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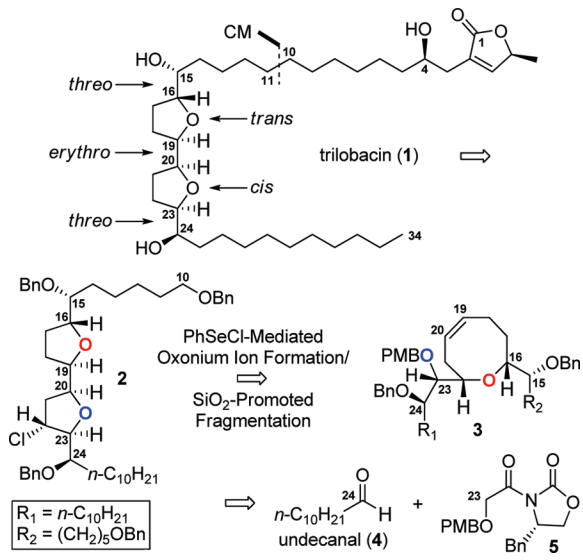
Abstract: An asymmetric total synthesis of trilobacin (**1**), an annonaceous acetogenin with potent anticancer activities, was accomplished wherein the construction of its *erythro*-bis(2,2′)-tetrahydrofuran core **2** featured a novel organoselenium-mediated oxonium ion formation/SiO_2-promoted fragmentation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

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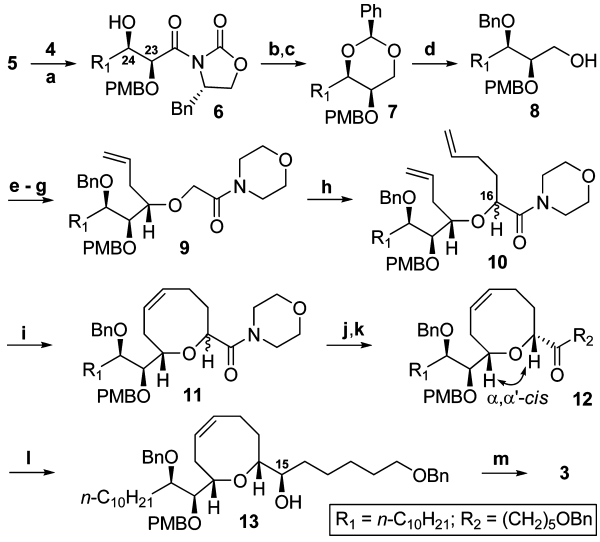
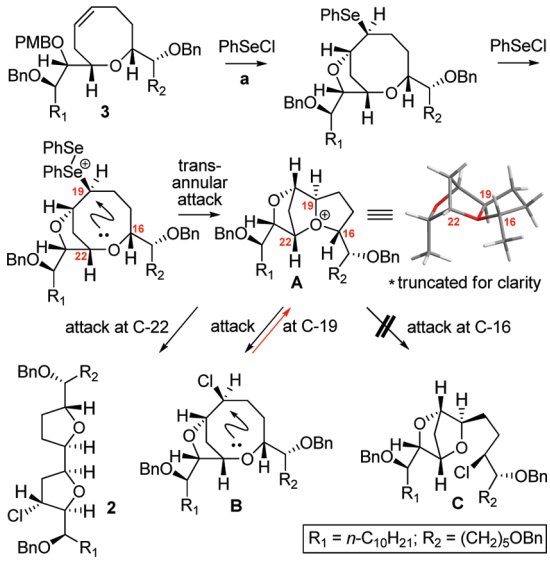
Scheme 2. Synthesis of Key Oxocene Intermediate **3**[a]



[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]

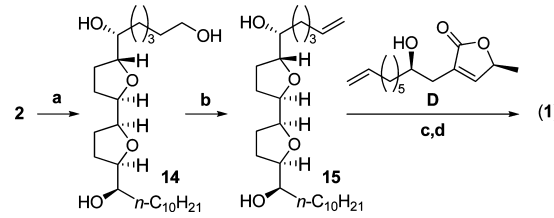


[a] *Reagents and conditions*: (a) PhSeCl, SiO_2, K_2CO_3, CH_2Cl_2, rt, 24 h, 83%.

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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(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%).
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JA106116V