A silicon controlled total synthesis of the antifungal agent (+)-preussin

Rekha Verma and Sunil K. Ghosh*

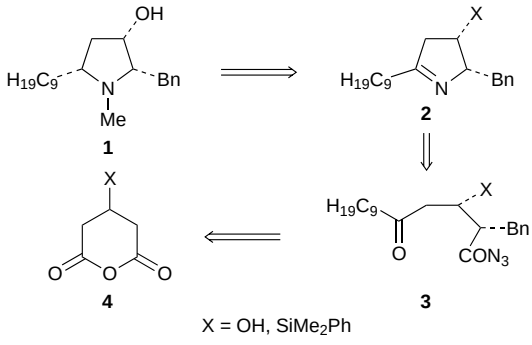
Bio-Organic Division, Bhabha Atomic Research Centre, Trombay, Mumbai 400 085, India

A stereoselective total synthesis of (+)-preussin has been achieved from a *meso* anhydride featuring a dimethyl(phenyl)silyl group as a masked hydroxy group which also restricts elimination reactions, stereodirects hydrogenation and ester enolate alkylation, and facilitates Curtius reaction.

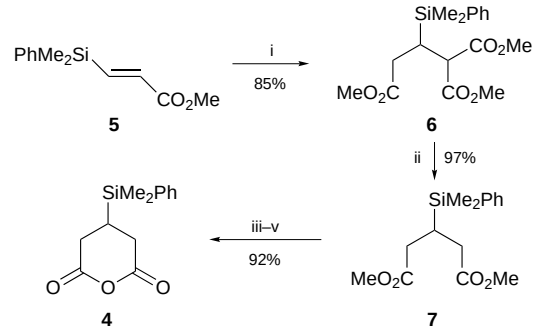
(+)-Preussin, (2*S*,3*S*,5*R*)-1-methyl-5-nonyl-2-benzylpyrrolidin-3-ol (also known as L-657,398), **1** was isolated from the fermentation broths of *Aspergillus ochraceus* ATCC 22947 and *Preussia sp.*[1] This structurally novel pyrrolidine alkaloid has broader spectrum antifungal activity against both filamentous fungi and yeasts than the structurally related antibiotic anisomycin. The first total synthesis of (+)-preussin was reported by Pak and Lee[2] taking D-glucose as a substrate. Four more syntheses have been published subsequently using (*S*)-phenylalanine[3] and its enantiomer[4] as starting materials.

A simple retrosynthetic analysis could be postulated for (+)-preussin **1** from *meso* anhydride **4**[5] *via* Δ^1-pyrroline **2** as shown in Scheme 1 (X = OH). However, as pointed out by Livinghouse,[3a] an intermediate like **2** is unstable due to the ease of elimination of the protected or unprotected OH group to provide a pyrrole derivative. Therefore, a substitute for this group is desirable which would resist elimination, could be stereospecifically converted to a hydroxy group when desired, could possibly stereodirect both saturation of the Δ^1-pyrroline system and introduction of the benzyl group, and possibly facilitate the Curtius reaction of **3**. Considering all these requirements, we envisaged that a dimethyl(phenyl)silyl ($PhMe_2Si$) group would be an ideal substitute. It is known to be a poor leaving group and, as shown by Fleming,[6] it can be stereospecifically converted to a hydroxy group with retention of configuration. They have further shown that β-silyl ester enolate alkylations occur with high *anti* stereoselectivity.[7] Moreover, we have found that a β-silicon group facilitates the Curtius reaction of acyl azides‡ in close analogy to silicon directed Bayer–Villiger oxidation of β-silyl ketones.[8]

The starting *meso* anhydride **4** could easily be obtained in a few steps from β-silyl acrylate **5**[9] *via* the triester **6** and Fleming's *meso* diester **7**[10] as depicted in Scheme 2. When **4** was opened up with (±)-naphthylethanol **8**, it was expected to show good diastereocontrol, as observed by Fleming and Ghosh[11] for the opening up of a 3,4-bis-silyl substituted *meso* adipic anhydride. However, we obtained an inseparable 85 : 15



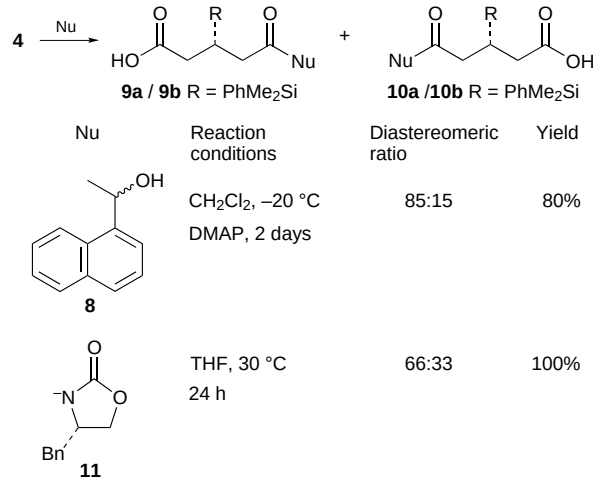
Scheme 1



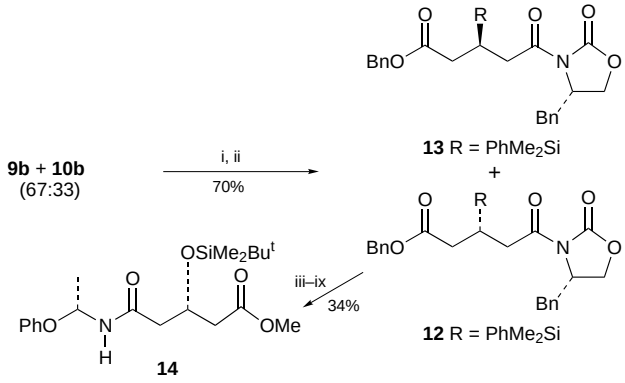
Scheme 2 *Reagents and conditions*: i, NaOMe, dimethyl malonate, room temp., 48 h; ii, NaCl, DMSO, H_2O, heat, 2.5 h; iii, KOH, MeOH, H_2O, room temp., 48 h; iv, dil. HCl; v, Ac_2O, reflux, 2.5 h

mixture of diastereoisomeric acids **9a** and **10a** (stereochemistry not determined) (Scheme 3) in 80% yield. In a related study, Theisen and Heathcock[5a] have also observed that 3-alkyl substituted glutaric anhydrides show poor diastereocontrol with increasing size of the alkyl groups. Alternatively, we opened up the anhydride with the lithium anion of the Evans' auxiliary[12] **11** which quantitatively provided a mixture of diastereoisomeric acids **9b** and **10b** in a ratio of *ca.* 67 : 33 (analysed as their methyl esters by NMR spectroscopy). To the best of our knowledge, this forms the first example of the desymmetrization of a *meso* anhydride using an anion of a chiral imide. Although the selectivity was low, the benzyl esters **12** and **13**‡ of these acids were easily separable by chromatography. The absolute stereochemistry of the major acid **9b** was established by converting it to a known derivative **14**[5b] following the reactions depicted in Scheme 4.

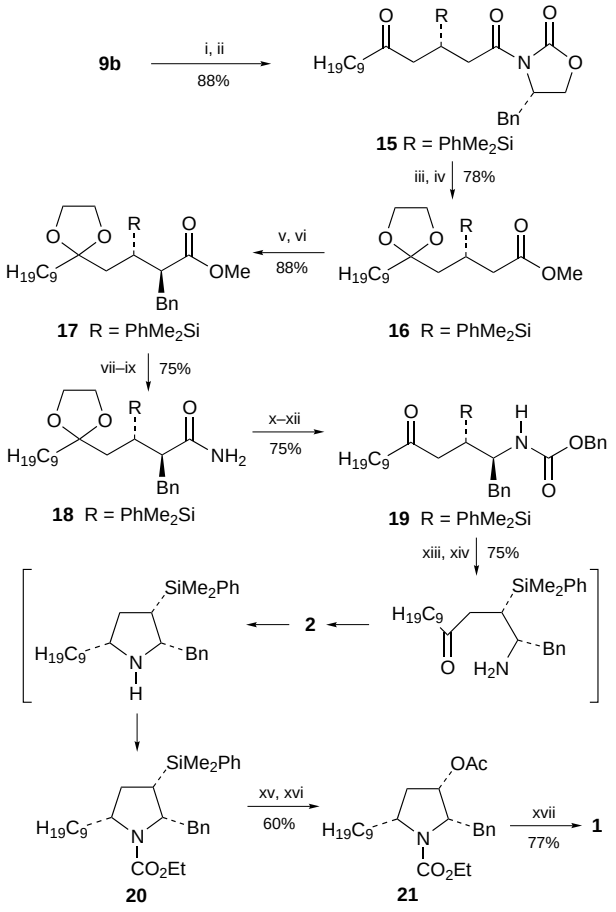
The major acid **9b** was converted to the ketone **15** in 60% yield (88% based on recovered **9b**) (Scheme 5), which was quantitatively protected[13] as the acetal and the auxiliary was removed[12] to provide the homochiral methyl ester **16** in 78% yield.§ We could recover the auxiliary in 78% yield (> 99% considering the wrong attack on the auxiliary) without any loss



Scheme 3



Scheme 4 *Reagents and conditions*: i, Et_3N, PivCl, −78 to 0 °C, 1 h; ii, BnOH, DMAP, room temp., 24 h; iii, chromatographic removal of **13**; iv, H_2, 10% Pd–C; room temp., 24 h; v, KBr, NaOAc, AcOOH, room temp., 24 h; vi, (*S*)-phenylethylamine, DCC, DMAP, room temp., 24 h; vii, LiOOH, THF, 0 °C, 40 min; viii, CH_2N_2; ix, Bu^tMe_2SiCl, DMF, imidazole, room temp., 15 h



Scheme 5 *Reagents and conditions*: i, Et_3N, PivCl, −78 to 0 °C, 1 h; ii, $C_9H_{19}MgBr$, −25 °C, 48 h; iii, 1,2-bis(trimethylsilyloxy)ethane, $Me_3SiOSO_2CF_3$, −20 °C, 48 h; iv, MgOMeBr, THF, 30 °C, 18 h; v, LiTMP, THF–DMPU, −78 °C, 1 h; vi, BnBr, −78 to −10 °C, 60 h; vii, KOH, MeOH, H_2O, 80 °C, 32 h; viii, Im_2CO, room temp., 30 min; ix, liq. NH_3; x, $Pb(OAc)_4$, BnOH, DMF, 100 °C, 15 h; xi, TsOH, acetone, H_2O, reflux, 2.5 h; xii, chromatographic removal of minor diastereoisomer; xiii, H_2, 10% Pd–C, EtOH, AcOH, 7 h; xiv, EtOCOCl, Et_3N, 0 °C, 15 h; xv, KBr, NaOAc, AcOOH, room temp., 20 h; xvi, Ac_2O, DMAP, CH_2Cl_2, room temp., 20 h; xvii, $LiAlH_4$, THF, room temp., 24 h

of optical purity. The ester enolate *C*-benzylation took place with high *anti* selectivity[7] (*anti*:*syn* = 93:7) to give ester **17** which was resistant to hydrazinolysis. This ester was hydrolysed, converted to primary amide **18** *via* its acid imidazolide and was subjected to modified Curtius reaction conditions[14] which smoothly† provided the expected benzyloxycarbonyl protected amine in good yield. The acetal protection was subsequently removed to give the ketone **19** in overall 75% yield from **17**. At this stage we could easily separate the unwanted minor diastereoisomer by chromatography. The ketone **19** was subjected to hydrogenolysis whereupon removal of the benzyloxycarbonyl group took place. The generated amino group condensed intramolecularly with the carbonyl group spontaneously to provide the Δ^1-pyrroline **2** (X = $PhMe_2Si$) which was *in situ* hydrogenated with hydrogens coming from the least hindered surface, *i.e*. away from the silicon and benzyl groups, to provide the pyrrolidine derivative with all three substituents having *cis* stereochemistry. Subsequently, the NH group was protected as ethoxycarbonyl derivative **20** and the silyl group in the molecule was converted to a hydroxy group[6] and then to its acetate **21**.¶ Lithium aluminium hydride reduction of this acetate provided (+)-preussin **1** in 77% yield. Since we started with the homochiral methyl ester **16,** and the synthetic sequence does not cause any epimerisation, the enatiomeric purity of (+)-preussin should undoubtedly be very high (>99%). This was confirmed from its specific rotation value ($[\alpha]_D^{25}$ + 31.1, *c* 1, $CHCl_3$) and spectral data.[2] The overall yield of (+)-preussin from the homochiral ester **16** was 17.2%.

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Footnotes and References

* E-mail: bod@magnum.barct1.ernet.in

† A silicon group at the β-position enhances the rate of Curtius reaction of acyl azides; details will be published elsewhere.

‡ We are in the process of converting this diastereoisomer to acetal **16**.

§ During the process, an undesired product (about 22%) was also formed by attack of the methoxide ion on the wrong carbonyl of the auxiliary.

¶ The NMR spectra of **20** and **21** could not be fully interpreted as these are known to be mixtures of amide geometrical isomers as well as atropisomers.

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