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AN EFFICIENT LARGE SCALE SYNTHESIS OF 2-METHOXYTETRAHYDROPHENANTHRIDINE.

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ABSTRACT. A practical and high yielding synthesis of 2-methoxy-7,8,9,10-tetrahydrophenanthridine suitable for large-scale preparation is described.

Recent work[1] in this laboratory required the preparation of various enediyne derivatives (e.g., **1**) as prodrugs for antibody-directed enzyme prodrug therapy (ADEPT).[2] This necessitated a convenient, large-scale synthesis of 2-substituted tetrahydrophenanthridine derivatives **2** as precursors for such enediynes.

A previous synthesis[3] of related enediynes had used a condensation reaction[4], which gave 2-methoxyphenanthridinone (**6**) in only 30% yield. Although we were able to replicate this result on a small scale, the cost of the precursors and low

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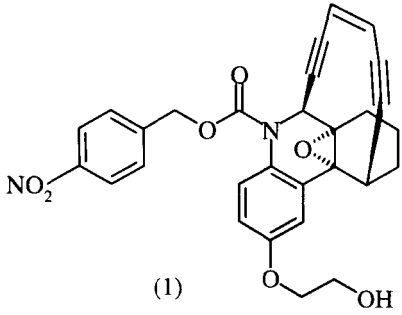
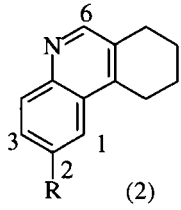
yield made this approach expensive, inefficient and unsuitable for large-scale preparation. An alternative synthesis[5] using acylthiazolidine derivatives as an activating agent for the amide coupling with subsequent deprotection of the ketone



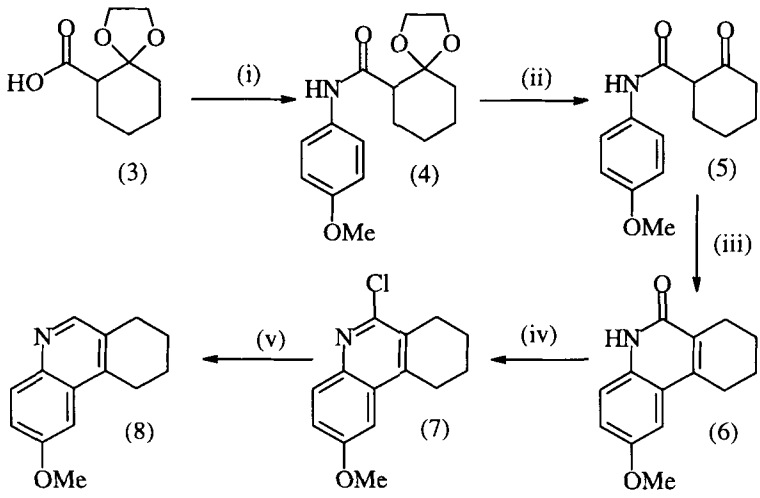
(1)



(2)

and condensation under acidic conditions was only facile with an electron-donating substituent in the 3-position. We found that incomplete reaction and decomposition in the 2-methoxy case resulted in tedious chromatography, undesirable for large-scale reactions. Use of a Mannich reaction[6] to construct the phenanthridine nucleus was not successful in our hands

We have developed a synthesis of 2-methoxy-7,8,9,10-tetrahydrophenanthridine (**8**), which is suitable for large-scale preparation and does not require chromatography. Thus the ketal acid **4**,[5] obtained from commercially available 2-cyclohexanone carboxylic acid (**3**), was activated as the acid chloride with oxalyl chloride and coupled to anisidine in 99% yield on a 0.23 mol scale. Deprotection of the ketal **4** with 70% perchloric acid gave the ketoamide **5** in 78% yield. Treatment of the ketoamide **5** with 90% H_2SO_4 for 20 minutes at 60°C gave the



Reagents: (i) a. $(COCl)_2$, DCM, b. anisidine, Et_3N, DCM; (ii) 70% $HClO_4$, DCM;(iii) 90% H_2SO_4, 60°C; (iv) $POCl_3$,100 °C; (v) H_2, Pd/C, EtOH.

FIG. 1.

lactam **6** in 74% yield. Treatment of ketoamide **5** with other dehydrating agents such as conc. H_2SO_4 at various temperatures, $POCl_3$ or PPA at 100°C gave only trace amounts of product **6**. Reaction of the lactam **6** with $POCl_3$ provided the chloride **7** which was hydrogenolysed to give 2-methoxy tetrahydrophenanthridine (**8**) in excellent yield as previously noted (no experimental detail was given).[3] This approach was extended to the parent tetrahydrophenanthridine (**2**, R=H) and the 2-methyl derivative (**2**, R=Me) (data not shown). However, attempts to extend this approach to electron-withdrawing substituents eg., 2-NO_2-tetrahydrophenanthridine (**2**, R=NO_2) failed at the condensation step. Extension of the reaction time led to extensive amide bond hydrolysis. Similarly reaction of 2-

amido substituted (**2**, R=CONHR) gave only poor yields of the product with amide hydrolysis predominating.

Thus, a practical and high yielding synthesis of 2-methoxy-7,8,9,10-tetrahydrophenanthridine (**8**) has been established which is suitable for the large-scale preparation of enediyne intermediates.

EXPERIMENTAL

Analyses were carried out by the Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on a Electrothermal 2300 melting point apparatus. NMR spectra were obtained on a Bruker AM-400 at 400 MHz (^{1}H) or 100 MHz (^{13}C) in $CDCl_3$ or d_6-DMSO, and are referenced to Me_4Si. Infrared spectra were obtained on a Midac FT-IR as KBr discs.

N-(2-Methoxyphenyl)-1,4-dioxaspiro[4.5]decane-6-carboxamide (**4**). Oxalyl chloride (60 mL, 0.684 mmol) was added dropwise to a stirred solution of 1,4-dioxaspiro[4.5]decane-6-carboxylic acid (**3**)[5] (42.4 g, 0.228 mmol) and DMF (3 drops) in DCM (200 mL) and the solution was stirred at 20 °C for 2 h. The solvent was removed under reduced pressure and the residue dissolved in DCM (150 mL) and added dropwise to a stirred solution of anisidine (28.06 g, 0.228 mmol) and Et_3N (95 mL, 0.684 mmol) in DCM (250 mL). The solution was stirred at 20 °C for 2 h and the mixture washed successfully with water (100 mL), 1 M HCl (2 x 100 mL), water (100 mL), diluted Na_2CO_3 (150 mL), water (100

mL), brine (100 mL) and dried (Na_2SO_4) to give **4** (65.32 g, 98%) mp (EtOAc/pet. ether) 129-131 °C; IR (KBr) υ_{max} 3272, 1659, 1514, 1248, 1171 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (br s, 1 H, CONH), 7.44 (ddd, J = 9.0, 3.4, 2.2 Hz, 2 H, H_{arom}), 6.84 (ddd, J = 9.0, 3.4, 2.2 Hz, H_{arom}), 3.92-4.03 (m, 4 H, $2CH_2O$), 3.78 (s, 3 H, OCH_3), 2.64 (dd, J = 11.4, 4.4 Hz, 1 H, CH), 1.98-2.04 (m, 1 H, CH_2), 1.89-1.97 (m, 1 H, CH_2), 1.82-1.86 (m, 1 H, CH_2), 1.67-1.72 (m, 2 H, CH_2), 1.51-1.60 (m, 1 H, CH_2), 1.41-1.48 (m, 1 H, CH_2), 1.28-1.36 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 169.7, 156.0, 131.6, 121.0 (2), 114.1 (2), 109.5, 64.6, 64.4, 55.4, 52.0, 34.9, 27.3, 24.1, 23.4; Anal. calcd for $C_{16}H_{21}NO_4$: C, 66.0; H, 7.3; N, 4.8; found C, 66.0; H, 7.3; N, 4.8%.

N-(2-Methoxyphenyl)-2-oxocyclohexane carboxamide (**5**). Perchloric acid (160 g, 1.12 mmol) was added to a stirred solution of **4** (65.3 g, 0.224 mmol) in DCM (500 mL) and stirred at 20 °C for 10 min. The solution was carefully poured into sat. aqueous $NaHCO_3$ solution (3 L) and stirred for 30 minutes. The organic fraction was removed and the aqueous fraction extracted with $CHCl_3$ (3 x 300 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was recrystallised from EtOAc/pet. ether to give **5** (43.2 g, 78%) mp (EtOAc/pet. ether) 116-117 °C, IR (KBr) υ_{max} 3372, 1707, 1678, 1602, 1510, 1236 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.19 (s, 1 H, CONH), 7.45 (ddd, J = 9.1, 3.5, 2.1 Hz, 2 H, H_{arom}), 6.86 (ddd, J = 9.1, 3.5, 2.1 Hz, 2 H, H_{arom}), 3.80 (s, 3 H OCH_3), 3.30 (ddd, J = 10.6, 5.5, 0.9 Hz, 1 H, CH),

2.49-2.58 (m, 2 H, CH_2), 2.39-2.47 (m, 1 H, CH_2), 1.94-2.11 (m, 3 H, CH_2), 1.74-1.88 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 211.5, 171.7, 156.4, 130.8, 121.8 (2), 114.1 (2), 55.7, 55.4, 42.4, 32.0, 27.5, 24.5; Anal. calcd for $C_{14}H_{21}NO_3$: C, 68.0; H, 6.9; N, 5.7; found C, 68.45; H, 7.0; N, 5.5%.

2-Methoxy-7,8,9,10-tetrahydrophenanthridone (**6**). A mixture of **5** (37.4 g, 0.151 mmol) and 90% H_2SO_4 (220 mL) was heated at 60 °C for 20 minutes (monitored by tlc). The reaction was poured into ice/water (2 L) and stirred for 10 minutes. The mixture was filtered and the solid dried to give **6** (25.56 g, 74%) mp 259-261 °C; IR (KBr) υ_{max} 3477, 1651, 1504, 1217, 1043 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.49 (s, 1 H, CONH), 7.30-7.33 (m, 1 H, H_{arom}), 7.08-7.11 (m, 2 H, H_{arom}), 3.87 (s, 3 H, OCH_3), 2.86 (br t, J = 6.2 Hz, 2 H, CH_2), 2.72 (br t, J = 6.1 Hz, 2 H, CH_2), 1.81-1.94 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 162.9, 155.1, 143.8, 130.8, 128.6, 121.3, 117.8, 117.3, 105.4, 55.7, 35.7, 29.9, 21.9, 21.8; Anal. calcd for $C_{14}H_{15}NO_2$: C, 73.3; H, 6.6; N, 6.1; found C, 73.3; H, 6.4; N, 6.0%.

2-Methoxy-6-chloro-7,8,9,10-tetrahydrophenanthridine (**7**). A mixture of **6** (28.5 g, 0.124 mmol) and $POCl_3$ (114 mL, 1.24 mmol) was heated at 100 °C for 2 h. The mixture was evaporated under reduced pressure and the residue slurried between sat. aqueous $NaHCO_3$ (2 L) and DCM (1 L). The organic fraction was dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was filtered through a short plug of silica eluting with 50% EtOAc/pet. ether to give **7**

(24.92 g, 81%) mp (EtOAc/pet. ether) 146-148 °C; IR (KBr) υ_{max} 1618, 1570, 1507, 1223, 1101 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86 (d, J = 9.1 Hz, 1 H, H 4), 7.28 (dd, J = 9.1, 2.7 Hz, 1 H, H 3), 7.08 (d, J = 2.7 Hz, 1 H, H 1), 3.92 (s, 3 H, OCH_3), 3.02 (dd, J = 5.7, 5.0 Hz, 2 H, CH_2), 2.86 (dd, J = 5.6, 5.0 Hz, 2 H, CH_2), 1.89-1.94 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 157.8, 149.9, 143.7, 141.3, 130.3, 128.9, 127.8, 120.8, 101.3, 55.5, 27.4, 26.0, 22.2, 21.8; Anal. calcd for $C_{14}H_{14}ClNO$: C, 67.9 H, 5.7; N, 5.7; found C, 68.1; H, 5.6; N, 5.7%.

2-Methoxy-7,8,9,10-tetrahydrophenanthridine (**8**). A mixture of **7** (5.0 g, 20.2 mmol) and Pd/C (100 mg) in EtOH (200 mL) was stirred under an atmosphere of H_2 (60 psi) for 16 h at 20 °C. The mixture was filtered though celite, washed with EtOH (2 x 25 mL). The solvent was removed under reduced pressure and the residue partitioned between DCM (300 mL) and sat. aqueous $NaHCO_3$ (300 mL). The aqueous fraction was washed with DCM (100 mL) and the combined organic extracts dried (Na_2SO_4) and the solvent removed under pressure to give **8** (4.10 g, 95%) mp (EtOAc/pet. ether) 111-113 °C; (lit.[6] mp (light petrol) 109-110.5 °C) ; IR (KBr) υ_{max} 1620, 1504, 1224, 1103 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.48 (s, 1 H, H 6), 7.94 (d, J = 9.1 Hz, 1 H, H 4), 7.27 (dd, J = 9.1, 2.8 Hz, 1 H, H 3), 7.12 (d, J = 2.8 Hz, 1 H, H 1), 3.93 (s, 3 H, OCH_3), 3.00-3.06 (m, 2 H, CH_2), 2.85-2.91 (m, 2 H CH_2), 1.95-2.00 (m, 2 H, CH_2), 1.85-1.90 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 157.7, 150.0, 142.3, 139.8, 131.3, 129.9, 128.5, 119.8, 101.1, 55.4, 27.2, 25.0, 22.5, 22.2.

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REFERENCES AND NOTES

1. Hay, M.P., Wilson, W.R., and Denny, W.A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2829.

2. Hay, M.P. and Denny, W.A. *Drugs of the Future*, **1996**, *21*, 917.

3. Nicolaou, K.C., Maligres, P., Suzuki, T., Wendeborn, S.V., Dai, W.-M., and Chadra, R.K. *J. Amer. Chem. Soc.* **1992**, *114*, 8890.

4. Masamune, T., Takasugi, M., Suginome, H., and Yokoyama, M. *J. Org. Chem.* **1964**, *29*, 681.

5. Nicoloau, K.C. and Dai, W.-M. *J. Amer. Chem. Soc.* **1992**, *114*, 8908.

6. Hollingsworth, B.L. and Petrow, V. *J. Chem. Soc*, **1948**, 1537.

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