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Total Synthesis of (−)-Dactylolide and Formal Synthesis of (−)-Zampanolide via Target Oriented β-*C*-Glycoside Formation

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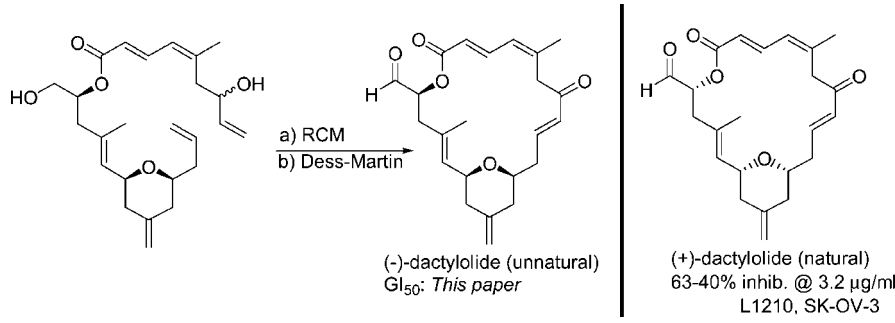

The total synthesis of (−)-dactylolide and formal synthesis of (−)-zampanolide via target oriented β-*C*-glycoside formation is described. The two key reactions involved a stereoselective reduction of the appropriate oxocarbenium cation and a highly chemo- and diastereoselective ring-closing metathesis protocol for the formation of the macrocyclic core. In addition to the described chemistry, in vitro screening of the antipode of natural dactylolide against the NCI's 60 cancer cell line helped to illuminate the critical importance of the *N*-acyl hemiaminal side chain of natural zampanolide for its reported potent nanomolar cytotoxicities. Furthermore, by means of the in vitro screen of (−)-dactylolide, a promising cancer therapeutic lead has now emerged for a variety of carcinomas. More specifically, (−)-dactylolide exhibited GI_{50} values in the nanomolar (25−99 ng/mL) range against the four cell lines HL-60, K-562, HCC-2998, and SF-539, while displaying modest LC_{50} values.

Introduction

First isolated and disclosed in 1996 by Higa and co-workers,[1] (−)-zampanolide (**1**) represented a novel macrolide which exhibited significant activity against a variety of tumor cell lines. In particular, **1** has proven to be noticeably active against the P388, A549, HT29, and MEL28 cell lines with IC_{50} values ranging from 1 to 5 ng/mL. Subsequently, Riccio isolated a structurally related compound, (+)-dactylolide (**2**), from the marine sponge *Dactylospongia*.[2] Due to the striking similarities between **1** and **2**, it was postulated that **2** is a potential biogenic precursor to that of **1**. Coupled with potent cytotoxicity and unusual structures of both **1** and **2**, there has been moderate synthetic interest in these targets culminating in the first total synthesis by Smith in which the relative and tentative absolute configuration of **1** and **2** was determined.[3,4] By means of Smith's account, it was observed that the common macrocyclic cores of **1** and **2** share an enantiomeric relationship with one another. Thus, the natural (−)-zampanolide can be degraded to the unnatural (−)-dactylolide (**3**) or, in the forward sense, (−)-dactylolide would serve as the macrocyclic precursor of natural zampanolide as shown in Figure 1. On the basis of the reports of Riccio and Higa, (+)-**2** displayed a modest biological profile with respect to that of (−)-**1**, thus initially suggesting that the *N*-acyl hemiaminal side chain resident in (−)-**1** is required for the impressive biological activity. However, the enantiomeric relationship between the macrocyclic cores of **1** and **2** may also play a dramatic role in the decreased biological profile of **2**

(1) Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535.

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

(3) (a) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426. (b) Smith, A. B., III; Safonov, I. G. *Org. Lett.* **2002**, *4*, 635. (c) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102.

(4) (a) Hoye, T. R.; Hu, M. *J. Am. Chem. Soc.* **2003**, *125*, 9576. (b) Aubele, D. L.; Wan, S. Y.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485. (c) Ding, F.; Jennings, M. P. *Org. Lett.* **2005**, *7*, 2321. (d) Sanchez, C. C.; Keck, G. E. *Org. Lett.* **2005**, *7*, 3053. (e) Louis, I.; Hungerford, N. L.; Humphries, E. J.; McLeod, M. D. *Org. Lett.* **2006**, *8*, 1117. (f) Loh, T. P.; Yang, J. Y.; Feng, L. C.; Zhou, Y. *Tetrahedron Lett.* **2002**, *43*, 7193. (g) Troast, D. M.; Porco, J. A., Jr. *Org. Lett.* **2002**, *4*, 991.

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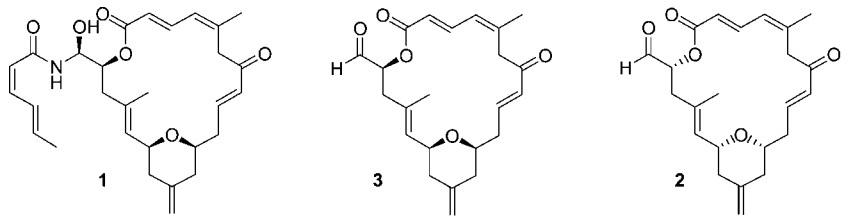
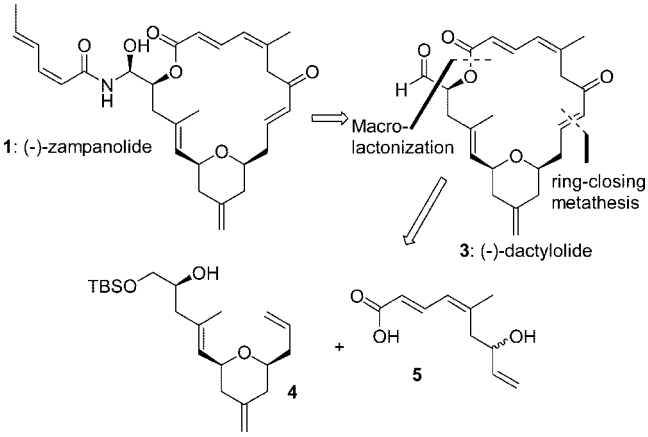


FIGURE 1. Structures and activities of **1**, **2**, and **3**.

SCHEME 1. Retrosynthetic Analyses of (−)-Zampanolide (1) and (−)-Dactylolide (3)



versus that of **1**. To the best of our knowledge, no biological testing of unnatural (−)-dactylolide (**3**) has been performed (vide infra). Thus, the unusual structures of both **1** and **2**, coupled with the unclear absolute configuration of **2**, and the uncertain origin of the impressive biological profile of **1** versus that of **2** make this class of natural products attractive targets for total synthesis and further investigation into their respective biological profiles.[4]

The retrosynthetic analysis of both (−)-dactylolide (**3**) and (−)-zampanolide (**1**) is illustrated in Scheme 1. As reported by Hoye, strategic disconnection at the *N*-acyl hemiaminal side chain would allow for the corresponding engagement of an "aluminum aza-aldol" sequence with the aldehyde moiety to **3** and should furnish the targeted natural product (−)-zampanolide.[4a] It was expected that disconnection of the macrolactone and the enone linkage of **3** would allow for utilization of olefin metathesis and esterification with **4** and **5** in anticipation of obtaining the macrolide skeleton.[4c,5]

Results and Discussion

The first major obstacle that was undertaken was the synthesis of the β-*C*-glycoside intermediate **4**. We initially surmised that a two directional approach might provide **4** via the hydride addition to an incipient oxocarbenium cation as initially described by Kishi.[6] Careful inspection of the two possible reactive conformers by utilizing the Woerpel models led us to believe that such a reduction protocol would indeed furnish the correct stereochemistry of the desired β-*C*-glycoside.[7] As described in Scheme 2, our initial approach to **4** centered on a vinyl lithium (**5**) addition to the protected lactone **8** followed by an oxocarbenium formation/reduction sequence. The vinyl lithium species would be derived from the stereodefined iodoolefin **6** by means of a lithium halogen exchange. In turn, olefin **6** was envisioned to be the result of a Negishi carboalumination reaction of the previously reported acetylenic diol **7**.[8,9] Synthesis of the other coupling partner **8** would be derived from an oxidation of lactenone **9**, which was envisaged to be the product of a ring-closing metathesis (RCM) reaction. The initial starting material leading to the RCM reaction process would be the previously reported homoallylic alcohol **10**.[10]

First Generation Retrosynthetic Analysis of β-*C*-Glycoside (4). With the initial synthetic blueprint in hand, we commenced the synthesis of **4** based on the Negishi carboalumination reaction process for the completion of olefin **6**. Thus, treatment of the commercially available (*R*)-glycidol (**11**) with the lithium acetylide•EDA complex provided the homopropargylic diol **7** in 79% yield and set the stage for the zirconium-catalyzed carboalumination reaction as delineated in Scheme 3.[9] Unfortunately, protecting the diol moiety of **7** as TBDPS or TBS ethers did not allow for the carboalumination reaction and led to decomposition of the starting material. Much to our delight, the free diol **7** did indeed undergo carboalumination with Cp_2ZrCl_2 and $AlMe_3$ to provide the assumed vinyl aluminum intermediate and subsequent quenching with I_2 allowed for the formation of the iodo-vinylic diol **12** in 45% yield over the two-step process. Ensuing silylation of the more accessible primary hydroxyl group with TDBPSCl and imidazole readily furnished the monoprotected diol **13** in 81% yield. Completion of the vinylic coupling partner **6** was accomplished in 72% yield by final protection of the remaining free hydroxyl moiety as a TES ether via standard silylation protocols (TESCl and imidazole).

With the vinylic coupling partner **6** in hand and in gram quantities, focus was then shifted to the synthesis of the protected β-hydroxy lactone **8** as shown in Scheme 4. Consequently, esterification of the previously reported homoallylic alcohol **10** with acryloyl chloride and Et_3N furnished the acrylate ester **14** in 88% yield. Ensuing treatment of ester **14** with Grubbs' second generation catalyst **15** provided swift access in 91% yield to lactenone **9** by means of a ring-closing metathesis

(5) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Rivkin, A.; Cho, Y. S.; Gabarda, A. E.; Yoshimura, F.; Danishefsky, S. J. *J. Nat. Prod.* **2004**, *67*, 139. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (d) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (e) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086.

(6) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(7) (a) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168. (b) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521.

(8) Van Horn, D. E.; Negishi, E.-I. *J. Am. Chem. Soc.* **1978**, *100*, 2252.

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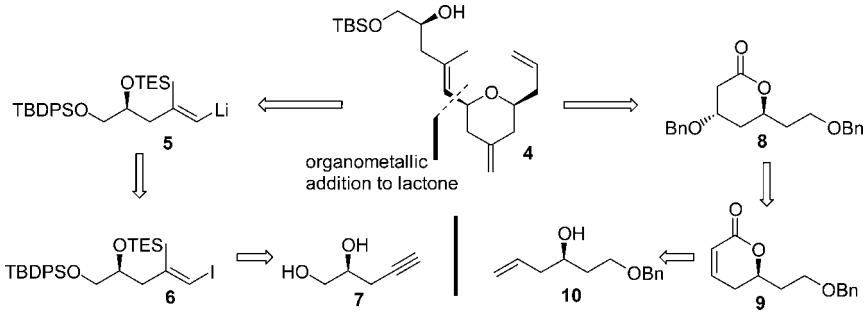
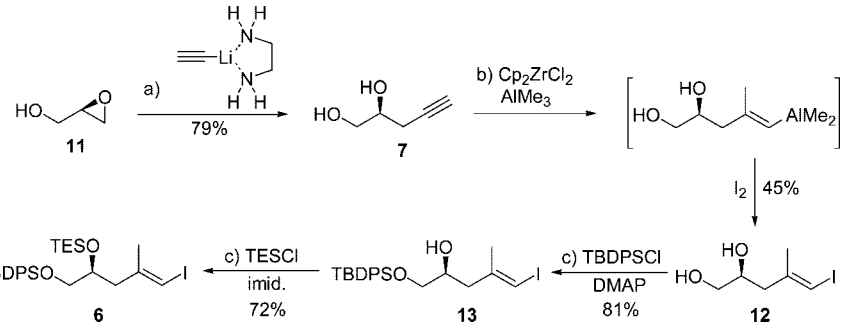
(10) Su, Q.; Panek, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1223.

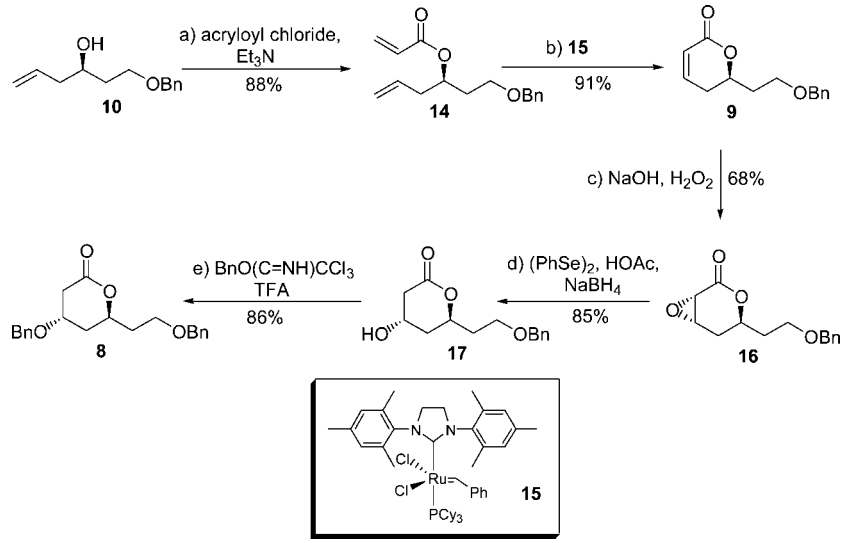
SCHEME 2. First Generation Retrosynthesis of 4



SCHEME 3. Synthesis of Protected Olefin Diol 6



SCHEME 4. Synthesis of Bisbenzyl-Protected Lactone 8

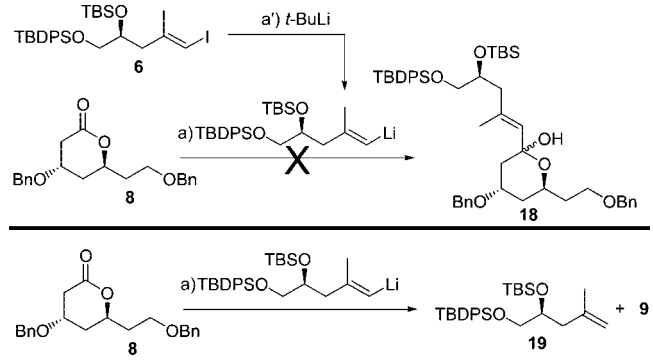


reaction.[11–13] With **15** in hand, diastereoselective introduction of the β-hydroxy group was envisioned to arise via an expoxidation/regioselective ring-opening sequence. The driving force behind the introduction of the hydroxy moiety was twofold. First, we postulated that the reactive conformer of the oxocarbenium reduction required the hydroxyl group to be C_3 axial position as described by Woerpel.[7] Thus, diastereoselective introduction of such a functional group would require a 1,3-*anti* relationship in compounds **17** and **8**. Second, the natural products **1** and **3** required an *exo*-methylene moiety in that specific location of the β-*C*-glycoside and the hydroxyl group would serve as an appropriate olefinic surrogate this early in the synthetic sequence. Consequently, stereoselective epoxidation of **9** with basic H_2O_2 was quite successful and afforded the epoxylactone **16** as a single diastereomer in 68% yield.

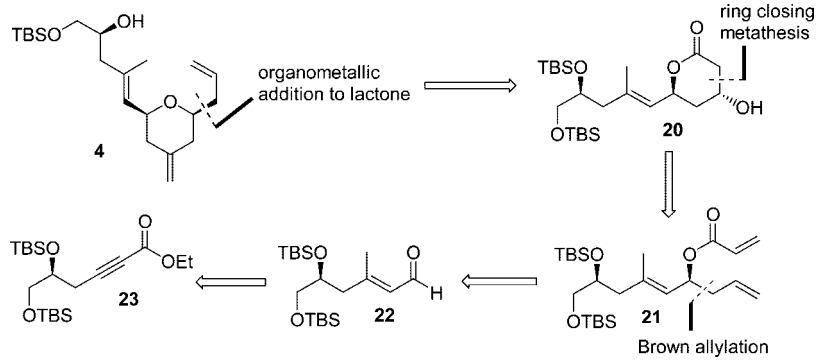
Subsequent regioselective ring opening of **16** was accomplished under Miyashita's conditions (Ph_2Se_2, HOAc, and $NaBH_4$)[14] and furnished the β-hydroxy lactone **17** in excellent yield.[15] The first attempted protection of the free hydroxyl group of **17** as a benzyl ether was unsuccessful under standard basic conditions (BnBr, TBAI, NaH) and led to starting material decomposition. However, treatment of **17** with the benzyl trichloroacetimidate [$BnO(C{=}NH)CCl_3$] reagent[16] and TFA efficiently provided the protected lactone **8** in excellent yield.

(11) Diez-Martin, D.; Kotecha, N. R.; Ley, S. V.; Mantegani, S.; Menendez, J. C.; Organ, H. M.; White, A. D.; Banks, B. J. *Tetrahedron* **1992**, *48*, 7899.
(12) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651.
(13) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(14) Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469.
(15) Miyazawa, M.; Matsuoka, E.; Sasaki, S.; Oonuma, S.; Maruyama, K.; Miyashita, M. *Chem. Lett.* **1998**, 109.

SCHEME 5. Attempted Synthesis of Lactol 18



SCHEME 6. Second Generation Synthetic Blueprint to *β*-*C*-Glycoside 4



With the two coupling partners **6** and **8** in hand, our attention was focused on first a lithium−halogen exchange of **6** and final nucleophilic addition to **8** to afford lactol **18** en route to the *β*-*C*-glycoside **4**, as illustrated in Scheme 5. Unfortunately, the sequential lithium−halogen exchange followed by addition to **8** did not progress as predicted based on the observed two final products **9** and **19**. As a result of the isolation of **9** and **19**, it was assumed that the lithium−halogen exchange did proceed to afford the vinyl lithium intermediate. However, the vinyl lithium species did not perform as a nucleophile as hoped, but functioned as a base and furnished the α,*β*-unsaturated lactone **9** via a presumed *β*-elimination of the benzyloxide anion. After multiple unsuccessful attempts of adding the vinyl lithium intermediate (derived from **6**) to lactone **8**, we decided to abandon the current route and redesigned a synthetic blueprint to take advantage of a nucleophilic addition of a less complex reagent to a more elaborated lactone.

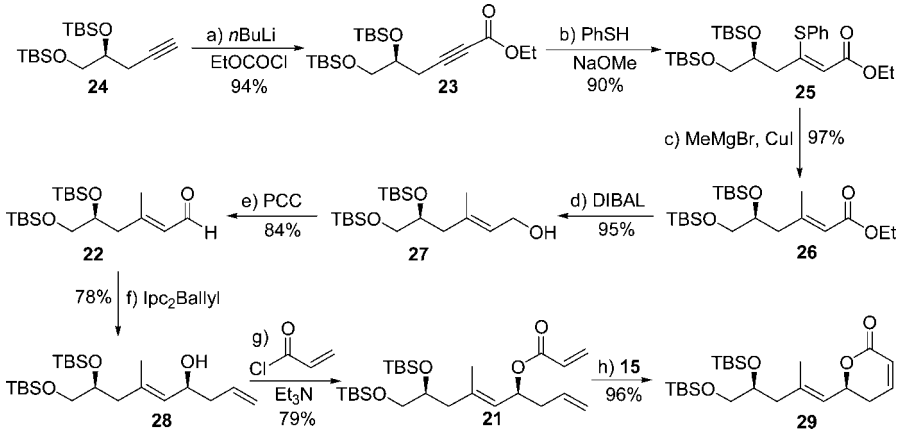
Second Generation Retrosynthetic Analysis of *β*-*C*-Glycoside (4). Our second synthetic blueprint of the *β*-*C*-glycoside (C_8−C_{20} subunit) **4** was designed to enlist a strategy based on a tandem organometallic allyl group addition to the corresponding lactone **20** followed by a diastereoselective axial reduction of an in situ generated oxocarbenium cation to forge the *cis*-2,6-disubstituted 4-*exo*-methylene tetrahydropyran ring after oxidation/olefination of the free hydroxyl moiety at C_8 as shown in Scheme 6. We envisioned that the lactone **20** would be the product of an oxidation (similar to that of **17**) after a chemoselective RCM reaction from the acrylate **21**, which in turn would be derived from a Brown allylation of the α,*β*-unsaturated aldehyde **22**. Finally, a stereoselective introduction of the required methyl group via a two-step thiolate addition−subsequent Grignard addition−thiolate elimination protocol would allow for the formation of **22** starting from the α,*β*-acetylenic ester **23**.

As delineated in Scheme 7, deprotonation of the previously reported propargylic alcohol **24**[17] with *n*-BuLi followed by electrophilic capture of ethyl chloroformate furnished the α,*β*-acetylenic ester **23** in a virtually quantitative (94%) yield. Subsequent conjugate addition of the thiolate anion derived from benzenethiol and NaOMe in MeOH diastereoselectively (9:1) provided the (*Z*)-α,*β*-unsaturated ester **23**. Replacement of the vinylic thiol ether by means of a copper-promoted MeMgBr addition followed by phenyl thiolate anion displacement afforded the α,*β*-olefinic ester **26** with complete retention of configuration with a 87% yield over the two-step procedure from **24**.[18] Subsequent reduction of the ester moiety to the allylic alcohol **27** was readily accomplished with DIBAL, and the corresponding free hydroxyl group was reoxidized to aldehyde **22** under slightly basic PCC conditions (buffered with NaOAc) in a combined yield of 89% from ester **26**. An asymmetric allylation−oxidation of **22** utilizing Brown's Ipc_2Ballyl reagent[19] furnished the homoallylic alcohol **28** with 90% de. Ensuing acrylate ester formation under the standard protocol (acryloyl chloride, Et_3N, DMAP) afforded the dienic ester **21** in 79% yield. Subjecting the acrylate ester **21** to Grubbs' catalyst **15**[13] readily allowed for the formation of lactenone **29** via a chemoselective ring-closing olefin metathesis.

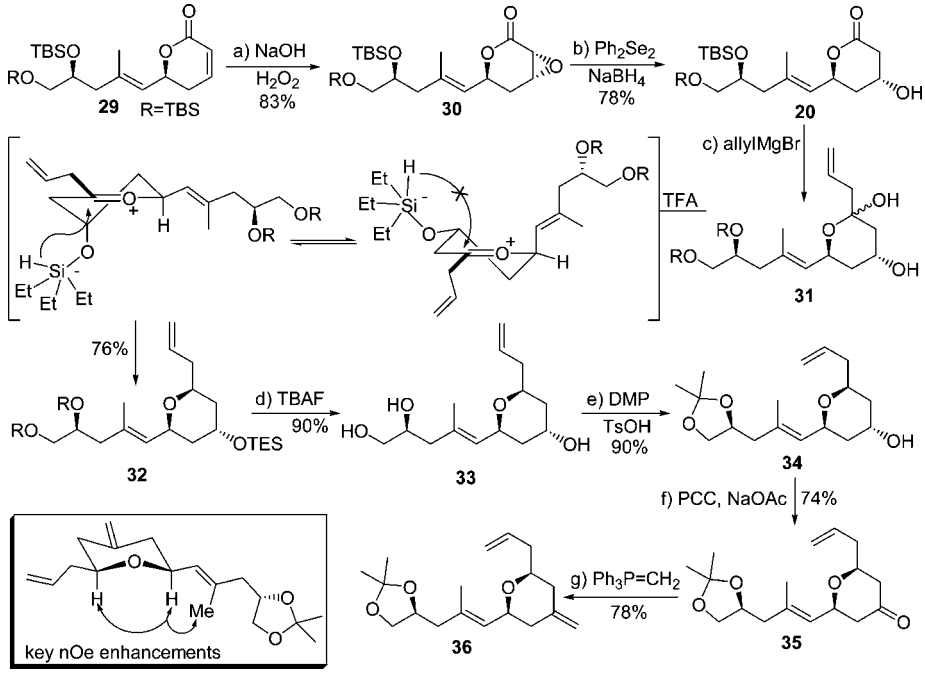
As shown in Scheme 8, an ensuing stereoselective epoxidation of the corresponding lactenone intermediate **29** with basic hydroperoxide provided the epoxy lactone **30**. A subsequent

(16) Wessel, H. P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.
(17) Nicolaou, K. C.; Jung, J.; Yoon, W. H.; Fong, K. C.; Choi, H.-S.; He, Y.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 2183.
(18) Hollowood, C. J.; Yamanoi, S.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 1664.
(19) (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.

SCHEME 7. Synthesis of Lactenone 29 via a Chemoselective Ring-Closing Metathesis



SCHEME 8. Synthesis of *β*-*C*-Glycoside 36 via Oxocarbenium Reduction Derived from 31



regioselective reduction of the oxirane under Miyashita's condition as above afforded intermediate **20** and set the stage for the tandem nucleophilic addition−oxocarbenium cation generation−diastereoselective reduction sequence in anticipation of providing the vital *β*-*C*-glycoside component. As observed in Scheme 5, we chose not to protect the free hydroxyl moiety of **20**, due to the concerns of a *β*-elimination as occurred with lactone **8**. Thus, nucleophilic addition of allyl magnesium bromide to *β*-hydroxy lactone **20** furnished the lactol **31**, which was immediately transformed into the oxocarbenium cation in the presence of TFA and consequently reduced with Et_3SiH to furnish the allyl *β*-*C*-glycoside **32** with a 76% yield from **20**.

As described in Scheme 8, it is believed that the more reactive oxocarbenium conformer places the hydroxyl group at C_8 in the axial position while the C_6 substituent favors the pseudoequatorial position. This is in agreement with Woerpel's observation that the C_3 hydroxyl moiety prefers the axial position during the reduction of monosubstituted oxocarbenium cations.[7] 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.[6,20] Unexpectedly, the C_{13} hydroxyl group was concomitantly protected as a TES ether under these conditions. This novel silylation reaction, presumably derived from the siliconate intermediate reagent, proceeds readily even at −78 °C. In all reality, this procedure allows for the silylation of free hydroxyl groups under acidic conditions (even with labile silicon groups such as the TES group) with concomitant hydride transfer to a reactive intermediate (i.e., oxocarbenium cation).[21] Selective deprotection of the TES group was unsuccessful upon the treatment of **32** with PPTS in methanol and other selective reagents such as Pd/C[22] and DDQ[23] also failed to provide the

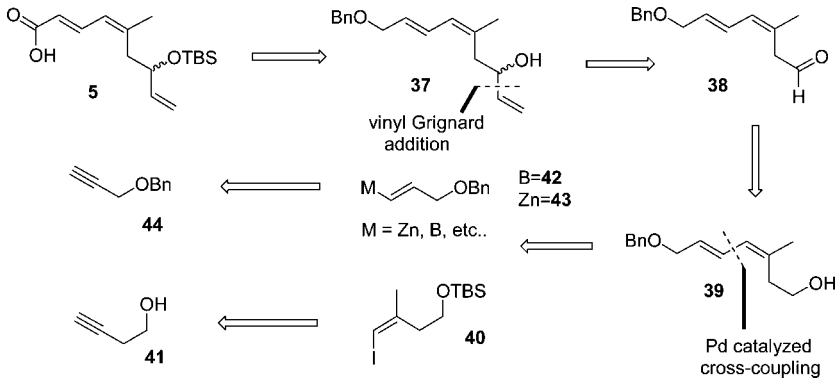
(20) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 1568.

(21) The silylation of the axial C_3 hydroxyl during oxocarbenium reduction with Et_3SiH has also been observed in three other instances within our laboratory; see: (a) Sawant, K. B.; Ding, F.; Jennings, M. P. *Tetrahedron Lett.* **2007**, *48*, 5177. (b) Sawant, K. B.; Jennings, M. P. *J. Org. Chem.* **2006**, *71*, 7911. (c) Sawant, K. B.; Ding, F.; Jennings, M. P. *Tetrahedron Lett.* **2006**, *47*, 939.

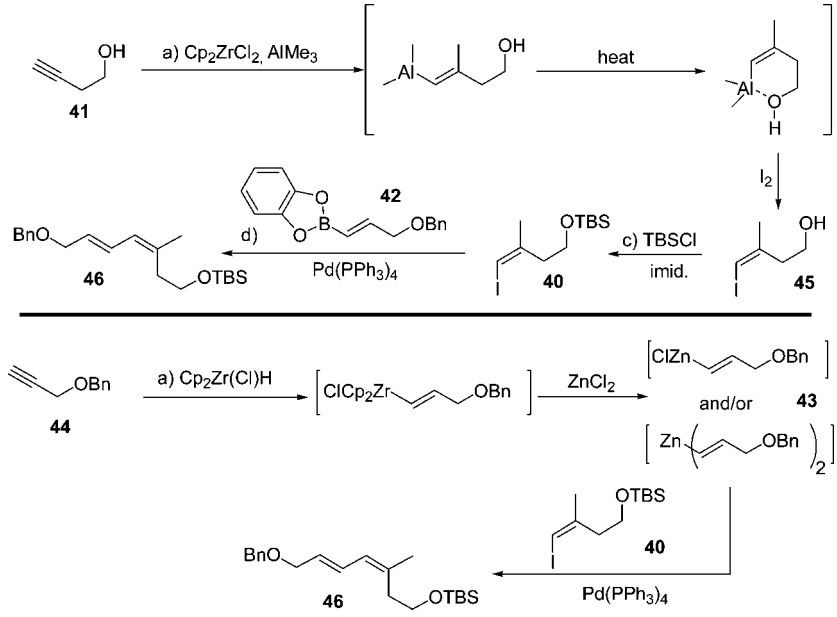
(22) Rotulo-Sims, D.; Prunet, J. *Org. Lett.* **2002**, *4*, 4701.

(23) Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2997.

SCHEME 9. First Generation Retrosynthetic Analysis of Triene 5



SCHEME 10. Attempted Synthesis of 46 via Pd Cross-Coupling



free hydroxy pyran. In lieu of selective deprotection, global desilylation of **32** was carried out with TBAF and the corresponding 1,2-diol **33** was reprotected as the acetonide **34** in 81% yield over two steps. Oxidation of the free hydroxyl group resident in **34** was accomplished with PCC to afford ketone **35**. Subsequent transformation of the carbonyl moiety, via the methylene Wittig reagent, to the *cis*-2,6-disubstituted 4-*exo*-methylene tetrahydropyran unit **36**, which possessed all the functionality required for the synthesis of **3**. The relative configuration of the β-*C*-glycoside subunit **36** was confirmed by NOE enhancements as shown in Scheme 8.

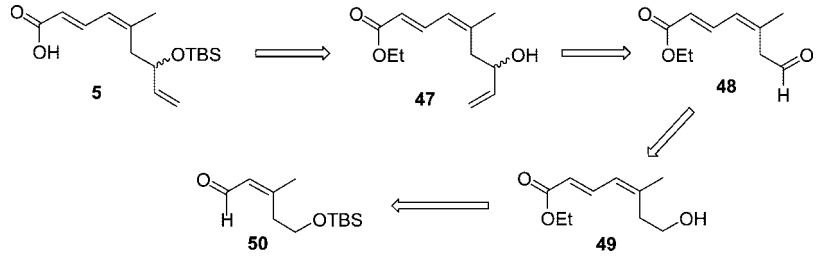
First Generation Retrosynthetic Analysis of Triene (5). With the completion of the β-*C*-glycoside **36**, our next objective was the completion of the triene subunit **5**. We initially envisaged that **5** would be derived from **37** after a series of protecting group shuffles and final oxidation of an allylic primary alcohol at C_1 as described in Scheme 9. In turn, **37** would be the product of a vinyl Grignard addition to the labile aldehyde moiety of **38**. The conjugated diene was envisioned to be the product of a Pd-catalyzed cross-coupling reaction with either the boronate **42** or zincate **43** and vinyl iodide **40**. Both of the nucleophilic coupling partners would be derived from either a hydroboration or a hydrozirconation→transmetalation of **44**.[24] The vinyl iodide **40** would be the product of a Negishi *anti*-carboalumination−iodination procedure of the homopropargylic alcohol **41**.[25]

With our design in mind for the completion of **5** by means of a Pd-catalyzed cross-coupling reaction, we initiated the synthesis of vinyl iodide **40** via a Negishi *anti*-carboalumination−iodination reaction sequence from commercially available **41**, as illustrated in Scheme 10. Interestingly, when $AlMe_3$ was used as a solution in hexane in conjunction with Cp_2ZrCl_2 under the reported conditions[25] ($ClCH_2CH_2Cl$ and 48 h at reflux), the *anti*-carboalumination/iodination reaction of **41** provided **45** in a low yield (~30%) and as a 3:1 mixture of *Z* to *E* isomers. Much to our delight, we found that using the neat $AlMe_3$ reagent provided a much higher yield and virtually isomerically pure vinyl iodide **45** under identical conditions. With **45** in hand, an ensuing silylation of the free hydroxyl group with TBSCl and imidazole furnished the protected electrophilic

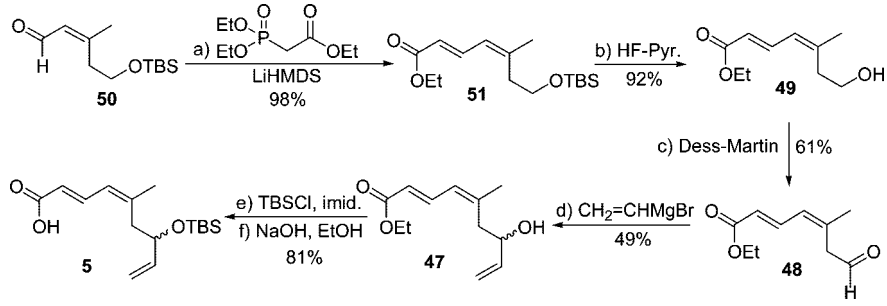
(24) For the seminal contribution from the Negishi laboratory, see: (a) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254. For a review on the synthetic utility of the zirconium transmetalation to zinc process, see: (b) Wipf, P.; Kendall, C. *Chem.—Eur. J.* **2002**, *8*, 1778.

(25) Ma, S.; Negishi, E.-I. *J. Org. Chem.* **1997**, *62*, 784.

SCHEME 11. Second Generation Retrosynthetic Analysis of Triene 5



SCHEME 12. Successful Completion of the Required Triene 5



coupling partner **40** in a 88% yield and set the stage for the Pd-catalyzed cross-coupling between **42** and **40**. Initial hydroboration of **44** with catecholborane readily provided the in situ formed vinyl boronate **42**, which subsequently underwent Pd-catalyzed cross-coupling with **40** via $Pd(PPh_3)_4$ and aq K_2CO_3 to furnish **46** as an isomerically pure diene but in a very low yield of 22%. After multiple unsuccessful attempts of improving the yield for the cross-coupling by changing the base (i.e., aq NaOH, $NaHCO_3$, CsF) and catalyst [$Pd(PPh_3)_2Cl_2$ and $Pd(dppf)Cl_2$] involved for the synthesis of **46**, we decided to investigate the possibility of utilizing a Negishi cross-coupling in place of the traditional Suzuki reaction.[26]

Similar to the hydroboration of **44**, we attempted a hydrozirconation of **44** with Schwartz's reagent[27] followed by transmetalation of the vinyl zirconcene with $ZnCl_2$ in anticipation of forming the vinyl (or bisvinyl) zinc compound **43** followed by an ensuing Pd-catalyzed cross-coupling with **40** to provide the much desired diene **46**. Unfortunately, we isolated only ∼5% of the desired diene **46**, with major decomposition of the vinyl iodide **40**. Since the two Pd-catalyzed cross-couplings failed to provide any useful amounts of **46**, we decided to abandon this specific synthetic plan and redesign a new route to the C_1-C_9 portion of **1**.

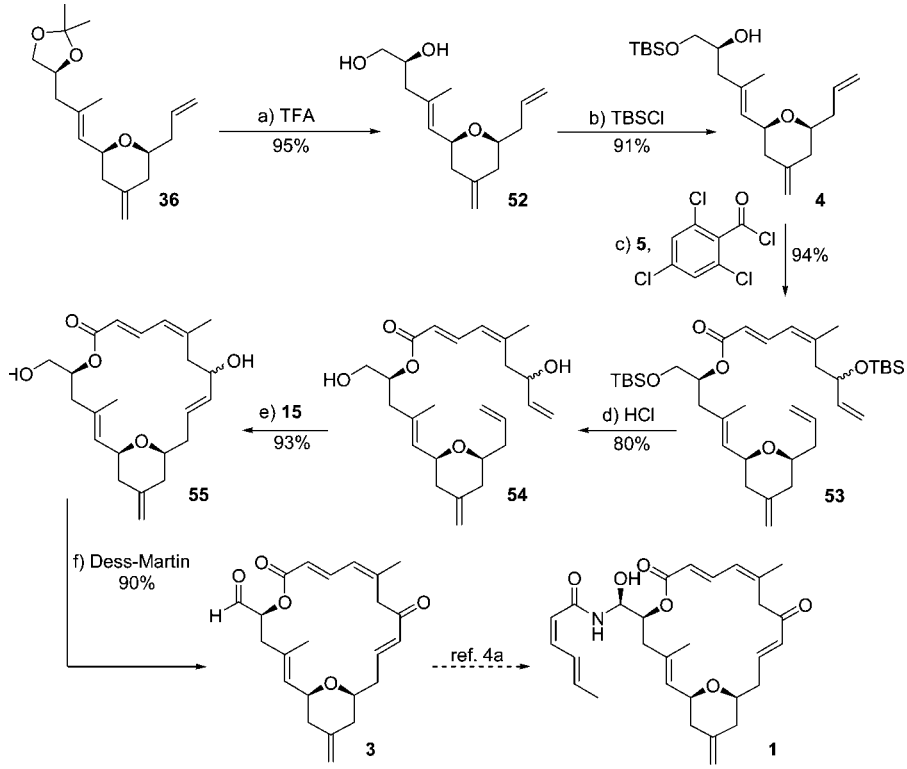
Second Generation Retrosynthetic Analysis of Triene (5). Our second approach to the "triene northern hemisphere" C_1-C_9 subunit **4** focused on a diastereoselective Horner−Emmons olefination in anticipation of providing the conjugated (*E*,*Z*)-diene **49** (Scheme 11), which in turn would allow for the introduction of the final terminal alkene moiety (as an inconsequential mixture of hydroxyl epimers at C_7) via a vinyl Grignard addition to the corresponding aldehyde **48**.

With the failed Pd-catalyzed cross-coupling route described above, attention was then focused on a second approach to the triene C_1-C_9 subunit. Accordingly, the known α,β-unsaturated aldehyde **50**[28] was treated with the corresponding Horner−Emmons reagent which afforded the expected (*E*,*Z*)-conjugated ester **51** in a virtually quantitative yield with an *E*/*Z* ratio of ∼10:1 as shown in Scheme 12. Subsequent HF-pyridine-mediated desilylation of the TBS group resident in **51** furnished the free hydroxyl intermediate **49** in a 90% yield over two steps. Ensuing Dess−Martin oxidation[29] of the corresponding homoallylic alcohol afforded the labile aldehyde **48** with a modest 61% yield. Presumably due to the highly acidic nature of the α-proton, addition of the vinyl Grignard reagent allowed for the formation of the desired allylic alcohol **47** as an inconsequential racemic mixture at C_7 with a moderate yield of 49%. Lastly, protection of the allylic alcohol as a TBS ether (TBSCl, imidazole) and hydrolysis (NaOH, EtOH) of the ester group provided the conjugated acid **5**, which positioned us for the convergence of the two synthetic intermediates **4** and **5**, followed by the completion of the targeted compound **2**.

Total Synthesis of (−)-Dactylolide via a Chemo- and Diastereoselective RCM Process. To commence the convergence of **4** and **5**, selective access to the stereogenic secondary alcohol of **36** was essential as delineated in Scheme 13. Along this line, the acetonide protecting group resident in **36** was cleaved under acidic conditions (TFA) to furnish diol **52** in 95% yield, and subsequently, the primary hydroxyl group of **52** was selectively reprotected as a TBS ether under standard conditions in virtually a quantitative yield providing **4**. The first attempted coupling of **4** and **5** utilizing DCC was unsuccessful, giving the desired ester **53** in low yield along with inseparable impurities. Fortunately, esterification proceeded smoothly under Yamaguchi conditions utilizing 2 equiv of **5**, affording the hexaenic ester intermediate **53** as a diastereomeric 3:1 mixture.[30] Apparently the two C_7 epimers of acid **5** display distinct kinetic reactivity toward the enantiopure alcohol **4**. An ensuing ring-closing olefin metathesis was then attempted on bis-TBS-protected hexaene **53**, employing a variety of reaction condi-

(26) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(27) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333.
(28) McLaughlin, M. J.; Hsung, R. P. *J. Org. Chem.* **2001**, *66*, 1049.
(29) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(30) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

SCHEME 13. Completion of 3 and Formal Synthesis of 1 via a Highly Chemoselective RCM



tions. In general, Grubbs' first generation catalyst[31] 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.[32] Unfortunately, cleavage of the silyl ethers was problematic, due to sensitive functional groups present in **53** giving rise to decomposed products under various reaction conditions including many fluoride reagents and weak acids.

Finally and much to our delight, aqueous HCl in MeOH was found to be the most satisfactory condition, providing the diol **54** in 80% yield. Subsequently subjecting the corresponding intermediate **52** to 10 mol % of catalyst **15** in a 1 mM solution in CH_2Cl_2 allowed for successful ring closure within 1 h at rt to afford the diastereomerically pure (with regards to the alkene geometries, but as an insignificant 3:1 diastereomeric mixture at C_7) macrolactone **53** in a 93% yield. Pleased by this result, the very late-stage intermediate **55** was then subjected to Dess−Martin periodinane (DMP), thus enabling the oxidation of both the primary and the allylic alcohols and consequently removing the redundant C_7 stereogenic center to afford (−)-dactylolide (**3**) as a single diastereomer. It is worth noting that the bisoxidation with DMP and the subsequent workup of **3** was conducted under strict anhydrous conditions as not to hydrate the labile aldehyde moiety (see the Experimental Section for details). The spectral data (^{1}H 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.[2–4] Finally, (−)-dactylolide could readily be converted to (−)-zampanolide via the "aluminum aza-aldol" sequence as reported by Hoye.[4a]

TABLE 1. Comparison Data between (−)-Zampanolide, (−)-Dactylolide, and (+)-Dactylolide

cell line	(−)-zampanolide	(−)-dactylolide	(+)-dactylolide
A549/ATCC	1−5 ng/mL	1.72 μg/mL	
HT29	1−5 ng/mL	0.101 μg/mL	
SK-Mel-28	1−5 ng/mL	2.0 μg/mL	
SK-OV-3		1.8 μg/mL	3.2 μg/mL[a]
P388	1−5 ng/mL		
L1210			3.2 μg/mL[b]

[a] IC_{50} or GI_{50} values. [b] GI_{40} value. [c] GI_{63} value.

In Vitro Evaluation of (−)-Dactylolide. As mentioned in the Introduction, the biological profile comparison between *nat* **1** and *nat* **2** is not the correct approach to evaluate the true importance of the *N*-acyl aminal side chain of **1** (remember that *nat* **1** and *unnat* **2** share the same enantiomeric macrocyclic core). Initially, we surmised that the enantiomeric relationship of the macrocyclic cores (Figure 1) may play a major role in the decreased biological activity of *nat* **2** versus *nat* **1**. With this in mind, we synthesized the *unnat* **2** and sent a 7 mg sample to the NCI for in vitro evaluation versus the 60-cell panel. The results from this screening are highlighted in Tables 1 and 2.

As shown in Table 1, a direct comparison between (−)-zampanolide, (−)-dactylolide (*unnat*), and (+)-dactylolide has been made. The data strongly suggest that the *N*-acyl hemiaminal side chain of zampanolide does indeed play a dramatic role in the nanomolar IC_{50} values against the four cell lines tested. Our sample of (−)-dactylolide, in a direct comparison with (−)-zampanolide against the A549, HT29, and SK-Mel-28 lines, was 10- to 1000-fold less active (GI_{50}) than that of (−)-zampanolide. These results suggest that the "double" hydrogen bonding network of (−)-zampanolide might be crucial for the reported nanomolar activities. On the basis of the limited

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(32) Hoye reported ring closure via olefin metathesis at the same C_8−C_9 alkene with a compound that is structurally related to **53**. Similar obstacles with respect to ring-closing olefin metathesis have been described; see: Matsuya, Y.; Kawaguchi, T.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2939.

TABLE 2. NCI 60 Cell Line In Vitro Data for (−)-Dactylolide

cell line	cancer type	GI_{50}	GI_{50} [M]	LC_{50} [M]
CCRF-CEM	Leukemia	0.148 μg/mL	3.84×10^{-7}	6.03×10^{-5}
HL-60(TB)	Leukemia	0.094 μg/mL	2.43×10^{-7}	$>1.00 \times 10^{-4}$
K-562	Leukemia	0.025 μg/mL	6.38×10^{-8}	$>1.00 \times 10^{-4}$
RPMI-8226	Leukemia	0.117 μg/mL	3.05×10^{-7}	$>1.00 \times 10^{-4}$
SR	Leukemia	0.175 μg/mL	4.54×10^{-7}	$>1.00 \times 10^{-4}$
HOP-92	Non-Small Cell Lung	0.193 μg/mL	5.02×10^{-7}	3.51×10^{-5}
COLO 205	Colon	0.147 μg/mL	3.81×10^{-7}	5.12×10^{-5}
HCC-2998	Colon	0.077 μg/mL	2.00×10^{-7}	3.16×10^{-5}
HCT-116	Colon	0.133 μg/mL	3.46×10^{-7}	5.49×10^{-6}
HCT-15	Colon	0.174 μg/mL	4.53×10^{-7}	4.62×10^{-5}
HT29	Colon	0.101 μg/mL	2.63×10^{-7}	4.87×10^{-5}
KM12	Colon	0.222 μg/mL	5.76×10^{-7}	8.57×10^{-5}
SW-620	Colon	0.173 μg/mL	4.50×10^{-7}	4.69×10^{-5}
SF-268	CNS	0.231 μg/mL	6.02×10^{-7}	9.56×10^{-5}
SF-539	CNS	0.099 μg/mL	2.58×10^{-7}	2.50×10^{-5}
SNB-75	CNS	0.120 μg/mL	3.12×10^{-7}	$>1.00 \times 10^{-4}$
U251	CNS	0.200 μg/mL	5.19×10^{-7}	4.07×10^{-5}
LOX IMVI	Melanoma	0.266 μg/mL	6.92×10^{-7}	4.07×10^{-5}
M14	Melanoma	0.108 μg/mL	2.81×10^{-7}	3.18×10^{-5}
IGROV1	Ovarian	0.185 μg/mL	4.81×10^{-7}	7.14×10^{-5}
OVCAR-3	Ovarian	0.316 μg/mL	8.22×10^{-7}	$>1.00 \times 10^{-4}$
786−0	Renal	0.324 μg/mL	8.41×10^{-7}	8.01×10^{-5}
SN12C	Renal	0.286 μg/mL	7.43×10^{-7}	6.52×10^{-5}
PC-3	Prostate	0.149 μg/mL	3.86×10^{-7}	8.03×10^{-5}
DU-145	Prostate	0.133 μg/mL	3.47×10^{-7}	2.32×10^{-5}
MCF7	Breast	0.076 μg/mL	1.98×10^{-7}	5.20×10^{-5}
NCI/ADR-RES	Breast	0.269 μg/mL	6.99×10^{-7}	$>1.00 \times 10^{-4}$
MDA-MB-435	Breast	0.122 μg/mL	3.16×10^{-7}	$>1.00 \times 10^{-4}$
BT-549	Breast	0.121 μg/mL	3.15×10^{-7}	3.74×10^{-5}
T-47D	Breast	0.295 μg/mL	7.67×10^{-7}	$>1.00 \times 10^{-4}$

bioassay data from Riccio, our data were compared to that of (+)-dactylolide against only one cell line. The natural (+)-dactylolide showed a GI_{40} value of 3.2 μg/mL against the SK-OV-3 line, whereas (−)-dactylolide exhibited a GI_{50} of 1.8 μg/mL. This result demonstrates that the unnatural (−)-dactylolide is roughly 2- to 3-fold times more active against this specific line than that of (+)-dactylolide and helps shed some preliminary light on the structural relationship between (−)-zampanolide, (−)-dactylolide, and (+)-dactylolide.

In addition to the comparisons shown in Table 1, the NCI in vitro assay data provided a much more detailed biological profile of the unnatural (−)-dactylolide, as shown in Table 2. First, only values of <0.350 μg/mL were placed into the table as the higher values GI_{50} were not included. A few trends are readily observable as described below.

The first is that (−)-dactylolide exhibits GI_{50} values in the nanomolar (25−99 ng/mL) range against the four cell lines HL-60, K-562, HCC-2998, and SF-539. This is important to note due to the fact that (+)-dactylolide was only tested on one human line and clearly illustrates the need for synthetic natural product molecules for the undertaking of in vitro biological testing. By simply synthesizing (−)-dactylolide and providing the NCI with a small sample for testing, a promising cancer therapeutic has now emerged for a variety of carcinomas. A second important fact that was uncovered by the NCI was that (−)-dactylolide exhibits extensive growth inhibition (GI_{50}) but is not excessively cytotoxic against most all of the leukemia and breast cell lines (and even other tumor lines as delineated in Table 2) due to the higher LC_{50} concentrations $>1.00 \times 10^{-4}$. Our next challenges include deciphering the true nature of the *N*-acyl hemiaminal side chain of **1** and understanding the mechanism of action of (−)-dactylolide and (−)-zampanolide analogues against specific tumor cell lines. The results from these future studies will be reported in due course.

Conclusion

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 oxocarbenium cation to forge the central β-*C*-glycoside subunit. 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. In addition, in vitro screening of the antipode of natural dactylolide against the NCI's 60 cancer cell line helped to illuminate the critical importance of the *N*-acyl hemiaminal side chain of natural zampanolide with respect to the potent nanomolar cytotoxicities as reported by Tanaka and Higa. Furthermore, by means of the in vitro screen of (−)-dactylolide, a promising cancer therapeutic lead has now emerged for a variety of carcinomas. More specifically, (−)-dactylolide exhibited GI_{50} values in the nanomolar (25−99 ng/mL) range against the four cell lines HL-60, K-562, HCC-2998, and SF-539, while displaying modest LC_{50} values. These results underscore the importance that (+)-dactylolide was only tested on one human tumor cell line and clearly illustrates the need for synthetic natural product molecules (or in this case the antipode) for the undertaking of in vitro biological testing. By simply synthesizing (−)-dactylolide and providing the NCI with a small sample for testing, a promising therapeutic has now emerged. Further investigations into determining the mechanism of action against a variety of tumors for **3** are underway and will be reported in due course.

Experimental Section

5,6-Bis(*tert*-butyldimethylsilanyloxy)hex-2-ynoic acid ethyl ester (23): To a solution of alkyne **24** (7.37 g, 22.5 mmol) in THF (63 mL) at −78 °C was added BuLi (1.6 M in hexanes, 21 mL, 33.7 mmol) dropwise and stirred for 15 min. Then, ethyl chloroformate (6.45 mL, 67.5 mmol) was added, and the solution was warmed to rt and stirred for 45 min before being quenched with a saturated $NaHCO_3$ solution (60 mL). The aqueous phase was extracted with Et_2O (3 × 60 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography (silica, 2% EtOAc in hexanes) afforded the pure alkynoate (R_f = 0.40, 2% EtOAc in hexanes) as a colorless oil (9.5 g, 94%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.2 Hz, 2H), 3.87 (m, 1H), 3.59 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.48 (dd, *J* = 10.2, 6.9 Hz, 1H), 2.65 (dd, *J* = 17.0, 4.7 Hz, 1H), 2.43 (dd, *J* = 17.0, 6.6 Hz, 1H), 1.29 (t, *J* = 7.2, 3H), 0.89 (s, 18H), 0.12 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 154.9, 87.2, 74.8, 71.4, 66.7, 62.1, 35.2, 26.1, 25.0, 23.3, 18.3, 14.2, −4.3, −4.6, −5.1, −5.2; $[\alpha]^{20}_D$ −6.4 (*c* 0.90, CH_2Cl_2); IR (CH_2Cl_2) 1710, 1471, 1115, 1082 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{41}O_4Si_2$ $(M + H)^+$ 401.2543, found 401.2528.

5,6-Bis(*tert*-butyldimethylsilanyloxy)-3-methylhex-2-enoic acid ethyl ester (26): To a stirred solution of NaOMe (61 mg, 1.1 mmol) in MeOH (54 mL) were added PhSH (2.86 mL, 28.0 mmol) and alkynoate **23** (9.0 g, 22.5 mmol) and stirred for 20 h at rt. The reaction mixture was then filtered through a silica plug with Et_2O as eluent. The filtrate was then concentrated under reduced pressure. Flash column chromatography (silica, 10% EtOAc in hexanes) afforded the alkenoate **25** (R_f = 0.40, 10% EtOAc in hexanes) as

a pale yellow oil (10.35 g, 90%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.35 (m, 3H), 5.94 (s, 1H), 4.21 (m, 2H), 3.63 (m, 1H), 3.33 (dd, J = 10.0, 5.0 Hz, 1H), 3.15 (dd, J = 10.0, 5.6 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 0.82 (s, 9H), 0.79 (s, 9H), −0.01 (s, 3H), −0.04 (s, 3H), −0.09 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.1, 156.9, 135.6, 131.5, 129.4, 115.9, 71.8, 67.6, 60.1, 41.8, 18.3, 15.5, 14.3, −4.2, −4.6, −5.2, −5.3; HRMS (ESI) calcd for $C_{21}H_{38}O_3Si$ $(M + H)^+$ 366.2590, found 366.2593.

A solution of MeMgBr (3.0 M in Et_2O, 473 μL, 1.42 mmol) was added dropwise into a suspension of CuI (296 mg, 1.56 mmol) in THF (4.7 mL) at −78 °C. The reaction mixture was warmed to rt and then recooled to −78 °C. Next, a solution of the thioether **25** (0.50 g, 0.98 mmol) in THF (0.5 mL) was added, and the resultant solution was warmed to 0 °C and allowed to stir for 1 h. Water (0.5 mL) was then added, and the mixture was diluted with Et_2O (20 mL). The organic phase was separated and then dried over Na_2SO_4. The resultant organic phase was then filtered through a silica plug, which was then eluted with Et_2O (10 mL). The combined organics were concentrated under reduced pressure to afford the product **26** (R_f = 0.55, 10% EtOAc in hexanes) as a colorless oil (395 mg, 97%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.70 (s, 1H), 4.14 (m, 2H), 3.81 (m, 1H), 3.54 (dd, J = 9.9, 5.0 Hz, 1H), 3.37 (dd, J = 9.9, 6.8 Hz, 1H), 2.45 (dd, J = 12.7, 3.8 Hz, 1H), 2.18 (d, J = 1.4 Hz, 3H), 2.15 (dd, J = 12.7, 7.9 Hz, 1H), 1.26 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H), 0.03 (s, 3H), 0.0 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.8, 156.9, 118.5, 71.8, 67.3, 59.6, 46.2, 26.2, 26.0, 25.7, 19.7, 18.5, 18.3, 15.5, 14.3, −4.2, −4.7, −5.1, −5.2; $[\alpha]^{20}_D$ −7.7 (*c* 2.35, CH_2Cl_2); IR (CH_2Cl_2) 1713, 1653, 1474, 1226, 1154, 1094 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{45}O_4Si_2$ $(M + H)^+$ 417.2856, found 417.2860.

8,9-Bis(*tert*-butyldimethylsilanyloxy)-6-methylnona-1,5-dien-4-ol (28): To a stirred solution of (−)-Ipc_2BOMe (10.0 g, 31.9 mmol) in anhydrous Et_2O (32 mL) at 0 °C was added allylmagnesium bromide (1.0 M solution in ether, 29.0 mL), and the reaction mixture was stirred at rt for 1 h before being cooled to −78 °C. The aldehyde **22** (7.18 g, 19.3 mmol) was then added dropwise into the Ipc_2Ballyl solution and allowed to stir for 1 h and then warm slowly to rt. An aqueous solution of NaOH (3 M, 12.8 mL) was then added, followed by slow addition of a 30% H_2O_2 solution (25.5 mL). The mixture was refluxed for 3 h to complete the oxidation process. After being cooled to rt, the biphasic solution was separated, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organics were dried over Na_2SO_4 and concentrated under vacuum to yield the crude product. Flash column chromatography (silica, 10% EtOAc in hexanes) afforded the homoallylic alcohol **28** (R_f = 0.50, 20% EtOAc in hexanes) as a colorless oil (5.70 g, 71%) along with other isomers (two diastereomers for each of the *Z/E* isomers, 88% combined yield, 90% de): ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.25 (dd, J = 8.5, 1.0 Hz, 1H), 5.12 (m, 2H), 4.41 (dd, J = 14.6, 6.3 Hz, 1H), 3.77 (ddd, J = 12.2, 11.2, 5.6 Hz, 1H), 3.49 (dd, J = 10.0, 4.5 Hz, 1H), 3.41 (dd, J = 10.0, 4.4 Hz, 1H), 2.31 (dd, J = 11.4, 6.5 Hz, 1H), 2.28 (m, 2H), 2.05 (dd, J = 11.4, 6.7 Hz, 1H), 1.72 (d, J = 1.2 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.055 (s, 3H), 0.047 (s, 6H), 0.045 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 136.1, 134.7, 130.2, 118.0, 72.3, 68.0, 67.2, 44.9, 42.3, 26.2, 26.1, 18.6, 18.4, 17.6, −4.05, −4.50, −5.05, −5.11; $[\alpha]^{20}_D$ −10.1 (*c* 1.3, CH_2Cl_2); IR (CH_2Cl_2) 1471, 1120, 1092 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{46}O_3Si_2Na$ $(M + Na)^+$ 437.2883, found 437.2885.

6-[4,5-Bis(*tert*-butyldimethylsilanyloxy)-2-methylpent-1-enyl]-5,6-dihydropyran-2-one (29): To a stirring solution of alcohol **28** (5.70 g, 13.8 mmol), Et_3N (4.29 mL, 30.4 mmol), and DMAP (84 mg, 0.70 mmol) in CH_2Cl_2 (138 mL) at rt was added acryloyl chloride (2.23 mL, 27.6 mmol) dropwise, and the resulting solution was stirred for 16 h, before brine (100 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organics were washed with brine (50 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash column chromatography (silica, 2% EtOAc in hexanes) afforded the acrylate **21** (R_f = 0.40, 10% EtOAc in hexanes) as a colorless oil (5.12 g, 79%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.37 (dd, J = 17.2, 1.3 Hz, 1H), 6.07 (dd, J = 17.2, 10.0 Hz, 1H), 5.78 (dd, J = 10.0, 1.3 Hz, 1H), 5.68 (m, 2H), 5.24 (dd, J = 9.3, 1.2 Hz, 1H), 5.06 (m, 2H), 3.75 (ddd, J = 12.5,11.6, 5.6 Hz, 1H), 3.48 (dd, J = 10.0, 5.4 Hz, 1H), 3.38 (dd, J = 10.0, 6.1 Hz, 1H), 2.40 (m, 2H), 2.31 (dd, J = 13.9, 6.0 Hz, 1H), 2.06 (dd, J = 13.9, 6.5 Hz, 1H), 1.75 (d, J = 1.1 Hz, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.04 (s, 6H), 0.03 (s, 3H), 0.0 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.7, 138.3, 133.7, 130.8, 129.5, 125.7, 118.2, 71.8, 70.7, 67.3, 45.0, 39.6, 26.2, 26.1, 18.6, 18.3, 17.7, −4.2, −4.6, −5,08, −5.13; $[\alpha]^{20}_D$ −8.2 (*c* 0.17, CH_2Cl_2); IR (CH_2Cl_2) 1715, 1409, 1201 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{48}O_4Si_2Na$ $(M + Na)^+$ 491.2989, found 491.2995.

To a solution of acrylate **21** (2.29 g, 4.90 mmol) in CH_2Cl_2 (300 mL) was added Grubbs' second generation catalyst (0.208 g, 0.245 mmol), and the solution was heated under reflux for 16 h until completion by TLC analysis. The solvent was removed under reduced pressure, and flash column chromatography (silica, 20% EtOAc in hexanes) afforded the lactenone **29** (R_f = 0.28, 20% EtOAc in hexanes) as a colorless oil (2.06 g, 96%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.87 (dddd, J = 13.2, 8.5, 3.6, 1.4 Hz, 1H), 6.03 (ddd, J = 13.2, 1.7, 1.7 Hz, 1H), 5.40 (dd, J = 8.4, 0.9 Hz, 1H), 5.15 (m, 1H), 3.77 (ddd, J = 11.6, 5.2, 1.4 Hz, 1H), 3.51 (dd, J = 10.0, 5.1 Hz, 1H), 3.39 (dd, J = 10.0, 6.5 Hz, 1H), 2.37 (m, 3H), 2.08 (dd, J = 13.5, 7.0 Hz, 1H), 1.76 (d, J = 1.4 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.05 (s, 12H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 164.6, 144.9, 140.6, 124.9, 122.0, 75.0, 72.4, 67.1, 44.6, 29.9, 26.2, 26.1, 18.5, 18.3, 18.1, −4.2, −4.5, −5.09, −5.12; $[\alpha]^{20}_D$ −12.2 (*c* 0.17, CH_2Cl_2); IR (CH_2Cl_2) 1719, 1424 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{45}O_4Si_2$ $(M + H)^+$ 441.2856, found 441.2860.

6-[4,5-Bis(*tert*-butyldimethylsilanyloxy)-2-methylpent-1-enyl]-4-hydroxytetrahydropyran-2-one (20): To a solution of the lactenone **29** (0.600 g, 1.36 mmol) in MeOH (6.8 mL) was added an aqueous H_2O_2 solution (30%, 488 mg, 4.58 mmol). The solution was cooled to 0 °C, and an aqueous NaOH solution (6.0 M, 0.14 mL, 0.82 mmol) was added dropwise and stirred for 10 min. The reaction mixture was then warmed to rt and kept stirring for 0.5 h, before being diluted with Et_2O (15 mL) and H_2O (15 mL). Concentrated aqueous HCl solution was added to adjust the pH to 4. The aqueous layer was extracted with Et_2O (2 × 15 mL), and the combined organics were washed with brine (10 mL). After being dried over Na_2SO_4, the organic solution was concentrated under reduced pressure. The residue was redissolved in benzene (3.4 mL), and the resultant solution was refluxed for 15 min using a Dean−Stark apparatus to remove water. After solvent evaporation, flash column chromatography (silica, 20% EtOAc in hexanes) afforded the epoxide **30** (R_f = 0.32, 20% EtOAc in hexanes) as a colorless viscous oil (515 mg, 83%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.22 (ddd, J = 18.7, 8.8, 3.0 Hz, 1H), 5.21 (d, J = 1.5, 1H), 3.75 (ddd, J = 11.8, 5.0, 1.8 Hz, 1H), 3.66 (dd, J = 6.8, 3.9 Hz, 1H), 3.58 (d, J = 4.1 Hz, 1H), 3.50 (dd, J = 10.0, 5.1 Hz, 1H), 3.37 (dd, J = 10.0, 6.6 Hz, 1H), 2.33 (m, 2H), 2.05 (m, 2H), 1.73 (d, J = 0.7 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.044 (s, 3H), 0.040 (s, 6H), 0.035 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.9, 140.5, 123.8, 72.2, 70.7, 67.1, 52.3, 49.3, 44.4, 30.1, 26.2, 26.1, 18.6, 18.3, 18.0, −4.2, −4.5, −5.08, −5.10, −5.12; $[\alpha]^{20}_D$ +34.2 (*c* 0.37, CH_2Cl_2); IR (CH_2Cl_2) 1738, 1473, 1363, 1112, 1080, 1013 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{45}O_5Si_2$ $(M + H)^+$ 457.2806, found 457.2805.

To a solution of $(PhSe)_2$ (482 mg, 1.55 mmol) in EtOH (8.2 mL) under Ar at rt was added $NaBH_4$ (118 mg, 3.09 mmol) and stirred for 5 min before being cooled to 0 °C. HOAc (176 μL, 3.09 mmol) was then added dropwise, and the solution was allowed to stir for 5 min before a solution of epoxide **30** (471 mg, 1.03 mmol) in EtOH (6.2 mL) was added. The reaction mixture was stirred for 15 min and then diluted with EtOAc (36 mL). The organic solution was washed with brine (9 mL), and the aqueous layer was then extracted with EtOAc (2 × 9 mL). The combined organic solution

was dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (silica, 1:1 EtOAc:hexanes) afforded the alcohol **20** (R_f = 0.30, 1:1 EtOAc/hexanes) as a pale yellow oil (368 mg, 78%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.42 (ddd, J = 8.8, 8.8, 3.4 Hz, 1H), 5.28 (d, J = 8.6 Hz, 1H), 4.37 (ddd, J = 7.6, 3.9, 3.9 Hz, 1H), 3.76 (ddd, J = 11.6, 5.5, 5.5 Hz, 1H), 3.50 (dd, J = 10.1, 5.5 Hz, 1H), 3.38 (dd, J = 10.1, 6.4 Hz, 1H), 2.71 (dd, J = 17.7, 4.9 Hz, 1H), 2.61 (ddd, J = 17.7, 3.4, 1.3 Hz, 1H), 2.34 (dd, J = 13.4, 4.9 Hz, 1H), 2.07 (dd, J = 13.4, 7.0 Hz, 1H), 1.93 (ddd, J = 14.2, 3.9, 3.9 Hz, 1H), 1.82 (dd, J = 14.2, 3.4 Hz, 1H), 1.76 (s, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.04 (s, 12H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.7, 139.6, 125.3, 73.0, 72.2, 67.1, 63.0, 44.5, 38.9, 36.3, 26.2, 26.1, 18.5, 18.3, 17.9, −4.21, −4.50, −5.10, −5.12; $[\alpha]^{20}_D$ +14.3 (*c* 0.20, CH_2Cl_2); IR (CH_2Cl_2) 1728, 1424 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{47}O_5Si_2$ $(M + H)^+$ 459.2962, found 459.2960.

2-Allyl-6-[4,5-bis(*tert*-butyldimethylsilanyloxy)-2-methylpent-1-enyl]-4-triethylsilanyloxytetrahydropyran (32): To a solution of lactone **20** (57 mg, 0.12 mmol) in Et_2O (1.2 mL) at −78 °C was added allylMgBr (1.0 M in Et_2O, 0.37 mL, 0.37 mmol) dropwise, and the suspension was stirred for 0.5 h, before being quenched with H_2O (1.2 mL) and then diluted with EtOAc (25 mL). The mixture was dried over Na_2SO_4, and the solvents were removed under reduced pressure to afford the hemiketal **31** (R_f = 0.60, 1:1 EtOAc:hexanes) as a colorless oil (53 mg). This material was used without further purification.

To a solution of the hemiketal **31** (53 mg, 0.11 mmol) in CH_2Cl_2 (1.1 mL) were added Et_3SiH (0.18 mL, 1.1 mmol) in one portion and TFA (41 μL, 0.55 mmol) sequentially. The solution was then warmed to −40 °C and kept stirring for 0.5 h, before being quenched with a saturated $NaHCO_3$ solution (1.1 mL). The mixture was diluted with Et_2O (25 mL) and dried over Na_2SO_4. The solvents were then removed under reduced pressure. Flash column chromatography (silica, 5% EtOAc in hexanes) afforded the tetrahydropyran **32** (R_f = 0.50, 10% EtOAc in hexanes) as a pale yellow oil (55 mg, 76%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.20 (d, J = 7.9 Hz, 1H), 5.07 − 4.99 (m, 2H), 4.54 (ddd, J = 13.5, 8.3, 5.2 Hz, 1H), 4.18 (m, 1H), 3.88 (m, 1H), 3.75 (ddd, J = 11.8, 11.8, 5.8 Hz, 1H), 3.52 − 3.36 (m, 2H), 2.33 − 2.25 (m, 2H), 2.13 (dd, J = 13.3, 6.8 Hz, 1H), 2.01 (dd, J = 13.3, 6.8 Hz, 1H), 1.70 (s, 3H), 1.64 − 1.19 (m, 4H), 0.96 (t, J = 8.0 Hz, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.58 (q, J = 8.0 Hz, 6H), 0.045 (s, 3H), 0.041 (s, 3H), 0.035 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 135.5, 135.3, 129.1, 116.5, 72.7, 71.3, 69.3, 67.5, 65.2, 44.9, 40.9, 39.8, 38.9, 26.2, 26.1, 18.6, 17.9, 7.1, 5.1, −4.2, −4.5, −5.06, −5.14; $[\alpha]^{20}_D$ −3.3 (*c* 0.30, CH_2Cl_2); IR (CH_2Cl_2) 1471, 1081 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{67}O_4Si_3$ $(M + H)^+$ 599.4347, found 599.4353.

2-Allyl-6-[3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2-methylpropenyl]-4-methylenetetrahydropyran (36): To a stirred solution of $MePh_3PBr$ (129 mg, 0.36 mmol) in anhydrous THF (2.1 mL) at −78 °C was added ^{n}BuLi (1.5 M solution in hexanes, 0.24 mL) dropwise, and the reaction mixture was stirred for 15 min, before being warmed to 0 °C for 20 min. A solution of ketone **35** (53 mg, 0.18 mmol) in THF (2.1 mL) was then added, and the reaction was allowed to stir at rt for 1.5 h until consumption of the starting material as determined by TLC analysis. The reaction was then quenched with H_2O (4 mL), and the aqueous layer was extracted with ether (3 × 4 mL). The combined organic solution was dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (silica, 5% EtOAc in hexanes) afforded the methylene tetrahydropyran **36** (R_f = 0.45, 20% EtOAc in hexanes) as a slightly yellow oil (41 mg, 78%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.30 (dd, J = 7.5, 1.0 Hz, 1H), 5.06 (m, 2H), 4.73 (dd, J = 1.5, 1.5 Hz, 2H), 4.22 (ddd, J = 13.2, 6.1, 6.1 Hz, 1H), 4.01 (m, 1H), 4.00 (dd, J = 7.6, 5.7 Hz, 1H), 3.54 (dd, J = 7.5, 7.5 Hz, 1H), 3.36 (m, 1H), 2.41 (dd, J = 14.0, 6.3 Hz, 2H), 2.27−2.12 (m, 2H), 2.03 (ddd, J = 11.5, 11.5, 1.2 Hz, 1H), 1.92 (ddd, J = 11.5, 11.5, 1.2 Hz, 1H), 1.72 (d, J = 1.0 Hz, 3H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 144.6, 135.7, 134.8, 128.4, 117.1, 109.1, 108.9, 78.0, 75.7, 74.8, 69.5, 43.8, 41.0, 40.2, 27.2, 26.0, 17.7; HRMS (EI) calcd for $C_{18}H_{28}O_3$ (M^+) 292.2038, found 292.2031.

7-Hydroxy-5-methylhepta-2,4-dienoic acid ethyl ester (49): To a solution of triethyl phosphonoacetate (6.91 mL, 34.5 mmol) in THF (34 mL) was added LiHMDS (1.0 M in THF, 34.5 mL, 34.5 mmol) dropwise, and the reaction was allowed to stir for 15 min at 0 °C. A solution of the enal **50** (3.95 g, 17.2 mmol) in THF (52 mL) was then added, and the reaction mixture was warmed to rt and stirred for 1 h, before being diluted with Et_2O (100 mL) and quenched with H_2O (30 mL). The aqueous solution was extracted with Et_2O (3 × 30 mL), and the combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (silica, 5% EtOAc in hexanes) afforded the dienoate **51** (R_f = 0.40, 10% EtOAc in hexanes) as a colorless oil (5.03 g, 98%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.54 (dd, J = 15.3, 11.8 Hz, 1H), 6.05 (d, J = 11.6 Hz, 1H), 5.75 (d, J = 15.1 Hz, 1H), 4.19 (g, J = 7.5 Hz, 2H), 3.70 (t, J = 6.5 Hz, 2H), 2.50 (t, J = 6.6 Hz, 2H), 1.90 (s, 3H), 1.29 (t, J = 7.4 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.7, 147.1, 141.1, 125.7, 119.5, 61.9, 60.2, 39.2, 36.7, 26.2, 25.2, 14.5, −5.1; IR (CH_2Cl_2) 1704, 1637, 1156, 1101 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{31}O_3Si$ $(M + H)^+$ 299.2042, found 299.2047.

To a solution of the silyl ether **51** (298 mg, 1.0 mmol) in THF (10 mL) was added a Py•HF solution (65% in Py, 0.3 mL, ∼10.0 mmol) and stirred for 4 h. The reaction mixture was then diluted with Et_2O (30 mL) and quenched with a saturated $NaHCO_3$ solution (10 mL) along with solid $NaHCO_3$ until no gas was evolved. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organics were dried over Na_2SO_4. Evaporation of solvents afforded the alcohol **49** (R_f = 0.30, 1:1 EtOAc/hexanes) as a pale yellow oil (169 mg, 92%) without further purification: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.54 (dd, J = 15.1, 11.7 Hz, 1H), 6.09 (d, J = 11.7 Hz, 1H), 5.77 (d, J = 15.5 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.72 (t, J = 6.7 Hz, 2H), 2.55 (t, J = 6.7 Hz, 2H), 1.90 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.9, 146.4, 140.5, 126.1, 119.7, 60.9, 60.4, 36.2, 24.7, 14.5; IR (CH_2Cl_2) 1704, 1637, 1154 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{17}O_3$ $(M + H)^+$ 185.1178, found 185.1168.

7-Hydroxy-5-methylnona-2,4,8-trienoic acid ethyl ester (47): To a stirred solution of alcohol **49** (1.00 g, 5.43 mmol) in CH_2Cl_2 at 0 °C was added Dess−Martin periodinane (15% in CH_2Cl_2, 17 mL, 8.14 mmol), and the reaction mixture was warmed to rt and allowed to stir for 1 h. After completion by TLC analysis, the reaction was quenched with isopropanol (6 mL) and the mixture was filtered through a silica gel plug using EtOAc as the eluent. The combined organics were concentrated under reduced pressure. Flash column chromatography (silica, 30% EtOAc in hexanes) afforded the aldehyde **48** (R_f = 0.35, 30% EtOAc in hexanes) as a pale yellow oil (602 mg, 61%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.59 (t, J = 1.8 Hz, 1H), 7.39 (dd, J = 15.1, 11.7 Hz, 1H), 6.21 (d, J = 11.7 Hz, 1H), 5.83 (d, J = 15.1 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.40 (s, 2H), 1.89 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 197.5, 167.2, 139.2, 139.0, 127.8, 121.4, 60.5, 47.9, 25.3, 14.4; IR (CH_2Cl_2) 1718, 1706, 1638, 1158 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{15}O_3$ $(M + H)^+$ 183.1021, found 183.1036.

To a solution of aldehyde **48** (67 mg, 0.37 mmol) in THF (2.8 mL) at −78 °C was added vinylMgBr (1.0 M in THF, 0.93 mL, 0.93 mmol), and the reaction mixture was stirred for 2 h, before being quenched with a saturated NH_4Cl solution (0.9 mL), warmed to rt, and diluted with EtOAc (20 mL). The organic solution was dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (silica, 30% EtOAc in hexanes) afforded the allylic alcohol **47** (R_f = 0.50, 1:1 EtOAc/hexanes) as a brown oil (38 mg, 49%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.53 (dd, J = 15.1, 11.7 Hz, 1H), 6.11 (d, J = 11.7 Hz, 1H), 5.88 (m, 1H), 5.77 (d, J = 15.1 Hz, 1H), 5.25 (d, J = 17.2 Hz, 1H), 5.11 (d, J = 10.4 Hz, 1H), 4.17 (d, J = 7.1 Hz, 2H), 2.62 (dd, J = 13.4, 8.2 Hz, 1H), 2.41 (dd, J = 13.4, 5.4 Hz, 1H), 1.91 (s, 3H), 1.27 (t, J = 7.1

Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.7, 145.7, 140.5, 140.3, 126.7, 120.0, 115.3, 71.6, 60.3, 40.6, 25.3, 14.5; IR (CH_2Cl_2) 1707, 1640, 1632, 1157 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{19}O_3$ $(M + H)^+$ 211.1334, found 211.1334.

7-(*tert*-Butyldimethylsilanyloxy)-5-methylnona-2,4,8-trienoic acid (5): To a stirred solution of the allylic alcohol **47** (195 mg, 0.93 mmol) and TBSCl (280 mg, 1.86 mmol) in DMF (2.0 mL) at rt was added imidazole (190 mg, 2.79 mmol), and the reaction was allowed to stir for 20 h, before being diluted with Et_2O (40 mL) and quenched with H_2O (10 mL). The organic solution was dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (silica, 10% EtOAc in hexanes) afforded the TBS ester (R_f = 0.32, 10% EtOAc in hexanes) as a pale yellow oil (254 mg, 85%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.53 (dd, J = 15.1, 11.6 Hz, 1H), 6.05 (d, J = 11.6 Hz, 1H), 5.83 (dd, J = 10.4, 6.1 Hz, 1H), 5.78 (dd, J = 10.4, 6.6 Hz, 1H), 5.75 (d, J = 15.3 Hz, 1H), 5.17 (ddd, J = 17.1, 1.4, 1.4 Hz, 1H), 5.04 (ddd, J = 10.3, 1.3, 1.3 Hz, 1H), 4.22 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.58 (dd, J = 13.2, 7.7 Hz, 1H), 2.34 (dd, J = 13.2, 5.4 Hz, 1H), 1.90 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.6, 146.2, 141.1, 141.0, 126.1, 119.3, 114.1, 73.0, 60.1, 41.7, 25.9, 25.7, 18.3, 14.4, −2.9, −4.4; IR (CH_2Cl_2) 1708, 1631 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{33}O_3Si$ $(M + H)^+$ 325.2199, found 325.2205.

To a solution of ester (241 mg, 0.74 mmol) in EtOH (3.7 mL) was added dropwise an aqueous NaOH solution (1.0 M, 1.85 mL) at 0 °C. The reaction mixture was then warmed to rt and stirred for 20 h before an aqueous HCl solution was added (1.0 M, 1.85 mL). EtOAc (20 mL) was added and allowed to partition. The aqueous layer was extracted with EtOAc (2 × 5 mL), and the organics were combined and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was redissolved in toluene (4 mL) and then rotavapped to afford the acid **5** (R_f = 0.56, EtOAc) as a pale yellow viscous oil (208 mg, 95%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.65 (dd, J = 15.0, 11.7 Hz, 1H), 6.10 (d, J = 11.7 Hz, 1H), 5.83−5.74 (m, 2H), 5.18 (ddd, J = 17.1, 1.4, 1.4 Hz, 1H), 5.06 (ddd, J = 10.4, 1.4, 1.4 Hz, 1H), 4.25 (dd, J = 12.7, 6.3 Hz, 1H), 2.60 (dd, J = 13.2, 7.7 Hz, 1H), 2.36 (dd, J = 13.2, 5.2 Hz, 1H), 1.93 (s, 3H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.1, 148.1, 143.7, 141.2, 126.2, 118.4, 114.4, 73.1, 42.0, 26.0, 18.3, −4.3, −4.7; IR (CH_2Cl_2) 1718, 1635 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{28}O_3Si$ $(M + H)^+$ 296.1808, found 296.1811.

5-(6-Allyl-4-methylenetetrahydropyran-2-yl)-1-(*tert*-butyldimethylsilanyloxy)-4-methylpent-4-en-2-ol (4): To a solution of the acetonide **36** (29 mg, 0.1 mmol) in EtOH (0.33 mL) and CH_2Cl_2 (0.33 mL) at 0 °C was added TFA (0.33 mL) dropwise and stirred for 10 min. The solvents were removed under reduced pressure, and the residue was coevaporated with PhMe (2 × 2 mL) to remove TFA and afforded the crude diol **52**.

To a solution of **52**, TBSCl (38 mg, 0.25 mmol), DMAP (2 mg, 16 μmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added Et_3N (56 μL, 0.4 mmol), and the reaction mixture was warmed to rt and stirred for 1.5 h until complete by TLC analysis. The reaction was then quenched with H_2O (0.5 mL), and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic washes were dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (silica, 20% EtOAc in hexanes) afforded the monoprotected alcohol **4** (R_f = 0.35, 20% EtOAc in hexanes) as a colorless oil (35 mg, 97%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.30 (d, J = 7.8 Hz, 1H), 5.10 − 5.03 (m, 2H), 4.73 (s, 2H), 4.01 (ddd, J = 10.8, 7.8, 2.7 Hz, 1H), 3.79 (dddd, J = 13.5, 10.6, 6.7, 3.8 Hz, 1H), 3.59 (dd, J = 10.0, 3.8 Hz, 1H), 3.44 (dd, J = 10.0, 6.6 Hz, 1H), 3.36 (m, 1H), 2.43−2.14 (m, 6H), 2.04 (dd, J = 11.3, 11.3 Hz, 1H), 1.92 (dd, J = 11.3, 11.3 Hz, 1H), 1.72 (d, J = 1.2 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 144.6, 136.0, 134.7, 128.6, 117.3, 108.8, 77.9, 75.7, 70.1, 66.7, 43.4, 40.8, 40.1, 26.1, 18.4, 17.4, −5.2; HRMS (ESI) calcd for $C_{21}H_{38}O_3Si$ $(M + H)^+$ 366.2590, found 366.2593.

(−)-Dactylolide (3): To a solution of the diol **55** (3.6 mg, 9.3 μmol) in CH_2Cl_2 (100 μL) was added dropwise a Dess−Martin solution (15% in CH_2Cl_2, 77 μL, 37.2 μmol) at 0 °C, and the reaction was allowed to warm to rt. The reaction mixture was stirred for 0.5 h, then diluted with CH_2Cl_2 (1.0 mL) and Et_2O (2.0 mL). Pyridine (5 μL, 91 μmol) was added, and the resulting mixture was filtered through a plug of Celite. The solvents were removed under reduced pressure, and flash column chromatography (silica, 1:1 EtOAc/hexanes) afforded dactylolide (**3**) (R_f = 0.46, 3:2 EtOAc/hexanes) as a colorless solid (3.2 mg, 90%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.63 (dd, J = 15.1, 11.6 Hz, 1H), 6.85 (ddd, J = 16.1, 8.6, 5.9 Hz, 1H), 6.15 (d, J = 11.6 Hz, 1H), 6.00 (d, J = 16.2 Hz, 1H), 5.96 (d, J = 15.1 Hz, 1H), 5.32 (dd, J = 11.4, 2.4 Hz, 1H), 5.24 (d, J = 8.0 Hz, 1H), 4.75 (s, 2H), 3.97 (ddd, J = 11.1, 8.1, 2.5 Hz, 1H), 3.95 (d, J = 14.3 Hz, 1H), 3.32 (dddd, J = 11.4, 9.1, 2.5, 2.5 Hz, 1H), 3.23 (d, J = 14.3 Hz, 1H), 2.54 (d, J = 14.0 Hz, 1H), 2.39−2.27 (m, 3H), 2.17 (ddd, J = 13.2, 1.6, 1.6 Hz, 1H), 2.11 (ddd, J = 13.0, 1.6, 1.6 Hz, 1H), 1.96 (m, 2H), 1.86 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 199.3, 197.6, 166.5, 146.2, 144.2, 140.6, 131.7, 131.1, 130.7, 125.8, 120.0, 109.5, 76.7, 75.9, 75.5, 45.1, 41.0, 40.6, 39.94, 39.90, 24.3, 16.3; $[\alpha]^{20}_D$ = −136 (*c* 1.2, MeOH); IR (CH_2Cl_2) 1722, 1703, 1668, 1638, 1283 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{29}O_5$ $(M + H)^+$ 385.2015, found 385.2023.

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Supporting Information Available: Experimental procedures and full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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