J|A|C|S
ARTICLES
Published on Web 11/15/2006

# A General Strategy for Synthesis of Both (6*Z*)- and (6*E*)-Cladiellin Diterpenes: Total Syntheses of (−)-Cladiella-6,11-dien-3-ol, (+)-Polyanthellin A, (−)-Cladiell-11-ene-3,6,7-triol, and (−)-Deacetoxyalcyonin Acetate

Hyoungsu Kim, Hyunjoo Lee, Jayoung Kim, Sanghee Kim, and Deukjoon Kim*

*Contribution from the Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, San 56-1, Shinrim-Dong, Kwanak-Ku, Seoul 151-742, Korea*

Received August 9, 2006; E-mail: deukjoon@snu.ac.kr

***Abstract:*** The first total synthesis of an (*E*)-cladiellin diterpene, (−)-cladiella-6,11-diene-3-ol (**1**), was accomplished featuring an intramolecular amide enolate alkylation−intramolecular Diels−Alder strategy. In addition, a highly stereo-, regio-, and chemoselective synthetic strategy for other members of the cladiellin diterpenes such as (+)-polyanthellin A (**2**), (−)-cladiell-11-ene-3,6,7-triol (**3**), and (−)-deacetoxyalcyonin acetate (**4**) was developed utilizing the synthetic (*E*)-cladiellin **1** as a common intermediate by taking advantage of the unique chemical properties of its C(6)-(*E*)-oxatricyclic skeleton.

## Introduction

The cladiellin diterpenes, the most abundant class of 2,11-cyclized cembranoid natural products, have been isolated from marine invertebrates.[1] These medium-sized oxatricyclic marine natural products possess a nine-membered ring, and both C(6)-(*E*)- and (*Z*)-isomers are found in nature. Owing to their fascinating molecular architecture and diverse biological activity, the 2,11-cyclized cembranoids have attracted considerable attention from the synthetic community over the past decade, leading to the total synthesis of several members of this family[2] along with a number of approaches to their synthesis.[3] However, total synthesis of the cembrane-derived diterpenes with a (6*E*)-oxonene unit has not been realized to date. With the notion that both the (6*Z*)- and (6*E*)-oxonene cores could be constructed by our intramolecular amide enolate alkylation (IAEA) methodology,[4] total synthesis of the more challenging and hitherto inaccessible (6*E*)-cladiellins was undertaken. In this article, we report an asymmetric total synthesis of (−)-cladiella-6,11-dien-3-ol (**1**),[5] which constitutes the first total synthesis of an (*E*)-cladiellin diterpene. Furthermore, the synthetic (*E*)-cladiellin **1** could be transformed into other members of the cladiellin diterpenes such as (+)-polyanthellin (**2**),[6] (−)-cladiell-11-ene-3,6,7-triol (**3**),[7] and (−)-deacetoxyalcyonin acetate (**4**)[8] in a highly stereo-, regio-, and chemoselective fashion by taking advantage of the unique chemical properties of its (6*E*)-oxatricyclic skeleton (vide infra).

## Results and Discussion

As shown in Scheme 1, we envisaged that (−)-cladiella-6,-11-dien-3-ol (**1**) could be elaborated from key oxatricycle **5**, which in turn could be prepared by an intramolecular Diels−Alder (IMDA) reaction of tetraene **6**. We further envisioned that 2,9-*cis*-disubstitued (*E*)-oxonene **7** could be secured through an intramolecular amide enolate alkylation of chloro amide **8**. Our preliminary studies suggested that the secondary nature of C(3) and the syn relative stereochemistry of C(2) and C(3) in key internal alkylation substrate **8** are vital for efficient

(1) (a) Rodriguez, A. D. *Tetrahedron* **1995**, *51*, 4571. (b) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531. (c) Sung, P.-S.; Chen, M.-C. *Heterocycles* **2002**, *57*, 1705.

(2) (a) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391. (b) Paquette, L. A.; Moradei, O. M.; Bernardelli, P.; Lange, T. *Org. Lett.* **2000**, *2*, 1875. (c) Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683. (d) Gallou, F.; MacMillan, D. W. C.; Overman, L. E.; Paquette, L. A.; Pennington, L. D.; Yang, J. *Org. Lett.* **2001**, *3*, 135. (e) 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. (f) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033. (g) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *Org. Lett.* **2003**, *5*, 1543. (h) Molander, G. A.; St. Jean, D. J., Jr.; Haas, J. *J. Am. Chem. Soc.* **2004**, *126*, 1642. (i) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264. (j) Crimmins, M. T.; Brown, B. H.; Plake, H. R. *J. Am. Chem. Soc.* **2006**, *128*, 1371. For total syntheses of briarellin and asbestinin diterpenes, see: (k) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650. (l) Crimmins, M. T.; Ellis, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 17200.

(3) (a) Xu, Q.; Weeresakare, M.; Rainier, J. D. *Tetrahedron* **2001**, *57*, 8029. (b) Jung, M. E.; Pontillo, J. *J. Org. Chem.* **2002**, *67*, 6848. (c) Jung, M. E.; Pontillo, J. *Tetrahedron* **2003**, *59*, 2729. (d) Chai, Y.; Vicic, D. A.; McIntosh, M. C. *Org. Lett.* **2003**, *5*, 1039. (e) Davidson, J. E. P.; Gilmour, R.; Ducki, S.; Davies, J. E.; Green, R.; Burton, J. W.; Holmes, A. B. *Synlett* **2004**, 1434. (f) Molander, G. A.; Czako, B.; St. Jean, D. J., Jr. *J. Org. Chem.* **2006**, *71*, 1172. (g) Hutchison, J. M.; Lindsay, H. A.; Dormi, S. S.; Jones, G. D.; Vicic, D. A.; McIntosh, M. C. *Org. Lett.* **2006**, *8*, 3663.

(4) (a) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2003**, *125*, 10238. (b) Lee, H.; Kim, H.; Baek, S.; Kim, S.; Kim, D. *Tetrahedron Lett.* **2003**, *44*, 6609. (c) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett.* **2005**, *7*, 75.

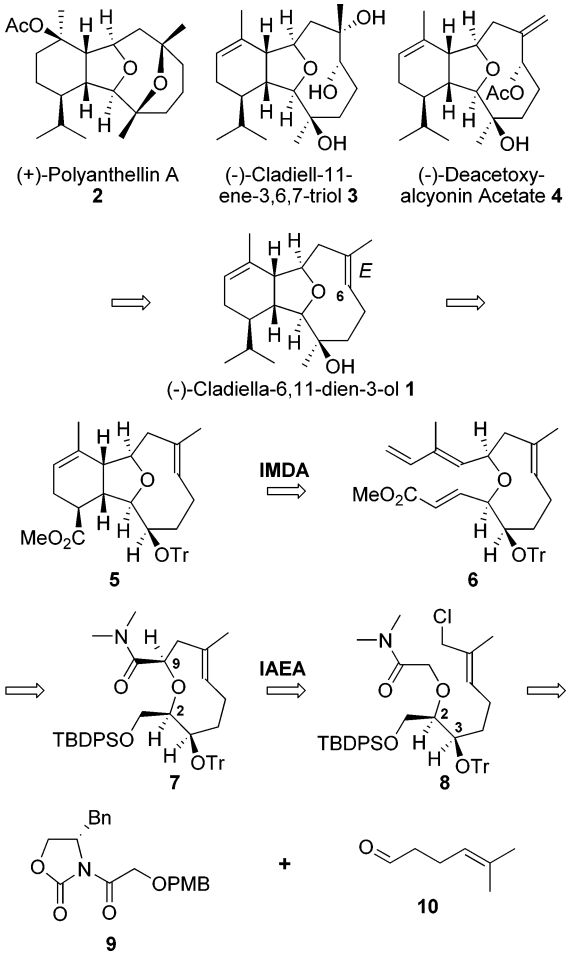
(5) (a) Hochlowski, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1980**, *21*, 4055. (b) Seo, Y.; Rho, J.-R.; Cho, K. W.; Shin, J. *J. Nat. Prod.* **1997**, *60*, 171.

(6) (a) Bowden, B. F.; Coll, J. C.; Vasilescu, I. M. *Aust. J. Chem.* **1989**, *42*, 1705. (b) Ospina, C. A.; Rodriguez, A. D.; Ortega-Barria, E.; Capson, T. L. *J. Nat. Prod.* **2003**, *66*, 357.

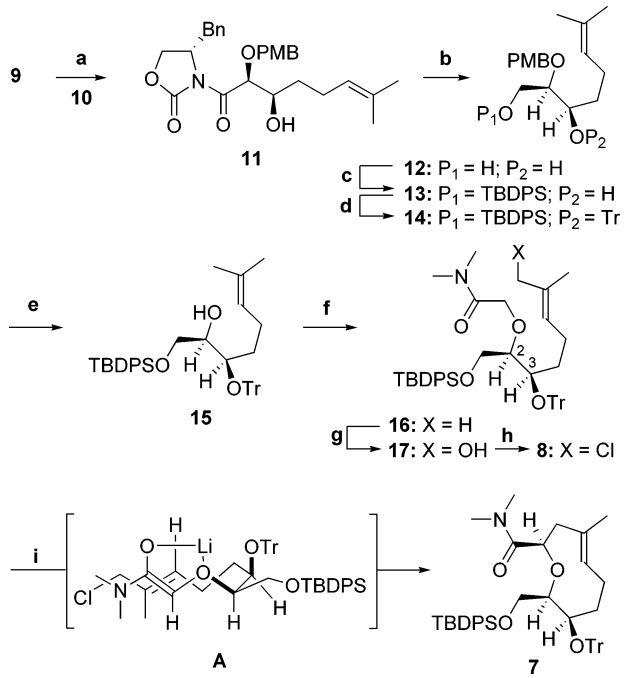
(7) Uchio, Y.; Nakatani, M.; Hase, T.; Kodama, M.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1989**, *30*, 3331.

(8) Uchio, Y.; Kodama, M.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1317.

***Scheme 1.*** Retrosynthetic Analysis




***Scheme 2.*** Synthesis of Key (*E*)-Oxonene **7** by IAEA[a]




[a] Reagents and conditions: (a) *n*-$Bu_2BOTf$, $Et_3N$, $CH_2Cl_2$, −78 to −40 °C, 30 min, then **10**, −78 to 0 °C, 2 h, 75%, (ds 98:2); (b) $NaBH_4$, THF/$H_2O$ (3:1), room temperature (rt), 2 h, 89%; (c) TBDPSCl, imidazole, 0 °C, 30 min, 92%; (d) trityl bromide, DMAP, pyridine, 100 °C, 6 h, 93%; (e) DDQ, $CH_2Cl_2$/pH 8.0 buffer (9:1), 0 °C, 1 h, 88%; (f) $ClCH_2CONMe_2$, NaH, THF, 0 °C to rt, 3 h, 88%; (g) $SeO_2$, pyridine, EtOH, 80 °C, 6 h, then $NaBH_4$, EtOH, 0 °C, 30 min, 76% (86% BRSM); (h) $Ph_3P$, $CCl_4$, pyridine, reflux, 2 h, 93%; (i) LiHMDS, THF, 45 °C, 1 h, 92%.

construction of strained[9] (6*E*)-oxonenes (vide infra).[10] The trityl protecting group for the C(3) hydroxyl function in **8** was chosen in view of the demonstrated importance of C(3) hydroxyl protection during the IMDA step for construction of the (6*Z*)-cladiellin skeleton.[2i,j,l] Further analysis indicated that the requisite internal alkylation precursor **8** could be prepared from known oxazolidinone **9** and aldehyde **10** by a glycolate aldol addition reaction.[11]

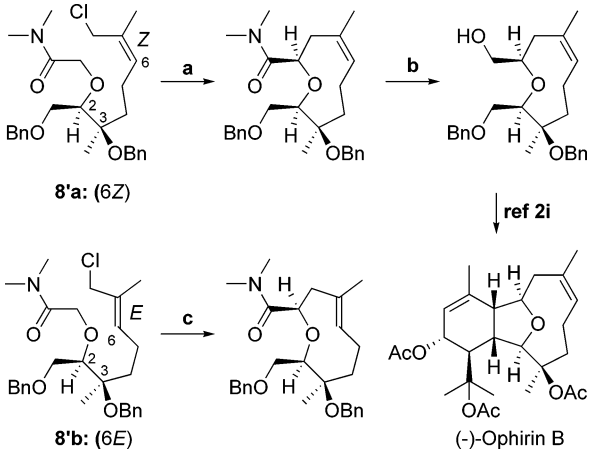
To commence the synthesis, the pivotal C(3) 2°/syn stereochemistry in alkylation substrate **8** was established by an aldol reaction of the dibutylboron enolate derived from readily available glycolate oxazolidinone **9**[12] with known aldehyde **10**[13] to yield the corresponding *syn*-aldol adduct **11** (75%, ds 98:2, $^1$H NMR analysis) (Scheme 2). Reductive cleavage of the chiral auxiliary in **11** and successive protection of the primary and secondary hydroxyl groups in the resulting diol **12** with TBDPSCl and trityl bromide, respectively, furnished the appropriately protected triol **14** in 76% overall yield for the three steps. Oxidative cleavage of the PMB group in **14** by the Yonemitsu method[14] and O-alkylation of the resulting alcohol **15** with *N*,*N*-dimethyl α-chloroacetamide afforded α-alkoxy amide **16** (77%, two steps). Stereoselective allylic oxidation of *gem*-dimethyl alkene **16** with $SeO_2$[15] and chlorination of the resulting (*E*)-allylic alcohol **17** by the Hooz protocol[16] produced (*E*)-allylic chloride **8** (80%, two steps), setting the stage for the crucial internal alkylation.

To our satisfaction, treatment of C(3) 2°/syn amide **8** with LiHMDS in THF at 45 °C for 1 h led to formation of the desired *cis*-(*E*)-oxonene **7** as a single diastereomer in excellent yield (92%), presumably through transition state **A**.[17] The corresponding *anti*-isomer of **8** did not produce any cyclization product under comparable conditions presumably due to a gauche effect in the transition state.

As outlined in Scheme 3, our preliminary study showed that internal alkylation of (*Z*)-C(3) 3°/syn substrate **8′a** proceeded smoothly to give the desired product in good yield (80%, unoptimized), which could be converted by a Superhydride reduction to a known Crimmins intermediate for (−)-ophirin B, a (6*Z*)-cladiellin.[2i,j,18] However, cyclization of the corresponding (*E*)-3°/syn isomer **8′b** was unsatisfactory in terms of chemical yield and reproducibility. Thus, our attempt to relieve the possible steric crowding in the transition state of cyclization of (*E*)-C(3) 3° substrate **8′b** by adopting C(3) 2° amide **8** as our cyclization precursor was rewarded. It is appropriate to

(9) Mancini, I.; Guella, G.; Zibrowius, H.; Pietra, F. *Helv. Chim. Acta* **2000**, *83*, 1561.
(10) In addition, the syn stereochemistry has been shown to play a critical role for controlling the diastereoselectivity of the intramolecular Diels−Alder reaction for construction of the (*Z*)-cladiellin skeleton (see ref 3e).
(11) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(12) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157.
(13) Kraus, G. A.; Kim, J. *Org. Lett.* **2004**, *6*, 3115.
(14) Oikawa, Y.; Yochika, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
(15) (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. (b) A small amount (~5%) of overoxidized α,α′-alkenediol was obtained.
(16) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.
(17) (a) For previous synthesis of (*E*)-oxonenes, see: Pohlmann, J.; Sabater, C.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 633. (b) Use of KHMDS as base did not effect internal alkylation, leading instead to decomposition.
(18) Kim, J. M.S. Thesis, Seoul National University, Seoul, Korea, 2006.

***Scheme 3.*** Intramolecular Amide Enolate Alkylation of (6*Z*)- and (6*E*)-C(3) 3°/syn Substrates[a]



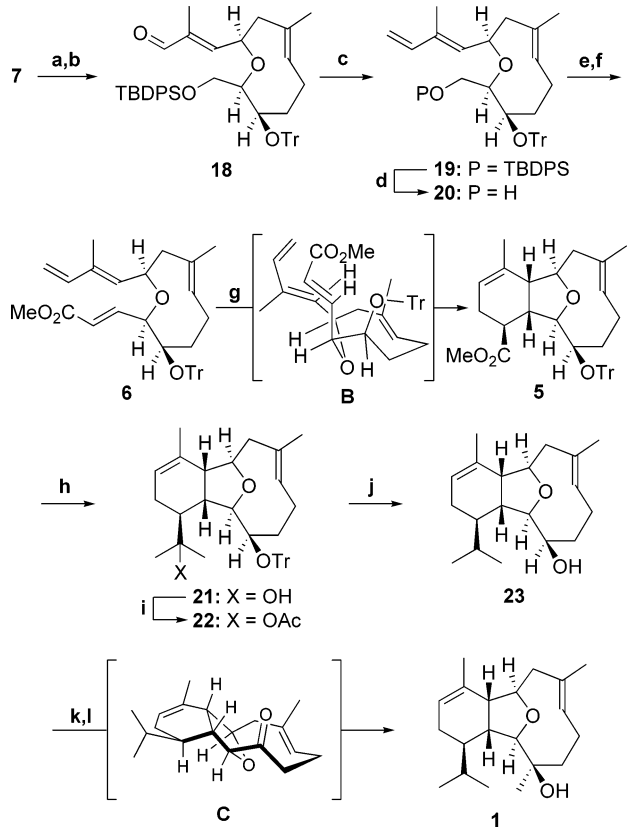

[a] Reagents and conditions: (a) KHMDS, THF, rt, 10 min, 80%; (b) Super-H, THF, rt, 2 h, 60%; (c) KHMDS, THF, rt, 10 min, ~40%.

mention at this point that the (*E*)-oxonenes were found to be quite unstable, especially under acidic conditions, and were stored as a solution in ethyl acetate containing a small amount of triethylamine.

With key IAEA product **7** in hand, we directed our efforts toward construction of the hydroisobenzofuran core in the natural product by an internal Diels−Alder strategy, which has been elegantly documented by both Crimmins and Holmes for the construction of (*Z*)-2,11-cyclized cembranoid skeleton (Scheme 4).[2i,j,l,3e] To this end, we prepared IMDA substrate **6** on the basis of successive Wittig olefinations, paying particular attention to the sensitivity of the (*E*)-oxonenes. The diene moiety of IMDA precursor **6** was installed first by a three-step sequence. Thus, partial reduction of the amide function in **7** with an ate complex,[19] followed by the Corey olefination protocol on the resulting aldehyde with α-lithio TMS-aldimine, furnished (*E*)-α,β-unsaturated aldehyde **18** (*E*:*Z* = 5:1, $^1$H NMR analysis) in 68% isolated yield for the two steps.[20] Wittig methylenation of (*E*)-enal **18** afforded (*E*)-1,3-diene **19** in 97% yield. With the diene moiety now installed, compound **19** was converted into the required IMDA intermediate **6** by desilyation, Dess−Martin oxidation,[21] and Wittig reaction (73%, three steps). Unlike the case of the (*Z*)-oxonenes,[2i,j,l,3e] refluxing tetraene **6** in xylene did not effect an intramolecular Diels−Alder reaction, leading instead to complete decomposition. However, we were pleased to find that addition of BHT to the reaction mixture produced the desired Diels−Alder adduct **5** in 85% yield, probably through exo transition state **B**.[22]

Having successfully assembled key oxatricyclic compound **5**, we embarked on the final stage of the synthesis of (−)-cladiella-6,11-dien-3-ol (**1**) by addressing the manipulation of the ester function to an isopropyl group in the presence of the reactive (6*E*)-oxonene, which turned out to be a challenge. For this purpose, ester **5** was first converted to the labile tertiary

***Scheme 4.*** Completion of Total Synthesis of (−)-Cladiella-6,11-dien-3-ol (**1**)[a]



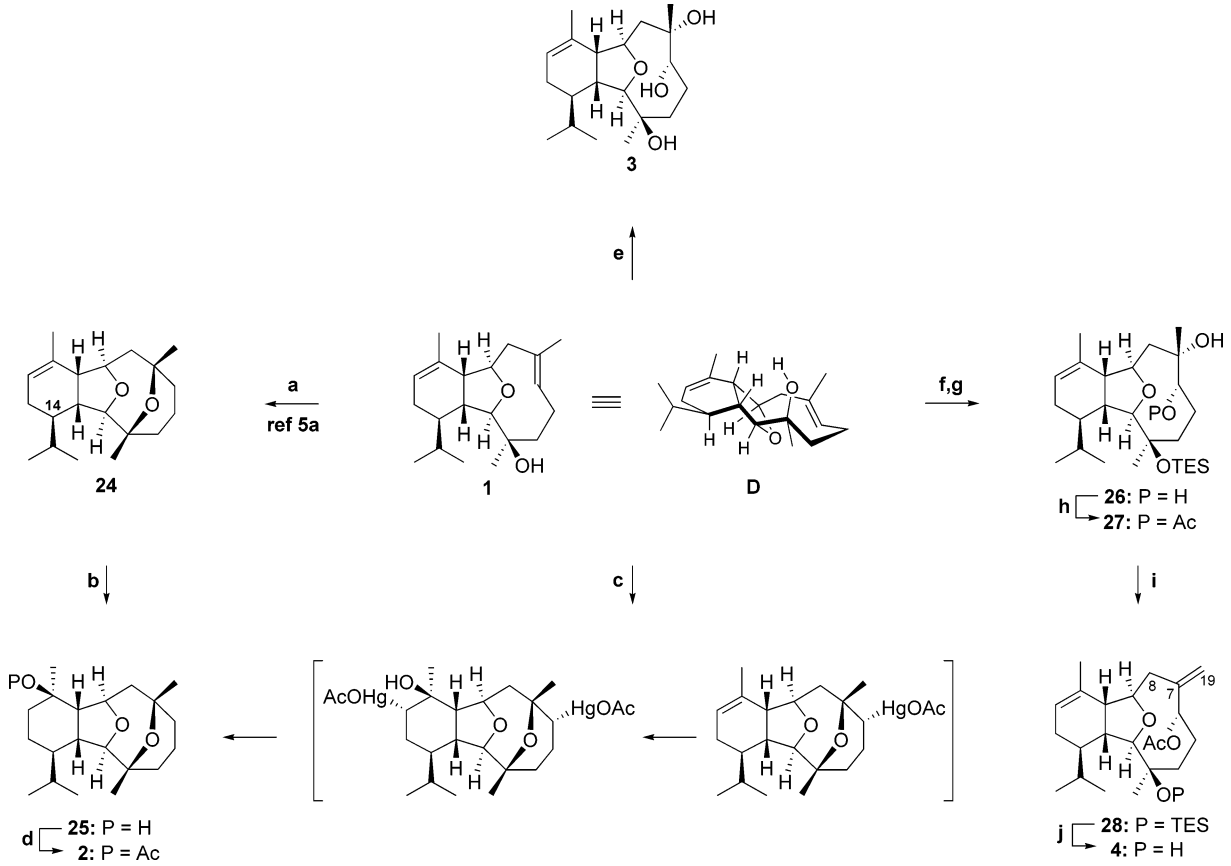

[a] Reagents and conditions: (a) DIBAL-H/*n*-BuLi (1:1), THF, 0 °C to rt, 30 min; (b) $CH_3CH(TMS)C{=}N$-*t*-Bu, *n*-BuLi, THF, −78 to 0 °C, 1 h, then the aldehyde from (a), −78 °C, 1 h, then oxalic acid, rt, 1 h, 68% for two steps, *E*:*Z* = 5:1; (c) $Ph_3P{=}CH_2$, THF, −78 °C to rt, 2 h, 97%; (d) TBAF, THF/DMF (2:1), rt, 16 h, 93%; (e) Dess−Martin periodinane, $NaHCO_3$, $CH_2Cl_2$, rt, 30 min; (f) $Ph_3P{=}CHCO_2Me$, $CH_2Cl_2$, rt, 1 h, 78% for two steps; (g) BHT, xylene, reflux, 1 h, 85%; (h) MeLi, $CeCl_3$, THF, −78 °C, 30 min, 89%; (i) $Ac_2O$, DMAP, $Et_3N$, $CH_2Cl_2$, rt, 48 h; (j) K, 18-crown-6, *t*-$BuNH_2$, THF, 1 h, 62% for two steps; (k) Dess−Martin periodinane, pyridine, $CH_2Cl_2$, rt, 30 min; (l) MeLi, $NaBF_4$, THF, −78 °C, 30 min, 82% for two steps.

acetate **22** by addition of MeLi in the presence of $CeCl_3$, followed by acetylation of the resulting tertiary alcohol **21**. After some experimentation, we were delighted to find that, upon subjection to dissolving metal reduction conditions (K, 18-crown-6, *t*-$BuNH_2$, THF),[23] tertiary acetate **22** underwent smooth chemoselective deoxygenation with concomitant cleavage of the trityl ether to deliver secondary alcohol **23** in 55% yield over three steps. Finally, Dess−Martin oxidation of alcohol **23** and subsequent treatment of the resulting unstable ketone with MeLi in the presence of $NaBF_4$ by the Paquette protocol[2b,e] gave rise to (−)-cladiella-6,11-dien-3-ol (**1**) in a stereoselective fashion, probably by nucleophilic attack from the molecular exterior of the preferred conformation **C**. The spectral characteristics and optical rotation of the synthetic material were in agreement with those of the natural product.[5]

With the initial mission accomplished, we were intrigued by the possibility that the synthetic (*E*)-cladiellin **1** might serve as a common intermediate for a highly stereo-, regio-, and chemoselective synthesis of other members of cladiellins such

(19) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717.
(20) (a) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, 7. (b) Attempt to isomerize the (*Z*)-enal under the Corey conditions was unsuccessful, leading to decomposition. See: Corey, E. J.; Weigel, L. O.; Floyd, D.; Bock, M. G. *J. Am. Chem. Soc.* **1978**, *100*, 2916.
(21) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Use of excess oxidant for a longer time caused allylic oxidation at the reactive (6*E*)-double bond.
(22) The corresponding tetraene with a benzyl protecting group at C(3) furnished the desired IMDA adduct in an inferior yield of 50%.
(23) Barrett, A. G. M.; Godfrey, C. R. A.; Hollinshead, D. M.; Prokopiou, P. A.; Barton, D. H. R.; Boar, R. B.; Joukhadar, L.; McGhie, J. F.; Misra, S. C. *J. Chem. Soc., Perkin Trans. I* **1981**, 1501.

***Scheme 5.*** Transformation of (−)-Cladiella-6,11-dien-3-ol (**1**) to Other Cladiellins[a]




[a] Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, $Et_2O$, rt, 30 min, 84%; (b) $Hg(OAc)_2$, $THF/H_2O$ (1:1), rt, 1 h, then $Et_3B$, $NaBH_4$, 62% (88% BRSM); (c) $Hg(OAc)_2$, THF, rt, 30 min, then $Hg(OAc)_2$, $H_2O$ to $THF/H_2O$ (1:1), 1 h, then $Et_3B$, $NaBH_4$, −20 °C to rt, overnight, 69%; (d) $Ac_2O$, DMAP, $Et_3N$, $CH_2Cl_2$, rt, 24 h, 78%; (e) $OsO_4$, NMO, $THF/H_2O$ (3:1), 0 °C, 1 h, 94%; (f) TESOTf, $CH_2Cl_2$, rt, 30 min, 97%; (g) $OsO_4$, NMO, $THF/H_2O$ (3:1), 0 °C, 5 h, 99%; (h) $Ac_2O$, DMAP, $Et_3N$, $CH_2Cl_2$, 0 °C, 30 min, 97%; (i) Burgess salt, toluene, 70 °C, 30 min; (j) TBAF, THF, 50 °C, 3 h, 92% for two steps.

as (+)-polyanthellin A (**2**), (−)-cladiell-11-ene-3,6,7-triol (**3**), and (−)-deacetoxyalcyonin acetate (**4**) as shown in Scheme 5. This attractive strategy relies on the following reasoning: (1) the trisubstituted (6*E*)-oxonene double bond in **1** might be more susceptible to electrophilic attack than the trisubstituted C(11) cyclohexene double bond, possibly due to a transannular interaction with the ring oxygen atom and ring strain[9,17,24] and (2) the (*E*)-oxonene moiety of the oxatricyclic skeleton is conformationally more rigid compared to that of the corresponding (*Z*)-oxonene, which should render peripheral attack in a highly stereoselective manner.[2e,9]

First, synthesis of (+)-polyanthellin A (**2**) was pursued along this line. A stereo- and regioselective oxymercuration−demercuration of oxatetracycle **24**, the known $BF_3{\cdot}Et_2O$-mediated cyclization product of **1**,[5a] in the presence of triethylborane[25a] to suppress $\beta$-elimination, furnished tertiary $\beta$-alcohol **25** (62%, 88% BRSM).[26] The observed stereochemical outcome could be rationalized by considering that the electrophile approaches from the α-face of the hexahydroisobenzofuran moiety to avoid steric interference from the pseudoaxially oriented C(14) isopropyl group. To our delight, exploration of a direct route to **25** led to an efficient one-pot protocol that consisted of sequential oxymercuration[25b] of the synthetic (*E*)-cladiellin **1** and exhaustive demercuration to furnish the desired tertiary $\beta$-alcohol in 69% optimized yield in a stereo- and regioselective manner. Acetylation of tertiary alcohol **25**, which is itself a natural product, furnished (+)-polyanthellin A (**2**). Both enantiomers of polyanthellin A have been found in nature, and the present synthesis establishes the absolute stereochemistry of the natural products. The enantiomer isolated by Bowden et al. corresponds to our synthetic (+)-polyanthellin A.[6]

For synthesis of (−)-cladiell-11-ene-3,6,7-triol (**3**), treatment of (−)-cladiella-6,11-dien-3-ol (**1**) with osmium tetroxide delivered the desired triol **3** in a highly stereo- and chemoselective fashion by peripheral attack by the electrophile on the preferred conformation **D** onto the more nucleophilic (6*E*)-double bond in 94% yield.[27−29]

Finally, protection of the hindered tertiary hydroxyl group of the sensitive (6*E*)-oxatricycle **1** with TESOTf and subsequent treatment of the resulting silyl ether with osmium tetroxide in a similar fashion provided diol **26** (96%, two steps).[30] Selective acetylation of the secondary hydroxyl group of diol **26** provided

(24) Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc.* **1992**, *114*, 3044.
(25) (a) Kang, S. H.; Lee, J. H.; Lee, S. B. *Tetrahedron Lett.* **1998**, *39*, 59. (b) Mercuriocyclization−demercuration of a related (6*Z*)-oxatricycle was shown to be completely nonregioselective (see ref 2e).
(26) In an exploratory experiment, oxatetracycle **24** could be converted to tertiary $\beta$-alcohol **25** in a conventional manner by successive treatment of **24** with aqueous NBS and methanolic $K_2CO_3$, followed by regioselective $LiAlH_4$ opening of the resultant $\beta$-epoxide (see ref 3f).
(27) A similar reaction of (−)-cladiellin, which possesses an *exo*-methylene-disubstituted double bond at C(11), with $OsO_4$ was reported: Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Schönholzer, P. *Tetrahedron Lett.* **1977**, 4643.
(28) Osmylation of a related (6*Z*)-oxatricycle was shown to be nonstereoselective (see refs 2d,e).
(29) The present synthesis also constitutes a formal synthesis of (−)-sclerophytin A (see ref 2f).

tertiary alcohol **27** for the crucial elimination step. After a considerable amount of experimentation, tertiary alcohol **27** furnished the desired *exo*-methylene regioisomer **28** upon exposure to Burgess salt[31] in excellent yield in a highly regioselective manner ($\Delta^{7,19}/\Delta^{7,8} = 20{:}1$, $^1$H NMR analysis).[32] Finally, desilylation of **28** with TBAF led to (−)-deacetoxyalcyonin acetate (**4**) whose spectral data and rotation were in good agreement with those of the natural material.

## Conclusion

In conclusion, an asymmetric total synthesis of (−)-cladiella-6,11-dien-3-ol (**1**) was accomplished in 21 steps in 6% overall yield from readily available starting materials **9** and **10** in a completely substrate-controlled manner, employing an intramolecular amide enolate alkylation and an intramolecular Diels−Alder reaction as key steps. This work constitutes the first total synthesis of an (*E*)-cladiellin. In addition, synthetic (−)-cladiella-6,11-dien-3-ol (**1**) was transformed in a highly stereo-, regio-, and chemoselective fashion into (+)-polyanthellin A (**2**), (−)-cladiell-11-ene-3,6,7-triol (**3**), and (−)-deacetoxyalcyonin acetate (**4**) by taking advantage of the unique properties of the (*E*)-oxonene moiety of **1**. Application of the present strategy to total synthesis of a variety of other 2,11-cyclized cembranoids is in progress in our laboratories.

**Acknowledgment.** This article is dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday. We thank Professors J. Shin (Seoul National University), A. D. Rodríguez (University of Puerto Rico), B. F. Bowden (James Cook University), and L. E. Overman (University of California, Irvine) for providing spectra of (−)-cladiella-6,11-dien-3-ol (**1**), (−)-polyanthellin A (**2**), (+)-(**2**) and (+)-deacetylpolyanthellin A (**25**), and natural and synthetic (−)-cladiell-11-ene-3,6,7-triol (**3**), respectively. This research was supported by the Korea Research Foundation Grant (KRF-2004-015-C00272) and the Brain Korea Project in 2005 and 2006.

**Supporting Information Available:** General experimental procedures, including spectroscopic and analytical data for all new compounds and copies of the $^1$H and $^{13}$C NMR spectra for **1**−**8**, **11**−**21**, and **23**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA065782W

(30) In view of the fact that C(3) hydroxyl groups of a considerable number of (6*E*)-cladiellins are acylated, our extensive attempt to acylate the C(3) hydroxyl function of (6*E*)-cladiellin **1** was unsuccessful unlike the case of (6*Z*)-cladiellins,[2e,i,j] possibly due to steric interference from C(7) methyl group in conformation **D**. For instance, treatment of **1** with acetic anhydride in the presence of $Bi(OTf)_3$ produced oxatetracycle **24** as the major product.

(31) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26 and references therein.

(32) Treatment of tertiary alcohol **27** with thionyl chloride furnished the corresponding $\Delta^{7,19}$- and $\Delta^{7,8}$-regioisomer in a roughly equal amount by $^1$H NMR analysis.