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Asymmetric Total Syntheses of (+)-3-(*Z*)-Laureatin and (+)-3-(*Z*)-Isolaureatin by "Lone Pair−Lone Pair Interaction-Controlled" Isomerization

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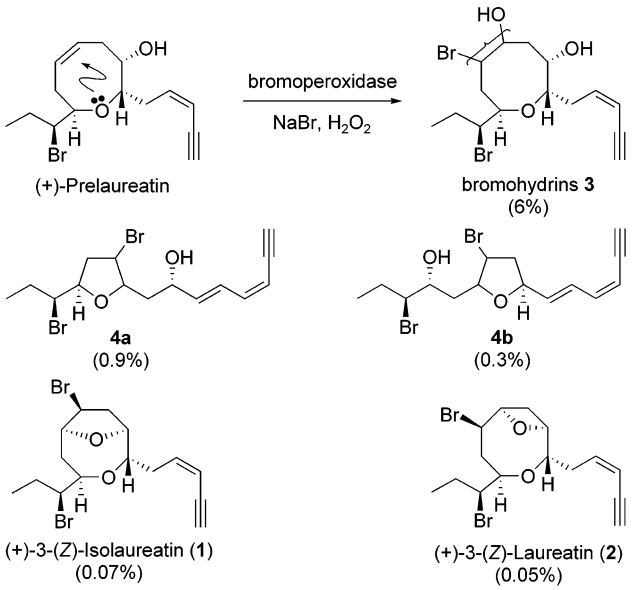
Abstract: The first asymmetric total syntheses of the dihalogenated medium-sized dioxabicyclic marine natural products (+)-3-(*Z*)-isolaureatin (**1**) and (+)-3-(*Z*)-laureatin (**2**) have been accomplished. Notable features of the highly stereo-, regio-, and chemoselective syntheses of these α,α′-*trans*-oxocene natural products include an intramolecular amide enolate alkylation to construct the α,α′-*cis*-oxocene, novel "lone pair−lone pair interaction-controlled" epimerizations to the α,α′-*trans*-oxocenes, various strategies for stereoselective introduction of halogen atoms, and novel olefin cross-metatheses for construction of the (*Z*)-enyne systems.

Introduction

(+)-3-(*Z*)-Isolaureatin (**1**) and (+)-3-(*Z*)-laureatin (**2**) were isolated from the red alga *Laurencia nipponica* by Irie and coworkers in 1968.[1] These marine natural products possess unique structural features: a rare dioxabicyclic ring system that is composed of a medium-sized oxocene moiety and a small ring, either an oxolane or an oxetane. Furthermore, these α,α′-*trans*-oxocene natural products contain six stereogenic centers in addition to a (*Z*)-enyne system in their compact C15 framework. The constitution as well as both the relative and absolute configurations of these marine natural products were proposed on the basis of spectroscopic studies, chemical correlations, and biogenetic considerations.[1] The proposed structures were firmly established by Lewis acid catalyzed isomerization[2] of (+)-3-(*Z*)-laureatin (**2**) to (+)-3-(*Z*)-isolaureatin (**1**), albeit in low yield, and by an X-ray crystallographic study[3] of (+)-3-(*Z*)-isolaureatin (**1**). In an enzymatic transformation[4] shown in Scheme 1, bromoperoxidase-catalyzed bromoetherification of (+)-prelaureatin by exposure to NaBr and H_2O_2 produced (+)-3-(*Z*)-isolaureatin (0.07%) and (+)-3-(*Z*)-laureatin (0.05%). However, monocyclic tetrahydrofurans **4a** (0.9%) and **4b** (0.3%) and a mixture of three bromohydrins **3** (6%) were formed as the major products. It is noteworthy that bromo oxolane **4a** was produced through transannular participation of the ring oxygen atom as depicted in the scheme.

Scheme 1. Enzymatic Transformation of (+)-Prelaureatin



These dihalogenated C15 metabolites were shown to possess strong activity as mosquito larvicides.[5] Although these medium-sized dioxabicyclic marine natural products have received a significant amount of attention due to their interesting molecular structure and potential as insecticides for mosquito vectors transmitting malaria, no total synthesis has been reported.[6−9] Our preliminary studies in this area suggested that successful execution of a synthesis of these natural products hinges upon stereoselective incorporation of halogen atoms into their oxocene skeletons, which is recognized to be demanding (vide infra).[7j,k] With this notion in mind, described herein are the first and highly stereo-, regio-, and chemoselective syntheses of (+)-3-

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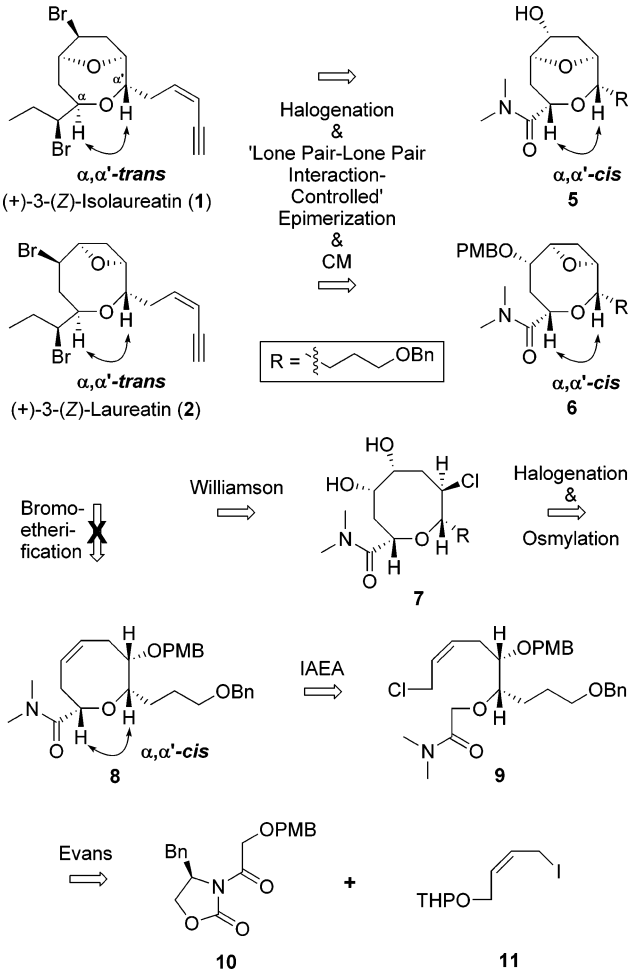
(1) (a) Irie, T.; Izawa, M.; Kurosawa, E. *Tetrahedron Lett.* **1968**, 2091. (b) Irie, T.; Izawa, M.; Kurosawa, E. *Tetrahedron Lett.* **1968**, 2735. (c) Irie, T.; Izawa, M.; Kurosawa, E. *Tetrahedron* **1970**, *26*, 851.
(2) Fukuzawa, A.; Kurosawa, E.; Irie, T. *J. Org. Chem.* **1972**, *37*, 680.
(3) Kurosawa, E.; Furusaki, A.; Izawa, M.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, 3857.
(4) (a) Ishihara, J.; Shimada, Y.; Kanoh, N.; Takasugi, Y.; Fukuzawa, A.; Murai, A. *Tetrahedron* **1997**, *53*, 8371.(b) The substrate used in the enzymatic transformation has deuterium at the alkyne terminus.
(5) (a) Watanabe, K.; Umeda, K.; Miyakado, M. *Agric. Biol. Chem.* **1989**, *53*, 2513. (b) For a recent review of prototypical insecticidal agents, see: El Sayed, K. D.; Dunbar, D. C.; Perry, T. L.; Wilkins, S. P.; Hamann, M. T. *J. Agric. Food Chem.* **1997**, *45*, 2765.

(*Z*)-isolaureatin (**1**) and (+)-3-(*Z*)-laureatin (**2**), featuring an intramolecular amide enolate alkylation (IAEA) to construct the α,α′-*cis*-oxocene, novel "lone pair−lone pair interaction-controlled" epimerizations to the α,α′-*trans*-oxocenes, various strategies for stereoselective introduction of halogen atoms, and novel olefin cross-metatheses for construction of the (*Z*)-enyne systems as key transformations.

Results and Discussion

Our retrosynthetic plan, which includes a multitude of halogenation steps, is shown in Scheme 2. We envisioned that the two α,α′-*trans*-oxocene natural products,[8] (+)-3-(*Z*)-isolaureatin (**1**) and (+)-3-(*Z*)-laureatin (**2**), could be elaborated from α,α′-*cis*-oxolane **5** and α,α′-*cis*-oxetane **6**, respectively, by a novel "lone pair−lone pair interaction-controlled" isomerization (vide infra). We further envisaged that chloro diol **7** could serve as a common intermediate for the regioselective construction of the oxolane and oxetane rings present in these natural products by an internal Williamson ether synthesis. It should be emphasized that our α,α′-*cis*-oxocene-based strategy possesses a definite advantage, in particular, for synthesis of Williamson substrate **7** (vide infra). Exploration of a direct route to these natural products by way of a bromoetherification was unsuccessful in our hands, probably due to the aforementioned transannular participation of the oxocene ring oxygen atom.[4] The requisite α,α′-*cis*-oxocene **8** in turn could be secured by our intramolecular amide enolate alkylation[7k,l] of chloro amide **9**. Further analysis indicated internal alkylation substrate **9** could be prepared from the known glycolate oxazolidinone **10** and allylic iodide **11** based on Evans methodology.[10]

Scheme 2. Retrosynthetic Plan for (+)-3-(*Z*)-Isolaureatin (**1**) and (+)-3-(*Z*)-Laureatin (**2**)



To commence the synthesis, key α,α′-*cis*-oxocene **8** was prepared in an efficient manner by a seven-step sequence identical to that employed for our synthesis of (+)-laurencin[7l] (35% overall yield from readily available glycolate oxazolidinone **10**[11] and the known allylic iodide **11**[12]). With α,α′-*cis*-oxocene **8** available in multigram quantities, we directed our attention to synthesis of key internal Williamson substrate **7** (Scheme 3). Chlorination of α,α′-*cis*-oxocene alcohol **12**, prepared by chemoselective removal of the PMB group in *cis*-oxocene **8** with wet DDQ,[13] by treatment with carbon tetrachloride and tri-*n*-octylphosphine in the presence of 1-methylcyclohexene,[14] efficiently furnished the desired chloride **13** with inversion of configuration at C(7).[15] Literature analogy[7f,16] and spectroscopic analysis suggest that α,α′-*cis*-oxocene alcohol **12**

(6) (a) Edwards, S. D.; Lewis, T.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, *40*, 4267. (b) Taylor, C. D.; Castillo, B. F., II; Howell, A. R. *Abstracts of Papers*, 232nd National Meeting of the American Chemical Society, San Francisco, CA, Sept 10−14, 2006; American Chemical Society: Washington, DC, 2006; ORGN-711. (c) Note added in proof: during the process of publishing this article, Suzuki and coworkers reported a total synthesis of (+)-3-(*Z*)-laureatin: Sugimoto, M.; Suzuki, T.; Hagiwara, H.; Hosi, T. *Tetrahedron Lett.* **2007**, *48*, 1109.

(7) For total syntheses of α,α′-*cis*-oxocene *Laurencia* natural products, see: (a) Murai, A.; Murase, H.; Matsue, H.; Masamune, T. *Tetrahedron Lett.* **1977**, 2507. (b) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248. (c) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345. (d) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958. (e) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **1996**, 983. (f) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483. (g) Krüger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499. (h) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029. (i) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (j) Boeckman, R. K., Jr.; Zhang, J.; Reeder, M. R. *Org. Lett.* **2002**, *4*, 3891. (k) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2003**, *125*, 10238. (l) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett.* **2005**, *7*, 75. (m) Fujiwara, K.; Yoshimoto, S.; Takizawa, A.; Souma, S.; Mishima, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 6819.

(8) For total synthesis of α,α′-*trans*-oxocene *Laurencia* natural products, see: (a) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473. (b) Fujiwara, K.; Souma, S.; Mishima, H.; Murai, A. *Synlett* **2002**, 1493. (c) Saitoh, T.; Suzuki, T.; Sugimoto, M.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2003**, *44*, 3175.

(9) For recent examples of C−C bond forming approaches to oxocene construction, see: (a) Suh, Y.-G.; Koo, B.-A.; Kim, E.-N.; Choi, N.-S. *Tetrahedron Lett.* **1995**, *36*, 2089. (b) Alvarez, E.; Delgado, M.; Diaz, M. T.; Hanxing, L.; Perez, R.; Martín, J. D. *Tetrahedron Lett.* **1996**, *37*, 2865. (c) Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919. (d) Coster, M. J.; De Voss, J. J. *Org. Lett.* **2002**, *4*, 3047. (e) Cossy, J.; Taillier, C.; Bellosta, V. *Tetrahedron Lett.* **2002**, *43*, 7263. (f) Kadota, I.; Uyehara, H.; Yamamoto, Y. *Tetrahedron* **2004**, *60*, 7361. (g) Rhee, H. J.; Beom, H. Y.; Kim, H.-D. *Tetrahedron Lett.* **2004**, *45*, 8019. (h) Clark, J. S.; Freeman, R. P.; Cacho, M.; Thomas, A. W.; Swallow, S.; Wilson, C. *Tetrahedron Lett.* **2004**, *45*, 8639. (i) Ortega, N.; Martin, T.; Martin, V. S. *Org. Lett.* **2006**, *8*, 871.

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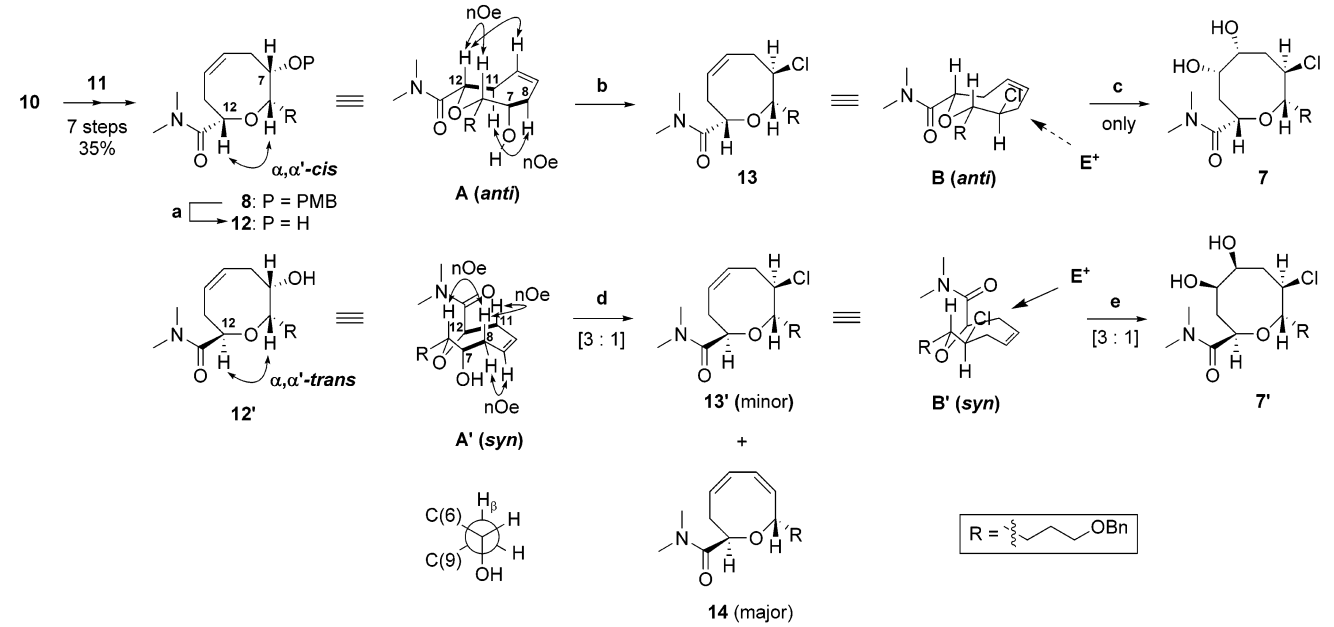
(15) We opted for the chloride instead of the corresponding bromide since the yield of the chlorination (>77%) was significantly better than that of the bromination (>60%) under comparable conditions.

(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) Norte, M.; Gonzalez, A. G.; Cataldo, F.; Rodriguez, M. L.; Brito, I. *Tetrahedron* **1991**, *45*, 9411.

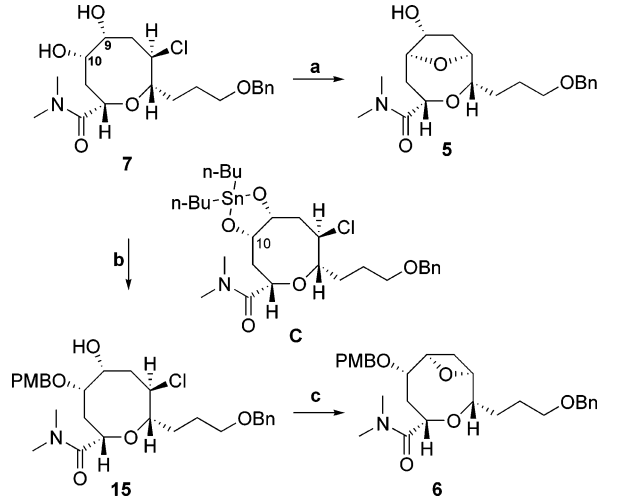
Scheme 3. Synthesis of Internal Williamson Substrate **7**[a]



[a] Reagents and conditions: (a) DDQ, CH_2Cl_2/pH 7.0 buffer (9:1), room temperature (rt), 2 h, 99%; (b) CCl_4, Oct_3P, 1-methylcyclohexene, toluene, 70 °C, 12 h; (c) OsO_4, NMO, acetone/H_2O (1:1), 0 °C, 4 h, 77% for two steps; (d) CCl_4, Oct_3P, 1-methylcyclohexene, toluene, 70 °C, 6 h; (e) OsO_4, NMO, acetone/H_2O (1:1), 0 °C, 21% for two steps.

assumes conformation **A**, where the double bond and its ring oxygen atom has an anti-relationship with respect to the best plane through carbons C(7), C(8), C(11), and C(12). On the other hand, the corresponding syn-conformation **A′** is preferred in the case of α,α′-*trans*-oxocene alcohol **12′**.[17] It is appropriate at this point to delineate our rationale for adopting α,α′-*cis*-oxocene **8** as our starting material. In contrast to α,α′-*cis*-oxocene alcohol **12**, our extensive experience in this field suggested that halogenation of the corresponding α,α′-trans-isomer **12′** might be quite problematic. In fact, attempted chlorination of *trans*-oxocene alcohol **12′** yielded the eliminated diene **14** as the major product (3:1) under the comparable conditions.[18] The difficulties encountered in the chlorination of α,α′-trans-isomer **12′** in its preferred syn-conformation **A′** can be attributed to the *β*-dimethylamide group at C(12) which sterically interferes with the incoming chloride. In addition, the trans-periplanar relationship between the C(7) α-hydroxyl function and the C(8) *β*-hydrogen atom in the syn-conformation **A′** might facilitate the observed elimination. Osmylation of α,α′-*cis*-chloro olefin **13** then yielded the desired α-*cis*-diol **7** exclusively in good overall yield for the two steps (77% from **12**) by electrophic attack from the sterically less congested α-face of the molecule in its preferred anti-conformation **B**. It is interesting to note that the corresponding α,α′-*trans*-chloro olefin **13′** in its syn-conformation **B′** undergoes electrophilic attack from the sterically less hindered *β*-face to produce *β*-*cis*-diol **7′** in a 3:1 *β*/α ratio under the comparable conditions, which further substantiates our choice of an α,α′-*cis*-oxocene-based strategy.

Scheme 4. Synthesis of Bicyclic Skeletons **5** and **6**[a]



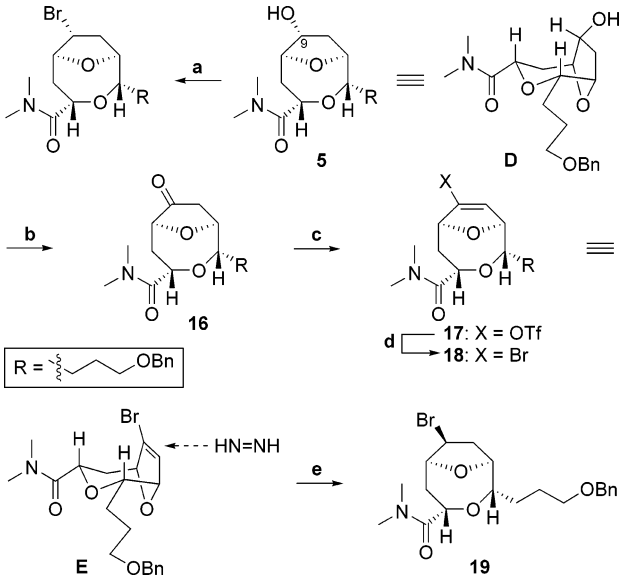
[a] Reagents and conditions: (a) NaH, THF, rt, 12 h, 98%; (b) (*n*-Bu)$_2$Sn(=O), toluene, reflux, then PMBCl, TBAI, 3 h, 80%; (c) DMF, NaH, rt, 12 h, 90%.

With key Williamson substrate **7** in hand, we embarked on the demanding task of installing the oxolane and oxetane moieties in a regioselective fashion (Scheme 4). First, treatment of chloro diol **7** with sodium hydride in THF afforded the desired five-membered ether **5**, a crucial intermediate for the synthesis of (+)-isolaureatin (**1**), in a highly regioselective manner in excellent yield (98%). With methodology for the regioselective construction of the oxolane moiety of (+)-3-(*Z*)-isolaureatin (**1**) secured, we focused our attention on the formation of the oxetane unit of (+)-3-(*Z*)-laureatin (**2**). The tendency of chloro diol **7** to form a five-membered ring under basic conditions thus necessitated development of a method for monoprotection at C(10) with a nonmigrating group[19] under nonbasic conditions. Unfortunately, an attempt to monoprotect chloro diol **7** under

(17) For the crystal structures of α,α′-*trans*-oxocene natural products, see: (a) Kinnel, R. B.; Dieter, R. K.; Meinwald, J.; Engen, D. V.; Clardy, J.; Eisner, T.; Stallard, M. O.; Fenical, W. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 3576. (b) Manzo, E.; Ciavatta, M. L.; Gavagnin, M.; Puliti, R.; Mollo, E.; Guo, Y.-W.; Mattia, C. A.; Mazzarella, L.; Cimino, G. *Tetrahedron* **2005**, *61*, 7456.

(18) Addition of $BnEt_3NCl$ by Boeckman's protocol[7j] afforded a 1:1 mixture of **14** and **13′**.

Scheme 5. Introduction of Bromine at C(9) of (+)-Isolaureatin (**1**)[a]

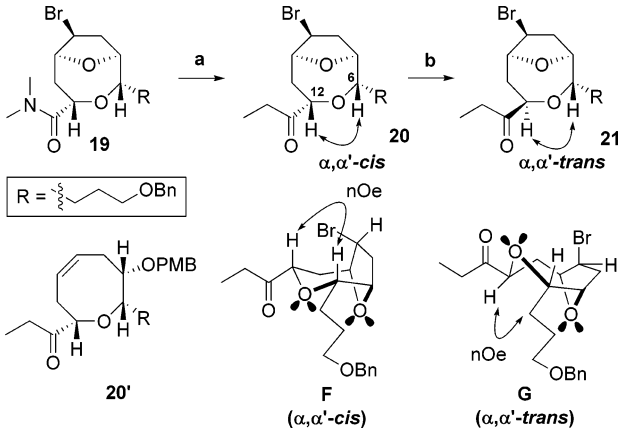


[a] Reagents and conditions: (a) CBr_4, Oct_3P, toluene, rt to 80 °C, 4 h, <10%; (b) TPAP, NMO, CH_2Cl_2, rt, 3 h, 92%; (c) KHMDS, THF, −78 °C, 30 min, then $PhNTf_2$, −78 °C, 1 h, 94%; (d) i. $Me_3SnSnMe_3$, $Pd(Ph_3P)_4$, LiCl, THF, reflux, 3 h, ii. Br_2, CH_2Cl_2, −20 °C, 1 h, 75%; (e) *p*-toluenesulfonylhydrazide, xylenes, reflux, 2 h, 88%.

the acidic conditions of Iversen and Bundle[20] was not regioselective. After a considerable amount of experimentation, we were pleased to find that the desired PMB ether **15** could be obtained in a regioselective fashion by way of the corresponding stannylene intermediate.[21] The regioselectivity here can be explained by invoking stannylene intermediate **C**, where the C(10) group assumes an equatorial position. It is reasonable that the sterically more exposed equatorial group undergoes preferential alkylation. Treatment of chloro alcohol **15** with NaH in DMF then provided oxetane **6**, a key intermediate for the synthesis of (+)-laureatin (**2**).[22]

With schemes for the regioselective syntheses of both **5** and **6** established, we next proceeded to address the remaining steps of the synthesis of (+)-isolaureatin (**1**). As we anticipated, introduction of bromine at C(9) with inversion of configuration turned out to be a challenge since the bromine atom must be incorporated from the sterically congested concave side of the molecule in its preferred conformation **D**. In fact, attempts to brominate secondary alcohol **5** under a variety of conditions generally proceeded with retention of configuration in low yields. To circumvent this problem, we were able to develop a four-step sequence featuring a diimide reduction of vinyl bromide **18** as a key step (Scheme 5). Thus, ketone **16**, prepared by TPAP oxidation[23] of secondary alcohol **5**, was converted to the corresponding enol triflate **17** by exposure to KHMDS and $PhNTf_2$ in a chemoselective manner.[24] Transformation of enol triflate **17** to the desired vinyl bromide **18** was achieved by

Scheme 6. Epimerization of α,α′-*cis*-Ketone **20**[a]



[a] Reagents and conditions: (a) EtMgBr, THF, rt, 1 h, 86%; (b) KOH, THF/MeOH/H_2O (3:2:1), rt, 48 h, 75% (93% BRSM), trans/cis = 4:1.

successive treatment with $Me_3SnSnMe_3$ and Br_2 by the Wulff protocol.[25] Finally, crucial diimide reduction[26] of vinyl bromide **18** from the less hindered convex face, as shown in conformation **E**, delivered the desired bromide **19** in a highly stereoselective fashion.

We next set out to tackle the formidable[27] task of epimerization at C(12), which constitutes a highlight of our synthetic endeavor. After tactical exploitation of the 6,12-cis-stereochemistry of oxocene **8** to develop the chlorination at C(7) and the osmylation step, it was imperative for us to find an opportune moment for the pivotal isomerization. After considerable experimentation, we elected to perform the epimerization on α,α′-*cis*-ketone **20** by taking advantage of its unique dioxabicyclic molecular structure. To this end, our direct ketone synthesis protocol on α-alkoxy amide **19** with ethylmagnesium bromide afforded α,α′-*cis*-ethyl ketone **20** in 86% yield (Scheme 6).[7k,l] We were delighted to find that, upon exposure to aqueous potassium hydroxide, bicyclic α,α′-*cis*-ketone **20** underwent a smooth isomerization to deliver the crucial α,α′-*trans*-ketone **21** in 75% isolated yield in a 4:1 trans/cis ratio, probably to minimize the unfavorable electrostatic repulsion between the oxygen lone pairs present in conformation **F**.[28] This novel "lone pair−lone pair interaction-controlled" isomerization is remarkable since the equilibrium lies completely in favor of the α,α′-cis-isomer in the case of monocyclic oxocene **20′**.[27]

After the correct configuration at C(12) was established, we moved on to assembly of the C(12) and C(6) side-chain appendages. For this purpose, highly stereoselective and efficient L-Selectride reduction of ketone **21** in a Felkin-Ahn sense, followed by side-chain bromination at C(13) of the resulting

(19) The monoprotected chloro diol derivative of **7** with a silyl or acyl protecting group at C(10) afforded the corresponding oxolane after migration of the group upon exposure to base.
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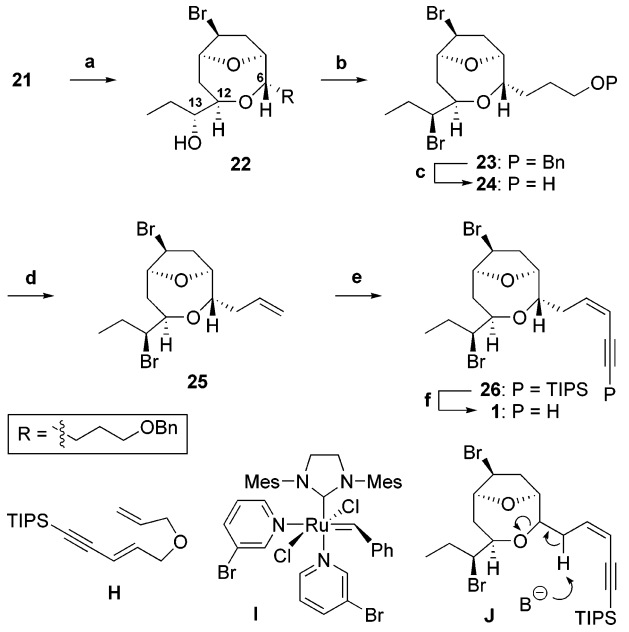
(28) For recent examples of controlling diastereoselectivity by the electrostatic repulsion between various types of lone pairs, see: (a) Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T.; Paquette, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 9021. (b) Ng, F. W.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812. (c) Lerchner, A.; Carreira, E. M. *Chem. Eur. J.* **2006**, *12*, 8208.

Scheme 7. Completion of Synthesis of (+)-Isolaureatin (**1**) by Olefin Cross-Metathesis[a]



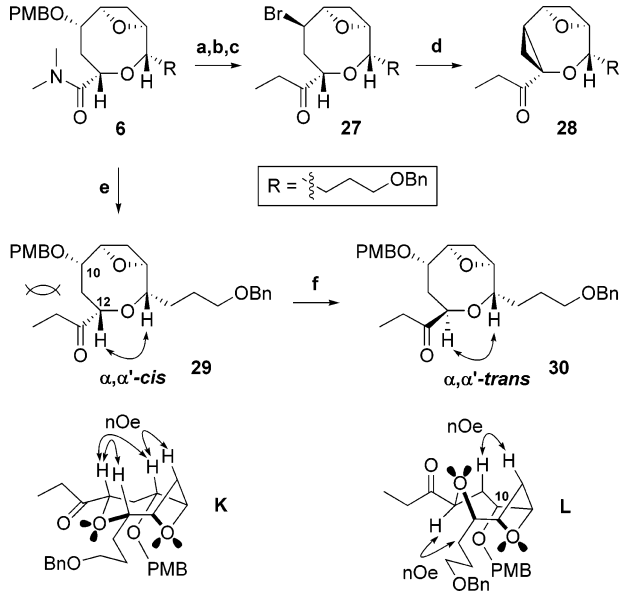
[a] Reagents and conditions: (a) L-Selectride, THF, −78 °C, 30 min, 94%; (b) CBr_4, Oct_3P, toluene, rt to 80 °C, 4 h, 84%; (c) H_2, Pd/C, EtOH/EtOAc (1:1), 2 h, 97%; (d) *o*-nitrophenylselenocyanide, Oct_3P, THF, rt, 2 h, then *m*-CPBA, 0 °C to rt, 3 h, 88%; (e) enyne **H**, Grubbs' catalyst **I**, benzene, 50 °C, 4 h, >76%, *Z*/*E* = 7:1; (f) TBAF, THF, −20 °C, 1 h, 96%.

secondary alcohol **22**, furnished key dibromo compound **23** in good yield (Scheme 7).

After functionalization of the C(12) side chain, we proceeded to address assembly of the unsaturated C(6) appendage. Thus, hydrogenolysis of the benzyl protecting group in **23**, followed by conversion of the resulting primary alcohol **24** into terminal olefin **25** by Grieco's protocol in a one-pot process,[29] set up the system for the crucial cross-metathesis for stereoselective introduction of the (*Z*)-enyne unit. Cross-metathesis of alkene **25** with enyne **H**[30] and Grubbs' catalyst **I**[31] using Lee's protocol[32] furnished a 76% isolated yield of (*Z*)-enyne **26** with a 7:1 *Z*/*E* stereoselectivity.[33] To the best of our knowledge, this constitutes the first application of the cross-metathesis protocol of Lee to the construction of a terminal (*Z*)-enyne system in natural product synthesis. It should be pointed out that (*Z*)-enyne **26** was found to be prone to ring opening under basic conditions as depicted in **J**. In fact, observation of the same phenomenon during a Wittig reaction to construct the (*Z*)-enyne unit in our preliminary studies led us to resort to the alternative CM strategy. Finally, careful removal of the TIPS group in **26** by treatment with fluoride at −20 °C to avoid the above-mentioned ring rupture furnished (+)-isolaureatin (**1**) in 96% yield. Spectral and optical rotation data of synthetic (+)-isolaureatin were identical to those of natural material.

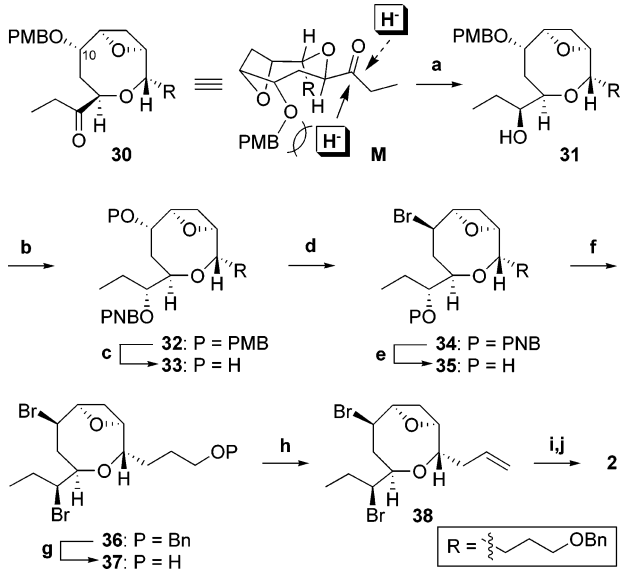
(29) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(30) Enyne **H** was prepared in two steps from the commercially available (*E*)-pent-2-en-4-yn-1-ol: (1) *n*-BuLi, THF, TIPSCl; (2) NaH, THF, allyl iodide.
(31) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035.
(32) (a) Kang, B.; Kim, D.-h.; Do, Y.; Chang, S. *Org. Lett.* **2003**, *5*, 3041. (b) Hansen, E. C.; Lee, D. *Org. Lett.* **2004**, *6*, 2035. (c) Kang, B. K.; Lee, J. M.; Kwak, J.; Lee, Y. S.; Chang, S. *J. Org. Chem.* **2004**, *69*, 7661.
(33) For recent representative reports on cross-metathesis, see: (a) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3171. (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

Scheme 8. Epimerization of α,α′-*cis*-Ketone **29**[a]



[a] Reagents and conditions: (a) DDQ, CH_2Cl_2/pH 7.0 buffer (9:1), rt, 1 h, 96%; (b) CBr_4, Oct_3P, pyridine, toluene, rt to 80 °C, 12 h; (c) EtMgBr, THF, rt, 1 h, 47% for two steps; (d) KOH, THF/MeOH/H_2O (3:2:1), rt, 12 h, 78%; (e) EtMgBr, THF, rt, 1 h, 94%; (f) KOH, THF/MeOH/H_2O (3:2:1), rt, 12 h, 95%.

Scheme 9. Completion of Synthesis of (+)-Laureatin (**2**)[a]



[a] Reagents and conditions: (a) L-Selectride, THF, −78 °C, 30 min, 96%; (b) DIAD, Ph_3P, *p*-nitrobenzoic acid, THF, rt to 40 °C, 12 h, 90%; (c) DDQ, CH_2Cl_2/pH 7.0 buffer (9:1), rt, 2 h, 95%; (d) CBr_4, Oct_3P, pyridine, toluene, rt to 80 °C, 4 h, 81%; (e) $LiAlH_4$, THF, 0 °C to rt, 1 h, 90%; (f) CBr_4, Oct_3P, 1-methylcyclohexene, toluene, rt to 80 °C, 4 h, 82%; (g) H_2, Pd/C, EtOH/EtOAc (1:1), 1 h, 98%; (h) *o*-nitrophenylselenocyanide, Oct_3P, THF, rt, 2 h, then *m*-CPBA, 0 °C to rt, 1 h, 88%; (i) enyne **H**, Grubbs' catalyst **I**, benzene, 50 °C, 4 h, >69%, *Z*/*E* = 7:1; (j) TBAF, THF, −20 °C, 1 h, 98%.

With our synthesis of (+)-isolaureatin (**1**) accomplished, we next turned to synthesis of (+)-laureatin (**2**) from the key oxabicyclic α,α′-*cis*-oxetane **6** as depicted in Scheme 8. Formation of cyclopropyl ketone **28** upon attempted base-promoted isomerization of bromo ketone **27** forced us to defer introduction of the bromine function at C(10) until after cis/

trans isomerization. Once again, our direct ketone synthesis protocol on α-alkoxy amide **6** with ethylmagnesium bromide (94% yield), followed by pivotal "lone pair−lone pair interaction-controlled" isomerization of the resultant α,α′-*cis*-ketone **29** (conformation **K**) by treatment with KOH in aqueous methanol, afforded the more stable α,α′-*trans*-ketone **30** (conformation **L**) exclusively in excellent yield (95%). The enhanced stereoselectivity here compared to bicyclic oxolane ketone **21** (trans/cis = 4:1) can be attributed to relief of additional unfavorable steric interactions between the C(10) and C(12) substituents in **29**.

To our great surprise, L-Selectride reduction of ketone **30** produced the undesired C(13)-(*S*) alcohol **31** exclusively in 96% yield, probably due to the PMB group at C(10) which blocks the *Si*-face of the carbonyl in Felkin-Ahn model **M** (Scheme 9). However, Mitsunobu inversion[34] of secondary alcohol **31** provided the desired *p*-nitrobenzoate **32** in 90% yield, setting the stage for the crucial sequential bromination at C(10) of the bicylic oxocene and C(13) of the acyclic side chain. Our experience dictated that ring bromination be carried out prior to side-chain bromination.[35] Thus, removal of the PMB protecting group of **32** and ring bromination of the resulting alcohol **33** furnished bromide **34** in 78% yield for the two steps. Reductive removal of the *p*-nitrobenzoate group in **34** with $LiAlH_4$, followed by side-chain bromination of the resulting alcohol **35**, yielded the requisite dibromide **36** in a satisfactory yield (74%, two steps). As with the isolaureatin intermediate, assembly of the C(6) side chain could be effected by the four-step CM protocol to give rise efficiently to (+)-laureatin (**2**) in 60% overall yield, whose spectral and optical rotation data were in good agreement with those reported for the natural product.

(34) Mitsunobu, O. *Synthesis* **1981**, 1.
(35) Reversal of the order of halogenation steps led to partial epimerization of the side-chain bromine.

Conclusion

In conclusion, the first and highly stereo-, regio-, and chemoselective asymmetric total syntheses of (+)-3-(*Z*)-isolaureatin (**1**) and (+)-3-(*Z*)-laureatin (**2**), unique medium-sized dioxabicyclic marine natural products with potent mosquito larvicide activity, were accomplished in a completely substrate-controlled manner. Our synthesis features a number of stereo-, regio-, and chemoselective transformations including an intramolecular amide enolate alkylation to construct the α,α′-*cis*-oxocene skeleton, novel "lone pair−lone pair interaction-controlled" epimerizations to the α,α′-*trans*-oxocenes, various strategies for the demanding stereoselective introduction of halogen atoms, and novel olefin cross-metatheses for construction of the (*Z*)-enyne systems.

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Supporting Information Available: General experimental procedures including spectroscopic and analytical data for all new compounds along with copies of the ^1H and ^{13}C NMR spectra for **1**, **2**, **5**−**9**, **12**−**38**, **12′**, and ^1H NMR of 13-*epi*-laureatin. This material is available free of charge via the Internet at http://pubs.acs.org.

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