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Total Synthesis of Tryprostatin A and B As Well As Their Enantiomers

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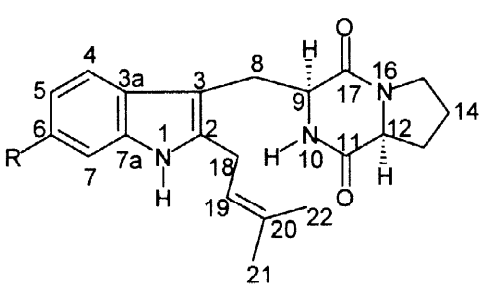
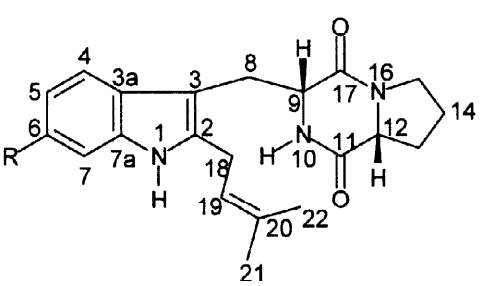
Abstract: *The 3-methylindoles **3a**, **3b** were converted into tryprostatin A (**1a**), B (**1b**) and their enantiomers **2a**, **2b** via prenylation at the indole 2-position by generation of the required 2-lithioindole derivatives (from **7a**, **7b**), followed by alkylation.* © 1998 Elsevier Science Ltd. All rights reserved.

Recently, tryprostatin A (**1a**) and B (**1b**) have been isolated as secondary metabolites of a marine fungal strain BM939. These indoles have been shown to completely inhibit cell cycle progression of tsFT210 cells in the G2/M phase at a final concentration of 50 μg/mL for **1a** and 12.5 μg/mL for **1b**, respectively.[1-3] Tryprostatin A (**1a**) and B (**1b**) contain a 2-isoprenyltryptophan moiety and a proline residue, which comprise the diketopiperazine unit. These indole alkaloids differ from representatives of the fumitremorgin series for ring-C has not been formed 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 **1a** and **1b** have been reported, to date. The biological activity and unique 2-isoprenyltryptophan units of **1a** and **1b** have prompted interest in such molecules. We report herein the enantiospecific total synthesis of the natural products as well as the enantiomers of tryprostatin A (**2a**) and B (**2b**) *via* an improved process.[5,6]

Figure 1



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



R = OMe, enantiomer of tryprostatin A (**2a**)
R = H, enantiomer of tryprostatin B (**2b**)

The synthesis began with indoles **3a** and **3b** which were available on large scale *via* a Japp-Klingmann/Fischer-indole protocol followed by hydrolysis and Cu/quinoline mediated decarboxylation reported earlier.[6,7] When indole **3a** or **3b** was stirred with di-*tert*-butyl dicarbonate in the presence of DMAP, *N*-BOC

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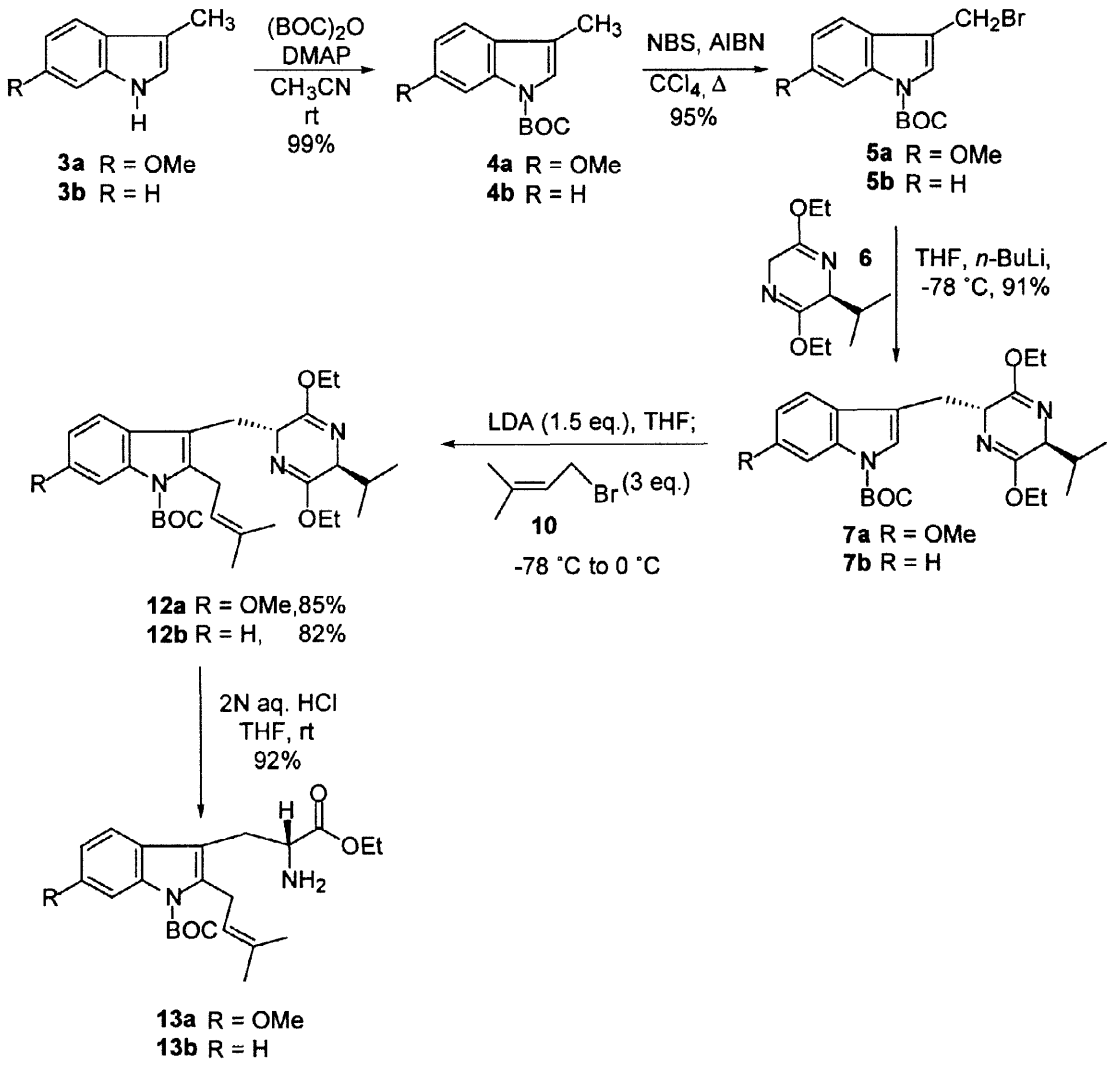
protected indoles **4a** or **4b** were realized, respectfully, in 99% yield. The protected 3-methylindoles **4a** and **4b** were then treated (individually) with NBS in the presence of AIBN to provide the 3-(bromomethyl)indoles **5a** and **5b**, as illustrated in Scheme 1. Not only did the BOC moiety promote the regiospecificity of the bromination sequence but it also provided the protected indole system necessary for alkylation with the Schöllkopf chiral auxiliary **6**. When bromides **5a**, **5b** were coupled, respectively, with the anion of the Schöllkopf chiral auxiliary **6** (derived from L-valine),[6-9] the desired *trans* diastereomers **7a** and **7b** were obtained with 100% diastereoselectivity. These diastereomers are required for the synthesis of the antipodes of tryprostatin A and B and are available by the *trans* transfer of asymmetry *via* the Schöllkopf chiral auxillary **6**.

Scheme 1

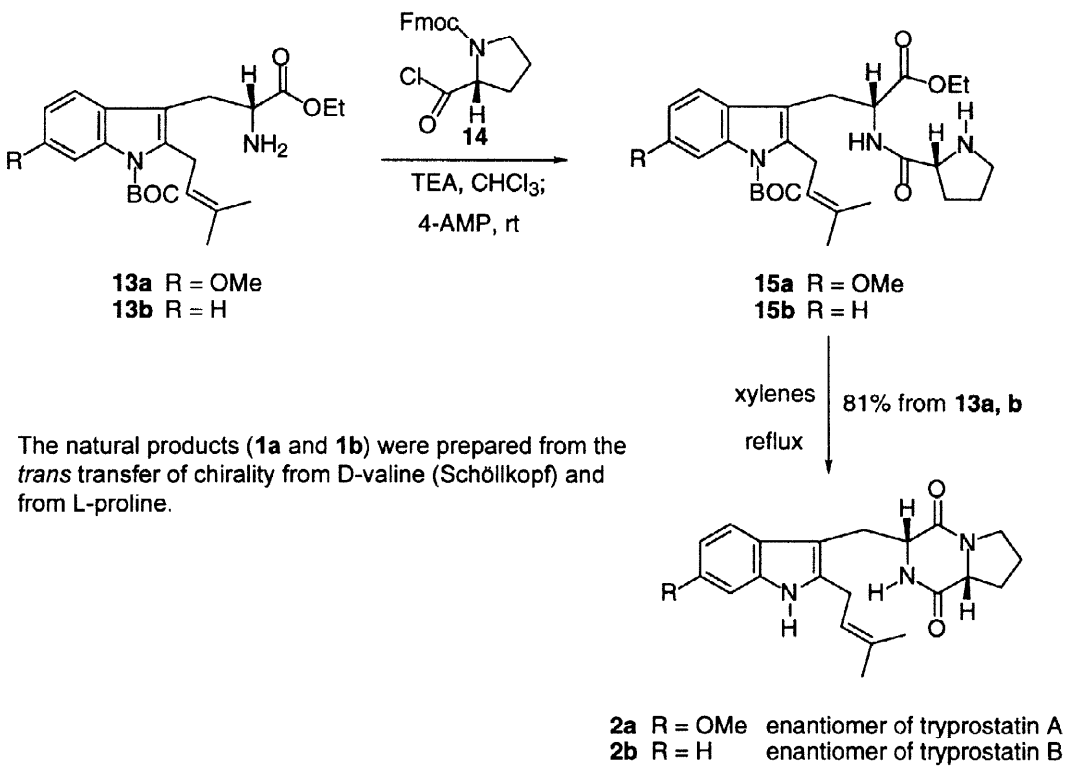


In order to introduce the isoprenyl group at the indole C(2) position of **7b** and decrease the number of steps earlier reported in the natural series,[6] LDA was employed to form the anion at the indole C(2) position.[10]

When **7b** was treated with LDA at -78 °C, and this was followed by addition of isoprenyl bromide **10**, 2-isoprenylpyrazine **12b** was isolated in 82% yield. This process represented an improvement in the synthesis of 2-isoprenylpyrazine **12b**, consequently the 6-methoxy analog **12a** was later prepared by the same method. Since the Schöllkopf chiral auxiliary can tolerate strongly alkaline conditions, it served as a protecting group for the amino acid functionality to prevent racemization. The pyrazine moiety was removed from **12a** or **12b** (individually) under acidic conditions (aqueous HCl, THF) in 94% yield to provide L-valine ethyl ester which can be recycled and the 2-isoprenyl tryptophan **13a** or **13b**, respectively.

When 2-isoprenyltryptophan **13a** or **13b** was stirred with *N*-Fmoc-D-prolyl chloride (**14**)[11] in the presence of triethylamine ($CHCl_3$) at room temperature and this was followed by removal of the Fmoc protecting group by addition of 4-(aminomethyl)-piperidine (4-AMP) to the above solution,[11] the desired dipeptide **15a** or **15b** was obtained, respectively. Formation of the diketopiperazine unit as well as removal of BOC protecting group from the indole N(H) function were achieved when dipeptide **15a** or **15b** was heated individually in refluxing xylenes.

Scheme 2



In summary, a stereospecific, enantiospecific total synthesis of the enantiomers of tryprostatin A (**2a**) and B (**2b**) was accomplished (from **3a** or **3b**, respectively) *via* alkylation of the corresponding 2-lithioindole derivatives. This approach was also employed to improve the total synthesis of natural tryprostatin A (**1a**) and to prepare tryprostatin B (**1b**). The optical rotations of the natural products and the enantiomers were identical

to that reported by Osada *et al*;[1-3] however, the sign of rotation of the latter compounds was opposite to that of the natural products. Completion of this work provides gram quantities of both the natural and unnatural enantiomers of tryprostatin A and B for biological screening. A thermally mediated cyclization of ester **15** provides a potential entry into alkaloids of the fumitremorgin series,[4] however, ring C of the tetrahydro β-carboline should precede formation of the diketopiperazide unit.

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