Natural Product Synthesis

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Total Synthesis of (−)-Dactylolide**

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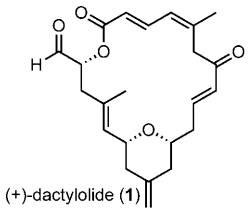
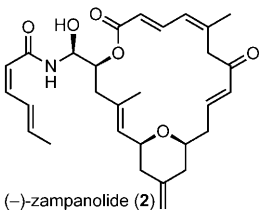
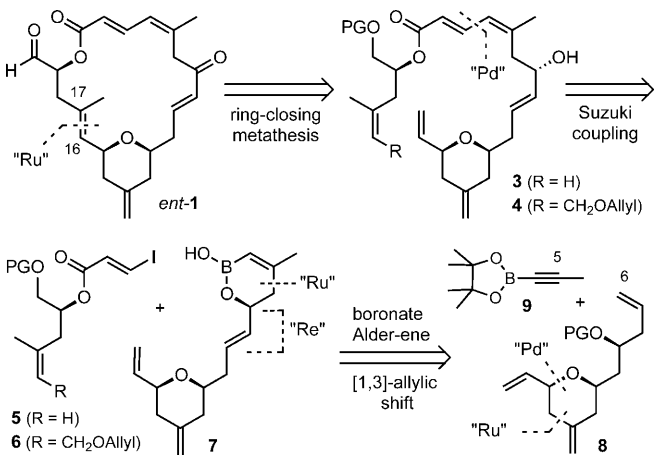
Since its discovery in 2001 by Riccio and co-workers,[1] dactylolide **1** has attracted considerable synthetic interest.[2] Several total syntheses of both natural (+)- and unnatural (−)-dactylolide have been reported. Extensive interest in dactylolide stems from not only its distinctive structural features, including a highly unsaturated 18-membered macrolactone with an embedded 2,6-disubstituted tetrahydropyran moiety, but also its biological activity toward several tumor cell lines such as L1210 and SK-OV-3 (63% and 40% inhibition, respectively, at 3.2 $\mu g\,mL^{-1}$).[1] Furthermore, a closely related natural product zampanolide **2**,[2b] has shown significantly more potent biological activity by blocking cell cycle in G2M transition through the stabilization of microtubules.[3–5] From a standpoint of the biosynthetic origin, it is interesting to note that the absolute configuration of the identical macrolide substructures contained in these two natural compounds is opposite.[6]





Recently, our research group has developed synthetic methods for efficient construction of trisubstituted *Z*-vinylboronates and 4-exomethylene-*cis*-2,6-disubstituted tetrahydropyrans. As an application to showcase these synthetic methods, herein we describe a concise route to (−)-dactylolide. Our retrosynthesis shown in Scheme 1 focuses on harnessing the power of transition-metal-catalyzed reactions to effect C–C and C–O bond formations. Often, the products from these reactions serve as the direct substrate for the next reaction,[7] thus minimizing the need for functional group transformations and protection/deprotection steps. We envision the macrocycle of (−)-**1** will be achieved through a late-



Scheme 1. Retrosynthesis of (−)-dactylolide (*ent*-**1**). PG = protecting group.

stage ring-closing metathesis (RCM) reaction[8] to form the C16–C17 double bond from **3** or relay metathesis substrate **4**.[9] To access **3** and **4**, we planned to use a Suzuki–Miyaura[10] coupling of iodoacrylate **5** and **6** and cyclic boronic acid half ester **7**. This is in turn accessed through the ruthenium-catalyzed Alder–ene reaction (RCAER)[11] to form the C5–C6 bond with the terminal double bond of **8** and alkynyl boronate **9** and subsequent rhenium-catalyzed allylic [1,3]-transposition.[12] The pyran subunit in **8** would be installed using a tandem RCAER and palladium-catalyzed ring closure.[13]

The synthesis of tetrahydropyran **8** commenced with the RCAER between ethyl carbonate **10** and homopropargylic alcohol **11**[14] and led to 1,4-diene **12** (Scheme 2). Treatment of **12** with palladium catalyst in the presence of Trost's chiral (+)-DPPBA[15] ligand afforded 2,6-*cis*-disubstituted tetrahydropyran **13** (11:1 diastereomeric ratio). This transformation was best achieved using a one-pot procedure,[16] and gave **13** in 72% yield. Removal of the pivalate group and oxidation of the resulting alcohol gave aldehyde **14**. Leighton allylation[17] and subsequent TBS protection afforded homoallyl silyl ether moiety of **8**. The RCAER of alkynyl boronate **9** occurred selectively with the least hindered double bond at C7 of **8**, and afforded vinyl boronate **15** (*cis/trans* = 5:1). The 1,3-transposition of the allyl alcohol of **15** with rhenium oxide in ether[18] afforded a relatively unstable cyclic boronic acid half ester **7**.

Subsequently, Suzuki coupling partner 2-iodoacrylate **5** was prepared from TBS-protected (*S*)-glycidol **16** (Scheme 3). The opening of the epoxide ring with 2-propenylmagnesium chloride and a subsequent Mitsunobu reaction[19] of **17** with 2-iodoacrylic acid **18**[20] provided ester **5**. The Suzuki coupling between **5** and **7** delivered **3** (79%). An attempted RCM with alcohol **3** did not yield the expected 18-membered lactone,

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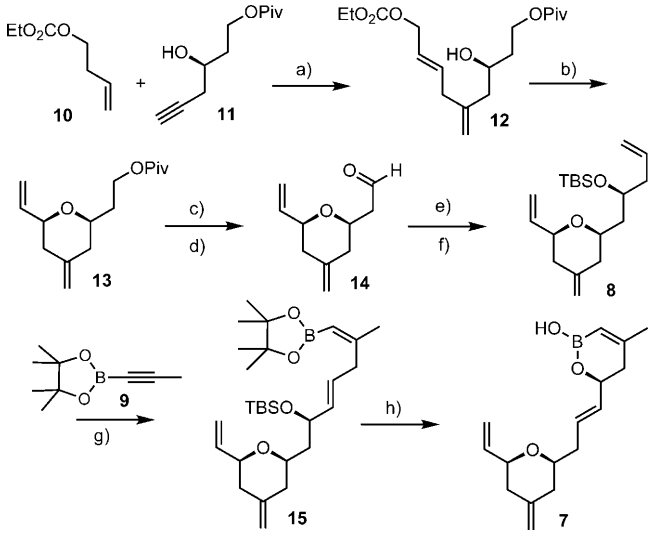
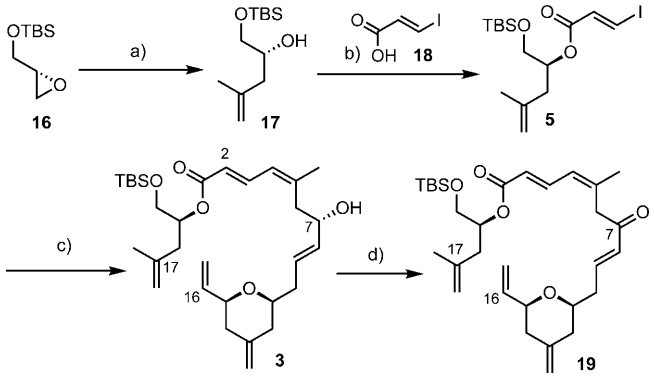


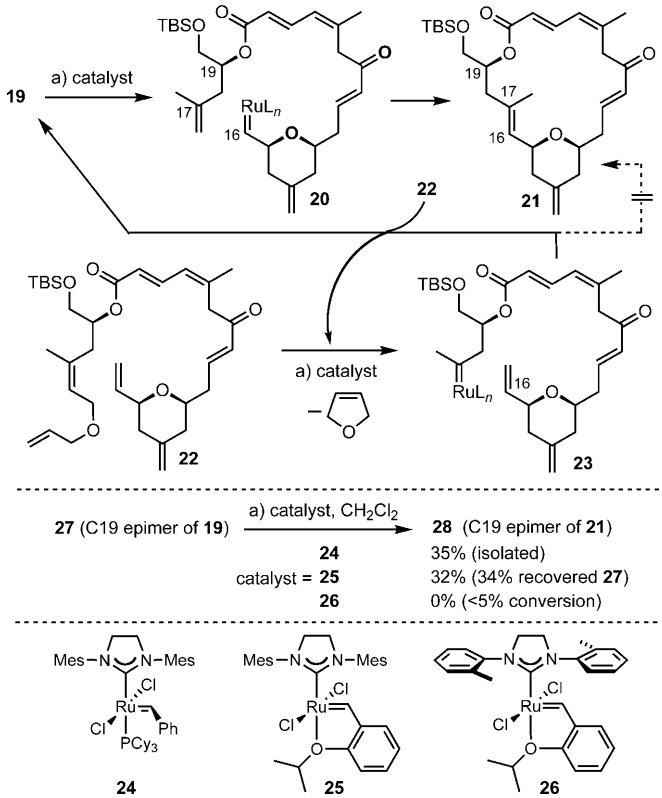
Scheme 2. a) 7 mol% $[RuCp(CH_3CN)_3]PF_6$, acetone, RT; b) 3 mol% $[Pd_2(dba)_3]\cdot CHCl_3$, 9 mol% (+)-DPPBA, CH_2Cl_2, −20°C to RT, 70% over two steps; c) DIBAL, CH_2Cl_2, −78°C, 96%; d) IBX, DMSO, 95%; e) (S,S)-Leighton reagent, CH_2Cl_2 −10°C, 85% (8:1 d.r.); f) TBSCl, imidazole, DMF, 98%; g) 10 mol% $[RuCp(CH_3CN)_3]PF_6$, acetone, RT, 65% (78% brsm), h) 10 mol% Re_2O_7, 65%. brsm = based on recovered starting material, Cp = cyclopentadienyl, dba = trans,trans-dibenzylideneacetone, DIBAL = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, DPPBA = 1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenyl-phosphinobenzoyl), IBX = 2-iodoxybenzoic acid, Piv = pivolyl, TBS = tert-butyldimethylsilyl.



Scheme 3. a) 2-Propenylmagnesium chloride, −30°C, THF, 82%; b) DIAD, PPh_3, THF, 0°C, 84%; c) **7**, $[Pd(PPh_3)_4]$, TlOEt, THF/H_2O (3:1), 79%; d) DMP, CH_2Cl_2, 89%. DIAD = diisopropyl azodicarboxylate, DMP = Dess–Martin periodinane, THF = tetrahydrofuran.

but instead generated a six-membered lactone through ring closure at C17–C2. Believing that the local conformation of the ketone at C7 should be similar to that of dactylolide, alcohol **3** was oxidized to α,β-unsaturated ketone **19** (89%).

With the pivotal RCM substrate **19** in hand, we explored various reaction conditions to maximize the formation of lactone **21** (Scheme 4). Treatment of **19** with the second-generation Grubbs catalyst **24** in the presence of benzoquinone[21] delivered the desired macrolactone **21** in 45% yield. Presumably, the RCM reaction occurred via the alkylidene intermediate **20**. Other catalysts **25** and **26** as well as the the first-generation Grubbs catalyst resulted in lower yield or no

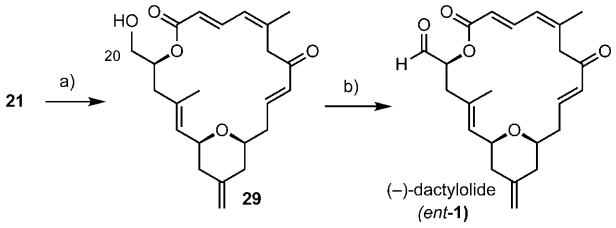


Scheme 4. a) 10 mol% **24**–**26**, 10 mol% benzoquinone, CH_2Cl_2, 65°C, 45%. Cy = cyclohexyl, Mes = mesityl.

reaction. We expected that the efficiency of the ring closure should be improved by generating an alternative alkylidene **23** because its ring closure with the less hindered double bond at C16 should be more facile. To test this hypothesis, we prepared an RCM substrate **22** that contains a relay metathesis tether. However, **22** did not cyclize directly into **21**, instead only to **19** by cleaving off the relay tether. This cleavage results from a faster methylene transfer from **22** to alkylidene **23** rather than its macrocyclic RCM. Based on this behavior and different modes of RCM with **3** and **19**, we surmised that the conformation of long linear substrates plays a more important role than the steric hindrance of the reacting double bond. To gain more insight into these divergent RCM behaviors, we examined RCM of diastereomeric substrate **27** (C19 epimer of **19**; Scheme 4). Interestingly, the RCM of **27** was similar to that of **21**, and gave macrolactone **28** (C19 epimer of **21**) with similar efficiency.[22] This outcome suggests that the RCM behavior of these substrates cannot be predicted simply on the basis of steric hindrance or local conformation.

Completion of (−)-dactylolide *ent*-**1** was accomplished by removal of the TBS group from **21**, thus generating **29** with an alcohol group at the C20—an intermediate reported by Smith and Safonov[2a] in their synthesis—and its subsequent oxidation with Dess–Martin periodinane (Scheme 5). The spectroscopic data of both **29** and *ent*-**1** are identical to those reported in the literature.

In conclusion, we have achieved a concise total synthesis of (−)-dactylolide. Several distinctive features in this syn-



Scheme 5. a) 1 N HCl, MeOH, 95%; b) DMP, pyridine, CH_2Cl_2, 90%.

thesis include: 1) a one-pot synthesis of *cis*-2,6-disubstituted-4-methylene tetrahydropyran through RCAER and palladium-catalyzed ring closure, 2) an Alder–ene reaction of alkynyl boronates and subsequent rhenium-catalyzed allylic transposition, and 3) a macrocyclic RCM to form an 18-membered lactone with concomitant installation of a trisubstituted double bond. The effectiveness and versatility of transition-metal-catalyzed transformations demonstrated in this synthetic maneuver can be further exploited in the synthesis of other complex molecular frameworks.

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[22] With catalyst **24**, no starting material **27** was recovered. However, 34 and >95% of **27** was recovered intact with catalyst **25** and **26**, respectively.

