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A Total Synthesis of (-)-Ruspolinone

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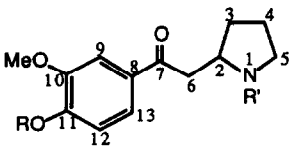
Abstract A synthesis of the pyrrolidine alkaloid (-)-ruspolinone (1) from (2S)-proline in 7 steps and 26% overall yield is presented which assigns the (2S) configuration to (-)-(1) The compound obtained by this route has $[\alpha]_D$ -29 73° compared to a value of zero for the material isolated from the plant suggesting racemisation had occurred during isolation

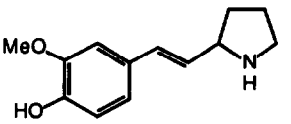
In 1978, three new pyrrolidine alkaloids were isolated from *Ruspolia hypercrateriformis*[1] Ruspolinone (1) and norruspolinone (2) were shown to possess the pyrrolidinylacetophenone skeleton whilst norruspoline (3) was shown to be based on the 1-aryl-2-pyrrolidin-2-ylethene structure It was recognised that ruspolinone (1) and norruspolinone (2) are plausible biosynthetic precursors to septicine (4), tylophorine (5), and related alkaloids[1] This possibility had been pointed out already, prior to the isolation of ruspolinone (1), and (1) had been synthesised[2] and used in a biomimetic synthesis of septicine (4)[2,3] and tylophorine (5)[3] The optical activity of septicine (4) and tylophorine (5) is well-established and the configuration of these alkaloids has been proven[4] although there are some questions regarding the optical purity of both isolated and synthetic septicine (4)[5] However, the ruspolinone (1) and norruspolinone (2) isolated from *Ruspolia hypercrateriformis* were found to be racemic[1] Given that septicine (4) and tylophorine (5) are optically active and given the known propensity for such β-amino ketones to undergo a reversible retro-Michael reaction[6], it seems likely that ruspolinone (1) and norruspolinone (2) were racemised during isolation Indeed, another very similar pyrrolidinylacetophenone alkaloid, (-)-phyllostone (6), has been isolated recently and shown to have a small negative optical rotation ($[\alpha]_D$ -5°)[7]. As part of a project concerned with the synthesis of single enantiomers from natural α-amino acids, we decided to attempt to prepare ruspolinone (1) in optically pure form In addition to the synthetic objective, we felt that such a synthesis would allow us to study the racemisation of ruspolinone (1) which might shed some light on its utilisation by the plant as a biosynthetic intermediate



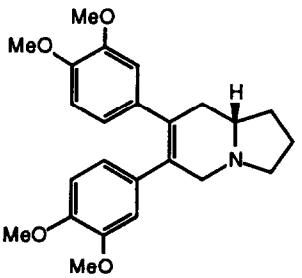
(1) R = Me, R' = H

(2) R = H, R' = H

(6) R = H, R' = Me



(3)



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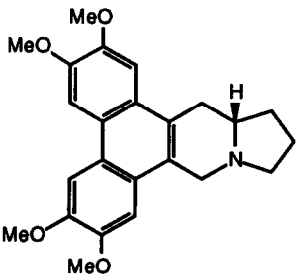
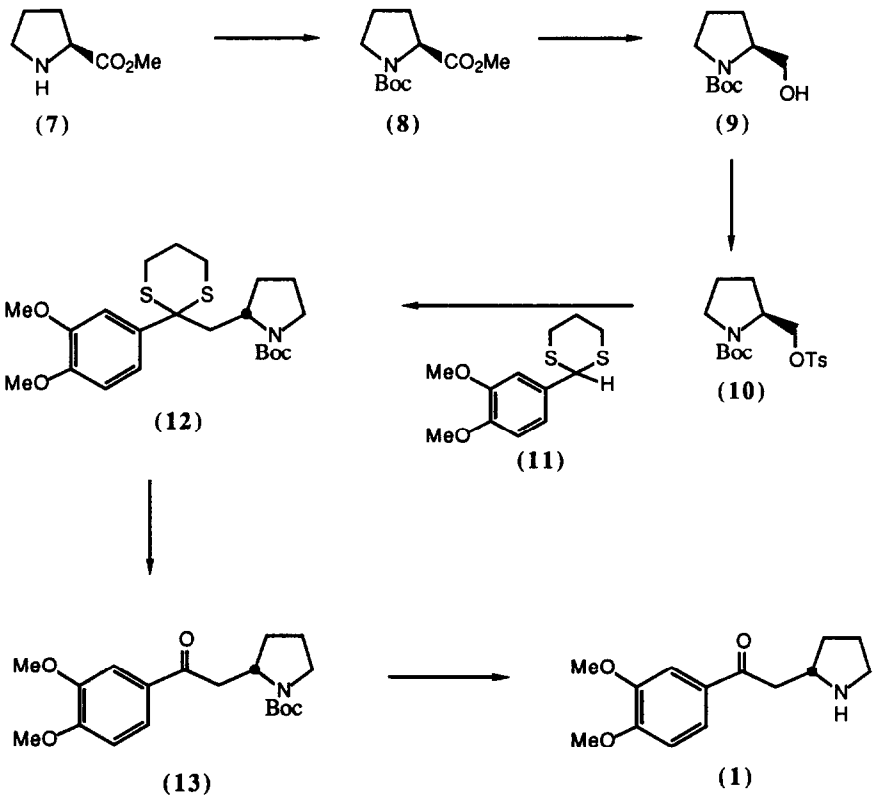


(5)

There have been two previous syntheses[2,8] of ruspolinone (1) neither of which addresses the problem of absolute stereochemistry Both utilise a disconnection of the C2/C6 bond at the chiral centre and consequently are not readily modified to incorporate absolute stereochemistry The first synthesis[2] involves condensation of a benzoylacetic acid with 1-pyrroline whilst the later[8] involves the condensation of a silyl enol ether with a 2-phenylsulphonylpyrrolidine In order to synthesise homochiral ruspolinone (1), we chose to explore the C6/C7 bond disconnection involving the reaction of a suitable prolinol derivative with a dithiane anion. We decided to begin the synthesis from (2S)-proline as this should give the correct optical isomer of ruspolinone (1) based on its presumed biosynthetic involvement.

The use of (2S)-proline in asymmetric synthesis has been recently reviewed[9] Our approach to ruspolinone is shown in the Scheme Reaction of (2S)-proline methyl ester (7)[10] with di-*t*-butyl dicarbonate in the presence of 4-dimethylaminopyridine (DMAP)[11] gave *N*-*t*-Boc-derivative (8) in 94% yield. Reduction of the ester function using $LiAlH_4$ in ether solution gave the *N*-*t*-Boc-prolinol (9) as a crystalline solid in 90% yield The optical purity of (9) was checked by comparison with a previous report[12] of the optical rotation of (9) which indicated our material to be of >97% e.e. and by synthesis of the Mosher's ester[13] Nmr studies revealed that the Mosher's ester of (9) was >95% one diastereomer[14]. Tosylation of (9) proceeded smoothly to give tosylate (10) in 83% yield after chromatography With tosylate (10) in hand, the stage was set for the crucial reaction with the lithiated dithiane derived from 3,4-dimethoxybenzaldehyde. Very few nucleophilic substitutions of such prolinol derivatives have been reported[15] However we were pleased to discover that

(10) reacted smoothly with the dithiane anion Treatment of dithiane (11)[16] with *n*-BuLi at -21°C generated the lithiated dithiane which underwent alkylation with tosylate (10) at the same temperature to give (12) in 76% yield. Thus, in spite of the relatively hindered primary centre in (10) and the presence of an electron-withdrawing group on the adjacent carbon, the crucial alkylation proceeded cleanly



Scheme

The remaining steps in the synthesis of ruspolinone (1) simply involve deprotection Removal of the dithiane group using NCS and silver nitrate[17] gave the *N*-*t*-Boc ruspolinone (13) as a crystalline solid in 73% yield Other methods for the removal of the dithiane group involving treatment with methyl iodide, $HgCl_2$, or chloramine-T gave considerably lower yields Finally, brief treatment of (13) with trifluoroacetic acid removed the *t*-Boc group to give (-)-ruspolinone (1) as a pale yellow powder in 87% yield The fact that this is the first time that ruspolinone (1) has been isolated as a crystalline solid could indicate that our material is of high optical purity The optical rotation of the (-)-ruspolinone (1) prepared by this route was measured as $[\alpha]_D^{25}$ -29 73° on freshly prepared material On standing in CH_2Cl_2 the observed rotation fell to zero over a period of 48 hours, a fact that shows how labile the chiral centre is in (1) and related alkaloids Although the magnitude of the optical rotation can be no guide to optical purity in this case, it is interesting to compare our value with that obtained for (-)-phyllostone (6) (see above). As these two molecules may be expected to

possess similar rotations, we would suggest that phyllostone (**6**) was partially racemised on isolation

In summary, we have prepared optically active (-)-ruspolinone (**1**) for the first time via a short (7 steps) high-yielding route (26% overall from (2S)-proline) Although we cannot be sure of the optical purity of our synthetic material owing to its facile racemisation, its optical rotation compares well with similar compounds In particular, we believe that the isolation techniques used to obtain ruspolinone (**1**) led to racemisation and those used to obtain phyllostone (**6**) led to partial racemisation Finally, we believe that naturally-occurring ruspolinone has the (2S)-configuration (from biosynthetic considerations) and this corresponds to (-)-ruspolinone

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Experimental

Solutions were dried over anhydrous magnesium sulphate and THF was distilled from potassium benzophenone ketyl immediately before use Purification was carried out by column chromatography using the flash chromatography technique Nmr were obtained on a Bruker AM360 operating at 360 MHz for ^{1}H and 90 MHz for ^{13}C and all spectra were recorded as solutions in $CDCl_3$ Mass spectra were run at the SERC Mass Spectrometry Centre, University College Swansea Optical rotations were obtained on a Perkin-Elmer 141 polarimeter at 25°C Melting points are uncorrected

(2S)-*N*-(*t*-Butoxycarbonyl)proline methyl ester (8)

To a solution of L-proline methyl ester (**7**) (0 71 g, 5 5 mmol) in dry dichloromethane (20 ml) was added *t*-butyl dicarbonate (2 64 g, 12 11 mmol), triethylamine (0 61 g, 6 05 mmol), and DMAP (0 74 g, 6 05 mmol) The mixture was stirred at room temperature under nitrogen for 18 hours It was then diluted with dichloromethane (50 ml) and washed with aqueous HCl (50 ml, 0 5 M), saturated $NaHCO_3$ solution (50 ml), and water (50 ml) The organic phase was dried and evaporation of the organic solution gave an oil that was purified by flash chromatography to give the product (**8**) as a clear oil (1 18 g, 94%), (Found C, 57 76, H, 8 44, N, 5 98, M^+, 229 1315 $C_{11}H_{19}NO_4$ requires C, 57 63, H, 8 35, N, 6 11%, M^+ 229 1314), $[\alpha]_D$ -52 47° (*c*0 99 in CH_2Cl_2), δ_H 1 40 (9H, s, *t*-Bu), 1 75 - 2 30 (4H, m, CH_2CH_2), 3 30 - 3 60 (2H, m, CH_2N), 3 70 (3H, s, OCH_3), 4 15 - 4 25 (1H, dd, *J*8 3 and 4 3 Hz, CHN), δ_C 23 6, 30 8 (CH_2CH_2), 28 2 ($C(\underline{C}H_3)_3$), 46 2 (CH_2N), 51 8 (OCH_3), 59 0 (CHN), 79.7 ($\underline{C}(CH_3)_3$), 153 7 (CON), 173 7 (COO), **m/z** 229 (M^+, 5%), 174 (30%), 128 (45%), 70 (100%)

(2S)-*N*-(*t*-Butoxycarbonyl) prolinol (9)

To a solution of the ester (**8**) (0 43 g, 2 0 mmol) in dry THF (10 ml) at 0°C under nitrogen was added $LiAlH_4$ solution (2 40 ml, 1 0 M) The mixture was stirred at 0°C for 2 hours and then ethyl acetate (5 ml) and KOH solution (10 ml, 20% w/v) added The mixture was extracted with ethyl acetate (50 ml) and the organic solution dried and evaporated The solid obtained was recrystallised from petroleum ether to give the product (**9**) (0 34 g, 90%), m p 57-58°C (Found C, 59 79, H, 9 57, N, 6 96, M^+, 201 1364 $C_{10}H_{19}NO_3$ requires C, 59 68, H, 9 51, N, 6 96%, M^+ 201 1365), $[\alpha]_D$ -47 24° (*c*0 91 in CH_2Cl_2), δ_H 1 45 (9H, s, *t*-Bu), 1 50 - 2 05 (4H, m, CH_2CH_2), 3 20 - 3 50 (2H, m, CH_2N), 3 50 - 3 65 (2H, m, CH_2O), 3 85 - 3 95 (1H, m, CHN), 3 90 - 4 10 (1H, br s, OH), δ_C 23 8 (CH_2CH_2), 28 4 ($C(\underline{C}H_3)_3$), 47 3 (CH_2N), 59 8 (CHN), 67 1 (CH_2O), 80 1 ($\underline{C}(CH_3)_3$), 156 2 (CON), **m/z** 202 (M^++H, 5%), 170 (15%), 146 (33%), 114 (40%), 70 (100%)

(2S)-*N*-(*t*-Butoxycarbonyl)-*O*-tosyl prolinol (10)

To a solution of the alcohol (**9**) (0 57 g, 2 84 mmol) in dry pyridine (5 ml) was added tosyl chloride (0 65 g, 3 40 mmol) The mixture was stirred at room temperature for 4 hours and then diluted with dichloromethane (50 ml) The solution was washed successively with dilute HCl (30 ml), saturated sodium bicarbonate solution (30 ml) and water (30 ml) The organic phase was dried and evaporated to give an oil which was purified by flash chromatography to give the product (**10**) (0 83 g, 83%) as a colourless oil (Found C, 57 39, H, 6 95, N, 3 88, M^+, 355 1450 $C_{17}H_{25}NO_5S$ requires C, 57 44, H, 7 09, N, 3 44%, M^+, 355 1453), $[\alpha]_D$ -39 57° (*c*0 74 in CH_2Cl_2), δ_H 1 45 (9H, s, *t*-Bu), 1 50-1 90 (4H, m, CH_2CH_2), 2 40 (3H, s, arylCH$_3$), 3 05-3 45 (2H, m, CH_2N), 3 75-3 85 (1H, m, CHN), 3 95-4 30 (2H, ABdd, *J*8 4 and 4 1 Hz, CH_2O), 7 30 (2H, d, *J*8 0 Hz, arylH), 7 70 (2H, d, *J*8 0 Hz, arylH), δ_C 21 4 (arylCH$_3$), 23 7, 28 5 (CH_2CH_2), 27 6 (C($\underline{C}H_3)_3$), 49 1 (CH_2N), 57 7 (CHN), 68 3 (CH_2O), 82 2 ($\underline{C}(CH_3)_3$), 127 5, 129 6, 133 9, 143 5 (arylC), 153 0 (CO), **m/z** 355 (M^+, 1%), 282 (12%), 170 (48%), 114 (91%), 91 (39%), 70 (100%)

(2"S)-2-(3',4'-Dimethoxyphenyl)-2-(*N*-*t*-butoxycarbonyl-2"-methylenepyrrolidine)-1,3-dithiane (12)

To a solution of 2-(3',4'-dimethoxyphenyl)-1,3-dithiane (**11**)[16] (0 26 g, 1 0 mmol) in dry THF (20 ml) under nitrogen at -21°C was added a solution of *n*-butyllithium in hexane (0 4 ml, 1 0 mmol) via syringe The pale yellow solution was stirred at -21°C for 30 minutes and a solution of the tosylate (**10**) (0 36 g, 1 0 mmol) in dry THF (10 ml) was added dropwise over 5 minutes Stirring was continued for one hour The reaction was quenched with saturated ammonium chloride solution (10 ml) and the product extracted with ether (50 ml) The ether layer was dried and evaporated to give an oil which was purified by flash chromatography to give the product (**12**) (0 34 g, 76%) as a colourless oil (Found. C, 60 02, H, 7 51, N, 3 25, M^+, 439 1851 $C_{22}H_{33}NO_4S_2$ requires C, 60 11, H, 7 57, N, 3 19%, M^+, 439 1851), $[\alpha]_D$ -35 34° (*c*2 1 in CH_2Cl_2), δ_H 1 25-1 40 (4H, m, CH_2CH_2), 1 45 (9H, s, *t*-Bu), 1 50-1 65 (2H, m, SSCCH$_2$), 1 75-2 00, 2 55-2 80 (6H, m, $CH_2CH_2CH_2$-dithiane), 3 10-3 35 (2H, m, CH_2N), 3 90 (6H, s, OCH_3), 4 05-4 15 (1H, m, CHN), 6 85 (1H, d, *J*8 3 Hz, C5'-H), 7 50 (1H, d, *J*2 3 Hz, C2'-H), 7 75 (1H, dd, *J*8 2 and 2 3 Hz, C6'-H), δ_C 24 9, 27 6 (C3",4"), 27 4 (C5), 28 2 (C($\underline{C}H_3)_3$), 31 2 (SSC$\underline{C}H_2$CHN), 45 8 (C1), 53 7 (CHN), 55 4 (OCH_3), 55 7 (OCH_3), 69 8 (CH_2N), 79 2 ($\underline{C}(CH_3)_3$), 110 7 (C5'), 112 0 (C2'), 121 4 (C6'), 133 7 (C1'), 147 8 (C3',4'), 154 (CO), **m/z** 439 (M^+, 2%), 276 (10%), 170 (28%), 114 (71%), 70 (91%), 41 (100%)

(2S)-*N*-*t*-Butoxycarbonyl ruspolinone (13)

To a solution of N-chlorosuccinimide (0 12 g, 0 91 mmol) and silver nitrate (0 17 g, 1 03 mmol), in 80% aqueous acetonitrile (10 ml) at room temperature was added the dithiane (**12**) (0 10 g, 0 23 mmol), and 2,6-lutidine (0 029 g, 0 27 mmol) dissolved in the same solvent (10 ml) The mixture was stirred for an hour and the precipitate filtered off and washed thoroughly with ethyl acetate (60 ml) Evaporation of the solvent gave an oil which was purified by flash chromatography to give (**13**) as an oil which solidified on standing This was recrystallised from petrol/dichloromethane to give (**13**) as colourless crystals (0 11 g, 73%), m p 99-100°C, (Found C, 65 31, H, 7 87, N, 3 94, M^+, 349 1889 $C_{19}H_{27}NO_5$ requires C, 65 39, H, 7 80, N, 4 01%, M^+, 349 1889), $[\alpha]_D$ -10 90° (*c*0 73 in CH_2Cl_2), δ_H 1 45 (9H, s, *t*-Bu), 1 70-2 10 (4H, m, CH_2CH_2), 2 65-2 80 (1H, m, $COCH_2$), 3 35-3 45 (1H, m, $COCH_2$), 3 30-3 40 (2H, m, CH_2N), 3 95 (6H, s, OCH_3), 4 25-4 35 (1H, m, CHN), 6 85 (1H, d, *J*8 4 Hz, C12-H), 7 55 (1H, m, C9-H), 7 65 (1H, m, C13-H), δ_C 23 1 (CH_2CH_2), 28 4 (C($\underline{C}H_3)_3$), 43 0 ($CO\underline{C}H_2$), 46 4 (CH_2N), 54 6 (CHN), 55 9 (OCH_3), 56 0 (OCH_3), 79 3 ($\underline{C}(CH_3)_3$), 109 9 (C12), 110 1 (C9), 123.1 (C13), 130 0 (C8), 148 9 (C10), 153 2

(C11), 154 3 (carbamate CO), 197 5 (ketone CO), **m/z** 349 (M^+, 1%), 248 (37%), 165 (84%), 70 (63%), 57 (100%)

(2S)-Ruspolinone (1)

To a solution of the carbamate (**13**) (0 15 g, 0 43 mmol) in dry dichloromethane (10 ml) was added trifluoroacetic acid (0.15 g, 1 29 mmol) The mixture was stirred at room temperature until no starting material could be observed by tlc Excess solvent was removed to leave an oil which was rapidly purified by flash chromatography (methanol ammonia solution dichloromethane, 17 1 2) The solid obtained was recrystallised from petrol/dichloromethane to give (2S)-ruspolinone (**1**) as a pale yellow powder (93 mg, 87%), m p 114-115°C (Found. C, 67 38, H, 7.65, N, 5 53, M^+, 249 1365 $C_{14}H_{19}NO_3$ requires C, 67 45, H, 7 68, N, 5 62, M^+, 249 1365), $[\alpha]_D$ -29 73° (*c*0 74 in CH_2Cl_2), δ_H 1 35-1 50, 1.70-1 90, 1 95-2 05 (4H, m, CH_2CH_2), 2 50 (1H, br s, NH), 2.92, 3 05 (2H, m, C5-H), 3.12 (1H, d, *J*7 Hz, C6-H), 3 13 (1H, d, *J*7 Hz, C6-H), 3 58 (1H, quintet, *J*7 Hz, C2-H), 3 91 (3H, s, OCH_3), 3 93 (3H, s, OCH_3), 6 86 (1H, d, *J*8 4 Hz, C12-H), 7 50 (1H, d, *J*2 Hz, C9-H), 7 58 (1H, dd, *J*8 4 and 2 Hz, C13-H) δ_H (protonated form) 1 75 (1H, m, CH_2CH_2), 2 05 (2H, m, CH_2CH_2), 2 80 (1H, m, CH_2CH_2), 3 33 (3H, m, C6-H_2 and C5-H), 3 67 (1H, dt, *J*17 and 7 7 Hz, C5-H), 3 86 (3H, s, OCH_3), 3 90 (3H, s, OCH_3), 4 07 (1H, quin, *J*7 Hz, C2-H), 6 80 (1H, 2d, *J*8 5 Hz, C12-H), 7 36 (1H, d, *J*2 1 Hz, C9-H), 7 47 (1H, dd, *J* 8 5 and 2 1 Hz, C13-H), 9 7 (br s, NH_2), δ_C 23 8, 30.7 (C3, C4), 40 2 (C6), 45 0 (C5), 55 7, 55 8, 56 0 (2xOCH_3, C2), 109 8 (C12), 110 1 (C9), 122 8 (C13), 129.1 (C8), 149 0 (C10), 153 7 (C11), 195 5 (C7), **m/z** 249 (M^+, 7%), 180 (53%), 165 (100%), 70 (70%)

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