A Short Synthesis of Preussin: Use of Allyldimethylsilyl as Masked Hydroxyl[1]

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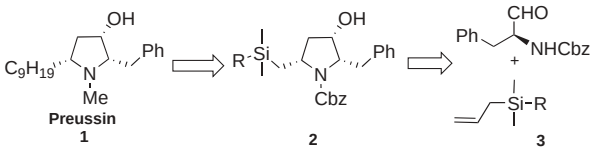
Abstract: A short and efficient synthesis of Preussin utilizing allyldimethylsilyl group as hydroxyl equivalent via an interesting (3+2) annulation reaction involving non-classical pentavalent silicon cation transition state, has been described.

Keywords: natural product, antifungal agents, (3+2) annulation, allydimethylsilyl, pyrrolidine alkaloid

Isolated originally from Preussia sp. and *Aspergillus ochraceus*[2a] and having strong inhibitory activity as broad-spectrum antibiotics against filamentous fungi,[2b] the pyrrolidine alkaloid Preussin has been the target of many synthetic endeavors due to its tri-*cis*-pyrrolidine structure.[3] Recent observations of the role of Preussin in inhibition of the fission yeast *ts* mutants defective on *cdc2*-regulatory genes,[4] apoptosis-induction, inhibition of cyclin-E kinase,[5] and inhibition of programmed-1 ribosomal frameshifting,[6] have rekindled interest in synthesis of Preussin and its analogs. Suitably substituted silyl group can be treated as synthetically equivalent to hydroxyl function[7] and a synthetic approach using dimethylphenylsilyl group in place of ring hydroxy function has been reported.[8] The possibility that silyl group can be treated as masked hydroxyl, prompted us to undertake and to report herein a short and efficient route to Preussin via 2-phenylmethyl-3-hydroxy-pyrrolidine-5-carboxaldehyde.

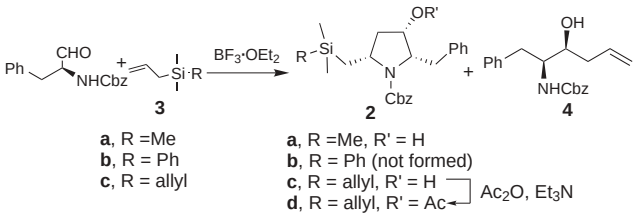


Scheme 1

While investigating the Sakurai–Hosomi reaction of allyltrimethylsilane with carbonyl compounds in presence of Lewis acid, Kiyooka et al. have observed an interesting (3+2) annulation reaction involving non-classical pentavalent silicon cation transition state where *cis*-2-substituted 3-hydroxy-5-trimethylsilylmethyl-pyrrolidines were obtained.[9]

We envisaged using allyldimethylphenylsilane in place of allyltrimethylsilane in order to obtain, in a similar reaction, corresponding 5-dimethylphenylsilanylmethylpyrrolidine, which might be converted to (2*S*,3*S*,5*S*)-2-benzyl-1-benzyloxycarbonyl-3-hydroxy-5-hydroxymethyl-pyrrolidine as an en route to Preussin (Scheme 1).

The reaction of allyl trimethylsilane with Cbz-Phe-al gave as reported, the *cis*-pyrrolidine **2a** in 55% yield along with open chain *syn*-alcohol **4** as minor product (<5%).[10] However, using allyldimethylphenylsilane under similar condition, no trace of cyclic product **2b** was seen and the allylic alcohol **4** was isolated as the only product. Failure to obtain cyclic product in this case can be rationalized to be due to the bulkiness of phenyl substitution in the crowded transition state involving pentavalent silicon (Scheme 2).



Scheme 2

Magar et al has shown that allyldimethyl silyl group can also be used as a hydroxy equivalent.[11] Thus using diallyldimethylsilane in place of trimethylsilane in the above reaction gave the cyclic product **2c** in good yield.[12] **2c** was converted to its acetate **2d** using Ac_2O and Et_3N.[13] Treatment of the acetate **2d** first with bromine in CH_2Cl_2 followed by HF–pyridine as fluoride source[13] gave the corresponding fluorosilane, which was not characterized and was directly reacted with H_2O_2–K_2CO_3 to provide (2*S*,3*S*,5*S*)-3-acetyl-2-benzyl-benzyloxycarbonyl-5-hydroxymethyl-pyrrolidine **5a** in good yield.[14] During the oxidative reaction under basic conditions, hydrolysis of the acetate group also occurred and dihydroxy compound **5b** was obtained in small amount. The formation of **5b** could be minimized using preformed H_2O_2–Na_2CO_3. Compound **5a** on Swern oxidation gave pyrrolidine aldehyde **6** in 60% yield (Scheme 3).[15] As a similarly protected aldehyde has already been converted to Preussin[16] in a few simple steps, this constitutes a formal synthesis of Preussin.

Thus, we have accomplished a short and efficient synthesis of the advanced aldehyde intermediate **6** having functionalities of requisite stereochemistry. We feel that this strategy is general in nature and can serve to give a range of novel Preussin analogs.

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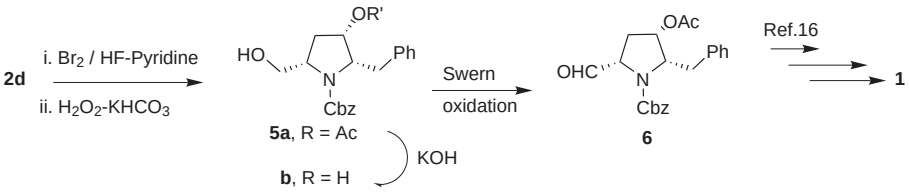

Scheme 3

Acknowledgment

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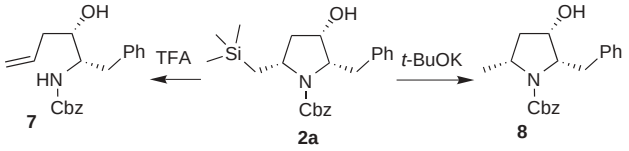

Scheme 4

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(10) (a) All the spectral data of compound **2a** and **4** matched fully with that of authentic sample, kindly provided by Prof. Kiyooka. (b) Our attempts to cleave trimethylsilyl group on **2a** to give synthetically useful intermediate met with no success. Reported TFA catalysed cleavage gave the ring open product **7**: Martin, D.; Gamal, M. *Synthesis* **1982**, 827. (c) While *t*-BuOK catalyzed cleavage conditions gave **8** (Scheme 4): Price, C. C.; Sowa, J. C. *J. Org. Chem.* **1967**, *32*, 4126.

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(12) **Synthesis of Compound 2c:** To a stirred soln of (*S*)-2-(*N*-benzyloxycarbonylamino)-3-phenyl-propanal (1 g, 3.5 mmol) in 20 mL of freshly dried CH_2Cl_2 at –10 °C was added $BF_3{\cdot}OEt_2$ (0.09 mL, 0.4 mmol). After 20 min a solution of diallyldimethylsilane (0.69 mL, 3.8 mmol) in freshly dried CH_2Cl_2 (4 mL) was added to it drop wise over a period of 10 min, the resultant mixture was stirred for 2 h at –10 °C, quenched with aq NH_4Cl solution (25 mL) and extracted with CH_2Cl_2 (50 mL × 3). Combined organic layer was washed with brine, dried over anhyd Na_2SO_4 and concentrated. The crude material was flash chromatographed over silica gel using 12% EtOAc–hexane as eluent to give pure **2c**. **Data of 2c**: Colourless oil (1.03 g, 70%); $[\alpha]_D$ = –61.09 (*c* 0.293, MeOH). IR(neat): 3432, 2956, 1680, 1502,1416 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.2 (m, 10 H), 5.7 (m, 1 H), 5.0 (d, *J* = 12 Hz, 2 H), 4.8 (dd, *J* = 15.8 and 11.0 Hz, 2 H), 4.2 (m, 2 H), 3.8 (m, 1 H), 2.9 (d, *J* = 5.3 Hz, 2 H), 2.2 (m, 1 H), 1.6 (m, 4 H), 0.81 (dd, *J* = 12.9 and 11.7 Hz, 1 H), –0.019 (s, 6 H). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 155.1, 139.3, 136.6, 134.6, 129.8, 129.5, 128.39, 128.32, 128.0, 127.9, 126.1, 113.1, 71.4, 66.7, 62.4, 53.9, 39.7, 36.0, 24.1, 23.5, –2.9, –3.2; FABMS: *m/z* = 424 (M + 1), 383, 292.

(13) **Synthesis of Compound 2d:** To a solution of **2c** (800 mg, 1.89 mmol) in CH_2Cl_2 (20 mL) at 0 °C were successively added Et_3N (2.6 mL, 18.9 mmol) and Ac_2O (0.9 mL, 9.4 mmol) followed by DMAP (50 mg) as catalyst. The resulting mixture was stirred at r.t. for 4 h, diluted with CH_2Cl_2 (50 mL), taken in a separating funnel and washed s uccessively with 5% HCl (25 mL), sat. $NaHCO_3$ (25 mL) and brine (25 mL). The organic layer was dried over anhyd Na_2SO_4, concd in vacuo and flash chromatographed over silica gel using 6% EtOAc–hexane as eluent. **Data of 2d**: Colorless oil (747 mg, 85%); $[\alpha]_D$ = –38.21(*c* 0.28, MeOH). IR (neat): 3020, 1737, 1690, 1413, 1219 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.2 (m, 10 H), 5.8 (m, 1 H), 5.0 (d, *J* = 12 Hz, 2 H), 4.9 (m, 1 H), 4.8 (m, 2 H), 4.4 (q, 1 H), 3.9 (m, 1 H), 2.8 (d, *J* = 8.1 Hz, 2 H), 2.3 (m, 1 H), 1.8 (s, 3 H), 1.7 (m, 2 H), 1.5 (m, 2 H), 0.7 (dd, *J* = 13.7 and 11.8, 1H), –0.011 (s, 6 H). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 170.4, 155.3, 138.9, 136.9, 134.8, 129.8, 128.8, 128.5, 128.4, 128.3, 126.5, 113, 72.7, 67.3, 60.2, 53.8, 37.3, 37.1, 24.5, 23.9, 21.1, –2.4, –2.8. FABMS: *m/z* = 466 (M + 1), 424.

(14) **Synthesis of Compound 5a:** To a solution of **2d** (500 mg, 1.07 mmol) in CH_2Cl_2 (30 mL) at 0 °C were added successively bromine (0.275 mL, 5.3 mmol) and HF–

pyridine (1.4 mL). The reaction mixture was stirred at r.t. for 3 h at the end of which excess of HF was destroyed by pouring the mixture over basic alumina. The resulting slurry was diluted with CH_2Cl_2 and filtered. The filtrate was dried over anhyd Na_2SO_4 and concentrated in vacuum. The material thus obtained was dissolved in a mixture of anhyd THF–MeOH (15 mL each) and $KHCO_3$ (215 mg, 2.15 mmol), KF (124 mg, 2.15 mmol), 30% H_2O_2 (2.68 mL, 21.5 mmol) were added successively to the soln under stirring. The resulting mixture was stirred at r.t. for 10 h, sodium thiosulphate solution (30%, 25 mL) was added to it and the quenched mixture was extracted with EtOAc (50 mL × 3). Combined organic layer was washed with brine (30 mL), dried over anhyd Na_2SO_4, concentrated in vacuo and flash chromatographed over silica-gel using 30% EtOAc–hexane as eluent. **Data of 5a**: Colorless oil (286 mg, 70%); $[\alpha]_D$ = –40.54 (*c* 0.259, MeOH). IR(neat): 3350, 3017, 2935, 1679, 1414 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.2 (m, 10 H), 5.1 (d, *J* = 12.5 Hz, 2 H), 4.4 (m, 1 H), 4.0 (m, 1 H), 3.6 (m, 3 H), 2.8 (d, *J* = 6 Hz, 2 H), 2.3 (m, 1 H), 1.9 (s, 3 H), 1.7 (m, 1 H). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 170.4, 156.1, 138.4, 136.2, 129.7, 128.9, 128.6, 126.7, 72.0, 68.1, 67.2, 60.7, 58.9, 36.7, 31.7,21.0. FABMS: *m/z* = 384 (M + 1), 340, 248. **Data of 5b**: Colorless oil (54.7 mg, 15%); $[\alpha]_D$ = –65.71 (*c* 0.035, MeOH). IR(neat): 3366, 2929, 1686, 1413 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.2 (m, 10 H), 5.0 (d, *J* = 12.2 Hz, 2 H), 4.1 (M, 1 H), 4.0 (m, 2 H), 3.9 (dd, *J* = 11.2 and 3.7 Hz, 1 H), 3.6 (dd, *J* = 11.2 and 3.7 Hz, 1 H), 3.0 (dd, *J* = 12.6 and 9.8 Hz, 2 H), 2.2 (m, 1 H), 1.8 (d, *J* = 13.7 Hz, 1 H), 1.7 (bs, 2 H). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 157.3, 139.6, 136.5, 129.9, 128.9, 128.7, 128.6, 126.5, 70.7, 67.8, 65.5, 60.2, 58.9, 36.4, 35.0; FABMS: *m/z* 342 (M + 1), 298.

(15) **Synthesis of Compound 6:** To a stirred solution of oxalylchloride (0.06 mL, 0.83 mmol) in CH_2Cl_2 (10 mL) at –78 °C under N_2 atmosphere was added DMSO (0.1 mL, 1.14 mmol) using a micro syringe. After stirring the mixture for 30 min, a solution of **5a** (200 mg, 0.52 mmol) in CH_2Cl_2 (2 mL) was added slowly over a period of 10 min. The reaction mixture was stirred for 30 min at –78 °C and diisopropylethyl amine (0.455 mL, 2.6 mmol) was added to it slowly in 10 min. The cooling was discontinued and the reaction was allowed to warm to r.t., diluted with CH_2Cl_2 (20 mL), washed with 5% HCl (20 mL), brine and water. The organic layer was dried over anhyd Na_2SO_4, concd under reduced pressure, and flash chromatographed over silica gel using 25% EtOAc–hexane as eluent to give **6** as viscous oil. **Data of 6**: Colourless oil (119 mg, 60%); $[\alpha]_D$ = –69.23 (*c* 0.156, MeOH). IR(neat): 2932, 1740, 1712, 1589, 1224 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.5 (br s, 1 H) 7.2 (m, 10 H), 5.0 (d, *J* = 12 Hz, 2 H), 4.3 (m, 3 H), 2.7 (dd, *J* = 13.6 and 9.5 Hz, 2 H), 2.1 (m, 2 H), 1.9 (s, 3 H). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 200.5, 169.9, 158, 138, 136.2, 129.6, 129, 128.8, 126.9, 72.7, 68.1, 64.4, 55.8, 33.0, 23.2, 21.1. FABMS: *m/z* = 382 (M + 1), 352, 248.

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