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The application of formyl group activation of bromopyrrole esters to formal syntheses of lycogarubin C, permethyl storniamide A and lamellarin G trimethyl ether

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ABSTRACT

Lycogarubin C, permethyl storniamide A, and lamellarin G trimethyl ether are pyrrole containing, natural products, which exhibit interesting biological properties. Such properties include anti-tumor activity on a variety of cancer cell lines including those that confer drug resistance, inhibition of HIV integrase, and vascular disrupting activity. We now describe the use of methyl and ethyl 3-bromo-2-formylpyrrole-5-carboxylate as building blocks for the formal synthesis of these three highly functionalized, bioactive pyrroles. These new building blocks will now provide ready access to the natural products and many novel analogs due to the ability to easily modify positions 2,3,4, and 5 of the pyrrole core.

1. Introduction

We have recently reported[1] the use of ethyl 3-bromo-2-formylpyrrole-5-carboxylate (1) as a very flexible and efficient pyrrole building block, which allows for Suzuki cross-coupling reactions. This becomes important, since various non-activated bromopyrroles have been reported[2–8] to be problematic in such cross-coupling reactions. In addition to the formyl group activating these transformations, a versatile carbonyl function is also introduced at the 2-position of the pyrrole and this is common to many pyrrole containing natural products. In our recent report, we described the utilization of this strategy for the formal synthesis of the natural products polycitone A and B and polycitrin A (Scheme 1).

Lycogarubin C, permethyl storniamide A, and lamellarin G trimethyl ether (Fig. 1) also represent novel and biologically significant, pyrrole containing natural products and we now describe our use of the formyl group activation strategy for the completion of formal syntheses of these substances.

2. Results and discussions

Steglich[9] and Asakawa[10] simultaneously reported the isolation of various members of the lycogarubin/lycogallic acid family of natural products from slime molds in 1994. It is interesting to note that Sherman [11] (2005) and Walsh[12] (2007) have suggested that lycogallic acid is a biosynthetic precursor to the important naturally occurring, antitumor agents rebeccamycin and staurosporin. Previous syntheses of members of the lycogarubin/lycogallic acid family of natural products have been accomplished by Steglich[9] (1994), Furstner[2] (2002), Onaka[13] (2006), Boger[14] (2010), Gribble[15] (2010), and more recently by Xie[16] (2014). The Boger and Gribble syntheses both rely on the Kornfeld-Boger ring contraction methodology to generate the pyrrole core. In the Gribble synthesis of lycogarubin C, the final precursor to the natural product was a bis-*N*,*N*-sulfonylated derivative of lycogarubin C and this material subsequently became our synthetic target. We initiated our synthetic strategy by preparing methyl 3-bromo-2-formylpyrrole-5-carboxylate (8) in a three step process analogous to ethyl 3-bromo-2-formylpyrrole-5-carboxylate, which we previously reported.[1] Such transformations proceed in very high yield with little if any purification required of the intermediate products and very significant amounts of the pyrrole building block (8) can be obtained very rapidly. It is fortunate that 1-(phenylsulfonyl)-3-indolylboronic acid pinacol ester (9) is commercially available and it was employed in our Suzuki cross-coupling reaction (Scheme 2) with our pyrrole building block (8) using reaction conditions described in our previous report.[1] The resulting cross-coupled product (10) was then oxidized with sodium chlorite in water/DMSO to produce the corresponding acid (11) in good yield. Subsequent treatment of this acid

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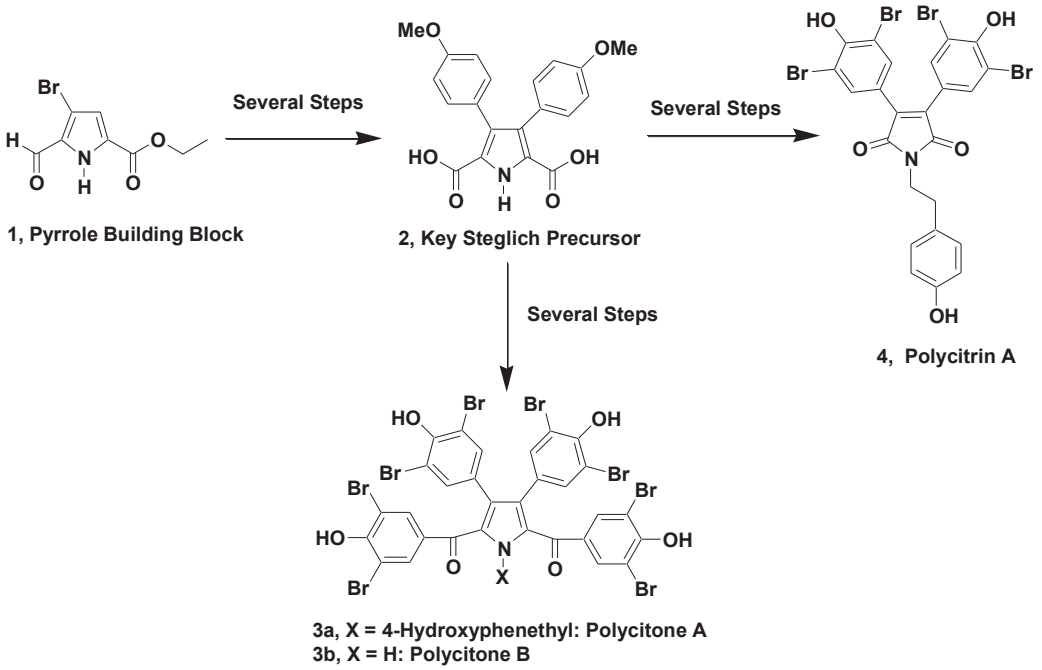

Scheme 1. Formyl group activation in the formal synthesis of polycitone A and B and polycitrin A.

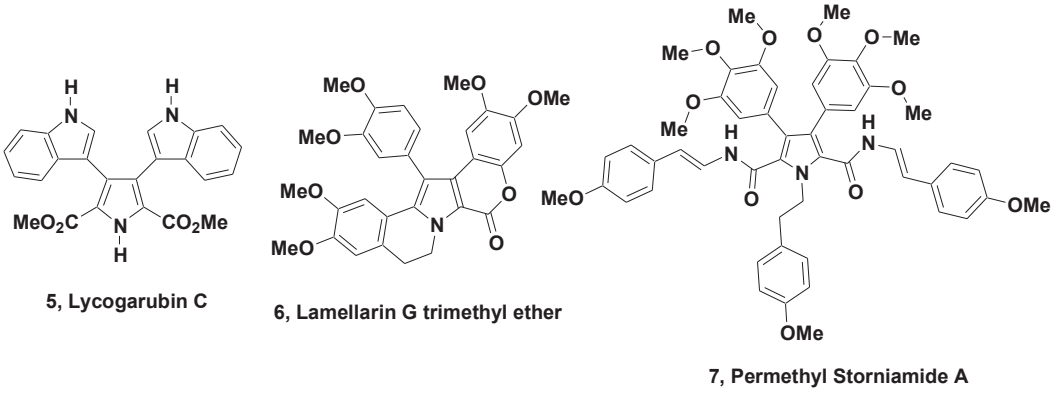

Fig. 1. Pyrrole containing natural products.

(11) with dicabonylimidazole and methanol generated the corresponding bis-methyl ester (12) also in good yield. This diester (12) was then brominated with KOH/NBS in DMF producing the corresponding 4-bromo compound (13) and this material was cross-coupled with 1-(phenylsulfonyl)-3-indolylboronic acid pinacol ester (9) under previously detailed conditions. The resulting product (14) was the Gribble lycogarubin C precursor, which was previously bis de-sulfonylated with magnesium/ammonium chloride in methanol by the Gribble group to yield the natural product (5). The overall yield of the Gribble precursor (14) in five steps from our pyrrole building block (8) was 37%. The proton and carbon NMR spectra for compound 14 were identical to the values reported by Gribble and co-workers.

In order to further demonstrate the utility of this synthetic strategy as it relates to rapidly generating analogs, which might be required in a biologically directed SAR study, we decided to utilize the mono cross-coupled aldehyde (10) as a precursor to such compounds. We selected boronic acids (16a, 16b, and 16c), which contain highly oxygenated phenyl groups given that many of the related pyrrole containing natural products possess such functionality. The resulting synthetic process is presented in Scheme 3. The presence of the aldehyde group in the final products (17) allows great flexibility for further synthetic manipulations.

Another very significant natural product derived compound is permethyl storniamide A (7, Fig. 1). The storniamide marine alkaloids were first isolated in 1996 by Seldes and co-workers[17] and subsequently Takamura[18] (2009), Iwao[19] (2003), Furstner[2] (2002), Boger[20] (1999), Steglich[21] (1998), and our group[22] (2008) reported either total or formal syntheses of permethyl storniamide A (7, Fig. 1).

Scheme 4 represents our bromoformylpyrrole methyl ester building block approach to the synthesis of the Boger storniamide intermediate[20] (23). We have previously prepared[22] this same compound via a vinamidinium salt based approach and compounds 21, 22, and 23 in Scheme 4 have been previously synthesized and fully characterized. The synthetic steps used in our approach are analogous to those used in our formal synthesis of lycogarubin C (Scheme 2). After an initial cross-coupling reaction of the bromoformylpyrrole ester (8) with 3,4,5-trimethoxyphenylboronic acid (18), the resulting pyrrole (19) was oxidized to the corresponding acid (20) and subsequently esterified (21) with iodomethane and base. Iodination of the pyrrole diester (21) generated the 3-