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Efficient Synthesis of *N*-Prenylpyrroloindoline and *N*-Prenylindole Alkaloids Based on a New Four-Reaction Anionic Domino Process

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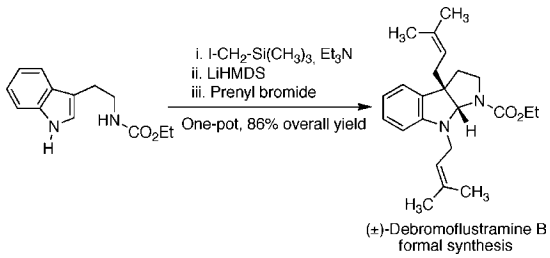
ABSTRACT



Treatment of 2,5-diketopiperazines or carbamates derived from tryptophan or tryptamine with iodomethyltrimethylsilane followed by lithium hexamethyldisilazane and a prenyl halide produced stereoselectively derivatives of the hexahydropyrrolo[2,3-*b*]indole system bearing prenyl substituents both at C-3a and at the indoline nitrogen in a one-pot procedure involving a novel four-reaction anionic domino process. The reaction was applied to the preparation of *N*-prenyltryprostatin B and to achieving a very efficient formal total synthesis of the biologically active marine natural product (±)-debromoflustramine B.

Alkaloids containing a hexahydropyrrolo[2,3-*b*]indole structural motif have been isolated from varied natural sources, including amphibians, plants, and marine organisms. Some examples are the okaramines, isolated from fermentation extracts of *Penicillium* simplicissimum and *Aspergillus aculeatus* cultured on okara, the residue from soymilk production,[1] and the ardeemins, from *Aspergillus fischeri*.[2] The simplest members of this family, which do not contain additional rings fused to the hexahydropyrrolo[2,3-*b*]indole fragment and normally bear a prenyl group at C-3a, are exemplified by flustramine B, debromoflustramine B, and flustramide B, isolated from the marine briozoan *Flustra foliacea*,[3] and the closely related pseudophyrnamines, e.g., pseudophrynaminol. These compounds are structurally and biogenetically related to the prenylindole family of alkaloids,[4] represented by the tryprostatins (Figure 1).

The pyrrolo[2,3-*b*]indole alkaloids exhibit a broad range of biological activities, some examples being the insecticidal activity found in the okaramines,[5] the reversal of multidrug

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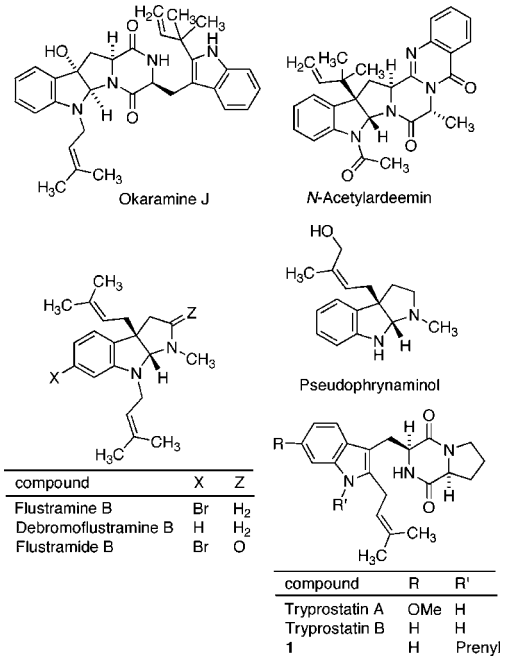


compound	X	Z
Flustramine B	Br	H_2
Debromoflustramine B	H	H_2
Flustramide B	Br	O

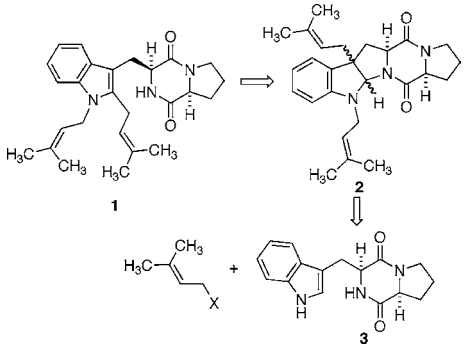
compound	R	R'
Tryprostatin A	OMe	H
Tryprostatin B	H	H
1	H	Prenyl

Figure 1. Structures of representative pyrroloindoline and prenylindole alkaloids

resistance[6] to antitumor agents (MDR)[2,7] and immunsuppresant activities[8] found in some natural and synthetic ardeemin derivatives, and the antibacterial,[9] muscle relaxant,[10] and potassium channel-blocking[11] activities of the flustramines. The related indole isoprene alkaloids are also very interesting from the biological point of view, and tryprostatin A is an inhibitor of BRP, a protein responsible for resistance to antitumor drugs in breast cancers.[12] Even more importantly, the tryprostatins have also been shown to prevent cell cycle progression at the G_2/M phase through a unique mechanism consisting of inhibition of the interaction between one of the microtubule-associated proteins (MAP-2) and the C-terminal end of tubuline.[13] In connection with this behavior, a diastereomer of tryprostatin B has been shown to have a more potent activity than the widely prescribed antitumor drug etoposide against three human cancer cell lines.[14] In this context, we proposed that the preparation of *N*-prenyltryprostatin B (**1**) would be of interest because the microtubule assembly inhibition activities of *N*-prenyl derivatives of *cyclo*-(L-Trp-L-Pro) are higher than those of tryprostatin itself.[15]

Our proposed approach to the synthesis of **1** was based on the use of a rearrangement of the prenyl chain in pentacyclic systems **2** with concomitant ring opening and aromatization of the indole ring (Scheme 1), a concept that we have previously exploited for achieving a very concise, biomimetic synthesis of tryprostatin B.[16] We present here the practical realization of this synthetic plan, involving the development of an efficient anionic reaction cascade leading to the one pot-synthesis of compound **2** from *cyclo*-(L-Trp-L-Pro). We also describe the extension of this new methodology to the one-pot formal total synthesis of (±)-debromoflustramine B.

Scheme 1. Retrosynthetic Analysis of *N*-Prenyltryprostatin B



Although compound **2** can be obtained as a minor product of the reaction between *cyclo*-(L-Trp-L-Pro) and prenyl bromide in acidic buffer,[16] we considered that *N*-prenylation would be favored by the use of basic reaction conditions and that perhaps these conditions could also be employed to induce the C_3-alkylation/cyclization cascade needed to create the pentacyclic ring system, thus allowing the one-pot preparation of **1**. Although the proposed transformation was unprecedented, a related literature example where C_3-alkylation/cyclization (but not *N*-alkylation) was achieved could be found in the reaction of *N*-methyltryptamine with methylmagnesium bromide as a base and prenyl bromide to give deoxypseudophrynaminol in a modest 19−22% yield.[17]

In the event, treatment of *cyclo*-(L-Trp-L-Pro) **3** with prenyl bromide in the presence of LHMDS under a variety of

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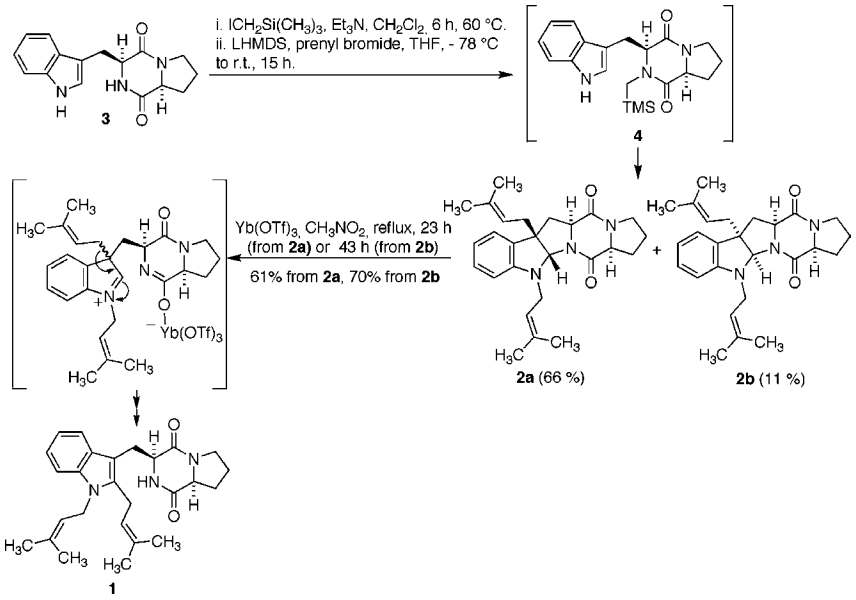
Scheme 2. Synthesis of *N*-Prenyltryprostatin B



conditions invariably gave very complex mixtures that contained only traces of pentacyclic compounds, the main reaction products arising from alkylation of the piperazine nitrogen atom, with or without epimerization of the starting material at the tryptophan stereocenter (see the Supporting Information). Therefore, protection of the piperazine nitrogen was considered necessary, although in principle it would have the disadvantage of preventing the desired *N*-alkylation from taking place in the same operation as the C_3-alkylation/cyclization. However, after assaying several protecting groups, we were pleased to find that the desired *C*-alkylation/cyclization, *and also the N-alkylation*, could be carried out in a single operation and in good yield by treatment of the starting material with iodotrimethyl-silane and triethylamine followed by evaporation and addition of the alkylating agent and LHMDS as a base. These conditions led to yields of 66% of compound **2a**[18] and 11% of its diastereomer **2b**, without isolation of the postulated intermediate **4**. Both **2a** and **2b** could be transformed later into the target compound **1**, together with a small amount (5%) of the previously known[19] N_{indole}-prenyl derivative of the starting material, by ytterbium triflate-induced rearrangement of the prenyl mechanism depicted in Scheme 2. From this result it must be assumed that iodomethyltrimethylsilane temporarily protects the piperazinedione nitrogen of the starting compound **3** to give the nonisolated intermediate **4**, thereby preventing the reaction of the piperazine nitrogen with prenyl bromide and allowing the desired N-1 indole alkylation to take place. This is followed by *N*-deprotection and tandem C_3-alkylation−cyclization (see below for a more detailed explanation).

The transformation of **3** into **2** represents a novel one-pot, stereoselective synthesis of a fused pyrrolo[2,3-*b*]indole system bearing prenyl substituents at both the C-3a and N-8 positions. The discovery of this reaction stimulated us to attempt its application in a concise total synthesis of a representative of the flustramine family, namely debromoflustramine B. Several racemic[20] and enantioselective[21] syntheses of this compound and the related flustramine B[20b,e,22] are known, which normally involve multistep sequences for the construction of the pyrrolo[2,3-*b*]indole system and the installation of the two prenyl substituents. In the shortest route, developed by Ganesan,[20f] treatment of a carbamate derived from tryptamine (compound **5**) with prenyl bromide in the presence of zinc triflate, DIPEA, and tetrabutylammonium iodide gave directly compound **7b** in 70% yield. We wished to ascertain if our method could provide the target compounds with similar or greater efficiency than the Lewis acid mediated procedure described by Ganesan, and this involved verifying the applicability of our procedure to a substrate containing a carbamate group rather than a diketopiperazine. Indeed, as shown in Scheme 3, treatment of **5** with trimethylsilylmethyl iodide and triethylamine followed by solvent evaporation and addition of LHMDS and allyl iodide or prenyl bromide gave compounds **7a** and **7b** in excellent 96% and 86% yields,

(18) Compound **2a** had been previously isolated as a minor product in the reaction of **3** with prenyl bromide or iodide in a buffered aqueous medium containing magnesium nitrate (see ref 16).

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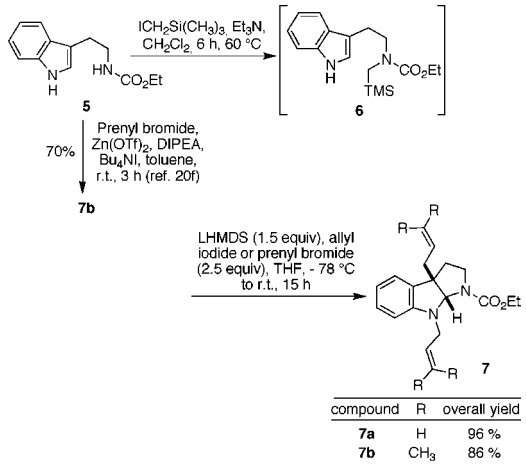
Scheme 3. Formal Synthesis of (±)-Debromoflustramine B

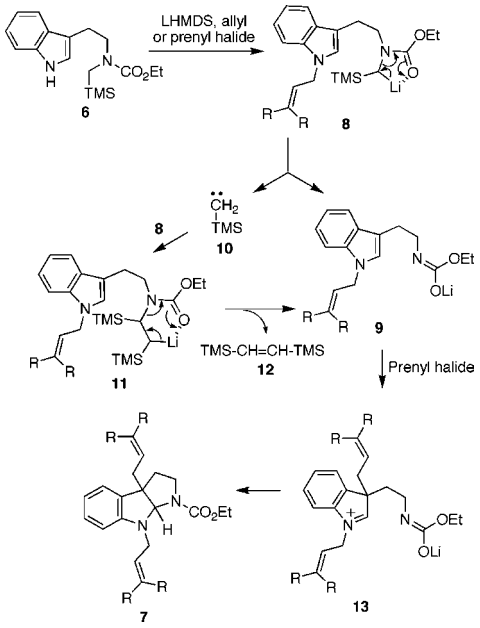


compound	R	overall yield
7a	H	96 %
7b	CH_3	86 %

respectively, both as rotamer mixtures.[23,24] The preparation of **7b** constitutes a formal synthesis of (±)-debromoflustramine B, since its transformation into the natural product by direct reduction has been previously described.[20f,25]

The one-pot process from **3** to **2** or **5** to **7** comprises five different reactions. After the initial *N*-protection of the amide or carbamate nitrogen, a four-reaction anionic domino process[26] takes place, involving prenylation at the indole nitrogen, in situ amide deprotection, indole alkylation at C-3, generating a C-2 iminium species, and final cyclization by trapping of the iminium cation by the nucleophilic nitrogen in the side chain. The *N*-deprotection presumably takes place through a mechanism similar to the one currently accepted for the debenzylation of *N*-benzylindoles with lithium bases.[27] Taking the case of the flustramine synthesis as an example, this mechanism would consist of deprotonation of **6** to give carbanion **8**,[28] whose stabilization is probably of a dipolar nature and is assisted by chelation and also by the presence of an α-silicon atom, since a silyl group can stabilize an α-carbanion by 14−20 kcal/mol[29] through p−d homoconjugation,[30] σ^*−n hyperconjugation,[31] or both.[32] α-Elimination from **8** must be faster than its competitive cyclization to a β-carboline derivative, since this compound has not been observed, and leads to the *N*-deprotected intermediate **9** and carbene **10**. Following the literature proposal for the *N*-debenzylation of indole derivatives,[27] subsequent evolution of **10** is assumed to occur by its addition to unreacted **8** to give anion **11**, which would then finally afford a second molecule of **9** and compound **12** by β-elimination. Finally, a domino alkylation−cyclization sequence would lead to the observed products **7** through the intermediacy of iminium derivative **13** (Scheme 4).

Scheme 4. Proposed Mechanism for the Anionic Domino Process Leading to Diprenylated Hexahydropyrrolo[2,3-*b*]indole Systems



In summary, we describe a new anionic domino process comprising four individual reactions that allows the efficient, one-pot synthesis of compounds derived from the pyrroloindoline architecture that contain prenyl substituents at the C-3a and N-8 positions. The scope of this sequence of reactions has been explored by its application to the preparation of a precursor to *N*-prenyltryprostatin B and to a formal total synthesis of (±)-debromoflustramine B.

Acknowledgment. We thank MEC (Grant No. CTQ2006-10930) and UCM-CAM (Grupos de Investigación, Grant No. 920234) for financial support.

Supporting Information Available: Representative experimental procedures, characterization data, and selected spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Clean spectra of these compounds were obtained in DMSO-d_6 at 80 °C (see the Supporting Information).

(24) For conformational studies of some *F. foliacea* alkaloids based on NMR and molecular modeling techniques, see: Morales-Ríos, M. S.; Santos-Sánchez, N. F.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *Magn. Reson. Chem.* **2002**, *40*, 677.

(25) Compounds closely related to **9** have been transformed into the corresponding *N*-methylamines by reductive cleavage of the carbamate group followed by methylation under reductive amination conditions. See refs 20a and 21c.

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