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Biomimetic Asymmetric Total Synthesis of (−)-Laurefucin via an Organoselenium-Mediated Intramolecular Hydroxyetherification

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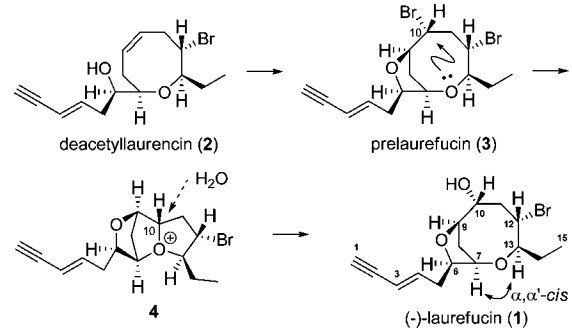
Abstract: The first asymmetric total synthesis of (−)-laurefucin (**1**), a unique C-15 acetogenin with a 2,8-dioxabicyclo[5.2.1]decane skeleton, has been accomplished in nine steps in 31% overall yield from known oxocene **10**. Highlights of the highly stereoselective synthesis include a novel organoselenium-mediated biomimetic hydroxyetherification.

Introduction

(−)-Laurefucin (**1**), the first C-15 acetogenin with a unique 2,8-dioxabicyclo[5.2.1]decane skeleton, was isolated by Irie and co-workers in 1972 from the red alga *Laurencia nipponica*.[1] Since then, a considerable number of congeners have been isolated from various marine sources.[2] The structure and absolute configuration of the α,α′-*cis* disubstituted medium ring marine natural product **1** were firmly established by X-ray crystallography.[3] Laurefucin (**1**) is reported to possess an interesting inhibitory activity for drug metabolism.[4]

On the basis of enzymatic and chemical considerations, it was proposed that (−)-laurefucin (**1**) might be biogenetically derived from deacetyllaurencin (**2**) through the intermediacy of bromoether **3**, which is designated as prelaurefucin.[2b,5] Displacement of the C-10 bromide functionality in **3** by transannular participation of the ring oxygen and subsequent nucleophilic attack by H_2O at the C-10 position in the resultant oxonium ion **4** with retention of configuration would lead to laurefucin as depicted in Scheme 1. It has been demonstrated that deacetyllaurencin (**2**) is transformed to laurefucin (**1**) by action of lactoperoxidase[5a] or bromoperoxidase.[5b] In addition, the possible involvement of prelaurefucin (**3**) in the biosynthetic pathway was supported by a facile conversion of hexahydroprelaurefucin, synthesized from natural laurefucin by a catalytic hydrogenation−bromination sequence, to hexahydrolaurefucin in aqueous solvents.[5a]

Scheme 1. Proposed Biogenetic Pathway of (−)-Laurefucin (1)



We have been involved in development of an efficient synthetic method for generation of the pivotal dioxatricyclic oxonium core in **4** in view of its possible involvement in the biosynthesis of other natural products such as notoryne (**5**)[2b,5a] and ocellenyne (**6**)[6] as well as laurefucin. As shown in Scheme 2, nucleophilic attack at C-7 in dioxatricyclic oxonium ion **4** by chloride would lead to notoryne, an adjacent bis-tetrahydrofuranoid marine natural product. Likewise, attack of bromide ion at C-13 would produce ocellenyne with a 2,5-dioxabicyclo[2.2.1]heptane skeleton. Described herein is a highly stereoselective, substrate-controlled asymmetric total synthesis of (−)-laurefucin (**1**), featuring a novel highly efficient

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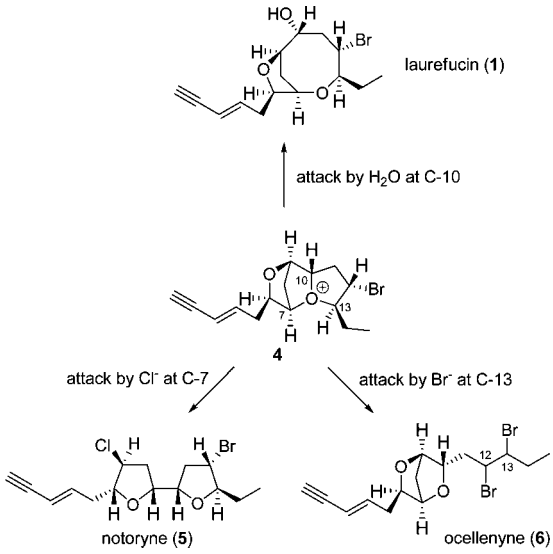
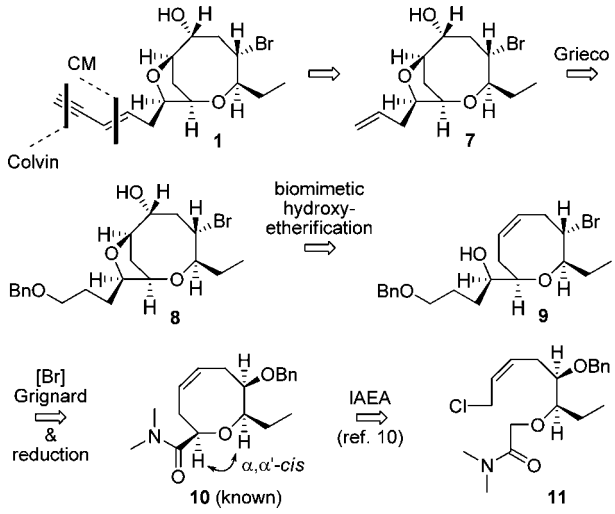
(1) Fukuzawa, A.; Kurosawa, E.; Irie, T. *Tetrahedron Lett.* **1972**, *13*, 3.
(2) (a) Wratten, S. J.; Faulkner, D. J. *J. Org. Chem.* **1977**, *42*, 3343. (b) Kikuchi, H.; Suzuki, T.; Kurosawa, E.; Suzuki, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1763. (c) König, G. M.; Wright, A. D. *J. Nat. Prod.* **1994**, *57*, 477.
(3) Furusaki, A.; Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, *14*, 4579.
(4) Kaul, P. N.; Kulkarni, S. K.; Kurosawa, E. *J. Pharm. Pharmacol.* **1978**, *30*, 589.
(5) (a) Fukuzawa, A.; Aye, M.; Nakamura, N.; Tamura, M.; Murai, A. *Tetrahedron Lett.* **1990**, *31*, 4895. (b) Fukuzawa, A.; Aye, M.; Takasugi, Y.; Nakamura, M.; Tamura, M.; Murai, A. *Chem. Lett.* **1994**, 2307.
(6) (a) Schulte, G. R.; Chung, M. C. H.; Scheuer, P. J. *J. Org. Chem.* **1981**, *46*, 3870. (b) The stereochemistry of the 12,13-dibromo moiety and of the side chains of the bicyclic system was not firmly established.

Scheme 2. Proposed Biogenetic Role of Oxonium Ion **4**



Scheme 3. Retrosynthetic Plan for (−)-Laurefucin (**1**)

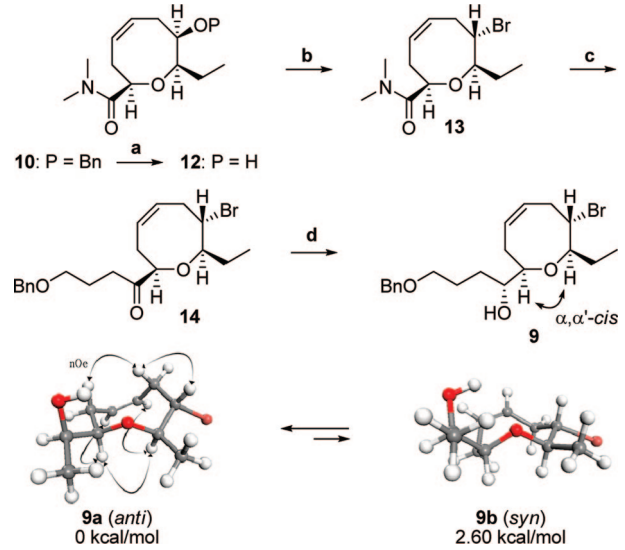


organoselenium-mediated hydroxyetherification that mimics the proposed biogenetic pathway.

Results and Discussion

As shown in Scheme 3, we envisioned that (−)-laurefucin (**1**) could be secured from alkene **7** by incorporation of the (*E*)-enyne moiety via an olefin cross-metathesis (CM)/Colvin alkyne synthesis strategy.[7] Terminal alkene **7** could in turn be readily elaborated from protected primary alcohol derivative **8** using Grieco's method.[8] Furthermore, we were intrigued by the possibility of implementing a biomimetic hydroxyetherification of γ,δ-unsaturated alcohol **9** for the synthesis of key intermediate **8** by a sequential intramolecular etherification−transannular cyclization process. However, we were concerned about potential transannular participation by the oxocene ring oxygen in **9** prior to the crucial internal etherification to form the 2,8-dioxabicyclo[5.2.1]decane skeleton, which would be problematic (vide infra).[9] Further retrosynthetic analysis suggested that key etherification substrate **9** should be accessible in an efficient manner from known oxocene amide **10**, which was prepared via our previously reported intramolecular amide enolate alkylation (IAEA) of chloro amide **11**.[10]

Scheme 4. Preparation of Key Etherification Substrate **9**[a]



[a] *Reagents and conditions*: (a) DDQ, $ClCH_2CH_2Cl$/pH 7.4 buffer (9:1), 50 °C, 5 h, 96%; (b) CBr_4, Oct_3P, pyridine, toluene, 70 °C, 2 h, 78%; (c) $BnO(CH_2)_3MgBr$, THF, room temperature (rt), 1 h, 70%; (d) L-Selectride, THF, −78 °C, 1 h, 96%.

Our synthesis commenced with the preparation of key cyclization substrate **9** from oxocene **10** (Scheme 4). Thus, oxidative cleavage of the benzyl group in oxocene **10** by the Yonemitsu method[11] and subsequent bromination of the resulting alcohol **12** by exposure to CBr_4 and Oct_3P[12] with inversion of configuration furnished bromo oxocene **13** in 75% overall yield for the two steps. Application of our direct ketone synthesis protocol[13] to α-alkoxy amide **13** with 3-benzyloxypropylmagnesium bromide, followed by Felkin–Ahn L-Selectride reduction[12a,14] of the resultant ketone **14**, provided the requisite secondary alcohol **9** as a single isomer (67%, two steps). The key NOE interactions observed for **9** as well as literature

(7) (a) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, 151. (b) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721. (c) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107.

(8) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(9) For examples of electrophilic transannular cyclization to form oxonium ion intermediates by a ring oxygen atom in Δ^4-oxocenes with halogen electrophiles, see: (a) Ishihara, J.; Shimada, Y.; Kanoh, N.; Takasugi, Y.; Fukuzawa, A.; Murai, A. *Tetrahedron* **1997**, *53*, 8371. (b) Sugimoto, M.; Suzuki, T.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2007**, *48*, 1109. With selenium electrophiles, see: (c) Clark, J. S.; Wong, Y.-S. *Chem. Commun.* **2000**, 1079. With Lewis acids, see: (d) Paquette, L. A.; Scott, M. K. *J. Am. Chem. Soc.* **1972**, *94*, 6751, and references therein. (e) Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386. (f) While our manuscript was undergoing review, Mascal and coworkers reported synthesis of an oxatriquinane oxonium ion: Mascal, M.; Hafezi, N.; Meher, N. K.; Fettinger, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 13532.

(10) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett.* **2005**, *7*, 75.

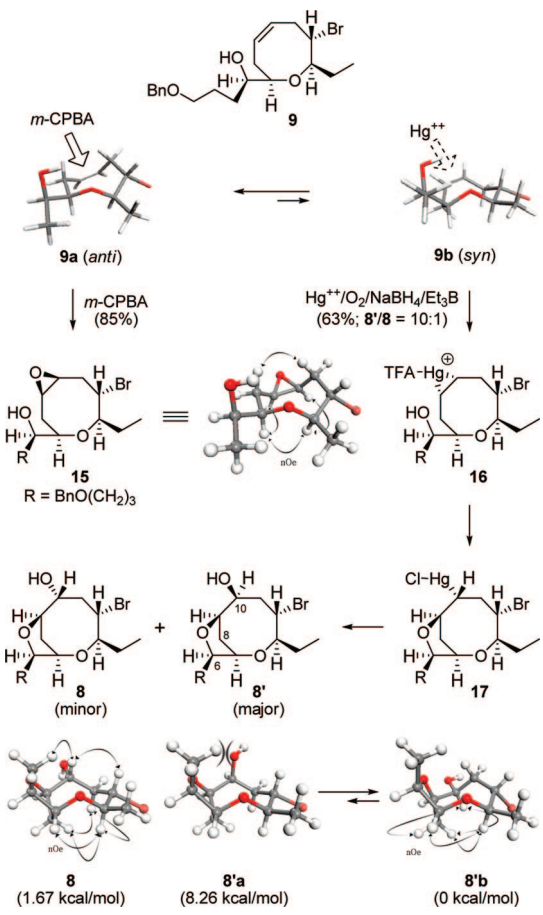
(11) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(12) (a) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345. (b) Suzuki, T.; Matsumura, R.; Oku, K.; Taguchi, K.; Hagiwara, H.; Hoshi, T.; Ando, M. *Tetrahedron Lett.* **2001**, *42*, 65.

(13) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2003**, *125*, 10238.

(14) Clark, J. S.; Holmes, A. B. *Tetrahedron Lett.* **1988**, *29*, 4333.

Scheme 5. Attempts to Synthesize Key Dioxabicyclic Intermediate **8**



analogy[15,16] suggested that α,α′-*cis*-oxocene **9** assumes the *anti*-conformation **9a**. This was further supported by computational analysis with structural optimizations of the two conformers (in truncated form), which predicted *anti*-conformer **9a** to be more stable than *syn*-conformer **9b** by 2.6 kcal/mol.[17]

With the key cyclization substrate **9** in hand, we proceeded to address construction of the 2,8-dioxabicyclo[5.2.1]decane skeleton of (−)-laurefucin (**1**). Examination of several conventional protocols for achieving the hydroxyetherification proved to be problematic as illustrated in Scheme 5. For instance, exposure of hydroxy oxocene **9** to *m*-CPBA led to exclusive formation of β-epoxide **15** by electrophilic attack from the less sterically hindered β-face of the molecule in its preferred *anti*-conformation **9a**, which precluded the desired intramolecular epoxide-opening route to **8**.[18] The observed NOE interactions for **15**, as depicted in the scheme, were consistent with a β-epoxide.

Likewise, oxidative mercuriocyclization of γ,δ-unsaturated alcohol **9** furnished the undesired C(10)-β-alcohol **8′** as the major product in 63% isolated yield in a 10:1 β/α ratio.[19,20] It is worthwhile mentioning at this point that only α-mercuronium ion **16**, produced from **9** in its *syn*-conformation **9b**, can undergo intramolecular etherification. The stereochemical nature of the desired minor isomer **8** was established by the NOESY studies illustrated in the scheme and further corroborated by crystallographic analysis of the final product (vide infra). It is interesting to note that, as suggested by careful analysis of the NOESY spectra, the undesired major β-alcohol **8′** adopts conformation **8′b** to alleviate the unfavorable nonbonding steric interactions between the C-6 benzyloxypropyl group and the C-10 β-hydroxyl function that are present in **8′a**. In this connection, our calculation predicted that **8′b** was more stable than **8′a** by 8.26 kcal/mol.[17] In addition, oxidation of the two alcohols **8** and **8′** gave the same ketone, confirming that they are epimeric at C-10.

Particularly disappointing was that treatment of γ,δ-unsaturated alcohol **9** with NBS in an attempt to synthesize the pivotal bromoether **19** produced a roughly 1:2 mixture of tetrahydrofurans **21** and **22** in 81% total yield (Scheme 6). It is of note that both the hydroxyl group and ring oxygen atom are properly situated to interact with α-bromonium ion **18**. Unlike the proposed biogenetic events, bromonium ion **18** undergoes transannular cyclization[9] via attack by the ring oxygen atom prior to the desired bromoetherification by the hydroxyl function to generate the unwanted oxonium ion **20**. Cationic rearrangement[9b] of **20** or intramolecular attack at the C-7 position by the benzyloxy oxygen then would yield tetrahydrofuranyl ketone **21** or tetrahydropyranyl tetrahydrofuran **22**, respectively. Although our attempt to obtain a crystalline derivative of **22** for an X-ray study was unsuccessful, the NOE interactions observed for the tetrahydrofuran moiety of **22** and the large vicinal coupling constant (J = 10.4 Hz) between hydrogens Ha and Hb in the corresponding *p*-bromobenzoate **22′**, indicative of a trans-diaxial relationship, are consistent with the proposed structure.

(15) (a) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483. (b) Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2007**, *129*, 2269.

(16) For the crystal structures of α,α′-*cis*-oxocene natural products, see: (a) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1965**, 638. (b) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc. (B)* **1969**, 559. (c) Gonzalez, A. G.; Martin, J. D.; Martin, V. S.; Norte, M.; Perez, R.; Ruano, J. Z. *Tetrahedron* **1982**, *38*, 1009. (d) Cardellina II, J. H.; Horseley, S. B.; Clardy, J.; Leftow, S. R.; Meinwald, J. *Can. J. Chem.* **1982**, *60*, 2675. (e) Norte, M.; Gonzalez, A. G.; Cataldo, F.; Rodriguez, M. L.; Brito, I. *Tetrahedron* **1991**, *45*, 9411.

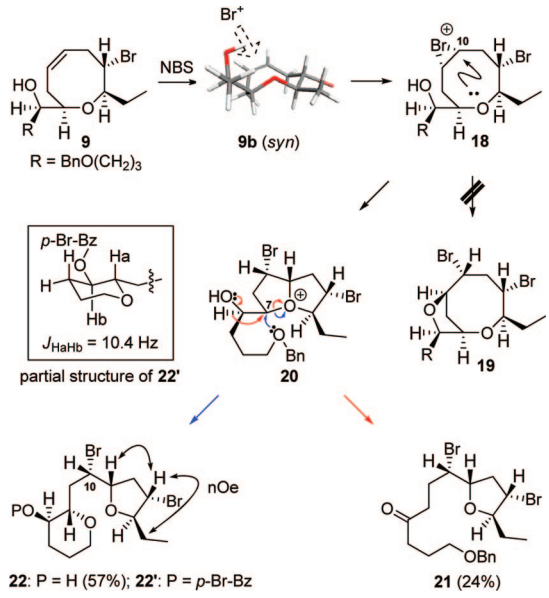
(17) See the Supporting Information for the optimized molecular geometries of **9a**, **9b**, **15**, **8**, **8′a**, and **8′b**. The energy-minimized conformations (Materials Studio 4.2, Systematic grid scan) were further optimized by the density functional theory method (PBE-GGA) at the DND level (Materials Studio 4.2, DMol3). Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623. Note that, in this approach, the benzyloxypropyl and ethyl substituents were replaced by methyl groups to expedite the PBE-GGA/DND optimizations.

(18) One of the reviewers pointed out that β-epoxide **15** might also arise from *syn*-conformation **9b** via a Henbest-like hydrogen-bonding interaction. Although this possibility cannot be ruled out completely, our rationalization of the stereochemical outcome of the epoxidation is strongly supported by the observations that the TBS ether of **9** produced the corresponding β-epoxide under comparable conditions. In addition, osmylation of a similar α,α′-*cis*-oxocene produced a β-*cis*-diol (see ref 15b).

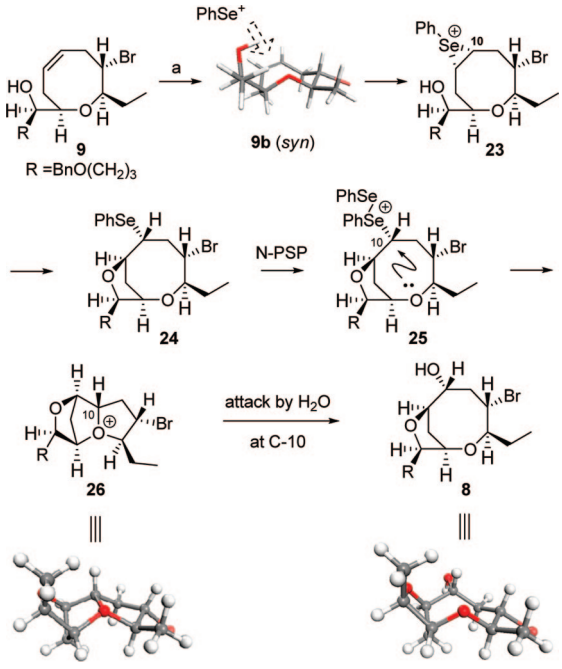
(19) (a) Broka, C. A.; Lin, Y.-T. *J. Org. Chem.* **1988**, *53*, 5876. (b) Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T.; Paquette, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 9021. (c) Kang, S.; Lee, S. *Chem. Commun.* **1998**, *7*, 761. (d) Kang, S.; Lee, J.; Lee, S. *Tetrahedron Lett.* **1998**, *39*, 59.

(20) (a) The oxidative mercuriocyclization proved to be somewhat capricious in our hands due to simple reductive demercuration and reversion to the starting material of the organomercurial intermediate. (b) Our preliminary attempts to convert C(10)-β-alcohol **8′** to the desired α-alcohol **8** in a stereoselective fashion by either an oxidation−reduction sequence or a Mitsunobu inversion were unsatisfactory. However, extensive efforts were not made for this purpose simply because the far more efficient organoselenium-based protocol was developed.

Scheme 6. Attempted Biomimetic Bromoetherification of **9**



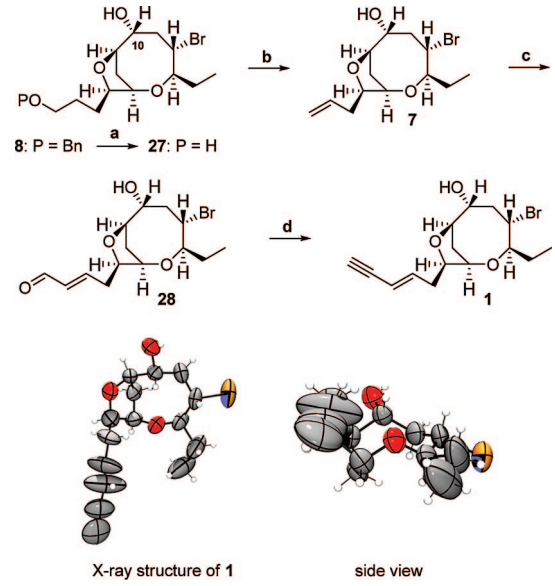
Scheme 7. Organoselenium-Mediated Biomimetic Hydroxyetherification[a]



[a] *Reagents and conditions*: (a) N-PSP (3 equiv), PTSA (0.2 equiv), CH_3CN/H_2O (9:1), 0.005 M, rt, 2.5 h, 100%.

After extensive experimentation, we were delighted to find that, upon exposure to an excess amount of *N*-phenylselenophthalimide (N-PSP)[21] in the presence of PTSA in CH_3CN/H_2O (9:1) at room temperature for 2.5 h, γ,δ-unsaturated alcohol **9** gave rise directly to the desired dioxabicyclic hydroxyether **8** in quantitative yield (Scheme 7).[22] We rationalize that intramolecular etherification of α-selenonium ion **23**, generated from **9** in its *syn*-conformation **9b** upon exposure to N-PSP, produces selenoether **24**.[23] Subsequent activation of the phenylselenyl group[24] in selenoether **24** by N-PSP, followed by transannular

Scheme 8. Completion of the Synthesis[a]



[a] *Reagents and conditions*: (a) H_2, 10% Pd/C, EtOH, rt, 30 min, 100%; (b) *o*-nitrophenylselenocyanide, Oct_3P, THF, rt, 30 min, then 30% H_2O_2, 0 °C to rt, 21 h, 72%; (c) crotonaldehyde, $(H_2IMes)(Cy_3P)Cl_2Ru{=}CHPh$, CH_2Cl_2, 40 °C, 1.5 h, then DMSO, rt, 12 h; (d) $TMSCH_2N_2$, LDA, THF, −78 to 0 °C, 2 h, 85% (two steps).

participation[2b,5a,9] by the ring oxygen in the resultant adduct **25**, would generate the pivotal putative biogenetic intermediate **26** as depicted in the scheme. It is worth noting that adduct **25** is expected to have a conformation similar to that of **8**, and would be favorably disposed for transannular cyclization through intramolecular attack by the oxocane oxygen atom. Ensuing nucleophilic attack by the water at C-10 in oxonium ion **26** would then lead to hydroxyether **8** with an overall double inversion. Several observations support this rationalization: (1) premature interruption of the reaction produced phenylselenoether **24** along with the desired hydroxyetherification product **8**; (2) resubjection of **24** to the reaction conditions produced hydroxyether **8**; (3) selenoether **24** did not undergo the transannular cyclization in the absence of N-PSP.

Significantly, while α-bromonium ion **18** apparently proceeds with transannular participation by the ring oxygen atom prior to cyclic ether formation (Scheme 6), the corresponding intermediates α-mercuronium ion **16** (Scheme 5) and α-selenonium ion **23** (Scheme 7) appear to undergo preferential nucleophilic attack by the side-chain hydroxyl group to produce organomercury species **17** and selenoether **24**, respectively. It is reasonable to assume that this divergence in reaction pathways (attack by the ring oxygen atom vs the hydroxyl) might be due to conformational differences between reactive intermediates **18** vs **16** and **23**. In addition, we note that these reactions take

(21) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

(22) (a) When PhSeBr or PhSeCl was used instead of N-PSP and PTSA under otherwise comparable conditions, the reaction proceeded more slowly to give the desired hydroxyether **8** in somewhat lower yields (rt, 24 h, 85% and rt, 48 h, 86%, respectively). (b) In the absence of water, bromoether **19** (45%) and the chloroether corresponding to **19** (76%) were obtained, respectively. The low yields observed in these organoselenium-mediated haloetherifications might be due to the instability of the corresponding haloethers, in particular bromoether **19**, towards water during chromatography.

(23) (a) Nicolaou, K. C. *Tetrahedron* **1981**, *37*, 4097, and references therein. (b) Brimble, M. A.; Pavia, G. S.; Stevenson, R. J. *Tetrahedron Lett.* **2002**, *43*, 1735, and references therein.

(24) Morella, A. M.; Ward, A. D. *Tetrahedron Lett.* **1984**, *25*, 1197.

place in different solvents, but the precise nature of these differences is unclear at the present time.

After construction of the requisite dioxabicyclic skeleton, we directed our attention to assembly of the (*E*)-enyne moiety to complete the synthesis (Scheme 8). To this end, we developed a protection-free four-step sequence based on a CM/Colvin−Ohira homologation protocol, which complements our recently reported CM-based (*Z*)-enyne synthesis.[15b] Thus, hydrogenolysis of the benzyl protecting group in **8**, followed by chemoselective conversion of the resulting diol **27** into terminal olefin **7** by Grieco's method,[8] set up the system for stereoselective introduction of the (*E*)-enyne unit. Cross-metathesis of alkene **7** with crotonaldehyde[25] using the Grubbs second-generation catalyst, followed by exposure of the resulting *trans*-α,*β*-unsaturated aldehyde **28** to lithio TMS-diazomethane,[7] delivered (−)-laurefucin (**1**) in 85% yield for the two steps. The spectral and optical rotation data for our synthetic material were in good agreement with those of the natural product.[2c] The structure of our synthetic laurefucin was further verified by X-ray crystallography.

Conclusion

In summary, the first asymmetric total synthesis of (−)-laurefucin (**1**), the first C-15 acetogenin containing a 2,8-dioxabicyclo[5.2.1]decane skeleton, has been accomplished in nine steps in 31% yield from known oxocene **10**.[26] The highly stereoselective synthesis features a novel, highly efficient organoselenium-mediated biomimetic-type intramolecular hydroxyetherification as a key step. Application of our organoselenium-based one-pot protocol for generating the pivotal dioxatricyclic oxonium intermediate to the synthesis of other natural products is under investigation in our laboratories.

Acknowledgment. This work was supported by the SRC/ERC program of MOST/KOSEF (R11-2007-107-02001-0).

Supporting Information Available: General experimental procedures including spectroscopic and analytical data for all new compounds along with copies of the ^{1}H and ^{13}C NMR spectra for **1**, **7**, **8**, **8′**, **9**, **12**−**15**, **21**−**22**, **22′**, **24**, **27**−**28**, X-ray crystallographic data for **1**, detailed experimental procedure of computational study, and the outcome of conformational optimization and energy minimization. This material is available free of charge via the Internet at http://pubs.acs.org.

JA806304S

(25) For examples of olefin cross-metathesis with crotonaldehyde, see: (a) Morgan, J. P.; Morrill, C.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 67. (b) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396.

(26) The asymmetric synthesis of (−)-laurefucin (**1**) has been accomplished in a completely substrate-controlled manner in 16 steps in 11% overall yield from the known (*S*)-4-benzyl-3-benzyloxyacetyl-2-oxazolidinone: Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029.