A Sulfone-mediated Synthesis of (+)-Preussin

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Abstract: The synthesis of the antifungal pyrrolidine (+)-preussin is described, utilising the 5-*endo-trig* cyclisation of a vinylic sulfone generated in situ to give the requisite pyrrolidine nucleus.

Key words: cyclisation, natural products, stereoselectivity, sulfones, total synthesis

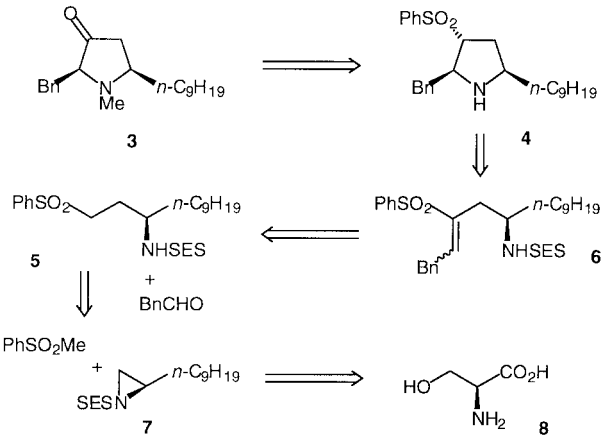
We have been evaluating the utility of 5-*endo-trig* cyclisations of sulfonyl-substituted amines and alcohols for the construction of heterocycles including pyrrolidines,[1] and reported quite recently the application of this methodology to the synthesis of the indolizidine alkaloid (+)-monomorine I **1** (Figure). The final stage in this synthesis was the reductive removal of the phenylsulfonyl moiety, and we were keen to exploit further the diverse reactivity of this versatile functional group.[2] It occurred to us that hydroxy-substituted pyrrolidines should be accessible from the 5-*endo-trig* cyclisation products simply by oxidation of the sulfone-stabilised carbanion[3] and subsequent reduction of the product ketone. Isolated and characterised in 1988,[4] the disubstituted hydroxypyrrolidine antifungal agent (+)-preussin **2** has been the subject of a number of synthetic approaches,[5] and the all-*syn* disposition of the pyrrolidine substituents made it an ideal target upon which to evaluate the proposed extension of our methodology. We report herein the sulfone-mediated total synthesis of **2** (Figure).

(+)-monomorine I
1

(+)-preussin
2

Figure

Our initial retrosynthetic analysis of (+)-preussin was adapted from the synthesis of (+)-monomorine I (Scheme 1). We had found[6] subsequent to the monomorine work that *N*-2-(trimethylsilyl)ethylsulfonyl-protected (*N*-SES-protected) vinylic sulfone-containing amines such as **6** could be synthesised in a one-pot olefination procedure by combination of aldehydes with the adducts of (phenylsulfonyl)methane and aziridines, such as **5**. This work had demonstrated further that sulfonamides related to **6** underwent desulfonylation and cyclisation in situ upon treatment with *n*-Bu_4NF, giving pyrrolidines analogous to **4**. For the synthesis of **2**, precursor ketone **3** would be made by oxidation of the sulfone-stabilised carbanion generated from the *N*-methyl derivative of **4**. In particular, it was felt that the use of readily enolisable phenylacetaldehyde as the coupling partner in the preparation of substrate **6** would provide a rigorous test of the applicability of this one-pot method. Precursor aziridine **7**, formally derived from a D-aminoacid would be accessed from L-serine **8** by reversing the relative oxidation levels at C1 and C3.



Scheme 1

Aziridine **7** was made using an adaptation of the work of Rapoport (Scheme 2).[7] Thus, addition of excess *n*-octylmagnesium iodide–*n*-butyllithium to *N*-tosyl-L-serine[8] provided ketone **9**, which was deoxygenated to give the *N*-protected amino alcohol **10** by conversion into the dithiane under standard conditions and subsequent treatment with Raney nickel. This was cyclodehydrated by treatment with TsCl-KOH[9] to provide the corresponding *N*-tosylaziridine **11** in near-quantitative yield. Finally, replacement of the *N*-tosyl protecting group with the SES function[10] was achieved by reductive desulfonylation followed by re-sulfonylation using SESCl-DMAP in the presence of base, giving **7** in 12% overall yield from L-serine (39% from ketone **9**). The instability of the SES protecting group towards the excess organometallic reagent used in the conversion **8**→**9** precluded its incorporation from the outset, necessitating the desulfonylation–resulfonylation sequence.

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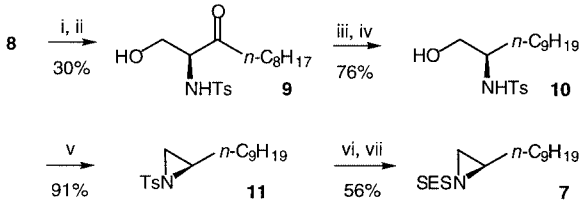
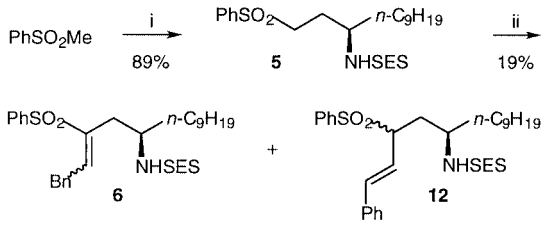


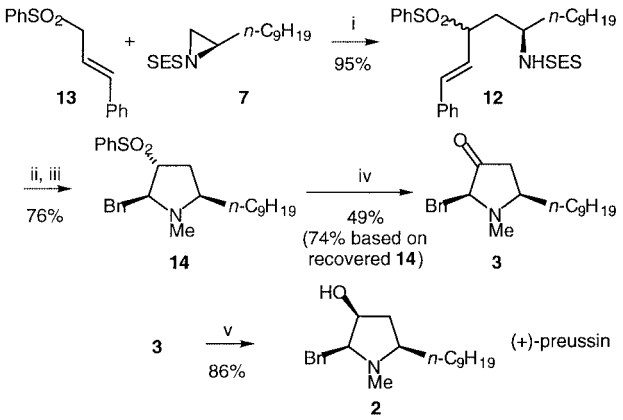
Scheme 2 *Reagents and conditions:* (i) 2 M NaOH, TsCl, H_2O, EtOAc; (ii) *n*-BuLi (2 equiv), $H_{17}C_8MgI$ (4 equiv), THF, Et_2O; (iii) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (iv) Ni*(R)*, EtOH, reflux; (v) KOH, TsCl, THF, r.t.; (vi) Na, naphthalene, THF, –78 °C; (vii) SESCl, DMAP, Et_3N, CH_2Cl_2, 0 °C

Aziridine **7** reacted smoothly with the lithio-anion of (phenylsulfonyl)methane to give the expected adduct **5**. Double deprotonation of **5** followed by sequential addition of phenylacetaldehyde and benzoyl chloride under the conditions which had been successful with less readily enolisable coupling partners[6] gave the *allylic* sulfone **12** in low yield, with virtually none of the desired vinylic sulfone **6** (Scheme 3).



Scheme 3 *Reagents and conditions:* (i) *n*-BuLi, THF, TMEDA, –78 °C, add **7**, –78 °C→r.t., 89%; (ii) *n*-BuLi, THF, –78 °C then phenylacetaldehyde, then BzCl

Though unwelcome, these observations appeared to be fully consistent with the greater thermodynamic stability of allylic sulfones compared with their vinylic isomers and the acidity of the phenylacetaldehyde α-protons. It occurred to us that **12** might itself be a substrate for 5-*endo-trig* cyclisation, since the fluoride-containing medium should be sufficiently basic to promote equilibration of unsaturated sulfone isomers **6** and **12**. This modified approach appeared especially attractive because substrate **12** could in principle be made simply by combining the appropriate allylic sulfone anion with **7**, thereby making the synthesis more convergent. In the event, reaction of the lithio-anion of *(E)*-3-phenyl-1-(phenylsulfonyl)-2-propene[11] **13** with **7** gave directly a diastereomeric mixture of the adducts **12** in excellent yield. Treatment of **12** with excess *n*-Bu_4NF gave pyrrolidine **4** in high yield as a single stereoisomer, having the 2,3-*anti*, 2,5-*syn* stereochemistry observed previously in 5-*endo-trig* cyclisations of this type.[1b,c] Although **4** could have been formed by direct 5-*exo-trig* cyclisation of **12**, it seems unlikely that an unsubstituted phenyl group would confer sufficient electrophilicity on the styryl linkage for cyclisation to occur. Also, although substrate **12** was an epimeric mixture at the sulfone centre, product **4** was a single diastereomer. Therefore, for 5-*exo-trig* cyclisation to have occurred either (i) the two epimers of **12** cyclised with mutually opposite stereochemistry relative to the phenylsulfonyl group, and epimerisation of the sulfonyl stereocentre in one of the isomers occurred post-cyclisation, or (ii) one of the two epimers of **12** was unreactive, equilibrating with the reactive isomer prior to stereoselective cyclisation; both these scenarios seem relatively unlikely given the facility of 5-*endo-trig* cyclisation in the absence of the competing 5-*exo* pathway.[1b,c] Compound **4** was next subjected to reductive amination[5i] to give the *N*-methyl derivative **14**. Reaction of the derived lithio-anion with TMSOOTMS[12] provided ketone **3**[5e] which was reduced to give (+)-preussin **2**. Compound **2** prepared in this way had spectral characteristics identical with those reported for the natural product.[4,5] The completion of the synthesis of **2** is depicted in Scheme 4.[13]



Scheme 4 *Reagents and conditions:* (i) add *n*-BuLi to **13**, THF, TMEDA, –78 °C, then add **7**, –78 °C→r.t.; (ii) TBAF (15 equiv), THF, reflux, 38 h; (iii) HCHO (aq), $NaCNBH_3$, AcOH, MeCN; (iv) *n*-BuLi, THF, then TMSOOTMS; (v) $LiAlH_4$, THF, –78 °C

In summary, a 12-step synthesis of (+)-preussin **2** from *(E)*-3-phenyl-1-(phenylsulfonyl)-2-propene and L-serine has been achieved. During the course of this investigation a new mode of 5-*endo-trig* cyclisation has been uncovered in which the requisite vinylic sulfone is generated in situ from a more readily available allylic precursor, and this renders the approach more convergent. We are currently evaluating the generality of this isomerisation–cyclisation process, and are assessing its utility in the synthesis of more complex pyrrolidine-containing targets. The results of these investigations will be reported in due course.

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(13) Preparation of **4**.
A solution of **12** (640 mg, 1.08 mmol) in TBAF (16.22 mL of a 1 M solution in THF, 16.22 mmol, 15 equiv) was heated under reflux under nitrogen for 38 h. MeOH (5 mL) was added to the cooled solution followed by water (50 mL). The mixture was extracted with EtOAc (2 × 50 mL) and the combined organic layers dried ($MgSO_4$), and concentrated under reduced pressure. Chromatographic purification (SiO_2; 30% EtOAc-petrol) of the crude product gave [2*S*,3*R*,5*R*]-2-benzyl-3-phenylsulfonyl-5-nonylpyrrolidine **4** (360 mg, 0.842 mmol, 78%) as a clear oil; $[\alpha]_D^{20}$ –9.6 (*c* 4.16, $CHCl_3$); ν_{max}(film) 3336, 3084, 3066, 3032, 3003, 2981, 2954, 2924, 2848, 2731, 2669, 1603, 1585, 1495, 1446, 1406, 1377, 1304, 1176, 1145, 1086, 1028 cm^{-1}; δ_H (300 MHz) 7.97–7.91 (2 H, m, Ar), 7.73–7.57 (3 H, m, Ar), 7.32–7.10 (5 H, m, Ar), 3.76 (1 H, ddd, *J* 9.0, 7.0, 3.5 Hz, H-2), 3.36 (1 H, ddd, *J* 10.5, 7.0, 3.5 Hz, H-3), 3.08 (1 H, dq, *J* 10.0, 6.5 Hz, H-5), 2.82 (1 H, dd, *J* 13.5, 3.5 Hz, C*H*HPh), 2.64 (1 H, dd, *J* 13.5, 9.0 Hz, CH*H*Ph), 2.40 (1 H, ddd, *J* 13.5, 6.5, 3.5 Hz, H-4), 1.88 (1 H, br s, N-H), 1.57 (1 H, dt, *J* 13.5, 10.0 Hz, H-4), 1.49–1.15 (16 H, m, $(CH_2)_8$), 0.89 (3 H, t, *J* 6.5 Hz, CH_3); δ_C (75 MHz) 139.0, 138.4, 134.0, 129.6, 129.4, 128.8, 128.7, 126.8, 67.3, 60.7, 58.4, 41.8, 35.9, 34.3, 32.0, 29.9, 29.7 (2 C), 29.5, 27.2, 22.8, 14.3; *m*/*z* (CI) 428 $[MH]^+$ (Found: $[MH]^+$, 428.2615; $C_{26}H_{37}NO_2S$ requires $[MH]^+$, 428.2623).

Preparation of **3**.
To a stirred solution of sulfone **14** (164 mg, 0.371 mmol) in THF (2 mL) at –78 °C under nitrogen was added *n*-BuLi (165 μL of a 2.7 M solution in hexanes, 0.446 mmol, 1.2 equiv) to give a pale yellow solution. After 15 min a solution of TMSOOTMS (86 mg, 0.483 mmol, 1.3 equiv) in THF (0.5 mL) was added via syringe. The solution was allowed to attain r.t. over 2 h, and then stirred at r.t. for a further 15 h. After quenching with saturated aqueous $NaHCO_3$ (15 mL) the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude product was purified by chromatography (SiO_2; 20% EtOAc-petrol) to give recovered starting material **14** (55 mg, 34%) and [2*S*,5*R*]-2-benzyl-1-methyl-5-nonyl-3-oxo-pyrrolidine **3** (57 mg, 49%, 74% based on recovered **14**) as a pale yellow oil; $[\alpha]_D^{20}$ –97.9 (*c* 1.43, $CHCl_3$); ν_{max}(film) 3055, 2956, 2927, 2856, 1751, 1411, 1379, 1265, 1151, 1115, 1082 cm^{-1}; δ_H (300 MHz) 7.32–7.15 (5 H, m, Ph), 3.08 (1 H, dd, *J* 14.0, 4.5 Hz, C*H*HPh), 2.87 (1 H, dd, *J* 14.0, 5.0 Hz, CH*H*Ph), 2.78 (1 H, distorted t, H-2), 2.55-2.44 (1 H, m, H-5), 2.41 (1 H, dd, *J* 17.5, 6.0 Hz, H-4), 2.33 (3 H, s, NMe), 1.79 (1 H, dd, *J* 18.0, 10.5 Hz, H-4), 1.40–1.10 (16 H, m, $(CH_2)_8$), 0.91 (3 H, t, *J* 6.5 Hz, CH_2CH_3); δ_C (75 MHz) 215.0, 138.7, 129.9, 128.2, 126.3, 74.5, 62.6, 42.9, 39.4, 36.1, 33.1, 32.1, 30.0, 29.7 (2C), 29.5, 25.8, 22.9, 14.3; *m*/*z* (CI) 306 $[MH]^+$ (Found: $[MH]^+$, 316.2637; $C_{21}H_{33}NO$ requires $[MH]^+$, 316.2640).