J|A|C|S COMMUNICATIONS

Published on Web 03/10/2009

Concise Enantioselective Synthesis of ent-Malbrancheamide B

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There is a growing family of fungi-derived alkaloids whose members feature a bicyclo[2.2.2]diazaoctane core as part of a more complex polycyclic structure.[1] Important examples include brevianamide B (**1**), paraherquamide A (**2**), stephacidin A (**3**), and the most recently added members of the group, the malbrancheamides **4** and **5** (Figure 1).[2]

These compounds combine synthetically challenging structures, intriguing biosynthetic origins, and, in many cases, potent biological activities. The malbrancheamides, recently isolated from the fungus *Malbranchea aurantiaca*, are unique in having a chlorinated indole nucleus, and compound **4** was shown to be a new calmodulin (CaM) inhibitor.[2a,3]

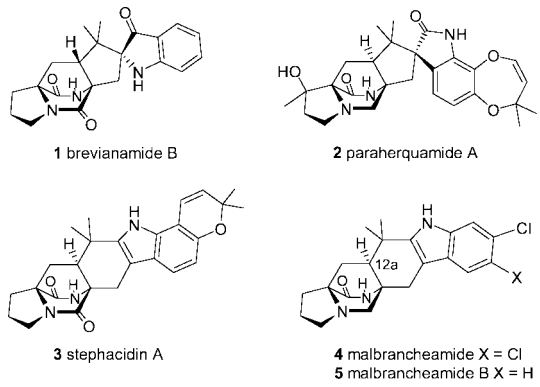


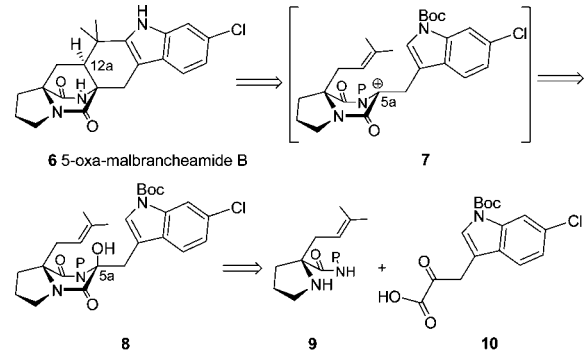
Figure 1. Structures of natural products containing bicyclo[2.2.2]-diazaoctane.

The synthesis and biosynthesis of these compounds have been probed for many years, most notably by the Williams group, which has established a biomimetic IMDA strategy as a concise access to several members of this family of natural products, including malbrancheamides **4** and **5**.[4] However, because of the prochiral nature of the key intermediate in this sequence, the products are necessarily racemic.[5] Herein, we describe a new and general enantioselective approach to this type of compound, which we illustrate with a concise synthesis of ent-malbrancheamide B (**5**).

Our chosen penultimate synthesis intermediate was 5-oxamalbrancheamide B (**6**), which had been previously synthesized by Williams[4a] and shown to be reduced to **5** by the action of DIBAL-H (Scheme 1). This compound would be formed by double cyclization of hydroxydiketopiperazine (hydroxy-DKP) compound **8** via the unusual α-amido *N*-acyliminium species **7**.

Model studies indicated that such a cyclization should predominantly give the stereochemistry at C-12a required for the malbrancheamides.[6] The key intermediate **8** would be

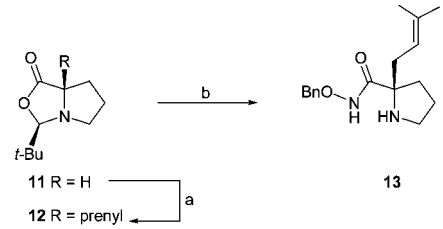
Scheme 1. Retrosynthetic Analysis of Malbrancheamide B



generated by union of a suitably protected prenylated proline amide **9** (P = protecting group) and the indole-3-pyruvic acid derivative **10**. As several other groups have done, we initially chose to explore our synthesis in the unnatural series, because of the relative cheapness of L-proline.

Potentially suitable proline amide derivatives conforming to the generic structure **9** were readily available using the Seebach "self-reproduction of chirality" approach.[7] After exploring a number of alternatives, we settled on the use of the *O*-benzylhydroxamic acid derivative **13**, which is easily prepared from the "Seebach acetal" **11** via prenylated derivative **12** (Scheme 2).[8]

Scheme 2. Synthesis of Hydroxamic Acid Derivative **13**a



[a] Reagents and conditions: (a) LDA, THF, −78 °C, prenyl bromide, 76%; (b) $BnONH_2$, *n*-BuLi, THF, −78 °C, 75%.

Attempts at direct coupling of such proline amides with pyruvic acid **10** were presumably thwarted by the intervention of the enol form of the keto acid, which completely undermined the usual amide-forming protocols.[9] To avoid this problem, we employed the tactic of coupling an enol ether derivative corresponding to **10**.

Readily prepared aldehyde **14** was condensed with ester **15** to give aldol adduct **16** as a 4:1 mixture of diastereomers (Scheme 3). This compound underwent ready elimination via mesylation and base treatment to give an unsaturated ester, which was then hydrolyzed to give acid **17** (3:1 *Z*/*E*).

With the troublesome α-keto acid function of the indole pyruvic acid system suitably protected, the required coupling with proline

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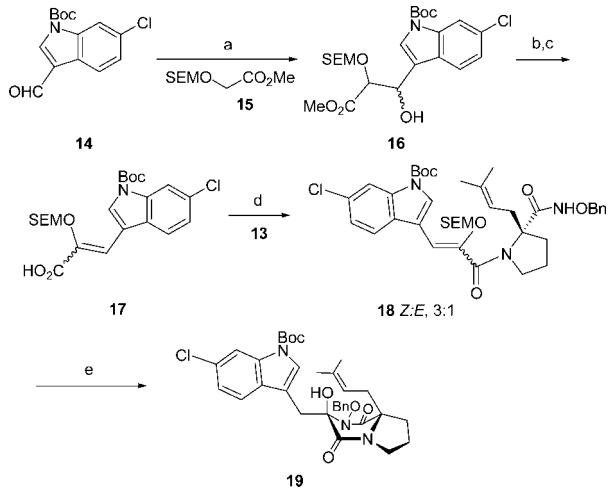
10.1021/ja900688y CCC: $40.75

Scheme 3. Amide Coupling and DKP Formation[a]



[a] Reagents and conditions: (a) LHMDS, THF, −78 °C, 97%; (b) MsCl, CH_2Cl_2, Et_3N, then DBU, 91%; (c) LiOH, THF(aq), 58% (+14% N−H derivative + 12% rec SM); (d) HATU, *i*-$PrNEt_2$, MeCN, 74%; (e) *i*-PrOH, CBr_4, 50 °C, 52%.

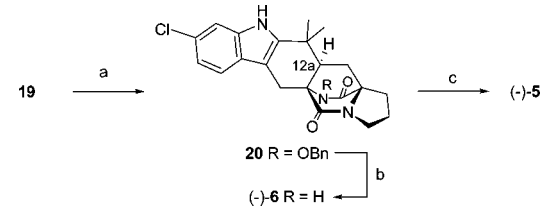
amide **13** proceeded smoothly to give the anticipated OSEM ether product **18** as a mixture of *Z* and *E* isomers. Unexpectedly, SEM ether **18** resisted all attempts at deprotection using TBAF, TBAT, or HF-py.[10] After screening alternative acidic conditions, we eventually established that conversion of **18** into the key DKP **19** was possible, albeit in moderate yield, by use of CBr_4 in warm *i*-PrOH.[11]

With our key precursor DKP **19** in hand, we were delighted to observe that treatment of this compound with TMSOTf in CH_2Cl_2 resulted in smooth cyclization accompanied by loss of the indole NBoc group (Scheme 4). The desired polycyclic DKP **20** was obtained in 64% yield as a separable 4:1 mixture favoring the desired C12a epimer.[12] The major product arises from a preferred conformation of the intermediate **7** in which the prenyl group is oriented away from the OBn group on nitrogen.

Conversion of **20** into ent-malbrancheamide B (**5**) was then accomplished by reductive cleavage of the N−OBn linkage using SmI_2 in the presence of excess LiCl[13] followed by reduction according to the published Williams protocol. Our synthetic ent-malbrancheamide B (**5**) displayed spectroscopic properties fully in accord with those published previously.[14]

The efficiency of our total synthesis of ent-malbrancheamide B is, at present, compromised by several steps having modest yields, especially the SEM removal leading to **19**, but the route is very concise, requiring only 10 steps from commercial 6-chloroindole. Further streamlining of the route and its application to other natural products in this family are underway.

Scheme 4. Completion of the Malbrancheamide B Synthesis[a]



[a] Reagents and conditions: (a) TMSOTf, CH_2Cl_2, 0 °C to RT, 64%, 4:1 dr; (b) SmI_2, LiCl, THF, RT, 70%; (c) DIBAL-H, toluene, RT, 63% (74%[4a]).

Acknowledgment. We acknowledge Pfizer, Sandwich, U.K., and the Universities of Nottingham and Birmingham for support of F.F. through a studentship. We also thank Dr. Richard Webster (Pfizer) for his support of this work.

Supporting Information Available: Complete experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) A number of alternatives, including *N*-PMB, *N*-DMB, and *N*-allyl were prepared but either proved incompatible with subsequent steps or could not be removed efficiently later on.
(9) Non-benzylic types of pyruvic acids can be coupled effectively. See: Siwicka, A.; Wojtasiewicz, K.; Rosiek, B.; Leniewski, A.; Maurin, J. K.; Czarnocki, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 975.
(10) More usual ethers, including OMe and OPMB types, were tried first, but this system appears to be unexpectedly stable toward acidic reagents, presumably because of the push−pull nature of the extended conjugated indole carboxamide. Forcing conditions resulted in destruction of the starting materials with no constructive cyclization.
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JA900688Y