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SYNTHESIS OF 3-CHLORO-2-FORMYLPYRROLE DERIVATIVES

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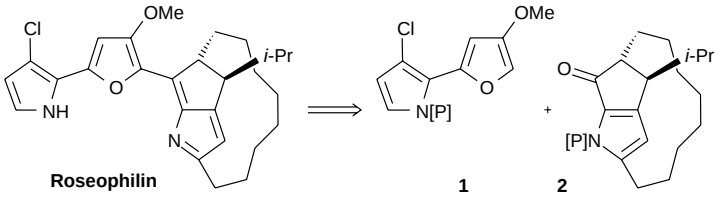
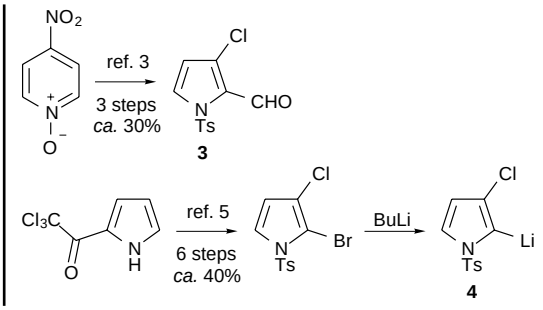
Abstract- Regioselective deprotonation of 3-chloro-1-tosylpyrrole is used to prepare the 2-formyl derivative. Application of this chemistry in a synthesis of the left hand pyrrolo-furan substructure of roseophilin is described.

The majority of reports concerning synthetic approaches to the cytotoxic antibiotic roseophilin[1] have focused on the preparation of a tricyclic pyrrolo-ketone 'right hand half' (**2**)[2] but the synthesis of the superficially simple bisheteroaromatic side-chain (**1**) is required for a total synthesis (Scheme 1). Only two syntheses of this fragment have appeared, both proceeding through 3-chloro-2-acylpyrrole derivatives at an early stage. Thus Terashima's route[3] initiates with pyrrole aldehyde (**3**) which was prepared in three steps from 4-nitropyridine *N*-oxide in an application of Streith's photochemical rearrangement optimised in the presence of Cu(II) salts.[4] Fürstner's route[5] proceeds through acylation of an organozinc species derived from 2-lithiopyrrole (**4**) in a sequence that is necessarily lengthy because these authors opted for a metal-halogen exchange method for generating the organometallic reagent (Scheme 2).



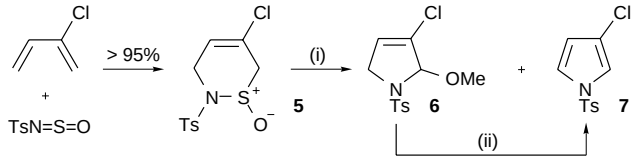
Scheme 1



Scheme 2

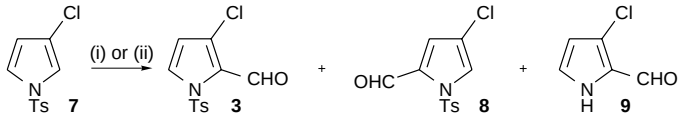
In this report we show that the 2-lithiopyrrole (**4**) can be obtained by direct deprotonation—which eases the synthesis of its immediate precursor—and that it can be formylated to give access to Terashima's intermediate (**3**). Furthermore we show that *in situ* detosylation of intermediate (**4**) can be used to advantage in a potential third synthesis of fragment (**1**). These results should be taken in the wider context of 3-halopyrrole synthesis since members of this class of molecules show a range of useful biological activities[6] and their general application in synthesis was highlighted recently by Ghosez.[7]

A short and efficient synthesis of 3-chloro-1-(*p*-toluenesulfonyl)pyrrole (**7**) from chloroprene has been described but in our hands the reported[8] procedure for the ring contraction of dihydrothiazine oxide (**5**) to the pyrrole was hampered by difficulties associated with separating the (assumed) trimethyl thiophosphate by-product and by the presence in the crude material of a second component assigned (by ^{1}H NMR spectroscopy, see EXPERIMENTAL) as the amino-acetal (**6**) (Scheme 3). Fortunately, stirring the crude product in MeOH in the presence of HCl (1 N, aq.) effected hydrolysis of the thiophosphate and completion of the aromatisation of compound (**6**) to the pyrrole (**7**). Reproducible yields of *ca.* 60 % were obtained under these conditions on a reasonable scale.



Scheme 3 *Reagents:* (i) Et_3N, $P(OMe)_3$, MeOH; (ii) aq. HCl, MeOH (59 %).

Deprotonation of pyrrole (**7**) with *n*-BuLi proved to be regioselective in favor of the 2-position (→ **4**), a further illustration of the *ortho*-effect of chlorine in directing aromatic deprotonations.[9] Thus, after quenching the deprotonated pyrrole with DMF, aqueous work-up provided three compounds: desired aldehyde (**3**), the regioisomer (**8**), and the detosylated compound (**9**). The ratio of these three products varied with the exact quantity of *n*-BuLi, and with the temperature and time of the deprotonation step and, to a lesser extent, of the formylation step. Conditions optimised for obtaining aldehyde (**3**) (in a 10:1 ratio with regioisomer (**8**)) are recorded in the Table. Whilst the *N*-tosylated products (**3**) and (**8**) could be readily separated from the free pyrrole (**9**) by chromatography they could not be separated from one another. However, that only detosylated compound (**9**) was formed in these reactions suggested that using an excess of *n*-BuLi during the deprotonation step would lead to selective detosylation[10] of regioisomer (**3**) to give separable pyrroles (**8**) and (**9**). This proved to be the case and conditions optimised for obtaining aldehyde (**9**) are also recorded in the Table.



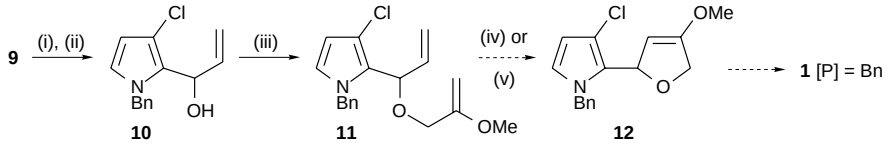
	Yield (%)		
Conditions	**3**	**8**	**9**
(i) *n*-BuLi (1.1 equiv.), THF, –78 °C, 1 h then DMF, –78 °C, 1 h	46	4.5	13
(ii) *n*-BuLi (2.5 equiv.), THF, –78 °C, 1.25 h then DMF, –78 °C, 1 h	—	21	64

Table

The regiochemistry of the formylation reaction and selective detosylation were supported by the ^{1}H NMR spectrum of pyrrole (**9**) which shows a characteristic five bond coupling constant between the formyl proton and 5-H (^5J = 1 Hz). This long range coupling has been attributed to a preferred *syn*- conformation

of the formyl group and a consequential zig-zag connectivity between the affected protons.[11]

From this aldehyde we envisaged a sequential RCM–oxidation route to complete the synthesis of the left hand half of roseophilin. Thus *N*-benzylation, Grignard addition (→ **10**), and etherification proceeded in high yield to generate metathesis precursor (**11**). However, whilst model studies[12] on compounds lacking the MeO- and Cl- substituents were promising this substrate could not be induced to form dihydrofuran (**12**), starting material being returned with Grubbs' ruthenium catalyst and decomposition predominating with the Schrock molybdenum catalyst.



Scheme 4 *Reagents:* (i) NaH, BnBr, THF (74 %); (ii) vinyl-MgBr, THF; (iii) NaH, 2-methoxyallyl bromide,[13] THF (80–92 % two steps); (iv) $Cl_2(Cy_3P)_2Ru{=}CHPh$ (0.2 equiv.), CH_2Cl_2; (v) 'Mo-F6' (0.2–1.0 equiv.), hexane.

In summary, we have shown that, under optimised conditions, 3-chloropyrrole (**7**) is deprotonated to give a 13:1 ratio of 2- and 5-lithio derivatives and that employing excess base results in selective detosylation to allow a single regioisomer of the 2-formyl derivative to be obtained in reasonable overall yield. Finally, we have provided preliminary results on an attempt to apply this chemistry to the synthesis of the pyrrolo-furan side chain (**1**) in roseophilin. Although it is disappointing that standard ring-closing metathesis conditions failed we are optimistic that alternative catalysts[14] will be more successful and investigations of this aspect are now underway.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer Paragon 1000 instrument; NMR spectra were run on Varian Gemini 200, Bruker DPX200, Bruker DPX400, and Bruker AMX500 machines; low resolution MS were recorded on either Micromass Platform APCI or VG Mass lab TRIO-1 GCMS spectrometers; HRMS were obtained by the EPSRC Mass Spectrometry Service Centre. Reagents were purified before use and reactions were routinely run in anhydrous solvents under an atmosphere of nitrogen or argon.

*3-Chloro-1-(*p-*toluenesulfonyl)pyrrole* (**7**)[8]

To a rapidly stirred solution of triethylamine (2.74 mL, 0.02 mol) and trimethyl phosphite (5.8 mL, 0.05 mol) in MeOH (200 mL) at rt was added dihydrothiazine oxide (**5**)[8] (12 g, 0.04 mol) and the mixture stirred for a further 14 h. The MeOH was removed *in vacuo*, the residue partitioned between ether and hydrochloric acid (1 N), and the organic layer was washed once with water then dried ($MgSO_4$), filtered, and concentrated to give an oil that by ^1H NMR spectroscopy contained the title compound (**7**) and amino-acetal (**6**) in a ratio of *ca.* 40:60 [characteristic peaks for **6**: δ_H (200 MHz, $CDCl_3$) 3.20 (3H, s), 3.97–4.20 (2H, m), 5.78 (1H, dd, *J* 4, 1.5 Hz), 5.99 (1H, apparent t, *J* 2.2 Hz)]. The oil was dissolved in MeOH (*ca.* 50 mL) and stirred with hydrochloric acid (1 N, *ca.* 25 mL) at rt for 1 h then the MeOH was removed

in vacuo, the residue dissolved in ether, and the organic solution washed successively with water and brine, then dried ($MgSO_4$), filtered, and concentrated to give a residue that was found to consist solely of pyrrole (**7**). Purification was achieved by flash chromatography (SiO_2, 20 % EtOAc/petrol) to yield the title compound (**7**) as a white solid (6.03 g, 59 %). Data as ref. 8.

*3-Chloro-2-formyl-1-(*p*-toluenesulfonyl)pyrrole* (**3**)[3]

To a solution of pyrrole (**7**) (127 mg, 0.5 mmol) in THF (12 mL) at –78 °C was added *n*-butyllithium (200 μL of a 2.5 M solution in hexanes, 0.5 mmol) and stirring continued for 1 h. DMF (40 μL, 0.52 mmol) was added and the mixture was stirred for a further 1 h at –78 °C then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. After warming to rt the mixture was partitioned between ether and water, the combined organic layers were washed with brine, then dried ($MgSO_4$), concentrated, and the residue purified by flash chromatography (SiO_2, 10 % EtOAc/petrol). The title compound (**3**)[3] was obtained as an inseparable mixture (yellow oil, 71 mg, 50 %) in a ratio of 10:1 with the regioisomer (**8**). ν_{max} (film)/cm^{-1} 3146m, 2849w, 1682s, 1595s, 1525s, 1372s, 1176s, 1127s, 1087s, 1030s, 946s, 767m; δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s), 6.39 (1H, d, *J* 3.4 Hz), 7.34 (2H, d, *J* 8.2 Hz), 7.68 (1H, d, *J* 3.4 Hz), 7.86 (2H, d, *J* 8.2 Hz), 9.88 (1H, s); δ_C (100 MHz, $CDCl_3$) 21.6, 113.3, 127.3, 128.4, 128.8, 130.2, 130.5, 134.6, 146.5, 177.2; *m/z* (C.I., NH_3) 174 (15), 157 (100), 156 (15 %); Anal. Calcd for $C_{12}H_{10}NO_3ClS$: C, 50.79; H, 3.55; N, 4.94. Found: C, 50.68; H, 3.33; N, 4.57. Key peaks for the minor regioisomer (**8**): δ_H (200 MHz, $CDCl_3$) 7.04 (1H, d), 7.52 (1H, d) and 9.97 (1H, s). Also obtained was the detosylated compound (**9**)[4] (9 mg, 14 %), data below.

3-Chloro-2-formylpyrrole (**9**)[4]

To a solution of pyrrole (**7**) (2.56 g, 0.01 mol) in THF (120 mL) at –78 °C was added *n*-butyllithium (15.6 mL of a 1.6 M solution in hexanes, 0.025 mol) and stirring continued for 1.25 h. DMF (2.3 mL, 0.03 mol) was added and the mixture was stirred for a further 1 h at –78 °C then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. After warming to rt the mixture was partitioned between ether and water, the combined organic layers were washed with brine, then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 10 % EtOAc/petrol) to give the title compound (**9**)[4] as a white solid (0.83 g, 64 %), mp 91–93 °C (lit.,[15] 100 °C); ν_{max} (KBr disk)/cm^{-1} 3255m, 1636s, 1409s, 1353s, 1289m, 780s, 742s; δ_H (200 MHz, $CDCl_3$) 6.30 (1H, apparent t, *J* 2.5 Hz), 7.03 (1H, apparent td, *J* 3.1, 1 Hz), 9.65 (1H, d, *J* 1 Hz), 10.0–10.9 (1H, br); *m/z* (C.I., NH_3) 149 (M(^{37}Cl)NH_4^+, 4), 147 (M(^{35}Cl)NH_4^+, 13), 132 (M(^{37}Cl)H^+, 28), 130 (M(^{35}Cl)H^+, 100 %).

1-Benzyl-3-chloro-2-formylpyrrole

To a suspension of NaH (170 mg of a 60 % dispersion in oil, 4.25 mmol) in THF (14 mL) at 0 °C was added pyrrole (**9**) (190 mg, 1.47 mmol). After 5 min, when evolution of hydrogen was complete, the cooling bath was removed and the mixture stirred for a further 0.5 h at rt then benzyl bromide (260 μL, 2.19 mmol) added. The reaction was complete (TLC) after *ca.* 36 h at rt. Water was added, the organic components were extracted into ether then the combined organic extracts were washed successively with

water and brine. The residue obtained after drying ($MgSO_4$) and removal of the solvent *in vacuo* was subjected to flash chromatography (SiO_2, 5 % EtOAc/petrol) to yield the product as a white solid (237 mg, 74 %), mp 51–52 °C; ν_{max} (KBr disk)/cm^{-1} 1661s, 1512w, 1407m, 1360m, 1328m, 773m, 718m; δ_H (200 MHz, $CDCl_3$) 5.52 (2H, s), 6.22 (1H, d, *J* 2.7 Hz), 6.88 (1H, d, *J* 2.7 Hz), 7.14–7.40 (5H, m), 9.78 (1H, s); *m/z* (C.I., NH_3) 222 ($M(^{37}Cl)H^+$, 25), 220 ($M(^{35}Cl)H^+$, 100), 91 ($C_7H_7^+$, 53 %); Accurate mass: Found 220.0529; $C_{12}H_{11}NOCl$ (MH^+) requires 220.0529.

1-Benzyl-3-chloro-2-(1-hydroxyprop-2-en-1-yl)pyrrole (**10**)

To a solution of 1-benzyl-3-chloro-2-formylpyrrole (520 mg, 2.37 mmol) in THF (50 mL) at 0 °C was added vinylmagnesium bromide (4.7 mL of a 1.0 M solution in THF, 4.7 mmol) and the mixture stirred for 30 min. The reaction was quenched with saturated NH_4Cl solution then partitioned between ether and water; the combined organic portions were washed with brine then dried ($MgSO_4$) and concentrated to yield the somewhat unstable crude product (**10**) as a yellow oil (593 mg, quant.) that was used directly in the next reaction. ν_{max} (film)/cm^{-1} 3681w, 3613w, 3020s, 1746w, 1670m, 1522m, 1421m, 1221s, 1028m, 929m, 730vs; δ_H (500 MHz, $CDCl_3$) 5.23 (2H, ABq, *J* 15.9 Hz), 5.20 (1H, apparent dt, *J* 10.4, 1.5 Hz), 5.30 (1H, apparent dt, *J* 17, 1.5 Hz), 5.5–5.58 (1H, m), 6.09 (1H, ddd, *J* 17, 10.4, 4.5 Hz), 6.16 (1H, d, *J* 3 Hz), 6.56 (1H, d, *J* 3 Hz), 7.09–7.40 (5H, m).

1-Benzyl-3-chloro-2-[1-(2-methoxyprop-2-en-1-yl)oxyprop-2-en-1-yl]pyrrole (**11**)

To a suspension of NaH (287 mg of a 60 % dispersion in oil, 7.18 mmol) in THF (50 mL) at 0 °C was added alcohol (**10**) (593 mg, 2.4 mmol) as a solution in THF (5 mL) and the mixture was stirred for 30 min. 2-Methoxyallyl bromide[13] (1.15 g, *ca.* 63 % pure, *ca.* 4.8 mmol) and tetrabutylammonium iodide (44 mg, 0.12 mmol) were added sequentially and the mixture was allowed to warm up to rt over 13 h. The reaction was quenched with water, the aqueous layer was extracted with ether, and the combined organic extracts were washed with brine then dried ($MgSO_4$) and concentrated to yield an oil. Purification by flash chromatography (SiO_2, 2:4:94 EtOAc:Et_3N:petrol) afforded the product (**11**) as a colorless oil (601 mg, 80 % from 1-benzyl-3-chloro-2-formylpyrrole). ν_{max} (film)/cm^{-1} 2936m, 1666m, 1630m, 1496m, 1453s, 1300s, 1258m, 1110s, 1079s, 926m; δ_H (500 MHz, $CDCl_3$) 3.55 (3H, s), 3.77 (2H, ABq, *J* 12.8 Hz), 4.05 (1H, d, *J* 2.2 Hz), 4.13 (1H, d, *J* 2.2 Hz), 4.91 (1H, d, *J* 6.7 Hz), 5.14 (2H, ABq, *J* 15.4 Hz), 5.13 (1H, apparent dt, *J* 10.6, 1.6 Hz), 5.20 (1H, apparent dt, *J* 17.3, 1.6 Hz), 5.99 (1H, ddd, *J* 17.3, 10.6, 6.7 Hz), 6.08 (1H, d, *J* 3 Hz), 6.46 (1H, d, *J* 3 Hz), 7.08 (2H, 2 x d, *J* 7.1 Hz), 7.25–7.32 (3H, m); δ_C (125 MHz, $CDCl_3$) 51.5, 54.9, 68.4, 72.6, 83.5, 107.8, 112.7, 116.1, 121.9, 125.3, 127.4, 127.5, 128.5, 136.4, 137.7, 159.8; *m/z* (C.I., NH_3) 320 ($M(^{37}Cl)H^+$, 3), 318 ($M(^{35}Cl)H^+$, 8), 261 (10), 232 (54), 230 (100), 91 (35), 89 (54 %); Anal. Calcd for $C_{18}H_{20}NO_2Cl$: C, 68.03; H, 6.34; N, 4.41. Found: C, 68.58; H, 6.00; N, 4.40; Accurate mass: Found 318.1259; $C_{18}H_{21}NOCl$ (MH^+) requires 318.1261.

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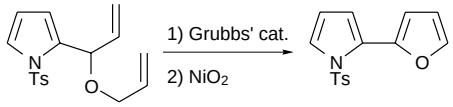

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