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An efficient synthesis for a new class antimalarial agent, 7-(2-carboxyethyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole

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ABSTRACT

Efficient synthesis is essential for antimalarial therapeutics. A four-step route has been established for the synthesis of 7-(2-carboxyethyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole **1** that is a potent new class boron-containing antimalarial agent in preclinical development with IC_{50} = 26 nM against the malaria parasite *Plasmodium falciparum.*

1. Introduction

Malaria represents a continuing public health problem for just under half of the world's population. *Plasmodium falciparum*, the principal malarial parasite, is transmitted by mosquitoes and is estimated to infect 250 million people worldwide and causes nearly 1 million deaths each year. Sadly, 85% of these infections occur in children under the age of five. Current therapies to treat falciparum malaria are heavily reliant on artemisinin-based combinations. However, resistance to artemisinins has recently been identified, and resistance to key artemisinin partner drugs is already widespread. Therefore, there is a great need for new antimalarial drugs with improved attributes over older therapies.[1] These new medicines need to be orally active, rapidly efficacious, safe in all age groups, including children and pregnant women, and inexpensive to produce.

Recently we identified a potent new class of boron-containing antimalarial agent, 7-(2-carboxyethyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole **1**, with an IC_{50} of 26 nM against the malaria parasite *P. falciparum*.[2] The initial route was lengthy and included nine chemical steps starting from 2-bromo-3-methylbenzoic acid **2** (Scheme 1).[2] An aryl nitrile reduction (**3** to aldehyde **4**) with Raney nickel in aqueous formic acid was particularly problematic because of low reproducibility and difficult scalability. In order to establish a shorter and scalable synthetic methodology, which is a requirement for a new antimalarial drug, we have investigated alternative syntheses of compound **1**, and wish to report an efficient, four-step synthesis of this compound.

2. Results and discussion

In order to avoid the cyano reduction from **3** to **4**, the second synthetic strategy shown in Scheme 2 was designed and investigated at a scale of 0.7 mol level. The methyl group in **5** was brominated with *N*-bromosuccinimide (NBS) to the bromomethyl derivative **6**, which was converted into the hydroxymethyl compound **7**. The benzyl alcohol **7** was oxidized with pyridinium chlorochromate (PCC) to the aldehyde **8**, which was further protected to give the acetal derivative **9**. Compound **9** was converted to the pinacolato boron compound **10** in a good yield by the catalytical boronylation method with bis(pinacolato)diboron (Pin_2B_2) as a boron-introducing agent and $Pd(PPh_3)_2Cl_2$ as a catalyst. The ester group in **10** was reduced resulting in a spontaneous cyclization with removal of pinacolato group forming the benzoxaborole moiety. This was followed by the acetal deprotection with the aqueous acid to provide **4**.[3] The aldehyde in **4** reacted with 2,2-dimethyl-1,3-dioxane-4,6-dione in the presence of formic acid and triethylamine to afford the carboxyethyl side chain of **1**. This reaction was remarkably efficient, which gave a convenient way for the conversion of **4** to **1** in a single step.

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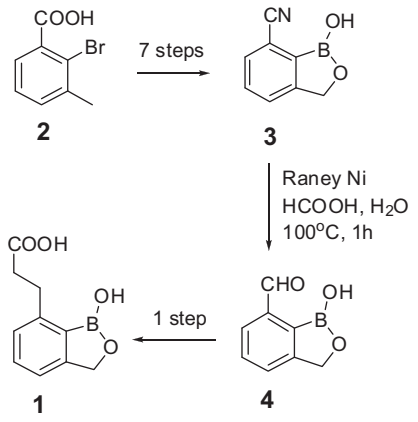
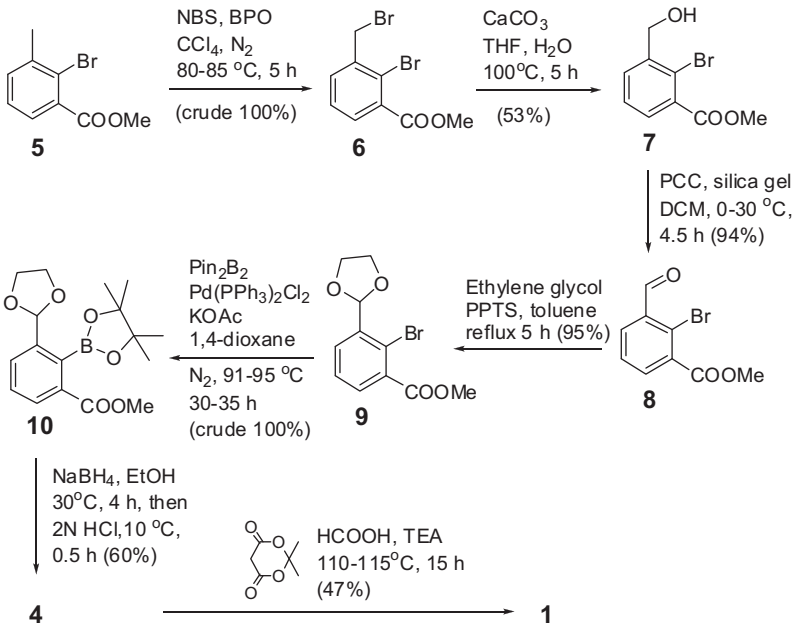


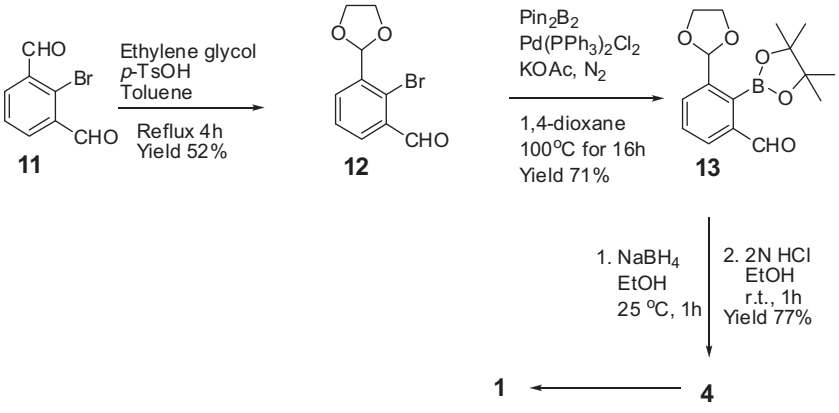
Scheme 1. An early method for the synthesis of **1**.

Although the second strategy was better than the first one in terms of fewer reaction steps and avoidance of the Raney nickel reduction of the cyano group, the challenge for developing the second route into a practical manufacturing process for the final product API still remained high because of the seven step process and the use of a toxic solvent (carbon tetrachloride—CCl_4) in the bromination step. It was very clear that a more efficient and shorter process for the preparation of compound **1** was required.

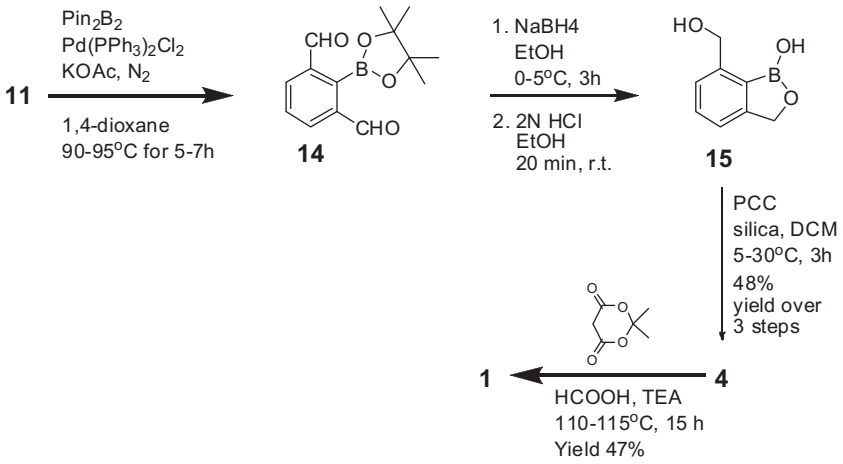
In order to shorten the synthetic route, a new building block, 2-bromoisophthalaldehyde **11**, was identified as the starting point for the third synthetic strategy, shown in Scheme 3. In the new route, one of the two aldehyde groups in **11** was protected with ethylene glycol to give **12**, and this compound was catalytically boronylated to produce the pinacolato boron intermediate **13**. Simple reduction of **13** followed by acidification generated **4**, which was further converted to the final product **1**. This synthetic scheme provided a short four-step route. The main problem of this route was the low yield of the first step because of concomitant reaction of the second aldehyde group in **11** to form a diacetal by-product. It was attempted to minimize this side-reaction by very slow addition of ethylene glycol to the reaction mixture, but the best yield obtained was 52%.



Scheme 2. Second strategy for the synthesis of **1**.



Scheme 3. Third strategy for the synthesis of **1**.



Scheme 4. Fourth strategy for the synthesis of **1**.

A fourth strategy was designed to further improve the overall yield. As shown in Scheme 4, compound **11** was subjected to a boronylation reaction to provide the boron intermediate **14**. The dialdehyde groups in **14** were reduced with sodium borohydride followed by acidification to produce **15**. Complete purification of the intermediate **15** was not performed because once the material was pure and solidified, it had very poor solubility in many solvents, even in DMSO or DMF. The crude oily **15** was soluble in organic solvents such as DCM and was then oxidized with PCC to give the aldehyde **4**. This compound was converted to the final compound as described above. This four-step synthetic route gave a better overall yield and provided an efficient methodology for the synthesis of **1**. This method has been used for a scale-up to more than a hundred grams of **1** in one batch, and further optimization of the reaction conditions is expected to provide kilogram quantities of **1**.

In summary, an efficient four-step route was established for the synthesis of 7-(2-carboxyethyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole **1**, which is a pre-clinical candidate being developed for the treatment of malaria.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.088.

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