

Natural Products

N-Heterocyclic Carbene Catalyzed Oxidative Macrolactonization: Total Synthesis of (+)-Dactylolide**

Kiyoun Lee, Hyungsu Kim,* and Jiyong Hong*

(+)-Dactylolide (**1**, Figure 1) is a cytotoxic 20-membered macrolide isolated from the Vanuatu sponge *Dactylospongia* sp by Riccio and co-workers.^[1] It possesses unique structural features which include a 2,6-*cis*-2-(4-oxo-2-butenyl)tetrahydropyran, a highly unsaturated 20-membered macrolac-

carbene (NHC)-catalyzed oxidative macrolactonization reaction for the synthesis of the 20-membered macrocycle in **1**.

Our retrosynthetic plan for **1** is outlined in Scheme 1. In pursuit of **1**, we were particularly interested in addressing the potential challenges associated with the formation of the

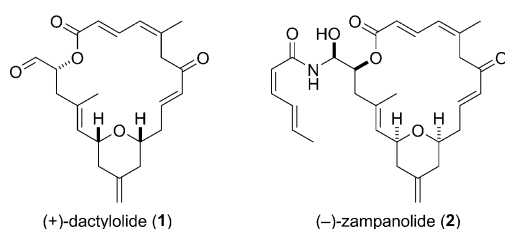
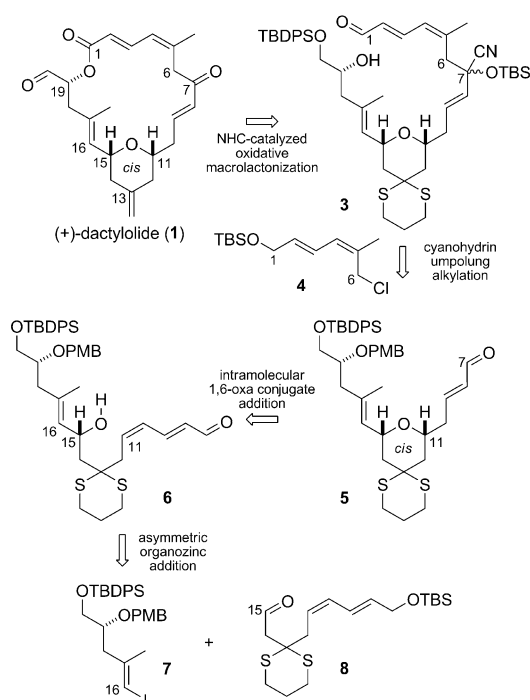


Figure 1. Structure of (+)-dactylolide (**1**) and (-)-zampanolide (**2**).

tone, and an α -chiral aldehyde. (+)-Dactylolide (**1**) displayed modest tumor cell growth inhibitory activities in leukemia and ovarian cancer cell lines^[1] and the mode of action has not been fully understood. Not surprisingly, as a result of the architectural complexity, biological profile, and enantiomeric relationship of the macrolactone core in **1** with natural (-)-zampanolide (**2**, Figure 1),^[2] **1**^[2b,3,5] and unnatural (-)-dactylolide^[2c-e,4,5] have attracted considerable interest from a number of synthetic groups, thus culminating in the first total synthesis by Smith and co-workers.^[2b,3a] The syntheses of **1** reported to date focus on the diastereoselective construction of the 2,6-*cis*-disubstituted tetrahydropyran subunit and the efficient formation of the 20-membered macrolactone core in **1**. Herein, we report a convergent synthesis of **1**, enlisting the 1,6-oxa conjugate addition reaction of a 2,4-dienal for the facile synthesis of the 2,6-*cis*-2-(4-oxo-2-butenyl)tetrahydropyran subunit in **1**, the umpolung alkylation reaction of a cyanohydrin, and the N-heterocyclic



Scheme 1. Retrosynthetic plan for (+)-dactylolide (**1**). PMB = *para*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

highly unsaturated 20-membered macrolactone. Dienoic substrates are known to be ineffective for macrolactonization under conventional reaction conditions.^[6] In particular, the macrolactonization of dienioic substrates for the synthesis of **1** either failed to proceed^[3c] or gave the desired macrolactones in unsatisfactory yields under Yamaguchi, Shiina, or Trost–Kita conditions.^[2d] We were also interested in the development of a concise approach to the 2,6-*cis*-2-(4-oxo-2-butenyl)tetrahydropyran subunit in **1**.

We anticipated that the 20-membered macrolactone in **1** could be constructed by intramolecular oxidative macrolactonization of ω -hydroxy aldehyde **3** catalyzed by an NHC. Conventional macrolactonization procedures require the use of a stoichiometric amount of activating agents and often need a protection/deprotection sequence. Recently, several

[*] K. Lee, Prof. Dr. J. Hong
Department of Chemistry, Duke University
Durham, NC 27708 (USA)
E-mail: jiyong.hong@duke.edu

Prof. Dr. H. Kim
College of Pharmacy, Ajou University
Suwon 443-749 (Korea)
E-mail: hkimajou@ajou.ac.kr

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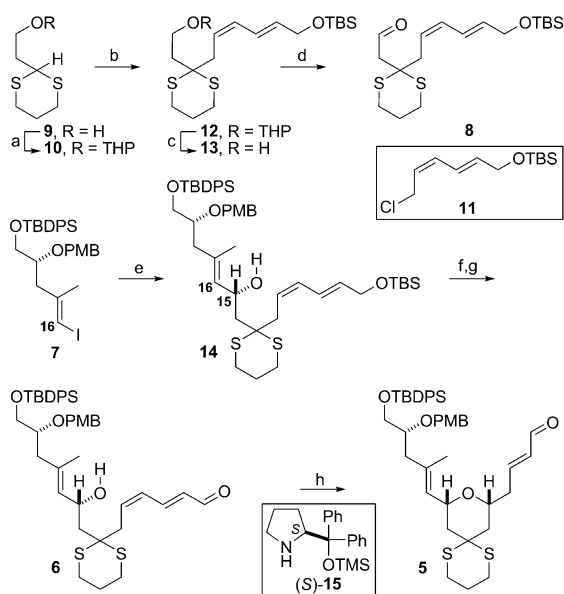
examples of inter- and intramolecular NHC-catalyzed oxidative esterification of aldehydes have been reported^[7] and clearly provide a new opportunity for the development of *catalytic* acyl transfer agents in macrolactonization reactions of ω -hydroxy aldehydes in the presence of oxidants.

The substrate for the macrolactonization reaction could be prepared by umpolung alkylation of the corresponding TBS-protected cyanohydrin of 2,6-*cis*-tetrahydropyran enal **5** with dienyli chloride **4**. We further envisioned that **5** could be constructed in a stereoselective manner through an intramolecular 1,6-oxa conjugate addition reaction of ω -hydroxy 2,4-dienal **6**.^[8] Despite the great potential as an elegant solution to the facile synthesis of 2-(4-oxo-2-butenyl) cyclic ethers, the 1,6-oxa conjugate addition has been extremely underutilized in natural product synthesis.^[9] Further analysis suggested that **6** could be accessible by the asymmetric addition of vinyl iodide **7** to aldehyde **8** in a reagent-controlled manner.

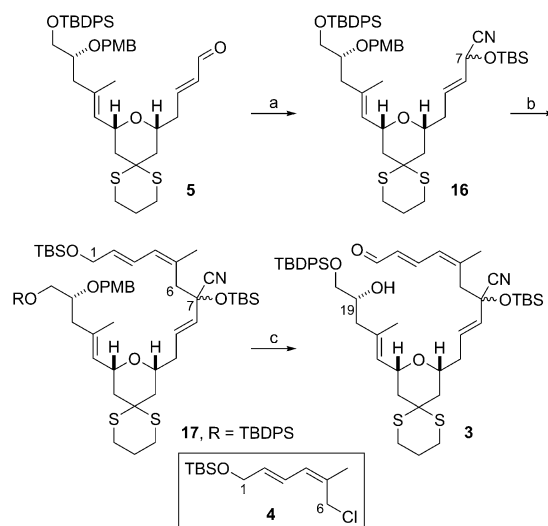
The synthesis of **1** started with the preparation of the ω -hydroxy 2,4-dienal **6** for the key intramolecular 1,6-oxa conjugate addition reaction (Scheme 2). The coupling of the dithiane **10**, prepared by THP protection of the known 1,3-dithiane-2-ethanol (**9**),^[10] and dienyli chloride **11**^[11] in the presence of *n*BuLi and *n*Bu₂Mg^[12] proceeded smoothly to provide **12**.^[13] Exposure of the THP ether **12** to ZnCl₂ with subsequent Parikh–Doering oxidation of the resulting alcohol

13 provided aldehyde **8**. With aldehyde **8** in hand, we attempted to stereoselectively install the C15 secondary carbinol by an asymmetric organozinc addition.^[14] We expected that the asymmetric addition of a highly functionalized bromozinc reagent derived from **7** to aldehyde **8** would be challenging because of the possible chelation of the oxygen atoms to zinc. Indeed, following the procedure described by Shair and co-workers,^[14b] the reaction gave **14** only with modest stereoselectivity (d.r. = 3.5:1). After an extensive search for the optimal reaction conditions, we were delighted to find that the slow addition (4 h) of **8** to a mixture of the corresponding bromozinc reagent of **7** and lithiated (1*S*,2*R*)-NME provided **14** in good stereoselectivity and yield (d.r. = 7.7:1, 71 %).^[15]

Removal of the TBS group in **14** and MnO₂ oxidation of the resulting allyl alcohol provided the ω -hydroxy 2,4-dienal **6**, thus setting the stage for the key intramolecular 1,6-oxa conjugate addition reaction. When **6** was treated with (*S*)-**15**^[16] at 0 °C, the organocatalytic 1,6-oxa conjugate addition reaction proceeded smoothly to provide the desired 2,6-*cis*-2-(4-oxo-2-butenyl)tetrahydropyran **5** with excellent stereoselectivity and yield (d.r. > 20:1, 98 %).^[17,18] When **6** was treated with either piperidine or (*R*)-**15**, the organocatalytic 1,6-oxa conjugate addition reaction provided **5** in 89 % (d.r. = 10:1) and 98 % (d.r. = 2:1), respectively (see the Supporting Information for details). To the best of our knowledge, this work is the first successful example of the construction of a tetrahydropyran through an intramolecular 1,6-oxa conjugate addition reaction.^[19] Having successfully prepared the desired 2,6-*cis*-tetrahydropyran enal **5** by employing the intramolecular 1,6-oxa conjugate addition reaction, we proceeded to install the C1–C6 fragment of the natural product using an acyl anion equivalent (Scheme 3). After extensive experimentation, we used a TBS-protected cyanohydrin^[20]



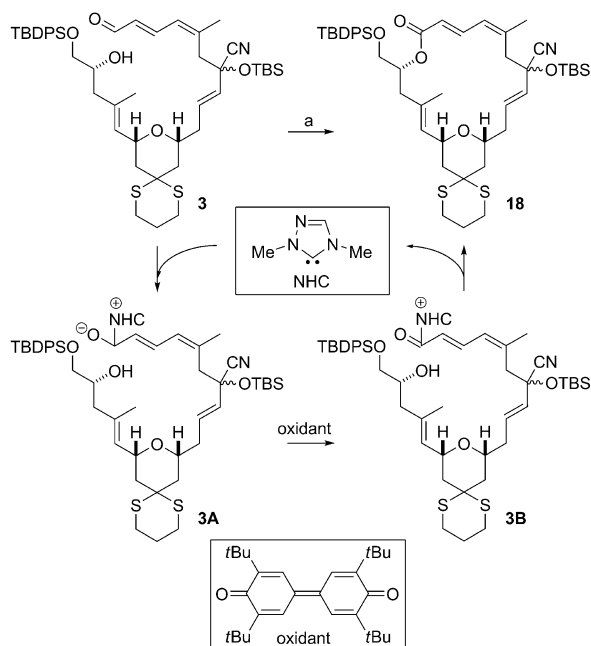
Scheme 2. A stereoselective synthesis of 2,6-*cis*-2-(4-oxo-2-butenyl)-tetrahydropyran: a) 3,4-dihydro-2*H*-pyran, camphorsulfonic acid, CH₂Cl₂, 0 °C, 1 h, 92 %; b) *n*BuLi/*n*Bu₂Mg (4:1), THF, 25 °C, 1 h; **11**, –78 to 0 °C, 1.5 h, 72 %; c) ZnCl₂, CH₂Cl₂, 25 °C, 3 h, 62 % (75 % brsm); d) SO₃·pyridine, DMSO, *i*Pr₂NEt, CH₂Cl₂, 0 °C, 1 h, 85 %; e) *t*BuLi, Et₂O, –78 °C, 1 h; ZnBr₂, Et₂O, 0 °C, 1 h; *n*BuLi/(1*S*,2*R*)-NME, toluene, 0 °C, 1 h; **8**, –20 °C, 4 h, 71 %, d.r. = 7.7:1; f) pyridinium *p*-toluenesulfonate, EtOH, 25 °C, 9 h, 69 % (81 % brsm); g) MnO₂, CH₂Cl₂, 25 °C, 20 min, 84 %; h) (*S*)-**15** (20 mol %), benzoic acid (20 mol %), toluene, 0 °C, 10 h, 98 %, d.r. > 20:1. brsm = based on recovered starting material, DMSO = dimethylsulfoxide, (1*S*,2*R*)-NME = (1*S*,2*R*)-*N*-methylephedrine, THF = tetrahydrofuran, THP = tetrahydropyranyl, TMS = trimethylsilyl.



Scheme 3. Preparation of ω -hydroxy aldehyde **3** for NHC-catalyzed oxidative macrolactonization: a) TBSCN, KCN, 18-crown-6, CH₂Cl₂, 25 °C, 1 h, 99 %; b) **4**, NaHMDS, THF, –78 °C, 20 min, 87 %; c) DDQ, pH 7 phosphate buffer/CH₂Cl₂ (1:10), 0 to 25 °C, 1.5 h, 96 %. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, HMDS = hexamethyldisilazide.

because of the easy preparation^[21] and preference for α -alkylation^[22] of the corresponding vinyl cyanohydrin anion. After the formation of the TBS-protected cyanohydrin **16** by treatment of **5** with TBSCN, the coupling of **16** and dienyl chloride **4** gave **17** in 87%. Concomitant removal of the PMB group and C1 oxidation of **17** was accomplished by treatment with DDQ to afford the ω -hydroxy aldehyde **3**, which set the stage for the pivotal NHC-catalyzed oxidative macrolactonization.

With the requisite ω -hydroxy aldehyde **3** in hand, we directed our attention to NHC-catalyzed oxidative macrolactonization (Scheme 4). Initial attempts for the macro-

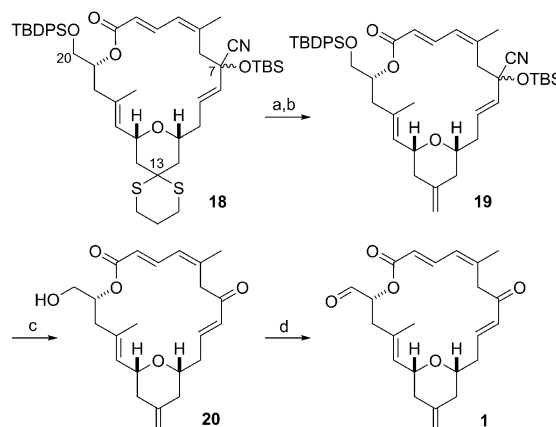


Scheme 4. NHC-catalyzed oxidative macrolactonization: a) 1,4-dimethyl-4*H*-1,2,4-triazolium iodide (30 mol %), 3,3',5,5'-tetra-*tert*-butyldiphenylquinone, DBU, DMAP, 4 Å M.S., CH₂Cl₂, 25 °C, 20 h, 65%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-(dimethylamino)pyridine, M.S. = molecular sieves.

lactonization in the presence of dimethyltriazolium iodide, DBU, MnO₂, and 4 Å molecular sieves in CH₂Cl₂ provided **18** in poor yield (< 10%). We were pleased to find that, however, the addition of DMAP,^[23] the use of 3,3',5,5'-tetra-*tert*-butyldiphenylquinone as an oxidant,^[24] and a slow addition of **3** (2 h) proved to be highly effective, thus leading to higher yield (65%).^[25] Since NHCs have not yet been exploited as acyl transfer agents in macrolactonization reactions, our report, therefore, constitutes the first example of the NHC-catalyzed oxidative macrolactonization of ω -hydroxy aldehydes. Because of significant benefits of the reaction, including the catalytic nature and mild reaction conditions of the reaction, the NHC-catalyzed oxidative macrolactonization reaction would provide a significant advance in the field of macrolactonization.

Having successfully assembled the macroketone **18**, we embarked on the completion of the synthesis of **1** by

elaborating the C13 *exo*-methylene group, unveiling the C7 carbonyl group, and oxidizing the C20 hydroxy group to the corresponding aldehyde (Scheme 5). Hydrolysis of the 1,3-



Scheme 5. Completion of total synthesis of (+)-dactylolide (**1**): a) MeI, CaCO₃, CH₃CN/H₂O (3:1), 40 °C, 30 h, 81%; b) CH₃Ph₃P⁺I⁻, *n*BuLi, THF, -78 to 25 °C, 1 h, 79%; c) TBAF, THF, -78 to 25 °C, 3 h, 75%; d) Dess–Martin periodinane, NaHCO₃, CH₂Cl₂, 0 to 25 °C, 1 h, 90%. TBAF = tetra-*n*-butylammonium fluoride.

dithiane group of **18** and Wittig olefination of the resulting ketone gave **19**. Concomitant removal of the TBS and TBDPS groups with subsequent Dess–Martin oxidation of alcohol **20** afforded **1**, which was identical in all respects to the natural product.

In conclusion, the total synthesis of (+)-dactylolide (**1**) has been accomplished in 19 steps for the longest sequence from commercially available 1,3-dithiane with an overall yield of 1.4% (1.9% brsm). Highlights of the synthesis include the organocatalytic 1,6-oxa conjugate addition reaction for the stereoselective synthesis of 2,6-*cis*-2-(4-oxo-2-butenyl)tetrahydropyran and the NHC-catalyzed oxidative lactonization for the construction of the 20-membered macrolactone. Other notable features in the synthesis are highly efficient carbon–carbon bond formations, including a 1,3-dithiane coupling reaction, asymmetric addition of an alkenylzinc reagent, and cyanohydrin alkylation, which allow a convergent approach to the carbon skeleton in **1**. We strongly believe that the NHC-catalyzed oxidative macrolactonization provides a new approach to a diverse set of macrolactones. The application of the NHC-catalyzed oxidative macrolactonization to other macrolactones and macrolide-containing natural products is underway and will be reported in due course.

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