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An Expedient Total Synthesis of (–)-Dactylolide and Formal Synthesis of (–)-Zampanolide

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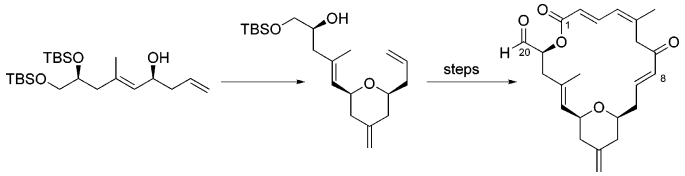
ABSTRACT



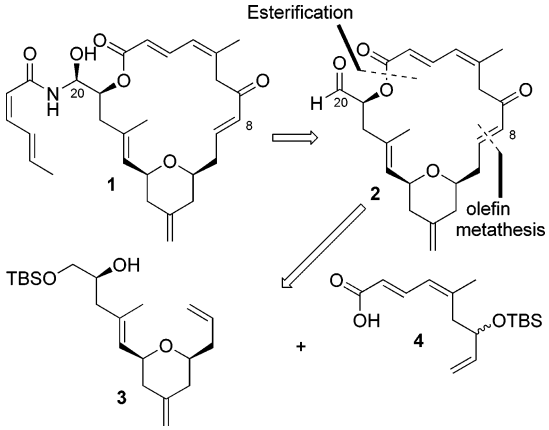
A highly convergent and efficient total synthesis of (–)-dactylolide and formal synthesis of (–)-zampanolide is reported.

First isolated and disclosed in 1996 by Higa and co-workers,[1] zampanolide (**1**) represented a novel macrolide that exhibited significant activity against a variety of tumor cell lines. In particular, **1** has proven to be active against the P388, A549, HT29, and MEL28 cell lines with IC_{50} values ranging from 1 to 5 ng/mL.[1] However, extensive biological tests have not been performed because of the lack of material, as only 3.9 mg were isolated from 0.480 kg (wet weight) of the marine sponge *Fasciospongia rimosa*. Subsequently, Riccio isolated a structurally related compound, dactylolide (**2**), from the marine sponge *Dactylospongia*.[2] However, **2** only displayed a modest biological profile (63% and 40% inhibition of L1210 and SK-OV-3 tumor cell lines at 3.2 μg/mL) with respect to that of **1**, thus suggesting that the *N*-acyl hemiaminal side-chain resident in **1** is required for the impressive biological activity.

In addition to a highly unsaturated macrolactone, both naturally occurring cytotoxins also feature a *cis*-2,6-disubstituted 4-*exo*-methylene tetrahydropyran ring system. Coupled with potent cytotoxicity and unusual structures of both **1** and **2,** there has been moderate synthetic interest in these targets.[3] By means of Smith's account, it was observed that the common macrocyclic cores of **1** and **2** share an enantiomeric relationship to one another. Thus, the natural (−)-zampanolide can be degraded to the unnatural (−)-dactylolide, or in the forward sense, (−)-dactylolide would serve as the macrocyclic precursor of natural zampanolide.

The retrosynthetic analysis of both (−)-dactylolide (**2**) and (−)-zampanolide is illustrated in Scheme 1. As reported by Hoye, strategic disconnection at the *N*-acyl hemi-aminal side chain would allow for the corresponding engagement of an "aluminum aza-aldol" sequence with the aldehyde moiety

Scheme 1



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(2) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.* **2001**, 775.

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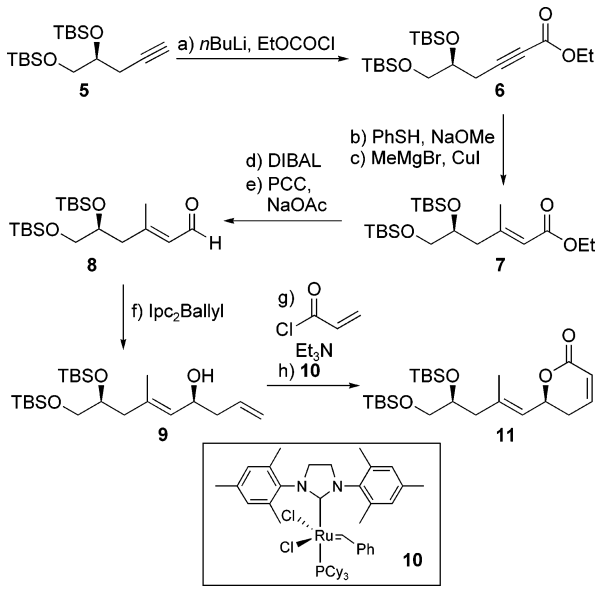
Scheme 2[a]



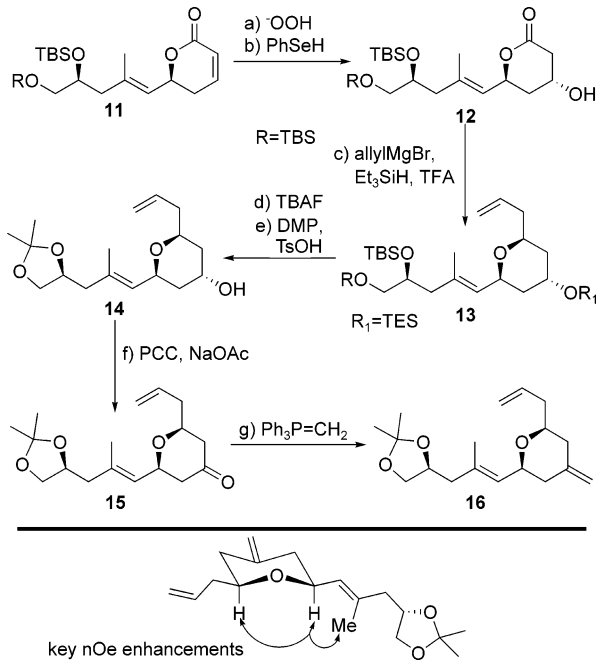
[a] (a) *n*-BuLi (2.0 equiv), THF, −78 °C, 15 min, then ClCOOEt (4.0 equiv), rt, 45 min, 100%. (b) PhSH (1.2 equiv), NaOMe (5 mol %), MeOH, rt, 20 h, 90%. (c) MeMgBr (1.5 equiv), CuI (1.6 equiv), THF, −78 °C to rt, 1 h, 97%. (d) DIBAL-H (2.2 equiv), CH_2Cl_2, −78 °C, 2 h, 95%. (e) PCC (2.0 equiv), NaOAc (0.8 equiv), CH_2Cl_2, rt, 1 h, 94%. (f) (i) (−)-Ipc_2BOMe (1.65 equiv), allylMgBr (1. 5 equiv), Et_2O, 0 °C to rt, 1 h, then **8**, −78 °C, 1 h; (ii) H_2O_2 (3.0 equiv), NaOH (2.2 equiv), H_2O/Et_2O, reflux, 3 h, 88%, 90% de. (g) acryloyl chloride (2.0 equiv), Et_3N (2.2 equiv), DMAP (5 mol %), CH_2Cl_2, rt, 16 h, 79%. (h) **10** (5 mol %), CH_2Cl_2, reflux, 18 h, 96%.

to **2** and should furnish the targeted natural product (−)-zampanolide. It was expected that disconnection of the macrolactone and the enone linkage of **2** would allow for utilization of olefin metathesis and esterification with **3** and **4** in anticipation of obtaining the macrolide skeleton.

Our synthetic blueprint of the C_8-C_{20} subunit (**3**) was designed to enlist a strategy based on a tandem organometallic allyl group addition to the corresponding lactone followed by a diastereoselective axial reduction of an in situ generated oxocarbenium cation to forge the *cis*-2,6-disubstituted 4-*exo*-methylene tetrahydropyran ring.[4] Our approach to the "triene northern hemisphere" C_1-C_9 subunit **4** focused on a diastereoselective Horner−Emmons olefination in anticipation of providing the conjugated (*E*,*Z*)-diene, which in turn would allow for the introduction of the final terminal alkene moiety (as an inconsequential mixture of hydroxyl enantiomers at C_7).

The approach to the synthesis of the central *cis*-pyran of **1** and **2** is shown in Schemes 2 and 3. Toward this end,

Scheme 3[a]



[a] (a) (i) H_2O_2 (3.5 equiv), NaOH (0.6 equiv), MeOH, 0 °C, 10 min, then rt, 0.5 h; (ii) PhH, reflux, 1 h, 83%. (b) $(PhSe)_2$ (1.5 equiv), $NaBH_4$ (3.0 equiv), EtOH, rt, 5 min, then HOAc (3.0 equiv), 0 °C, 5 min, then epoxide, 15 min, 78%. (c) (i) allylMgBr (3.0 equiv), Et_2O, −78 °C, 0.5 h. (ii) Et_3SiH (10 equiv), TFA (5 equiv), CH_2Cl_2, −78 °C to −40 °C, 0.5 h, 76%. (d) (i) TBAF (4.0 equiv), THF, 6 h. (e) 2,2-dimethoxypropane (5.0 equiv), TsOH (0.1 equiv), CH_2Cl_2, rt, 16 h, 81%. (f) PCC (2.0 equiv), NaOAc (0.8 equiv) CH_2Cl_2, rt, 1.5 h, 74%. (g) Ph_3PMeBr (2.0 equiv), *n*-BuLi (2.0 equiv), THF, −78 °C, 15 min, then 0 °C, 20 min, then **15**, rt, 1.5 h, 78%. TFA = tirfluoroacetic acid, TsOH = *p*-toluenesulfonic acid, PCC = pyridinium chlorochromate.

deprotonation of the known propargylic alcohol **5**[5] with *n*-BuLi followed by electrophilic quench with ethyl chloroformate furnished the acetylenic ester **6** in a virtually quantitative yield. Ensuing conjugate addition of the thiolate anion derived from benzenethiol upon treatment with NaOMe in MeOH selectively provided the (*Z*)-α,*β*-unsaturated ester.[6] Replacement of the vinylic phenyl thiol ether by means of a copper-promoted MeMgBr addition afforded the methylated α,*β*-olefinic ester **7** with complete retention of configuration with an 87% yield over the three-step procedure from **5**. Subsequent reduction of the ester moiety to the allylic alcohol was readily accomplished with DIBAL, and the corresponding free hydroxyl group was reoxidized to aldehyde **8** under slightly basic PCC conditions (buffered with NaOAc) in a combined yield of 89% from ester **7**.

An asymmetric allylation−oxidation of **8** utilizing Brown's reagent[7] provided the homo-allylic alcohol **9** with 90% de

(3) (a) Smith, A. B., III; Safonov, I. G.;. Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426. (b) Hoye, T. R.; Hu, M. *J. Am. Chem. Soc.* **2003**, *125*, 9576. (c) Smith, A. B., III; Safonov, I. G. *Org. Lett.* **2002**, *4*, 635. (d) Smith, A. B., III; Safonov, I. G.;. Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102. (e) Troast, D. M.; Porco, J. A., Jr. *Org. Lett.* **2002**, *4*, 991. (f) Loh, T. P.; Yang, J. Y.; Feng, L. C.; Zhou, Y. *Tetrahedron Lett.* **2002**, *43*, 7193.

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(7) (a) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

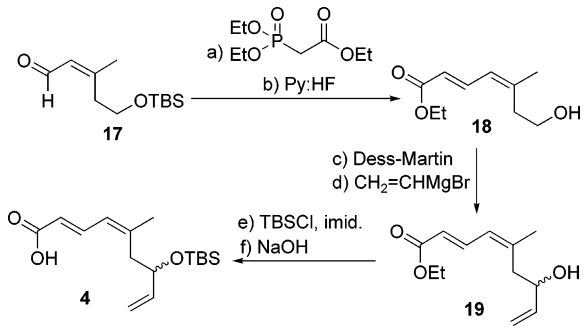
followed by successive acrylate ester formation under the standard protocol (acryloyl chloride, Et_3N, DMAP) afforded the dienic-ester. Subjecting the acrylate ester to Grubbs' carbene catalyst **10**[8] readily allowed for the formation of lactenone **11** via a ring-closing olefin metathesis[9] with a combined yield of 67% over two steps from **9**.

As shown in Scheme 3, an ensuing stereoselective epoxidation of the corresponding lactenone intermediate **11** with basic hydroperoxide provided the epoxy-lactone followed by a subsequent regioselective reduction of the oxirane by means of the in situ generated PhSeH[10] afforded intermediate **12** and set the stage for the tandem nucleophilic addition−oxonium cation generation−diastereoselective reduction sequence in anticipation of providing the vital β-*C*-glycoside component**.** Thus, nucleophilic addition of allylmagnesium bromide to β-hydroxy lactone **12** furnished the lactol, which was immediately transformed into the oxocarbenium cation in the presence of TFA and consequently reduced with Et_3-SiH to furnish the *cis*-2,6-disubstituted tetrahydropyran **13** with a 76% yield from **12**.[11] To avoid removal of the TBS groups during the reduction, TFA was employed instead of BF_3•OEt_2 as used in Kishi's conventional procedure. Unexpectedly, the C_{13} hydroxyl group was concomitantly protected as a TES ether under these conditions.

Selective deprotection of the TES group was unsuccessful upon the treatment of **13** with PPTS in methanol, and other selective reagents such as Pd/C[12] and DDQ[13] also failed to provide the free hydroxy-pyran. In lieu of selective deprotection, global desilylation of **13** was carried out with TBAF, and the corresponding 1,2-diol was reprotected as the acetonide **14** in 81% yield over two steps. Oxidation of the free hydroxyl group resident in **14** was accomplished with PCC, and ketone **15** was subsequently transformed via the methylene Wittig reagent to the *cis*-2,6-disubstituted 4-*exo*-methylene tetrahydropyran unit **16**, which possessed all the functionality required for the synthesis of **2**. The relative configuration of the β-*C*-glycoside subunit **16** was confirmed by NOE enhancements as shown in Scheme 3.

With the C_8-C_{20} intermediate in hand, attention was focused on the synthesis of the triene C_1-C_9 subunit. Accordingly, the known α,β-unsaturated aldehyde **17**[14] was treated with the corresponding Horner−Emmons reagent, which afforded the expected (*E*,*Z*)-conjugated ester. Subsequent HF−pyridine-mediated desilylation of the TBS group furnished the free hydroxyl intermediate **18** in a 90% yield over two steps. Dess−Martin oxidation of the corresponding homoallylic alcohol afforded the labile aldehyde with a modest 61% yield. Because of the highly acidic nature of the α-proton, addition of the vinyl Grignard reagent allowed

Scheme 4[a]



[a] (a) triethyl phosphonoacetate (2.0 equiv), LiHMDS (2.0 equiv), THF, 0 °C, 15 min, 98%. (b) pyridine-HF (10 equiv), THF, rt, 4 h, 92%. (c) Dess−Martin periodinane (1.5 equiv), CH_2Cl_2, rt, 1 h, 61%. (d) vinylMgBr (2.5 equiv), THF, −78 °C, 2 h, 49%. (e) TBSCl (2.0 equiv), imidazole (3.0 equiv), DMF, 20 h, 85%. (f) NaOH (1.0 M, 2.5 equiv), EtOH, 0 °C to rt, 20 h, 95%. LiHMDS = lithium salt of 1,1,1,3,3,3-hexamethyldisilazane, Dess−Martin periodinane = 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxo-3-(*1H*)-one, TBSCl = *tert*-butyldimethylsilyl chloride.

for the formation of the desired allylic alcohol **19** as an inconsequential racemic mixture at C_7 with a moderate yield. Finally, protection of the allylic alcohol as a TBS ether (TBSCl, imid.) and hydrolysis (NaOH, EtOH) of the ester group provided the conjugated acid **4**, which positioned us for the convergence of the two synthetic intermediates **3** and **4,** followed by the completion of the targeted compound **2**.

To commence the convergence of **3** and **6**, selective access to the stereogenic secondary alcohol of **3** was essential. Along this line, the acetonide protecting group was cleaved under acidic conditions (TFA), and the primary hydroxyl group was selectively reprotected as a TBS ether under standard conditions in a quantitative yield.The first attempted coupling **3** and **4** utilizing DCC was unsuccessful, giving the desired ester **20** in low yield along with inseparable impurities. Fortunately, esterification proceeded smoothly under Yamaguchi conditions[15] utilizing two equivalents of **4**, affording the hexaeneic ester intermediate **20** as a diastereomeric 3:1 mixture. Apparently, the two C_7 epimers of acid **4** displayed distinct kinetic reactivity toward the enantiopure alcohol **3**. Ring-closing olefin metathesis was then attempted on bis-TBS-protected hexaene **20** employing a variety of reaction conditions. In general, Grubbs' first-generation catalyst led to recovery of the starting material, while the second-generation catalyst resulted in decomposed starting material even at room temperature. At this point, we conjectured that the TBS protecting group on allylic alcohol was impeding the ring closure.[16] Unfortunately, cleavage of the silyl ethers was problematic, because of sensitive functional groups present in **20** giving rise to

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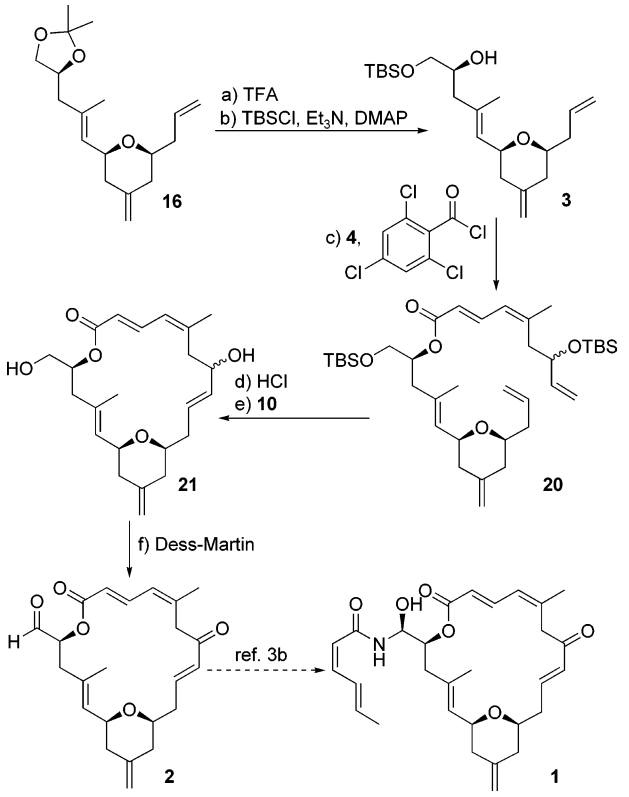
(16) Hoye reported ring closure via olefin metathesis at the same C_8-C_9 alkene with a compound that is somewhat structurally related to **20**. Similar obstacles with respect to ring-closing olefin metathesis have been described, see: Matsuya, Y.; Kawaguchi, T.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2939.

Scheme 5[a]



[a] (a) 1:1:1 TFA/EtOH/CH_2Cl_2, 0 °C, 10 min. (b) TBSCl (2.5 equiv), Et_3N (4.0 equiv), DMAP (16 mol %), CH_2Cl_2, 0 °C to rt, 1.5 h, 97%. (c) **4** (2.0 equiv), 2,4,6-$Cl_3C_6H_2COCl$ (3.0 equiv), Et_3N (4.0 equiv), PhMe, rt, 1 h, then **3** (1.0 equiv), DMAP (1.2 equiv), rt, 1 h, 100%. (d) HCl (1.0 M, 2.0 equiv), 4:1 MeOH/CH_2Cl_2, rt, 4.5 h, 80%. (e) catalyst **10** (10 mol %), CH_2Cl_2 (1 mM), rt, 1 h, 93%. (f) Dess-Martin periodinane (4.0 equiv), CH_2Cl_2, 0 °C to rt, 0.5 h, 90%. TFA = trifluoroacetic acid, TBSCl = *tert*-butyldimethylsilyl chloride, DMAP = 4-(dimethylamino)pyridine, Dess−Martin periodinane = 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxo-3-(*1H*)-one.

decomposed products under various reaction conditions, including many fluoride reagents and weak acids. Finally, aqueous HCl in MeOH was found to be the most satisfactory condition, providing the diol in 80% yield. Subsequently subjecting the corresponding diol intermediate to 10 mol % catalyst **10** in a 1mM solution in CH_2Cl_2 allowed for successful ring closure within 1 h at room temperature to afford the diastereomerically pure (with regard to the alkene geometries, but as an insignificant 3:1 diastereomeric mixture at C_7) macrolactone **21.** As we were delighted by this result, the very late stage intermediate **21** was then subjected to Dess−Martin periodinane, thus enabling the oxidation of both the primary and allylic alcohols and consequently removing the redundant C_7 stereogenic center to afford (−)-dactylolide as a single diastereomer. The spectral data (^1H NMR, 500 MHz; ^{13}C NMR, 125 MHz), optical rotation ($[\alpha]^{rt}_D$ −136°, *c* 1.2, MeOH), and HRMS data of synthetic (−)-dactylolide were in complete agreement with those previously reported.[2,3] Finally, (−)-dactylolide could readily be converted to (−)-zampanolide via the "aluminum azaaldol" sequence reported by Hoye.[3]

In conclusion, we have completed a highly convergent total synthesis of (−)-dactylolide and a formal synthesis of (−)-zampanolide. Key features of the synthetic strategy included a chemo- and diastereoselective 20-membered macrocyclization via a ring-closing olefin metathesis utilizing Grubbs' second-generation catalyst and a tandem nucleophilic addition−diastereoselective axial reduction of an in situ generated oxonium cation to forge the *cis*-2,6-disubstituted 4-*exo*-methylene tetrahydropyran ring. The prospect of a late-stage addition of the amide framework to (−)-dactylolide now allows for the synthesis of a variety of analogues to examine bioactivity of structurally diverse "zampanolide-like" compounds against a variety of tumor cell lines.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2**−**4, 6**−**9, 11**−**16, 18**−**21.** This material is available free of charge via the Internet at http://pubs.acs.org.

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