J|A|C|S COMMUNICATIONS

Published on Web 08/11/2010

Asymmetric Total Synthesis of Trilobacin via Organoselenium-Mediated Oxonium Ion Formation/SiO_2-Promoted Fragmentation

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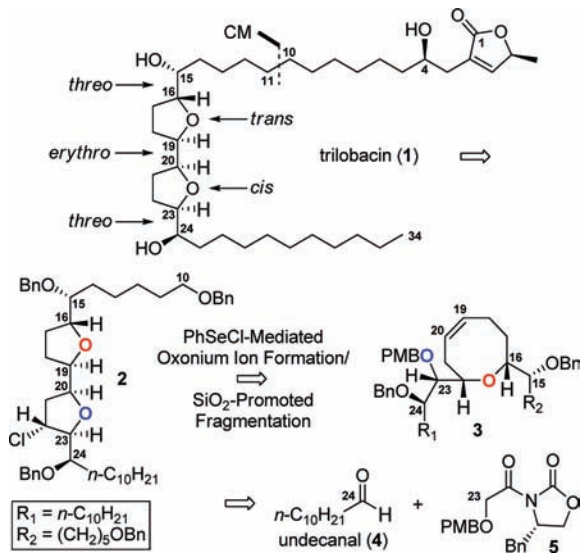
Abstract: An asymmetric total synthesis of trilobacin (**1**), an annonaceous acetogenin with potent anticancer activities, was accomplished wherein the construction of its *erythro*-bis(2,2′)-tetrahydrofuran core **2** featured a novel organoselenium-mediated oxonium ion formation/SiO_2-promoted fragmentation of α,α′-*cis*-oxocene **3**.

Trilobacin (**1**), the first known member of adjacent bis-tetrahydrofuran (THF) annonaceous acetogenins with a *threo*, *trans*, *erythro*, *cis*, *threo* backbone, was isolated from *Asmina triloba* by McLaughlin and co-workers in 1992.[1] The impressive potency of the annonaceous acetogenin against human solid-tumor cell lines, coupled with the fascinating structure and limited availability, has attracted considerable attention from the synthetic community.[2,3] In this communication we report an asymmetric total synthesis of trilobacin featuring a novel organoselenium-mediated oxonium ion formation/SiO_2-promoted fragmentation process for the construction of its *erythro*-bis(2,2′)-THF core.

As shown in Scheme 1, our strategy focuses on the elaboration of *erythro*-bis(2,2′)-THF fragment **2**, and the requisite butenolide chain would be incorporated using an existing method such as olefin cross-metathesis (CM) at the indicated position to achieve the target trilobacin (**1**).[4] We were intrigued by the possibility that key adjacent bis-THF intermediate **2** could in turn be constructed from α,α′-*cis*-oxocene **3** by a novel organoselenium-mediated oxonium ion formation/SiO_2-promoted fragmentation (*vide infra*). Furthermore, we were confident from previous experience[5] that the requisite oxocene substrate **3** could be synthesized from undecanal (**4**) and glycolate oxazolidinone **5**.

To commence the synthesis, Evans *syn*-aldol reaction[6] of oxazolidinone **5** with undecanal (**4**) furnished *syn*-aldol product **6** with the requisite C(23)/C(24) relative stereochemistry in 74% yield (Scheme 2). Reductive cleavage of the chiral auxiliary in **6** with $NaBH_4$ and subsequent regioselective DIBAL-H reduction of benzylidene acetal **7**, derived from the resultant 1,3-diol, afforded primary alcohol **8** (70%; 3 steps). Alcohol **8** was then smoothly transformed into α-alkoxy amide **9** in good overall yield (85%) by a three-step sequence: (1) DMSO oxidation, (2) chelation-controlled nucleophilic addition of allyltributylstannane,[7] (3) *O*-alkylation with *N*-(chloroacetyl) morpholine. Alkylation of **9** by successive treatment with LiHMDS and 3-butenol triflate then furnished homoallylated product **10** as a 1.4:1 mixture of *anti* and *syn* isomers (85%).[8] We reasoned that the desired oxymethine stereochemistry at C(16) could be secured subsequently due to the greater stability of the incipient α,α′-*cis*-oxocene vs the corresponding *trans* isomer.[5a,9] Ring-closing metathesis (RCM)[10] of diene **10** with the first-generation Grubbs' Ru catalyst, followed by application of our direct ketone synthesis protocol[11] to the resultant α-alkoxy morpholine amide **11** with 5-benzyloxypentylmagnesium bromide, yielded the desired α,α′-*cis*-oxocene ketone **12** in excellent overall yield (88%, 3 steps, α,α′-*cis*/*trans* = 17:1) after epimerization[5a,9] with aqueous KOH. Finally, L-Selectride reduction[11a,12] of α-alkoxy ketone

Scheme 1. Retrosynthetic Plan



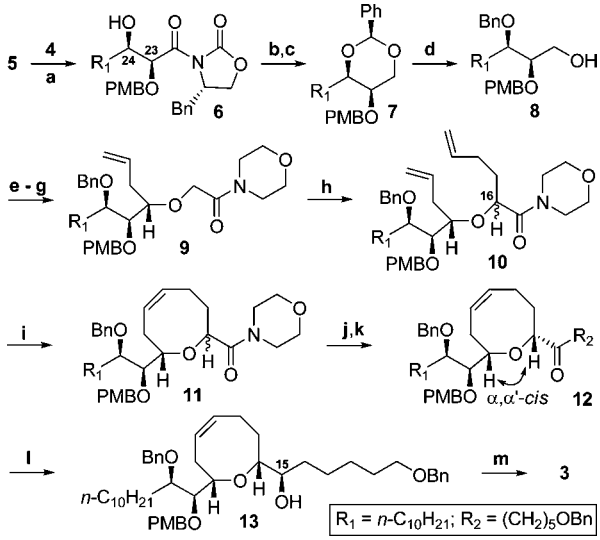
12 with Felkin−Ahn selectivity and subsequent protection of the resulting alcohol **13** as a benzyl ether gave rise to oxocene **3** (81%, 2 steps, 15*R*/15*S* = 34:1). This 13-step synthesis is quite efficient, and we have used it to generate multigram quantities of key intermediate **3**.

We next proceeded to address the construction of the crucial bis(2,2′)-THF core in **2**, which constitutes the keystone of our synthesis. After some experimentation, we were delighted to find that treatment of γ,δ-unsaturated PMB-ether **3** with PhSeCl (activated SiO_2[13]/K_2CO_3/CH_2Cl_2/rt/24 h) produced the desired *erythro*-bis(2,2′)-THF **2** in 83% yield in a stereo-, regio-, and chemoselective fashion, without the need for prior deprotection of the PMB group.[14] Upon exposure to PhSeCl, α,α′-*cis*-oxocene **3** would generate dioxatricyclic oxonium ion **A** by our organoselenium-based protocol, which consists of phenylseleno-etherification and activation of the phenylselenyl group with a second equivalent of reagent, followed by transannular ring closure as depicted in the Scheme 3.[15] *A priori*, nucleophilic attack by chloride at C(22), C(19), or C(16) in oxonium ion **A** could produce the desired bis(2,2′)-THF **2**, 2,8-dioxabicyclo[5.2.1]decane **B**, or 2,5-dioxabicyclo[2.2.1]-heptane **C**, respectively. The major kinetic product chloro ether **B**[16] is in equilibrium with oxonium ion **A**, which undergoes SiO_2-promoted fragmentation[17] to provide the desired bis(2,2′)-THF **2**.[18] Interestingly, the precursor that would give rise to a derivative of oxonium ion **A** that is unsubstituted at C(16) produced a 2,5-dioxabicyclo[2.2.1]heptane related to **C** as the major product.

With the requisite C(10)−C(34) segment in hand, global deprotection of **2** with concurrent removal of the chlorine using Raney-Ni gave triol **14** in 92% yield (Scheme 4). Chemoselective transformation of the primary hydroxyl group in **14** into terminal alkene **15** by Grieco's protocol[19] (88%) set the stage for the end

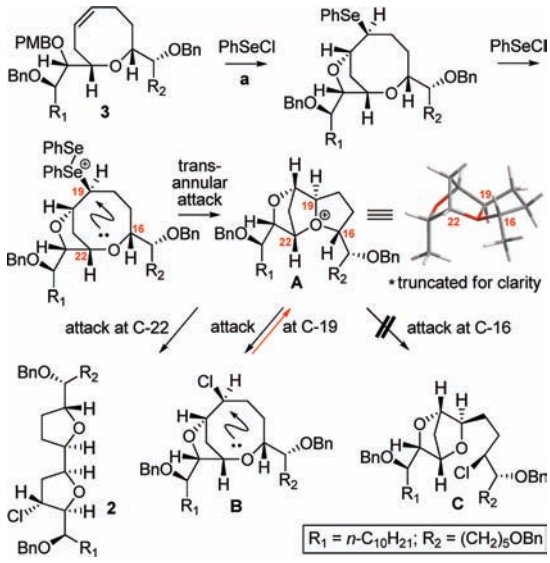
10.1021/ja106116v

Scheme 2. Synthesis of Key Oxocene Intermediate **3**[a]



[a] *Reagents and conditions*: (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C, 2 h, 74%; (b) $NaBH_4$, THF/H_2O (3:1), rt, 1 h, 85%; (c) $PhCH(OCH_3)_2$, PPTS, CH_2Cl_2, rt, 12 h, 90%; (d) DIBAL-H, CH_2Cl_2, −78 °C to rt, 3 h, 92%; (e) SO_3·pyridine, Et_3N, CH_2Cl_2/DMSO (4:1), 0 °C to rt, 1.5 h; (f) allyltributyltin, $MgBr_2$·Et_2O, CH_2Cl_2, −78 °C to rt, 2 h 86% (2 steps), *syn* only; (g) $ClCH_2CON(CH_2CH_2)_2O$, NaH, DMF, 0 °C to rt, 2 h, 99%; (h) LiHMDS, CH_2=$CHCH_2CH_2OTf$, THF, −78 °C to rt, 15 min, 85% (88% BRSM), *anti*/*syn* = 1.4:1; (i) $(Cy_3P)_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, 2 h, then DMSO, rt, 15 h, 95%; (j) $BnO(CH_2)_5MgBr$, THF, rt, 1.5 h, 97%; (k) 13 M KOH, THF/MeOH (3:2), rt, 3 h, 95%, *cis*/*trans* = 17:1; (l) L-Selectride, THF, −78 °C, 30 min, 86%, 15*R*/15*S* = 34:1; (m) Bn−Br, NaH, DMF, rt, 2 h, 94%.

Scheme 3. Oxonium Ion Formation/Fragmentation[a]

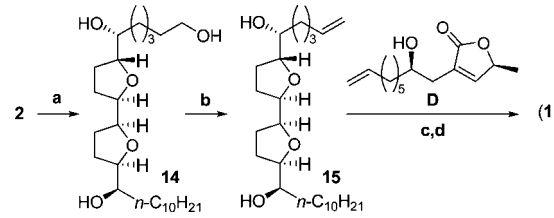


[a] *Reagents and conditions*: (a) PhSeCl, SiO_2, K_2CO_3, CH_2Cl_2, rt, 24 h, 83%.

game to deliver the natural product. Cross-metathesis of alkene **15** with known butenolide **D**[4b] followed by a chemoselective diimide reduction[20] led to trilobacin (**1**), the spectral and optical rotation data for which were in good agreement with those reported for the natural material.

In conclusion, we have accomplished an asymmetric total synthesis of trilobacin (**1**), an annonaceous acetogenin with potent anticancer activity, in 18 steps and 14% overall yield from readily available starting materials **4** and **5**. Our synthesis illustrates the potential of our novel organoselenium-mediated oxonium ion formation/SiO_2-promoted fragmentation protocol to generate this hitherto unattainable adjacent bis-THF moiety with high selectivity.

Scheme 4. Completion of the Synthesis[a]



[a] *Reagents and conditions*: (a) Raney-Ni, EtOH, reflux, 2 h, 92%; (b) (i) *o*-NO_2−PhSeCN, *n*-Oct_3P, THF, rt, 30 min, (ii) 30% H_2O_2, THF, rt, 48 h, 88%; (c) $(Cy_3P)_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, 6 h, then DMSO, rt, 15 h, 73% (86% BRSM); (d) $TsNHNH_2$, NaOAc, DME, reflux, 6 h, 91%.

Acknowledgment. This work was supported by the NRF grant funded by the MEST, Korea (No. 20100001710) and RIPS.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The silica gel (Merck, Kieselgel 60, 70−230 mesh) was activated by heating at 160 °C for 3 h under vacuum.

(14) The structure of **2** was substantiated by conversion to intermediates prepared by Marshall (ref 3b) in the synthesis of trilobin and comparison with their published spectra; see the Supporting Information.

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(16) Premature interruption of the reaction at 15 min produced chloro ether **B** as the major product (85%) along with the desired bis-THF **2** (15%).

(17) This behavior of structurally related halo ethers in the presence of silica gel was first observed during column chromatography in the course of the structure determination of laurefucin by Fukuzawa and co-workers and was later confirmed by Suzuki and co-workers: (a) Furusaki, A.; Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, *14*, 4579. (b) Kikuchi, H.; Suzuki, T.; Kurosawa, E.; Suzuki, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1763.

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(20) A small amount (∼5%) of the over-reduced product was formed.

JA106116V