Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), www.mdpi.org/ecsoc-4.htm, September 1-30, 2000

[C0023]

Brief synthesis of the cell cycle inhibitor tryprostatin B and its alanine analogue

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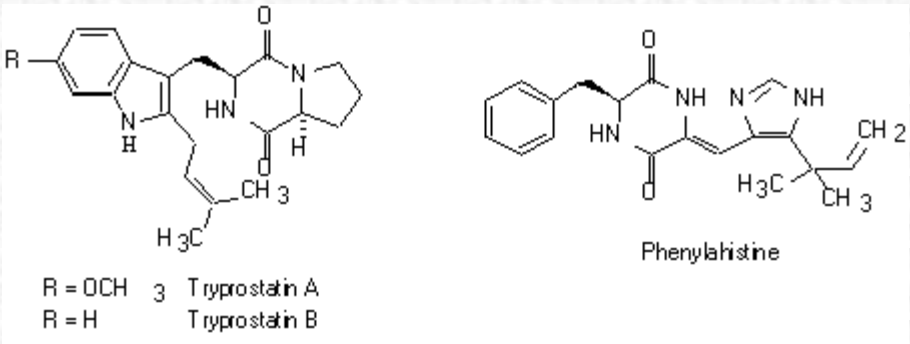
Received: 7 August 2000 / Uploaded: 10 August

Abstract.- Tryprostatin B and its analogue containing alanine instead of proline were synthesized from *cyclo*-(L-Trp-L-Pro) and *cyclo*-(L-Trp-L-Ala), respectively, by tandem C-3 prenylation/cyclization, followed by acid-catalyzed migration of the prenyl group to the indole C2 position.

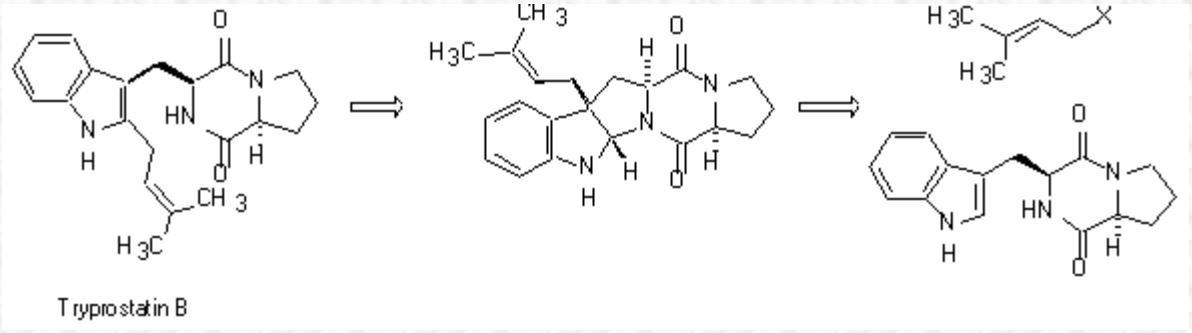
Introduction

The cell cycle is an attractive target for the development of chemotherapeutic agents, with much current interest being focused on the search for anti-mitotic agents [1]. Recently, the group led by Osada has reported the structure and biological properties of tryprostatins A and B, two novel cell cycle inhibitors isolated from a strain of *Aspergillus fumigatus*[2,3]. These compounds act as inhibitors of the cell cycle progresion through inhibition of microtubule assembly through a novel mechanism [4,5], and are therefore promising lead compounds in the search for new antitumour agents. Related natural products, like phenylahistin, are also inhibitors of the mammalian cell cycle [6].



All total [7,8,9] and formal [10] syntheses of the tryprostatins published to date rely on the preparation of a suitable 2-prenylindole intermediate. We describe here an alternative strategy, based on the prenylation-cyclization of *cyclo*-(L-

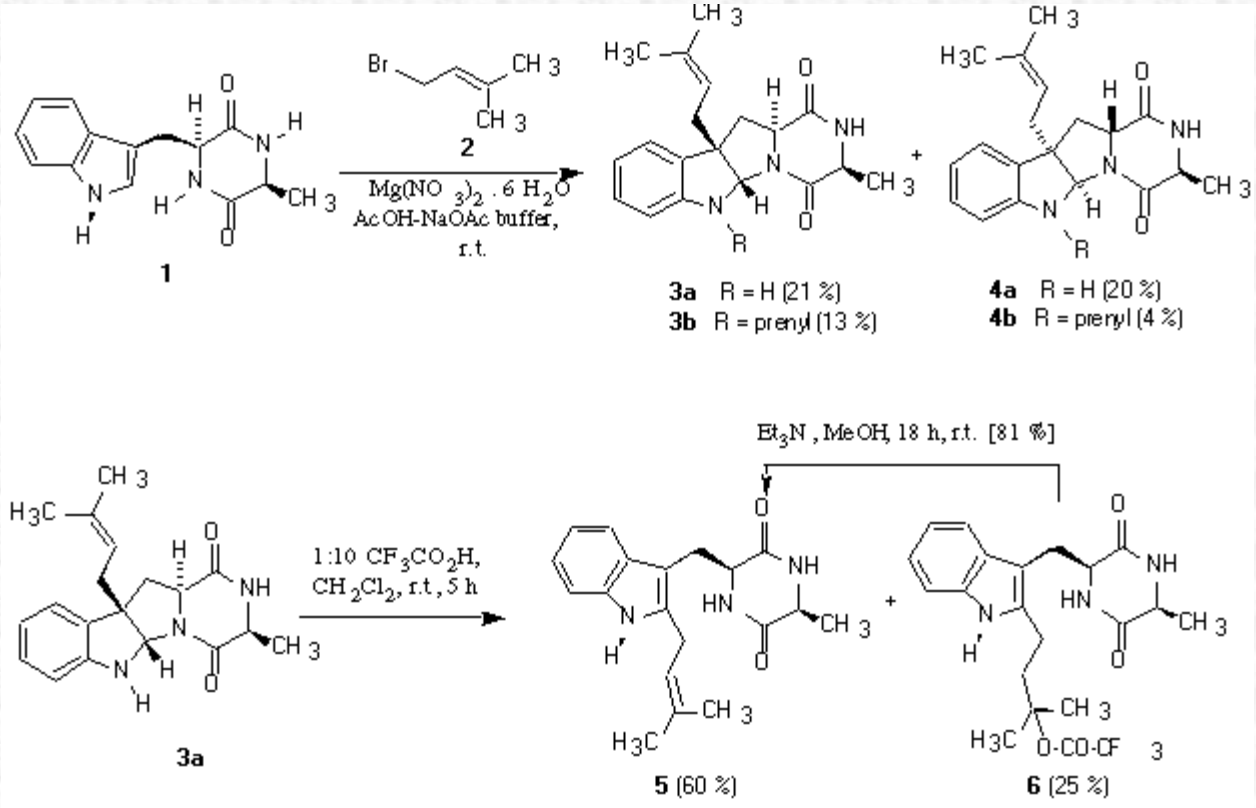
Trp-L-Pro) followed by rearrangement of the prenyl chain with concomitant ring opening and rearomatization of the indole system (Scheme 1). By replacing L-Pro by other amino acids as the starting material, this route should also allow the preparation of tryprostatin analogues.



Scheme 1

Results

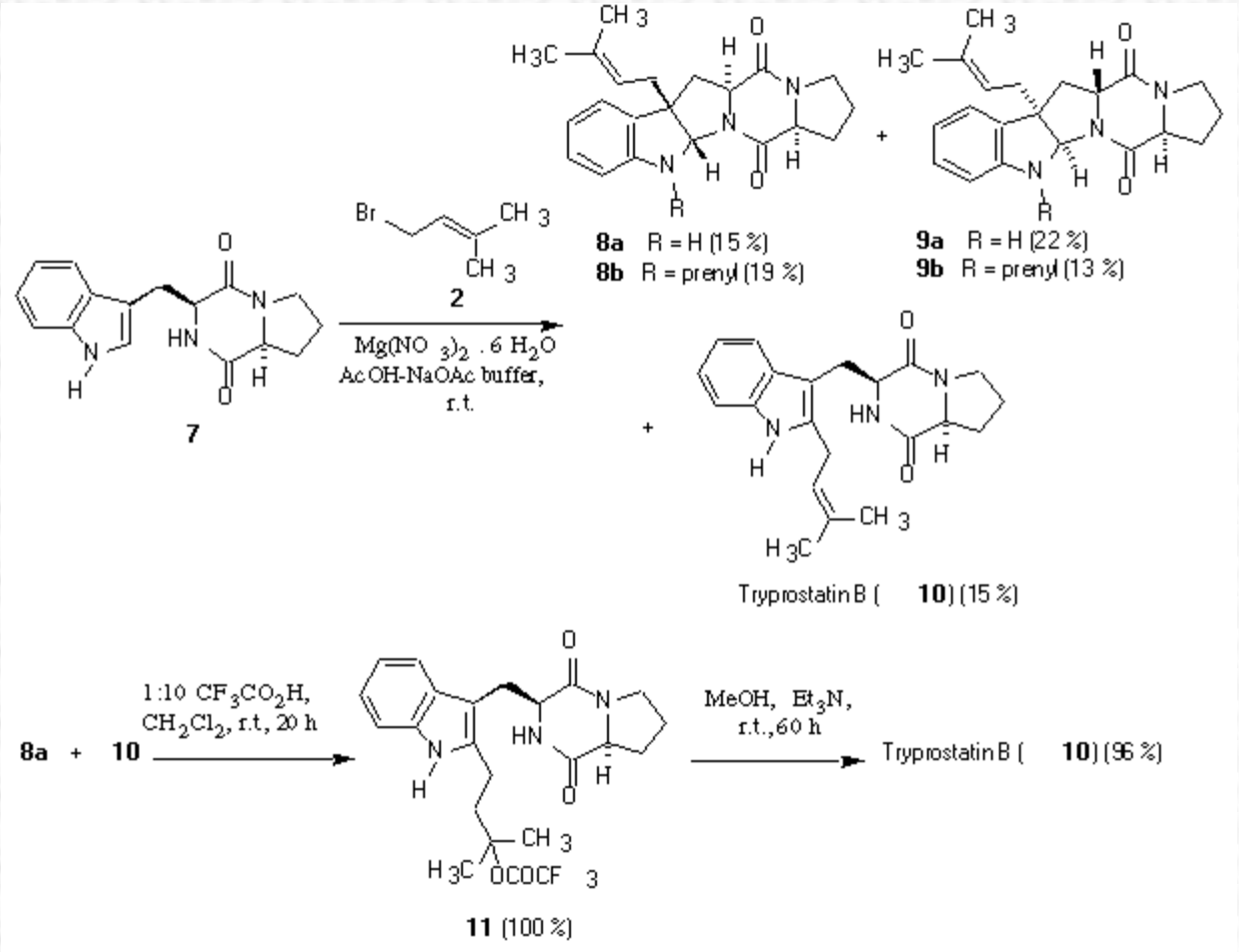
Slow addition of prenyl bromide to a solution of *cyclo*-(L-Trp-L-Ala) (**1**) gave a mixture of compounds (**3a**, **4a**) arising from alkylation of the indole ring at C-3 followed by cyclization by nucleophilic attack of the neighbouring piperazinedione nitrogen, together with their N-prenylated derivatives **3b** and **4b**. The viability of the required rearrangement step was studied on compound **3a**, which upon treatment with dilute trifluoroacetic acid gave the desired tryprostatin analog **5** in 60% yield together with 25% of **6**, from addition of trifluoroacetic acid to the double bond of **5**. Compound **6** could be transformed into **5** in 81% yield by reaction with triethylamine in methanol (Scheme 2).



Scheme 2

A similar method was used for the preparation of the natural product, as summarized in Scheme 3. It is noteworthy that in this case the alkylation step gave some tryprostatin B (**10**), probably by acid-catalyzed rearrangement of **8a** under the reaction conditions. Exposure of the inseparable mixture of **8a** and **10** gave **11** in 100% yield, and treatment of the

latter with triethylamine in methanol gave tryprostatin B in 96 % yield.



Scheme 3

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Acknowledgements

We thank CICYT for financial support of this research through grant SAF-2000-0130.

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