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. We have
previously developed a new aza-Diels–Alder reaction, using thio-substituted 3-sulfolenes (1) 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). 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. (+)-Pumiliotoxin 251D was isolated from the frogs (Dendrobates pumilio) in South America, and some
total syntheses and many formal syntheses have been reported. (+)-Awajanomycin was isolated
more recently from the marine-derived fungus (Acremonium sp. AWA16-1), also with some syntheses
being reported. Herein we report that compounds 3 can also be utilized to achieve a formal synthesis
of (±)-pumiliotoxin 251D and (±)-awajanomycin (Figure 1).
**RESULTS AND DISCUSSION**

Treatment of compound 1a with p-toluenesulfonyl isocyanate (PTSI) in refluxing toluene in the presence of hydroquinone (HQ) and NaHCO₃ afforded the cycloaddition product 2a. The reaction of compound 2a with N-bromosuccinimide (NBS) in refluxing acetonitrile provided the allylic 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 Bu₃SnH/AIBN 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) 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. Since compound 8 has also been converted to pumiliotoxin 251D, 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, we have also carried out some synthetic transformations of compound 6 (Scheme 3). Treatment of compound
6 with mesyl chloride in the presence of Et₃N in CH₂Cl₂ 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), which indicates that the substitution reaction of compound 9 with the azide anion proceeds with inversion of configuration, probably through the SₐN₂ mechanism. As we have previously shown, 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 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, and have shown interesting biological activities.

Scheme 3. Synthetic transformations of compound 6

Figure 3. X-Ray crystal structure of compound 10
We previously reported the synthesis of allylic alcohol 4b from the bromide 3b (Scheme 1, $R^1 = H, R^2 = Me$), and we have now used compound 4b to achieve a formal synthesis of awajanomycin (Scheme 4). Treatment of compound 4b with $\text{t-butyl}dime\text{thylsilanyl chloride (TBSCl)}$ and Et$_3$N in the presence of a catalytic amount of 4-dimethylaminoapyridine (DMAP) gave the TBS-protected ether 12. Detosylation by Bu$_3$SnH/AIBN 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. Thus we have achieved a formal synthesis of (±)-awajanomycin.

Because some of the piperidine derivatives we previously made have shown novel biological activities, we have also carried out some synthetic transformations of compound 4b (Scheme 5). The $N$-tosyl group of compound 4b was removed by Bu$_3$SnH/AIBN 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), 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.
temperature to afford the azido product 17. The structure of compound 17 was established by X-ray crystallography (Figure 6). 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
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(3H)-one (2a)

A mixture of compound 1a (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 ºC; $\nu_{\text{max}}$ (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,
trans-5-Bromo-6-(3-chloropropyl)-4-(phenylthio)-1-tosyl-5,6-dihydropyridin-2(1H)-one (3a)

A mixture of compound 2a (1000 mg, 2.29 mmol) and NBS (450 mg, 2.52 mmol) in MeCN (15 cm³) was heated at reflux under N₂ 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 131.1–131.2 °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; δ₁H (300 MHz; CDCl₃) 8.07 (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), 3.61–3.52 (1H, m), 2.41 (3H, s), 2.13–1.99 (4H, m); δ₁C (75 MHz; CDCl₃) 158.8, 156.9, 145.1, 135.4, 135.2, 130.7, 130.1, 129.7, 128.9, 126.6, 115.9, 62.4, 44.4, 44.1, 31.6, 29.1, 21.6. HRMS (FAB) Found: M⁺, 512.9828. C₂₁H₂₁BrClNO₃S₂ requires 512.9835.

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

To a solution of compound 3a (50 mg, 0.11 mmol) in MeCN (1 cm³) was added Et₃N (0.3 cm³) and H₂O (0.45 cm³). The mixture was heated at 80 °C under N₂ for 4 h. After cooling, EtOAc (30 cm³) was added. The mixture was washed with brine (2 × 30 cm³), dried (MgSO₄), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 3 : 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; δ₁H (300 MHz; CDCl₃) 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), 3.60–3.54 (1H, m), 2.64 (1H, br s), 2.40 (3H, s), 2.09–1.97 (4H, m); δ₁C (75 MHz; CDCl₃) 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. C₂₁H₂₂ClNO₃S₂ requires 451.0679.

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

To a refluxing solution of compound 4a (1000 mg, 2.22 mmol) in degassed toluene (22 cm³) was added slowly a solution of Bu₃SnH (2.66 mmol) and AIBN (218.4 mg, 1.33 mmol) in toluene (40 cm³) 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% Et₃N and 5% CH₂Cl₂ 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; δ₁H (300 MHz; CDCl₃) 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); δ₁C (75 MHz; CDCl₃) 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. C₁₄H₁₆ClNO₂S requires 297.0590.

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

To a solution of compound 6 (100 mg, 0.34 mmol) in THF (20 cm³) at room temperature under N₂ was added t-BuOK (77.9 mg, 0.68 mmol) in one portion. After refluxing for 2 h, EtOAc (20 cm³) was added, and the mixture was filtered to remove the solid. The organic solution was dried (MgSO₄), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 2 : 1 : 1) containing 5% Et₃N and 5% CH₂Cl₂ 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; δ₁H (300 MHz; CDCl₃) 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); δ₁C (75 MHz; CDCl₃) 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. C₁₄H₁₃NO₂S requires 261.0823.

trans-8-Hydroxy-2,3,6,7,8,8a-hexahydropyridizin-5(1H)-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 cm³) was heated at reflux under N₂ for 2 h. The reaction mixture was then passed through a short pad of Celite, rinsed with MeOH (20 cm³), and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography using CH₂Cl₂–MeOH (10 : 1) as eluent to give 8 (23 mg, 78%) as a yellow oil. Its spectral data were identical with the literature values.

trans-5-(Methanesulfonyl)-6-(3-chloropropyl)-4-(phenylthio)-5,6-dihydropyridin-2(1H)-one (9)
To a solution of compound 6 (1.44 g, 5.99 mmol) in CH₂Cl₂ (3 cm³) in an ice bath was added Et₃N (1.9 cm³, 1.4 mmol). Methanesulfonyl chloride (0.5 cm³, 0.73 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for 12 h. Sat. aq NaHCO₃ (20 cm³) was added slowly, and the mixture was extracted with CH₂Cl₂ (3 × 20 cm³), dried (MgSO₄), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 2–1 : 1) containing 5% Et₃N as eluent to give 9 (179.3 mg, 71%) as a white solid; mp 141.0–142.0 °C; νmax (film/cm⁻¹) 3126, 3058, 3024, 2971, 1667, 1594, 1469, 1442, 1416, 1359, 1277, 1176, 1144, 1107, 1023, 923, 837; δH (300 MHz; CDCl₃) 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); δC (75 MHz; CDCl₃) 162.7, 148.6, 135.4, 130.7, 130.4, 127.0, 119.6, 58.7, 54.2, 44.3, 39.3, 30.7, 28.6. HRMS (FAB) Found: M⁺, 375.0369. C₁₅H₁₈ClNO₂S requires 375.0366.

cis-5-Azido-6-(3-chloropropyl)-4-(phenylthio)-5,6-dihydropyridin-2(1H)-one (10)
To a solution of compound 9 (100 mg, 0.27 mmol) in DMF (2 cm³) in an ice bath was added NaN₃ (69.3 mg, 1.08 mmol) in one portion. The mixture was stirred at room temperature for 12 h. Brine (20 cm³) was added, and the mixture was extracted with EtOAc (3 × 30 cm³). 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; νmax (film/cm⁻¹) 3195, 3073, 2922, 2851, 2102, 1660, 1591, 1441, 1412, 1339, 1262, 1176, 1111, 1068, 1023, 924, 859; δH (300 MHz; CDCl₃) 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); δC (75 MHz; CDCl₃) 164.7, 152.1, 135.6, 130.7, 130.4, 127.0, 119.6, 57.5, 54.3, 44.3, 39.3, 30.7, 28.6. HRMS (FAB) Found: M⁺, 322.0657. C₁₄H₁₅ClNO₂S requires 322.0655.

cis-6-(3-Chloropropyl)-5-(4-phenyl-1H-1,2,3-triazol-1-yl)-4-(phenylthio)-5,6-dihydropyridin-2(1H)-one (11)
To a solution of compound 10 (30 mg, 0.09 mmol) in THF–H₂O (1:1, 2 cm³) were added sodium ascorbate (NaASC, 1.8 mg, 0.01 mmol) and CuSO₄·5H₂O (1.2 mg, 0.0045 mmol). Phenylacetylene (17 cm³, 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 CH₂Cl₂ (20 cm³) was added. The organic solution was dried (MgSO₄), and evaporated under vacuum. The crude product was purified by recrystallization from CH₂Cl₂–hexane to give 11 (25.7 mg, 65%) as a white solid; mp 203.1–204.2 °C; νmax (film/cm⁻¹) 3081, 3037, 2928, 2304, 1650, 1596, 1457, 1415, 1352, 1265, 1226, 1085, 1024, 978, 857; δH (300 MHz; CDCl₃) 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); δC (75 MHz; CDCl₃) 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. C₂₂H₂₁ClN₄O₂S requires 424.1125.

trans-5-(tert-Butyldimethylsilyloxy)-6-methyl-4-(phenylthio)-1-tosyl-5,6-dihydropyridin-2(1H)-one (12)
To a solution of compound 4b (90 mg, 0.23 mmol) and DMAP (2.8 mg, 0.02 mmol) in CH₂Cl₂ (3 cm³) were added sequentially Et₃N (0.18 cm³, 1.16 mmol) and TBSCl (97 mg, 0.58 mmol). The reaction mixture was heated at 60 °C for 24 h, and sat. aq NaHCO₃ (10 cm³) was added. The mixture was
extracted with CH₂Cl₂ (2 × 30 cm³), the combined organic solutions dried (MgSO₄), 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; mp 154.7–156.4 °C; νmax (film/cm⁻¹) 3062, 2954, 2929, 2857, 1675, 1599, 1463, 1441, 1385, 1351, 1237, 1169, 1097, 948, 882, 839; δ₁H (300 MHz; CDCl₃) 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); δC (75 MHz; CDCl₃) 161.0, 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. C₁₂H₁₃NO₂Si requires 503.1620.

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

To a refluxing solution of compound 12 (80 mg, 0.16 mmol) in degassed toluene (16 cm³) was added a solution of Bu₃SnH (0.09 cm³, 0.35 mmol) and AIBN (15.6 mg, 0.09 mmol) in toluene (4 cm³) 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% Et₃N and 5% CH₂Cl₂ as eluent to give 13 (50.5 mg, 91%) as a white solid; mp 123.9–125.5 °C; νmax (film/cm⁻¹) 1675, 1599, 1463, 1441, 1385, 1351, 1237, 1169, 1097, 948, 882, 839; δ₁H (300 MHz; CDCl₃) 7.50–7.40 (5H, m), 7.37 (5H, m), 7.23 (2H, d, J = 1.8 Hz), 4.98 (1H, d, J = 3.9 Hz), 4.00 (1H, d, J = 6.9 Hz), 0.95 (9H, s), 0.26 (3H, s), 0.24 (3H, s); δC (75 MHz; CDCl₃) 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. C₁₂H₁₃NO₂Si requires 503.1620.

trans-5-(tert-Butyldimethylsilyloxy)-6-methyl-3,4,5,6-tetrahydropyridin-2(1H)-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 cm³) was heated at reflux under N₂ 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 cm³), evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 2) containing 5% Et₃N as eluent to give 14 (24.2 mg, 73%) as a white solid; mp 101.5–103.1 °C. Its spectral data were identical with the literature values.¹₈

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

To a refluxing solution of compound 4b (200 mg, 0.51 mmol) in degassed toluene (51 cm³) was added a solution of Bu₃SnH (0.31 cm³, 1.13 mmol) and AIBN (50.5 mg, 0.31 mmol) in toluene (14 cm³) 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% Et₃N and 5% CH₂Cl₂ as eluent to give 15 (101.5 mg, 84%) as a white solid; mp 213.5–215.4 °C; νmax (film/cm⁻¹) 3335, 2923, 2852, 1597, 1415, 1272, 1121, 750; δ₁H (300 MHz; CDCl₃) 7.55–7.40 (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); δC (100 MHz; DMSO-d₆) 163.7, 160.9, 129.4, 129.4, 113.9, 71.8, 53.2, 18.6. HRMS (EI) Found: M⁺, 235.0670. C₁₂H₁₃NO₂Si requires 235.0667.

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

To a solution of compound 15 (99 mg, 0.42 mmol) in CH₂Cl₂ (2.5 cm³) in an ice bath was added Et₃N (0.25 cm³, 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 NaHCO₃ (15 cm³) was added slowly, and the mixture was extracted with CH₂Cl₂ (2 × 20 cm³), dried (MgSO₄), and evaporated under vacuum. The crude product was purified by flash chromatography using EtOAc–hexane (1 : 1) containing 5% Et₃N as eluent to give 16 (93.6 mg, 71%) as a white solid; mp 147.4–149.0 °C; νmax (film/cm⁻¹) 3196, 3058, 2895, 1667, 1592, 1441, 1356, 1174, 941, 908, 850; δ₁H (300 MHz; CDCl₃) 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 =
cis-5-Azido-6-methyl-4-(phenylthio)-5,6-dihydropyridin-2(1H)-one (17)

To a solution of compound 16 (20 mg, 0.06 mmol) in DMF (1 cm³) in an ice bath was added NaN₃ (16.6 mg, 0.26 mmol) in one portion. The mixture was stirred at room temperature for 20 h. Brine (10 cm³) was added, and the mixture was extracted with CH₂Cl₂ (2 × 20 cm³). The combined solutions were evaporated under vacuum, and the crude product was purified by flash chromatography using EtOAc–hexane (1 : 2) containing 5% Et₃N as eluent to give 17 (12.6 mg, 76%) as a white solid; mp 136.5–138.3 °C; v_max (film/cm⁻¹) 3184, 3064, 2896, 2105, 1659, 1584, 1475, 1402, 1330, 1261, 1233, 1023, 998, 850; δ_H (300 MHz; CDCl₃) 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; CDCl₃) 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. C₁₂H₁₂N₄O requires 260.0732.

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

A mixture of compound 17 (10 mg, 0.04 mmol), Et₃N (0.011 cm³, 0.08 mmol) and 10% Pd/C (1.2 mg, 0.002 mmol) in acetic anhydride (2 cm³) was placed in a high pressure bottle under 5 bar of hydrogen at room temperature for 6 h. Then 5% aq NaHCO₃ (15 cm³) 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% Et₃N and 5% CH₂Cl₂ as eluent to give 18 (6.1 mg, 57%) as a white solid; mp 215.4 °C (decomp); v_max (film/cm⁻¹) 3255, 3188, 3050, 2922, 2856, 1667, 1590, 1543, 1440, 1334, 1298, 1105, 1006, 859; δ_H (300 MHz; CDCl₃) 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; CDCl₃) 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. C₁₄H₁₆N₂O₂S requires 276.0932.

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

To a solution of compound 17 (45 mg, 0.17 mmol) in THF–H₂O (2 : 1, 1.5 cm³) were added sodium ascorbate (NaASC, 3.4 mg, 0.02 mmol) and CuSO₄·5H₂O (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 CH₂Cl₂–hexane to give 19a (41 mg, 65%) as a white solid; mp 251.5 °C (decomp); v_max (film/cm⁻¹) 3380, 3081, 2924, 2174, 1729, 1659, 1593, 1560, 1539, 1408, 1344, 1114, 1040, 863; δ_H (300 MHz; CDCl₃) 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; CDCl₃): 164.7, 153.2, 148.4, 135.5, 130.8, 130.4, 130.2, 129.0, 128.6, 125.9, 118.7, 118.2, 60.0, 50.1, 16.3. HRMS (FAB) Found: M⁺, 362.1197. C₂₀H₁₀N₄O₂S requires 362.1201.

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

To a solution of compound 17 (10 mg, 0.04 mmol) in THF–H₂O (2 : 1, 1.5 cm³) were added sodium ascorbate (NaASC, 0.75 mg, 0.004 mmol) and CuSO₄·5H₂O (0.48 mg, 0.002 mmol). 1-Hexyne (4.4 μL, 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 CH₂Cl₂–hexane to give 19b (7.5 mg, 57%) as a white solid; mp 223.7–225.6 °C; v_max (film/cm⁻¹) 3389, 2923, 2853, 2325, 1653, 1592, 1464, 1405, 1340, 1117, 1020, 856; δ_H (300 MHz; CDCl₃) 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; CDCl₃) 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_{4}O requires 342.1514.

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REFERENCES AND NOTES


21. Crystallographic data (excluding structure factors) for compounds 7, 10, 15 and 17 in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 977117–977120. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).