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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.

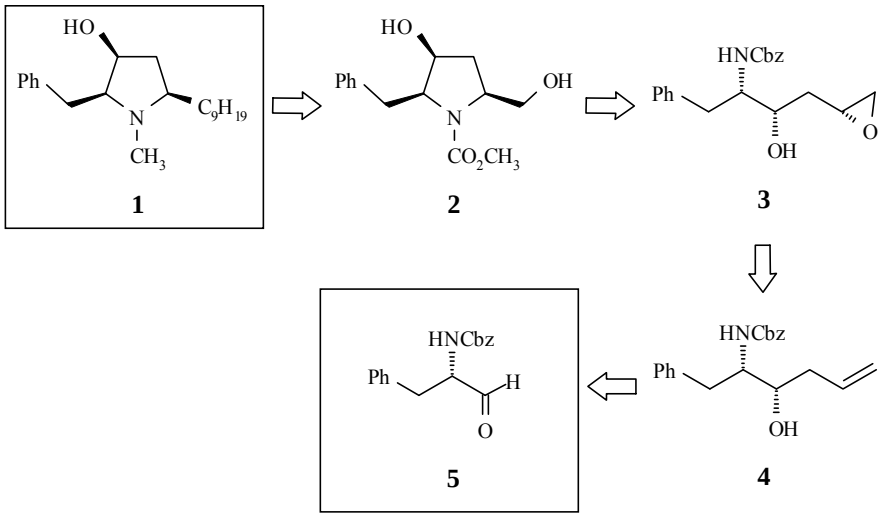
Stereocontrolled transformation of α–amino acids has long been of great interest due to their importance as chiral building blocks in the synthesis of biologically active molecules.[1] In our recent studies involving the synthesis of antibiotic amino sugars, we have found that suitably protected α–amino 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*-adducts[3] 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.

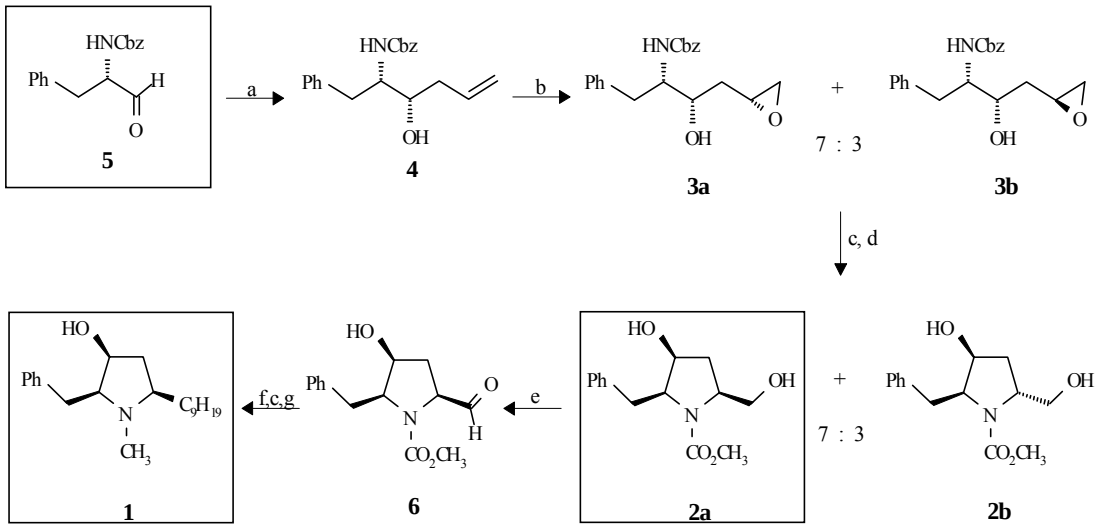
Addtition of allyltrimethylsilane to aldehyde (**5**) in the presence of one equiv. of $SnCl_4$ at -78˚C, afforded with very high diastereoselectivity (98:2) the *syn*-adduct (**4**)[13] in 77% yield. Olefin (**4**) was subjected to the vanadium-catalyzed epoxidation reaction,[14] furnishing in 87% yield 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 procedure[12] to furnish the known aldehyde (**6**).[9] Final transformation of **6** *via* the Wittig reaction with n-$C_8H_{17}P^+Ph_3I^-$, followed by Pd/C hydrogenation and $LiAlH_4$ reduction afforded the desired (2*S*,3*S*,5*R*)-(+)-preussin (**1**)[16] in good overall yield and correct stereochemistry.



Scheme 2. Reagents and conditions: (a) $AllSi(CH_3)_3$, $SnCl_4$, CH_2Cl_2, -78°C, 77%; (b) *t*-C_4H_9OOH, $VO(acac)_2$ 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., $AcOC_2H_5$-$PhCH_3$ 1:1, -5°C, 72%; (f) *n*-$C_8H_{17}P^+Ph_3I^-$, *n*-C_4H_9Li, 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 appriopriate *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*-C_4H_9OOH epoxidation with *syn*-selectivity or the $Al(Ot\text{-}C_4H_9)_3$/*t*-C_4H_9OOH 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.

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REFERENCES AND NOTES

1. (a) J. Martens, *Topics Curr. Chem*., 1984, **125**, 165. (b) G. M. Coppola and H. F. Schuster 'Asymmetric Synthesis : Construction of Chiral Molecules Using Amino Acids,' Wiley, New York, 1987. (c) J. Jurczak and A. Gołębiowski, *Chem. Rev*., 1989, **89**, 149. (d) M. T. Reetz, *Chem. Rev*., 1999, **99**, 1121.
2. (a) A. Gołębiowski and J. Jurczak, *Synlett*, 1993, 241. (b) K. Kiciak, U. Jacobsson, A. Gołębiowski, and J. Jurczak, *Polish J. Chem*., 1994, **68**, 199.
3. (a) D. Gryko, Z. Urbańczyk-Lipkowska, and J. Jurczak, *Tetrahedron*, 1997, **53**, 13373. (b) J. Jurczak and P. Prokopowicz, *Tetrahedron Lett*., 1998, **39**, 9835.
4. J. Jurczak, P. Prokopowicz, and A. Gołębiowski, *Tetrahedron Lett*., 1993, **34**, 7107.
5. D. Gryko and J. Jurczak, *Tetrahedron Lett*., 1997, **38**, 8275.
6. G. Veeresha and A. Datta, *Tetrahedron Lett*., 1997, **38**, 5223.
7. J. H. Johnson, D. W. Phillipson, and A. D. Kahle, *J. Antibiot*., 1989, **42**, 1184.
8. (a) R. E. Schwartz, J. Liesch, O. Hensens, L. Zitano, S. Honeycutt, G. Garrity, and R. A. Fromtling, *J. Antibiot*., 1988, **41**, 1774. (b) R. E. Schwartz, J. C. Onishi, R. L. Monaghan, J. M. Liesch, and O. D. Hensens, U.S. Patent 4,847,284, 1989 (*Chem. Abstr*., 1990, **112**, 75313u).
9. C. W. Pak and G. H. Lee, *J. Org. Chem*., 1991, **56**, 1128.
10. (a) M. Shimazaki, F. Okazaki, F. Nakajima, T. Ishikawa, and A. Ohta, *Heterocycles*, 1993, **36**, 1823. (b) P. L. McGrane and T. Livinghouse, *J. Am. Chem. Soc*., 1993, **115**, 11485. (c) W. Deng and L. E. Overman, *J. Am. Chem. Soc*., 1994, **116**, 11241. (d) M. Overhand and S.M. Hecht, *J.Org. Chem*., 1994, **59**, 4721. (e) H. Yoda, H. Yamazaki, and K. Takabe, *Tetrahedron Asymm*., 1996, **7**, 373. (f) R.

Verma and S. K. Ghosh, *Chem. Commun*., 1997, 1601. (g) C. Beier and E. Schaumann, *Synthesis*, 1997, 1296. (h) I. Kadota, S. Saya, and Y. Yamamoto, *Heterocycles*, 1997, **46**, 335. (i) P. D. Armas, F. Tellado-Garcia, J. J. Tellado-Marrero, and J. Robles, *Tetrahedron Lett*., 1998, **39**, 131. (j) A. Kanazawa, S. Gillet, P. Delair, and A. E. Greene, *J. Org. Chem*., 1998, **63**, 4660. (k) G. Veeresa and A. Datta, *Tetrahedron*, 1998, **54**, 15673. (l) R. Verma and S. K. Ghosh, *J. Chem. Soc. Perkin Trans. 1*, 1999, 265.

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 $LiBH_4$ to give *N*-Cbz-L-phenylalaninol. Finally, oxidation of this amino alcohol using the TEMPO procedure[12] afforded the desired aldehyde (**5**).
12. (a) M. R. Leanna, T. J. Sowin, and H. E. Morton, *Tetrahedron Lett*., 1992, **33**, 5029. (b) J. Jurczak, D. Gryko, E. Kobrzycka, H. Gruza, and P. Prokopowicz, *Tetrahedron*, 1998, **54**, 6051.
13. Selected data: mp 62-64°C (CH_2Cl_2/hexane); $[\alpha]_D$ –35.0° (c 1.0, $CHCl_3$); LSIMS HR calcd for $(M+H)^+$ ($C_{20}H_{24}NO_3$) 326.1756, found 326.1791; ^{1}H NMR (500 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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.
14. E. D. Mihelich, K. Daniels, and D. J. Eickhoff, *J. Am. Chem. Soc*., 1981, **103**, 7690.
15. Selected data: mp 84-87°C (CH_2Cl_2/hexane); $[\alpha]_D$ –35.2° (c 1.0, $CHCl_3$); EIMS HR calcd for M^+ ($C_{14}H_{19}NO_4$) 265.1314, found 265.1282; ^{1}H 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); ^{13}C 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: $[\alpha]_D$ +23.4° (c 2.0, $CHCl_3$) [lit.,[7] $[\alpha]_D$ +22.0° (c 1.0, $CHCl_3$)]; LSIMS HR calcd for $(M+H)^+$ ($C_{21}H_{36}NO$) 318.2797, found 318.2792; ^{1}H NMR (500 MHz, $CDCl_3$):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); ^{13}C NMR (125 MHz, $CDCl_3$): 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.