Synthesis of the necine base (−)-supinidine from (*S*)-glutamic acid

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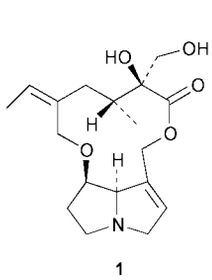
A route is described towards the pyrrolizidine† nucleus from derivatives of 5-acetylpyrrolidin-2-one using an intramolecular Wittig reaction with vinylphosphonium salts. The acetoxy ketone **15**, derived from (*S*)-*N*-benzyloxycarbonylpyroglutamic acid,‡ affords **16**, a known precursor of (−)-supinidine.

Introduction

The pyrrolizidine alkaloids such as retrorsine **1** are usually composed of two moieties, namely a necine base (a pyrrolizidine alcohol, exemplified by retronecine **2** and supinidine **3**) and a necic acid (usually a hydroxy carboxylic acid).[1] They have attracted much synthetic interest over recent years, partly because of their interesting range of biological activities, but also because they provide challenging targets for testing new synthetic methods. In particular, a range of methods has been reported towards the necine bases, resulting in both racemic and optically pure products.[1a–d] Many approaches to these pyrrolizidine alcohols build a second five-membered ring on to a preformed, functionalised pyrrolidine, though the final bond formed in the synthesis can be N–C3, C7a–C1 or C1–C2 (Fig. 1). Amongst many elegant approaches, those involving radicals,[2] acyliminium ions[3] and dipolar cycloadditions[4] are noteworthy.



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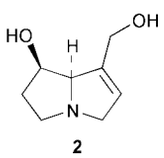

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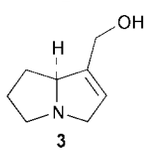
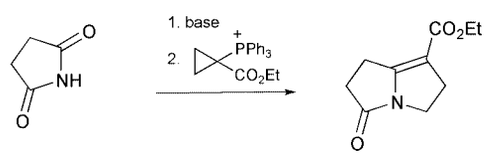


3

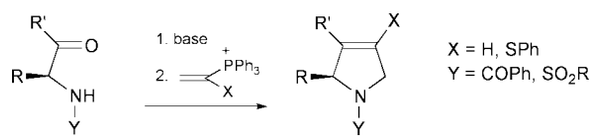
An approach using a Wittig reaction to effect ring closure (C7a–C1 bond formation) on to the carbonyl group of a succinimide derivative has also been reported (Scheme 1).[5]



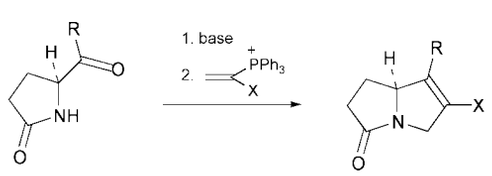
Scheme 1

We have previously described the use of the intramolecular Wittig reaction to form a range of carbocyclic[6] and heterocyclic compounds,[7] including a demonstration that the stereochemistry present in the reacting carbonyl compound is retained in the process (Scheme 2). We therefore hoped that necine bases should be obtainable by a related process (C1–C2 bond formation) using an appropriately functionalised pyrrolidin-2-one (Scheme 3), and we describe here the outcome of studies towards that end.

Fig. 1 Numbering system for pyrrolizidine nucleus.



Scheme 2



Scheme 3

Early development was directed towards (±)-supinidine **3**, and the procedure was then modified to provide the same compound in enantiomerically pure form.

Results and discussion

Treatment of (*S*)-glutamic acid with acetic anhydride–triethylamine–4-dimethylaminopyridine (Dakin–West reaction)[8] produced 1,5-diacetylpyrrolidin-2-one **4** which underwent base hydrolysis to give 5-acetylpyrrolidin-2-one **5**.[9] Unfortunately the Dakin–West reaction racemises the original α-amino acid so inevitably any alkaloid produced from **5** will be racemic, but it provides a readily available precursor to test the concept of the synthesis. Treatment of **5** with sodium hydride and the appropriate vinylphosphonium salt **6** or **7** gave the corresponding pyrrolizidine **8** (40%) or **9** (68%). In the latter case there was some difficulty in purification since the product co-chromatographed with triphenylphosphine oxide. This problem could be circumvented by using vinylphosphine oxide **10**[10] which afforded **9** (84%), in this case the phosphorus containing

† The IUPAC name for pyrrolizidine is hexahydro-1*H*-pyrrolizine.
‡ The IUPAC name for pyroglutamic acid is 5-oxopyrrolidine-2-carboxylic acid.

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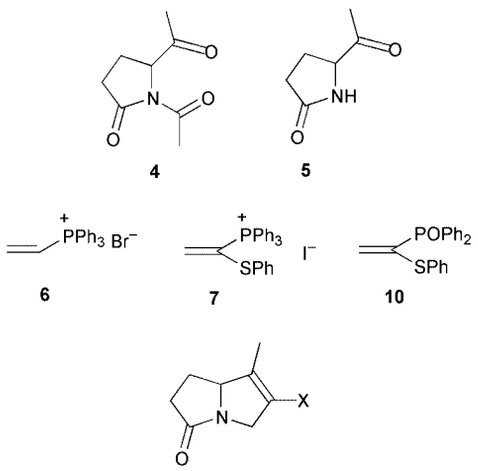
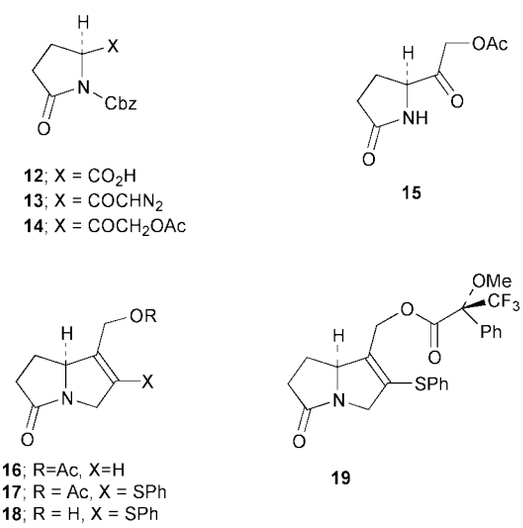
by-products being water soluble. The phenylthio group could be removed from **9** by treatment with Raney nickel (acetone–H_2O), giving **8** (47%), although this method was somewhat capricious and over reduction was often observed. The same transformation could be achieved less erratically by oxidation to the sulfone **11** which was reduced with sodium dithionite§[11] to provide **8** (40% from **9**). The ^{1}H NMR spectrum of **8** was in agreement with that described by Hart and co-workers,[12] who have previously converted to it to (±)-supinidine **3** by allylic acetoxylation followed by $LiAlH_4$ reduction.



The method was then extended to provide (−)-supinidine in the following way. The readily available (*S*)-*N*-benzyloxycarbonylpyroglutamic acid **12**[13] was converted to its acid chloride and then, by treatment with diazomethane, to the diazoketone **13** (84%) which was heated with acetic acid to provide the acetoxy ketone **14** (78%). The Cbz group was then removed from **14** by hydrogenolysis to give the pyrrolidin-2-one **15** which was cyclised with the vinylphosphonium salts **6** and **7** to provide the pyrrolizidines **16** (58%) and **17** (62%) respectively. In the latter case there was no advantage in using the vinylphosphine oxide **10**. The ^{1}H NMR spectrum of **16** was in total agreement with that previously described.[12]



Under the basic conditions of the cyclisation there is the possibility of **15** being racemised. In order to investigate the optical purity of the pyrrolizidine products, the ester **17** was hydrolysed to the corresponding alcohol **18** (77%) which was converted to the Mosher's ester **19**. Analysis of the ^{1}H and ^{13}C NMR spectra of **19** showed that it was >95% a single diastereoisomer and hence that there is little or no racemisation in the cyclisation reactions leading to **15** and **16**. Since **16** has been reduced[12,14] to supinidine, our route constitutes a new approach to the natural enantiomer of this necine base.

Experimental

General methods

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. Specific rotations were determined using a Perkin-Elmer 241 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were obtained on an ATI Mattson Genesis Series FTIR spectrophotometer. NMR spectra were obtained on a Bruker 250AC spectrometer. *J* values are quoted in Hz. Mass spectra and high resolution mass spectra were obtained on a VG Micromass 70/70F mass spectrometer fitted with a MSS data system. TLC was performed on Merck 555 Alufolien Kieselgel 60F_{254} plates, and flash chromatography was performed on Sorbsil C-60H (40–60 μm) silica gel. Light petroleum refers to the fraction boiling between 40 and 60 °C. Solvents were dried and distilled prior to use.

5,6,7,7a-Tetrahydro-1-methyl-2-phenylthiopyrrolizin-5(3*H*)-one 9

5-Acetylpyrrolidin-2-one **5** (1.51 g, 11.9 mmol) was dissolved in a mixture of THF (10 cm^3) and acetonitrile (40 cm^3) and sodium hydride (60% dispersion, 0.48 g, 12 mmol) was added. The mixture was stirred for 0.5 h and then diphenyl(1-phenylthiovinyl)phosphine oxide **10** (2.00 g, 6.0 mmol) was added and the stirring was continued overnight. After removal of the solvents, the residue was purified by flash chromatography with ethyl acetate–light petroleum (1 : 1) to give the product **9** as an oil (2.46 g, 84%) (Found M$^+$ 245.0852. $C_{14}H_{15}NOS$ requires 245.0874); ν_{max} (film)/cm^{-1} 3100, 1690, 1580; δ_H (250 MHz; $CDCl_3$) 1.83 (3H, s, CH_3), 1.90–2.95 (4H, m, CH_2CH_2), 3.55 (1H, m, NCH), 4.05–4.76 (2H, m, NCH_2), 7.15 (5H, br s, ArH); *m*/*z* 245(M$^+$), 230, 189, 136, 121, 55.

5,6,7,7a-Tetrahydro-1-methylpyrrolizin-5(3*H*)-one 8

(a) Prepared as described above for **9** but using vinyltriphenylphosphonium bromide. Oil (40%) (Found M$^+$ 137.0857. $C_8H_{11}NO$ requires 137.0841); ν_{max} (film)/cm^{-1} 1710, 1650; δ_H (250 MHz; $CDCl_3$) 1.70 (3H, s, CH_3), 1.90–2.95 (4H, m, CH_2CH_2), 3.50 (1H, m, NCH), 4.05–4.60 (2H, m, NCH_2), 5.26 (1H, br s, C=CH); *m*/*z* 137(M$^+$), 122, 81. (b) 5,6,7,7a-Tetrahydro-1-methyl-2-phenylthiopyrrolizin-5(3*H*)-one **9** (0.64 g, 2.6 mmol) was dissolved in methanol (50 cm^3) and a solution of Oxone® (6.2 g, 13.5 mmol) in water (50 cm^3) was added. The mixture was stirred overnight at room temperature, the methanol was removed on the rotary evaporator and the residue was diluted with water (50 cm^3) and extracted with ethyl acetate (3 × 25 cm^3). The organic extracts were dried ($MgSO_4$) and evaporated to give the crude sulfone **11**. This was dissolved in DMF (50 cm^3) and a solution of sodium hydrogen carbonate (1.1 g, 13 mmol) and sodium dithionite§ (1.1 g, 7 mmol) in water (50 cm^3) was added. The mixture was refluxed for 4 h, cooled and partitioned between 2 M aq. HCl (50 cm^3) and DCM (50 cm^3). The aqueous layer was extracted with DCM (2 × 20 cm^3) and the combined organic layers were washed with 2 M aq. HCl (2 × 20 cm^3), dried ($MgSO_4$) and evaporated to provide the crude product which was purified by flash chromatography with ethyl acetate–light petroleum (1 : 1) to give **8** as an oil (0.14 g, 40%) identical with that from (a) above.

§ The IUPAC name for sodium dithionite is sodium hydrosulfite.

(*S*)-*N*-Benzyloxycarbonyl-5-diazoacetylpyrrolidin-2-one 13

(*S*)-*N*-Benzyloxycarbonylpyroglutamic acid (6 g, 23 mmol) was dissolved in dry THF (50 cm^3) and cooled to 0 °C. Oxalyl chloride (6.43 g, 101 mmol) was added slowly with stirring. The mixture was then stirred at room temperature for 3 h and evaporated to leave the crude acid chloride. This was dissolved in dry THF (100 cm^3) and into it was distilled an ethereal solution of diazomethane obtained from diazald¶ (38 g) and potassium hydroxide (10.25 g). The reaction mixture was left to stand overnight and then concentrated under reduced pressure to give the product **13** as a pale yellow solid (8.68 g, 84%); mp 121–123 °C (MeOH) (Found: C, 58.3; H, 4.35; N, 14.35. $C_{14}H_{13}N_3O_4$ requires C, 58.52; H, 4.56; N, 14.63%); $[a]_D^{22}$ −27.2 (*c* 2.10 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3010, 2930, 2100, 1780, 1720, 1630; δ_H (250 MHz; $CDCl_3$) 2.03 (1H, m), 2.28 (1H, m), 2.50 (1H, m), 2.69 (1H, m), 4.57 (1H, m, NCH), 5.26 (3H, m, CHN_2 + OCH_2Ph), 7.34 (5H, m, ArH); *m*/*z* 287(M^+), 197, 115, 107, 91, 83, 55, 41.

(*S*)-5-Acetoxyacetyl-*N*-benzyloxycarbonylpyrrolidin-2-one 14

(*S*)-*N*-Benzyloxycarbonyl-5-diazoacetylpyrrolidin-2-one **13** (6.46 g, 23 mmol) was added to acetic acid (65 cm^3) and the mixture was refluxed for 1 h. The excess acetic acid was removed *in vacuo* to give the crude product which was purified by flash chromatography with ethyl acetate to give the product **14** as a white solid (5.6 g, 78%); mp 62–64 °C (Found: C, 66.6; H, 5.85; N, 4.65. $C_{16}H_{17}NO_6$ requires C, 66.89; H, 5.96; N, 4.88%); $[a]_D^{22}$ −38.4 (*c* 2.25 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3100, 2940, 1730, 1680; δ_H (250 MHz; $CDCl_3$) 2.13 (3H, s, CH_3), 2.01–2.63 (4H, m, 2 × CH_2), 4.57 (1H, d, *J* 17.0, OCH), 4.78 (1H, dd, *J* 9.5, 3, NCH), 4.83 (1H, d, *J* 17.0, OCH), 5.21 (2H, s, OCH_2Ph), 7.34 (5H, m, ArH); δ_C (62.5 MHz; $CDCl_3$) 20.6, 20.7, 31.2, 61.2, 66.4, 68.9, 128.4, 128.9, 129.0, 127.9, 131.3, 135.1, 151.3, 170.5, 173.2 and 201.3; *m*/*z* 319(M^+), 295, 218, 174, 107, 91, 85, 64, 43.

(*S*)-5-Acetoxyacetylpyrrolidin-2-one 15

(*S*)-5-Acetoxyacetyl-*N*-benzyloxycarbonylpyrrolidin-2-one **14** (3.0 g, 9.4 mmol) was dissolved in methanol (40 cm^3), 10% palladium on charcoal (0.5 g) was added and the mixture was stirred under hydrogen for 6 h. The catalyst was filtered off and the filtrate evaporated to give the product **15** as a white solid (1.51 g, 87%); mp 35–36 °C (Found: C, 51.7; H, 5.8; N, 7.75. $C_8H_{11}NO_4$ requires C, 51.89; H, 5.99; N, 7.56%); $[a]_D^{23}$ −24.1 (*c* 1.54 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3400–3300, 2940, 1740, 1700; δ_H (250 MHz; $CDCl_3$) 2.08 (3H, s, CH_3), 2.01–2.53 (4H, m, 2 × CH_2), 4.33 (1H, m, NCH), 4.76 (2H, s, CH_2), 7.66 (1H, s, NH); δ_C (62.5 MHz; $CDCl_3$) 20.6, 24.1, 29.6, 60.1, 66.2, 170.6, 179.9 and 203.0; *m*/*z* 185(M^+), 154, 84, 41.

(*S*)-5,6,7,7a-Tetrahydro-1-acetoxymethylpyrrolizin-5(3*H*)-one 16

(*S*)-5-Acetoxyacetylpyrrolidin-2-one **15** (0.23 g, 1.24 mmol) was dissolved in a mixture of THF (5 cm^3) and acetonitrile (20 cm^3) and sodium hydride (60% dispersion, 0.06 g, 1.5 mmol) was added. The mixture was stirred for 0.5 h and then vinyltriphenylphosphonium bromide (0.55 g, 1.5 mmol) was added and the stirring was continued overnight. After removal of the solvents the residue was purified by flash chromatography with ethyl acetate to give the product **16** as a pale yellow solid (0.14 g, 58%); mp 89–91 °C (Found: C, 61.3; H, 6.55; N, 6.95. $C_{10}H_{13}NO_3$ requires C, 61.53; H, 6.71; N, 7.17%); $[a]_D^{22}$ −19.8 (*c* 1.24 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3000–2880, 1740, 1700, 1650; δ_H (250 MHz; $CDCl_3$) 1.84–2.03 (1H, m), 2.09 (3H, s, CH_3), 2.29–2.46 (2H, m), 2.64–2.79 (1H, m), 3.72 (1H, br d, *J* 16.0, NCH), 4.40 (1H, br d, *J* 16.0, NCH), 4.65 (1H, m, NCH), 4.69 (2H, s, CH_2OCO), 5.81 (1H, s, C=CH); δ_C (62.5 MHz; $CDCl_3$) 21.0, 29.7, 33.7, 49.9, 60.1, 68.1, 123.5, 136.5, 170.8, 177.6; *m*/*z* 195(M^+), 135, 134, 122, 106, 93, 80, 79, 68, 55, 53, 52, 43.

(*S*)-5,6,7,7a-Tetrahydro-1-acetoxymethyl-2-phenylthiopyrrolizin-5(3*H*)-one 17

(*S*)-5-Acetoxyacetylpyrrolidin-2-one **15** (0.28 g, 1.51 mmol) was dissolved in a mixture of THF (5 cm^3) and acetonitrile (20 cm^3) and sodium hydride (60% dispersion, 0.07 g, 1.75 mmol) was added. The mixture was stirred for 0.5 h and then 1-(phenylthiovinyl)triphenylphosphonium iodide **7** (0.95 g, 1.8 mmol) was added and the stirring was continued overnight. After removal of the solvents the residue was purified by flash chromatography with ethyl acetate to give the product **17** as an oil (0.24 g, 62%) (Found M^+ 303.0920. $C_{16}H_{17}NO_3S$ requires 303.0929); $[a]_D^{22}$ −10.7 (*c* 1.10 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3080, 3000–2900, 2880, 1740, 1700, 1585; δ_H (250 MHz; $CDCl_3$) 1.81–2.02 (1H, m), 2.08 (3H, s, CH_3), 2.25–2.44 (2H, m), 2.60–2.78 (1H, m), 3.56 (1H, dd, *J* 14.7, 2.2, NCH), 4.27 (1H, br d, *J* 15.0, NCH), 4.72 (1H, m, NCH), 4.89 (2H, br s, CH_2OCO), 7.28 (5H, m, ArH); δ_C (62.5 MHz; $CDCl_3$) 21.0, 29.4, 33.5, 52.5, 58.5, 69.2, 127.6, 128.8, 129.7, 130.9, 132.8, 136.4, 170.9, 177.6; *m*/*z* 303(M^+), 277, 245, 244, 230, 210, 188, 186, 149, 134, 121, 109, 91, 77, 71, 55, 43.

(*S*)-5,6,7,7a-Tetrahydro-1-hydroxymethyl-2-phenylthiopyrrolizin-5(3*H*)-one 18

(*S*)-5,6,7,7a-Tetrahydro-1-acetoxymethyl-2-phenylthiopyrrolizin-5(3*H*)-one **17** (0.3 g, 1.15 mmol) was dissolved in methanol (5 cm^3), 2 M aq NaOH (20 cm^3), was added and the solution was stirred for 5 h. After removal of the methanol the residue was extracted with DCM (3 × 20 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue with ethyl acetate gave the product **18** as an oil (0.2 g, 77%) (Found M^+ 261.0839. $C_{14}H_{15}NO_2S$ requires 261.0824); $[a]_D^{22}$ −12.9 (*c* 1.10 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3400, 3100, 2960–2900, 1680, 1630; δ_H (250 MHz; $CDCl_3$) 1.92–2.95 (5H, m), 3.5 (1H, br s), 4.25 (2H, t, *J* 2, CH_2O), 4.45 (1H, m), 4.80 (1H, m), 7.1 (5H, m, ArH); δ_C (62.5 MHz; $CDCl_3$) 29.5, 33.3, 52.4, 58.5, 62.5, 127.4, 128.6, 129.7, 130.7, 132.9, 136.1, 177.6.

Mosher's ester 19

(*S*)-5,6,7,7a-Tetrahydro-1-hydroxymethyl-2-phenylthiopyrrolizin-5(3*H*)-one **18** (0.10 g, 0.35 mmol) was dissolved in DCM (10 cm^3) and (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (0.088 g, 0.38 mmol), DCC (0.083 g, 0.4 mmol) and DMAP (0.01 g) were added. The mixture was stirred at room temperature for 8 h, after which the consumption of **18** was complete, and filtered. The filtrate was washed with 2 M aq. HCl (10 cm^3), 2 M aq. NaOH (10 cm^3), and water (10 cm^3), dried ($MgSO_4$) and evaporated to give the crude product which was purified by flash chromatography with ethyl acetate–light petroleum (1 : 1) to give the product **19** as a colourless oil (0.14 g, 77%) (Found M^+ 478.1288. $C_{24}H_{23}F_3NO_4S$ requires 478.1300); δ_H (250 MHz; $CDCl_3$) 1.7–1.9 (1H, m), 2.15–2.4 (2H, m,), 2.6 (1H, ddd, *J* 16.2, 12.7, 8.3 Hz), 3.6 (4H, m + s), 4.25 (1H, dd, *J* 15.6, 3.6), 4.6 (1H, m), 5.1 (2H, s), 7.3–7.5 (10H, m); δ_C (62.5 MHz; $CDCl_3$) 28.6, 33.1, 52.4, 55.5, 59.8, 68.7, 121.3, 125.8, 127.4, 128.6, 128.8, 129.6, 129.8, 130.4, 132.1, 132.7, 134.5, 136.0, 166.5, 177.3.

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¶ The IUPAC name for diazald is *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide.

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