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SYNTHESIS AND REACTIONS OF 2-PYRIDO-FUSED BICYCLIC COMPOUNDS

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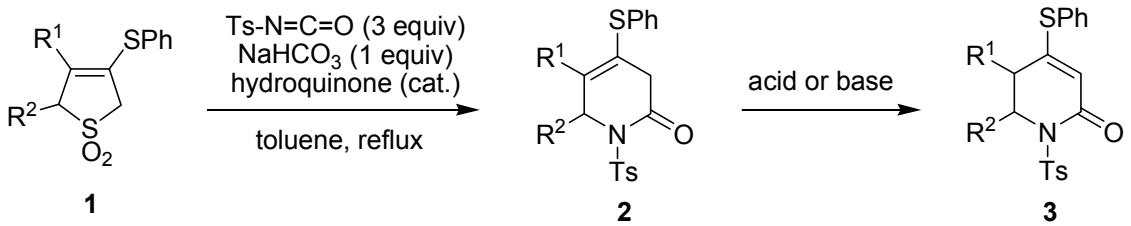
Abstract – Dihydropyridones derived from the aza-Diels–Alder reaction of 3-phenylthio-3-sulfolenes with *p*-toluenesulfonyl isocyanate (PTSI) gave readily the epoxy sulfones, which upon treatment with base afforded the 2-pyrido-fused bicyclic compounds. Some synthetic transformations of these compounds are also reported.

INTRODUCTION

Aza-Diels–Alder reactions are quite useful for constructing the piperidine derivatives.[1] We have previously developed a new aza-Diels–Alder reaction,[2] using thio-substituted 3-sulfolenes (**1**)[3] to react with *p*-toluenesulfonyl isocyanate (PTSI) to give the cycloaddition products **2**, which can be treated with acid or base to afford the 5,6-dihydro-2-pyridones **3** (Scheme 1). We have also used this method to prepare some indolizidines and quinolizidines,[4] and other heterocyclic compounds.[5] Some of these compounds showed novel biological activities.[6]



Scheme 1. Synthesis of 4-(phenylthio)-5,6-dihydro-2-pyridones (**3**)

The 2-pyrido-fused bicyclic structures (Figure 1) comprise the skeleton of some natural products, such as the antitumor agent camptothecin[7] and the alkaloid isosophoramine.[8] There are many methods for synthesizing one or two such bicyclic structures,[9–15] but very few methods have been developed for

constructing all three such skeletons.[16–18] We now report a new method for the synthesis of all these three systems of 2-pyrido-fused bicyclic compounds.

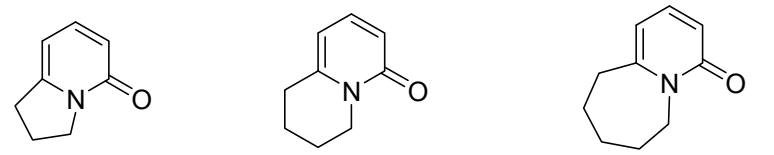
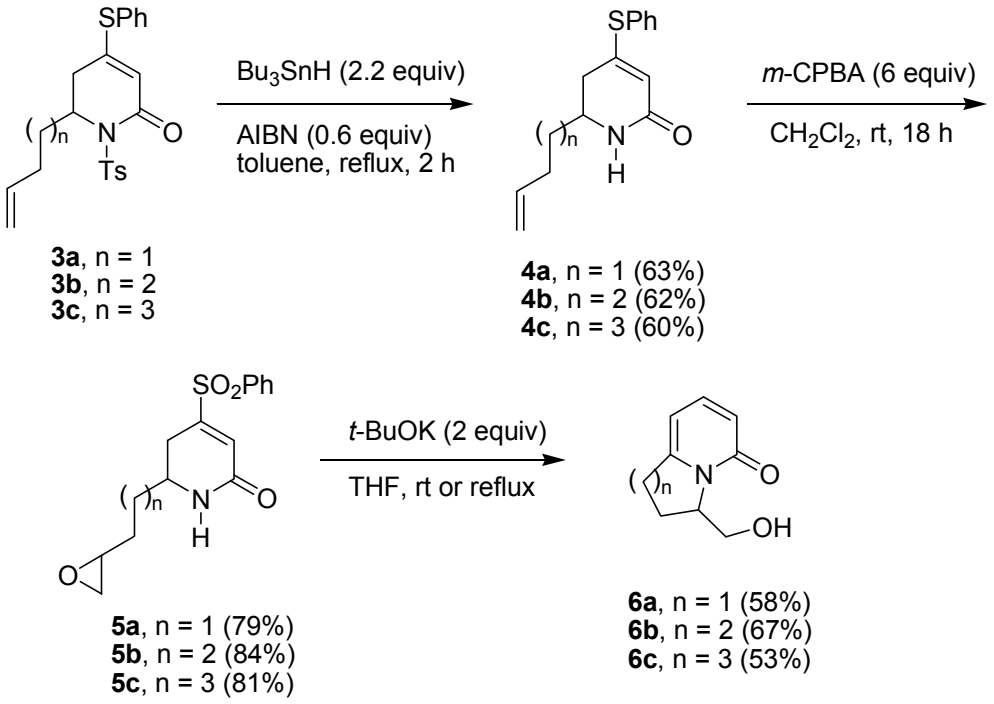


Figure 1. 2-Pyrido-fused bicyclic structures

RESULTS AND DISCUSSION

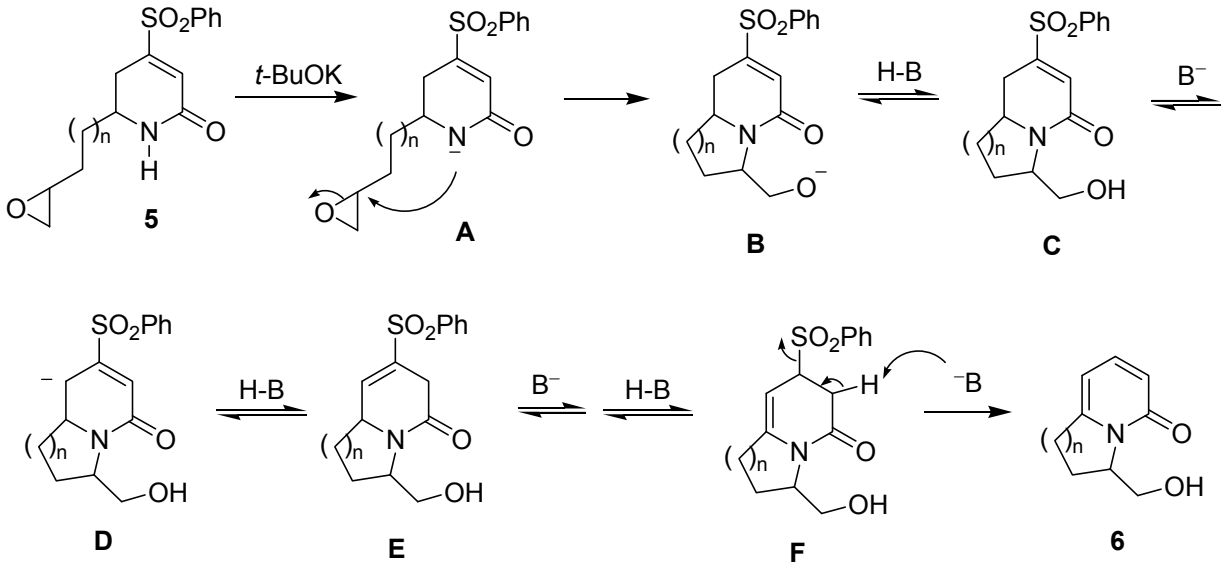
Treatment of compounds **3a**[4], **3b**[2] and **3c** with Bu_3SnH/AIBN[19] gave the secondary amides **4a**–**c**, respectively (Scheme 2). Further oxidation of compounds **4a**–**c** with *m*-CPBA (6 equiv) at room temperature led to the corresponding epoxy sulfones **5a**–**c** in good yields. If less amounts of *m*-CPBA were used, a mixture of sulfoxides, sulfones and epoxy sulfones was obtained. This indicates that the



Scheme 2. Synthesis of 2-pyrido-fused bicyclic compounds **6**

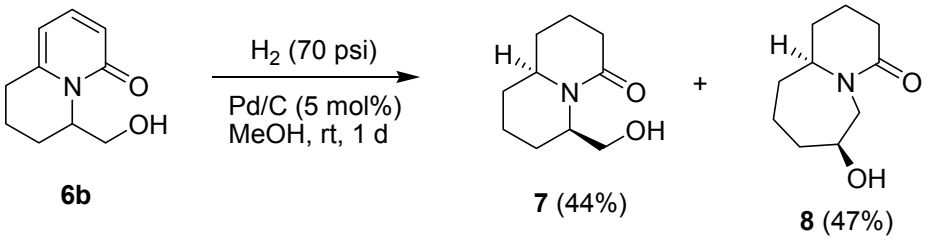
oxidation of compounds **4** proceeded first at the thio group, followed by the reaction with the terminal alkenyl group. The ^{1}H and ^{13}C NMR spectra of compounds **5a**–**c** showed that compound **5a** was a 1 : 1 diastereomeric mixture, whereas compounds **5b** and **5c** only existed as one diastereomer. It seems that the larger alkenyl groups present in compounds **5b** and **5c** make the epoxidation stereoselectively. Treatment of compounds **5a**–**c** with *t*-BuOK in THF (at room temperature for **5b**, and at reflux for **5a** and **5c**) gave the bicyclic products **6a**–**c**, respectively.

A plausible mechanism for the formation of compounds **6** from compounds **5** by treatment with base is shown in Scheme 3. Deprotonation of compounds **5** by *t*-BuOK would generate the amide anions **A**, which can undergo intramolecular cyclization to give intermediates **B**. A series of protonation and deprotonation at equilibrium would then lead to intermediates **F**, which would undergo irreversible elimination of benzenesulfinic acid to give the stable bicyclic products **6**.



Scheme 3. Plausible mechanism for the formation of compounds **6** from compounds **5**

Because some of the piperidine derivatives (including the bicyclic analogs) we previously made have shown novel biological activities,[6] we have also carried out some synthetic transformations of compound **6b**. Treatment of a solution of compound **6b** in MeOH with atmospheric hydrogen at room temperature using Pd/C or PtO_2 as the catalyst did not give any reaction. However, the reaction of compound **6b** with hydrogen in a sealed bottle at 70 psi in the presence of 5 mol% of Pd/C gave the expected reduction product **7**, together with the ring expansion product **8** (Scheme 4). The stereochemistry of compound **7** was determined by comparing with the spectral data of its *trans* diastereomer.[16] The structure of compound **8** was established by X-ray crystallography (Figure 2),[20] and has the interesting moiety of pyrido[1,2-*a*]azepines.[21]



Scheme 4. Hydrogenation of compound **6b**

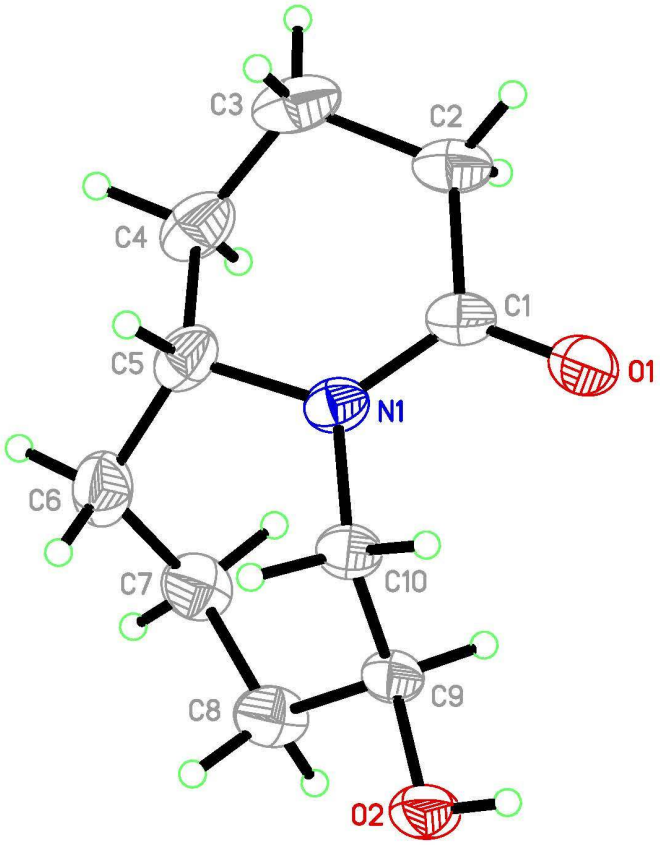
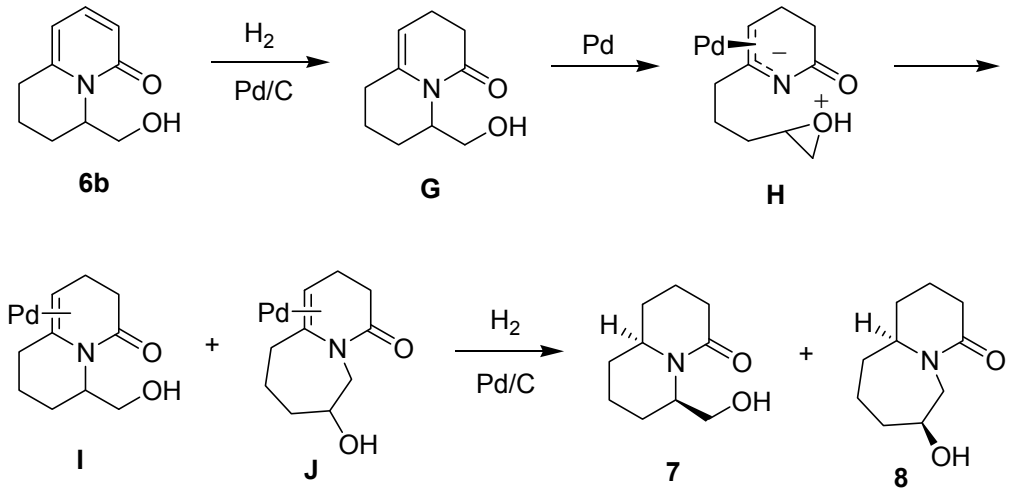


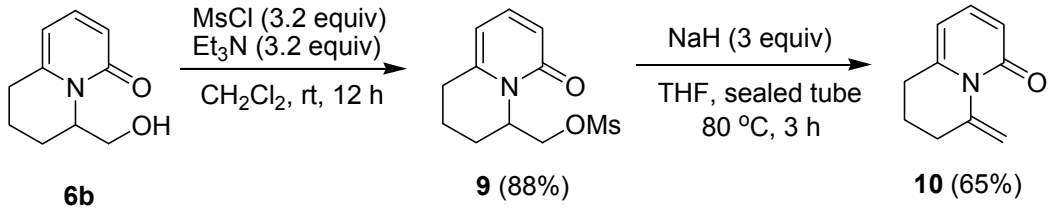
Figure 2. X-Ray crystal structure of compound **8**

A plausible mechanism for the formation of compounds **7** and **8** from hydrogenation of compound **6b** is shown in Scheme 5. Hydrogenation of compound **6b** would occur first at the C3-C4 double bond to give an intermediate **G**, which would then be converted to the palladium π-allyl complex **H**. Intramolecular cyclization would give generate a mixture of intermediates **I** and **J**, as shown in a similar case without the metal complex.[16] Finally, hydrogenation at the C5-C6 double bond from the less hindered side would give the products **7** and **8**.



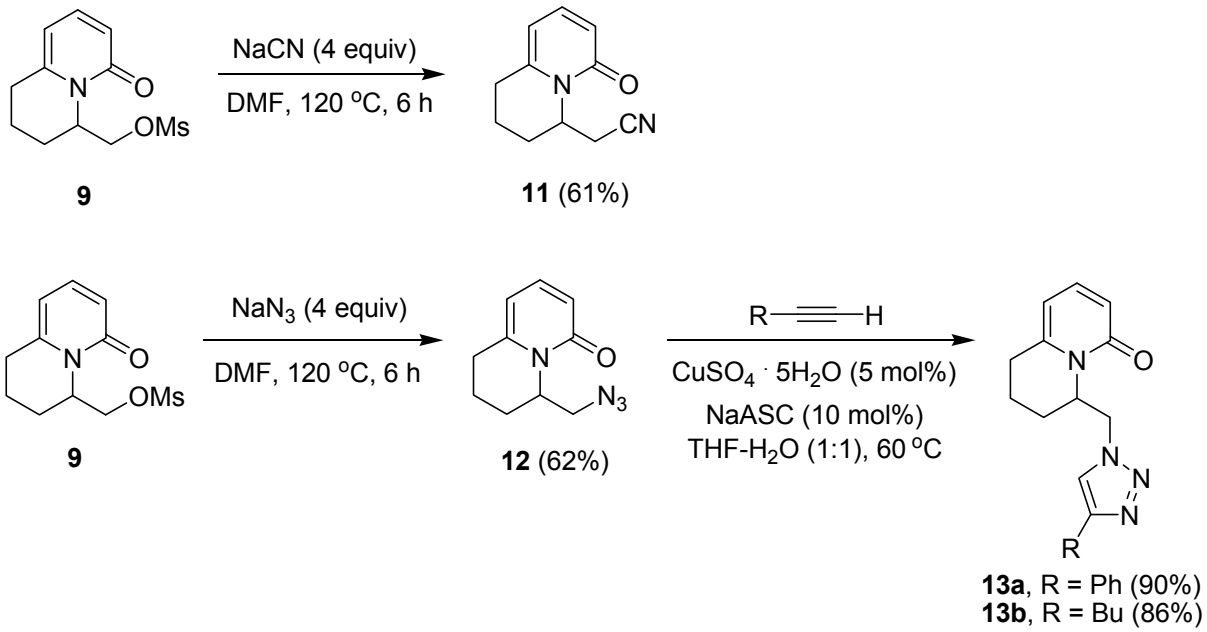
Scheme 5. Plausible mechanism for the formation of products **7** and **8** from compounds **6b**

Treatment of compound **6b** with methanesulfonyl chloride (MsCl) in the presence of Et_3N in CH_2Cl_2 gave the corresponding mesylate **9** in good yield (Scheme 6). Further reaction of compound **9** with NaH in THF at 80 °C gave the elimination product **10** with formation of the exocyclic double bond.



Scheme 6. Preparation of compound **10** from compound **6b**

We have also carried out some synthetic transformations of compound **9** (Scheme 7). Reaction of mesylate **9** with sodium cyanide in DMF at 120 °C afforded the substitution product **11**. Similarly, treatment of mesylate **9** with sodium azide provided the product **12**. Compound **12** could further undergo the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction[22] with phenylacetylene and 1-hexyne in the presence of cupric sulfate and sodium ascorbate (NaASC) to give the triazoles **13a** and **13b**, respectively. The regiochemistry of compound **13a** was established by the HMBC technique (Figure 3). Many triazoles have been made by the click chemistry,[23] and have shown interesting biological activities.[24]



Scheme 7. Synthetic transformations of compound **9**

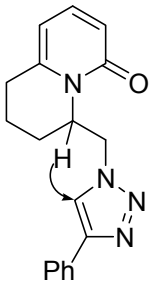


Figure 3. HMBC correlations of compound **13a**

CONCLUSION

In summary, we have developed a new method for synthesizing all three classes (including the [6,5], [6,6], and [6,7] ring systems) of 2-pyrido-fused bicyclic compounds **6** from the epoxy sulfones **5**, which are readily obtained from the aza-Diels–Alder reaction of 3-phenylthio-3-sulfolenes **1** with *p*-toluenesulfonyl isocyanate (PTSI). We have also studied some useful synthetic transformations of compound **6b**.

EXPERIMENTAL

Melting points were determined with a SMP3 melting apparatus. Infrared spectra (ATR) were recorded with a Perkin Elmer 100 series FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were mostly 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 mass spectrometer Finnigan/Thermo Quest MAT 95XL. Flash column chromatographic purifications were performed using Merck 60 H silica gel.

6-(Hex-5-enyl)-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (4c)

To a refluxing solution of compound **3c** (250 mg, 0.57 mmol) in degassed toluene (10 cm^3) was added slowly a solution of Bu_3SnH (0.33 cm^3, 1.23 mmol) and AIBN (56 mg, 0.34 mmol) in toluene (20 cm^3) over a period of 2 h. The solvent was then evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 1) containing 5% Et_3N as eluent to give **4c** (98 mg, 60%) as a white solid; mp 150.1−152.4 °C; ν_{max} (film/cm^{-1}) 3194, 3076, 2937, 1648, 1588, 1463, 1442, 1400, 1328, 1163, 1085, 1025, 911, 854, 750, 691; δ_H (300 MHz; $CDCl_3$) 7.52−7.40 (5H, m), 5.85−5.71 (1H, m), 5.68 (1H, br s), 5.25 (1H, s), 5.03−4.95 (2H, m), 3.65−3.55 (1H, m), 2.51−2.31 (2H, m), 2.10−2.03 (2H, m), 1.66−1.52 (2H, m), 1.50−1.40 (4H, m); δ_C (75 MHz; $CDCl_3$) 165.9, 155.2, 138.4, 135.5, 130.1, 129.9, 128.2, 114.9, 114.1, 51.0, 34.8, 34.7, 33.6, 28.6, 24.8. HRMS (EI) Found: M^+, 287.1339. $C_{17}H_{21}NOS$ requires 287.1344.

6-(3,4-Epoxybutyl)-4-(phenylsulfonyl)-5,6-dihydropyridin-2(1*H*)-one (5a)

To a solution of compound **4a** (41 mg, 0.16 mmol) in CH_2Cl_2 (2 cm^3) at 0 °C was added in portions of *m*-CPBA (70% in H_2O, 220.2 mg, 0.96 mmol). The mixture was stirred at room temperature for 18 h, diluted with CH_2Cl_2 (30 cm^3), and then sequentially washed with saturated sodium thiosulfate solution (15 cm^3) and saturated sodium bicarbonate solution (15 cm^3). The organic layer was dried ($MgSO_4$), evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 2) containing 5% Et_3N as eluent to give **5a** (38.8 mg, 79%) as a white solid; mp 95.8−96.7 °C. The ^1H and ^{13}C NMR of compound **5a** indicates that it is a 1 : 1 mixture of diastereomers. ν_{max} (film/cm^{-1}) 3241, 3064, 2930, 2858, 1671, 1623, 1554, 1447, 1330, 1161, 1086, 998, 964, 802, 730, 689; δ_H (300 MHz; $CDCl_3$) 7.95 (2H, d, J = 7.2 Hz), 7.72 (1H, d, J = 7.2 Hz), 7.61 (2H, d, J = 7.2 Hz), 7.44 (0.5 H, br s), 7.29 (0.5 H, br s), 6.63 (1H, d, J = 0.9 Hz), 3.72−3.65 (1H, m), 2.86 (1H, dt, J = 6.6, 3.3 Hz), 2.76−2.63 (2H, m), 2.47−2.45 (1H, m), 2.34−2.23 (1H, m), 1.81−1.78 (3H, m), 1.44−1.28 (1H, m); δ_C (75 MHz; $CDCl_3$) 164.2, 164.0, 150.6, 150.5, 137.0 (2×), 134.5 (2×), 129.6 (2×), 128.5 (2×), 127.3 (2×), 51.6, 51.4, 50.4, 50.2, 47.0, 46.8, 31.1, 30.9, 28.0, 27.7, 27.5 (2×). HRMS (ESI) Found: M^+, 307.0867. $C_{15}H_{17}NO_4S$ requires 307.0878.

6-(4,5-Epoxypentyl)-4-(phenylsulfonyl)-5,6-dihydropyridin-2(1*H*)-one (5b)

A similar procedure as for compound **5a** was used to give **5b** (73 mg, 84%) as a white solid; mp 111.0−111.9 °C; ν_{max} (film/cm^{-1}) 3310, 3066, 2927, 1730, 1677, 1621, 1447, 1311, 1154, 1017, 998, 810, 757, 688; δ_H (300 MHz; $CDCl_3$) 7.92−7.90 (2H, m), 7.74−7.69 (1H, m), 7.63−7.58 (2H, m), 6.62 (1H, s), 6.11 (1H, br s), 3.65−3.63 (1H, m), 2.89−2.77 (1H, m), 2.77−2.66 (2H, m), 2.45 (1H, dd, J = 4.8, 2.7 Hz), 2.33−2.28 (1H, m), 1.68−1.51 (6H, m); δ_C (75 MHz; $CDCl_3$) 167.4, 137.7, 136.0, 134.2, 133.4, 129.6, 128.4, 53.8, 51.8, 46.9, 35.7, 31.9, 29.0, 21.2. HRMS (FAB) Found: M^+, 321.1037. $C_{16}H_{19}NO_4S$ requires 321.1035.

6-(5,6-Epoxyhexyl)-4-(phenylsulfonyl)-5,6-dihydropyridin-2(1*H*)-one (5c)

A similar procedure as for compound **5a** was used to give **5c** (57 mg, 81%) as a white solid; mp 121.3−123.0 °C; ν_{max} (film/cm^{-1}) 3296, 2928, 1677, 1621, 1447, 1310, 1154, 1085, 729, 688; δ_H (300 MHz; $CDCl_3$) 7.92−7.89 (2H, m), 7.71−7.69 (1H, m), 7.63−7.58 (2H, m), 6.73 (1H, br d, J = 7.5 Hz), 6.62 (1H, s), 3.63−3.59 (1H, m), 2.89−2.87 (1H, m), 2.77−2.64 (2H, m), 2.47−2.44 (1H, m), 2.25 (1H, dd, J = 17.1, 9.9 Hz), 1.61−1.28 (8H, m); δ_C (75 MHz; $CDCl_3$) 164.1, 151.0, 137.1, 134.6, 129.7, 128.7, 127.4, 52.1, 50.9, 47.0, 34.6, 32.1, 27.7, 25.8, 24.9. HRMS (FAB) Found: M^+, 335.1194. $C_{17}H_{21}NO_4S$

requires 335.1191.

3-(Hydroxymethyl)-2,3-dihydroindolizin-5(1*H*)-one (6a)
To a solution of compound **5a** (60 mg, 0.20 mmol) in THF (10 cm^3) at room temperature under N_2 was added *t*-BuOK (22.4 mg, 0.40 mmol) in one portion. After refluxing for 3 h, the solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 1) as eluent to give **6a** (19.0 mg, 58%) as a white solid; mp 109.4−110.8 °C; ν_{max} (film/cm^{-1}) 3332, 2961, 2926, 2854, 1650, 1557, 1459, 1438, 1311, 1260, 1158, 1139, 1086, 797; δ_H (300 MHz; $CDCl_3$) 7.35 (1H, dd, *J* = 9.0, 6.9 Hz), 6.46 (1H, d, *J* = 9.0 Hz), 6.18 (1H, d, *J* = 6.9 Hz), 5.57 (1H, br s), 4.87−4.81 (1H, m), 3.89−3.86 (2H, m), 3.16−2.95 (2H, m), 2.39−2.29 (1H, m), 1.95−1.83 (1H, m); δ_C (125 MHz; $CDCl_3$) 162.9, 152.4, 142.4, 116.3, 105.8, 66.7, 64.9, 30.8, 24.5. HRMS (ESI) Found: M^+, 165.0780. $C_9H_{11}NO_2$ requires 165.0790.

4-(Hydroxymethyl)-3,4-dihydro-1*H*-quinolizin-6(2*H*)-one (6b)
A similar procedure as for compound **6a** was used to give **6b** (47 mg, 67%) as a white solid; mp 116.4−118.2 °C; ν_{max} (film/cm^{-1}) 3329, 2928, 2857, 1649, 1615, 1552, 1450, 1369, 1261, 1160, 1143, 1064, 797; δ_H (300 MHz; $CDCl_3$) 7.21 (1H, dd, *J* = 9.0, 6.9 Hz), 6.46 (1H, dd, *J* = 9.0, 0.9 Hz), 6.02 (1H, d, *J* = 6.9 Hz), 4.66 (1H, d, *J* = 13.8 Hz), 4.31−4.13 (1H, m), 4.07 (1H, br s), 3.93−3.71 (1H, m), 2.84−2.69 (2H, m), 2.08−1.93 (2H, m), 1.88−1.78 (1H, m), 1.68−1.59 (1H, m); δ_C (75 MHz; $CDCl_3$) 164.2, 152.2, 139.5, 117.5, 106.0, 67.4, 49.2, 36.9, 34.1, 23.0. HRMS (FAB) Found: M^+, 179.0949. $C_{10}H_{13}NO_2$ requires 179.0946.

6-(Hydroxymethyl)-7,8,9,10-tetrahydropyrido[1,2-*a*]azepin-4(6*H*)-one (6c)
A similar procedure as for compound **6a** was used to give **6c** (50 mg, 53%) as a white solid; mp 122.8−124.0 °C; ν_{max} (film/cm^{-1}) 3331, 2951, 2853, 1651, 1625, 1552, 1450, 1330, 1262, 1161, 1140, 1069, 799; δ_H (300 MHz; $CDCl_3$) 7.32 (1H, dd, *J* = 9.0, 6.9 Hz), 6.53 (1H, d, *J* = 9.0 Hz), 6.14 (1H, d, *J* = 6.9 Hz), 5.47 (1H, br s), 5.01−4.94 (1H, m), 4.31−4.01 (2H, m), 2.87−2.78 (1H, m), 2.74−2.64 (1H, m), 2.14−1.73 (3H, m), 1.60−1.48 (1H, m), 1.29−1.16 (2H, m); δ_C (75 MHz; $CDCl_3$) 165.9, 152.1, 140.1, 117.6, 107.6, 72.9, 48.6, 33.9, 32.7, 32.1, 29.8. HRMS (EI) Found: M^+, 193.1103. $C_{11}H_{15}NO_2$ requires 193.1103.

***cis*-4-(Hydroxymethyl)-3,4,7,8,9,9a-hexahydro-1*H*-quinolizin-6(2*H*)-one (7) and *cis*-7-Hydroxy-1,2,3,7,8,9,10,10a-octahydropyrido[1,2-*a*]azepin-4(6*H*)-one (8)**
To a solution of compound **6b** (60 mg, 0.34 mmol) in methanol (2 cm^3) in a pressure bottle was added Pd/C (2 mg, 0.02 mmol). Hydrogen gas was then filled to 70 psi, and the reaction was carried out at room temperature for 24 h. The reaction mixture was diluted with EtOAc, and was filtered through Celite. The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 2) as eluent to give compound **7** (26 mg, 44%) and compound **8** (29 mg, 47%). Compound **7**: a colorless liquid; ν_{max} (neat/cm^{-1}) 3404, 2936, 1622, 1614, 1416, 1338, 1284, 1160, 1055, 636; δ_H (300 MHz; $CDCl_3$) 4.53 (1H, d, *J* = 5.1 Hz), 4.47 (1H, dd, *J* = 14.7, 2.4 Hz), 4.03 (1H, br s), 3.56−3.48 (1H, m), 2.94 (1H, dd, *J* = 14.7, 3.0 Hz), 2.44−2.40 (2H, m), 1.95−1.54 (9H, m), 1.45−1.36 (1H, m); δ_C (75 MHz; $CDCl_3$) 173.6, 70.7, 59.5, 53.7, 36.5, 36.2, 31.6, 29.3, 19.4, 18.5. HRMS (FAB) Found: M^+, 183.1262. $C_{10}H_{17}NO_2$ requires 183.1259. Compound **8**: a white solid; mp 132.8−134.0 °C; ν_{max} (film/cm^{-1}) 3372, 2936, 1616, 1472, 1343, 1055; δ_H (300 MHz; $CDCl_3$) 4.27 (1H, dd, *J* = 13.0, 3.9 Hz), 3.92−3.86 (1H, br s), 3.66−3.59 (1H, m), 3.33−3.26 (1H, m), 2.68 (1H, dd, 13.0, 10.2 Hz), 2.44−2.21 (2H, m), 2.04−1.97 (1H, m), 1.91−1.42 (9H, m); δ_C (75 MHz; $CDCl_3$) 170.9, 68.5, 57.9, 51.6, 36.9, 34.9, 32.0, 29.9, 19.3, 18.3. HRMS (FAB) Found: M^+, 183.1259. $C_{10}H_{17}NO_2$ requires 183.1259.

4-(Methanesulfonyloxy)-3,4-dihydro-1*H*-quinolizin-6(2*H*)-one (9)
To a solution of compound **7** (21.5 mg, 0.12 mmol) in CH_2Cl_2 (1 cm^3) in an ice bath was added Et_3N (59 μL, 0.42 mmol). Methanesulfonyl chloride (32 μL, 0.42 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for 18 h. Sat. aq $NaHCO_3$ (10 cm^3) was added slowly, and the mixture was extracted with CH_2Cl_2 (2 × 10 cm^3), dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 3) containing 5% Et_3N as eluent to give **9** (27.0 mg, 88%) as a white solid; mp 112.4−113.8 °C; ν_{max} (film/cm^{-1}) 3015, 2936, 2864, 1661, 1583, 1554, 1467, 1429, 1350, 1241, 1173, 1085, 1070, 963, 909, 798, 692; δ_H (300 MHz; $CDCl_3$) 7.23 (1H, dd, *J* = 9.0, 6.9 Hz), 6.44 (1H, d, *J* = 9.0 Hz), 6.01 (1H, d, *J* = 6.9 Hz), 4.74−4.70 (1H, m), 4.63−4.50 (2H, m), 3.19 (3H, s), 2.87−2.72 (2H, m), 2.19−2.00 (3H, m), 1.99−1.96 (1H, m); δ_C (75 MHz; $CDCl_3$) 163.4, 150.9, 139.7, 117.9, 105.8, 76.7, 45.7, 38.5, 35.9, 33.6, 22.4. HRMS (FAB) Found: M^+, 257.0726. $C_{11}H_{15}NO_4S$ requires 257.0722.

4-Methylene-3,4-dihydro-1*H*-quinolizin-6(2*H*)-one (10)
A solution of compound **9** (50 mg, 0.19 mmol) in THF (1.5 cm^3) and NaH (28 mg, 0.57 mmol) was heated in a sealed tube at 80 °C for 3 h. After cooling to room temperature, the solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 4) as eluent to give **10** (20 mg, 65%) as a white solid; mp 96.4−97.8 °C; ν_{max} (film/cm^{-1}) 3052, 2930, 2861,1663, 1581, 1548, 1447, 1427, 1374, 1209, 1142, 1085, 1058, 969, 850, 798, 755; δ_H (300 MHz; $CDCl_3$) 7.25 (1H, dd, *J* = 9.3, 8.4 Hz), 6.92 (1H, d, *J* = 8.4 Hz), 6.48 (1H, d, *J* = 9.3 Hz), 6.06 (1H, d, *J* = 6.6 Hz), 6.02−5.94 (1H, m), 2.65 (2H, t, *J* = 6.5 Hz), 2.20−2.04 (4H, m); δ_C (75 MHz; $CDCl_3$) 163.1, 150.0, 139.6, 127.3, 123.8, 118.1, 105.9, 31.9, 30.0, 23.6. HRMS (EI) Found: M^+, 161.0841. $C_{10}H_{11}NO$ requires 161.0841.

4-(Cyanomethyl)-3,4-dihydro-1*H*-quinolizin-6(2*H*)-one (11)
A solution of compound **9** (90 mg, 0.35 mmol) and NaCN (69 mg, 1.4 mmol) in DMF (1.5 cm^3) was heated at 120 °C for 6 h. After cooling to room temperature, CH_2Cl_2 (35 cm^3) was added, and the reaction mixture was washed sequentially with water (10 cm^3) and brine (10 cm^3). The organic solution was dried ($MgSO_4$), the solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 3) containing 5% Et_3N as eluent to give **11** (40 mg, 61%) as a white solid; mp 110.8−111.3 °C; ν_{max} (film/cm^{-1}) 3434, 2917, 2247, 1647, 1618, 1544, 1462, 1261, 1163, 1094, 810, 739; δ_H (300 MHz; $CDCl_3$) 7.42 (1H, dd, *J* = 9.3, 6.9 Hz), 6.44 (1H, d, *J* = 9.3 Hz), 6.11 (1H, d, *J* = 6.9 Hz), 3.10−3.05 (1H, m), 2.78 (2H, d, *J* = 6.6 Hz), 2.71−2.65 (2H, m), 2.07−1.81 (4H, m); δ_C (75 MHz; $CDCl_3$) δ 163.9, 149.9, 139.5, 123.7, 118.2, 105.2, 55.7, 38.6, 31.4, 30.1, 23.8. HRMS (FAB) Found: M^+, 188.0945. $C_{11}H_{12}N_2O$ requires 188.0950.

4-(Azidomethyl)-3,4-dihydro-1*H*-quinolizin-6(2*H*)-one (12)
A solution of compound **9** (90 mg, 0.35 mmol) and NaN_3 (105 mg, 1.4 mmol) in DMF (1.5 cm^3) was heated at 120 °C for 6 h. After cooling to room temperature, CH_2Cl_2 (35 cm^3) was added, and the reaction mixture was washed sequentially with water (10 cm^3) and brine (10 cm^3). The organic solution was dried ($MgSO_4$), the solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 3) containing 5% Et_3N as eluent to give **12** (44 mg, 62%) as a white solid; mp 99.8−101.3 °C; ν_{max} (film/cm^{-1}) 2922, 2851, 2102, 1661, 1586, 1552, 1466, 1428, 1325, 1255, 1142, 1104, 969, 795; δ_H (300 MHz; $CDCl_3$) 7.22 (1H, dd, *J* = 9.0, 6.6 Hz), 6.47 (1H, d, *J* = 9.0 Hz), 5.97 (1H, d, *J* = 6.6 Hz), 4.64 (1H, d, *J* = 13.8 Hz), 4.31 (1H, dd, *J* = 13.8, 8.7 Hz), 3.71 (1H, d, *J* = 6.6 Hz), 2.84−2.70 (2H, m), 1.85−2.10 (3H, m), 1.73 (1H, dd, *J* = 8.1, 5.1 Hz); δ_C (75 MHz; $CDCl_3$) 163.5, 151.1, 139.3, 118.1, 105.6, 58.2, 45.6, 34.2, 33.9, 23.1. HRMS (ESI) Found: M^+, 204.0997. $C_{10}H_{12}N_4O$ requires 204.1011.

4-((4-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-3,4-dihydro-1*H*-quinolizin-6(2*H*)-one (13a)
To a solution of compound **12** (8 mg, 0.04 mmol) in THF–H_2O (1:1, 2 cm^3) were added sodium ascorbate (NaASC, 1.6 mg, 0.008 mmol) and $CuSO_4 \cdot 5H_2O$ (1.0 mg, 0.004 mmol). Phenylacetylene (17.5 μL, 0.16 mmol) was then added via a syringe. The mixture was heated at 60 °C for 1 h. The solvent was evaporated under vacuum, and CH_2Cl_2 (20 cm^3) was added. The organic solution was dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by recrystallization from CH_2Cl_2 to give **13a** (11 mg, 90%) as a white solid; mp 142.3－142.8 °C; ν_{max} (film/cm^{-1}) 3129, 3088, 2942, 2862, 1658, 1553, 1461, 1427, 1379, 1298, 1234, 1140, 1080, 952, 794, 767, 696; δ_H (300 MHz; $CDCl_3$) 7.96 (1H, s), 7.85－7.82 (2H, m), 7.49－7.40 (2H, m), 7.34－7.27 (1H, m), 7.24 (1H, dd, *J* = 9.0, 6.6 Hz), 6.44 (1H, d, *J* = 9.0 Hz), 6.04 (1H, d, *J* = 6.6 Hz), 5.29 (1H, *J* = 14.1 Hz), 4.56－4.48 (1H, m), 4.34 (1H, dd, *J* = 14.1, 9.1 Hz), 3.04－2.82 (2H, m), 2.64－2.50 (1H, m), 2.43－2.39 (1H, m), 2.34－2.25 (1H, m), 1.79－1.67 (1H, m); δ_C (75 MHz; $CDCl_3$) 163.4, 151.1, 147.8, 139.7, 130.5, 128.8 ,128.3, 125.8, 119.6, 118.2, 105.8, 58.8, 47.2, 35.0, 33.6, 24.4. HRMS (ESI) Found: M^+, 306.1475. $C_{18}H_{18}N_4O$ requires 306.1481.

4-((4-Butyl-1*H*-1,2,3-triazol-1-yl)methyl)-3,4-dihydro-1*H*-quinolizin-6(2*H*)-one (13b)
To a solution of compound **12** (10 mg, 0.049 mmol) in THF–H_2O (1:1, 2 cm^3) were added sodium ascorbate (NaASC, 1.9 mg, 0.098 mmol) and $CuSO_4 \cdot 5H_2O$ (1.2 mg, 0.0049 mmol). 1-Hexyne (22.5 μL, 0.196 mmol) was then added via a syringe. The mixture was heated at 60 °C for 1 h. The solvent was evaporated under vacuum, and CH_2Cl_2 (20 cm^3) was added. The organic solution was dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by recrystallization from CH_2Cl_2 to give **13b** (12 mg, 86%) as a white solid; mp 133.3－134.8 °C; ν_{max} (film/cm^{-1}) 3130, 2929, 2858, 1661, 1581, 1552, 1466, 1428, 1380, 1260, 1140, 1044, 953, 796, 731; δ_H (300 MHz; $CDCl_3$) 7.42 (1H, s), 7.23 (1H, dd, *J* = 9.3, 6.6 Hz), 6.47 (1H, d, *J* = 9.3 Hz), 6.01 (1H, d, *J* = 6.6 Hz), 5.27 (1H, d, *J* = 13.8 Hz), 4.42－4.38 (1H, m), 4.25 (1H, dd, *J* = 13.8, 9.3 Hz), 2.98－2.89 (1H, m), 2.89－2.87 (1H, m), 2.72 (2H, t, *J* = 7.8 Hz), 2.56－2.51 (1H, m), 2.38－2.24 (2H, m), 1.71－1.66 (3H, m), 1.43－1.35 (2H, m), 0.94 (3H, t, *J* = 7.2 Hz); δ_C (75 MHz; $CDCl_3$) 163.4, 151.1, 146.8, 139.7, 120.9, 118.2, 105.9, 58.8, 47.2, 34.9, 33.7, 31.5, 29.8, 29.2, 25.2, 24.3. HRMS (EI) Found: M^+, 286.1792. $C_{16}H_{22}N_4O$ requires 286.1794.

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