ORGANIC LETTERS

1999
Vol. 1, No. 9
1471−1473

Cytotoxic Alkaloids Motuporamines A–C: Synthesis and Structural Verification

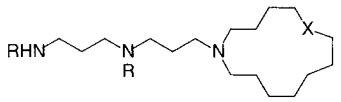
William P. D. Goldring* and Larry Weiler

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia V6T 1Z1, Canada

billg@chem.ubc.ca

Received September 8, 1999

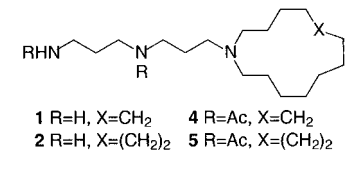
ABSTRACT



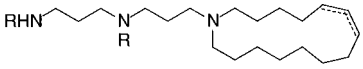
X=CH_2, $(CH_2)_2$, CH=$CHCH_2$, CH_2CH=CH
R=H, Ac

The unusual structure and biological properties of the marine alkaloids motuporamines A–C, as well as the uncertainty as to the position of the olefin within the ring of motuporamine C, led us to synthesize these compounds. The strategy utilized the ring-closing metathesis reaction to form the 14- and 15-membered rings and Michael addition and amidation chemistry to introduce the spermine-like unit. The syntheses, structure assignment verifications, and also the determination of the position of the olefin in motuporamine C are described.

The cytotoxic alkaloids motuporamines A (**1**), B (**2**), and C (**3**) were recently isolated from the marine sponge *Xestospongia exigua* (Kirkpatrick).[1] Crude mixtures of motuporamines A−C were not readily separated. Preparation of the diacetylated derivatives, which were easily separated by reversed-phase HPLC, provided pure samples of diacetylmotuporamines A (**4**), B (**5**), and C (**6**). The structures of **4**, **5**, and **6** (Figure 1) were elucidated via analysis of spectral data. However, it was not possible to determine the position of the double bond within the macrocyclic ring of **6**, although it was determined to have the *Z* configuration. Analysis of the NMR data obtained for **6** eliminated all of the positional isomers except **6a** and **6b**.



1 R=H, X=CH_2 **4** R=Ac, X=CH_2
2 R=H, X=$(CH_2)_2$ **5** R=Ac, X=$(CH_2)_2$



3 R=H, **6** R=Ac

Figure 1. Motuporamines A (**1**), B (**2**), and C (**3**).

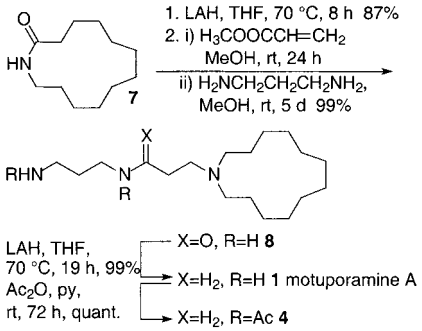
The unusual structure and biological properties of the motuporamines combined with the unresolved structure ambiguity in motuporamine C led us to synthesize these compounds. During the preparation of this manuscript the synthesis of motuporamines A and B appeared.[2] In an attempt to resolve the structural ambiguity in motuporamine C, compounds **6a** and **6b** were prepared. A general two-part synthetic strategy involving the formation of the macrocyclic amine in the first stage, and the formation of a spermine-like unit from the nitrogen of this ring in the second stage was employed in the synthesis of each compound. Recent developments in our laboratory regarding the formation of macrocyclic lactams via ring-closing metathesis (RCM)[3] led us to form the ring portions of **5**, **6a**, and **6b** by this method.

The synthesis of motuporamine A (**1**) (Scheme 1) began with the reduction of 2-azacyclotridecanone (**7**) with LAH. The resulting macrocyclic amine was reacted with methyl

(1) Williams, D. E.; Lassota, P.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 4838.
(2) Baldwin, J. E.; Vallmer, H. R.; Lee, V. *Tetrahedron Lett.* **1999**, *40*, 5401.
(3) Goldring, W. P. D.; Hodder, A. S.; Weiler, L. *Tetrahedron Lett.* **1998**, *39*, 4955.

10.1021/ol991029e CCC: $18.00
Published on Web 09/28/1999

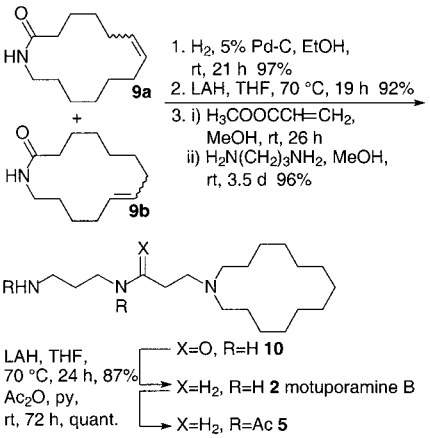
Scheme 1



acrylate. After removal of the solvent and excess reagent in vacuo, the resulting β-amino ester was reacted with a 10-fold excess of 1,3-diaminopropane.[4] Evaporation of the solvent and excess reagent in vacuo provided analytically pure amide **8**. Compound **8** was reduced with LAH to provide motuporamine A (**1**) in an overall yield of 85%. Finally, reaction of **1** with acetic anhydride in pyridine gave diacetylmotuporamine A (**4**) in quantitative yield.[5]

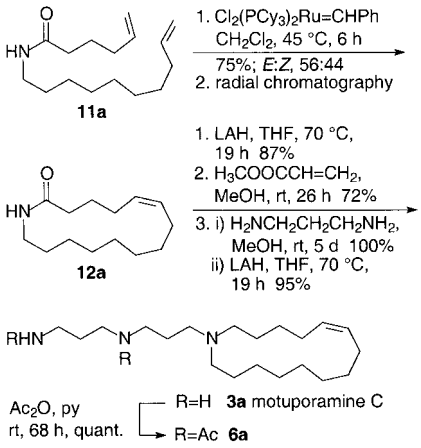
The synthesis of motuporamine B (**2**) (Scheme 2) began with the hydrogenation of a mixture of 2-azacyclotetradecenones (**9a** and **9b**), independently formed by RCM,[3] to provide the saturated 14-membered lactam. The lactam was converted into motuporamine B (**2**), using the same sequence of steps as in the synthesis of **1** from **7** (Scheme 1), in an overall yield of 75%. Finally, reaction of **2** with acetic anhydride in pyridine gave diacetylmotuporamine B (**5**) in quantitative yield.

Scheme 2



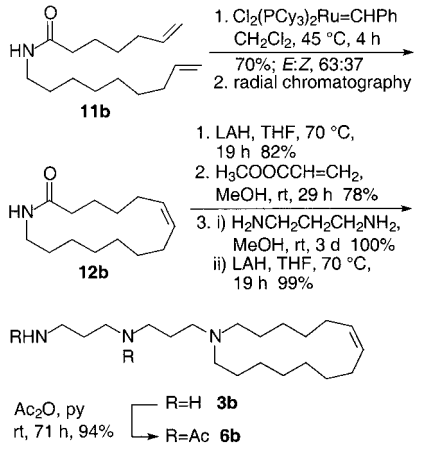
The synthesis of **3a** (Scheme 3) began with the formation of the 15-membered lactam from diene−amide **11a** via RCM, using 5 mol % $Cl_2(PCy_3)_2Ru{=}CHPh$. Following chromatographic separation of the *E* and *Z* isomers,[6] the *Z* lactam **12a** was converted into **3a**, using the same sequence of steps as in the synthesis of **1** from **7** (Scheme 1), in an overall yield of 45%. Finally, reaction of **3a** with acetic anhydride in pyridine gave **6a** in quantitative yield.

Scheme 3



Compound **3b** was formed from **11b** (Scheme 4), following the same sequence of steps as in the synthesis of **3a** from **11a** (Scheme 3), in an overall yield of 44%. Finally, reaction of **3b** with acetic anhydride in pyridine gave **6b** in 94% yield.

Scheme 4



The ^1H, ^{13}C, COSY, HMQC, and HMBC NMR data, as well as mass spectral data, for compounds **4** and **5** was compared with the corresponding data reported for authentic samples of diacetylmotuporamines A and B,[1] respectively. These comparisons allowed us to verify the structures as assigned.

The NMR and mass spectral data for compounds **6a** and **6b** were compared with the corresponding data reported for an authentic sample of diacetylmotuporamine C.[1] This comparison led us to conclude that compound **6a** and the

(4) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Macromolecules* **1986**, *19*, 2466.

(5) All new compounds were characterized by ^1H and ^{13}C NMR, IR, and LRMS and HRMS.

(6) Morris, L. J. *Chem. Ind.* **1962**, 1238.

authentic sample of diacetylmotuporamine C were identical. Thus, the position of the double bond within the authentic sample of motuporamine C is as it appears in **3a**.

The synthesis of **1**, **2**, **3a**, and **3b** and their diacetylated derivatives **4**, **5**, **6a**, and **6b** proceeded in excellent yields, using a small number of steps, and without the use of protective groups. The synthesis of **3a**, **3b**, **6a**, and **6b** represents the first such synthesis of these compounds and demonstrated the utility of ring-closing metathesis to form 15-membered lactams. The comparison of spectral data from the synthetically prepared compounds to that of the authentic samples of diacetylmotuporamines A−C allowed us to verify the assigned structure of each alkaloid. In addition, the position of the double bond within motuporamine C was determined to be in the same position as in **3a**.

Acknowledgment. We thank Professor R. J. Andersen and Dr. Michael Pungente for assistance in the preparation of this manuscript, and Dr. David E. Williams for providing the NMR data of authentic diacetylmotuporamines A−C. We are grateful for the financial support of the Natural Sciences and Engineering Research Council of Canada.

OL991029E