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Enantiospecific Total Synthesis of Tryprostatin A

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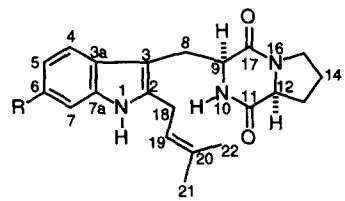
Abstract:: *The 3-methyl-6-methoxyindole **3** was converted into tryprostatin A (**1**) via a regiospecific bromination process coupled with the Schöllkopf chiral auxillary **7** to provide the 2-bromo-6-methoxy-tryptophan **8a** as a key intermediate.* © 1997 Elsevier Science Ltd. All rights reserved.

Tryprostatins A (**1**) and B (**2**) have been isolated as secondary metabolites of a marine fungal strain BM939 and shown to completely inhibit cell cycle progression of tsFT210 cells in the G2/M phase at a final concentration of 50 μg/mL of **1** and 12.5 μg/mL of **2**, respectively.[1-3] Tryprostatins A (**1**) and B (**2**) contain a 2-isoprenyltryptophan moiety and a proline residue, the latter of which is located in the diketopiperazine unit. These indole alkaloids differ from the representatives of the fumitremorgin series for ring-C has been cleaved between the positions designated C(18) and N(10).[4] Although bases in the fumitremorgin series have been studied extensively,[4] only a few natural products structurally related to **1** and **2** have been reported to date. The biological activity and unique 2-isoprenyltryptophan units of **1** and **2** prompted interest in such molecules. We wish to report the first enantiospecific total synthesis of tryprostatin A *via* a regiospecific bromination procedure developed in our laboratory as the key process.[5]

Figure 1



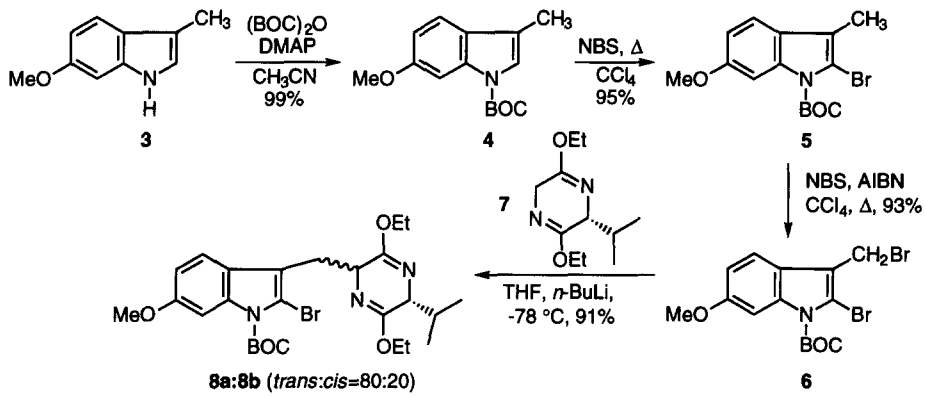
R = OMe, tryprostatin A (**1**)
R = H, tryprostatin B (**2**)

In the course of studies directed toward the synthesis of ring-A oxygenated indole alkaloids,[6,7] the regiospecific bromination of various substituted 3-methylindoles at either the C(2) or the C(3)alkyl position was developed *via* an electrophilic or free radical bromination process, respectively.[5] The 3-bromomethyl group could then be coupled with the Schöllkopf chiral auxiliary[8,9] to furnish the desired tryptophan unit, moreover, the 2-bromo moiety would serve as a synthon for the isoprenyl group. Consequently, this method

would appear to provide an enantiospecific route for the synthesis of either L or D-2-isoprenyltryptophan related natural products.

Since the enantiospecific synthesis of 6-methoxy-(D)-tryptophan had recently been developed by Hamaker[10] and Liu[11] in our laboratory, tryprostatin A (**1**) was chosen as the synthetic target. The synthesis began with 6-methoxy-3-methylindole **3** which was readily available *via* a Japp-Klingmann/Fischer-indole protocol followed by hydrolysis and Cu/quinoline mediated decarboxylation.[12] After protection of the N(1) position with a BOC group, regiospecific bromination at the indole C(2) position was carried out to yield 2-bromoindole **4** in 95% yield under electrophilic conditions. Furthermore when **4** was reacted with NBS under free radical conditions (AIBN, Δ), dibromide **6** was obtained (Scheme 1). Not only did the BOC moiety control the regiochemistry of the bromination sequence but also provided the protected indole system necessary for alkylation with the Schöllkopf chiral auxiliary. When dibromide **6** was coupled with the anion of the Schöllkopf chiral auxiliary **7** (derived from D-valine)[10-13] at -78 °C, a mixture of diastereomers **8a** and **8b** in a ratio of 80:20 was obtained in 91% yield. Since the enantioselectivity of formation of **8a**:**8b** was disappointing, another approach to **1** was developed.

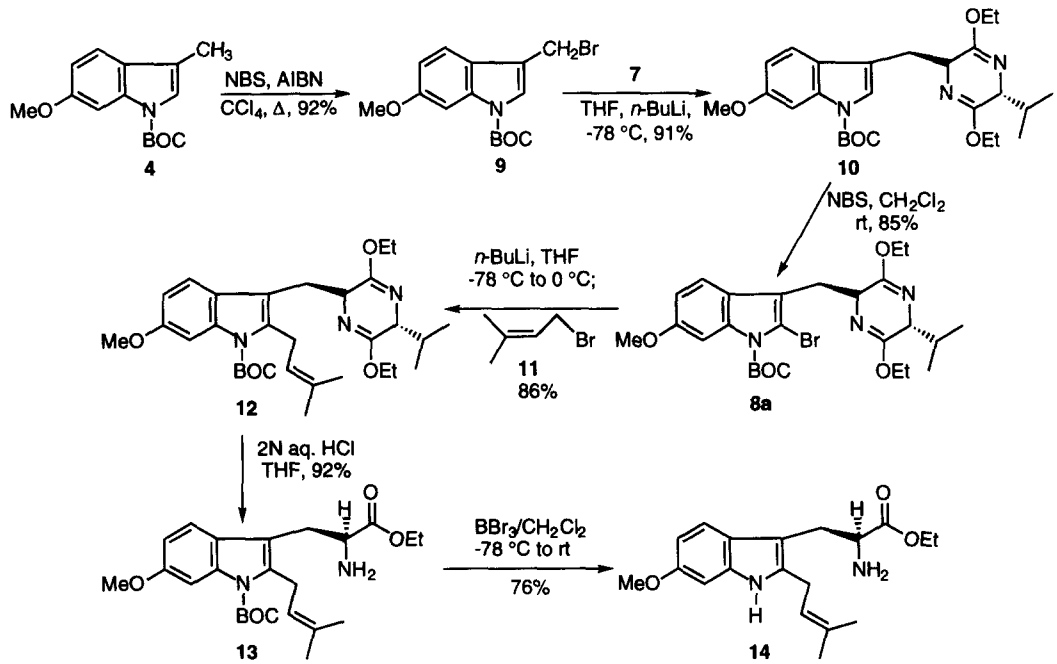
Scheme 1



As illustrated in Scheme 2, the indole **4** was reacted with NBS under free radical conditions (AIBN) to afford the 3-bromomethylindole **9** in 92% yield. The benzylic bromide **9** which resulted was stirred with the anion of **7** at -78 °C to provide only one diastereomer **10** (C-13 NMR) in 93% yield. Regiospecific bromination of **10** at the indole C(2) position was accomplished in 85% yield when **10** was stirred with NBS in CH_2Cl_2 at room temperature. In this manner diastereomer **8a** was obtained in enantiospecific fashion. When bromide **8a** was treated with *n*-butyllithium at -78 °C and isoprenyl bromide **11** was added to the solution, 2-isoprenyl pyrazine **12** was isolated (86% yield). Since the Schöllkopf chiral auxiliary can tolerate strongly alkaline conditions, it served as a protecting group for the amino acid functionality to prevent any racemization. The pyrazine **12** was then hydrolyzed under acidic conditions (aq. HCl, THF) to remove the D-valine ethyl ester, which can readily be recovered by Kugelrohr distillation and reused.[10-13] Finally, the BOC protecting group was removed on stirring **13** with boron tribromide to provide the 2-isoprenyl-6-methoxy-(L)-

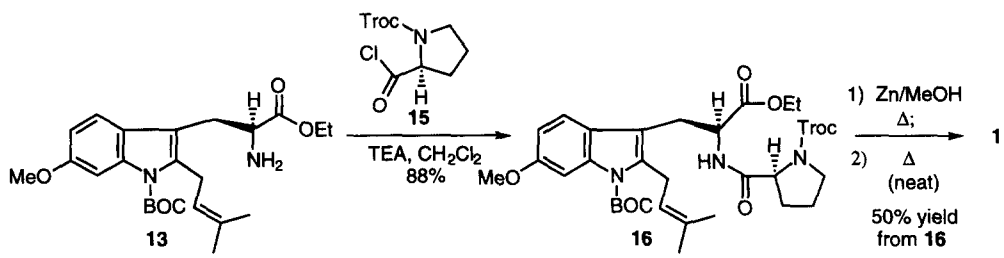
tryptophan ethyl ester **14**. Use of the enantiomer of the Schöllkopf chiral auxiliary **7** (derived from L-valine) furnished the D-enantiomer of 2-isoprenyl-6-methoxytryptophan ethyl ester **14** also in optically active form.

Scheme 2



The tryptophan ethyl ester intermediate **13** was then stirred with trichloroethoxycarbonyl (Troc)-L-prolyl chloride **15**[14] in the presence of triethylamine in CH_2Cl_2 at 0 °C. The proline substituted intermediate **16** which resulted was heated with Zn (dust) in refluxing MeOH, followed by heating at 160 °C (neat) to furnish tryprostatin A (**1**) in 50% overall yield from **16**.

Scheme 3



In summary, an enantiospecific synthesis of tryprostatin A (**1**) was accomplished(from **3**) *via* a regiospecific bromination process. In addition the key 2-isoprenyltryptophan ethyl ester **14** was also prepared. The success of this method rests on the ability to prepare either antipode of the Schöllkopf chiral auxiliary on

greater than 300 gram scale[10-13] and facile preparation of 6-methoxy-3-methylindole **3** *via* the Japp-Klingmann/ Fischer-indole protocol.[11,12] This approach should also provide a route for the synthesis of other unusual tryptophans or indoles which carry substituents at the indole(2) position. Further work in this areas is in progress and will be reported in due course.

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