

**EFFICIENT STEREOSELECTIVE SYNTHESIS
OF (2*S*,3*S*,5*R*)-(+)-PREUSSIN***

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Abstract - Allyltrimethylsilane reacted with *N*-carbobenzoxy-L-phenylalaninal to afford with high diastereoselectivity *syn*-adduct which was subsequently transformed into (2*S*,3*S*,5*R*)-(+)-preussin.

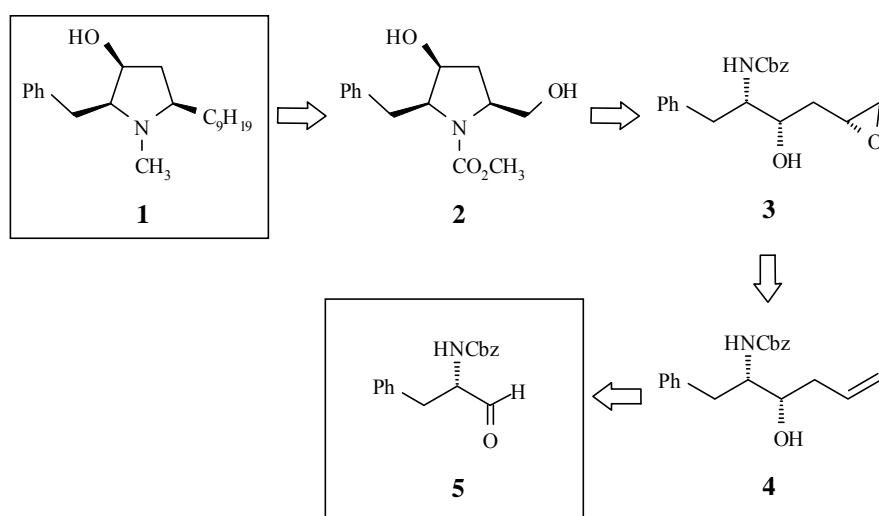
Stereocontrolled transformation of α -amino acids has long been of great interest due to their importance as chiral building blocks in the synthesis of biologically active molecules.¹ In our recent studies involving the synthesis of antibiotic amino sugars, we have found that suitably protected α -amino aldehydes are very convenient and versatile chirons.² For example, addition of allyltrimethylsilane to *N*-mono- and *N,N*-diprotected α -amino aldehydes offers an easy access to almost enantiomerically pure both *syn*- and *anti*-adducts³ which are readily transformed into natural products, such as 3-hydroxyproline,⁴ 1,3-dideoxynojirimycin,⁵ and statine.⁶

Now we report a new application of our methodology to the stereoselective and short synthesis of (2*S*,3*S*,5*R*)-(+)-preussin (**1**),⁷ also known as L-657,398,⁸ a naturally occurring pyrrolidine alkaloid isolated from the fermentation of *Aspergillus ochraceus* ATCC 22947 and *Preussia* sp., a similar but better antifungal agent, as compared with anisomycin. Since pioneering synthesis by Pak *et al.*,⁹ several asymmetric syntheses of **1** have been reported.¹⁰

Retrosynthetic analysis, shown in Scheme 1, suggested that *N*-carbobenzoxy-L-phenylalaninal (**5**)¹¹ and allyltrimethylsilane could serve as starting materials.

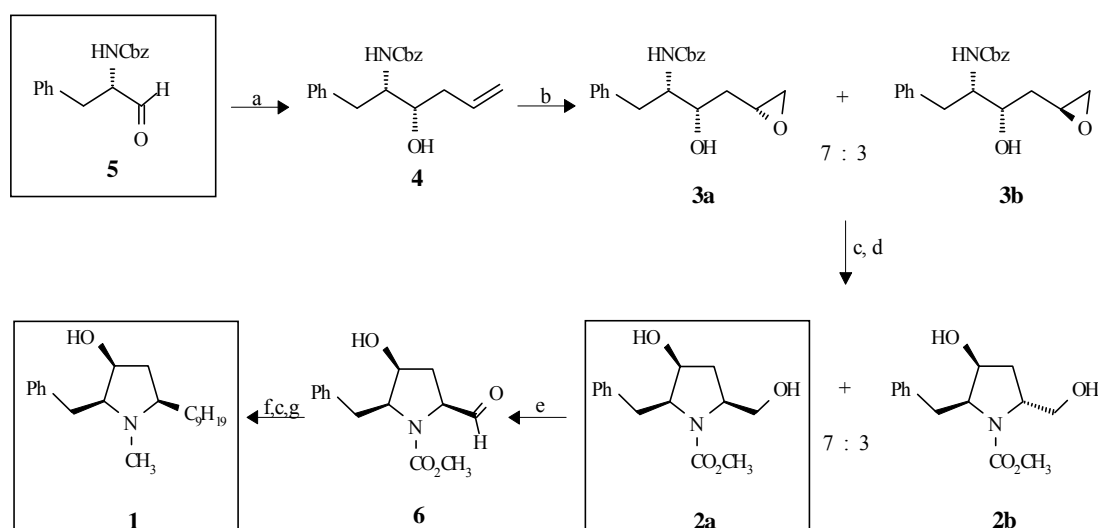
Addition of allyltrimethylsilane to aldehyde (**5**) in the presence of one equiv. of SnCl₄ at -78°C, afforded with very high diastereoselectivity (98:2) the *syn*-adduct (**4**)¹³ in 77% yield. Olefin (**4**) was subjected to the vanadium-catalyzed epoxidation reaction,¹⁴ furnishing in 87% yield a chromatographically unseparable mixture of diastereoisomeric epoxides (**3a**) (*syn*) and (**3b**) (*anti*) in a ratio of 7:3. Hydrogenation of this mixture on palladium on charcoal as a catalyst caused deprotection of the amino

* Dedicated to Professor Sho Ito on the occasion of his 77th birthday.



Scheme 1 Retrosynthetic analysis

group and subsequent cyclization to afford a mixture of diastereoisomeric pyrrolidines, which was treated with methyl chloroformate and subjected to chromatographic separation to give two pure diastereoisomers (**2a**)¹⁵ and (**2b**) in the same ratio as in the case of their precursors (**3a**) and (**3b**) (Scheme 2). The major diastereoisomer (**2a**), isolated in 59% yield, calculated on a starting mixture of epoxides (**3**), was oxidized using the TEMPO procedure¹² to furnish the known aldehyde (**6**).⁹ Final transformation of **6** *via* the Wittig reaction with $n\text{-C}_8\text{H}_{17}\text{P}^+\text{Ph}_3\Gamma$, followed by Pd/C hydrogenation and LiAlH_4 reduction afforded the desired (*2S,3S,5R*)-(+)-preussin (**1**)¹⁶ in good overall yield and correct stereochemistry.



Scheme 2. Reagents and conditions: (a) $\text{AllSi}(\text{CH}_3)_3$, SnCl_4 , CH_2Cl_2 , -78°C , 77%; (b) $t\text{-C}_4\text{H}_9\text{OOH}$, $\text{VO}(\text{acac})_2$ cat., CH_2Cl_2 , rt, 87%; (c) H_2 , 5% Pd/C, CH_3OH , rt, quant.; (d) ClCO_2CH_3 , CH_2Cl_2 , sat. aq NaHCO_3 , rt, 83%; (e) sat. aq NaHCO_3 , 4% aq NaOCl , 10% aq NaBr , TEMPO cat., $\text{AcOC}_2\text{H}_5\text{-PhCH}_3$ 1:1, -5°C , 72%; (f) $n\text{-C}_8\text{H}_{17}\text{P}^+\text{Ph}_3\Gamma$, $n\text{-C}_4\text{H}_9\text{Li}$, THF/HMPA 9:1, -78°C , 80%; (h) LiAlH_4 , THF, reflux, 85%.

It is noteworthy that allyl addition to *N*-Bn-*N*-Cbz analogue of **5**, carried out under Barbier conditions,^{3a} afforded the appropriate *anti*-adduct with good selectivity (86:14) and in high yield (98%). The *syn*-adduct (**4**) and its *anti*-isomer as well as their *N*-Bn-*N*-Cbz analogues can undergo the catalytic VO(acac)₂/*t*-C₄H₉OOH epoxidation with *syn*-selectivity or the Al(*Ot*-C₄H₉)₃/*t*-C₄H₉OOH epoxidation with high *anti*-selectivity. Combination of those possibilities provides selective access to all diastereoisomers of **2** and, as a consequence, to all diastereoisomers of preussin.

ACKNOWLEDGEMENTS

This work was supported by the State Committee for Scientific Research (Project PBZ 6.05/T09/1999).

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11. The L-phenylalanine derivative (**5**) was obtained in 87% overall yield on the following route: L-phenylalanine methyl ester hydrochloride was treated with benzyl chloroformate in the presence of sodium bicarbonate, affording *N*-Cbz-L-phenylalanine methyl ester which was then reduced with LiBH₄ to give *N*-Cbz-L-phenylalaninol. Finally, oxidation of this amino alcohol using the TEMPO procedure¹² afforded the desired aldehyde (**5**).
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13. Selected data: mp 62-64°C (CH₂Cl₂/hexane); [α]_D -35.0° (c 1.0, CHCl₃); LSIMS HR calcd for (M+H)⁺ (C₂₀H₂₄NO₃) 326.1756, found 326.1791; ¹H NMR (500 MHz, CDCl₃): 7.31-7.21 (m, 10H), 5.73 (m, 1H), 5.17 (d, J=9.2 Hz, 1H), 5.12-5.03 (m, 4H), 3.90-3.75 (m, 1H), 3.64-3.57 (m, 1H), 2.96-2.83 (m, 2H), 2.27-2.16 (m, 2H), 2.05 (d, J=3.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): 156.42, 138.10, 136.56, 134.17, 129.30, 128.48, 128.04, 127.94, 126.42, 118.68, 69.83, 66.68, 55.73, 39.22, 38.84.
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15. Selected data: mp 84-87°C (CH₂Cl₂/hexane); [α]_D -35.2° (c 1.0, CHCl₃); EIMS HR calcd for M⁺ (C₁₄H₁₉NO₄) 265.1314, found 265.1282; ¹H NMR (500 MHz, DMSO-*d*₆): 7.27-7.11 (m, 5H), 5.20 (d, J=5.4 Hz, 1H), 4.94 (br s, 1H), 4.15-4.02 (m, 1H), 3.89 (q, J=6.6 Hz, 1H), 3.79-3.67 (m, 1H), 3.60-3.49 (m, 2H), 3.30 (s, 3H), 2.92 (dd, J=13.1, 6.7 Hz, 1H), 2.13-2.05 (m, 1H), 1.86-1.80 (m, 1H); ¹³C NMR (125 MHz, DMSO-*d*₆): 155.60, 140.06, 129.35, 127.69, 125.41, 69.16, 62.51, 57.83, 51.52, 34.63.
16. Selected data: [α]_D +23.4° (c 2.0, CHCl₃) [lit.,⁷ [α]_D +22.0° (c 1.0, CHCl₃)]; LSIMS HR calcd for (M+H)⁺ (C₂₁H₃₆NO) 318.2797, found 318.2792; ¹H NMR (500 MHz, CDCl₃): 7.31-7.17 (m, 5H), 3.85-3.77 (m, 1H), 2.89 (dd, J=13.2, 10.1 Hz, 1H), 2.84 (dd, J=13.2, 4.6 Hz, 1H), 2.33 (s, 3H), 2.31-2.25 (m, 1H), 2.24-2.09 (m, 2H), 2.07-1.92 (br s, 1H), 1.76-1.68 (m, 1H), 1.46-1.40 (m, 1H), 1.37-1.21 (m, 15H), 0.88 (t, J=6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): 139.42, 129.34, 128.36, 126.05, 73.61, 70.45, 65.83, 39.31, 38.57, 34.88, 33.67, 31.87, 29.88, 29.61, 29.55, 29.29, 26.27, 22.66, 14.08.