

Studies Toward the Total Synthesis of Combretastatin D4

Wilson S. Nascimento,* Walter R. Martinez, Arisson T. Silva, Antônio A. S. Paulino,
Paulo H. Menezes and Roberta A. Oliveira

Departamento de Química Fundamental, CCEN, UFPE, 50670-901, Recife-PE, Brasil

*e-mail: wilsonnascimento1q@hotmail.com

Keywords: combretastatin D-4, potassium organotrifluoroborates, macrocyclic lactones

INTRODUCTION

Compounds isolated from Combretaceae are of great interest and include the bioactive stilbenes and the 17-membered macrocyclic lactones Combretastatins D2 and D4 (Figure 1).¹

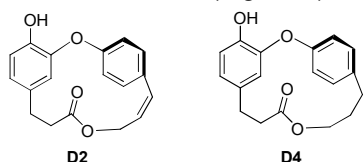
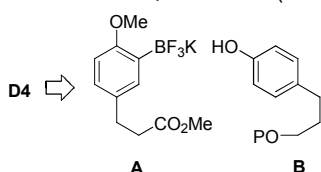


Figure 1. Combretastatins D2 and D4

Different approaches for the synthesis of Combretastatin D2 have been described, but due to date no synthetic approaches as well as cytotoxicity studies have been reported for Combretastatin D4 (CA-D4). The interest in the design and synthesis of angiogenesis inhibitors prompted us to design a new, convergent route to this class of compounds with a view to further studies of biological properties of the natural product and its analogues.

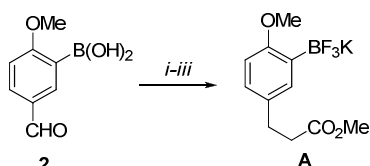
RESULTS AND DISCUSSION

In our disconnection approach, CA-D4 was divided in two main intermediates, **A** and **B** (Scheme 1).



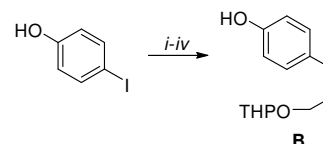
Scheme 1

Fragment A was synthesized in 67% overall yield after three steps (Scheme 2).²



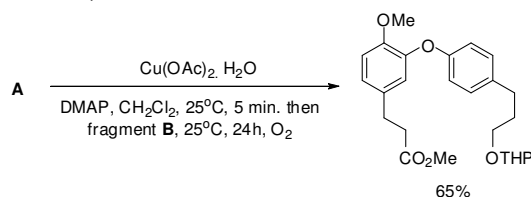
Scheme 2. Reagents and conditions: (i) KHF_2 , $\text{MeOH:H}_2\text{O}$, 0°C , 0.5h (90%); (ii) $\text{Ph}_3\text{PCHCO}_2\text{Me}$, H_2O , 90°C , 12h, (86%); (iii) H_2 , Pd/C , MeOH , 12h, 25°C (85%).

Fragment B was synthesized in four steps from the commercially available 4-iodo-phenol in 55% overall yield (Scheme 3).



Scheme 3. Reagents and conditions: (i) Ac_2O , I_2 , 5h, 25°C (92%); (ii) $\text{HC}\equiv\text{CCH}_2\text{OTHP}$, $\text{PdCl}_2(\text{PPh}_3)_2$, CuI , $\text{MeCN:Et}_3\text{N}$, 25°C (82%); (iii) NH_4OH , THF:MeOH , 12h, 25°C (80%); (iv) H_2 , Pd/C , MeOH , 5h, 25°C (90%).

The obtained fragments were then coupled using an Ullmann type reaction³ to yield an advanced intermediate in the synthesis of the target molecule (Scheme 4).



Scheme 4.

CONCLUSION

In summary, an advanced intermediate in the synthesis of CA-D4 was achieved. The synthesis features the use of a potassium aryltrifluoroborate as a *synthon* and using this approach, all carbon atoms present in the structure were installed. Further progress toward the synthesis will be reported in the due course.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge CNPq, CAPES, FACEPE and INCT-INAMI for the financial support.

REFERENCES

- Cirla, A.; Mann, J. *Nat. Prod. Rep.*, **2003**, *20*, 558–564.
- Oliveira, R. A.; Molander G. A. *Tetrahedron Lett.* **2008**, *49*, 1266–1268.
- Quach, T. D.; Batey, R.A. *Org. Lett.* **2003**, *5*, 1381–1384.