Studies Toward the Total Synthesis of Combretastatin D4


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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. Combretastatines D2 and D4](image)

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](image)

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

![Scheme 2](image)

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

![Scheme 3](image)

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](image)

CONCLUSION

In summary, an advanced intermediate in the synthesis of CA-D4 was achieved. The synthesis features the use of a potassium ary trifluoroborate 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.

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REFERENCES


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