI-MS: *m*/*z* (%) = 313 (M^+ + 2, 2.4), 311 (M^+, 6), 164 (22), 135 (34), 122 (32), 120 (100).

EI-HRMS: *m*/*z* calcd for $C_{15}H_{18}ClNO_2S$: 311.0747; found: 311.0742.

trans-1-Hydroxy-2-(phenylthio)-7,8,9,9a-tetrahydro-1*H*-quinolizin-4(6*H*)-one (7)

To a solution of compound **6** (30 mg, 0.10 mmol) in THF (3 mL) at –78 °C under N_2 was added dropwise a solution of BuLi (2.5 M in hexane, 77 μL, 0.19 mmol). After slowly warming to r.t. in 1 h, the reaction mixture was heated at reflux for 7 h, and then poured into sat. aq NH_4Cl (20 mL). The mixture was extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexanes (1:4-1:2) containing 5% Et_3N and 5% CH_2Cl_2 as eluent; yield: 23.4 mg (88%); yellow oil.

IR (ATR, film): 3275, 3058, 2936, 2856, 2709, 1619, 1579, 1468, 1439, 1419, 1266 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.40 (5 H, m), 5.30 (1 H, d, *J* = 2.1 Hz), 4.43 (1 H, br d, *J* = 13.0 Hz), 4.04 (1 H, d, *J* = 5.1 Hz), 3.44 (1 H, ddd, *J* = 11.5, 5.1, 2.4 Hz), 2.53 (1 H, td, *J* = 13.0, 3.1 Hz), 1.90–1.86 (2 H, m), 1.67 (1 H, d, *J* = 11.1 Hz), 1.58–1.26 (3 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 155.1, 135.5, 130.0 (2 ×), 128.2, 115.9, 70.5, 63.0, 44.1, 30.6, 25.1, 24.1.

EI-MS: *m*/*z* (%) = 275 (M^+, 45), 164 (35), 135 (66), 97 (20), 91 (24), 85 (33), 84 (100), 59 (20), 55 (36).

EI-HRMS: *m*/*z* calcd for $C_{15}H_{17}NO_2S$: 275.0980; found: 275.0982.

trans-1-Hydroxy-2,3,7,8,9,9a-hexahydro-1*H*-quinolizin-4(6*H*)-one (8)

A mixture of compound **7** (20 mg, 0.09 mmol) and W-2 Raney Ni (192.5 mg, 1.8 mmol) in 95% EtOH (1.5 mL) was heated at reflux under N_2 for 2 h. The reaction mixture was then passed through a short pad of Celite, rinsed with MeOH (20 mL), and the solvent was evaporated under vacuum. The residue was washed with EtOAc–hexanes (1:95) several times to remove the unwanted top layer material. After evaporation of the solvent under vacuum in an ice bath, product **8** (12 mg, 83%) was obtained as a yellow oil. Its spectral data were identical with the literature values.[10]

6-Methyl-4-(phenylthio)-1-tosyl-1,6-dihydropyridin-2(3*H*)-one (9)

A mixture of 2-methyl-4-(phenylthio)-3-sulfolene (1.44 g, 5.99 mmol),[12a] $NaHCO_3$ (502.1 mg, 5.99 mmol), hydroquinone (33 mg, 0.3 mmol), and PTSI (2.7 mL, 17.97 mmol) in toluene (14 mL) was heated at reflux under N_2 for 2.5 h. After cooling in an ice bath, 5% aq NaOH (100 mL) was slowly added to decompose the excess of PTSI. The mixture was then extracted with EtOAc (3 × 40 mL), dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexanes (1:6) as eluent; yield: 1.58 g (71%); white solid; mp 120.3–121.7 °C.

IR (ATR, film): 3055, 2988, 1687, 1594, 1476, 1441, 1376, 1341, 1265, 1248, 1186, 1168, 1153, 1088, 1025 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.92 (2 H, d, *J* = 8.4 Hz), 7.40–7.30 (7 H, m), 5.88 (1 H, dd, *J* = 5.7, 2.7 Hz), 5.11–5.07 (1 H, m), 3.18 (1 H, dt, *J* = 21.0, 2.6 Hz), 2.94 (1 H, dd, *J* = 21.0, 0.6 Hz), 2.43 (3 H, s), 1.51 (3 H, d, *J* = 6.6 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 145.0, 136.3, 133.1, 130.7, 130.0, 129.3, 129.1, 128.9, 128.7, 125.9, 54.5, 37.9, 23.2, 21.7.

EI-MS: *m*/*z* (%) = 373 (M^+, 5), 358 (62), 218 (36), 200 (43), 155 (38), 91 (47), 17 (100).

HRMS: *m*/*z* calcd for $C_{19}H_{19}NO_3S_2$: 373.0806; found: 373.0803.

trans-5-Bromo-6-methyl-4-(phenylthio)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (10)

A mixture of compound **9** (1.00 g, 2.68 mmol) and NBS (524.7 mg, 2.95 mmol) in MeCN (12 mL) was heated at reflux under N_2 for 1 h. The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexanes (1:6) as eluent; yield: 1.17 g (97%); white solid; mp 189.1–190.0 °C.

IR (ATR, film): 2966, 1665, 1587, 1475, 1442, 1384, 1346, 1306, 1245, 1190, 1161, 1085 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.00 (2 H, d, *J* = 8.4 Hz), 7.50–7.39 (5 H, m), 7.29 (2 H, d, *J* = 8.4 Hz), 5.28 (1 H, s), 5.07 (1 H, qd, *J* = 6.9, 1.7 Hz), 4.44 (1 H, d, *J* = 1.7 Hz), 2.40 (3 H, s), 1.51 (3 H, d, *J* = 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 156.8, 145.0, 136.0, 135.5, 130.8, 130.2, 129.4, 129.2, 128.1, 126.9, 116.0, 58.8, 45.9, 21.7, 20.2.

FAB-MS: *m*/*z* (%) = 454 (M + 2 + H, 42), 452 (M + H, 37), 155 (41), 136 (56), 91 (80), 73 (100).

FAB-HRMS: *m*/*z* calcd for $C_{19}H_{19}{}^{79}BrNO_3S_2$: 451.9989; found: 452.0002.

trans-5-Hydroxy-6-methyl-4-(phenylthio)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (11)

To a solution of compound **10** (25 mg, 0.06 mmol) in MeCN (1 mL) was added Et_3N (0.25 mL) and H_2O (0.30 mL). The mixture was heated at 70 °C under N_2 for 24 h. After cooling, EtOAc (30 mL)

was added and the mixture was washed with brine (2 × 30 mL), dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexanes (1:4) as eluent; yield: 16 mg (74%); white solid; mp 129.2–131.1 °C.

IR (ATR, film): 3354, 3260, 3056, 2926, 1671, 1598, 1386, 1341, 1298, 1265, 1158, 1095, 813, 703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.94 (2 H, d, *J* = 7.8 Hz), 7.49–7.38 (5 H, m), 7.26 (2 H, d, *J* = 7.8 Hz), 5.20 (1 H, s), 4.92 (1 H, qd, *J* = 6.9, 2.1 Hz), 4.04 (1 H, br, s), 2.72 (1 H, d, *J* = 5.1 Hz), 2.40 (3 H, s), 1.38 (3 H, d, *J* = 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 158.0, 144.7, 136.5, 135.3, 130.7, 130.2, 129.3, 129.0, 127.1, 115.0, 70.1, 57.8, 21.7, 18.7.

EI-MS: *m*/*z* (%) = 325 (20), 155 (24), 135 (31), 134 (100), 91 (51).

EI-HRMS: *m*/*z* calcd for $C_{19}H_{19}NO_4S_2$: 389.0755; found: 389.0760.

***trans*-1-Hydroxy-2-(phenylsulfonyl)-7,8,9,9a-tetrahydro-1*H*-quinolizin-4(6*H*)-one (12)**

To a solution of compound **7** (19.7 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) at 0 °C was slowly added a solution of MCPBA (30% in H_2O, 42 mg, 0.48 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at r.t. for 2 h, diluted with CH_2Cl_2 (20 mL), and then sequentially washed with sat. aq $Na_2S_2O_3$ (20 mL) and sat. aq $NaHCO_3$ (20 mL). The organic layer was dried (K_2CO_3), evaporated, and the residue was recrystallized from EtOAc; yield: 16.5 mg (75%); white solid; mp 131–132 °C.

IR (ATR, film): 3340, 3063, 2926, 2856, 2724, 1719, 1663, 1613, 1468, 1447, 1373, 1309, 1152, 1033 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.93 (2 H, m), 7.74–7.59 (3 H, m), 6.66 (1 H, s), 4.52 (1 H, br d, *J* = 13.0 Hz), 4.28 (1 H, d, *J* = 2.1 Hz), 3.63 (1 H, dt, *J* = 12.4, 2.1 Hz), 3.34 (1 H, br, s), 2.63 (1 H, td, *J* = 13.0, 2.7 Hz), 1.87–1.37 (5 H, m), 1.14–1.00 (1 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 148.9, 137.6, 134.7, 129.7, 129.4, 128.8, 64.9, 64.5, 45.1, 30.7, 25.4, 24.4.

FAB-MS: *m*/*z* (%) = 307 (M^+, 3), 281 (16), 221 (13), 207 (19), 154 (40), 136 (76), 107 (30), 91 (50), 73 (97), 55 (100), 41 (86), 39 (39), 29 (29).

FAB-HRMS: *m*/*z* calcd for $C_{15}H_{17}NO_4S$: 307.0878; found: 307.0877.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are ^1H and ^{13}C NMR spectra for compounds **3**–**12**, and X-ray crystal structures for compounds **10**–**12**.

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