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SYNTHESIS OF PENICOLINATES A, C AND D

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Dedicated with respect and affection to Professor Somsak Ruchirawat on the occasion of his 80th birthday to honour his long commitment to the chemistry of both heterocycles and natural products

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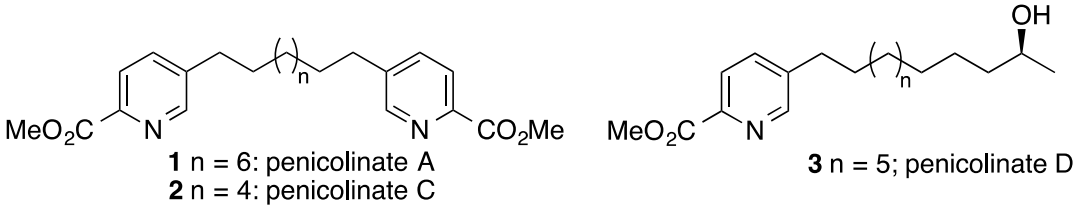
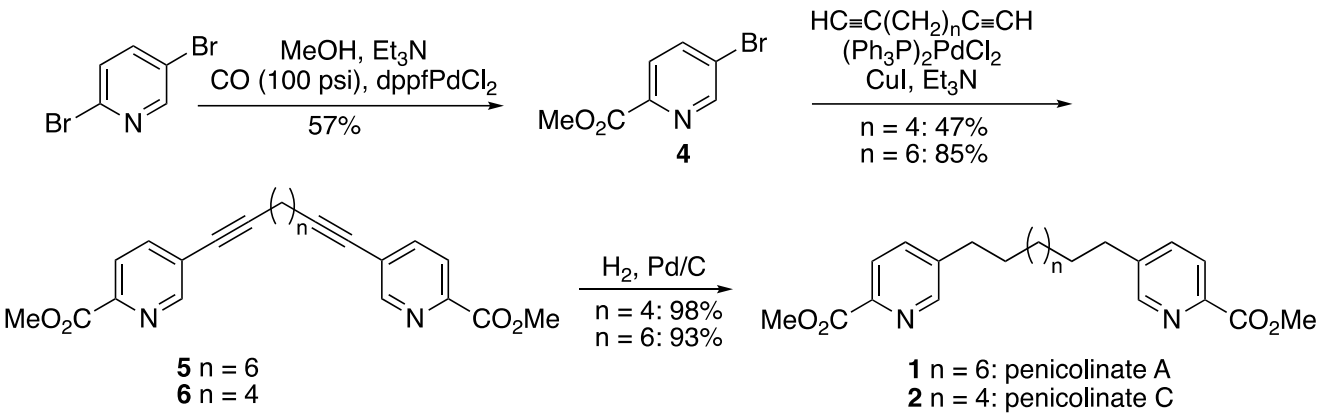
Abstract – Penicolinates A, C and D are synthesized using the Sonogashira coupling reaction as a key step. By comparison of the optical rotation, the stereochemistry of penicolinate D is determined to be (*S*).

Penicolinates A-E were recently isolated from a *Penicillium* fungus collected in Doi Suthep-Pui National Park near to Chiang Mai, Thailand.[2] Penicolinate A **1** has also been isolated from a *Bionectria* fungus from Cameroon.[3] These compounds were found to be 3-substituted pyridines, a reasonably well known structure amongst natural products.[4] Penicolinates A and C, **1** and **2**, were determined to be symmetrical bispyridines, differing only in the length of the alkyl tether, while penicolinate D **3** was found to be a mono-pyridine bearing a secondary alcohol moiety (Scheme 1). The absolute stereochemistry of penicolinate D **3** was not determined. Penicolinates A and C, **1** and **2**, were found to show both anti-tubercular and anti-malarial activity, although data for penicolinate D **3** was not reported. Penicolinate A **1** has also been found to show potent cytotoxicity against an ovarian cancer cell line.[3]



Scheme 1. Penicolinates A, C and D

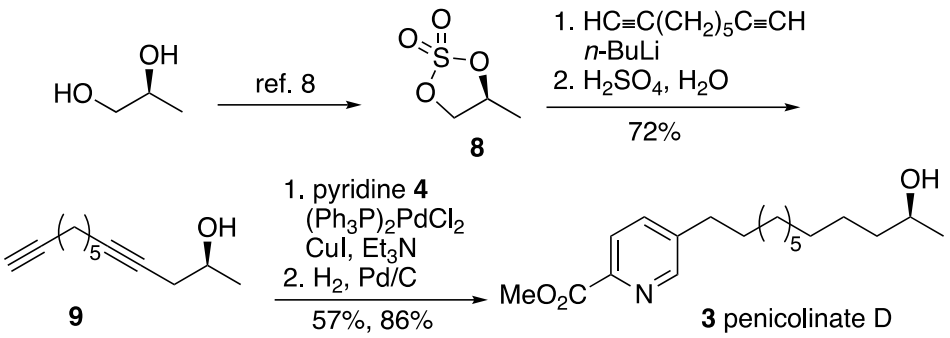
We anticipated that a double Sonogashira coupling[5] of the known bromopyridine **4** with appropriate diynes followed by catalytic hydrogenation would yield penicolinates A and C, **1** and **2** (Scheme 2). Bromopyridine **4** is readily available by methoxycarbonylation of 2,5-dibromopyridine.[6] In contrast to the observations of Song and Yee,[6] in our hands this reaction proceeds best using dppfPdCl$_2$ as the catalyst rather than triphenylphosphine palladium complexes, delivering the product of carbonylation at the 2-position, which is presumably electronically activated, in 57% yield. A small amount of the diester can also be isolated. Sonogashira coupling of bromopyridine **4** proceeded smoothly with both 1,7-octadiyne and with 1,9-decadiyne to give the expected doubly coupled products **5** and **6**. It is notable that the yield is lower when octadiyne is employed. This may be due to chelate of the palladium by the diyne. Hydrogenation then yielded the two natural products, penicolinates A and C, **1** and **2**. Spectroscopic data for the synthetic samples was in good agreement with that reported for the natural compounds.[2]



Scheme 2. Synthesis of Penicolinates A and C

Turning to penicolinate D **3**, an alkynol was required. For synthetic convenience, we proposed to employ the ring opening of a cyclic sulfate[7] with an acetylide anion[8] as this would allow us to specifically prepare a single defined enantiomer and, thus, determine the stereochemistry of the natural product. Initial attempts at the ring opening of (*S*)-cyclic sulfate **8** with 1,8-nonadiyne using *n*-BuLi as the base gave disappointing results. Simply using an excess of the base and a large excess of the diyne gave a good yield of the desired ring opening product, diyne **9**. The Sonogashira coupling of diyne **9** with bromopyridine **4** proceeded in satisfactory yield. Catalytic hydrogenation of coupling product **10** then gave penicolinate D **3**. The spectroscopic data was in good agreement with that reported for the natural product. The optical rotation for the synthetic material was determined to be $[\alpha]_D^{22}$ +32.6 (c 1.44, $CHCl_3$). While this is larger than the reported value of $[\alpha]_D^{26}$ +5.04 (c 0.10, $CHCl_3$),[2] both measurements show the compound to be dextrorotatory. The (*S*)-cyclic sulfate used in our work was obtained from the corresponding (*S*)-diol **7** which was prepared by the method of Jacobsen.[9] Thus, it can be determined that

penicolinate D **3** has (*S*) configuration and is homochiral with the related natural product fusarinolic acid.[6,10]



Scheme 3. Synthesis of Penicolinate D

EXPERIMENTAL

General experimental

All reagents were obtained from commercial suppliers and used without further purification. Reactions requiring anhydrous or air free conditions were performed under an atmosphere of nitrogen. Glassware was oven dried at 120 °C and cooled under vacuum. Anhydrous THF was distilled from sodium metal and benzophenone under nitrogen. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 spectrometer or a JEOL ECA400 UltraShield in $CDCl_3$. Chemical shifts are given in parts per million (ppm) with residual protic solvent as the internal standard. Coupling constants are given in Hertz. Analytical thin layer chromatography was performed on Merck DC pre coated TLC plates with 0.25 mm Kieselgel 60 F_{254}. The plates were visualised with a 254 nm UV lamp, or by staining with ammonium molybdate or potassium permanganate. Flash chromatography was performed on silica gel 230-400 mesh.

Diyne (5):

1,9-Decadiyne (41 μL, 0.25 mmol) and triethylamine (1 mL) were added to a solution of methyl 5-bromopicolinate (120 mg, 0.55 mmol), $PdCl_2(PPh_3)_2$ (18 mg, 0.03 mmol), and CuI (10 mg, 0.06 mmol) in anhydrous THF (10 mL). The reaction mixture was heated at reflux for 22 h and then allowed to cool to room temperature. The mixture was filtered through Celite® and concentrated under vacuum to afford a dark brown oil, which was purified by flash column chromatography on silica gel (30% EtOAc/Hexane) to give diyne (**5**) (87 mg, 85% yield) as an off-white solid, mp 117-119 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 1.8 Hz, 2H), 8.05 (d, *J* = 8.0 Hz, 2H), 7.79 (dd, *J* = 2.3, 8.0 Hz, 2H), 4.01 (s, 6H), 2.48 (t, *J* = 7.3 Hz, 4H), 1.68 (m, 4H), 1.54 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.3, 152.1, 145.5, 139.3, 124.7, 124.4, 97.3, 52.9, 28.4, 28.2, 19.5; **IR** (*Nujol* mull) 1643, 1732 cm^{-1}; **EI-MS** *m/z* (+ion mode): 405.4 $[M + H]^+$; **HR-MS** (ESI): $C_{24}H_{24}N_2O_4Na$ $[M+Na]^+$ calculated: 427.1634, found: 427.1653.

Diyne (6):

1,7-Octadiyne (30 μL, 0.22 mmol) and triethylamine (1 mL) were added to a solution of methyl 5-bromopicolinate (102 mg, 0.47 mmol), $PdCl_2(PPh_3)_2$ (16 mg, 0.02 mmol), and CuI (9 mg, 0.04 mmol) in anhydrous THF (10 mL). The mixture was heated at reflux for 22 h and then allowed to cool to room temperature. The mixture was filtered through Celite®, and concentrated under vacuum to afford a dark brown oil, which was purified by flash column chromatography on silica gel (30% EtOAc/Hexane) to give diyne (**6**) (40 mg, 47% yield) as an off-white solid, mp 116-117 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 1.8 Hz, 2H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.81 (dd, *J* = 2.3, 8.0 Hz, 2H), 4.01 (s, 6H), 2.54 (t, *J* = 6.4 Hz, 4H), 1.82 (quin, *J* = 1.4 Hz, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.2, 152.1, 145.6, 139.2, 132.1, 132.0, 128.5, 128.4, 124.5, 124.4, 96.9, 52.9, 27.5, 19.1; **IR** (*Nujol* mull) 1643, 1732 cm^{-1}; **EI-MS** *m/z* (+ion mode): 377.3 $[M + H]^+$; HR-MS (ESI): $C_{22}H_{20}N_2O_4Na$ $[M+Na]^+$ calculated: 399.1321, found: 399.1324.

Penicolinate A (1):

A solution of diyne (**5**) (42 mg, 0.04 mmol) in MeOH/EtOAc (1:1) (10 mL) containing 10% palladium on activated charcoal (10 mg). The reaction mixture was stirred under H_2 gas (1 atm). After stirring for 24 h at room temperature, the reaction mixture was filtered through Celite®, and concentrated under vacuum to afford penicolinate A (**1**) (40 mg, 93% yield) as an off-white solid, mp 114-115 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.8 Hz, 2H), 8.05 (d, *J* = 7.8 Hz, 2H), 7.63 (dd, *J* = 1.8, 7.8 Hz, 2H), 3.99 (s, 6H), 2.68 (t, *J* = 7.8 Hz, 4H), 1.61 (quin, *J* = 7.3 Hz, 4H), 1.29 (m, 12H); **^{13}C NMR** (100 Hz, $CDCl_3$) δ 165.9, 150.0, 145.5, 142.2, 136.6, 124.9, 52.8, 33.0, 30.8, 29.4, 29.3, 29.0; **IR** (*Nujol* mull) 2922, 1636, 1732 cm^{-1}; **EI-MS** *m/z* (+ion mode): 413.3 $[M + H]^+$; **HR-MS** (ESI): $C_{24}H_{32}N_2O_4Na$ $[M+Na]^+$ calculated: 435.2260, found: 435.2280.

Penicolinate C (2):

A solution of diyne (**6**) (20 mg, 0.05 mmol) in MeOH/EtOAc (1:1) (5 mL) containing 10% palladium on activated charcoal (5 mg) was stirred under H_2 gas (1 atm). After stirring for 24 h at room temperature, the mixture was filtered through Celite®, and concentrated under vacuum to afford penicolinate C (**2**) (20 mg, 98% yield) as an off-white solid, mp 83-84 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.8 Hz, 2H), 8.06 (d, *J* = 7.8 Hz, 2H), 7.63 (dd, *J* = 1.8, 8.2 Hz, 2H), 3.99 (s, 6H), 2.68 (t, *J* = 7.3 Hz, 4H), 1.63 (quin, *J* = 6.9 Hz, 2H), 1.25 (m, 10H); **^{13}C NMR** (100 Hz, $CDCl_3$) δ 165.8, 150.0, 145.5, 142.1, 136.6, 124.9, 52.8, 33.0, 30.8, 29.2, 29.0; **IR** (*Nujol* mull) 2922, 1636, 1732 cm^{-1}; **EI-MS** *m/z*: 385.3 $[M + H]^+$; **HR-MS** (ESI): $C_{22}H_{28}O_2N_4Na$ $[M+Na]^+$ calculated: 407.1947, found: 407.1938.

(*S*)-Dodeca-4,11-diyn-2-ol (9):

n-BuLi in cyclohexane (2.0 M, 3.5 mL, 6.94 mmol) was added dropwise to a solution of diyne (2.5 g, 0.02 mmol) in anhydrous THF (20 mL) at −78 °C. The clear solution was stirred for 1 h at this

temperature. A solution of cyclic sulfate **8** (0.6 g, 3.47 mmol) in THF (5 mL) was added via cannula. The mixture was stirred for 2 h at −78 °C and then allowed to warm to room temperature over 30 min. Water (100 μL) and conc. sulfuric acid (50 μL) was added and the mixture turned opaque. The cloudy mixture was stirred for another 15 min and the excess acid was neutralized by addition of aqueous $NaHCO_3$ solution. The mixture was extracted twice with Et_2O (50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residual colourless oil was purified by flash column chromatography (15% EtOAc/Hexane) to give the (*S*)-dodeca-4,11-diyn-2-ol (**9**) (0.41 g, 72% yield) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.13 – 3.69 (m, 1H), 2.46 – 2.10 (m, 6H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.83 (brs, 1H), 1.66 – 1.39 (m, 6H), 1.23 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 84.6, 83.0, 76.5, 68.5, 66.7, 29.5, 28.6, 28.1, 28.1, 22.4, 18.8, 18.4; IR (neat) 3404, 3295, 2972, 2935, 2862, 2114, 1432, 1117, 1083, 938, 626 cm^{-1}; EI-MS *m/z* $[M+H]^+$ 179.0; **HR-MS** (ESI): $C_{12}H_{19}O$ $[M+H]^+$ calculated: 179.1436, found: 179.1437; $[\alpha]_D^{22}$ +11.68 (c 1.13, $CHCl_3$).

Methyl (*S*)-5-(11-hydroxydodeca-1,8-diyn-1-yl)picolinate (10): Diynol **9** (80 mg, 0.49 mmol) and triethylamine (1 mL) were added to a solution of methyl 5-bromopicolinate (105 mg, 0.49 mmol), $PdCl_2(PPh_3)_2$ (34.2 mg, 0.05 mmol), and CuI (19 mg, 0.09 mmol) in anhydrous THF (10 mL). The mixture was stirred at reflux for 22 h and then allowed to cool to room temperature. The mixture was filtered through Celite®, and concentrated under vacuum to afford a residue dark brown oil, which was purified by flash column chromatography on silica gel (30% EtOAc/Hexane) to give diyne **10** (87 mg, 57% yield) as a pale yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.69 (d, *J* = 1.9 Hz, 1H), 8.03 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.78 (dd, *J* = 8.1, 2.1 Hz, 1H), 3.98 (s, 3H), 3.94 – 3.81 (m, 1H), 2.45 (t, *J* = 6.9 Hz, 2H), 2.40 – 2.14 (m, 4H), 1.97 (s, 1H), 1.65 – 1.52 (m, 6H), 1.20 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.4, 152.2, 145.6, 139.4, 124.81, 124.5, 97.4, 82.8, 77.3, 76.6, 66.6, 53.0, 29.5, 28.5, 28.2, 28.0, 22.3, 19.6, 18.7; IR (neat) 3422, 2935, 2860, 2231, 1742, 1724, 1438, 1311, 1234, 1122 cm^{-1}; EI-MS *m/z* $[M+H]^+$ 314.2; $C_{19}H_{23}NO_3Na$ $[M+Na]^+$ calculated: 336.1576, found: 336.1588; $[\alpha]_D^{22}$ +10.64 (c 0.89, $CHCl_3$).

Penicolinate D (3):

A solution of diyne **10** (50 mg, 0.16 mmol) and Pd/C (10 mg, 20% w/w) in MeOH (7 mL) was stirred under hydrogen (1 atm) for 24 h at room temperature. The reaction mixture was filtered through Celite® and the filtrate was concentrated under reduced pressure. Further purification by flash chromatography (30% EtOAc: Hexane, v/v) gave penicolinate D **3** as an off-white solid (44 mg, 86% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.54 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 3.98 (s, 3H), 3.87 – 3.64 (m, 1H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.69 – 1.57 (m, 2H), 1.40 – 1.25 (m, 16H), 1.16 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.0, 150.2, 145.7, 142.3, 136.7, 125.0, 68.3, 52.9, 39.5, 33.1, 31.0,

29.7, 29.7, 29.6, 29.6, 29.4, 29.2, 25.9, 23.6; IR (*Nujol* mull, cm^{-1}) 3393, 1717; $[\alpha]_D^{30}$ +8.27 (c 0.0068, $CHCl_3$); EI-MS *m/z* $[M+H]^+$ 322.3; HR-MS (ESI): $C_{19}H_{31}NO_3Na$ $[M+Na]^+$ calculated: 344.2202, found: 344.2207; $[\alpha]_D^{22}$ +32.6 (c 1.44, $CHCl_3$).

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