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Diastereoselective Formal Synthesis of the Antifungal Agent, (+)-Preussin. A New Entry to Chiral Pyrrolidines

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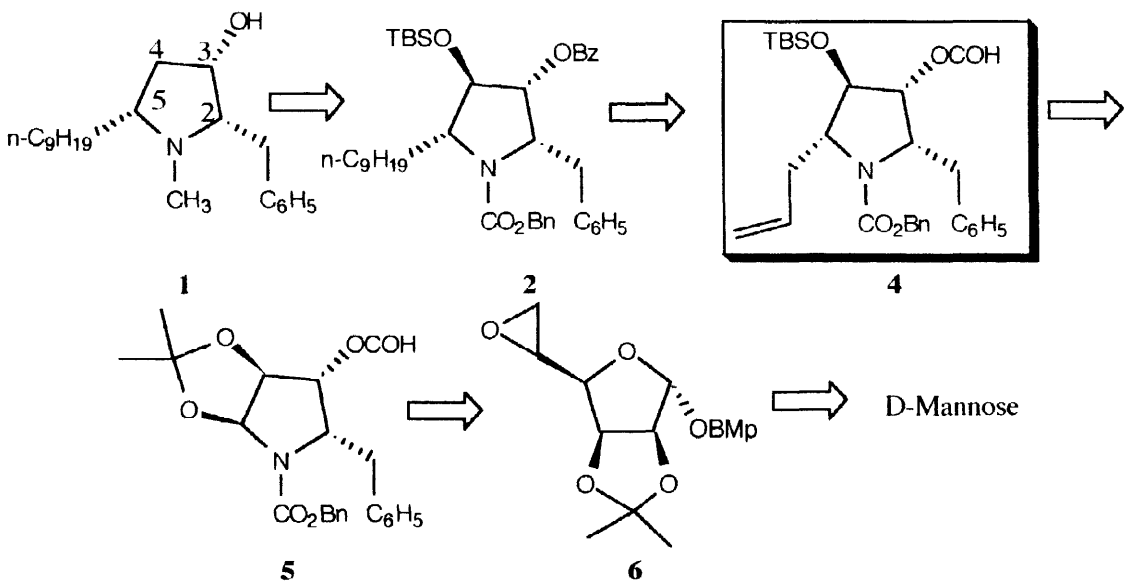
Abstract: A formal total synthesis of (+)-Preussin was achieved by using D-mannose as the starting material . The key step involved diastereoselective addition of allyltrimethylsilane to the bicyclic ketal **5.**

The potent antifungal antibiotic (+)-Preussin (L-675,398) **1**, has benn isolated from the microorganisms *Preussia sp* and *Aspergillus ochraceus* ATCC 22947.[1]

Due to its interesting activities, to the best of our knowledge six total syntheses of **1** have been described.[2] These strategies employ different procedures for the installation of the R configuration of the C5 nonyl side chain.

Here we describe a diastereoselective formal synthesis of (+)-Preussin. Our synthetic strategy is outlined in Scheme 1.



The key step, is the Lewis acid-promoted addition of allyltrimethylsilane to the bicyclic ketal **5** to introduce the correct R configuration at C5.

Several authors[3,4] have shown that under certain conditions the stereochemical course of the Lewis acid-aided reactions of acetal with nucleophile is an SN2 like displacement. Also, compound **5** incorporats the required C2, C3 stereochemistry for **1**, which are transfered from D-mannose.

Our synthesis, commenced with that of the epoxide **6** (Scheme2). This was readly obtained from commercially available 1,2:3,5-di-0-isopropylidene-α-D-mannofuranose in 60% overall yield. The ring opening[5] of epoxide **6** with PhMgCl, catalized by CuI, gave the secondary alcohol **7**. Conversion to the

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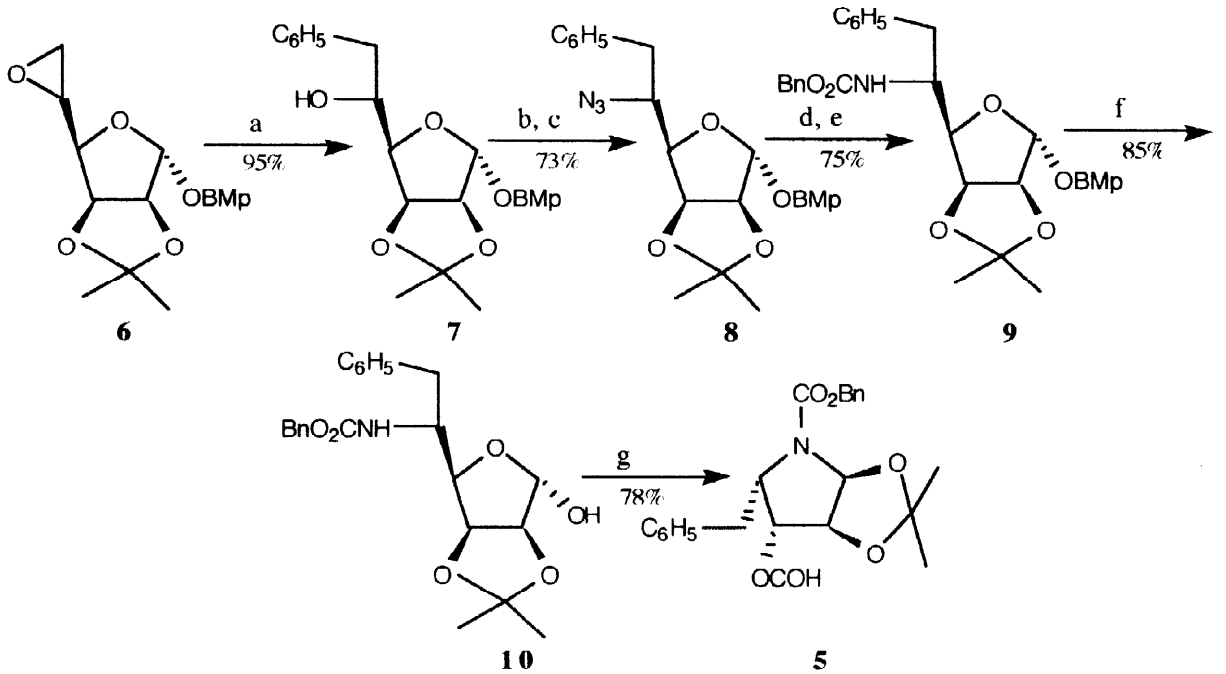
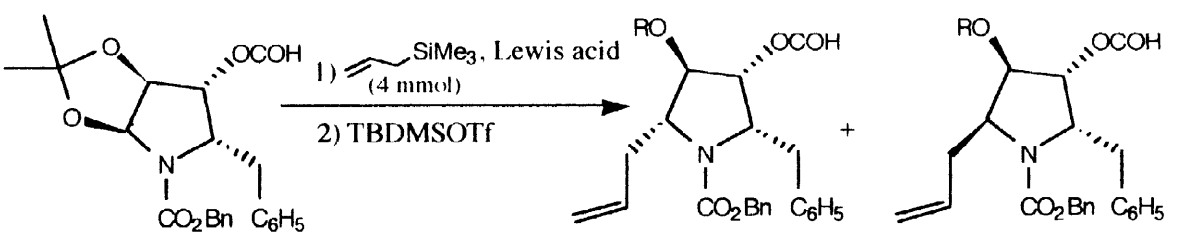
trifluoromethanesulphonate ester, followed by treatment with sodium azide in dimethylformamide, gave the inverted azide **8**. Reduction of **8** and benzyloxy-carbonylation gave the carbamate **9**. The cyclic[6] derivative **5** was obtained in good yield (67%, 2 steps) by removal of the anomeric protecting group and ionic cyclization[7] of **10** promoted by $PhIO/I_2$.



Scheme 2: (a) PhMgCl, CuI, (10 mol%), THF, -30 °C, 3h; (b) $(CF_3SO_2)_2O$, Py, CH_2Cl_2, N_2, -78 °C, 1h; (c) NaN_3, DMF, N_2, rt, 1h; (d) $LiAlH_4$,THF, 0 °C→rt, 1h; (e) $ClCO_2Bn$, Py, DMAP, 0 °C→rt, 16h; (f) DDQ, CH_2Cl_2:H_2O, 19:1, N_2, rt, 2h; (g) PhIO(3 mmol), I_2, (1 mmol), CH_2Cl_2(wet), rt, 2h.

At this stage we were ready to explore the stereoselectivity in the addition reaction of allyltrimethylsilane to the ketal **5** (Eq 1).

(Eq 1)



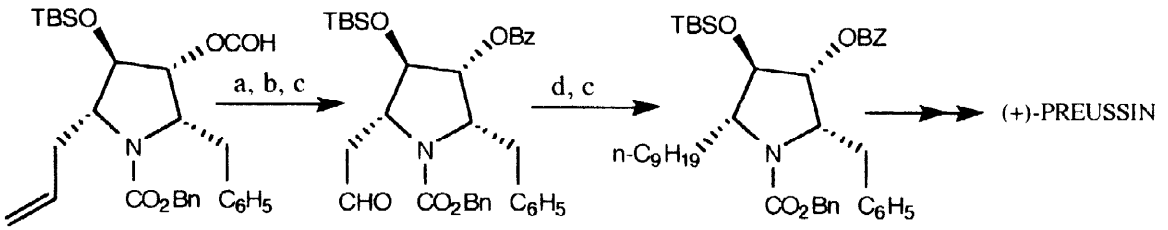
5 **3a** R = H **3b**
4a R = TBDMS **4b**

Lewis Acid	Reaction Conditions	Yield (DS Ratio)
(2mmol) $BF_3.OEt_2$	CH_2Cl_2, -78 °C/5min, rt/50 min	62% (>95:5)
(2mmol) $BF_3.OEt_2$/TMSOTf	CH_2Cl_2, -78 °C/5min, rt/50 min	92% (70:30)

Thus, treatment[8] of **5** with allyltrimethylsilane in the presence of $BF_3.OEt_2$ gave **3a:3b** in good yield (65%) in a ratio > 95:5. With a combination of $BF_3.OEt_2$ /TMSOTf a **3a:3b** mixture was obtained in 92% yield but the diastereoselectivity decreased to 70:30.

The stereochemistry of the major stereoisomer was unambiguously determined from the ^1H-^1H coupling constant (in particular HC2-HC3 appear as broad singlet[9]) and NOESY experiments.

The carbon bond chain was extended by oxidative cleavage of the alkene and then Wittig reaction of the resulting aldehyde and hydrogenation gave **2** in 41% overall yield from **4a**.



4a **12** **2**

Scheme 3: (a) $NaCO_3$, MeOH, rt, 45 min; (b) PhCOCl, Py, rt, 16 h; (c) i. OsO_4, MNO, H_2O: Me_2CO: ^tBuOH; ii. H_2O, $NaIO_4$; (d) I. $CH_3(CH_2)_6{}^+PPh_3I^-$, BuLi, THF, -78°C, 10 min; ii. 10% Pd/C, H_2 (1atm), EtOH, rt, (41% from **4a**)

In summary, we have described a diastereoselective formal synthesis of (+)-Preussin, using a stereocontrolled allylation of the bicyclic ketal **5**.

This procedure may be extended to the synthesis of different chiral pyrrolidines. Further work is in progress to study the scope and limitation of the allylation reaction as well as t the synthesis of new pyrrolidine and pyrrolizidine antibiotic analogues.

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References and Notes.

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6 Procedure for the synthesis of **5**: a solution of compound **10** (452 mg, 1.1 mmol) in wet CH_2Cl_2 (35 ml) containing iodosylbenzene (723 mg, 3.3 mmol) and iodine (278 mg, 1.1 mmol) was stirred at room temperature for 4 h. The reaction mixture was then poured into water and extracted with dichloromethane. The organic layer was washed with aqueous sodium thiosulfate and water. Concentration and purification by flash chromatography (n-hexane/ethyl acetate 8:2 v/v) gave **5** (353 mg, 78%) as a colourless oil. $[\alpha]_D$ +36.76° ($CHCl_3$); IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 200 Mhz) 1.3 (3H, s), 1.4 (3H, s), 2.8 (2H, dd, J 13.8, 9.8 Hz), 4.27 (1H, dd, J 4.8, 2.6 Hz), 4.5 (1H, q, J 4.9 Hz), 5.03 (1H, m), 5.26 (2H, dd, J 16.2 Hz), 5.78 (1h, d, J 4.8 Hz), 7.25 (10H, m), 8.06 (1H, s). ^{13}C NMR 26.45, 27.37, 32.98, 60.51, 67.26, 74.90, 79.90, 89.02, 112.85, 126.74, 128.70, 129.33, 136.25, 137.10, 154.80, 159.47.HRMS calcd for ($C_{23}H_{25}O_6N$) (M^+) 411.1681, found 411.1664.

7 (a) For a mechanistic discussion see. de Armas, P.; Garcia-Tellado, F.; Marrero-Tellado, J.; Robles, J. *Tetrahedron Lett.* **1997**, in press. In the present case the oxidation to oxonium ion is favoured by changing benzene for wet dichloromethane, which is captured by an internal nucleophile. (b) During the manuscript praparation we had knowledge of Prof. Suarez' preliminary results in the synthesis of azasugars using a similar procedure.

8 Procedure for the synthesis of **4a**: a solution of **5** (206mg, 0.63mmol) and allyltrimethylsilane (0.8 ml, 5 mmol) in CH_2Cl_2 (7 ml) in a dry flask under an argon atmosphere. The mixture was cooled to -78°C, and $BF_3.Et_2O$ (0.16 ml, 1.26 mmol) was slowly added. After 5min, the cooling bath was removed, and the mixture was stirred for 50min. The organic phase was washed once with saturated $NaHCO_3$ and once with water and dried over $MgSO_4$. Concentration and purification by flash chromatography (n-hexane/ethyl acetate 7:3 v/v) gave an inseparable mixture of **3a** and **3b** (135 mg, 62% yield).TBSOTf (0.21 ml, 0.9 mmol) was added to a solution of the mixture **3a,b** (135mg, 0.34 mmol) and Py (0.17 ml, 1.4 mmol) at 0°C and the resulting mixture was stirred at 0°C for 15 min and then warmed to rt.The mixture was cooled back to 0°C and poured into cold sat. aq. $NaHCO_3$.The separated aqueous layer was extracted with ether. Concentration and purification by flash chromatography (benzene/n-hexane 7:3 v/v) gave **4a** (130.3mg, >95%) as a less polar product and **4b** (4.7 mg, <5%) as a more polar product. **4a** : colourless oil $[\alpha]_D$= + 16.13° ($CHCl_3$); IR ($CHCl_3$) 1725, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) 0.03 (3H, s), 0.04 (3H, s), 0.82 (9H, s), 2.54 (2H, m), 2.78 (2H, dd, J 10.3, 13.5 Hz), 3.81 (1H, m), 4.07 (1H, br s), 4.49 (1H, m), 4.91 (1H, dd, J 3.5, 6.1 Hz), 5.05 (2H, m), 5.14 (2H, d, J 11.7 Hz), 5.76 (1H, m), 7.19-7.35 (20H, m), 7.92 (1H,s); ^{13}C NMR -3.89, -4.32, 18.38, 26.20, 36.00, 37.23, 60.90, 65.96, 67.65, 76.09, 78.26, 118.47, 118.56, 126.99, 128.41, 128.62, 128.98, 129.11, 129.65, 134.89, 138.58, 156.41, 159.95, 160.02, HMRS calcd for $C_{26}H_{34}O_5NSi$ [(M^+-CH2CHCH2)] 468.2206, found 468.2244.

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