ORGANIC LETTERS

2007
Vol. 9, No. 26
5357−5359

Synthesis of (+)-Didemniserinolipid B via Ketalization/Ring-Closing Metathesis

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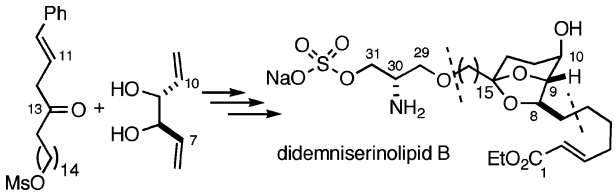
Received October 8, 2007

ABSTRACT



A modular synthesis of didemniserinolipid B is reported. Central to this synthesis was the use of a ketalization/ring-closing metathesis (K/RCM) strategy to establish the 6,8-dioxabicyclo[3.2.1]octane core. The C10 axial alcohol was established via a selective epoxidation, followed by reductive *trans*-diaxial epoxide opening. The serinol and unsaturated ester side chains were introduced by a Williamson etherification and cross metathesis, respectively.

Didemniserinolipid B (**1** in Figure 1) is one of three unusual serinolipids isolated from a cytotoxic extract of the tunicate *Didemnum* sp. by Jiménez and co-workers.[1] Ultimately, none of these purified serinolipids possessed any cytotoxicity. Subsequently, Faulkner and co-workers discovered a related macrocycle-containing serinolipid, cyclodidemniserinol trisulfate, an inhibitor of HIV-1 integrase.[2] A synthesis of didemniserinolipid B has been reported by Ley and co-workers.[3] Their work resulted in both the elucidation of the stereochemistry within the serinol fragment and in a structural revision with the identification of an *O*-sulfate at C31.

Our interest in didemniserinolipid B was stimulated by the central 6,8-dioxabicyclo[3.2.1]octane core. Traditional routes to such bicyclic ketals involve intermolecular carbon−carbon bond formation followed by intramolecular ketalization via dehydration of a keto diol. Recently, we have developed a nontraditional approach to these structures which reverses this sequence.[4] One advantage of intermolecular ketalization followed by intramolecular carbon−carbon bond formation via ring-closing alkene metathesis[5] (K/RCM) is that the use of protecting groups can be minimized. Fur-

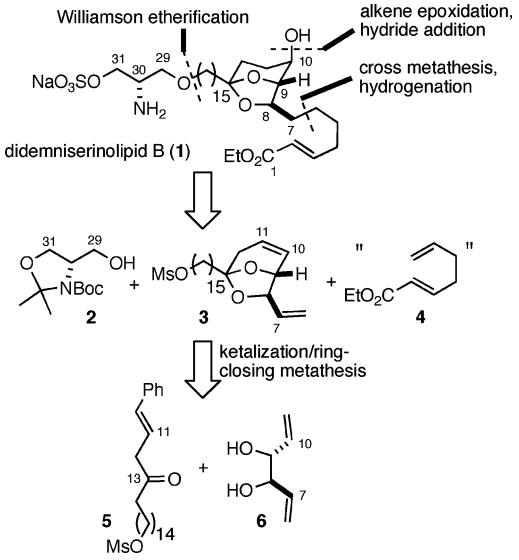


Figure 1. Didemniserinolipid B structure and retrosynthesis.

(1) González, N.; Rodriguez, J.; Jiménez, C. *J. Org. Chem.* **1999**, *64*, 5705.

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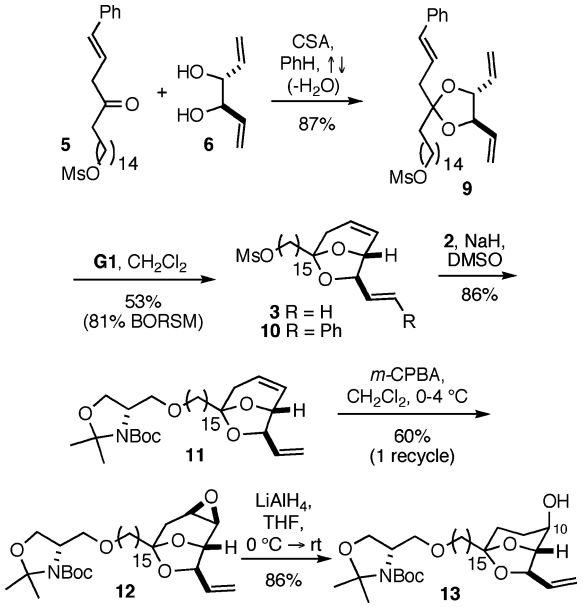
10.1021/ol702454m CCC: $37.00
Published on Web 11/30/2007

thermore, stereoselective functional group introduction is facilitated by the rigid, facially biased dioxabicyclic core. In the context of didemniserinolipid B, we felt that by first constructing the bicyclic ketal core via K/RCM we could develop an efficient and modular synthesis which could be amenable to diversification of the chains appended to this core for future analogue preparation.

Our retrosynthesis is shown in Figure 1. We imagined installing the C1−C6 α,β-unsaturated ester fragment via an alkene cross metathesis (CM) followed by saturation of the isolated C6−C7 double bond. The axial C10 alcohol would arise from a substrate-controlled epoxidation of the endocyclic alkene in **3**,[6] followed by hydride delivery via *trans*-diaxial opening of the epoxide (Scheme 1).[7] The C29−C31

Scheme 1. Synthesis of Bicyclic Ketal **3**, Williamson Etherification, and Installation of C10 Alcohol



serinol fragment would be installed via Williamson etherification[8] involving known serinol derivative **2**[9] and mesylate **3**. Bicyclic ketal **3** would be directly accessible from a K/RCM sequence involving ketone **5** and C_2-symmetric (*R*,*R*)-diene diol **6**.[10] While providing a rapid and convenient route to **3**, K/RCM has additional strategic advantages in that the C_2-symmetric diene diol **6** is desymmetrized, and one of the vinyl groups is left unreacted and thus available for later CM with **4**.

Our synthesis commenced with the combination of ketone **5** and diene diol **6** with azeotropic removal of water to provide ketal **9** in 87% yield (57% overall yield from **7**).[11] Two features of ketone **5** deserve comment. The γ-phenyl group was essential, as it promoted a 5:1 mixture of β,γ- to α,β-alkenes. Additionally, the mesylate served both as an alcohol protecting group and as a reactive leaving group for subsequent etherification.

Ketal **9** underwent RCM upon treatment with Grubbs' first generation metathesis catalyst (**G1**, Figure 2) to afford

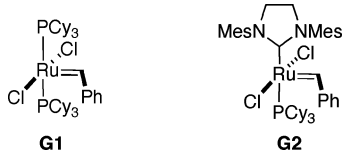


Figure 2. Grubbs first and second generation metathesis catalysts.

bicyclic acetal **3** (53% isolated, 81% BORSM). Prolonged reaction times led to decreased isolated yields due to dimerization of **3** and the formation of significant amounts of **10**, resulting from cross metathesis of **3** with the styrene byproduct of the RCM.

Etherification of **3** with the sodium alkoxide of **2** proceeded cleanly to yield **11** with only trace amounts (~3%) of elimination product. Bicyclic diene **11** underwent chemo- and stereoselective epoxidation at the endocyclic double bond upon treatment with 1 equiv of *m*-CPBA and warming from 0 to 4 °C overnight. After one recycle of recovered **11**, epoxide **12** could be obtained in 60% yield. *trans*-Diaxial reductive epoxide opening was then achieved by treatment of *exo*-epoxide **12** with LAH in THF, thus providing the C10 axial alcohol **13** in 86% yield.

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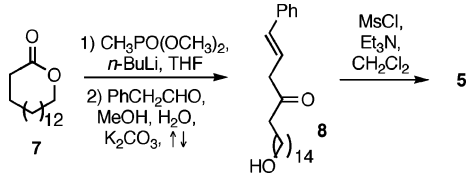
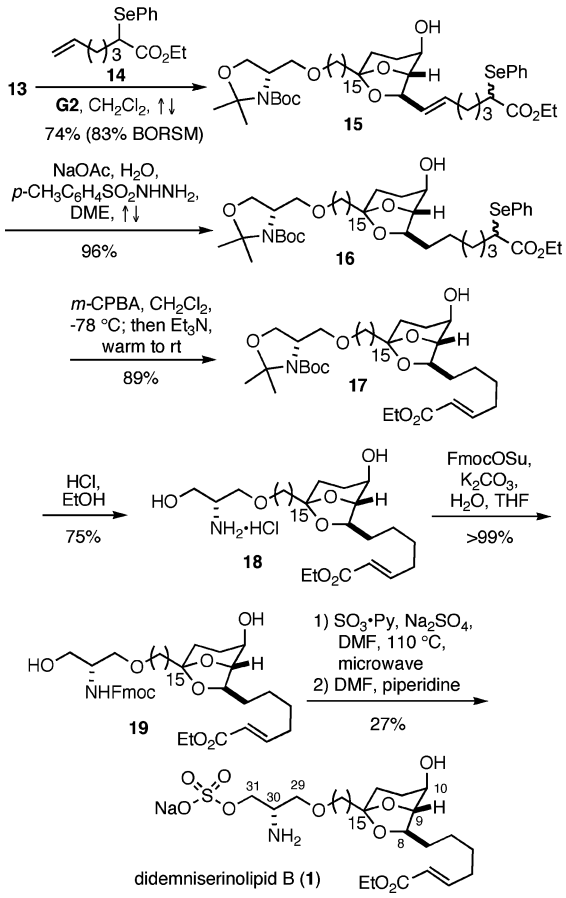
(10) Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 71.

(11) 16-Hexadecanolide **7** was opened with lithiated dimethyl methylphosphonate to generate a β-ketophosphonate and immediately subjected to Horner−Wadsworth−Emmons olefination with phenylacetaldehyde to yield β,γ-unsaturated ketone **8**. The presence of the phenyl ring promoted isomerization of the double bond from the α,β- to the β,γ-position, which was essential for the required RCM. Standard mesylation conditions provided **5**.



Completion of the synthesis of didemniserinolipid B required elaboration of the vinyl group in **13** to the C1−C7 enoate-containing side chain. We initially explored the alkene cross metathesis of **13** and **4**[12] (proceeding in 57% yield, not shown) but were unable to selectively hydrogenate the $\Delta^{6,7}$ double bond without concomitant reduction of the α,β-unsaturated ester. A successful alternative route to install the correct C1−C7 functionality is shown in Scheme 2. In the course of an isomigrastatin synthesis, Danishefsky reported that selenides were compatible with RCM conditions.[13] Cross metathesis of **13** with racemic alkenyl selenide **14**[13] proceeded in 74% yield to give only the *E* isomer of **15** as an inconsequential 1:1 diastereomeric mixture using second generation Grubbs' catalyst (**G2**).[14] Although attempts to reduce the C6−C7 alkene in **15** were unsuccessful with Pd/C and 1 atm of hydrogen, **16** was obtained via diimide reduction.[15] Selenoxide elimination of **16** promoted by *m*-CPBA introduced the α,β-unsaturation to provide **17**.[16] The serinol moiety was then liberated using 1 N HCl in EtOH to afford **18**, the HCl salt of Jiménez's originally proposed didemniserinolipid structure. The final three steps to didemniserinolipid B followed those described in the Ley synthesis.[3] The amine was masked in nearly quantitative yield with an Fmoc protecting group. Treatment of **19** with 1 equiv of SO_3•Py at 110 °C for 1 h under microwave irradiation,[17] followed by Fmoc deprotection with piperidine, provided (+)-didemniserinolipid B (**1**).[18] Synthetic (+)-didemniserinolipid B thus obtained was identical with the natural product by ^{1}H and ^{13}C NMR, MS, IR, and optical rotation.[19]

Scheme 2. Completion of Didemniserinolipid B



In summary, didemniserinolipid B has been prepared in 2.6% overall yield via a concise route with a longest linear sequence (LLS) of 12 steps from ketone **5** and diene diol **6** (15 step LLS from commercially available materials). The use of K/RCM to establish the central bicyclic ketal facilitated a synthesis wherein the serinol and C1−C7 side chains could be appended in a modular fashion. This total synthesis further showcases the merits of a K/RCM strategy in the construction of bicyclic ketals and their derivatives.[4]

Acknowledgment. Financial support for this work from NIH Grants GM069352 and CA108488 and NIH CBI training Grant T32 GM008505 (C.C.M.) is gratefully acknowledged, as is support of the departmental NMR facilities by grants from the NIH 1 S10 RR0 8389-01 and NSF CHE-9208463. We also thank Matt Dodge (University of Wisconsin−Madison) for obtaining the high-field ^{1}H and ^{13}C NMR data for synthetic **1**.

Supporting Information Available: Experimental procedures and NMR spectra for compounds **3**, **5**, **9**−**13**, and **15**−**19** and comparison of **1** with literature data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702454M

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(18) Ley and co-workers reported a two-step yield of 49% for this sequence. See ref 3.
(19) See the Supporting Information.