ORGANIC LETTERS

2011
Vol. 13, No. 2
347−349

Concise and Protective Group-Free Syntheses of (±)-Hamigeran B and (±)-4-Bromohamigeran B†

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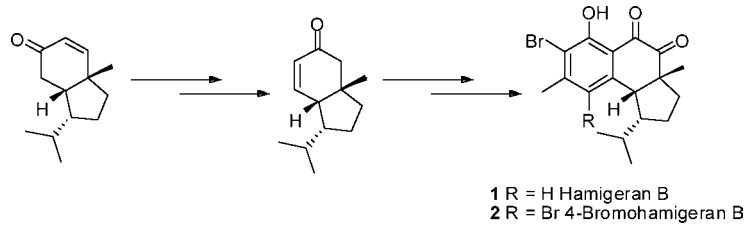
Received November 16, 2010

ABSTRACT



1 R = H Hamigeran B
2 R = Br 4-Bromohamigeran B

Concise and protective group free syntheses of (±)-hamigeran B and (±)-4-bromohamigeran B are reported. The key reactions include an enone migration and a Diels−Alder cyclization to provide the requisite tricyclic skeleton.

Hamigeran B (**1**) and 4-bromohamigeran B (**2**) were first isolated from the poecilosclerid sponge *Hamigera tarangensis* Bergquist and Fromont (family Anchinoidae, syn. Phorbasidae) and reported by Cambie and co-workers in 2000.[1] While most members of the hamigeran family of natural products, including **2**, possess mild antitumor activity toward P-388, hamigeran B also possesses potent antiviral activity. The challenging nature of its unique structure has been highlighted by recent syntheses of hamigeran B.[2−7] Herein we report an alternative synthesis to hamigeran B and also to 4-bromohamigeran B that is extremely concise and does not require the use of protective groups.

A similar feature of the previous syntheses is that the aromatic A ring is already present as part of their respective starting precursors, upon which the B and C rings are incorporated (Figure 1). In contrast, we sought to first construct the B and C rings and envisaged an intermolecular Diels−Alder cyclization as the key step in forming the A ring toward the latter part of the synthesis (Scheme 1). Although studies toward a direct route to **4** via cyclopen-

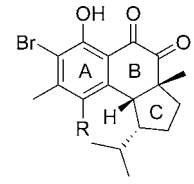


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Figure 1. Hamigeran B and 4-bromohamigeran B listing the A−C rings.

† Dedicated to the memory of the late Professor Edward Piers.

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(1) Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79.

(2) (a) Nicolaou, K. C.; Gray, D.; Tae, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3675. (b) Nicolaou, K. C.; Gray, D.; Tae, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3679. (c) Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613.

(3) (a) Clive, D. L. J.; Wang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3406. (b) Clive, D. L. J.; Wang, J. *Tetrahedon Lett.* **2003**, *44*, 7731. (c) Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2004**, *69*, 2773. (d) For a review of pre-2005 syntheses, see: Clive, D. L. J.; Wang, J. *Org. Prep. Proc. Int.* **2005**, *37*, 1.

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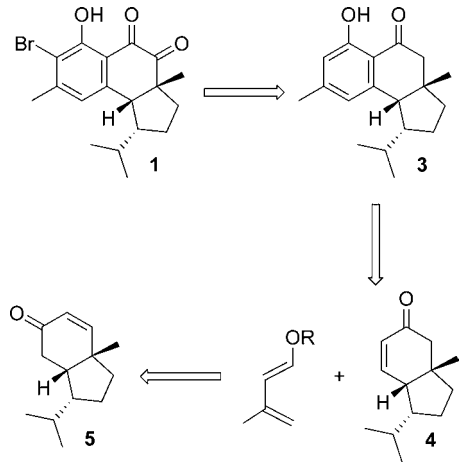
10.1021/ol102780s
Published on Web 12/02/2010

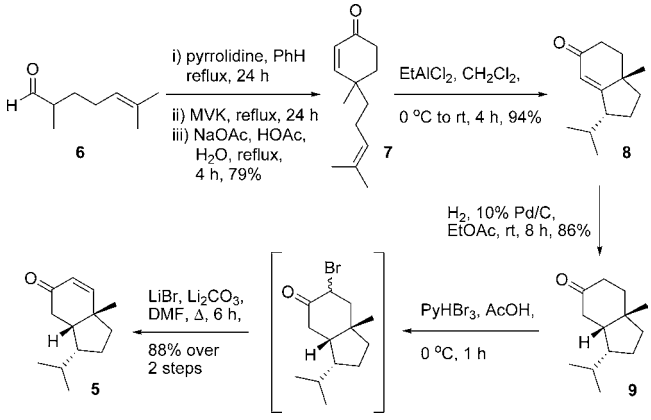
Scheme 1. Retrosynthetic Analysis of Hamigeran B



tenone annulation chemistry developed in the Piers laboratory[8] showed limited success, we were able to take advantage of some previously reported work in order to build the desired enone **4** through an enone migration protocol on enone **5**.[9]

Enone **5** was synthesized on the basis of work performed by Snider and co-workers[10] and by Corey and Engler[11] in order to obtain bicyclic ketone **9** stereospecifically, containing the requisite relative stereochemistry of the three contiguous chirality centers in hamigeran B (Scheme 2). Introduction

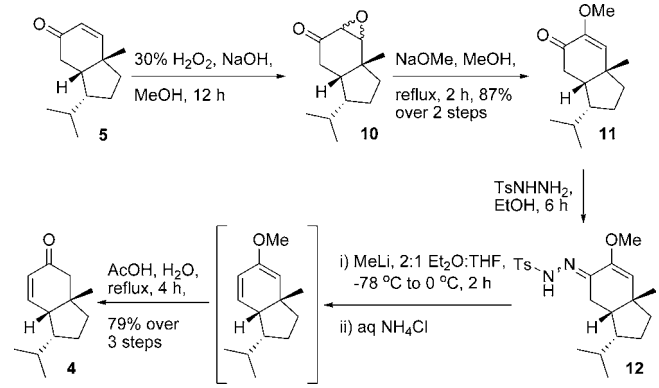
Scheme 2. Synthesis of Enone **5**



of the unsaturation was accomplished by the regioselective α-bromination of **9** using pyridinium tribromide in acetic acid,[12] followed by elimination of HBr with lithium carbonate and lithium bromide in hot dimethylformamide,[13] to provide the desired enone **5** in 88% yield.[14]

With enone **5** in hand, a Reusch enone migration[15] protocol was performed (Scheme 3).[16] Enone **5** was treated

Scheme 3. Enone Migration Protocol



with 30% hydrogen peroxide and catalytic sodium hydroxide in methanol to furnish epoxide **10**. Without purification, the epoxide was opened with sodium methoxide in methanol, providing the α-methoxy enone **11** in 87% yield over two steps. Enone **11** was then treated with tosyl hydrazide in ethanol to furnish the hydrazone **12** as a mixture of geometric isomers. Again without purification, hydrazone **12** was subjected to Shapiro conditions[17] using 4 equiv of methyllithium at −78 °C and then warming from −78 to 0 °C. An in situ hydrolysis of the resulting methyl enol ether with refluxing aqueous acetic acid afforded the desired enone **4** in 79% yield from **11**.

Surprisingly, enone **4** was a poorly reactive dienophile and required the use of ketene acetal **13** as the reactive diene. Acetal **13** was synthesized from 3,3-dimethylacrylic acid in 77% yield following a procedure developed by Boehler and Konopelski (Scheme 4).[18]

Diene **13** and dienophile **4** were mixed in a 4:1 ratio, respectively, with 10 mol % of K_2CO_3 (as a proton scavenger) and heated to 150 °C in a sealed vial for 4 days

(7) For approaches to hamigeran B, see: (a) Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2003**, *44*, 7049. (b) Cai, Z.; Harmata, M. *Org. Lett.* **2010**, *12*, 5668.

(8) Piers, E.; Cook, K. L.; Rogers, C. *Tetrahedron Lett.* **1994**, *35*, 8573.

(9) Enone **5** had been previously reported as a minor byproduct: Attah-Poku, S. K.; Chau, F.; Yadav, V. K.; Fallis, A. G. *J. Org. Chem.* **1985**, *50*, 3418.

(10) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.

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(16) Each of the intermediates **10** and **12** were used in the following transformation without purification and were not fully characterized. All other compounds were isolated, purified, and exhibited spectra in accord with assigned structures and gave satifactory elemental analyses or molecular mass determinations.

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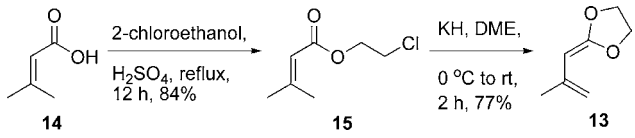
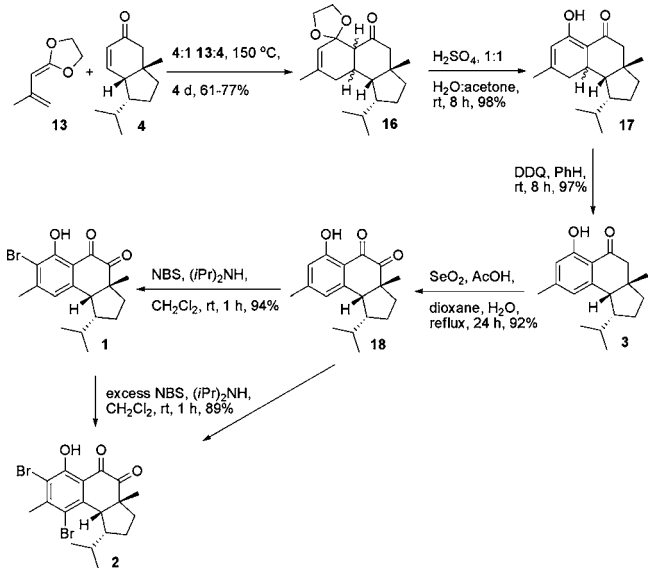
(18) (a) Konopelski, J. P.; Boehler, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4515. (b) Boehler, M. A.; Konopelski, J. P. *Tetrahedron* **1991**, *47*, 4519.

Scheme 4. Preparation of Ketene Acetal **13**



to afford the Diels−Alder adduct **16** as primarily a single diastereomer (Scheme 5),[19] with yields ranging from 61%

Scheme 5. Diels−Alder Cyclization and End Game



(83% based on recovered starting material) to 77% (complete consumption of the enone). Heating of the reaction for longer periods in order to completely consume the enone tended to lower the yield. Furthermore, use of fewer equivalents of diene resulted in a sluggish reaction. For example, when **13**: dienophile **4** were mixed in a 2:1 ratio, respectively, for 4 d at 150 °C, only 23% conversion was observed.

With the cyclized compound **16** in hand, hydrolysis of the ketal functionality[20] using sulfuric acid in wet acetone gave enol **17** quantitatively. Compound **17** was then aromatized using DDQ[21] in benzene at rt to give ketone **3** also in high yield. The 1,2-diketone functionality was introduced using selenium dioxide[22] with catalytic acetic acid in refluxing wet dioxane to form **18** in 92% yield.

Careful *o*-bromination of the phenol using NBS with diisopropylamine in methylene chloride[23] afforded hamigeran B, whose spectral data were in agreement with reported data.[1] Use of an excess of NBS with rapid addition to the phenol resulted in the dibromination of phenol **18** to form 4-bromohamigeran B, whose spectral data were also in agreement with reported data.[1]

In summary, we report a novel, concise, and stereospecific synthesis of (±)-hamigeran B and of (±)-4-bromohamigeran B that does not require the use of any protective groups.

Acknowledgment. We thank NSERC and AHFMR for funding.

Supporting Information Available: Full experimental details and spectroscopic data for compounds **1**−**5**, **7**−**13**, and **15**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102780S

(19) Approximate 10:1 ratio by ^{1}H NMR. As the stereochemistry of the newly formed stereogenic centers of **16** were to be destroyed through subsequent aromatization, no attempt was made to determine their configuration.

(20) Note that the use of the acetal functionality in **13** was to both activate the diene and to provide the enol functionality in the cyclized product. Consequently, the ketal formed in **16** as a result of the Diels−Alder cyclization does not actually serve as a protective group.

(21) For a review, see: Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153.

(22) For a review, see: Rabjohn, N. *Org. React.* **1976**, *24*, 261.

(23) Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576.