Highly regioselective epoxide hydrogenolysis aiming at the bulgecinine synthesis

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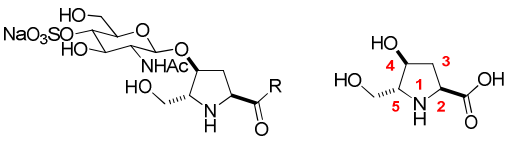
INTRODUCTION

Bulgecins are bacterial metabolites[1] that interfere with the cell-wall synthesis of Gram-negative bacteria when used in combination with β-lactams antibiotics. These compounds consist in a glucosamine linked to the non-proteinogenic amino acid **1** called bulgecinine



The biological acitivity of bulgecins is unique as they operate inhibiting specific enzymes not present in mammals. This feature makes bulgecinine an important target to synthesize, as well as a template to find biologically active molecules more potent than the natural entity.

RESULTS AND DISCUSSION

The synthesis of bulgecinine and analogues started from 3-pyrroline **3,** which was prepared according to the Correia's protocol.[2]

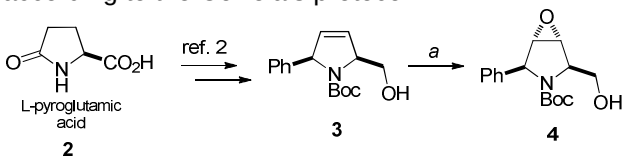
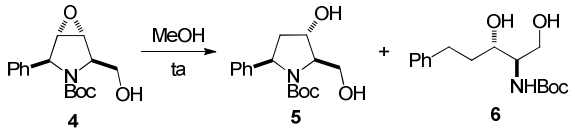


Figure 1. *a)* OXONE®, EDTA, $NaHCO_3$, H_2O, $CF_3C(O)CH_3$, 6h (77%).

The epoxide **4** was submitted to hydrogenolytic conditions cleaving exclusively the C-O bond closer to the phenyl ring (table 1). Along with the desired pyrrolidine **5,** the product **6,** (C-N benzylic bond cleavage) was isolated (entries 1, 2). Palladium catalyst loading higher than 25mol% (entries 3, 4) resulted in a complete selectivity favoring compound **5**. The structures of aminoalcohols **5** and **6** were confirmed by X-ray analysis.

After diol protection of **5**, the phenyl ring was converted into the acid **7** using Lemieux-von Rudloff

Table 1. Hydrogenolysis of epoxypyrrolidine **4**



#	Pd/C 10%	t	P_{H2}	5:6	Rend. [b]
1	10mol%	72h	1 atm	56:44	54%
2	25mol%	24h	1 atm	68:32	93%
3	50mol%	24h	1 atm	100:0	83%
4	1,0 eq.	24h	4 atm	100:0	89%

oxidation. The obtained pyrrolidine **7** is a useful intermediate which can be transformed into 2-*epi*-bulgecinine (**8**) after deprotection.

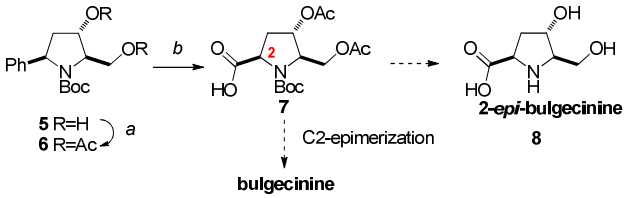


Figure 2. *a)* Ac_2O, Et_3N, CH_2Cl_2, 4h (82%). *b)* $RuCl_3$ cat, $NaIO_4$, CH_3CN, H_2O, 3h, (49%).

CONCLUSION

It was possible to prepare the carbon framework of a bulgecinine epimer **8** using a highly selective epoxide opening. This concise strategy also allows the synthesis of the natural product bulgecinine **1** through base mediate epimerization of C2. Studies to determine the factors that control hydrogenolysis selectivity are ongoing.

ACKNOWLEDGEMENTS

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