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Efficient synthesis of polyfunctionalised enantiopure diazepanone scaffolds

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Abstract—The synthesis of polyfunctionalised enantiopure 1,4-diazepan-3-one scaffolds from L-serine derivatives and azidoepoxides readily available from either L-ascorbic or D-isoascorbic acid, allowing access to various configurations at chiral centres, is described. The key steps are the nucleophilic opening of the epoxide by the amine of serine followed by a lactonisation–lactamisation sequence.

In the context of an ongoing programme directed to the synthesis and biological evaluation of new potential antibacterial, we are aiming at developing efficient and flexible routes to versatile scaffolds allowing access to libraries of compounds. Indeed, the design of scaffolds[1] is often the most suitable plan to reach large families of compounds because it can take advantage of multiple functional groups which facilitate the further introduction of pharmacophoric groups. Furthermore, scaffolds generally display cyclic structures that reduce the entropic cost associated with the loss of conformational degrees of freedom upon binding to the target protein and finally they may allow solid phase synthesis. Our goal is the inhibition of the bacterial translocase MraY, which catalyses the first membrane step of peptidoglycan biosynthesis.[2] Indeed, this essential enzyme[3] represents a target of prime interest when searching for new antibiotics because it has been shown that the inhibition of any enzyme involved in peptidoglycan biosynthesis leads to bacterial lysis and furthermore this enzyme is currently the target of no drugs used in therapeutics. The transmembrane localisation of that enzyme,[4] making it difficult to purify and to study, is responsible for the limited interest dedicated to MarY for a long time. Nevertheless, this enzyme has now been recently purified to homogeneity[5] and tests allowing high-throughput screening of inhibitors have been developed.[6] Our goal is to achieve the synthesis of a library of inhibitors displaying analogous and simplified structures as compared to liposidomycins[7] (Fig. 1) which are naturally occurring inhibitors of MraY. However, probably due to the high hydrophilicity of these compounds, although they are powerful inhibitors of MraY, their antibacterial

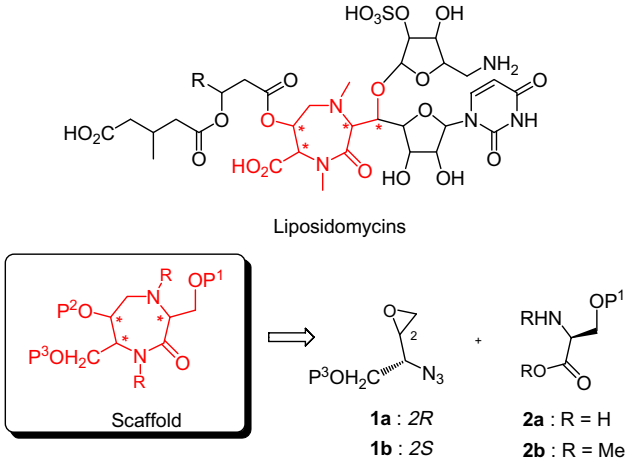

Figure 1. Structure of liposidomycins and of the target scaffold.

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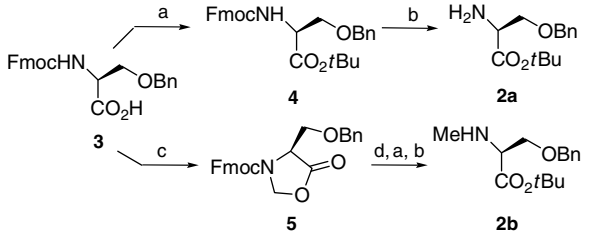
activity is weak. Consequently, crucial objective of the project will be to adjust the physico-chemical properties of the synthesised inhibitors to promote their passive diffusion through membranes barriers. The structure of the target scaffold (Fig. 1), retaining the central core of liposidomycins, is a 1,4-diazepan-3-one with various well-differentiated functions such as primary and secondary alcohols and amine.[8] It has to be noted that this structure has not been exploited yet for MraY inhibition, so that the proposed inhibitors will display original structures as compared to those existing.[9] A special attention has been paid to the introduction of orthogonal protections on the various functions, thus allowing further sequential deprotection and introduction of key structural fragments required for biological activity. Finally, the accessibility to several configurations at chiral centres of the scaffold should increase the diversity of the future library.

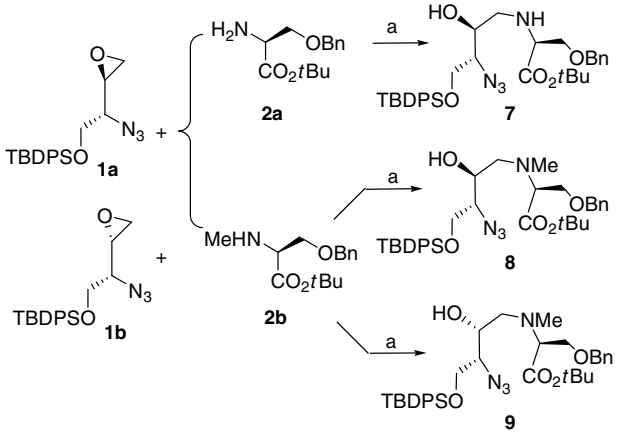
Retrosynthetic analysis towards the target compound **1** (Fig. 1) involves two key steps which are the regiospecific nucleophilic opening of an enantiomerically pure azido epoxide by the amine of a conveniently protected L-serine derivative[10] and a peptidic coupling involving the amine, resulting from azide reduction, and the carboxylic acid of the serine. According to this plan, the preparation of two serine derivatives with either a primary or a secondary amine function has been carried out from commercially available *O*-benzyl-*N*-Fmoc-L-serine **3** (Scheme 1). On one hand, esterification with *tert*-butyl trichloroacetimidate followed by *N*-Fmoc deprotection in the presence of 20% piperidine afforded the *tert*-butyl *O*-benzyl L-serine **2a** in quantitative overall yield. On the other hand, according to Freidinger method,[11] serine **3** was condensed with *p*-formaldehyde in the presence of *p*-toluenesulfonic acid in refluxing toluene to give oxazolidinone **5**. Then acid-catalysed reductive alkylation led to the corresponding amino acid which was then submitted to esterification and *N*-Fmoc deprotection as previously described to afford **2b**.



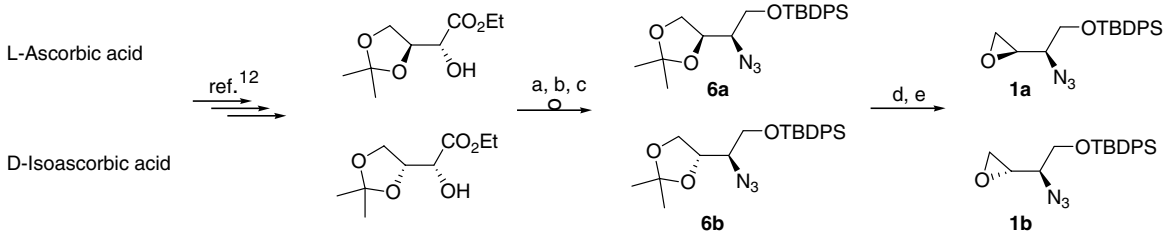
Scheme 1. Reagents and conditions: (a) $Cl_3CC(NH)OtBu$, cyclohexane, CH_2Cl_2, 100% for **4**; (b) piperidine, rt, 100% for **2a**, 83% overall yield from **5**; (c) $(CH_2O)_n$, *p*-toluenesulfonic acid, toluene reflux, 97%; (d) Et_3SiH, TFA, $CHCl_3$, rt.

The preparation of azido epoxides **1a** and **1b** (Scheme 2) was, respectively, performed from ethyl 1,2-*O*-methylethylidene L-threonate and D-erythronate readily obtained from L-ascorbic and D-isoascorbic acids according to known routes.[12] $LiAlH_4$ reduction of the esters was followed by selective protection of the resulting primary alcohol with *tert*-butyldimethylsilyl chloride followed by the activation of the secondary alcohol function as the corresponding triflate and nucleophilic substitution with excess sodium azide affording the azido derivatives **6a**[13] and **6b**. Acidic hydrolysis in the presence of trifluoroacetic acid in H_2O/THF was followed by epoxidation under Sharpless conditions[14] affording epoxides **1a** and **1b** in good yields.

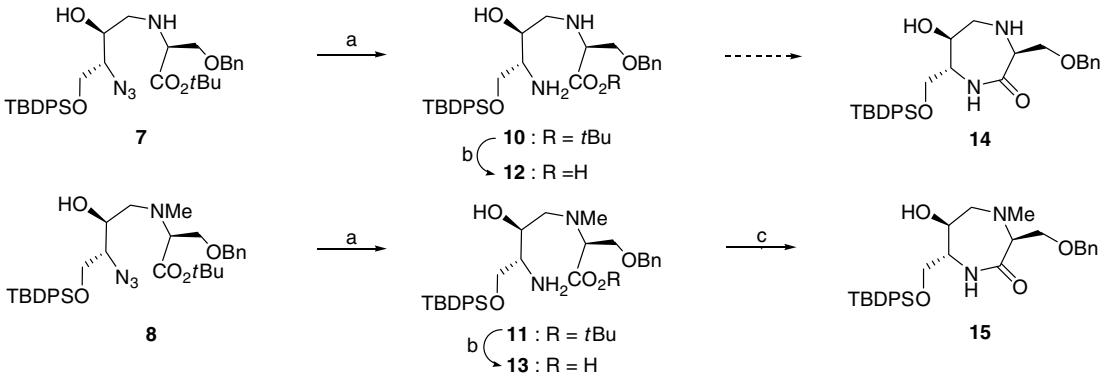
With both synthons in hands, we next turned to the first key step (Scheme 3) which involved nucleophilic opening of the azido epoxide **1a** with either the *tert*-butyl *O*-benzyl L-serine **2a** or its *N*-methyl analog **2b** in the presence of ytterbium triflate in dichloromethane leading to **7** or **8**, respectively, in 65–70% yield.[15] Alternatively, to reach another configuration at carbon C_5 of the target scaffold, the same reaction involving the



Scheme 3. Reagents and conditions: (a) $Yb(OTf)_3$, CH_2Cl_2, rt, up to a week (see Ref. 15), 65–70%.



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, rt then reflux 2 h, 98%; (b) TBDPSCl, imidazole, DMF, −10 °C, 97%; (c) (i) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; (ii) NaN_3, DMF, 0 °C to rt, 89%; (d) TFA/H_2O/THF, 0 °C to rt, 75% and 70%, respectively, from **6a** and **6b**; (e) (i) $CH_3C(OCH_3)_3$, PPTS, CH_2Cl_2, rt; (ii) AcBr, Et_3N, 0 °C to rt; (iii) K_2CO_3, MeOH, rt, 87% overall yield.



Scheme 4. Reagents and conditions: (a) $(Ph_2PCH_2)_2$, THF, H_2O, rt, 85% for **10** and 70% for **11**; (b) TFA, CH_2Cl_2, rt; (c) HATU/HOBt in excess, DIPEA, DMF, rt, 30% overall yield from **13**.

diastereoisomeric epoxide **1b** and *N*-methyl amine **2b** was carried out and led to compound **9** in similar yield.

For prior testing of the peptidic coupling reaction, chemical modifications of the molecules were required (Scheme 4). Thus, reduction of the azido group of **7** or **8**, respectively, under Staudinger conditions in the presence of 1,2-bis(diphenylphosphino)ethane in THF followed by H_2O addition afforded the corresponding amine **10** or **11**, respectively, and was followed by subsequent acidolysis of *tert*-butyl ester in the presence of trifluoroacetic acid in dichloromethane to give **12** and **13** which were used without further purification. We next turned to the lactame formation which was first assayed on derivative **12**. Various conditions were tried and notably involved EDCI/HOBt in CH_2Cl_2 as coupling agents but revealed unsuccessful for this cyclisation. Indeed, modelisation (Fig. 2) of compound **12** was performed with calculations being run on a Silicon Graphics computer using the Biosym software INSIGHT II and DISCOVER with the CVFF force field from Dauber-Osguthorpe anf Hagler.[16] It showed hydrophobic interactions between aromatic rings of the TBDPS and the benzyl O-protecting groups leading to a distorted conformation of the molecule. Furthermore, several hydrogen bonds, in particular between the secondary amine and the oxygen atom of the *O*Bn residue, remove the protagonists of the reaction, primary amine and carboxylic acid, to a distance of 6 Å from each other, probably avoiding the cyclisation.

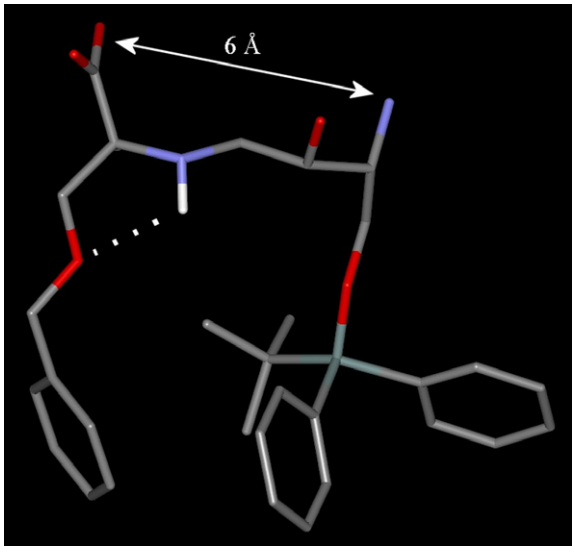
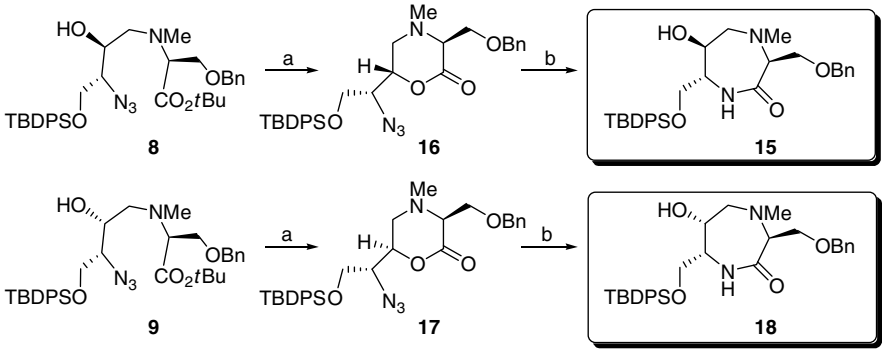


Figure 2. Modelisation of aminoacid **12** showing hydrophobic interactions between aromatic rings and hydrogen bond between –*N*H– and –*O*Bn.

Finally, in order to limit possible hydrogen bonds within the molecule, further assays were run on the *N*-methyl derivative **13** and we showed that the best conditions



Scheme 5. Reagents and conditions: (a) TFA, CH_2Cl_2, rt, 80%; (b) $HCOO^-$, NH_4^+, Pd/C 10%, EtOAc, rt, 84%.

for performing the cyclisation in lactam ring were HATU/HOBt in excess with diisopropylethylamine in DMF. Indeed, these conditions allowed the obtention of the expected diazepanone **15**, although in a modest 30% yield. Obviously, further goal was to improve the yield of the diazepanone formation and that was finely done by inverting the order of the last steps of the synthesis (Scheme 5). Thus, acidolysis of *tert*-butyl ester of **8** was first carried out by treatment with trifluoroacetic acid in CH_2Cl_2 and concommitant lactonisation occurred leading lactone **16** in 80% yield.

Then, reduction of the azido group of **16** by hydrogenolysis in the presence of ammonium formate and Pd/C led to simultaneous isomerisation of the lactone into the required lactam **15** in 84% yield. In an analogous manner, the diastereoisomeric diazepanone **18** could be obtained from the azido derivative **9** through the intermediate lactone **17**. The latter conditions involving a lactonisation–lactamisation two-step sequence revealed much more powerful in terms of both yield and purification as compared to the initial route.

In conclusion, we developed a straightforward route to two enantiomerically pure polyfunctionalised diazepanone scaffolds from easily available L-serine derivative and azido epoxide resulting from L-ascorbic or D-isoascorbic acid. The described synthesis relies on three key reactions which are nucleophilic opening of the epoxide by the secondary amine of the amino acid followed by a two-step procedure involving a lactonisation–lactamisation sequence and affording the targeted diazepanone in 45% overall yield. The achievement of 1,4-diazepan-3-one synthesis in good yield and displaying orthogonally protected highly differentiated functions and various configurations is of general interest in the scaffold field. It should now allow the obtention of a library of liposidomycins analogs. Current work is in progress towards this goal.

Acknowledgements

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