Total Synthesis of (+)-Preussin: Control of the Stereogenic Centers by Enantioselective Allyltitanations

Sophie Canova, Véronique Bellosta, Janine Cossy*

Laboratoire de Chimie Organique, associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France
Fax +33(1)40794660; E-mail: janine.cossy@espci.fr

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Abstract: (+)-Preussin was synthesized in ten steps with an overall yield of 6.4% from phenylacetaldehyde. The three stereogenic centers were controlled by enantioselective allyltitanations of aldehydes.

Key words: preussin, allyltitanation, cross-metathesis

Preussin (Figure 1), a naturally occuring pyrrolidine alkaloid has been isolated from fermentation broths of *Aspergillus ochraceus* ATCC 22947 and from *Preussia* sp., and exhibits antifungal and antibacterial activities.[1] Recently, it has been discovered that preussin is a selective inhibitor for cell growth of the fission yeast *ts* mutants defective on *cdc2*-regulatory genes,[2] and its activity in apoptosis-induction and as a potent inhibitor of cyclin E kinase in human tumor cells were also reported.[3] The impressive biological activity and interesting structural features have thus made preussin an attractive target for synthesis.[4] Almost all of the published syntheses employ a chiral pool starting material to introduce the chirality except for the syntheses reported by Greene,[4j] Ghosh,[4l] and Rhagavan[4s] which are enantioselective.

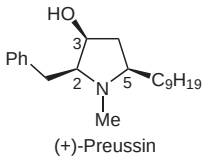


Figure 1

Among the different methods that allow the formation of a pyrrolidine ring, the intramolecular nucleophilic displacement of an activated alcohol moiety (e.g. tosylate, mesylate or triflate) by an amine is certainly one of the most useful and reliable methods when 2,5-disubstituted pyrrolidines have to be synthesized. This approach requires that the stereochemistry has already been established in the previous steps by using either chiral pool-derived cyclization precursors or stereoselective C-O and/or C-N bond formation with the appropriate configuration. Our interest was to develop a versatile route for preussin, which could be readily extendable to the preparation of structural analogs possessing various substituents at C2, C3 and C5 for biological screening. With this aim in view, we envisaged to use enantioselective allyltitanations employing the chiral cyclopentadienyl-dialkoxytitanium(IV) complexes[5] **I** and **II** (Figure 2) to create the three stereogenic centers present in (+)-preussin.

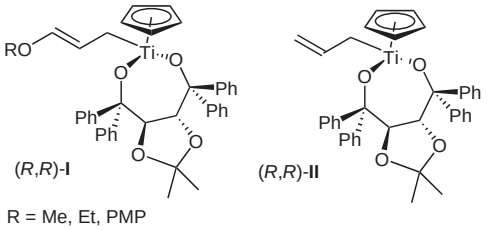
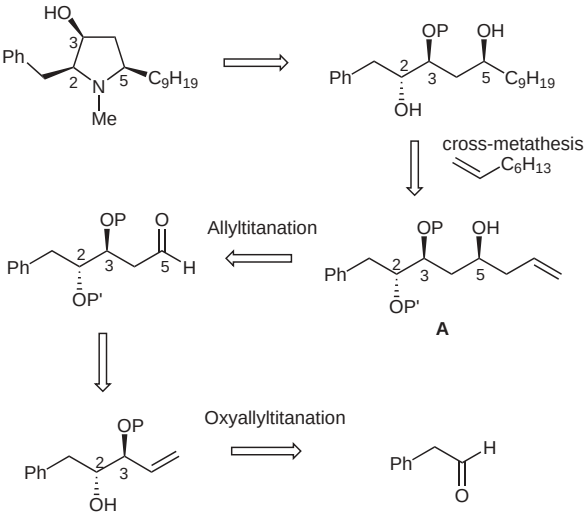


Figure 2

Herein, we would like to report the synthesis of (+)-preussin by employing a double nucleophilic substitution of an activated γ-diol by *N*-methylamine to build up the pyrrolidine ring and an enantioselective oxyallyltitanation of an aldehyde to control at first the C2 and C3 stereogenic centers and then an allyltitanation to control the C5 stereogenic center. Furthermore, a chain elongation of **A**, by using a cross-metathesis reaction has been envisaged for the installation of the nonyl alkyl side-chain present at C5 (Scheme 1).



Scheme 1

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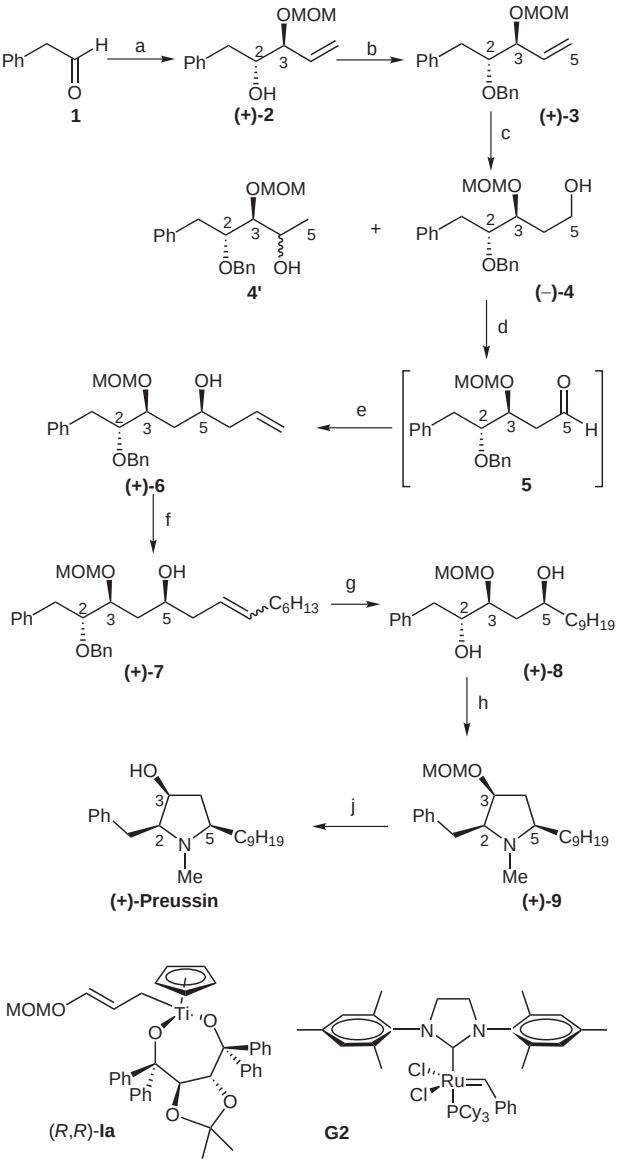
Enantioselective oxyallyltitanations with complex of type **I** are known to lead to *anti*-1,2-diols with good diastereoselectivity and enantioselectivity.[5] The first step of our synthesis required an oxyallytitanation of phenylacetaldehyde **1** to install at this stage a protected alcohol at C3, which could be easily deprotected at the end of the synthesis. Therefore, we decided to perform the MOM-oxyallyltitanation of phenylacetaldehyde **1** with complex (*R*,*R*)-**Ia** (R = MOM)[6] in diethyl ether at –78 °C. The desired *anti*-1,2-diol **2** was obtained with a 91:9 diastereomeric ratio. After purification by flash chromatography, compound (+)-**2** was isolated in 63% yield as a single diastereomer with an enantiomeric excess of 90%.[7] Protection of (+)-**2** as a benzyl ether (NaH, THF, HMPA, BnBr, *n*-Bu_4NI) led to compound (+)-**3** (87% yield) which was transformed to the desired primary alcohol (–)-**4** in 56% yield by hydroboration–oxidation (BH_3·THF, 0 °C then NaOH, H_2O_2). It is noteworthy that the secondary alcohol **4′** was also formed in 35% yield.[8,9] After a Dess–Martin oxidation of (–)-**4** (Dess–Martin periodinane = DMP, pyridine), the obtained aldehyde **5** was added directly to the highly face-selective allyltitanium complex (*R*,*R*)-**II**,[5] to give the homoallylic alcohol (+)-**6** with a 96:4 diastereoselectivity and in 88% overall yield (for the last two steps). The next step was the introduction of the alkyl side chain present at C5 in (+)-preussin, by using a cross-metathesis reaction (Scheme 2). When homoallylic alcohol (+)-**6** was treated with the 'second generation' Grubbs' catalyst[10] **G2** (10 mol%) in refluxing methylene chloride in the presence of oct-1-ene (20 equiv), the corresponding disubstituted olefin (+)-**7** was obtained (84% yield) and hydrogenated (H_2, Pd/C, EtOAc–MeOH 4:1) to produce the mono-protected triol (+)-**8** in 73% yield. The transformation of (+)-**8** to pyrrolidine (+)-**9** was achieved in two steps. The monoprotected triol (+)-**8** was first treated with methanesulfonyl chloride (MsCl, Et_3N, THF). The resulting bis-mesylate was reacted slowly with aqueous *N*-methylamine (DMF, 50 °C, 4 d) to produce the desired cyclized product (+)-**9** as a single diastereomer via two nucleophilic substitution (S_N2 and then S_Ni). Pyrrolidine (+)-**9** was isolated in 48% yield[11] (for the last two steps).

After acidic removal of the methoxymethyl protecting group (6 N HCl, THF), (+)-preussin was isolated in 81% yield. The spectral and physical data of (+)-**1** are in accordance with the literature [1b,4m]{$[\alpha]_D^{25}$ = +21 (*c* 0.2, $CHCl_3$), lit.[1b] $[\alpha]_D^{25}$ = +22 (*c* 1.0, $CHCl_3$)]}.

The use of two enantioselective allyltitanations and a cross-metathesis reaction allowed the synthesis of (+)-preussin in ten steps with an overall yield of 6.4%. Because of the biological potential of (+)-preussin, the synthesis of analogs is certainly a topic of current interest and due to the versatility of the enantioselective allyltitanations and the cross-metathesis reaction, the synthesis of analogs are still being pursued in our laboratories. The results along these lines will be reported in due course.



Scheme 2 (a) (*R*,*R*)-**Ia**, Et_2O, –78 °C, 4 h, 63%, ee = 90%; (b) NaH, HMPA, THF; BnBr, Bu_4NI, r.t., 2 h, 87%; (c) BH_3·THF, THF, 0 °C to r.t., 2 h, (–)-**4** (56%), **4′** (35%); (d) DMP, pyridine, CH_2Cl_2, r.t., 3 h; (e) (*R*,*R*)-**II**, –78 °C, Et_2O, 4 h, 88% (2 steps), dr = 96:4; (f) **G2** (10 mol%), oct-1-ene (20 equiv), CH_2Cl_2, reflux, 8 h, 84%; (g) Pd/C 10%, H_2, EtOAc–MeOH (4:1), r.t., 2 h, 73%; (h) i. MsCl, Et_3N, THF, <0 °C, 2 h.; ii. aq $MeNH_2$, DMF, 50 °C, 4 d, 48% (2 steps); (j) 6 N HCl, THF, r.t., 3 d, 81%.

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(6) Complex (*R*,*R*)-**Ia** (R = MOM) was formed in situ after deprotonation of 3-methoxymethoxypropene by *s*-BuLi and transmetallation with the correponding chlorocyclopentadienyldialkoxytitanium(IV) complex.

(7) The enantiomeric excess of (+)-**3** was determined by ^{1}H NMR after its derivatization with (*S*)- and (*R*)-methoxyphenylacetic acid.

(8) Secondary alcohol **4′** was isolated as a mixture of two diastereomers in a 75:25 ratio. After debenzylation (H_2, Pd/C, quantitative yield), the resulting 1,3-diols were transformed to the corresponding acetonides (dimethoxypropane, PPTS, 90%). According to the ^{1}H NMR and ^{13}C NMR data, the major product has the *anti-anti* structure (Figure 3):

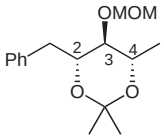

Figure 3

(9) Decomposition of the starting material or non-reactivity were observed when other boranes were used [9-BBN, $(Cy)_2BH$].

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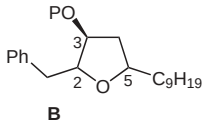
(11) The formation of tetrahydrofuran **B** as secondary product could be observed during the cyclization process (Figure 4).



B

Figure 4