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Synthesis of Pinacolylboronate-Substituted Stilbenes and their application to the synthesis of boron capped polyenes

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ABSTRACT

A series of novel 4,4,5,5-tetramethyl-2-(4-substitutedstyrylphenyl)-1,3,2 dioxaborolane derivatives has been synthesized. 4-(4,4,5,5-tetramethyl-1,3,2-dioxaboratophenyl)-methyl triphenylphosphonium bromide (4) was treated with 3 equiv of tBuONa, various aldehydes in the presence of DMF, and stirred at room temperature 4–6 h to yield the corresponding boron containing stilbene derivatives 1a-n in 71–94% yields. A one-pot protocol transformation has also been developed and used this methodology to synthesize boron containing resveratrol analogues. Simple and clean reactions, high yield of the products are the salient features of this methodology. We used this reaction to synthesize the boron capped polyenes. These boron containing polyene systems are potential intermediate to synthesize conjugated polyene as new material for LCD (Liquid Crystal Display) technology. The biological testing of these compounds is currently underway to identify potential therapeutic for Neurodegenerative diseases.

1. Introduction

The idea of using zebrafish to screen small molecules for possible drug activity is recent but now well validated by a number of studies. There are two common approaches. 1) Screening a very large random library, or 2) screening smaller “drug” libraries, e.g. FDA-approved or drugs of known action. An alternative approach, which is newer and less common, is to generate small but novel libraries based on derivatives that are predicted by design to interact with key path-ways. We call this LRD (Limited Rational Design) because it is still a screen for unknown activities, but based on a strong biological prediction. Using our LRD approach, in the context of an ongoing chemical biology project focused on the Retinoic acid, Oxidative, and TGF-beta (Transforming Growth Factor-beta) pathway in developing zebrafish embryos [1–3], we envisioned developing a pinacolylboronate-substituted resveratrol analogues.

Our hypothesis to develop boron-containing resveratrol analogues is based on two expectations. First, it is expected that the boron atoms introduced into biologically active molecular frameworks might interact with a target protein not only through hydrogen bonds but also through covalent bonds, and this interaction would pro-duce potent biological activity [4,5]. The use of boron atoms in pharmaceutical drug design possesses a high potential for discovery of new biological activity [6]. Among various boron compounds synthesized, much attention has been paid to boronic acid containing pep-tides such as Velcade and DPP-IV inhibitors [7,8]. In these boropeptides, a carboxylic acid has been replaced by a boronic acid group. Second, from a literature search we found that reseveratrol (trans-3,4/, 5-trihydroxystilbene) (Fig. 1) is a polyphenolic compound that modulates TGF-beta signaling pathway and potential therapeutic agent for the treatment of Alzheimer's disease [9,17]. In this context we under-took a project to synthesize boron containing resveratrol analogues. In the process of synthesizing boron-containing reseveratol analogues, we developed a synthetic methodology to synthesize boron-containing stilbene derivatives and used this methodology to synthesize our target compound **1o** (Fig. 1).

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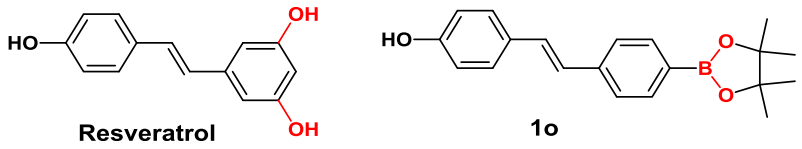


Fig. 1. Resveratrol and boron-containing resveratrol.

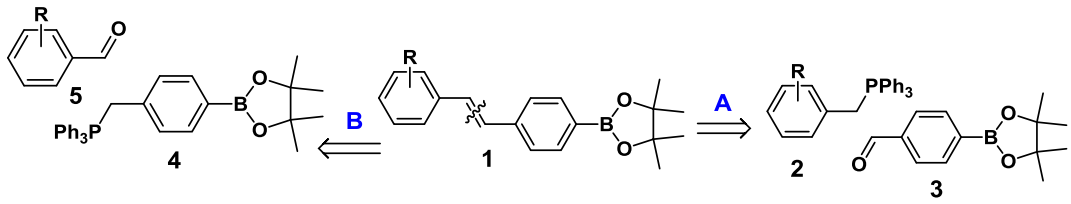


Fig. 2. Retrosynthetic approach for pinacolylboronate-substituted stilbene derivatives **1**.

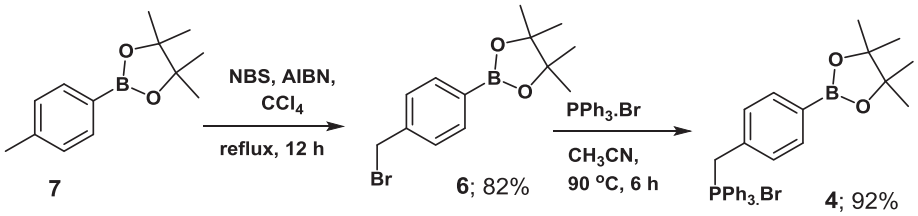
2. Results and discussion

The most familiar and general strategy for synthesis of boron-containing stilbenes **1** is based on disconnection A (Fig. 2) and involves the Wittig reaction of the various substituted benzyl phosphonium ylide **2** with the pinacol ester of boronate aldehyde **3** [10]. To our surprise, literature search failed to uncover any examples of pinacol ester of boronato phosphonium ylide. We report herein the employment of this strategy to prepare novel pinacolylboronate-substituted stilbene derivatives. Although Wittig and Horner–Wadsworth–Emmons reactions have been carried out on aldehyde derivatives of boronate esters [11–13], the problem with this approach A (Fig. 2) to synthesize boron-containing stilbene derivatives requires various substituted benzyl phosphonium ylides and boron containing aldehydes. Boron-containing aldehydes are very prone to self-dimerization and oxidation and decomposed for longer storage, so this method is limited in scope. To overcome this problem, we undertook the disconnection B approach (Fig. 2), envisaging the use of the pinacol ester of boronato phosphonium ylide **4**, which has not previously been explored.

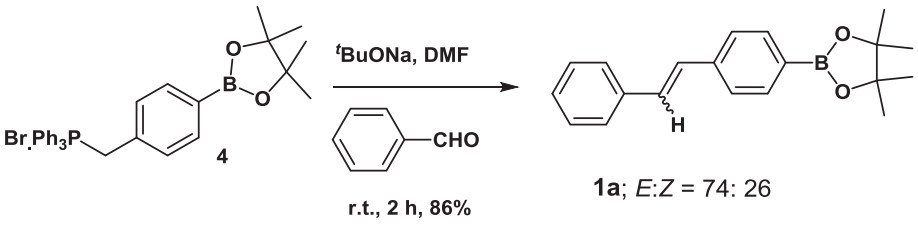
Our methodology is complementary to their finding, but more practical applicable as it contains boronic esters and acids which are biological active. Because there is no dearth of pinacol esters of boronato phosphonium ylide **4** in the literature, the route appeared highly attractive. Compound **4** is stable in air, so different phenyl and alkyl aldehydes are easily available or can be derivatized to synthesize a library of boron-containing stilbene derivatives. Herein, we report the success of this new route based on disconnection B (Fig. 1), the preparation of pinacol ester of boronato phosphonium ylide **4**, followed by the novel synthesis of pinacolylboronate-substituted stilbene derivatives via the direct Wittig bromide (**4**) from the corresponding 2-[4/-(bromomethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 6 in the presence of 1.01 equiv of tri-phenylphosphine in acetonitrile at reflux condition (Scheme 1).

Compound **6** [14] was prepared starting from 4,4,5,5-tetramethyl-2-p-tolyl-1,3,2-dioxaborolane **7**, NBS and AIBN in carbon tetrachloride were refluxed for 12 h. In our initial attempt 4-(4,4,5,5-tetramethyl-1,3,2-dioxaboratophenyl)-methyl triphenylphosphonium bromide **4** was isolated as a white solid in 92% yield. The minor excess of PPh3 was removed from the product by trituration with ether 2–3 times and the product was found to be stable under normal atmospheric conditions. Subsequently, we optimized the Wittig reaction of the ylide derived from this salt using benzaldehyde (Scheme 2).

It is noteworthy that the three equivalents of sodium tert-butoxide in DMF at room temperature led to the highest yield of **1a** (Table 1, entry 1). With this optimized condition in hand, we



Scheme 1. Synthesis of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaboratophenyl)-methyl triphenylphosphonium bromide **4**.



Scheme 2. Proposed synthesis of stibene **1**.