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SYNTHESIS OF THE PRECURSORS OF PUMILIOTOXIN 251D AND AWAJANOMYCIN AND RELATED STUDIES

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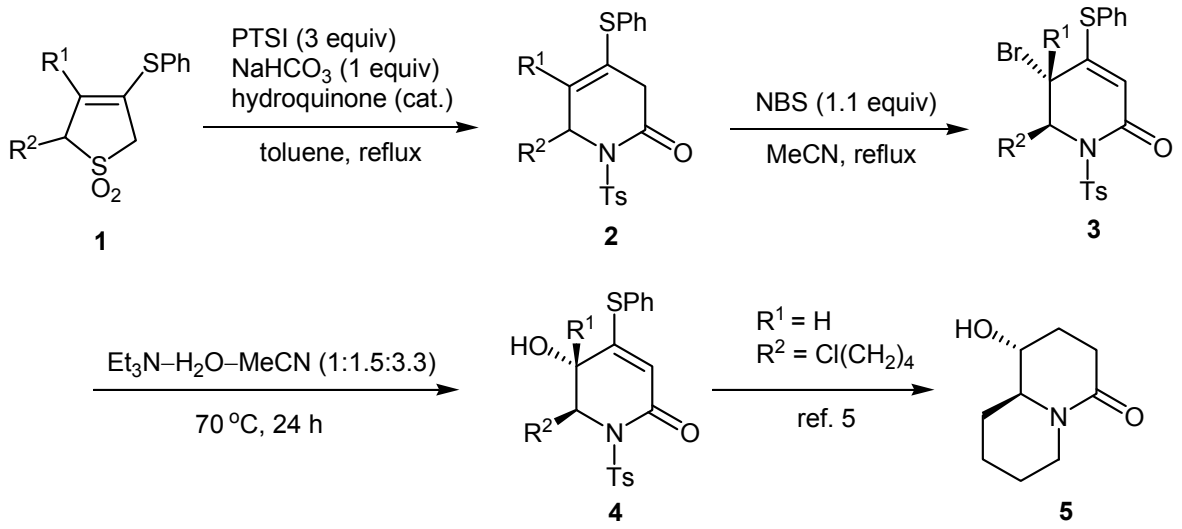
Abstract – The aza-Diels–Alder reaction of 3-phenylthio-3-sulfolenes with *p*-toluenesulfonyl isocyanate (PTSI) gave *trans*-5,6-dihydropyridinones, which upon treatment with NBS afforded the trans-allylic bromides. Hydrolysis of the bromides provided the allylic alcohols with retention of configuration. Further synthetic transformations led to the formal synthesis of pumiliotoxin 251D and awajanomycin. Some related syntheses 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 *N*-bromosuccinimide (NBS) to afford the *trans*-allylic bromides **3** (Scheme 1).[4] The allylic bromides were hydrolyzed to give the alcohols **4** with retention of configuration. One of these alcohols was further converted to 1-hydroxyquinolizidin-4-one (**5**), constituting a formal synthesis of (±)-epiquinamide and (±)-homopumiliotoxin 223G.[5]

(+)-Pumiliotoxin 251D was isolated from the frogs (*Dendrobates pumilio*) in South America,[6] and some total syntheses[7,8] and many formal syntheses[9-16] have been reported. (+)-Awajanomycin was isolated more recently from the marine-derived fungus (*Acremonium sp.* AWA16-1),[17] also with some syntheses being reported.[18,19] Herein we report that compounds **3** can also be utilized to achieve a formal synthesis of (±)-pumiliotoxin 251D and (±)-awajanomycin (Figure 1).



Scheme 1. Synthesis of 1-hydroxyquinolizidin-4-one (**5**)

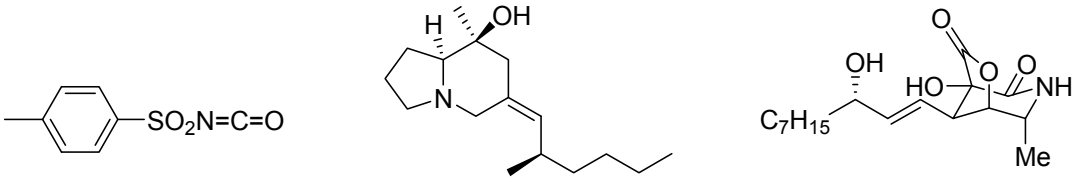
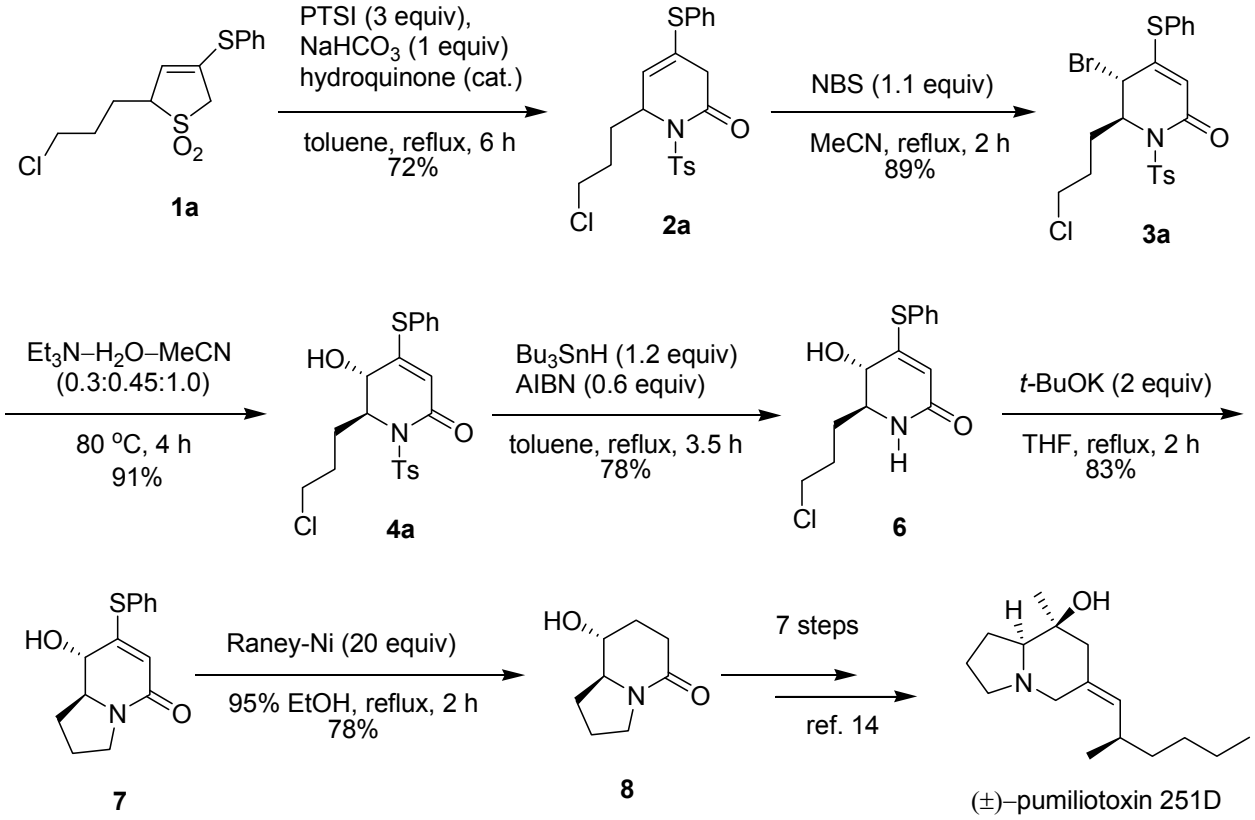


Figure 1

RESULTS AND DISCUSSION

Treatment of compound **1a**[3] with *p*-toluenesulfonyl isocyanate (PTSI) in refluxing toluene in the presence of hydroquinone (HQ) and $NaHCO_3$ afforded the cycloaddition product **2a**. The reaction of compound **2a** with *N*-bromosuccinimide (NBS) in refluxing acetonitrile provided the allyic bromide **3a** (Scheme 2). Subsequent reaction of bromide **3a** with triethylamine in aqueous acetonitrile at reflux gave the allylic alcohol **4a** in excellent yield. The tosyl group of compound **4a** was effectively cleaved by Bu_3SnH/AIBN[20] to give the amide **6**, which was converted to the indolizidine **7** by refluxing with *t*-BuOK in THF. The X-ray crystal structure of compound **7** (Figure 2)[21] shows that the hydroxyl group is *trans* to the five-membered ring. This also indirectly proves the *trans* relationship of the two side groups of compounds **3a**, **4a** and **6**. We propose that NBS approaches compound **2a** from the opposite side of the 3-chloropropyl group, resulting in the formation of the *trans*-product **3a**. Similar to what we proposed previously,[5] hydrolysis of compound **3a** proceeds through an S_N1 mechanism to generate an allylic carbocation, which is then attacked by water from the opposite side of the chloropropyl group to give the *trans*-product **4a**. Removal of the tosyl group of compound **4a** by tributyltin radical should not change the stereochemistry of the side groups so that the *trans* compound **6** would be obtained. Treatment of

compound **7** with Raney nickel in refluxing 95% EtOH cleaved the phenylthio group and also reduced the C=C double bond to give compound **8**, the spectral data of which are identical with the literature report.[8] Since compound **8** has also been converted to pumiliotoxin 251D,[14] we have thus achieved a formal synthesis of (±)-pumiliotoxin 251D.



Scheme 2. Formal synthesis of (±)-pumiliotoxin 251D

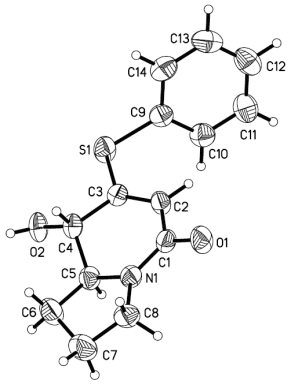
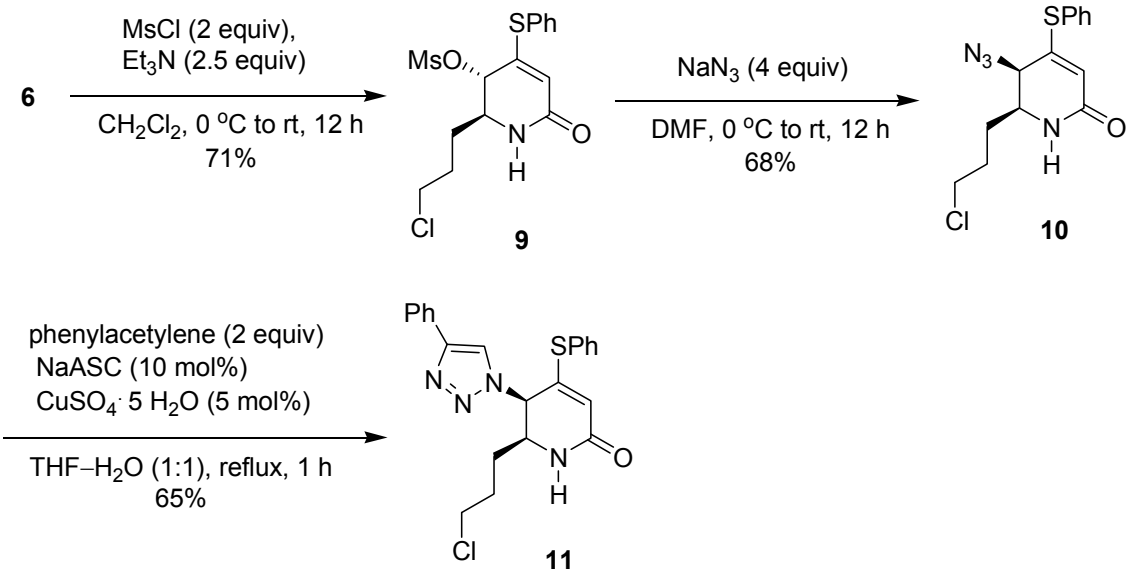


Figure 2. X-Ray crystal structure of compound **7**

Because some the piperidine derivatives we previously made have shown novel biological activities,[22] we have also carried out some synthetic transformations of compound **6** (Scheme 3). Treatment of compound

6 with mesyl chloride in the presence of Et_3N in CH_2Cl_2 gave the corresponding mesylate **9**, which was reacted with sodium azide in DMF to afford the azide **10**. The X-ray structure of compound **10** shows that the azido group is *cis* to the 3-chloropropyl group (Figure 3),[21] which indicates that the substitution reaction of compound **9** with the azide anion proceeds with inversion of configuration, probably through the S_N2 mechanism. As we have previously shown,[5] once the *N*-tosyl group is cleaved from the 5,6-dihyro-2-pyridones (such as compounds **6** and **9**), the two *trans* groups at C-5 and C-6 would occupy the diequatorial positions. Thus, the azide anion can undergo the back-side attack at the C-5 of compound **9** from the axial direction without suffering steric hindrance of the equatorial C-6 substituent. Compound **10** could further undergo the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction[23] with phenylacetylene in the presence of cupric sulfate and sodium ascorbate (NaASC) to give the triazole **11**. The regiochemistry of compound **11** was established by the HMBC technique (Figure 4). Many triazoles have been made by the click chemistry,[24] and have shown interesting biological activities.[25]



Scheme 3. Synthetic transformations of compound **6**

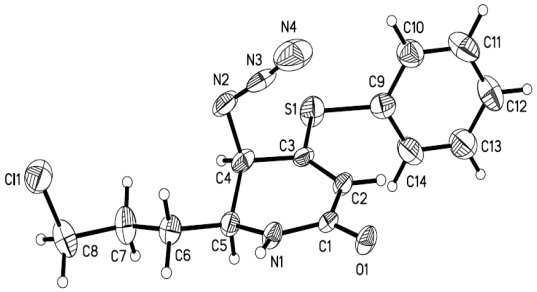
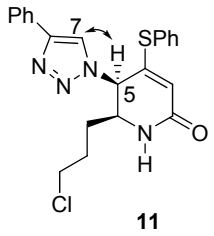


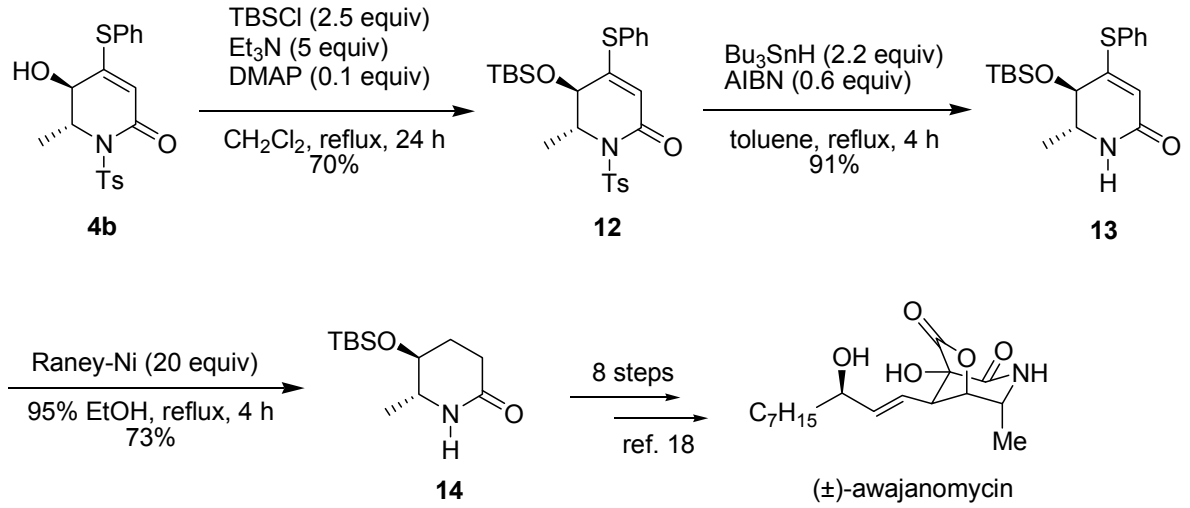
Figure 3. X-Ray crystal structure of compound **10**



11

Figure 4. HMBC correlations of compound **11**

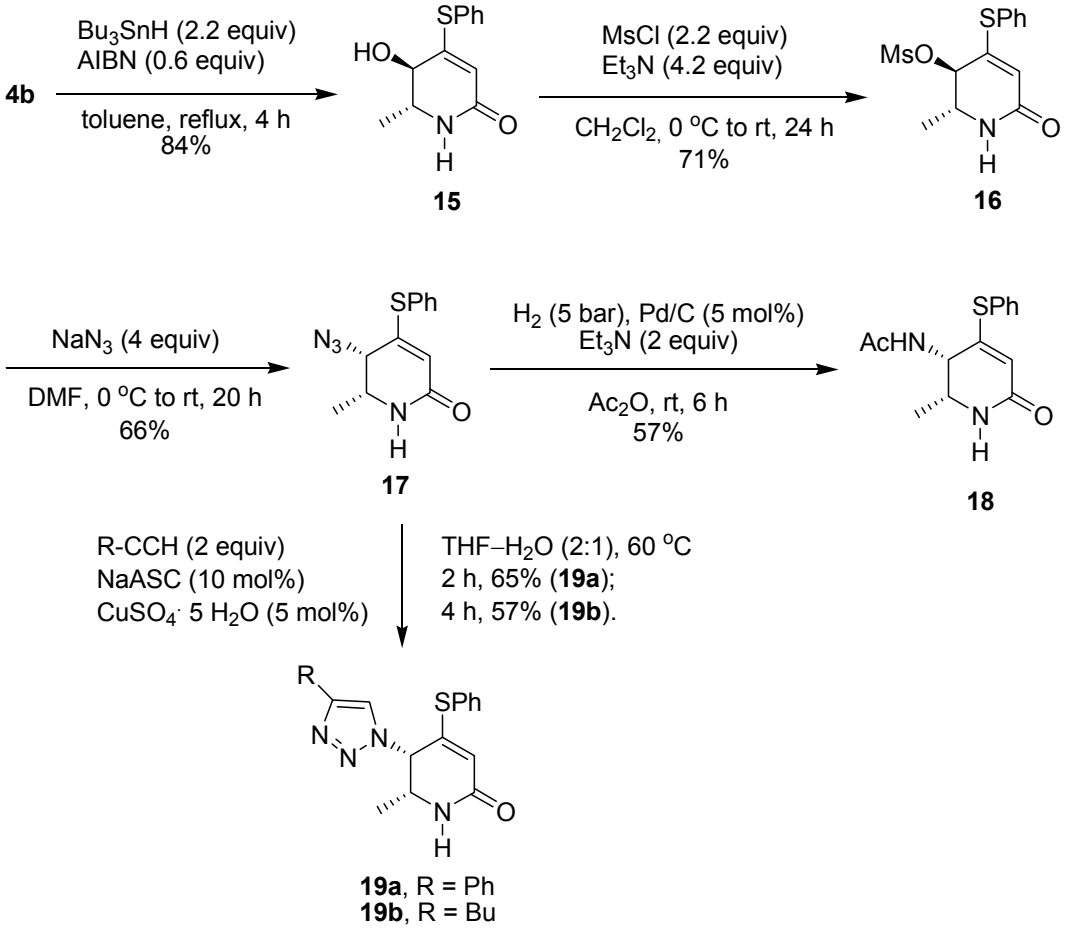
We previously reported the synthesis of allylic alcohol **4b** from the bromide **3b** (Scheme 1, R^1 = H, R^2 = Me),[5] and we have now used compound **4b** to achieve a formal synthesis of awajanomycin (Scheme 4). Treatment of compound **4b** with *t*-butyldimethylsilyl chloride (TBSCl) and Et_3N in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) gave the TBS-protected ether **12**. Detosylation by Bu_3SnH/AIBN[20] then afforded the amide **13** in excellent yield. Treatment of compound **13** with Raney nickel in refluxing 95% EtOH cleaved the phenylthio group and also reduced the C=C double bond to give compound **14**, which is identical with what has previously been converted to awajanomycin.[18] Thus we have achieved a formal synthesis of (±)-awajanomycin.



Scheme 4. Formal synthesis of (±)-awajanomycin

Because some of the piperidine derivatives we previously made have shown novel biological activities,[22] we have also carried out some synthetic transformations of compound **4b** (Scheme 5). The *N*-tosyl group of compound **4b** was removed by Bu_3SnH/AIBN[20] to give the secondary amide **15**; the presence of the hydroxyl group in compound **4b** did not affect the success of this reaction. The structure of compound **15** was established by X-ray crystallography (Figure 5),[21] which also shows that both the methyl and hydroxyl groups occupy the equatorial positions. The hydroxyl group of compound **15** was then converted in the usual way to the mesylate **16**, which was reacted with sodium azide in DMF at room

temperature to afford the azido product **17**. The structure of compound **17** was established by X-ray crystallography (Figure 6).[21] It can be seen that the azido group is *cis* to the methyl group in compound **17**, which suggests that the azide anion undergoes an S_N2 reaction with the mesylate **16**. Attempted reduction of the azido group of compound **17** by thioacetic acid to the acetamido group at various reaction temperatures only recovered the starting material. However, hydrogenation of compound **17** at high pressure in the presence of acetic anhydride and Et_3N gave the acetamide **18** in fair yield. Compound **17** could also undergo the CuAAC reaction with phenylacetylene and 1-hexyne to give the triazoles **19a** and **19b**, respectively. The regiochemistry of compounds **19** was established by the HMBC technique.



Scheme 5. Synthetic transformations of compound **4b**

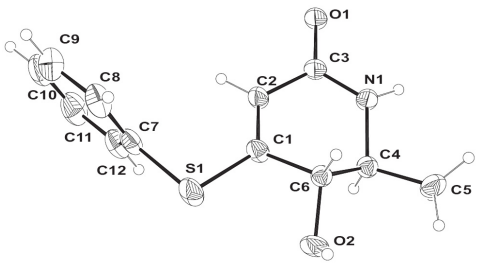


Figure 5. X-Ray crystal structure of compound **15**

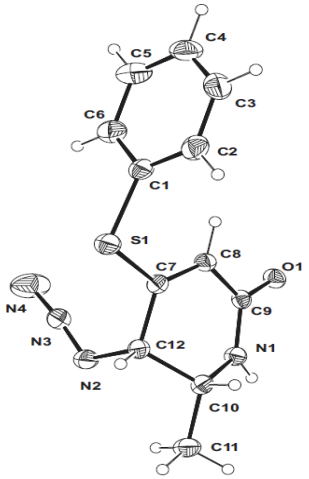


Figure 6. X-Ray crystal structure of compound **17**

CONCLUSION

In summary, we have used the aza-Diels–Alder reaction of 3-phenylthio-3-sulfolenes **1** with *p*-toluenesulfonyl isocyanate (PTSI) to give *trans*-5,6-dihydropyridinones **2**, which upon treatment with NBS afforded the *trans*-allylic bromides **3**. Hydrolysis of the bromides provided the allylic alcohols **4** with retention of configuration. Further synthetic transformations led to compounds **8** and **14**, which constitute a formal synthesis of (±)-pumiliotoxin 251D and (±)-awajanomycin, respectively. Some useful synthetic transformations have been achieved.

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

A mixture of compound **1a**[3] (1000 mg, 3.31 mmol), $NaHCO_3$ (277.7 mg, 3.31 mmol), hydroquinone (36.4 mg, 0.33 mmol), and PTSI (1.52 cm^3, 9.93 mmol) in toluene (15 cm^3) was heated at reflux under N_2 for 6 h. After cooling in an ice bath, 5% aq NaOH (50 cm^3) was slowly added to decompose the excess PTSI. The mixture was then extracted with EtOAc (3 × 30 cm^3), the combined organic extracts dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 6) as eluent to give **2a** (1107 mg, 76%) as a white solid; mp 152.2–158.1 °C; ν_{max} (film/cm^{-1}) 3061, 2957, 1668, 1595, 1386, 1346, 1225, 1186, 1167, 1117, 1089, 1069, 1025, 957, 894, 849; δ_H (300 MHz; $CDCl_3$) 7.90 (2H, d, *J* = 8.4 Hz), 7.39–7.26 (7H, m), 5.84 (1H, dd, *J* = 5.7, 2.7 Hz), 5.08 (1H, d, *J* = 5.1 Hz), 3.52 (2H, t, *J* = 12.6 Hz), 3.17 (1H, dt, *J* = 21.3, 2.4 Hz), 2.92 (1H, d, *J* = 21.3 Hz), 2.39 (3H, t, *J* = 18.0 Hz), 2.08–1.93 (2H, m), 1.81–1.69 (2H, m). δ_C (75 MHz; $CDCl_3$) 167.0, 145.1,

135.9, 133.2, 130.5, 129.6 (2 ×), 129.3, 129.1, 128.8, 123.6, 57.6, 44.4, 38.2, 34.3, 27.5, 21.7. HRMS (FAB) Found: M^+, 435.0731. $C_{21}H_{22}ClNO_3S_2$ requires 435.0730.

***trans*-5-Bromo-6-(3-chloropropyl)-4-(phenylthio)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (3a)**

A mixture of compound **2a** (1000 mg, 2.29 mmol) and NBS (450 mg, 2.52 mmol) in MeCN (15 cm^3) 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–hexane (1 : 6) as eluent to give **3a** (1049 mg, 89%) as a white solid; mp 138.1–139.2 °C; ν_{max} (film/cm^{-1}) 3061, 2959, 2925, 2863, 1674, 1593, 1441, 1387, 1351, 1307, 1293, 1234, 1168, 1134, 1087, 1023, 942, 887, 857; δ_H (300 MHz; $CDCl_3$) 8.03 (2H, d, J = 8.2 Hz), 7.50–7.39 (5H, m), 7.28 (2H, d, J = 8.2 Hz), 5.29 (1H, d, J = 2.4 Hz), 4.95 (1H, td, J = 6.6, 2.8 Hz), 4.54–4.53 (1H, m), 3.71–3.64 (1H, m), 3.60–3.52 (1H, m), 2.41 (3H, s), 2.13–1.99 (4H, m); δ_C (75 MHz; $CDCl_3$) 158.8, 156.9, 145.1, 135.4, 135.2, 130.7, 130.1, 129.7, 128.9, 126.6, 115.9, 62.2, 44.4, 44.1, 31.6, 29.1, 21.6. HRMS (FAB) Found: M^+, 512.9828. $C_{21}H_{21}BrClNO_3S_2$ requires 512.9835.

***trans*-6-(3-Chloropropyl)-5-hydroxy-4-(phenylthio)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (4a)**

To a solution of compound **3a** (50 mg, 0.1 mmol) in MeCN (1 cm^3) was added Et_3N (0.3 cm^3) and H_2O (0.45 cm^3). The mixture was heated at 80 °C under N_2 for 4 h. After cooling, EtOAc (30 cm^3) was added. The mixture was washed with brine (2 × 30 cm^3), dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 3–1 : 2) as eluent to give **4a** (40 mg, 91%) as a white solid; mp 134.1–135.7 °C; ν_{max} (film/cm^{-1}) 3466, 2924, 2855, 1671, 1654, 1596, 1456, 1377, 1344, 1237, 1187, 1167, 1131, 1088, 932, 893; δ_H (300 MHz; $CDCl_3$) 7.94 (2H, d, J = 8.1 Hz), 7.48–7.38 (5H, m), 7.27 (2H, d, J = 8.1 Hz), 5.19 (1H, d, J = 0.6 Hz), 4.82 (1H, td, J = 7.1, 2.1 Hz), 4.14–4.11 (1H, m), 3.73–3.65 (1H, m), 3.62–3.54 (1H, m), 2.64 (1H, br s), 2.40 (3H, s), 2.09–1.97 (4H, m); δ_C (75 MHz; $CDCl_3$) 159.7, 158.1, 144.9, 136.0, 135.3, 130.8, 130.3, 129.3, 129.1, 126.8, 114.9, 68.7, 61.3, 44.7, 30.2, 29.1, 21.7. HRMS (FAB) Found: M^+, 451.0670. $C_{21}H_{22}ClNO_4S_2$ requires 451.0679.

***trans*-6-(3-Chloropropyl)-5-hydroxy-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (6)**

To a refluxing solution of compound **4a** (1000 mg, 2.22 mmol) in degassed toluene (22 cm^3) was added slowly a solution of Bu_3SnH (2.5 cm^3, 2.66 mmol) and AIBN (218.4 mg, 1.33 mmol) in tolune (40 cm^3) over a period of 3.5 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 and 5% CH_2Cl_2 as eluent to give **6** (513.7 mg, 78%) as a white solid; mp 130.3–131.5 °C; ν_{max} (film/cm^{-1}) 3343, 2942, 2854, 2333, 1712, 1660, 1457, 1377, 1261, 1167, 1090, 1020, 805; δ_H (300 MHz; $CDCl_3$) 7.54–7.44 (5H, m), 6.97 (1H, br s), 5.29 (1H, d, J = 1.2 Hz), 3.98 (2H, br s), 3.58–3.53 (3H, m), 1.90–1.61 (4H, m); δ_C (75 MHz; $CDCl_3$) 164.6, 157.3, 135.3, 130.1 (2 ×), 128.1, 115.0, 68.8, 57.2, 44.7, 30.5, 28.7. HRMS (FAB) Found: M^+, 297.0590. $C_{14}H_{16}ClNO_2S$ requires 297.0590.

***trans*-8-Hydroxy-7-(phenylthio)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (7)**

To a solution of compound **6** (100 mg, 0.34 mmol) in THF (20 cm^3) at room temperature under N_2 was added *t*-BuOK (77.9 mg, 0.68 mmol) in one portion. After refluxing for 2 h, EtOAc (20 cm^3) was added, and the mixture was filtered to remove the solid. The organic solution was dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 2–1 : 1) containing 5% Et_3N and 5% CH_2Cl_2 as eluent to give **7** (72.9 mg, 83%) as a yellow oil; ν_{max} (film/cm^{-1}) 3271, 3057, 1623, 1559, 1439, 1092, 1021, 817; δ_H (300 MHz; $CDCl_3$) 7.52–7.38 (5H, m), 5.13 (1H, d, J = 2.1 Hz), 4.46 (1H, d, J = 11.1 Hz), 3.70–3.58 (2H, m), 3.50–3.41 (1H, m), 2.72 (1H, br s), 2.44–2.30 (1H, m), 2.09–2.02 (1H, m), 1.91–1.85 (2H, m); δ_C (75 MHz; $CDCl_3$) 162.1, 159.1, 135.6, 130.1 (2 ×), 128.4, 115.4, 74.0, 62.4, 44.7, 31.9, 23.1. HRMS (EI) Found: M^+, 261.0833. $C_{14}H_{15}NO_2S$ requires 261.0823.

***trans*-8-Hydroxy-2,3,6,7,8,8a-hexahydroindolizin-5(1*H*)-one (8)**

A mixture of compound **7** (50 mg, 0.19 mmol) and W-2 Raney Ni (406.2 mg, 3.8 mmol) in 95% EtOH (3 cm^3) 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 cm^3), and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography using CH_2Cl_2–MeOH (10 : 1) as eluent to give **8** (23 mg, 78%) as a yellow oil. Its spectral data were identical with the literature values.[8]

***trans*-5-(Methanesulfonyloxy)-6-(3-chloropropyl)- 4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (9)**
To a solution of compound **6** (1.44 g, 5.99 mmol) in CH_2Cl_2 (3 cm^3) in an ice bath was added Et_3N (1.9 cm^3, 1.4 mmol). Methanesulfonyl chloride (0.5 cm^3, 0.73 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for 12 h. Sat. aq $NaHCO_3$ (20 cm^3) was added slowly, and the mixture was extracted with CH_2Cl_2 (3 × 20 cm^3), dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 2–1 : 1) containing 5% Et_3N as eluent to give **9** (179.3 mg, 71%) as a white solid; mp 141.0–142.0 °C; ν_{max} (film/cm^{-1}) 3216, 3058, 3024, 2957, 2930, 2871, 1667, 1594, 1469, 1442, 1416, 1359, 1277, 1176, 1144, 1107, 1023, 923, 837; δ_H (300 MHz; $CDCl_3$) 7.54–7.43 (5H, m), 6.82 (1H, br s), 5.48 (1H, d, J = 1.5 Hz), 4.97 (1H, d, J = 2.1 Hz), 3.88–3.81 (1H, m), 3.63–3.49 (2H, m), 3.22 (3H, s), 2.00–1.85 (4H, m); δ_C (75 MHz; $CDCl_3$) 162.7, 148.6, 135.4, 130.7, 130.4, 127.0, 119.6, 75.1, 55.7, 44.3, 39.3, 30.7, 28.6. HRMS (FAB) Found: M^+, 375.0369. $C_{15}H_{18}ClNO_4S_2$ requires 375.0366.

***cis*-5-Azido-6-(3-chloropropyl)-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (10)**
To a solution of compound **9** (100 mg, 0.27 mmol) in DMF (2 cm^3) in an ice bath was added NaN_3 (69.33 mg, 1.08 mmol) in one portion. The mixture was stirred at room temperature for 12 h. Brine (20 cm^3) was added, and the mixture was extracted with EtOAc (3 × 30 cm^3). The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 2) as eluent to give **10** (58.4 mg, 68%) as a white solid; mp 160.1–161.3 °C; ν_{max} (film/cm^{-1}) 3195, 3073, 2922, 2851, 2102, 1660, 1591, 1441, 1412, 1339, 1262, 1176, 1111, 1068, 1023, 924, 859; δ_H (300 MHz; $CDCl_3$) 7.56–7.47 (5H, m), 6.64 (1H, br s), 5.46 (1H, s), 3.71–3.66 (2H, m), 3.57 (2H, t, J = 11.1 Hz), 1.94–1.81 (4H, m); δ_C (75 MHz; $CDCl_3$) 164.7, 152.1, 135.6, 130.6, 130.3, 127.3, 117.1, 58.7, 54.3, 44.2, 28.2 (2 ×). HRMS (FAB) Found: M^+, 322.0657. $C_{14}H_{15}ClN_4OS$ requires 322.0655.

***cis*-6-(3-Chloropropyl)-5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (11)**
To a solution of compound **10** (30 mg, 0.09 mmol) in THF–H_2O (1:1, 2 cm^3) were added sodium ascorbate (NaASC, 1.8 mg, 0.01 mmol) and $CuSO_4 \cdot 5H_2O$ (1.2 mg, 0.0045 mmol). Phenylacetylene (17 cm^3, 0.18 mmol) was then added via a syringe. The mixture was heated at reflux 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–hexane to give **11** (25.7 mg, 65%) as a white solid; mp 203.1–204.2 °C; ν_{max} (film/cm^{-1}) 3081, 3037, 2928, 2304, 1650, 1596, 1457, 1415, 1352, 1265, 1226, 1085, 1024, 978, 857; δ_H (300 MHz; $CDCl_3$) 7.86 (2H, d, J = 7.2 Hz), 7.76 (1H, s), 7.49–7.27 (8H, m), 5.87 (1H, br s), 5.65 (1H, d, J = 1.5 Hz), 5.39–5.37 (1H, m), 4.07 (1H, td, J = 7.1, 3.9 Hz), 3.59–3.41 (2H, m), 2.17–2.04 (1H, m), 1.90–1.79 (1H, m), 1.44–1.35 (2H, m); δ_C (75 MHz; $CDCl_3$) 164.6, 153.2, 148.5, 135.5, 130.9, 130.4, 130.1, 129.0, 128.6, 126.7, 125.9, 118.5, 118.2, 58.7, 54.2, 43.9, 28.0 (2 ×). HRMS (ESI) Found: M^+, 424.1125. $C_{22}H_{21}ClN_4OS$ requires 424.1125.

***trans*-5-(*tert*-Butyldimethylsilyloxy)-6-methyl-4-(phenylthio)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (12)**
To a solution of compound **4b** (90 mg, 0.23 mmol) and DMAP (2.8 mg, 0.02 mmol) in CH_2Cl_2 (3 cm^3) were added sequentially Et_3N (0.18 cm^3, 1.16 mmol) and TBSCl (97 mg, 0.58 mmol). The reaction mixture was heated at 60 °C for 24 h, and sat. aq $NaHCO_3$ (10 cm^3) was added. The mixture was

extracted with CH_2Cl_2 (2 × 30 cm^3), the combined organic solutions dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 3) as eluent to give **12** (81.4 mg, 70%) as a white solid; mp154.7–156.4 °C; ν_{max} (film/cm^{-1}) 3062, 2954, 2929, 2857, 1675, 1599, 1463, 1441, 1385, 1351, 1237, 1169, 1097, 948, 882, 839; δ_H (300 MHz; $CDCl_3$) 7.92 (2H, d, *J* = 8.2 Hz), 7.46–7.37 (5H, m), 7.23 (2H, d, *J* = 8.2 Hz), 5.11 (1H, d, *J* = 0.9 Hz), 4.78 (1H, qd, *J* = 6.9, 2.1 Hz), 4.00 (1H, dd, *J* = 2.1, 0.9 Hz), 2.38 (3H, s), 1.40 (3H, d, *J* = 6.9 Hz), 0.95 (9H, s), 0.26 (3H, s), 0.24 (3H, s); δ_C (75 MHz; $CDCl_3$) 160.0, 157.8, 144.4, 136.9, 135.2, 130.5, 130.2, 129.2, 128.8, 127.5, 114.8, 70.9, 58.4, 25.8, 21.7, 18.9, 18.2, –4.3, –4.4. HRMS (EI) Found: M^+, 503.1622. $C_{25}H_{33}NO_4S_2Si$ requires 503.1620.

***trans*-5-(*tert*-Butyldimethylsilyloxy)-6-methyl-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (13)**

To a refluxing solution of compound **12** (80 mg, 0.16 mmol) in degassed toluene (16 cm^3) was added a solution of Bu_3SnH (0.09 cm^3, 0.35 mmol) and AIBN (15.6 mg, 0.09 mmol) in tolune (4 cm^3) over a period of 4 h. The solvent was then evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 2–1 : 1) containing 5% Et_3N and 5% CH_2Cl_2 as eluent to give 13 (50.5 mg, 91%) as a white solid; mp 123.9–125.5 °C; ν_{max} (film/cm^{-1}) 3371, 2920, 2324, 1647, 1590, 1540, 1488, 1416, 1361, 1120; δ_H (300 MHz; $CDCl_3$) 7.50–7.40 (5H, m), 6.80 (1H, br s), 5.09 (1H, s), 4.16 (1H, d, *J* = 7.5 Hz), 3.56 (1H, qd, *J* = 6.6, 7.5 Hz), 1.23 (3H, d, *J* = 6.6 Hz), 0.96 (9H, s), 0.26 (3H, s), 0.15 (3H, s); δ_C (75 MHz; $CDCl_3$) 164.6, 159.8, 135.6, 130.0, 128.7 (2 ×), 114.0, 73.0, 53.8, 26.0, 19.1, 18.3, –3.8, –3.9. HRMS (EI) Found: M^+, 349.1531. $C_{18}H_{27}NO_2SSi$ requires 349.1532.

***trans*-5-(*tert*-Butyldimethylsilyloxy)-6-methyl-3,4,5,6-tetrahydropyridin-2(1*H*)-one (14)**

A mixture of compound **13** (48 mg, 0.14 mmol) and W-2 Raney Ni (288.8 mg, 2.7 mmol) in 95% EtOH (1.5 cm^3) was heated at reflux under N_2 for 4 h. The reaction mixture was then passed through a short pad of Celite, and the solvent was evaporated under vacuum. The residue was rinsed with hexane containing 5% EtOAc (3 × 10 cm^3), 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 **14** (24.2 mg, 73%) as a white solid; mp101.5–103.1 °C. Its spectral data were identical with the literature values.[18]

***trans*-5-Hydroxy-6-methyl-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (15)**

To a refluxing solution of compound **4b** (200 mg, 0.51 mmol) in degassed toluene (51 cm^3) was added a solution of Bu_3SnH (0.31 cm^3, 1.13 mmol) and AIBN (50.5 mg, 0.31 mmol) in tolune (14 cm^3) over a period of 4 h. The solvent was then evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 2–1 : 1) containing 5% Et_3N and 5% CH_2Cl_2 as eluent to give **15** (101.5 mg, 84%) as a white solid; mp 213.5–215.4 °C; ν_{max} (film/cm^{-1}) 3335, 2923, 2852, 1597, 1415, 1272, 1121, 750; δ_H (300 MHz; $CDCl_3$) 7.55–7.42 (5H, m), 5.64 (1H, br s), 5.19 (1H, d, *J* = 1.8 Hz), 4.14 (1H, d, *J* = 7.2 Hz), 3.70–3.60 (1H, m), 2.85 (1H, br s), 1.31 (1H, d, *J* = 6.6 Hz); δ_C (100 MHz; DMSO-d_6) 163.7, 160.9, 135.8, 130.5, 130.4, 129.4, 113.9, 71.8, 53.2, 18.6. HRMS (EI) Found: M^+, 235.0670. $C_{12}H_{13}NO_2S$ requires 235.0667.

***trans*-5-(Methanesulfonyloxy)-6-methyl-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (16)**

To a solution of compound **15** (99 mg, 0.42 mmol) in CH_2Cl_2 (2.5 cm^3) in an ice bath was added Et_3N (0.25 cm^3, 1.77 mmol). Methanesulfonyl chloride (72 μL, 0.93 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for 24 h. Sat. aq $NaHCO_3$ (15 cm^3) was added slowly, and the mixture was extracted with CH_2Cl_2 (2 × 20 cm^3), dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 1) containing 5% Et_3N as eluent to give **16** (93.6 mg, 71%) as a white solid; mp 147.4–149.0 °C; ν_{max} (film/cm^{-1}) 3196, 3058, 2895, 1667, 1592, 1441, 1356, 1174, 941, 908, 850; δ_H (300 MHz; $CDCl_3$) 7.55–7.42 (5H, m), 6.88 (1H, br s), 5.41 (1H, d, *J* = 1.8 Hz), 4.98 (1H, d, *J* = 3.9 Hz), 4.00–3.90 (1H, m), 3.22 (3H, s), 1.32 (3H, d, *J* =

6.9 Hz); δ_C (75 MHz; $CDCl_3$) 163.1, 149.3, 135.4, 130.6, 130.3, 127.1, 118.8, 76.8, 51.8, 39.2, 19.2. HRMS (FAB) Found: M^+, 313.0443. $C_{13}H_{15}NO_4S_2$ requires 313.0442.

***cis*-5-Azido-6-methyl-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (17)**

To a solution of compound **16** (20 mg, 0.06 mmol) in DMF (1 cm^3) in an ice bath was added NaN_3 (16.6 mg, 0.26 mmol) in one portion. The mixture was stirred at room temperature for 20 h. Brine (10 cm^3) was added, and the mixture was extracted with CH_2Cl_2 (2 × 20 cm^3). The combined solutions were 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 **17** (12.6 mg, 76%) as a white solid; mp 136.5–138.3 °C; ν_{max} (film/cm^{-1}) 3184, 3064, 2896, 2105, 1659, 1584, 1475, 1402, 1330, 1261, 1233, 1023, 998, 850; δ_H (300 MHz; $CDCl_3$) 7.57–7.42 (5H, m), 6.32 (1H, br s), 5.48 (1H, d, *J* = 1.8 Hz), 3.86 (1H, qd, *J* = 6.9, 3.3 Hz), 3.58 (1H, dd, *J* = 3.3, 1.8 Hz), 1.35 (3H, d, *J* = 6.9 Hz); δ_C (75 MHz; $CDCl_3$) 164.7, 152.2, 135.6, 130.6, 130.3, 127.4, 117.0, 60.3, 50.5, 16.7. HRMS (FAB) Found: M^+, 260.0727. $C_{12}H_{12}N_4OS$ requires 260.0732.

***cis*-5-(Acetamido)-6-methyl-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (18)**

A mixture of compound **17** (10 mg, 0.04 mmol), Et_3N (0.011 cm^3, 0.08 mmol) and 10% Pd/C (1.2 mg, 0.002 mmol) in acetic anhydride (2 cm^3) was placed in a high pressure bottle under 5 bar of hydrogen at room temperature for 6 h. Then 5% aq $NaHCO_3$ (15 cm^3) was added dropwise at 0 °C. The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 1) containing 5% Et_3N and 5% CH_2Cl_2 as eluent to give 18 (6.1 mg, 57%) as a white solid; mp 215.4 °C (decomp); ν_{max} (film/cm^{-1}) 3255, 3188, 3050, 2922, 2856, 1667, 1590, 1543, 1440, 1404, 1334, 1298, 1105, 1006, 859; δ_H (300 MHz; $CDCl_3$) 7.51–7.42 (5H, m), 6.48 (1H, br s), 5.83 (1H, br s), 5.27 (1H, d, *J* = 1.0 Hz), 4.67 (1H, ddd, *J* =10.0, 3.5, 1.0 Hz), 3.88–3.83 (1H, m), 2.02 (3H, s), 1.18 (3H, d, *J* = 6.6 Hz); δ_C (125 MHz; $CDCl_3$) 170.3, 165.7, 158.0, 135.4, 130.4, 130.1, 127.8, 114.9, 50.0, 49.0, 23.1, 16.1. HRMS (FAB) Found: M^+, 276.0926. $C_{14}H_{16}N_2O_2S$ requires 276.0932.

***cis*-6-Methyl-5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (19a)**

To a solution of compound **17** (45 mg, 0.17 mmol) in THF–H_2O (2 : 1, 1.5 cm^3) were added sodium ascorbate (NaASC, 3.4 mg, 0.02 mmol) and $CuSO_4 \cdot 5H_2O$ (2.2 mg, 0.009 mmol). Phenylacetylene (39 μL, 0.35 mmol) was then added via a syringe. The mixture was heated at 60 °C for 2 h. The solvent was evaporated under vacuum, and the crude product was purified by recrystallization from CH_2Cl_2–hexane to give **19a** (41mg, 65%) as a white solid; mp 251.5 °C (decomp); ν_{max} (film/cm^{-1}) 3380, 3081, 2924, 2174, 1729, 1659, 1593, 1560, 1539, 1408, 1344, 1114, 1040, 863; δ_H (300 MHz; $CDCl_3$) 7.87 (2H, d, *J* = 7.0 Hz), 7.76 (1H, s), 7.49–7.34 (8H, m), 5.82 (1H, br s), 5.68 (1H, s), 5.30 (1H, d, *J* = 4.0 Hz), 4.24–4.19 (1H, m), 1.04 (3H, d, *J* = 6.5 Hz); δ_C (125 MHz; $CDCl_3$): 164.7, 153.2, 148.4, 135.5, 130.8, 130.4, 130.2, 129.0, 128.6, 126.8, 125.9, 118.7, 118.2, 60.0, 50.1, 16.3. HRMS (FAB) Found: M^+, 362.1197. $C_{20}H_{19}N_4OS$ requires 362.1201.

***cis*-5-(4-Butyl-1*H*-1,2,3-triazol-1-yl)-6-methyl-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (19b)**

To a solution of compound **17** (10 mg, 0.04 mmol) in THF–H_2O (2 : 1, 1.5 cm^3) were added sodium ascorbate (NaASC, 0.75 mg, 0.004 mmol) and $CuSO_4 \cdot 5H_2O$ (0.48 mg, 0.002 mmol). 1-Hexyne (4.4μL, 0.075 mmol) was then added via a syringe. The mixture was heated at 60 °C for 4 h. The solvent was evaporated under vacuum, and the crude product was purified by recrystallization from CH_2Cl_2–hexane to give **19b** (7.5 mg, 57%) as a white solid; mp 223.7–225.6 °C; ν_{max} (film/cm^{-1}) 3389, 2923, 2853, 2325, 1653, 1592, 1464, 1405, 1340, 1117, 1020, 856; δ_H (300 MHz; $CDCl_3$) 7.50–7.39 (5H, m), 7.28 (1H, s), 5.99 (1H, br s), 5.60 (1H, d, *J* = 1.8 Hz), 5.23 (1H, dd, *J* = 3.6, 1.8 Hz), 4.20–4.12 (1H, m), 2.74 (2H, t, *J* = 7.5 Hz), 1.70–1.62 (2H, m), 1.45–1.32 (2H, m), 1.05 (3H, d, *J* = 7.5 Hz), 0.96 (3H, d, *J* = 7.2 Hz); δ_C (125 MHz; $CDCl_3$) 164.7, 153.3, 149.2, 135.5, 130.7, 130.3, 127.0, 119.3, 118.4, 59.8, 50.1, 31.5, 25.5,

22.4, 16.2, 13.9. HRMS (FAB) Found: M^+, 342.1513. $C_{18}H_{22}N_4OS$ requires 342.1514.

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