Improved synthesis of natural and unnatural marinoquinolines for biological studies.

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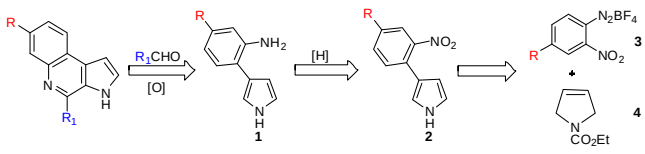
Introduction

Nitrogen containing heteroaromatic compounds have been playing a crucial role in the treatment of many types of diseases. A less known class of heteroaromatic compounds displays as its main core structure the uncommon tricyclic system 3*H*-pyrrolo[2,3-*c*]quinoline. Isolated from extracts of the *Rapidithrix thailandica* bacteria the marinoquinoline A was the first reported natural product having this skeleton[1,2]. Five other analogues were discovered later, namely the marinoquinolines B-F, which were extracted from *Ohtaekwangia kribensis* bacteria[3]. These compounds have demonstrated moderate antiprotozoal activity against *Plasmodium falciparum* K1 lineage resistant to chloroquine (IC_{50} between 1.7 and 15 μM) and *Trypanosoma cruzi* (IC_{50} between 21.8 and 53.1 μM), as well as cytotoxic activity against tumor cell lineages L929, MCF-7 and KB-3-1.

Results and discussion

We describe herein an improved and divergent total synthesis of natural and unnatural marinoquinolines by means of a *Pictet–Spengler* reaction of the key aryl-pyrrole derivative **1** with the appropriate aldehyde, followed by in situ aromatization. The aryl-pyrrole 1 is synthesized from the nitro compounds **2**, which in turn are prepared via a Heck-Matsuda reaction between *N*-protected 3-pyrroline 4 and the aryldiazonium salts **3** following a strategy previously developed in our research group. (**Scheme 1**).[4]



R= H, OMe, CF3, Br

Scheme 1: Retrosynthetic analysis.

Table 1 shows some preliminary results regarding key improvements in the *Pictet-Spengler* reaction.

Table 1: Pictet–Spengler reactions with different aldehydes.

Entry	R	R_1	yield %
1	OMe	CH_3	50
2	OMe	CH_2Bn	63
3	OMe	Bn(*p*-Cl)	88
4	OMe	$CH_2CH(CH_3)_2$	67
5	OMe	Bn	76
6	OMe	Bn(3,5-OMe)	69

Studies are on going to prepare a larger and diversified library of marinoquinoline analogues for pharmacological screening.

Conclusion

Improved syntheses of natural and unnatural marinoquinolines featuring a Heck-Matsuda arylation and the Pictet-Spengler reaction were accomplished. Using this new approach the natural marinoquinolines (A, B, C, and E) and many unnatural analogues were prepared in a concise and efficient manner amenable to biological studies.

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