Natural Products

DOI: 10.1002/anie.201201653

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

Kiyoun Lee, Hyoungsu 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 macrolactone, 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 carbene (NHC)-catalyzed oxidative macrolactonization reaction for the synthesis of the 20-membered macrocyle in **1**.

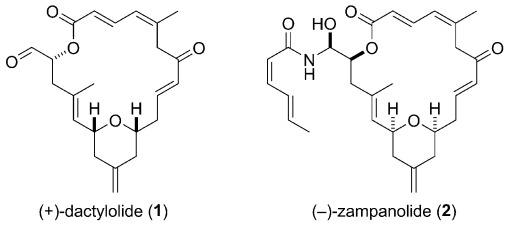
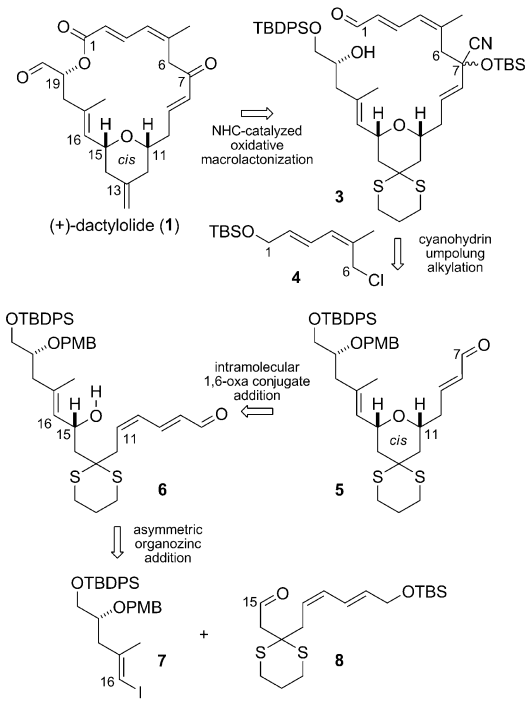


Figure 1. Structure of (+)-dactylolide (**1**) and (−)-zampanolide (**2**).

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 highly unsaturated 20-membered macrolactone. Dienoic substrates are known to be ineffective for macrolactonization under conventional reaction conditions.[6] In particular, the macrolactonization of dienoic 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**.



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

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

[**] We are grateful to Duke University for funding this work, to the North Carolina Biotechnology Center (NCBC; Grant No. 2008-IDG-1010) for funding of the NMR instrumentation, and to the National Science Foundation (NSF) MRI Program (Award ID No. 0923097) for funding mass spectrometry instrumentation.

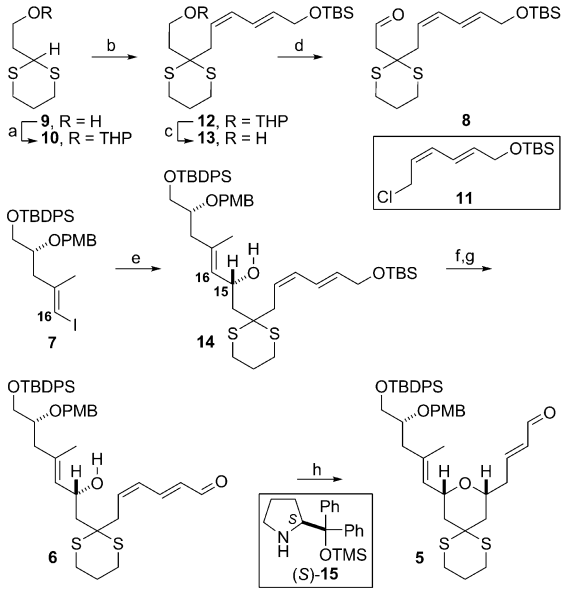
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201201653.

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.

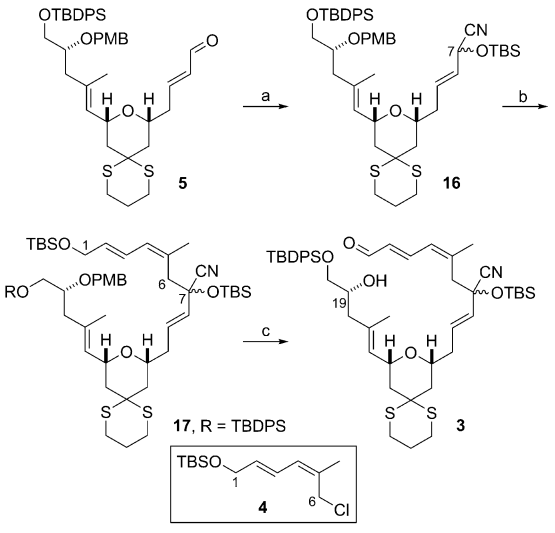
The substrate for the macrolactonization reaction could be prepared by umpolung alkylation of the corresponding TBS-protected cyanohydrin of 2,6-*cis*-tetrahydropyran enal **5** with dienyl chloride **4**. We further envisioned that **5** could be constructed in a stereoselective manner through an intramolecular 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 dienyl chloride **11**[11] in the presence of *n*BuLi and nBu$_2$Mg[12] proceeded smoothly to provide **12**.[13] Exposure of the THP ether **12** to $ZnCl_2$ 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 MnO_2 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]



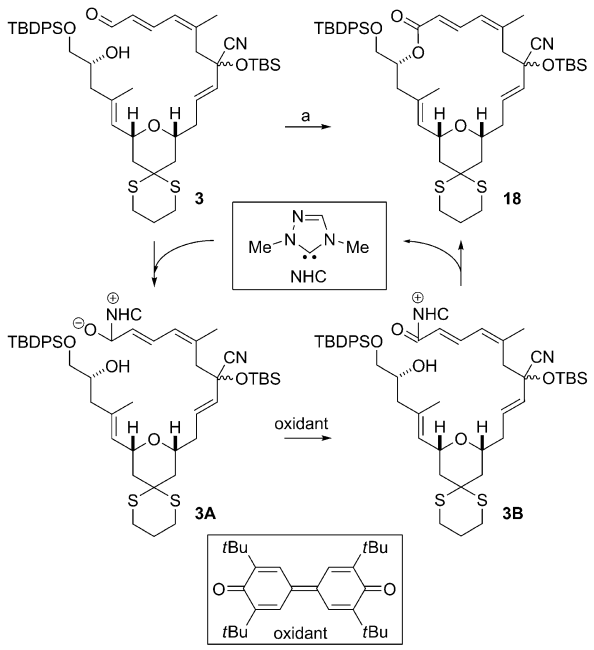
Scheme 2. A stereoselective synthesis of 2,6-*cis*-2-(4-oxo-2-butenyl)-tetrahydropyran: a) 3,4-dihydro-2*H*-pyran, camphorsulfonic acid, CH_2Cl_2, 0 °C, 1 h, 92 %; b) *n*BuLi/nBu$_2$Mg (4:1), THF, 25 °C, 1 h; **11**, −78 to 0 °C, 1.5 h, 72 %; c) $ZnCl_2$, CH_2Cl_2, 25 °C, 3 h, 62 % (75 % brsm); d) SO_3·pyridine, DMSO, *i*Pr$_2$NEt, CH_2Cl_2, 0 °C, 1 h, 85 %; e) *t*BuLi, Et_2O, −78 °C, 1 h; $ZnBr_2$, Et_2O, 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) MnO_2, CH_2Cl_2, 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, CH_2Cl_2, 25 °C, 1 h, 99 %; b) **4**, NaHMDS, THF, −78 °C, 20 min, 87 %; c) DDQ, pH 7 phosphate buffer/CH_2Cl_2 (1:10), 0 to 25 °C, 1.5 h, 96 %. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, HMDS = hexamethyldisilazide.

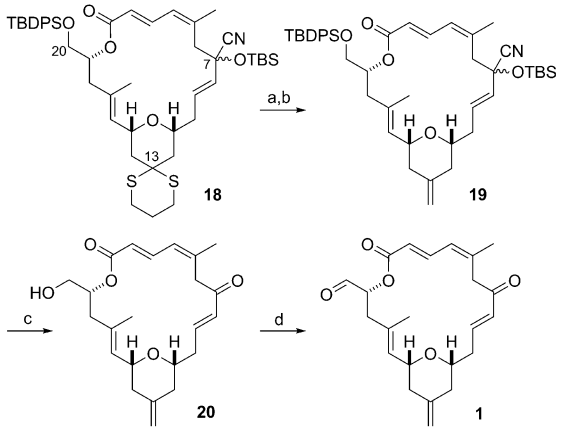
because of the easy preparation[21] and preference for α-alkylation[22] of the corresponding vinyl cyanohydrin anion. After the formation of the TBS-protected cyanohydrin **16** by treatment of **5** with TBSCN, the coupling of **16** and dienyl chloride **4** gave **17** in 87%. Concomitant removal 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 macrolactonization in the presence of dimethyltriazolium iodide, DBU, MnO_2, and 4 Å molecular sieves in CH_2Cl_2 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*-butyldiphenoquinone 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.



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*-butyldiphenoquinone, DBU, DMAP, 4 Å M.S., CH_2Cl_2, 25 °C, 20 h, 65%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-(dimethylamino)-pyridine, M.S. = molecular sieves.

Having successfully assembled the macrolactone **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-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.



Scheme 5. Completion of total synthesis of (+)-dactylolide (**1**): a) MeI, $CaCO_3$, CH_3CN/H_2O (3:1), 40 °C, 30 h, 81%; b) $CH_3Ph_3P^+I^-$, *n*BuLi, THF, −78 to 25 °C, 1 h, 79%; c) TBAF, THF, −78 to 25 °C, 3 h, 75%; d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 to 25 °C, 1 h, 90%. TBAF = tetra-*n*-butylammonium flouride.

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.

Received: February 29, 2012
Published online: ■■ ■■, ■■■■

Keywords: lactones · natural products · N-heterocyclic carbenes · total synthesis · umpolung

[1] A. Cutignano, I. Bruno, G. Bifulco, A. Caspullo, C. Debitus, L. Gomez-Paloma, R. Riccio, *Eur. J. Org. Chem.* **2001**, 775–778.

[2] For total synthesis of zampanolide, see: a) A. B. Smith III, I. G. Safonov, R. M. Corbett, *J. Am. Chem. Soc.* **2001**, *123*, 12426 – 12427; b) A. B. Smith III, I. G. Safonov, R. M. Corbett, *J. Am. Chem. Soc.* **2002**, *124*, 11102 – 11113; c) T. R. Hoye, M. Hu, *J. Am. Chem. Soc.* **2003**, *125*, 9576 – 9577; d) J. Uenishi, T. Iwamoto, J. Tanaka, *Org. Lett.* **2009**, *11*, 3262 – 3265; e) A. K. Ghosh, X. Cheng, *Org. Lett.* **2011**, *13*, 4108 – 4111.

[3] a) A. B. Smith III, I. G. Safonov, *Org. Lett.* **2002**, *4*, 635 – 637; b) D. L. Aubele, S. Wan, P. E. Floreancig, *Angew. Chem.* **2005**, *117*, 3551 – 3554; *Angew. Chem. Int. Ed.* **2005**, *44*, 3485 – 3488; c) C. C. Sanchez, G. E. Keck, *Org. Lett.* **2005**, *7*, 3053 – 3056.

[4] a) F. Ding, M. P. Jennings, *Org. Lett.* **2005**, *7*, 2321 – 2324; b) I. Louis, N. L. Hungerford, E. J. Humphries, M. D. McLeod, *Org. Lett.* **2006**, *8*, 1117 – 1120; c) F. Ding, M. P. Jennings, *J. Org. Chem.* **2008**, *73*, 5965 – 5976; d) D. Zurwerra, J. Gertsch, K.-H. Altmann, *Org. Lett.* **2010**, *12*, 2302 – 2305; e) S. Y. Yun, E. C. Hansen, I. Volchkov, E. J. Cho, W. Y. Lo, D. Lee, *Angew. Chem.* **2010**, *122*, 4357 – 4359; *Angew. Chem. Int. Ed.* **2010**, *49*, 4261 – 4263.

[5] For synthetic studies, see: a) T.-P. Loh, J.-Y. Yang, L.-C. Feng, Y. Zhou, *Tetrahedron Lett.* **2002**, *43*, 7193 – 7196; b) C. R. Reddy, B. Srikanth, *Synlett* **2010**, 1536 – 1538.

[6] For an example, see: D. Amans, V. Bellosta, J. Cossy, *Org. Lett.* **2007**, *9*, 4761 – 4764.

[7] a) H. Inoue, K. Higashiura, *J. Chem. Soc. Chem. Commun.* **1980**, 549 – 550; b) K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126 – 8127; c) N. T. Reynolds, J. R. Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518 – 9519; d) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.* **2007**, *9*, 371 – 374; e) B. E. Maki, K. A. Scheidt, *Org. Lett.* **2008**, *10*, 4331 – 4334; f) L. Wang, K. Thai, M. Gravel, *Org. Lett.* **2009**, *11*, 891 – 893; g) K. Zeitler, C. A. Rose, *J. Org. Chem.* **2009**, *74*, 1759 – 1762; h) J. R. Struble, J. W. Bode, *Tetrahedron* **2009**, *65*, 4957 – 4967; i) C. A. Rose, K. Zeitler, *Org. Lett.* **2010**, *12*, 4552 – 4555.

[8] For our reports on tetrahydropyran synthesis through the oxa-conjugate addition, see: a) H. Kim, Y. Park, J. Hong, *Angew. Chem.* **2009**, *121*, 7713 – 7717; *Angew. Chem. Int. Ed.* **2009**, *48*, 7577 – 7581; b) H. Kim, J. Hong, *Org. Lett.* **2010**, *12*, 2880 – 2883; c) K. Lee, H. Kim, J. Hong, *Org. Lett.* **2011**, *13*, 2722 – 2725; d) H. Park, H. Kim, J. Hong, *Org. Lett.* **2011**, *13*, 3742 – 3745; e) S. R. Byeon, H. Park, H. Kim, J. Hong, *Org. Lett.* **2011**, *13*, 5816 – 5819; f) K. Lee, H. Kim, J. Hong, *Eur. J. Org. Chem.* **2012**, 1025 – 1032.

[9] For the synthesis of a tetrahydrofuran through the 1,6-oxa conjugate addition, see: S. S. Ko, L. L. Klein, K.-P. Pfaff, Y. Kishi, *Tetrahedron Lett.* **1982**, *23*, 4415 – 4418.

[10] M. J. Gaunt, A. S. Jessiman, P. Orsini, H. R. Tanner, D. F. Hook, S. V. Ley, *Org. Lett.* **2003**, *5*, 4819 – 4822.

[11] F. Caussanel, P. Deslongchamps, Y. L. Dory, *Org. Lett.* **2003**, *5*, 4799 – 4802.

[12] a) M. Ide, M. Yasuda, M. Nakata, *Synlett* **1998**, 936 – 938; b) M. Ide, M. Nakata, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491 – 2499; c) T. Ichige, Y. Okano, N. Kanoh, M. Nakata, *J. Org. Chem.* **2009**, *74*, 230 – 243.

[13] The coupling of **9** and (2*E*,4*E*) or (2*Z*,4*E*)-dienyl chloride in the presence of *n*BuLi or *t*BuLi resulted in the formation of the desired coupling product in low yields (< 40 %).

[14] a) W. Oppolzer, R. N. Radinov, *Tetrahedron Lett.* **1991**, *32*, 5777 – 5780; b) M. E. Layton, C. A. Morales, M. D. Shair, *J. Am. Chem. Soc.* **2002**, *124*, 773 – 775.

[15] The configuration of the C15 stereocenter of **14** was determined using the procedure reported by Kakisawa and co-workers (see the Supporting Information for details).

[16] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804 – 807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794 – 797; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284 – 4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212 – 4215.

[17] The relative stereochemistry of **5** was assigned as *cis* by 2D NMR spectroscopy (see the Supporting Information for details).

[18] It should be noted that the 1,4-oxa conjugate addition reaction of an ester provided the 2,6-*cis*-tetraydropyran in low stereoselectivity (d.r. = 1.8:1), see Ref. [2d].

[19] For attempts for the synthesis of a tetrahydropyran by the 1,6-oxa conjugate addition, see: a) B. Wang, T. M. Hansen, T. Wang, D. Wu, L. Weyer, L. Ying, M. M. Engler, M. Sanville, C. Leitheiser, M. Christmann, Y. Lu, J. Chen, N. Zunker, R. D. Cink, F. Ahmed, C.-S. Lee, C. J. Forsyth, *J. Am. Chem. Soc.* **2011**, *133*, 1484 – 1505; b) S. R. Houghton, L. Furst, C. N. Boddy, *J. Org. Chem.* **2009**, *74*, 1454 – 1463.

[20] a) G. Stork, L. Maldonado, *J. Am. Chem. Soc.* **1971**, *93*, 5286 – 5287; b) A. Kalir, D. Balderman, *Synthesis* **1973**, 358 – 359; c) K. Deuchert, U. Hertenstein, S. Hünig, *Synthesis* **1973**, 777 – 779.

[21] Initially, we envisioned the 1,3-ditinane coupling reaction for C6–C7 bond formation. However, the preparation of the corresponding dithiane from **5** failed because of the 1,4-conjugate addition of 1,3-propanedithiol to **5**.

[22] a) T. Takahashi, H. Nemoto, J. Tsuji, *Tetrahedron Lett.* **1983**, *24*, 2005 – 2008; b) R. M. Jacobson, G. P. Lahm, J. W. Clader, *J. Org. Chem.* **1980**, *45*, 395 – 405.

[23] The NHC-catalyzed oxidative macrolactonization of **3** in the absence of DMAP resulted in lower yield (32 %), thus suggesting that DMAP may play an important role in the reaction mechanism. Further study would be required for determining the exact role of DMAP.

[24] S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190 – 1191.

[25] The macrolactonization reaction of the corresponding carboxylic acid of aldehyde **3** utilizing Shiina's procedure afforded macrolactone **18** in 81 % (see the Supporting Information for details). Since structurally similar substrates without the cyanohydrin group failed to afford the corresponding macrolactone[3c] or resulted in low to modest yields (21–48 %) under a variety of macrolactonization conditions,[2d] it is noteworthy to mention that TBS-protected cyanohydrin at the C7-position plays an important role in the NHC-catalyzed oxidative macrolactonization through the *gem*-disubstituent effect. To the best of our knowledge, this is the first example where a cyanohydrin elicits the *gem*-disubstituent effect.[26]

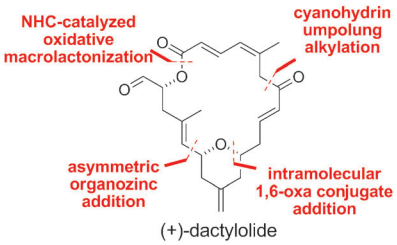
[26] During the review of the manuscript, an independent report on the *gem*-disubstituent effect by a cyanohydrin appeared in literature, see: Z. Cai, N. Yongpruksa, M. Harmata, *Org. Lett.* **2012**, *14*, 1661 – 1663.

Communications

Natural Products

K. Lee, H. Kim,* J. Hong* ____ ■■■■–■■■■

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



Three key steps constitute the total synthesis of (+)-dactylolide: 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, the umpolung alkylation reaction of a cyanohydrin, and the NHC-catalyzed oxidative macrolactonization reaction for the synthesis of the 20-membered macrocyle. NHC = N-heterocyclic carbene.