Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: H. Reissig, A. Hausherr and G. Siemeister, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C8OB02645A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

Alkoxyallene-Based Syntheses of Preussin and Analogs and Their Cytotoxicity

Arndt Hausherr,[a] Gerhard Siemeister[b] and Hans-Ulrich Reissig*[a]

[a] Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin (Germany)
E-mail: hans.reissig@chemie.fu-berlin.de
[b] Bayer AG, Research & Development, Pharmaceuticals Müllerstraße 178, 13353 Berlin (Germany)

Electronic supplementary information (ESI) available: Experimental details and spectra of all products.

Abstract: Short syntheses of oxa-preussin, racemic preussin and (-)-preussin are reported. Starting from a racemic 3-nonyl-substituted methoxyallene derivative, its lithiation and addition to phenylethanal provided the corresponding allenyl alcohol that was converted into two diastereomeric dihydrofuran derivatives by silver nitrate-catalyzed 5-*endo-trig* cyclization. The acidic hydrolysis of the enol ether moiety gave heterocyclic ketones and subsequent highly stereoselective reductions with L-Selectride furnished 2-benzyl-5-nonylfuran-3-ol derivatives in good overall yield. The major all-c*is*-diastereomer has the skeleton and relative configuration of preussin and is hence called oxa-preussin. An analogous sequence with the same allene, but an *N*-sulfonyl imine as electrophile, finally led to racemic preussin. The stereoselectivities of the individual steps are discussed in detail. With an enantiopure 2-benzyl-5-nonylpyrrolidin-3-one intermediate the preparation of (-)-preussin with an enantiomeric ratio of >95:5 could be accomplished in a few steps. The sign of the optical rotation of this product finally proved the absolute configurations of its precursors and demonstrated that our chiral auxiliary-based route led to the antipode of the natural product. The cytotoxicity of several of the prepared heterocycles against MCF-7 tumor cells was investigated and five compounds, including racemic and enantiopure (-)-preussin, were identified as highly cytotoxic with IC_{50} values in the range of 3–6 μM.

Introduction

Compounds with hydroxylated pyrrolidine, pyrrolizidine or indolizidine skeletons are frequently occurring natural products with many interesting biological activities.[1] Applying suitably substituted alkoxyallenes[2] and imines we developed short and stereoselective syntheses of the amino acid (-)-detoxinine[3] and the biologically active alkaloids (-)-anisomycin[4] and (+)-codonopsinine.[5] Employing an arabinose-derived nitrone and the requisite alkoxyallenes the preparation of (+)-australine and (+)-casuarine[6] or (-)-hyacinthacine B_4 and hyacinthacine C_5 epimers[7] could be achieved in a close collaboration with the Goti research group (Fig. 1). As a related interesting target compound we planned to prepare the pyrrolidin-3-ol natural product preussin and analogs such as its oxygen congener oxa-preussin.

View Article Online
DOI: 10.1039/C8OB02645A

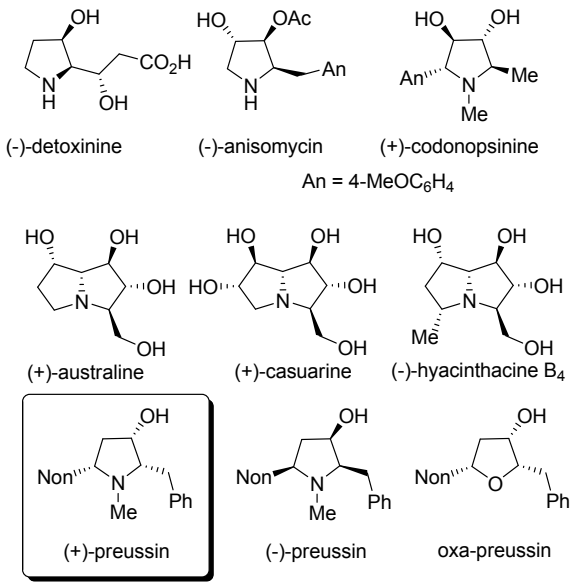
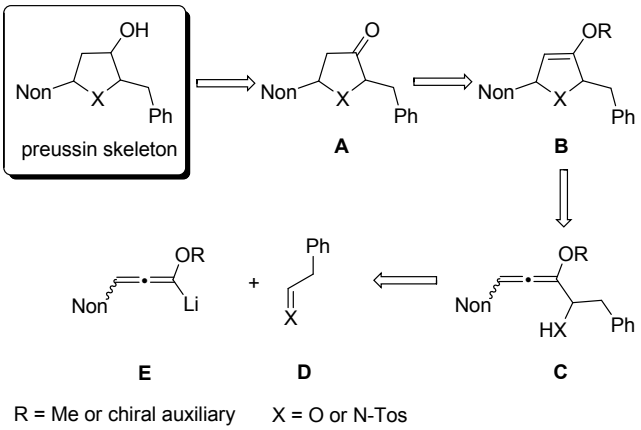


Fig. 1 Hydroxylated pyrrolidine and pyrrolizidine natural products.

The naturally occurring (+)-preussin was isolated independently by two research groups either from the fermentation broth of *Aspergillus Ochraceus* (ATCC 22947)[8] or of a *Preussia species*.[9] This pyrrolidin-3-ol alkaloid has a broad activity spectrum against bacteria and filamentous fungi[8,9] and 1997 Yoshida et al. also described the cytotoxic activity against rat fibroblast cells 3Y1.[10] Later Müller et al. reported that the compound directly interferes in the cell cycle and induces apoptosis of human tumor cells.[11] It could be shown with different human cell lines that (+)-preussin inhibits in vitro the cyclin E kinase (CDK2-cyclin E)[12] with an IC_{50} value of ca. 0.5 µM by blocking the cell cycle progression into S phase. It was also found that (+)-preussin inhibits the -1 programmed ribosomal frameshifting and virus propargation.[13] More recently, the closely related (+)-preussin B (a compound with a 5-heptyl instead of a 5-nonyl substituent) was isolated from *Simplicillium lanosoniveum* and its biosynthesis was elucidated.[14] In 2018 Kijjoa et al. isolated together with 14 other compounds a second close relative of (+)-preussin from the marine sponge-associated fungus *Aspergillus Candidus* KUFA0062: preussin C is the *N*-demethylated version of (+)-preussin.[15] These authors found that preussin C has cytotoxic effects against different tumor cell lines, but that the *N*-methyl group of (+)-preussin seems to be crucial for antibiotic and high cytotoxic activity.

As consequence of these interesting biological activities and the moderate structural complexity of this natural product, it became a popular target for the proof of new synthetic concepts or methods. A large number of syntheses of (+)-preussin, a few of its antipode (-)-preussin and of the racemic compound have been reported.[16] Since most of these syntheses are based on chiral pool compounds, there is still room for improved selectivity and flexibility with respect to an access to analogs. For the envisioned preparation of compounds with the preussin skeleton we planned stereoselective reductions of ketones of type **A** that should be available from the corresponding heterocyclic compounds **B** bearing an enol ether moiety (Scheme 1). These 2,5-dihydrofuran or 2,5-dihydropyrrole derivatives **B** should be prepared from the corresponding allenyl alcohols[17] or amines **C**, [18] respectively, by suitable 5-*endo*-*trig* cyclizations.[19] Hence this analysis leads to starting materials such as lithiated 3-nonyl-substituted alkoxyallenes **E** as crucial nucleophilic component and phenylethanal or its imine congener **D** as electrophiles.

View Article Online
DOI: 10.1039/C8OB02645A



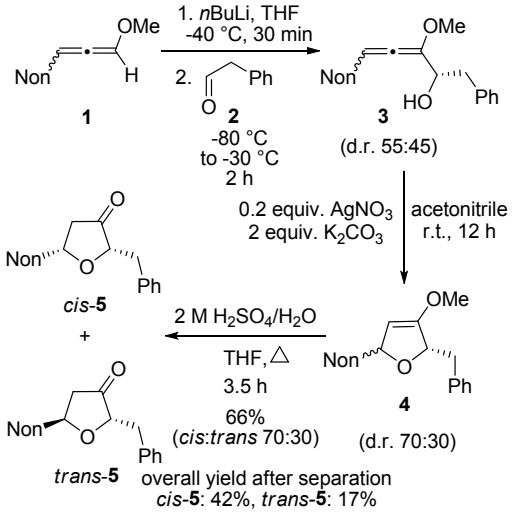
Scheme 1 Retrosynthetic analysis of compounds with preussin skeleton leading via heterocyclic ketones **A**, enol ethers **B**, and allenyl alcohols or allenyl amines **C** to nucleophilic building blocks **E** and electrophiles **D**.

The synthesis and lithiation of 3-alkyl-substituted alkoxyallenes and the addition to electrophiles had been reported by our group in preceding publications.[20] These model reactions revealed that only low diastereoselectivities in additions of the axially chiral allenes to prochiral electrophiles are to be expected.[21] In addition, we also investigated the feasibility of this (3+2) route to five-membered heterocycles using allenes with carbohydrate-derived auxiliaries at the oxygen, that led to highly enantio-enriched pyrrolidine building blocks.[22]

Results and Discussion

First, the short synthesis of racemic oxa-preussin (X = O) is described. The axially chiral 3-nonyl-substituted methoxyallene **1**[20] was used in racemic form, lithiated with *n*-butyllithium under standard conditions and treated with phenylethanal (**2**) at -80 °C. After warm-up and aqueous quench crude allenyl alcohol **3** was quantitatively obtained (Scheme 2). The low diastereoselectivity in the addition step was expected since in model reaction of lithiated **1** or related allenes with various electrophiles similarly unselective additions were observed.[21] The slim nonyl group of **1** seems to be too far away from the C-C bond forming event to have strong influence on this step. Since allenyl alcohols such as **3** rapidly undergo decomposition, crude **3** was treated with 0.2 equivalents of silver nitrate in the presence of potassium carbonate[17d] to furnish the expected 2,5-dihydrofuran derivative **4**. The diastereomeric ratio was slightly shifted in favor of the *cis*-compound (assignments after the next step). This is likely due to a partial equilibration at the allenyl alcohol stage by silver(I) catalysis and a faster cyclization of the pro-*cis*-allenyl alcohol **3** to furnish *cis*-**4** in slight excess. This behavior has also been found and explained in allenyl amine cyclizations.[22] Intermediate **4** was not purified but directly hydrolyzed to furan-3-one derivatives **5** obtained in 66% overall yield after column chromatography. This good yield demonstrates the efficacy of each step of this approach to specifically substituted furan-3-ones. The separation of the two isomers by HPLC provided *cis*-**5** and *trans*-**5** in 42% and 17% overall yield, respectively.

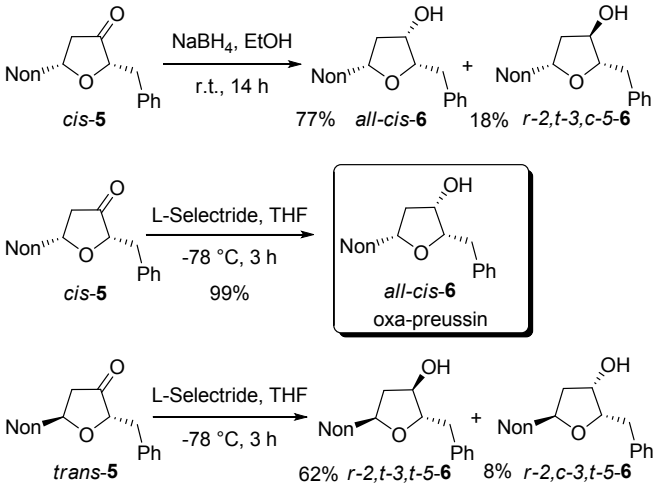
View Article Online
DOI: 10.1039/C8OB02645A



Scheme 2 Synthesis of *cis*- and *trans*-furan-3-one **5** by lithiation of alkoxyallene **1** and addition to phenylethanal (**2**) followed by silver nitrate-promoted cyclization and acidic hydrolysis of **4**. (The shown formulas refer to the relative configurations; the compounds are racemic mixtures).

In order to obtain oxa-preussin, the stereoselective reduction of ketones *cis*-**5** and *trans*-**5** were studied (Scheme 3). Treatment of *cis*-**5** with sodium borohydride in ethanol afforded a 3:1 mixture of the desired *all-cis*-**6** and *r-2*,*t-3*,*c-5*-**6**, that were isolated after purification in 77% and 18% yield, respectively. Gratifyingly, the use of L-Selectride in tetrahydrofuran at -78 °C exclusively gave *all-cis*-**6** in essentially quantitative yield. A NOESY experiment confirmed the configurational assignment of all-*cis*-**6**. Starting from alkoxyallene **1**, the synthesis of oxa-preussin (*all-cis*-**6**) was accomplished in four steps with an overall yield of 42%.

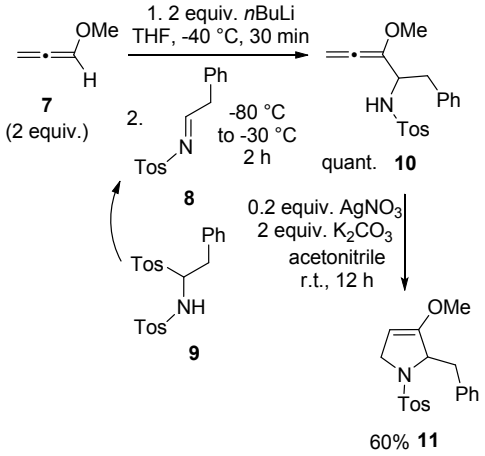
The reduction of *trans*-**5** with L-Selectride was less selective furnishing a mixture of the two possible diastereomers in 62% and 8% yield (Scheme 3). The depicted configurations are based on our observations with related pyrrolidin-3-ones showing that in *trans*-compounds the substituent at C-5 has a stronger influence on the reduction than the C-3 substituent.[21] The *r-2*,*t-3*,*t-5* configuration of the major diastereomer of **6** is thus very likely.



Scheme 3 Synthesis of oxa-preussin (*all-cis*-**6**) by stereoselective reduction of *cis*-**5** and reduction of *trans*-**5**. (The shown formulas refer to the relative configurations; the compounds are racemic mixtures).

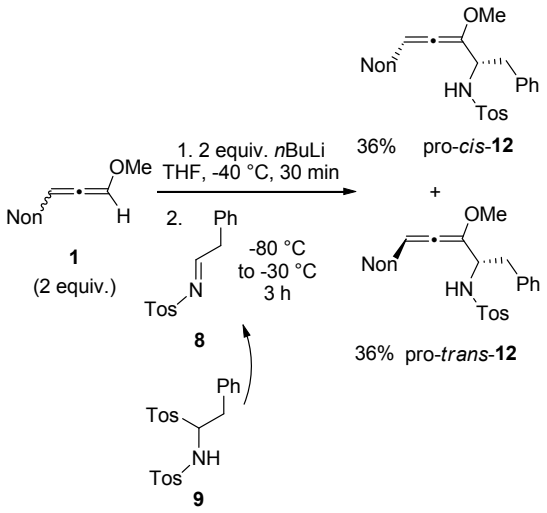
View Article Online
DOI: 10.1039/C8OB02645A

For the synthesis of preussin we planned the use of *N*-tosyl imine **8** since this electrophile should be highly reactive. The N-tosyl group also leads to fairly stable products and on the other hand, it can easily be removed under mild conditions at later stages. However, compound **8** is not particularly stable due to its fast isomerization into the corresponding enamine tautomer.[23] Therefore we examined the *C*,*N*-ditosyl amine **9** as precursor, since under basic conditions this compound undergoes smooth elimination of sulfinate to provide in situ imine **8** that can be trapped by nucleophiles.[24] In most cases the employed base and nucleophile are identical. In a first model reaction, two equivalents of methoxyallene (**7**) were lithiated and imine precursor **9** was added at -80 °C giving the expected allenyl amine **10** quantitatively (Scheme 4). This intermediate was cyclized with silver nitrate to furnish the expected 2,5-dihydropyrrole derivative **11** in 60% overall yield. This experiment taught us that **9** should be a suitable building block for the preparation of the target compound preussin.



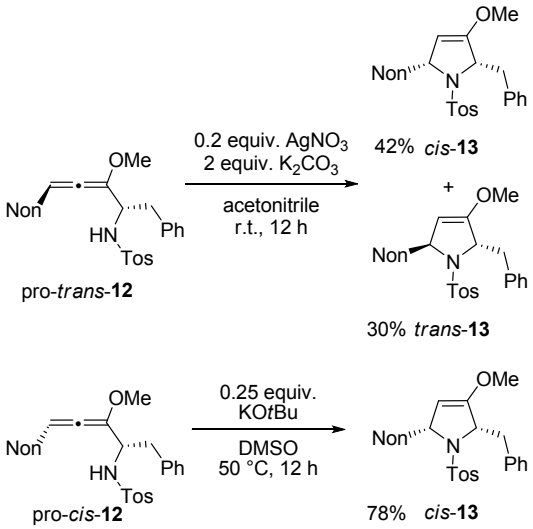
Scheme 4 Synthesis of model compound **11** by lithiation and addition of methoxyallene (**7**) to in situ generated imine **8** and subsequent cyclization of allenyl amine **10**.

With the knowledge gained during the preparation of oxa-preussin and the model reaction above we combined racemic 3-nonyl-substituted methoxyallene **1** with imine precursor **9** (Scheme 5). Two equivalent of lithiated **1** and **9** afforded the expected diastereomers pro-*cis*-**12** and pro-*trans*-**12** in good yield, but with no selectivity. The two isomers were separated by conventional column chromatography and both were isolated in good quantities in 36% yield. The excess of **1** required in this experiment could be re-isolated and used again.



Scheme 5 Synthesis of diastereomeric allenyl amines pro-*cis*-**12** and pro-*trans*-**12** by lithiation of 3-nonyl-substituted methoxyallene **1** and addition to in situ generated imine **8**. (The shown formulas refer to the relative configurations; the compounds are racemic mixtures).

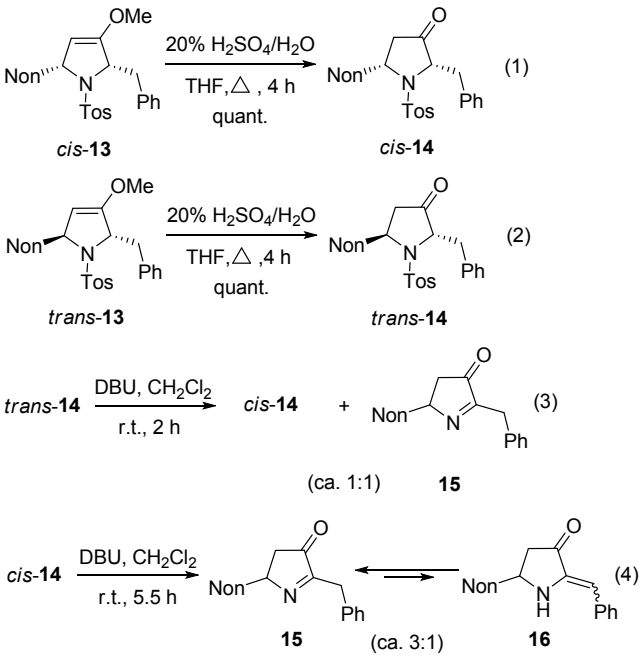
Next, two methods were used for the cyclization step in order to receive the required *cis*-**13** from both diastereomeric precursors.[21] The cyclization of pro-*trans*-**12** with silver nitrate under buffered conditions led to a mixture of *cis*-**13** and *trans*-**13** in 87% yield (Scheme 6). The two isomers were separated by HPLC to furnish the two crystalline isomers in 42% and 30% yield, respectively. Whereas this method is not stereospecific due to the already mentioned equilibration at the allenyl amine stage, the alternative cyclization under strongly basic conditions with potassium *tert*-butoxide in dimethyl sulfoxide proceeds stereospecifically.[21] Starting with pro-*cis*-**12** after 12 h the desired 2,5-disubstituted dihydropyrrole derivative *cis*-**13** was isolated exclusively in good yield. The ^{1}H NMR data allow an unambiguous assignment of the relative configurations of the compounds. Altogether, preussin precursor *cis*-**13** was isolated in 43% overall yield when the results of Schemes 5 and 6 are combined.



Scheme 6 Cyclizations of diastereomeric allenyl amines **12** to *cis*- and *trans*-configured dihydropyrrole derivatives **13** under silver nitrate or potassium *tert*-butoxide promotion. (The shown formulas refer to the relative configurations; the compounds are racemic mixtures).

The hydrolysis of *cis*-**13** and *trans*-**13** could be routinely achieved with 20% aqueous sulfuric acid, furnishing the required 2,5-disubstituted pyrrolidin-3-ones *cis*-**14** and *trans*-**14** quantitatively (Scheme 7, equations 1 and 2). A *cis*/*trans*-equilibration via the corresponding enol form might be possible due to the CH acidic position at C-2, however, even under the relatively harsh hydrolysis conditions no cross-over between *cis*-**14** and *trans*-**14** was found. Since only *cis*-**14** has the required relative configuration to approach preussin, we also examined the equilibration under basic conditions. Whereas no reaction was observed with weak bases (K_2CO_3 or NEt_3), 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) converted *trans*-**14** within 2 h into the thermodynamically more stable *cis*-**14**. Unfortunately, a second compound was formed in similar quantities (Scheme 7, equation 3) whose NMR data reveal the constitution of product **15**. Apparently, a base-promoted sulfinate elimination competes with the desired *trans*/*cis*-equilibration. The conversion into **15** could be completed by applying DBU for longer reaction times (Scheme 7, equation 4). Without the disturbing NMR signals of compound *cis*-**14** we could detect that compound **15** is in equilibrium (ratio ca. 3:1) with its tautomer **16** (*E*/*Z* ca. 1:1).

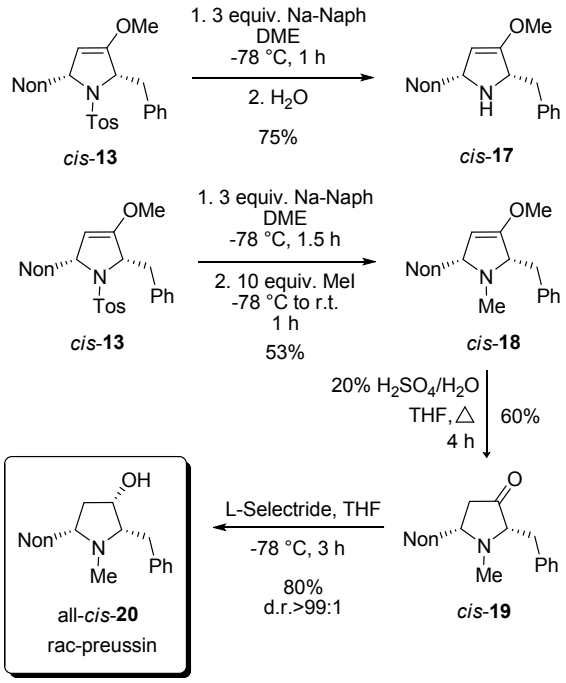
View Article Online
DOI: 10.1039/C8OB02645A



Scheme 7 Hydrolysis of the enol ether moiety of 2,5-dihydropyrroles *cis*-**13** and *trans*-**13** to pyrrolidin-3-ones *cis*-**14** and *trans*-**14** and equilibration experiments finally leading to **15** and **16**. (The shown formulas refer to the relative configurations; the compounds are racemic mixtures).

For the completion of the synthesis of rac-preussin the *N*-tosyl group of *cis*-**13** has to be replaced by an *N*-methyl group. Among the several possibilities to reductively remove *N*-sulfonyl substituents we examined sodium naphthalenide as reagent.[25] At -78 °C compound *cis*-**13** was smoothly converted into *cis*-**17** when the mixture was quenched with water (Scheme 8). The analogous reaction, similarly executed but quenched with an excess of methyl iodide, furnished *cis*-**18** in 53% yield. The moderate efficacy of this step is probably due to the formation of the quarternary ammonium salt. Compound *cis*-**18** was transformed by acidic hydrolysis into 2,5-disubstituted pyrrolidin-3-one derivative *cis*-**19** in 60% yield. The final reduction with sodium borohydride provided an 80:20 mixture of the two possible diastereomers, but with L-Selectride it proceeded with high diastereoselectivity and exclusively gave all-*cis*-**20** in good yield. The NMR data of the sample were in full agreement with those published for preussin in the literature.[26] In conclusion, we could accomplish a synthesis of rac-preussin in five steps (from alkoxyallene **1** and imine precursor **9**). The moderate overall yield of 11% is mainly due to the unselective formation of pro-*cis*-**12** from alkoxyallene **1** and imine **8**. On the other hand, the isolation of pro-*trans*-**12** in similar quantities should allow the preparation of diastereomeric analog of rac-preussin with *trans* orientation of the benzyl and nonyl substituents at C-2 and C-5. Starting with differently 3-alkyl-substituted alkoxyallenes the preparation of other preussin analoga, e.g. the new relative preussin B, should be easily possible.

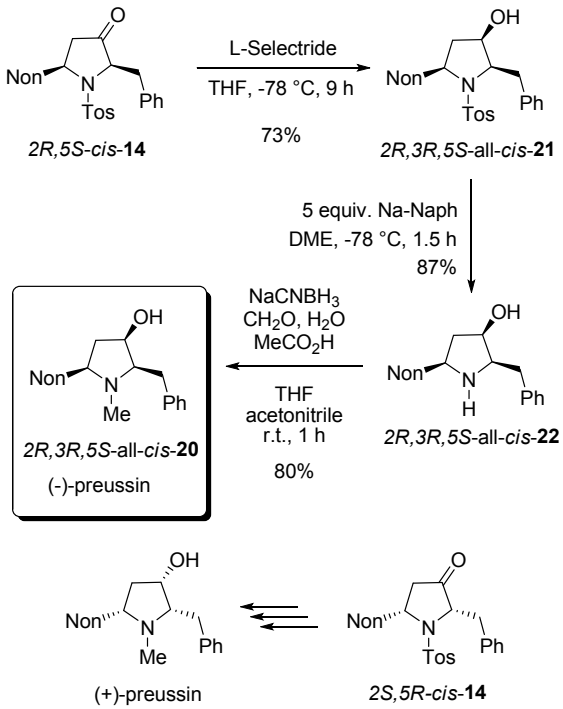
View Article Online
DOI: 10.1039/C8OB02645A



Scheme 8 Synthesis of rac-preussin (all-*cis*-**20**) by reductive removal of the *N*-tosyl group of *cis*-**13**, *N*-methylation to *cis*-**18**, conversion into pyrrolidin-3-one *cis*-**19** followed by stereoselective reduction. (The shown formulas refer to the relative configurations; the compounds are racemic mixtures).

As a result of our systematic studies of 3-alkyl-substituted alkoxyallenes bearing carbohydrate-derived auxiliaries, the pyrrolidin-3-one *cis*-**14** was also available in enantiopure form.[22] Enantiomers 2*R*,5*S*-*cis*-**14** and 2*S*,5*R*-*cis*-**14** had been prepared in a three-step sequence employing the diacetone fructose-derived alkoxyallene congener of **1** and imine **8** as crucial precursors. Without knowing the absolute configuration by certainty,[22] we converted the obtained major isomer *cis*-**14** into enantiopure preussin whose optical rotation showed that we have prepared the unnatural (-)-enantiomer (Scheme 9). Hence the configuration of the used *cis*-**14** could finally be confirmed to be 2*R*,5*S*. For the preparation of (-)-preussin we slightly modified the sequence of steps, starting with the reduction of the ketone moiety and finalizing it by a reductive amination to introduce the *N*-methyl group. Whereas the reduction of 2*R*,5*S*-*cis*-**14** was unselective with sodium borohydride giving an 80:20 mixture of the two diastereomers, the use of L-Selectride exclusively afforded 2*R*,3*R*,5*S*-all-*cis*-**21** in good yield. The subsequent reductive removal of the *N*-tosyl group furnished gave 2*R*,3*R*,5*S*-all-*cis*-**22** that is the optical antipode of the recently isolated preussin C. Since we had learned during the synthesis of racemic preussin that the direct *N*-methylation of the intermediate amide anion with methyl iodide proceeded only with moderate efficacy (Scheme 8), we employed a literature known method[27] for a reductive methylation with aqueous formaldehyde and sodium cyanoborohydride under acidic conditions. The obtained 2*R*,3*R*,5*S*-all-*cis*-**20** was isolated in 80% yield and its NMR data agree very well with those of the literature.[26]

View Article Online
DOI: 10.1039/C8OB02645A



Scheme 9 Synthesis of enantiopure (-)-preussin by stereoselective reduction of 2*R*,5*S*-*cis*-**15** followed by transformations into all-*cis*-**22** and all-*cis*-**20**.

The negative sign of the optical rotation of the final product revealed that we have obtained the unnatural enantiomer and the absolute value of -25.8 (in chloroform) indicated the high enantiomeric purity.[28] The optical purity was further evidenced by converting the sample of all-*cis*-**20** into its Mosher ester. NMR and HPLC analyses showed that the obtained product has a ratio of diastereomers of > 95:5 indicating an ee of at least 90%.

Summing up, our route to (-) preussin involved six steps (starting from the diacetone fructose-derived allene and imine precursor **9**), but the overall yield of only 16% is due to the formation of diastereomers during the route to the required allenyl amine. It should also be mentioned that the 2*S*,5*R*-*cis*-**14** isomer, also available in lower quantities by this route,[22] will allow the reparation of the natural (+) preussin in analogous fashion.

Twenty-one racemic or enantiopure precursors and analogs of preussin (including oxa-preussin) obtained in this study and the preceding report were investigated in vitro for their cytotoxicity against MCF-7 tumor cells during 96 hours of incubation. Only five compounds were found to be cytotoxic with IC_{50} values in the range of 3 to 6 µM (Fig. 2). Racemic preussin showed an IC_{50} value of 6 µM whereas for the (-)-preussin 3.5 µM were determined. In the literature an IC_{50} value of 4.1 µM is reported for the naturally occurring (+)-preussin.[11] These results indicate that the absolute configuration of the preussin enantiomers are not decisive for its cytotoxicity. This is also in accordance with an investigation of the eight stereoisomers with preussin constitution that revealed that the relative and absolute configuration of the compounds has no crucial effect on their inhibitory activity against the cell growth of fission yeast.[28b]

View Article Online
DOI: 10.1039/C8OB02645A

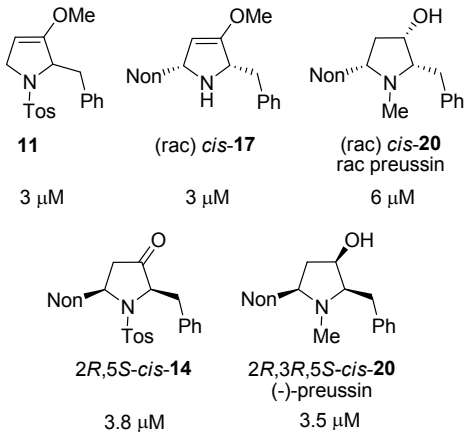


Fig. 2 IC_{50} values of cytotoxic compounds of this studies against the human tumor cell line MCF-7.

As mentioned in the introduction, it was reported that (+)-preussin directly intervenes in the cell cycle and inhibits the entry to the S phase.[11] In order to confirm this finding, the five cytotoxic compounds depicted in Figure 2 were additionally investigated in a cyclinE/CDK2-assay. However, none of the compounds inhibited this kinase. The cellular active compounds **11**, *cis*-**17** and *cis*-**20** [(-)-preussin] were tested as inhibitors of other kinases, but none showed activity. A final conclusion about the mode of action of this type of compounds is therefore not possible.

Conclusions

The routes to racemic preussin and its oxa-analog oxa-preussin based on 3-nonyl-substituted methoxyallene **1** as key precursor are short and flexible. The diastereoselectivity of the addition of the lithiated allene to the electrophiles is low, but this stereodivergent step opens the way for the synthesis of diastereomeric target compounds. A synthesis of the antipode of the natural product – (-)-preussin – proceeds efficiently by starting from highly enantio-enriched 2*R*,5*S*-*cis*-**14** and proves the absolute configuration of this compound and its precursors. On the way to (-)-preussin its demethylated relative (-)-preussin C was passed by that is the antipode of a recently isolated natural product. Our approach to compounds with preussin skeleton is highly flexible since we do not follow a chiral pool but an auxiliary-based strategy. As a consequence, the 3-alkyl group of the starting allene and the C-substituent of the imine can easily be varied and a broad range of target compounds with differing substituents at C-2 and C-5 should easily be accessible, e.g. preussin B or related compounds. Racemic preussin and (-)-preussin showed IC_{50} values against MCF-7 tumors cells in the range of 3.5-6 μM, similar to a literature reported value for (+)-preussin. Unexpectedly, the absolute configuration of the compounds does not play no essential role for its cytotoxicity.

Experimental

For general information and details of remaining experiments, see ESI.

Starting materials: 1-methoxydodeca-1,2-diene (**1**)[20b], imine precursor **9**[24].

General procedure for the addition of lithiated alkoxyallenes to aldehydes or imines (GP1)

View Article Online
DOI: 10.1039/C8OB02645A

For generation of the lithiated alkoxyallene, the corresponding alkoxyallene was dissolved in THF and *n*-butyllithium was added at -40 °C. After 30 min, the solution was cooled to -80 °C and the corresponding electrophile was added. The mixture was allowed to warm up to -30 °C and stirred for the time given in the individual experiments. After quenching with saturated aqueous $NaHCO_3$ solution (10 mL/), the organic phase was separated and the aqueous phase was extracted with diethyl ether (3 x 15 mL/mmol of alkoxyallene). The combined organic phases were dried (Na_2SO_4), filtered and evaporated in vacuo to provide the crude product that was used directly or purified as given in the individual experiment. The yields refer to the amount of electrophile used.

3-Methoxy-1-phenyltetradeca-3,4-diene-2-ol (3)

According to **GP1**, 1-methoxydodeca-1,2-diene (**1**) (0.620 g, 3.16 mmol), *n*-butyllithium (1.30 mL, 3.16 mmol of 2.43 M solution in hexanes) and phenylethanal (**2**) (0.380 g, 3.16 mmol) in THF (40 mL) provided after 2 h crude **3** (1.13 g, d.r. 55:45) as light yellow oil that was cyclized without purification.

^{1}H NMR ($CDCl_3$, 270 MHz), major diastereomer: δ = 0.89 (t, J = 6.6 Hz, 3 H, Me), 1.15–1.40, 1.85–2.00 (2 m, 14 H, 2 H, CH_2), 2.01 (d, J = 5.9 Hz, 1 H, OH), 2.88, 2.98 (AB part of ABX system, J_{AB} = 13.6 Hz, J_{AX} = 7.4 Hz, J_{BX} = 2.6 Hz, 1 H each, 1-H), 3.41 (s, 3 H, OMe), 4.28–4.44 (m, 1 H, 2-H), 5.84 (d, J = 7.0 Hz, 1 H, 5-H), 7.10–7.40 ppm (m, 5 H, Ph); the following signals of the minor diastereomer are distinguishable from those of the major isomer: δ = 2.15 (d, J = 5.9 Hz, 1 H, OH), 2.88, 3.00 (AB part of ABX system, J_{AB} = 13.6 Hz, J_{AX} = 7.4 Hz, J_{BX} = 3.3 Hz, 1 H each, 1-H), 5.89 ppm (td, J = 6.8 Hz, J = 1.7 Hz, 1 H, 5-H). ^{13}C NMR ($CDCl_3$, 67.9 MHz), major diastereomer: δ = 14.0 (q, Me), 22.6, 28.5, 29.1, 29.2, 29.4, 29.5, 31.4, 31.8 (8 t, CH_2), 40.9 (t, C-1), 55.9 (q, OMe), 71.2 (d, C-2), 109.8 (d, C-5), 126.2, 128.1, 129.4 (3 d, Ph), 134.1 (s, C-3), 138.0 (s, Ph),188.8 ppm (s, C-4); the following signals of the minor diastereomer are distinguishable from those of the major isomer: δ = 31.5 (t, CH_2), 41.1 (t, C-1), 72.5 (d, C-2), 108.8 (d, C-5), 129.5 (d, Ph), 135.0 (s, C-3), 137.8 (s, Ph), 188.5 ppm (s, C-4). IR (film): $\tilde{\nu}$ = 3460 (OH), 3030–2855 (C-H), 1950 cm^{-1} (C=C=C). MS (EI, 80 eV): *m/z* (%) = 316 (1) [M$^+$], 301 (1) [M$^+$ - Me], 239 (21) [M$^+$ - Ph], 227 (65), 91 (100) [Bn$^+$].

General procedure for silver nitrate-promoted cyclization (GP2)

To a solution of the corresponding allenyl alcohol or amine in acetonitrile (5 mL/mmol) were added under a stream of argon via a funnel potassium carbonate and silver nitrate. The resulting mixture was stirred at room temperature under light exclusion for 12 h, then filtered and evaporated. The residue was dissolved in a small amount ethyl acetate and filtered through a pad of Celite (elution with ethyl acetate). After removal of the solvents in vacuo, the crude product was purified as indicated in the individual experiments.

2-Benzyl-3-methoxy-5-nonyl-2,5-dihydrofuran (4)

According to **GP2**, crude allenyl alcohol **3** (1.13 g, d.r. 55:45) in acetonitrile (40 mL) was treated with $AgNO_3$ (0.107 g, 0.63 mmol) and K_2CO_3 (0.873 g, 6.30 mmol) for 12 h to provide crude **4** (1.11 g, d.r. 70:30) as brown oil, that was directly hydrolyzed in the next step. The *cis*/*trans* assignments are based on the assignments of *cis*-**5** and *trans*-**5**.

General procedure for acid-promoted hydrolysis of 2,5-dihydrofurans and 2,5-dihydropyrroles (GP3)

A solution of the corresponding substrate in THF was heated under reflux with aqueous sulfuric acid (2 M or 20%) for the time given in the individual experiments (progress of conversion was followed by TLC). After cooling to room temperature the mixture was cautiously neutralized with saturated aqueous $NaHCO_3$ solution and the organic phase was separated. The aqueous phase was extracted with diethyl ether (2 x 15 mL). The combined organic phases were dried (Na_2SO_4), filtered and evaporated in vacuo. The purification is indicated in the individual experiments.

2-Benzyl-5-nonyltetrahydrofuran-3-one (5)

According to **GP3**, crude **4** (1.11 g, d.r. 70:30) in THF (20 mL) and H_2SO_4 (14 mL of 2 M aqueous solution) provided after 3.5 h crude **5** (1.06 g, d.r. 70:30) as yellow oil. Purification by column chromatography (silica gel, hexanes/ethyl acetate 10:1) furnished **5** (0.630 g, 66%, d.r. 70:30) as colorless oil and subsequent separation of the diastereomers by HPLC (hexanes/ethyl acetate 97:3) afforded *trans*-**5** (0.165 g, 17%, containing minor impurities) and *cis*-**5** (0.402 g, 42%) as colorless oils. Overall yield for three steps: 59%.

Data of *cis*-**5**: ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.88 (t, J = 6.9 Hz, 3 H, Me), 1.20–1.40, 1.47–1.60 1.62–1.70, (3 m, 14 H, 1 H each, CH_2), 1.83 (dd, J = 17.9 Hz, J = 10.6 Hz, 1 H, 4-H), 2.45 (dd, J = 17.9 Hz, J = 5.6 Hz, 1 H, 4-H), 2.87, 3.08, 4.00 (ABX system, J_{AB} = 14.4 Hz, J_{AX} = 6.9 Hz, J_{BX} = 3.9 Hz, 1 H each, PhCH_2, 2-H), 4.06 (ddt, J = 10.6 Hz, J = 5.9 Hz, J = 5.6 Hz, 1 H, 5-H), 7.20–7.32 ppm (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 22.7, 25.2, 29.3, 29.4, 29.5*, 31.9, 35.5, 37.2, 41.2 (9 t, CH_2, C-4, PhCH_2,), 75.9, 81.9 (2 d, C-2, C-5), 126.5, 128.1, 129.7, 137.2 (3 d, s, Ph), 216.0 ppm (s, C-3); * signal with higher

View Article Online
DOI: 10.1039/C8OB02645A

intensity. IR (film): $\tilde{\nu}$ = 3090–2855 (C-H), 1740 cm^{-1} (C=O). MS (EI, 80 eV): *m/z* (%) = 302 (20) [M$^+$], 181 (16), 91 (100) [Bn$^+$]. $C_{20}H_{30}O_2$ (302.5): calcd. C 79.42, H 10.00; found C 79.34, H 9.75.

Data of *trans*-**5**: ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.88 (t, *J* = 6.7 Hz, 3 H, Me), 1.20–1.40, 1.45–1.60, 1.60–1.75 (3 m, 14 H, 1 H each, CH_2), 2.15, 2.34 (AB part of ABX system, J_{AB} = 18.0 Hz, J_{AX} = 7.3 Hz, J_{BX} = 6.8 Hz, 1 H each, 4-H), 2.90, 2.98, 4.23 (ABX system, J_{AB} = 14.2 Hz, J_{AX} = 6.8 Hz, J_{BX} = 4.6 Hz, 1 H each, PhC*H*$_2$, 2-H), 4.03–4.16 (m, 1 H, 5-H), 7.16–7.31 ppm (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 22.6, 25.4, 29.2, 29.4, 29.5*, 31.8, 35.6, 37.0, 42.6 (9 t, CH_2, C-4, Ph*C*H$_2$), 75.5, 80.0 (2 d, C-2, C-5), 126.5, 128.3, 129.5, 137.1 (3 d, s, Ph), 216.4 ppm (s, C-3); * signal with higher intensity. IR (film): $\tilde{\nu}$ = 3065–2855 (C-H), 1755 cm^{-1} (C=O). MS (EI, 80 eV): *m/z* (%) = 302 (6) [M$^+$], 136 (16), 120 (18), 91 (100) [Bn$^+$].

General procedure for sodium borohydride-promoted reductions of cyclic ketones (GP4)

The corresponding substrate was dissolved in dry ethanol and at 0 °C sodium borohydride was added under a stream of argon via a funnel. After stirring at room temperature for the time indicated, the mixture was treated with 2 N HCl until the precipitate dissolved and was extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (until the extract is neutral), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by chromatography.

(all-*cis*)- and (*r*-2,*t*-3,*c*-5)-2-Benzyl-5-nonyltetrahydrofuran-3-ol (6)

According to **GP4**, a solution of *cis*-**5** (0.027 g, 0.09 mmol), $NaBH_4$ (0.007 g, 0.17 mmol) in EtOH (3 mL) provided after 14 h crude **6** (0.032 g, d.r. 75:25) as a colorless oil. Column chromatography (silica gel, hexanes/ethyl acetate 5:1) furnished *all-cis*-**6** (0.021 g, 77%) as colorless crystals (m.p. 49–50 °C) and *r*-2,*t*-3,*c*-5-**6** (0.005 g, 18%) as colorless crystals (m.p. 42–43 °C).

Data of *all-cis*-**6**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.88 (t, *J* = 6.5 Hz, 3 H, Me), 1.20–1.40 (m, 14 H, CH_2), 1.54 (ddd, *J* = 13.9 Hz, *J* = 6.5 Hz, *J* = 1.8 Hz, 1 H, 4-H), 1.51–1.58 (m, 1 H, CH_2), 1.68 (d, *J* = 7.5 Hz, 1 H, OH), 1.66–1.78 (m, 1 H, CH_2), 2.34 (ddd, *J* = 13.9 Hz, *J* = 8.2 Hz, *J* = 6.3 Hz, 1 H, 4-H), 3.01 (d, *J* = 7.1 Hz, 2 H, PhC*H*$_2$), 3.75 (td, *J* = 7.1 Hz, *J* = 3.3 Hz, 1 H, 2-H), 3.79 (dq, *J* = 8.2 Hz, *J* = 6.5 Hz, 1 H, 5-H), 4.05–4.13 (m, 1 H, 3-H), 7.15–7.33 ppm (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 14.1 (q, Me), 22.7, 26.2, 29.3, 29.5, 29.6*, 31.9, 36.8, (7 t, CH_2), 35.1 (t, Ph*C*H$_2$), 41.6 (t, C-4), 72.3 (d, C-3), 77.8 (d, C-5), 83.8 (d, C-2), 126.2, 128,4, 129.2, 138.6 ppm (3 d, s, Ph); * signal with higher intensity. IR (KBr): $\tilde{\nu}$ = 3410 (O-H), 3030–2850 cm^{-1} (C-H). MS (EI, 80 eV): *m/z* (%) = 304 (10) [M$^+$], 213 (100) [M$^+$ - Bn], 177 (34) [M$^+$ - C_9H_{19}]. $C_{20}H_{30}O_2$ (304.5): calcd. C 78.90, H 10.59; found C 78.73, H 10.57.

Data of *r*-2,*t*-3,*c*-5-**6**: ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.88 (t, *J* = 6.6 Hz, 3 H, Me), 1.20–1.50 (m, 16 H, CH_2), 1.62 (ddd, *J* = 13.1 Hz, *J* = 9.6 Hz, *J* = 6.6 Hz, 1 H, 4-H), 1.55–1.70 (m, 1 H, OH), 1.87 (ddd, *J* = 13.1 Hz, *J* = 5.7 Hz, *J* = 2.4 Hz, 1 H, 4-H), 2.71, 2.96, 3.94 (ABX system, J_{AB} = 13.7 Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.0 Hz, 1 H each, PhC*H*$_2$, 2-H), 4.07 (dtd, *J* = 9.6 Hz, *J* = 6.0 Hz, *J* = 5.7 Hz, 1 H, 5-H), 4.08–4.16 (m, 1 H, 3-H), 7.20–7.35 ppm (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 22.7, 26.0, 29.3, 29.6*, 29.7, 31.9, 35.1, 35.8, 40.6 (9 t, CH_2, C-4, Ph*C*H$_2$), 75.7 (d, C-3), 78.2 (d, C-5), 87.1 (d, C-2), 126.4, 128.4, 129.4, 137.9 ppm (3 d, s, Ph); * signal with higher intensity. IR (KBr): $\tilde{\nu}$ = 3410 (O-H), 3085, 3020, 2955, 2920, 2820 cm^{-1} (C-H). MS (EI, 80 eV): *m/z* (%) = 304 (13) [M$^+$], 213 (100) [M$^+$ - Bn], 177 (37) [M$^+$ - C_9H_{19}]. HRMS (EI, 80 eV): calcd. for $C_{20}H_{32}O_2$: 304.2402; found 304.2444.

General procedure for the reduction of cyclic ketones with L-Selectride (GP5)

The corresponding substrate was dissolved in THF and at –78 °C an excess of L-Selectride (1 M in THF) was added dropwise. The mixture was stirred at this temperature for the time indicated and then quenched by addition of water (10 mL). The aqueous phase was separated and the organic phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and the solvents were removed in vacuum. The crude product was purified by chromatography.

(all-*cis*)-2-Benzyl-5-nonyltetrahydrofuran-3-ol (6)

According to **GP5**, a solution of *cis*-**5** (0.036 g, 0.12 mmol), L-Selectride (0.18 mL of 1 M solution in THF, 0.18 mmol) in THF (3 mL) provided after 3 h crude **6** (0.061 g). Purification by column chromatography (silica gel, hexanes/ethyl acetate 5:1) afforded *all-cis*-**6** (0.036 g, 99%) as colorless crystals (m.p. 49–50 °C). The spectroscopic data agree with those of the sample obtained before.

(*r*-2,*t*-3,*t*-5)- and (*r*-2,*c*-3,*t*-5)-2-Benzyl-5-nonyltetrahydrofuran-3-ol (6)

According to **GP5**, a solution of *trans*-**5** (0.147 g, 0.49 mmol), L-Selectride (0.73 mL of 1 M solution in THF, 0.73 mmol) in THF (20 mL) provided after 3 h the crude product (0.250 g, d.r. 90:10). The ratio of diastereomers was determined by HPLC. Purification by column chromatography (silica gel, hexanes/ethyl acetate 5:1) and subsequent separation by HPLC (hexanes/ethyl acetate 5:1) afforded *r*-2,*t*-3,*t*-5-**6** (0.091 g, 62%) as colorless crystals (m.p. 54–55 °C) and *r*-2,*c*-3,*t*-5-**6** (0.010 g, 8%) as colorless oil.

Data of *r*-2,*t*-3,*t*-5-**6**: H NMR ($CDCl_3$, 270 MHz): δ = 0.88 (t, *J* = 6.5 Hz, 3 H, Me), 1.20–1.45 (m, 15 H, CH_2), 1.55–1.73 (m, 2 H, OH, CH_2), 1.70 (ddd, *J* = 13.4 Hz, *J* = 9.5 Hz, *J* = 4.4 Hz, 1 H, 4-H), 2.08 (dd, *J* = 13.4 Hz, *J* = 6.1 Hz, 1 H, 4-H), 2.96, 3.01, 4.05 (ABX system, J_{AB} = 13.5 Hz, J_{AX} = 7.7 Hz, J_{BX} = 6.7 Hz, 1 H each, PhCH_2, 2-H), 4.09–4.17 (m, 1 H, 3-H), 4.28 (dq, *J* = 9.5 Hz, *J* = 6.1 Hz, 1 H, 5-H), 7.17–7.33 ppm (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 22.7, 26.0, 29.3, 29.5, 29.6*, 31.9, 35.3, 36.3, 41.6 (9 t, CH_2, C-4, PhCH_2), 72.7 (d, C-3), 77.5 (d, C-5), 83.6 (d, C-2), 126.2, 128.4, 129.2, 138.5 ppm (3 d, s, Ph); * signal with higher intensity. IR (KBr): $\tilde{\nu}$ = 3420 (O-H), 3035–2850 cm^{-1} (C-H). MS (EI, 80 eV): *m/z* (%) = 304 (18) [M^+], 213 (100) [M^+ - Bn], 91 (81) [Bn^+]. HRMS (EI, 80 eV): calcd. for $C_{20}H_{32}O_2$: 304.2402; found 304.2434.

Data of *r*-2,*c*-3,*t*-5-**6**: ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.87 (t, *J* = 6.9 Hz, 3 H, Me), 1.15–1.73 (m, 17 H, OH, CH_2), 1.57 (ddd, *J* = 13.2 Hz, *J* = 7.3 Hz, *J* = 5.6 Hz, 1 H, 4-H), 2.33 (dd, *J* = 13.2 Hz, *J* = 6.3 Hz, 1 H, 4-H), 2.71, 2.92 (AB part of ABX system, J_{AB} = 13.6 Hz, J_{AX} = 7.2 Hz, J_{BX} = 6.3 Hz, 1 H each, PhCH_2), 3.95–4.05, 4.08–4.16 (2 m, 3 H, 2-H, 3-H, 5-H), 7.17–7.35 ppm (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 22.7, 26.0, 29.3, 29.5, 29.6, 29.7, 31.9, 36.6, 39.4, 40.3 (10 t, CH_2, C-4, PhCH_2), 75.9, 77.4, 85.0 (3 d, C-2, C-3, C-5), 126.4, 128.5, 129.3, 137.8 ppm (3 d, s, Ph). IR (film): $\tilde{\nu}$ = 3410 (O-H), 3085–2855 cm^{-1} (C-H). MS (EI, 80 eV): *m/z* (%) = 304 (11) [M^+], 213 (100) [M^+ - Bn], 91 (96) [Bn^+]. HRMS (EI, 80 eV): calcd. for $C_{20}H_{32}O_2$: 304.2402; found 304.2439.

***N*-(3-Methoxy-1-phenyltetradeca-3,4-dien-2-yl)-*p*-toluenesulfonamide (12)**

According to **GP1**, 1-methoxydodeca-1,2-diene (**1**) (1.32 g, 6.71 mmol), *n*-butyllithium (2.80 mL, 6.71 mmol of 2.40 M solution in hexanes) and **9** (1.44 g, 3.35 mmol) in THF (50 mL) provided after 3 h crude **12** (2.34 g, d.r. 50:50) as light yellow oil. The crude product was purified by column chromatography (alumina III, hexanes/ethyl acetate 5:1) to give **12** (0.778 g), pro-*cis*-**12** (0.569 g, 36%) as light yellow solid (melting range 36–40 °C) and pro-*trans*-**12** (0.566 g, 36%) as light yellow crystals (m.p. 48 °C).

Data of pro-*cis*-**12**: ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.89 (t, *J* = 6.3 Hz, 3 H, Me), 1.00–1.40, 1.60–1.70 (2 m, 14 H, 2 H, CH_2), 2.40 (s, 3 H, Tos-Me), 2.92, 2.99 (AB part of ABX system, J_{AB} = 13.8 Hz, J_{AX} = 7.0 Hz, J_{BX} = 5.9 Hz, 1 H each, 1-H), 3.20 (s, 3 H, OMe), 4.05–4.18 (m, 1 H, 2-H), 4.56 (d, *J* = 9.6 Hz, 1 H, NH), 5.45 (t, *J* = 5.9 Hz, 1 H, 5-H), 7.09 (d, *J* = 7.4 Hz, 2 H, Ph), 7.15–7.30 (m, 5 H, Ph, Tos), 7.66 ppm (d, *J* = 8.1 Hz, 2 H, Tos). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 21.5 (q, Tos-Me), 22.7, 28.7, 29.2, 29.3, 29.4, 29.6, 31.2, 31.9 (8 t, CH_2), 40.1 (t, C-1), 58.8, 55.4 (q, d, OMe, C-2), 109.7 (d, C-5), 126.5, 127.1, 128.1, 129.3, 129.8 (5 d, Ph, Ts), 131.2 (s, C-3), 136.5*, 142.9 (2 s, Ph, Ts), 189.0 ppm (s, C-4); * signal with higher intensity. IR (KBr): $\tilde{\nu}$ = 3255 (N-H), 3065, 2925, 2850 (C-H), 1965 (C=C), 1325, 1165 cm^{-1} (Tos-N). MS (pos. FAB): *m/z* (%) = 470 (9) [M^+ + H], 456 (11) [M^+ + H - Me], 378 (5) [M^+ - Bn], 274 (34), 154 (73), 136 (66), 91 (100) [Bn^+].

Data of pro-*trans*-**12**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.89 (t, *J* = 7.0 Hz, 3 H, Me), 1.00–1.45, 1.50–1.60 (2 m, 14 H, 2 H, CH_2), 2.40 (s, 3 H, Tos-Me), 2.89, 2.97 (AB part of ABX system, J_{AB} = 13.2 Hz, J_{AX} = 8.8 Hz, J_{BX} = 5.7 Hz, 1 H each, 1-H), 3.06 (s, 3 H, OMe), 4.05–4.13 (m, 1 H, 2-H), 4.86 (d, *J* = 9.4 Hz, 1 H, NH), 5.42 (t, *J* = 6.7 Hz, 1 H, 5-H), 7.08 (d, *J* = 7.1 Hz, 2 H, Ph), 7.10–7.30 (m, 5 H, Ph, Ts), 7.67 ppm (d, *J* = 8.4 Hz, 2 H, Ts). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 14.2 (q, Me), 21.5 (q, Tos-Me), 22.7, 28.4, 29.1, 29.3, 29.4, 29.5, 30.9, 31.9 (8 t, CH_2), 40.1 (t, C-1), 55.5, 57.4 (q, d, OMe, C-2), 108.0 (d, C-5), 126.4, 128.6, 128.9, 129.1, 130.0 (5 d, Ph, Ts), 136.9, 137.8, 142.9 (3 s, Ph, Ts)*, 189.3 ppm (s, C-4) ppm; * signal of C-3 is hidden by the aryl signals. IR (KBr): $\tilde{\nu}$ = 3270 (N-H), 3065, 2925, 2855 (C-H), 1965 (C=C), 1335, 1160 cm^{-1} (Tos-N). MS (pos. FAB): *m/z* (%) = 470 (21) [M^+ + H], 438 (7) [M^+ - OMe], 378 (12) [M^+ - Bn], 314 (22), 299 (44), 91 (100) [Bn^+].

***cis*- and *trans*-2-Benzyl-3-methoxy-5-nonyl-1-tosyl-2,5-dihydro-pyrrole (13)**

According to **GP2**, allenyl amine pro-*trans*-**12** (0.200 g, 0.43 mmol) in acetonitrile (8 mL) was treated with $AgNO_3$ (0.015 g, 0.09 mmol) and K_2CO_3 (0.118 g, 0.86 mmol) for 12 h to provide crude **13** (0.220 g, d.r. 55:45) as brown oil that was purified by column chromatography (silica gel, hexanes/ethyl acetate 9:1) to give the pure diastereomers of **13** (0.174 g, 87%). Separation HPLC (hexanes/ethyl acetate 93:7) furnished *trans*-**13** (0.060 g, 30%) as colorless crystals (m.p. 66 °C) and *cis*-**13** (0.083 g, 42%) as colorless crystals (m.p. 57–58 °C).

Data of *cis*-**13**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.89 (t, *J* = 6.6 Hz, 3 H, Me), 0.95–1.41 (m, 16 H, CH_2), 2.42 (s, 3 H, Tos-Me), 3.06, 3.17 (AB part of ABX system, J_{AB} = 13.6 Hz, J_{AX} = 2.6 Hz, J_{BX} = 5.5 Hz, 1 H each, PhCH_2), 3.54 (s, 3 H, OMe), 3.94–4.02 (m, 1 H, 5-H), 4.27 (s, 1 H, 4-H), 4.37–4.43 (m, 1 H, 2-H), 7.15–7.27 (m, 5 H, Ph), 7.30, 7.71 ppm (2 d, *J* = 8.1 Hz, 2 H each, Tos). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 14.0 (q, Me), 21.5 (q, Tos-Me), 22.7, 28.7, 25.6, 28.7, 29.3, 29.4, 29.5, 31.9 (8 t, CH_2), 38.8 (t,

View Article Online
DOI: 10.1039/C8OB02645A

PhCH$_2$), 56.6 (q, OMe), 65.0, 65.2 (2 d, C-2, C-5), 94.4 (d, C-4), 126.3, 127.5, 127.7, 129.8, 131.0 (5 d, Ph, Tos), 134.3, 136.4, 143.3 (3 s, Ph, Tos), 154.0 ppm (s, C-3). IR (KBr): $\tilde{\nu}$ = 3060, 3030, 2925, 2855 (C-H), 1670 (C=C), 1345, 1165 cm^{-1} (Tos-N). MS (EI, 80 eV): *m/z* (%) = 469 (0.3) [M$^+$], 378 (100) [M$^+$ - Bn], 342 (20) [M$^+$ - C_9H_{19}], 91 (100) [Bn$^+$]. $C_{28}H_{39}NO_3S$ (469.3): calcd. C 71.61, H 8.37, N 2.98; found C 71.62, H 8.22, N 2.91.

Data of *trans*-**13**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.88 (t, *J* = 7.1 Hz, 3 H, Me), 0.90–1.31, 1.80–1.88 (2 m, 15 H, 1 H, CH$_2$), 2.42 (s, 3 H, Tos-Me), 3.01 (dd, *J* = 13.7 Hz, *J* = 2.2 Hz, 1 H, PhC*H*$_2$), 3.56 (s, 3 H, OMe), 3.74 (dd, *J* = 13.7 Hz, *J* = 4.5 Hz, 1 H, PhC*H*$_2$), 3.97–4.02 (m, 1 H, 5-H), 4.23 (s, 1 H, 4-H), 4.71 (s_{br}, 1 H, 2-H), 7.19–7.28 (m, 3 H, Ph), 7.27 (d, *J* = 8.1 Hz, 2 H, Tos), 7.35 (d, *J* = 6.9 Hz, 2 H, Ph), 7.77 ppm (d, *J* = 8.1 Hz, 2 H, Tos). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 14.1 (q, Me), 21.4 (q, Tos-Me), 22.6, 25.1, 29.2, 29.4*, 29.5, 31.8, 33.9, (8 t, CH$_2$), 38.4 (t, PhCH$_2$), 56.3 (q, OMe), 65.7 (2 d, C-2, C-5), 94.6 (d, C-4), 126.1, 126.6, 127.6, 129.3, 130.5 (5 d, Ph, Tos), 136.5, 140.1, 142.6 (3 s, Ph, Tos),153.8 ppm (s, C-3); signal with higher intensity. IR (KBr): $\tilde{\nu}$ = 3030, 2925, 2855 (C-H), 1675 (C=C), 1335, 1160 cm^{-1} (Tos-N). MS (EI, 80 eV): *m/z* (%) = 469 (0.5) [M$^+$], 378 (100) [M$^+$ - Bn], 342 (12) [M$^+$ - C_9H_{19}], 91 (50) [Bn$^+$]. HRMS (EI, 80 eV): calcd. for $C_{28}H_{39}NO_2S$: 469.2651; found 469.2636. $C_{28}H_{39}NO_3S$ (469.3): calcd. C 71.61, H 8.37, N 2.98; found C 71.65, H 8.33, N 2.95.

2-Benzyl-3-methoxy-5-nonyl-1-tosyl-2,5-dihydropyrrole (*cis*-13)

A solution of pro-*cis*-**12** (0.520 g, 1.11 mmol) in 15 mL of dry DMSO was heated to 50 °C. In a stream of argon, freshly sublimed KO*t*Bu (0.031 g, 0.28 mmol) was added via a funnel and the mixture was stirred at this temperature for 12 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ solution (10 mL) was added. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 x 20 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (2 x 20 mL), dried (Na_2SO_4), filtered and evaporated in vacuo to provide crude *cis*-**13** (0.534 g) as yellow oil. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate) to furnish *cis*-**13** (0.405 g, 78%) as colorless crystals (m,p. 57–58 °C). For the analytical data see above.

2-Benzyl-5-nonyl-1-tosylpyrrolidin-3-one (*cis*-14)

According to **GP3**, *cis*-**13** (0.120 g, 0.26 mmol) in THF (6 mL) and 20% aqueous H_2SO_4 (4 mL) provided after 4 h crude *cis*-**14** (0.189 g) as light yellow oil. Purification by column chromatography (silica gel, hexanes/ethyl acetate 7:1) furnished *cis*-**14** (0.116 g, quant.) as colorless crystals (m.p. 63–65 °C).

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.90 (t, *J* = 6.7 Hz, 3 H, Me), 0.90–1.40 (m, 16 H, CH$_2$), 1.76, 2.14 (AB part of ABX system, J_{AB} = 18.2 Hz, J_{AX} = 3.0 Hz, J_{BX} = 9.3 Hz, $J_{B,CH}$ = 1.3 Hz, 1 H each, 4-H), 2.43 (s, 3 H, Tos-Me), 3.22, 3.27, 3.93 (ABX system, J_{AB} = 13.5 Hz, J_{AX} = 5.7 Hz, J_{BX} = 4.0 Hz, 1 H each, PhC*H*$_2$, 2-H), 3.77–3.88 (m, 1 H, 5-H), 7.20–7.30 (m, 5 H, Ph), 7.33, 7.73 ppm (2 d, *J* = 8.3 Hz, 2 H each, Tos). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 21.5 (q, Tos-Me), 22.6, 25.8, 29.0, 29.2, 29.3, 29.4, 31.8, 37.0, 37.9, 42.2 (10 t, CH$_2$, PhCH$_2$, C-4,), 56.8, 65.4 (2 d, C-2, C-5), 126.9, 127.5, 128.2, 130.0, 130.9 (5 d, Ph, Tos), 134.1, 136.2, 144.1 (3 s, Ph, Tos), 211.3 ppm (s, C-3). IR (KBr): $\tilde{\nu}$ = 3060–2855 (CH), 1760 (C=O), 1355, 1155 cm^{-1} (Tos-N). MS (EI, 80 eV): *m/z* (%) = 455 (7) [M$^+$], 364 (100) [M$^+$ - Bn], 155 (88) [Tos$^+$], 91 (82) [Bn$^+$].

2-Benzyl-5-nonyl-1-tosylpyrrolidin-3-one (*trans*-14)

According to **GP3**, *trans*-**13** (0.060 g, 0.13 mmol) in THF (4 mL) and 20% aqueous H_2SO_4 (2 mL) provided after 4 h crude *trans*-**14** (0.058 g, quant.) as light yellow solid that was not purified but directly used in the epimerization experiments.

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.87 (t, *J* = 6.8 Hz, 3 H, Me), 0.90–1.35, 1.60–1.70 (2 m, 15 H, 1 H, CH$_2$), 1.65, 1.99 (AB part of ABX system, J_{AB} = 17.2 Hz, J_{AX} = 1.0 Hz, J_{BX}=9.0 Hz, 1 H each, 4-H), 2.44 (s, 3 H, Tos-Me), 3.12 (dd, *J* = 13.7 Hz, *J* = 3.2 Hz, 1 H, PhC*H*$_2$), 3.64 (dd, *J* = 13.7 Hz, *J* = 5.1 Hz, 1 H, PhC*H*$_2$), 3.94 (dd, *J* = 5.0 Hz, *J* = 3.2 Hz, 1 H, 2-H), 4.00–4.10 (m, 1 H, 5-H), 7.20–7.36 (m, 7 H, Ph, Tos), 7.77 ppm (d, *J* = 8.3 Hz, 2 H, Tos). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 21.5 (q, Tos-Me), 22.6, 24.6, 27.4, 29.3,* 29.4, 31.8, 33.2, 37.9, 42.8 (9 t, CH$_2$, PhCH$_2$, C-4), 57.6, 64.8 (2 d, C-2, C-5), 127.0, 127.2, 128.3, 129.7, 130.6 (5 d, Ph, Tos), 135.3, 137.8, 143.6 (3 s, Ph, Tos), 210.9 ppm (s, C-3); * signal with higher intensity.

2-Benzyl-3-methoxy-1-methyl-5-nonyl-2,5-dihydropyrrole (*cis*-18)

A solution of sodium naphthalenide (0.98 mL of a 1 M solution in DME, prepared according to ref. 25) was added to a solution of *cis*-**13** (0.153 g, 0.33 mmol) in DME (17 mL) at -78 °C. After 1.5 h the mixture was quenched at this temperature with methyl iodide (0.468 g, 3.30 mmol), then stirred at room temperature for 1 h and concentrated in vacuo. The residue was taken up in saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried

View Article Online
DOI: 10.1039/C8OB02645A

(Na_2SO_4), filtered and evaporated in vacuo to obtain the crude product (0.250 g) as yellow solid. Purification by column chromatography (alumina III, hexanes/ethyl acetate 25:1 + 1% of NEt_3) gave *cis*-**18** (0.057 g, 53%) as yellow oil.

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.88 (t, J = 6.6 Hz, 3 H, Me), 1.05–1.40 (m, 16 H, CH_2), 2.19 (s, 3 H, Me), 2.67, 2.95 (AB part of ABX system, J_{AB} = 13.2 Hz, J_{AX} = 5.9 Hz, J_{BX} = 4.4 Hz, 1 H each, PhCH_2), 3.08–3.17, 3.46–3.53 (2 m, 1 H each, 2-H, 5-H), 3.57 (s, 3 H, OMe), 4.39 (s, 1 H, 4-H), 7.10–7.30 ppm (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 22.7, 25.7, 29.4, 29.6, 29.7, 30.0, 31.9, 36.8 (8 t, CH_2), 40.1, 40.9 (t, q, PhCH_2, NMe), 56.5 (q, OMe), 69.5, 71.7 (2 d, C-2, C-5), 95.0 (d, C-4), 125.5, 127.6, 130.1, 139.5 (3 d, s, Ph), 157.7 ppm (s, C-3). IR (film): $\tilde{\nu}$ = 3085–2775 (C-H), 1660 cm^{-1} (C=C). MS (EI, 80 eV): *m/z* (%) = 329 (0.7) [M$^+$], 328 (3) [M$^+$ - H], 238 (100) [M$^+$ - Bn], 202 (48) [M$^+$ - C_9H_{19}], 91 (25) [Bn$^+$].

2-Benzyl-1-methyl-5-nonylpyrrolidin-3-one (*cis*-19)

According to **GP3**, *cis*-**18** (0.054 g, 0.16 mmol) in THF (4 mL) and 20% aqueous H_2SO_4 (4 mL) provided after 4 h crude *cis*-**19** (0.053 g) as yellow oil. Purification by column chromatography (alumina III, hexanes/ethyl acetate 20:1 + 1% of NEt_3) furnished *cis*-**19** (0.031 g, 60%) as light yellow oil.

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.88 (t, J = 6.7 Hz, 3 H, Me), 1.10–1.38, 1.68–1.84 (2 m, 15 H, 1 H, CH_2), 1.76 (dd, J = 17.4 Hz, J = 10.3 Hz, 1 H, 4-H), 2.31 (s, 3 H, NMe), 2.38 (dd, J = 17.4 Hz, J = 5.9 Hz, 1 H, 4-H), 2.37–2.53 (m, 1 H, 5-H), 2.75 (X part of ABX system, J_{AX} = 5.1 Hz, J_{BX} = 4.7 Hz, 1 H, 2-H), 2.84, 3.05 (AB part of ABX system, J_{AB} = 14.2 Hz, J_{AX} = 5.1 Hz, J_{BX} = 4.7 Hz, 1 H each, PhCH_2), 7.14–7.29 ppm (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 22.7, 25.6, 29.3, 29.5, 29.6, 29.8, 31.9, 32.9, 35.9, 42.8 (10 t, CH_2, PhCH_2, C-4), 39.2 (q, NMe), 62.5, 74.3 (2 d, C-2, C-5), 126.1, 128.0, 129.7, 138.5 (3 d, s, Ph), 214.8 ppm (s, C-3). IR (film): $\tilde{\nu}$ = 3060–2855 (C-H), 1755 cm^{-1} (C=O). MS (EI, 80 eV): *m/z* (%) = 315 (1.5) [M$^+$], 224 (100) [M$^+$ - Bn], 91 (21) [Bn$^+$]. HRMS (EI, 80 eV): calcd. for $C_{21}H_{33}NO$ [M$^+$]: 315.2562; found 315.2539; calcd. for $C_{14}H_{26}NO$ [M$^+$ - Bn] 224.2014; found 224.2042.

2-Benzyl-1-methyl-5-nonylpyrrolidin-3-ol (all-*cis*-20), rac-preussin

According to **GP5**, a solution of *cis*-**19** (0.010 g, 0.04 mmol), L-Selectride (0.06 mL of 1 M solution in THF, 0.73 mmol) in THF (4 mL) provided after 3 h the crude product (0.038 g) as yellow oil. Purification by column chromatography (silica gel, dichloromethane/methanol 9:1) provided pure all-*cis*-**20** (0.008 g, 80%, d.r. >99:1 according to HPLC) as light yellow oil.

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.88 (t, J = 6.6 Hz, 3 H, Me), 1.15–1.36 (m, 16 H, CH_2), 1.42 (ddd, J = 13.0 Hz, J = 5.5 Hz, J = 1.4 Hz, 1 H, 4-H), 1.65–1.78 (m, 1 H, OH), 2.05–2.15 (m, 1 H, 5-H), 2.18 (dd, J = 13.0 Hz, J = 6.4 Hz, 1 H, 4-H), 2.27, 2.84, 2.89 (X part and AB part of ABX system, J_{AB} = 13.4 Hz, J_{AX} = 5.3 Hz, J_{BX} = 9.1 Hz, 1 H each, 2-H, PhCH_2), 2.34 (s, 3 H, NMe), 3.76–3.84 (m, 1 H, 3-H), 7.16–7.32 ppm (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 22.7, 26.3, 29.3, 29.5, 29.6, 29.9, 31.9, 33.7, 34.9, 39.2 (10 t, CH_2, PhCH_2, C-4), 38.6 (q, NMe), 65.8, 70.4, 73.6 (3 d, C-2, C-3, C-5), 126.0, 128.4, 129.3, 139.4 ppm (3 d, s, Ph). The spectroscopic data of the sample agree with those reported in literature.[26]

(2*R*,3*R*,5*S*)-2-Benzyl-5-nonyl-1-tosylpyrrolidin-3-ol (all-*cis*-21)

According to **GP5**, a solution of 2*R*,5*S*-*cis*-**15** (0.055 g, 0.12 mmol), L-Selectride (0.24 mL of 1 M solution in THF, 0.24 mmol) in THF (5 mL) provided after 6 h the crude product that still contained starting material. It was treated again with L-Selectride (0.96 mL of 1 M solution in THF, 0.96 mmol) in THF (5 mL) for 3 h and finally furnished crude 2*R*,3*R*,5*S*-all-*cis*-**21** (0.080 g) as yellow oil., d.r. 90:10). Pre-purification by column chromatography (silica gel, hexanes/ethyl acetate 4:1) and purification by HPLC (hexanes/ethyl acetate 4:1) afforded diastereomerically pure 2*R*,3*R*,5*R*-all-*cis*-**21** (0.040 g,73%) as colorless oil.

Optical rotation: $[\alpha]_D^{20}$ = -20.4 (c = 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.89 (t, J = 6.4 Hz, 3 H, Me), 1.20–1.40, 1.50–1.80, 1.90–2.10 (3 m, 14 H, 4 H, 1 H, CH_2, 4-H, OH), 2.42 (s, 3 H, Tos-Me), 3.08, 3.24 (AB part of ABX system, J_{AB} = 13.9 Hz, J_{AX} = 9.0 Hz, J_{BX} = 3.9 Hz, 1 H each, PhCH_2), 3.55–3.70 (m, 1 H, 5-H), 3.80–3.90 (m, 2 H, 2-H, 3-H), 7.17–7.30 (m, 7 H, Ph, Tos), 7.71 ppm (d, J = 8.0 Hz, 2 H, Tos). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 21.5 (q, Tos-Me), 22.7, 26.5, 29.3, 29.4, 29.5, 29.6, 31.9, 37.1, 37.3, 37.8 (10 t, CH_2, C-4, PhCH_2), 59.9, 65.6, 71.6 (3 d, C-2, C-3, C-5), 126.3, 127.6, 128.5, 129.4, 129.7 (5 d, Ph, Tos), 135.0, 128.9, 143.4 ppm (3 s, Ph, Tos). IR (film): $\tilde{\nu}$ = 3520 (OH), 3085–2855 (C-H), 1600 (Ph), 1340, 1160 cm^{-1} (Tos-N). MS (EI, 80 eV): *m/z* (%) = 457 (0.1) [M$^+$], 456 (0.2) [M$^+$ - H], 366 (100) [M$^+$ - Bn], 155 (20) [Tos$^+$], 91 (52) [Bn$^+$]. HRMS (EI, 80 eV): calcd. for $C_{27}H_{39}NO_3S$ [M$^+$]: 457.2651; found 457.2677; calcd. for $C_{27}H_{38}NO_3S$ [M$^+$-H]: 456.2572; found 456.2547.

(2*R*,3*R*,5*S*)-2-Benzyl-5-nonylpyrrolidin-3-ol (all-*cis*-22)

A solution of sodium naphthalenide (0.44 mL of a 1 M solution in DME, 0.44 mmol, prepared according to ref. 25) was added to a solution of all-*cis*-**21** (0.040 g, 0.09 mmol) in DME (7 mL) at -78 °C. After 1.5 h the mixture was quenched with water (5 mL) and

View Article Online
DOI: 10.1039/C8OB02645A

concentrated in vacuo. The residue was taken up in saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and evaporated in vacuo to obtain the crude product (0.090 g) as yellow solid. Purification by column chromatography (silica gel, hexanes/ethyl acetate 1:3, + 1% of NEt_3) gave all-*cis*-**22** (0.021 g, 87%) as light yellow crystals (melting range 96-100 °C; ref. 29: m.p. of the enantiomer: 101-102 °C). The spectroscopic data agree with those of the enantiomer.[29]

Optical rotation: $[\alpha]_D^{20}$ = +14.1 (c = 0.4, $CHCl_3$); for the enantiomer $[\alpha]_D^{20}$ = -15.6 (c = 1.0, MeOH).[29] ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.86 (t, *J* = 6.6 Hz, 3 H, Me), 1.20–1.38 (m, 14 H, CH_2), 1.35 (ddd, *J* = 14.2 Hz, *J* = 6.7 Hz, *J* = 1.5 Hz, 1 H, 4-H), 1.45–1.60 (m, 2 H, CH_2), 2.08–2.25 (m, 2 H, OH, NH), 2.26 (ddd, *J* = 14.2 Hz, *J* = 8.6 Hz, *J* = 6.2 Hz, 1 H, 4-H), 2.85, 2.94 (AB part of ABX system, J_{AB} = 13.0 Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.6 Hz, 2 H, PhCH_2), 2.89–3.07 (m, 2 H, 2-H, 5-H), 3.99 (ddd, *J* = 6.2 Hz, *J* = 3.4 Hz, *J* = 1.5 Hz, 1 H, 3-H), 7.16–7.36 ppm (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.0 (q, Me), 22.7, 27.2, 29.3, 29.5, 29.6, 29.7, 31.9, 35.6, 37.5, 42.0 (10 t, CH_2, PhCH_2, C-4), 57.0, 65.7, 72.2 (3 d, C-2, C-3, C-5), 126.1, 128.5, 128.9, 139.9 ppm (3 d, s, Ph). IR (KBr): $\tilde{\nu}$ = 3420 (N-H), 3065, 3030, 2925, 2855 cm^{-1} (C-H). MS (EI, 80 eV): *m/z* (%) = 303 (0.5) [M^+], 302 (2) [M^+ - H], 212 (100) [M^+ - Bn], 176 (22) [$C_9H_{19}^+$], 91 (16) [Bn^+]. HRMS (EI, 80 eV): calcd. for $C_{18}H_{20}NO$ [M^+]: 303.2562; found 303.2575; calcd. for $C_{18}H_{19}NO$ [M^+ - H]: 302.2484; found 302.2442.

(2*R*,3*R*,5*S*)-2-Benzyl-1-methyl-5-nonylpyrrolidin-3-ol (all-*cis*-20), (-)-Preussin

2*R*,3*R*,5S-all-*cis*-**22** (0.019 g, 0.06 mmol) was dissolved in a 1:1 mixture of THF/acetonitrile (4 mL) and aqueous formaldehyde (0.03 mL, 35%, 0.38 mmol) was added dropwise. After 5 min sodium cyanoborohydride (0.008 g, 0.13 mmol) and after 1 h stirring at room temperature acetic acid (0.5 mL) were added. After 30 min solid $NaHCO_3$ was added, with aqueous 2 N NaOH the solution adjusted to pH 10 and the organic phase was separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried (Na_2SO_4). After filtration and evaporation of solvents in vacuo the residue was purified by column chromatography (silica gel, dichloro-methane/methanol 9:1) to afford pure 2*R*,3*R*,5*S*-all-*cis*-**20** (0.016 g, 80 %) as yellow oil.

Optical rotation: $[\alpha]_D^{20}$ = -25.8 (c = 0.8, $CHCl_3$); for literature values see ref. 28. The NMR data agree with those of rac-preussin (see above).

MCF-7 cell proliferation assay

MCF-7 cells (ATCC HTB-22, USA) were seeded in RPMI 1640 medium (Biochrome, Germany) supplemented with fetal calf serum (10%; PAA, Austria), l-glutamine (2 mM), estradiol (0.1 nM), and insulin (1 U/mL) at 5000 cells per well in 96-well plates. Cells were allowed to adhere for 24 h, and then fresh growth medium plus compound was added. The final concentration of DMSO was 0.5%. After four days of continuous incubation, the cells were fixed with glutaraldehyde and stained with crystal violet, and the absorbance was recorded at 595 nm using Tecan Sunrise equipment. All measurements were performed in quadruplicate. The values were normalized to the absorbance of solvent-treated cells (100 %), and the absorbance of a reference plate which was fixed at the time point of compound application (0 %). Half-maximal growth inhibition (IC50) was determined as the compound concentration required to achieve 50% inhibition of cell growth.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

Generous support of this work by the Fonds der Chemischen Industrie (Kekulé fellowship for Arndt Hausherr), the Deutsche Forschungsgemeinschaft and Schering AG is most gratefully acknowledged. We thank Winfried Münch and Christiane Groneberg for their assistance in analytical work and Dr. Reinhold Zimmer for his great help during preparation of the manuscript.

Notes and references

1 (a) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435–446; (b) N. Asano, R. J. Nash, R. J. Molyneux and G. W. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645−1680; (c) J. R. Liddell, *Nat. Prod. Rep.* **2002**, *19*, 773–781; (d) H. Yoda, *Curr. Org. Chem.* **2002**, *6*, 223–243; (e) P. Compain and O. R. Martin, *Iminosugars: from Synthesis to Therapeutic*

View Article Online
DOI: 10.1039/C8OB02645A

Applications, Wiley-VCH: Weinheim, New York, **2007**; (f) J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 191–222; (g) V. Desvergnes and Y. Landais, *Stud. Nat. Prod. Chem.* **2014**, *42*, 373−419.

2 Reviews on the use of alkoxyallenes in organic synthesis: (a) R. Zimmer, *Synthesis* **1993**, 165–178; (b) M. Brasholz, H.-U. Reissig and R. Zimmer, *Acc. Chem. Res.* **2009**, *42*, 45–56; (c) F. Pfrengle and H.-U. Reissig, *Chem. Soc. Rev.* **2010**, *39*, 549–557; (d) A. Nedolya, O. Tarasova, O. G. Volostnykh, A. L. Albanov, L. V. Klyba and B. A. Trofimov, *Synthesis* **2011**, 2192–2204; (e) R. Zimmer and H.-U. Reissig, *Chem. Soc. Rev.* **2014**, *43*, 2888–2903; (f) M. A. Tius, *Chem. Soc. Rev.* **2014**, *43*, 2979–3002; (g) H.-U. Reissig and R. Zimmer, *Synthesis* **2017**, *49*, 3291–3302.

3 O. Flögel, M. G. Okala Amombo, H.-U. Reissig, G. Zahn, I. Brüdgam and H. Hartl, *Chem. Eur. J.* **2003**, *9*, 1405–1415.

4 S. Kaden, M. Brockmann and H.-U. Reissig, *Helv. Chim. Acta* **2005**, *88*, 1826–1838.

5 M. A. Chowdhury and H.-U. Reissig, to be published. For a synthesis of the racemic compound, see: M. A. Chowdhury and H-U. Reissig, *Synlett* **2006**, 2383–2386.

6 C. Parmeggiani, F. Cardona, L. Giusti, H.-U. Reissig and A. Goti, *Chem. Eur. J.* **2013**, *19*, 10595–10604.

7 T. Pecchioli, F. Cardona, H.-U. Reissig, R. Zimmer and A. Goti, *J. Org. Chem.* **2017**, *83*, 5835-5844.

8 R. E. Schwartz, J. Liesch, O. Hensens, L. Zitano, S. Honeycutt, G. Garrity, R. A. Fromtling, J. Onishi and R. Monagahn, *J. Antibiot.* **1988**, *41*, 1774–1779.

9 J. H. Johnson, D. W. Phillipson and A. D. Kahle, *J. Antibiot.* **1989**, *42*, 1184–1185.

10 K. Kasahara, M. Yoshida, J. Eishima, K. Takesako, T. Beppu and S. Horinouchi, *J. Antibiot.* **1997**, *50*, 267–269.

11 T. V. Achenbach, E. P. Slater, H. Brummerhop, T. Bach and R. Müller, *Antimicrob. Agents Chemother.* **2000**, *44*, 2794–2801.

12 For selected reviews on cyclin-dependent kinase inhibitors, see: (a) T. M. Sielecki, J. F. Boylan, P. A. Benfield and G. L. Trianor, *J. Med. Chem.* **2000**, *43*, 1–18; (b) P. L. Toogood, *Med. Res. Rev.* **2001**, *21*, 487–498; (c) A. Huwe, R. Mazitschek and A. Giannis, *Angew. Chem.* **2003**, *115*, 2170–2187; *Angew. Chem. Int. Ed.* **2003**, *42*, 2122–2138; (d) Q. Wang, L. Su, N. Liu, L. Zhang, W. Xu and H. Fang, *Curr. Med. Chem.* **2011**, *18*, 2025–2043; (e) M. Tutone and A. M. Almerico, *Eur. J. Med. Chem.* **2017**, *142*, 300–315.

13 T. G. Kinzy, J. W. Harper, A. Carr-Schmid, J. Kwon, M. Shastry, M. Justice and J. D. Dinman, *Virology* **2002**, *300*, 60–70.

14 T. Fukuda, Y. Sudoh, Y. Tsuchiya, T. Okuda and Y. Igarashi, *J. Nat. Prod.* **2014**, *77*, 813–817.

15 S. Buttachon, A. A. Ramos, A. Inácio, T. Dethoup, L. Gales, M. Lee, P. M. Costa, A. M. S. Silva, N. Sekeroglu, E. Rochan, M. M. M. Pinto, J. A. Pereira and A. Kijjoa, *Mar. Drugs* **2018**, *16*, Nr. 119.

16 For an excellent compilation and analysis of preussin syntheses including the year 2002, see: a) B. Basler, A. Spiegel and T. Bach, *Top. Curr. Chem.* **2005**, *243*, 1–42 (for a list of these references see ESI). For new syntheses including formal total syntheses since 2003 (abbreviations for the type of synthesis: CP = chiral pool; AUX = auxiliary-based; AC = asymmetric catalysis ; KR = kinetic resolution; rac = synthesis of the racemic compound): (b) S. Raghavan and M. A. Rasheed, *Tetrahedron* **2003**, *59*, 10307–10312 (CP); (c) D. K. Dikshit, L. N. Goswami and V. S. Singh, *Synlett* **2003**, 1737–1739 (CP); (d) P.-Q. Huang, T.-J. Wu and Y.-P. Ruan, *Org. Lett.* **2003**, *5*, 4341–4344 (AUX); (e) F. A. Davis and J. Deng, *Tetrahedron* **2004**, *60*, 5111–5115 (AUX); (f) S. Canova, V. Bellosta and J. Cossy, *Synlett* **2004**, 1811–1813 (AUX); (g) M. Bertrand and J. P. Wolfe, *Org. Lett.* **2006**, *8*, 2353–23256 (AUX); (h) N. Gogoi, J. Boruwa and N. C. Barua, *Eur. J. Org. Chem.* **2006**, 1722–1725 (AC); (i) J. J.

Caldwell, D. Craig and S. P. East, *ARKIVOC* **2007**, *12*, 67–90 (CP); (j) M. Bertrand, M.L. Leathen and J. P. Wolfe, *Org. Lett.* **2007**, *9*, 457–460 (rac); (k) F. A. Davis, J. Zhang, H. Qiu and Y. Wu, *Org. Lett.* **2008**, *10*, 1433–1436 (AUX); (l) R. Chowdhury and S. K. Ghosh, *Org. Lett.* **2009**, *11*, 3270–3273 (AC); (m) J. A. Draper and R. Britton, *Org. Lett.* **2010**, *12*, 4034–4037 (AC); (n) K.-J. Xiao, Y. Wang, K.-Y. Ye and P.-Q. Huang, *Chem. Eur. J.* **2010**, *16*, 12792–12796 (CP); (o) Y.-H. Wang, W. Ou, L. Xie, J.-L. Ye and P.-Q. Huang, *Asian J. Org. Chem.* **2012**, *1*, 359–365 (CP); (p) E. B. Arevalo-Garcia, *Heterocyclic Commun.* **2014**, *20*, 47–50 (CP); (q) Y. Natori, S. Kikuchi, T. Kondo, Y. Saito, Y. Yoshimura and H. Takahata, *Org. Biomol. Chem.* **2014**, *12*, 1983–1994 (CP); (r) I. G. Rosset, R. M. P. Dias, V. D. Pinho and A. C. B. Burtoloso, *J. Org. Chem.* **2014**, *79*, 6748–6453 (rac); (s) Q.-R. Zhou, X.-Y. Wei, Y.-Q. Li, D. Huang and B.-G. Wei, *Tetrahedron* **2014**, *70*, 4799–4808 [AUX to (-)-preussin]; (t) P.-Q. Huang, H. Geng, Y.-S. Tian, Q.-R. Peng and K.-J. Xiao, *Science China, Chemistry*, **2015**, *58*, 478–482 (CP); (u) M. Buchman, K. Csatayová, S. G. Davies, A. M. Fletcher, I. T. T. Houlsby, P. M. Roberts, S. M. Rowe and J. E. Thomson, *J. Org. Chem.* **2016**, *81*,4907–4922(AUX); (v) Y. Natori, T. Imahori and Y. Yoshimura, *J. Synth. Org. Chem. Jpn* **2016**, *74*, 335–349 (KR); (w) C.-M. Si, L.-P. Shao, Z.-Y. Mao, W. Zhou and B.-G. Wie, *Org. Biomol. Chem.* **2017**, *15*, 649–661 (KR); (x) H.-J. Rong, J.-J. Yao, J.-K. Li and J. Qu, *J. Org. Chem.* **2017**, *82*, 5557–5565 (rac); (y) H. Mao, H. Jeong, J. Yang, H.-J. Ha and J. W. Yang, *Chem. Eur. J.* **2018**, *24*, 2370–2374 (AC).

17 Typical examples: a) S. Hoff, L. Brandsma and J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609–619; (b) D. Gange and P. Magnus, *J. Am. Chem. Soc.* **1978**, *100*, 7746–7747; (c) S. Hormuth and H.-U. Reissig, *J. Org. Chem.* **1994**, *59*, 67–73; (d) O. Flögel and H.-U. Reissig, *Eur. J. Org. Chem.* **2004**, 2797–2804; (e) M. Brasholz and H.-U. Reissig, *Angew. Chem.* **2007**, *119*, 1659–1662; *Angew. Chem., Int. Ed.* **2007**, *46*, 1634–1637; (f) S. Cai, B. K. Gorityala, J. Ma, M. L. Leow and X.-W. Liu, *Org. Lett.* **2011**, *13*, 1072–1075.

18 Typical examples: a) M. G. Okala Amombo, A. Hausherr and H.-U. Reissig, *Synlett* **1999**, 1871–1874; (b) O. Flögel and H.-U. Reissig, *Synlett* **2004**, 895–897; (c) M. G. Okala Amombo, O. Flögel, S. Kord Daoroun Kalai, S. Schoder, U. Warzok and H.-U. Reissig, *Eur. J. Org. Chem.* **2017**, 1965–1972; for a review of other allenyl amine cyclizations, see: d) B. Alcaide, P. Almendros, *Adv. Synth. Catal.* **2011**, *353*, 2561–2576.

19 Recent computational study: F. Cumine, A. Young, H.-U. Reissig, T. Tuttle and J. A. Murphy, *Eur. J. Org. Chem.* **2017**, 6867–6871.

20 (a) A. Hausherr, B. Orschel, S. Scherer and H.-U. Reissig, *Synthesis* **2001**, 1377–1385; (b) A. Hausherr and H.-U. Reissig, *Synthesis* **2018***, 50*, 2546–2554.

21 A. Hausherr and H.-U. Reissig, *Eur. J. Org. Chem.* **2018**, 4071–4080.

22 A. Hausherr, R. Zimmer and H.-U. Reissig, *Synthesis* **2018***, 50*, doi.org/10.1055/s-0037-1609942.

23 M. Haddad, F. Dahan, J.-P. Legros, L. Lopez, M.-T. Boisdon and J. Barrans, *J. Chem. Soc., Perkin Trans. 2* **1992**, 671-678.

24 F. Chemla, V. Hebbe and J.-F. Normant, *Synthesis* **2000**, 75-77.

25 A. B. Smith, T. A. Rano, N. Chida, A. G. Sulikowski and J. L. Wood, *J. Am. Chem. Soc.* **1992**, *114*, 8008–8022.

26 See for instance: a) T. Bach, H. Brummerhop and K. Harms, *Chem. Eur. J.* **2000**, *6*, 3838–3848.

27 (a) H. M. Davies, J. J. Matasi, L. M. Hodges, N. J. S. Huby, C. Thornley, N. Kong and J. H. Houser, *J. Org. Chem.* **1997**, *62*, 1095-1105; (b) R. Lin, J. Castells and H. Rapoport, *J. Org. Chem.* **1998**, *63*, 4069-4078.

28 Optical rotations reported for (-)-preussin: (a) -21.6 (c 1.0, $CHCl_3$): W. Deng and L. E. Overman, *J. Am. Chem. Soc.* **1994**, *116*, 11241–11250; b) -28.8 (c 1.01 CHCl3) M. Okue, H. Watanabe, K. Kasahara, M. Yoshida, S.

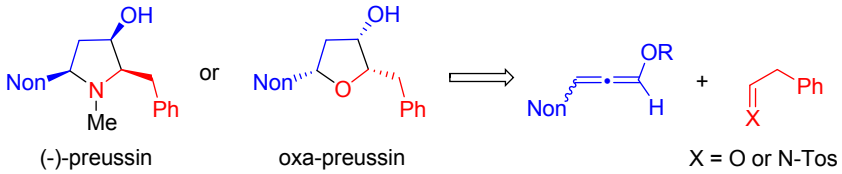
Horinouchi and T. Kitahara, *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1093–1096; (c) -34.7 (c 0.5, $CHCl_3$) in ref. 16s.

View Article Online
DOI: 10.1039/C8OB02645A

29 A. Kanazawa, S. Gillet, P. Delair and A. E. Greene, *J. Org. Chem.* **1998**, *63*, 4660–4663.

Alkoxyallene-Based Syntheses of Preussin and Analogs and Their Cytotoxicity

Arndt Hausherr, Gerhard Siemeister and Hans-Ulrich Reissig



(-)-preussin oxa-preussin X = O or N-Tos

Preussin made in Prussia! Axially chiral alkoxyallenes provided oxa-preussin, racemic and enantiopure (-)-preussin (cytotoxicities: IC_{50} = 3-6 µM).