Natural Product Synthesis

Total Synthesis of (+)-Dactylolide through an Efficient Sequential Peterson Olefination and Prins Cyclization Reaction**

*Danielle L. Aubele, Shuangyi Wan, and Paul E. Floreancig**

Dedicated to Professor Peter Dervan on the occasion of his 60th birthday

Dactylolide (**1**, Figure 1) is a bicyclic macrolactone that was isolated from the Vanuatu sponge *Dactylospongia* in 2001 by Riccio and co-workers.[1] While dactylolide is moderately cytotoxic toward L1210 (lymphatic leukemia) and SK-OV-3 (ovarian cancer) cells, causing 63% and 40% growth inhibition, respectively, at 3.2 $\mu g\,mL^{-1}$ (8.3 μM), the structurally related natural product zampanolide (**2**)[2] shows significantly greater cytotoxic activity, with IC_{50} values of 1–5 nM against several cell lines. Upon completing the syntheses of **1** and **2**,[3] Smith et al. concluded, on the basis of optical rotation data, that the common macrolide cores of these compounds have opposite absolute configurations. The incongruence in optical rotations between natural ($[\alpha]_D = +30°$, $c = 1$, MeOH) and synthetic ($[\alpha]_D = +235°$, $c = 0.52$, MeOH[3] or $-128°$, $c = 0.39$, MeOH, antipode[4]) dactylolide, however, preclude a firm conclusion regarding its absolute stereochemistry. Hoye and Hu's demonstration[4] that dactylolide can be converted into zampanolide through an aza-aldol addition shows that both compounds can be accessed through a common strategy, provided the route can be used to access either enantiomer. Herein, we report a convergent and efficient route to dactylolide that employs an acetal linkage to fuse two complex fragments and a Prins reaction that proceeds under remarkably mild conditions to form the methylene tetrahydropyran group. In this sequence stereogenicity is derived from asymmetric catalysts that are readily available as either enantiomer, which makes the route also applicable to the synthesis of zampanolide.

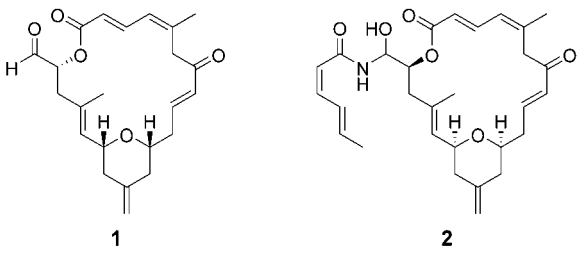

Figure 1. (+)-Dactylolide and (−)-zampanolide.

We established two key objectives for the synthesis of dactylolide (Figure 2): to maximize convergency by coupling two functionalized subunits at a reasonably late stage in the sequence, and to minimize the number of carbon–carbon bond-forming reactions. We postulated that the former objective could result from the union of two advanced fragments through an acetal linkage.[5] This somewhat underutilized approach to increasing molecular complexity is quite attractive in both the efficiency of the coupling and the capacity for acetals to serve as precursors for structurally diverse ethers. We envisioned asymmetric vinylogous Mukaiyama aldol reactions[6] to be effective vehicles for achieving the latter objective. Thus **1** can be accessed from diol **3**, which, in turn, results from transposed allylic alcohol **4** (Figure 2). Acetal **5**, prepared through the union of **6** and **7**, serves as the precursor for the methylene tetrahydropyran. We recently reported[7] that acetals of this general structure undergo Prins reactions under very mild conditions, with promotion of the process in water by Lewis acid surfactant catalysts.[8] Sequences that employ catalytic, asymmetric vinylogous Mukaiyama aldol reactions can be designed to access **6** and **7** from *p*-methoxybenzyloxyacetaldehyde and 2-butynol, respectively.

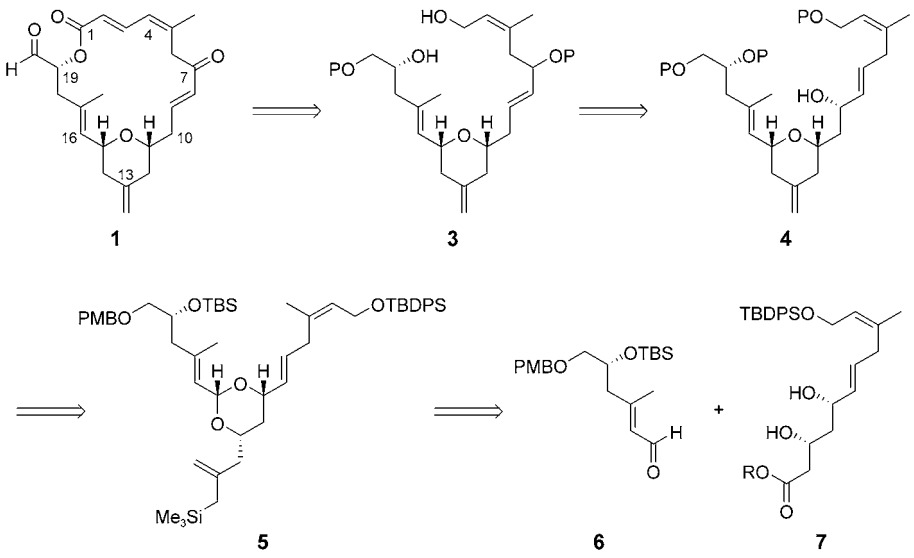

Figure 2. Retrosynthetic analysis of dactylolide. P = protecting group, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

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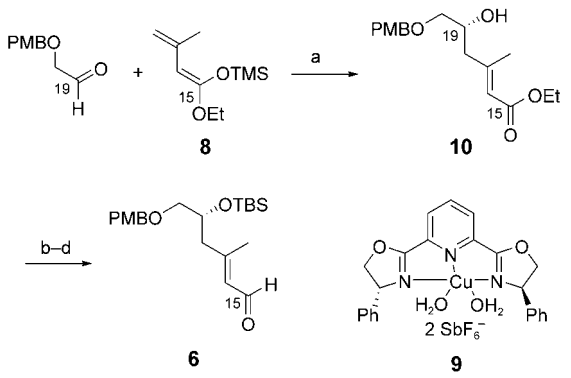
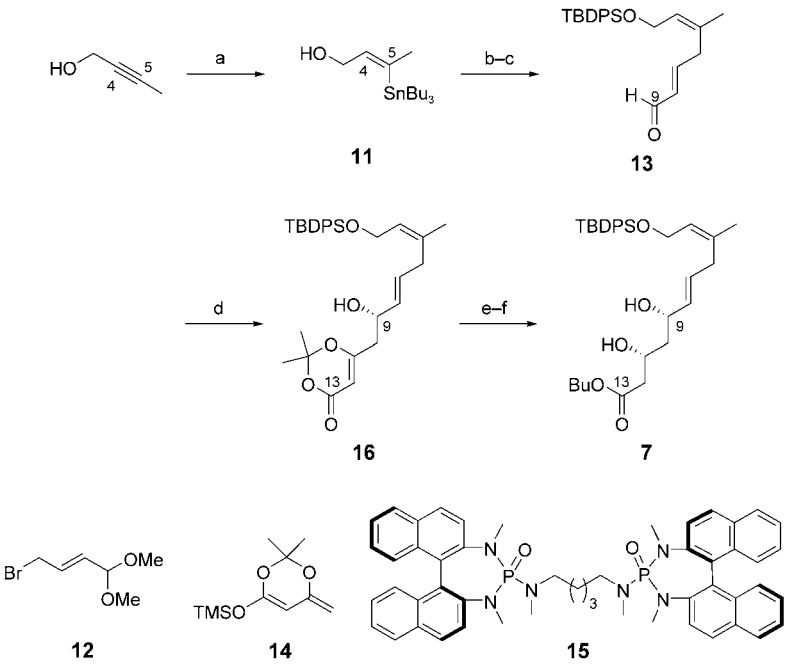
The synthesis of **6** (Scheme 1) requires a high level of control over both the stereocenter at C19 and the geometry of the trisubstituted alkene. Our route to **6** follows the sequence devised by Evans et al. in their synthesis of callipeltoside.[9]



Scheme 1. a) **9**, CH_2Cl_2, −78 °C, 82 %, 95 % *ee*; b) TBSCl, imidazole, DMF, 89 %; c) $LiAlH_4$, Et_2O; d) MnO_2, CH_2Cl_2, 80 %, 2 steps. DMF = *N*,*N*-dimethylformamide.

Condensation of silyl ketene acetal **8** with *p*-methoxybenzyloxyacetaldehyde in the presence of Cu·pybox catalyst **9**[10] provided **10** in 82 % yield and 95 % *ee*, with the alkene formed as a single isomer. Conversion of **10** into **6** proceeded through a straightforward three-step sequence of protection, reduction, and oxidation.

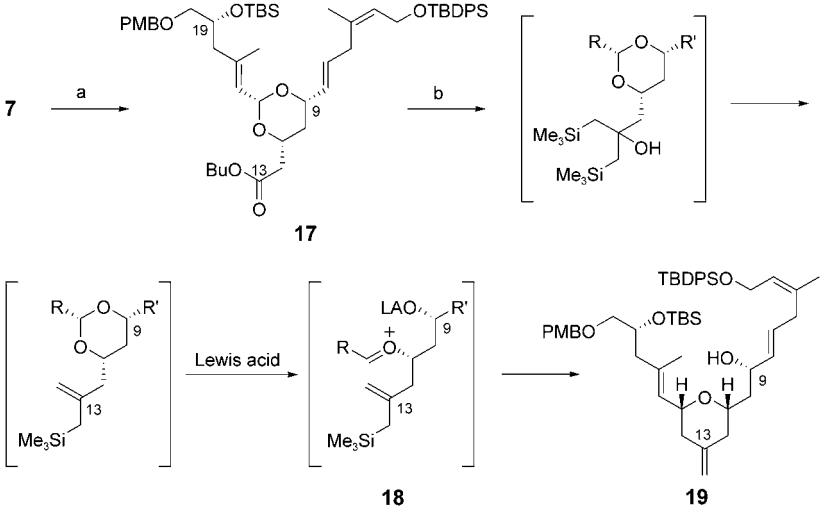
As an entry into **7** (Scheme 2), the geometry of the $\Delta^{4,5}$-trisubstituted olefin was set through a hydroalumination reaction of 2-butynol with Red-Al[11] followed by quenching with Bu_3SnCl to form vinyl stannane **11** in 93 % yield. Following protection of the primary hydroxyl group, palladium-mediated coupling[12] with bromide **12**[13] and acetal hydrolysis in situ provided enal **13** in 80 % yield. To the best of our knowledge, this is the first report of **12** serving as an electrophilic surrogate for crotonaldehyde in a cross-coupling reaction. The absence of a chelating group in **13** precluded the use of the Cu·pybox complex as a promoter of aldol chemistry. Therefore we utilized Denmark's bisphosphoramide catalytic system **15**[14] and $SiCl_4$ to effect coupling between **13** and ketene acetal **14** to yield alcohol **16** in 93 % *ee* and 67 % yield at 83 % conversion (83 % yield based on recovered starting material). Notably, this reaction proceeded with even higher selectivity than the corresponding reaction with cinnamaldehyde that was reported in the original manuscript,[15] which suggests that this catalyst is well suited for applications in the synthesis of complex molecules. Thermolysis of **16** in BuOH followed by *syn*-reduction of the resulting keto ester with Et_2BOMe and $NaBH_4$[16] completed the synthesis of diol **7**.



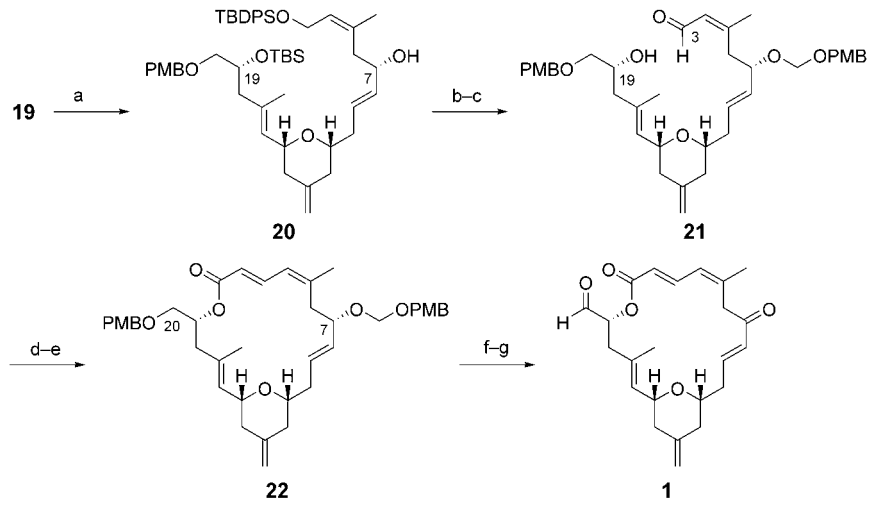
Scheme 2. a) Red-Al, THF, then Bu_3SnCl, 93 %; b) TBDPSCl, imidazole, DMF, 87 %; c) **12**, $[(CH_3CN)_2PdCl_2]$, PPh_3, $CHCl_3$, 65 °C, then HCO_2H, CH_2Cl_2, 80 %; d) **15**, $SiCl_4$, **14**, CH_2Cl_2, −78 °C, 67 % at 83 % conversion, 93 % *ee*; e) *n*BuOH, reflux, 74 %; f) Et_2BOMe, $NaBH_4$, THF, −78 °C, 83 %. Red-Al = sodium bis(2-methoxyethoxy)aluminumhydride.

Formation of the acetal linkage between **6** and **7** (Scheme 3) through standard acid catalysis was complicated by competitive isomerization of the trisubstituted alkene in the enal. Conversion of **7** into its bis-trimethylsilyl ether and coupling with **6** using Noyori's TMSOTf-mediated protocol,[17] however, provided acetal **17** in high yield and without isomerization. In preparation for the Prins reaction, we subjected **17** to excess $TMSCH_2MgCl$ and $CeCl_3$ followed by an acidic workup.[18] To our surprise the major product isolated from this reaction was methylene tetrahydropyran **19**, the desired subunit of dactylolide, which resulted from allylsilane formation, followed by acetal ionization to provide oxocarbenium ion **18**, and cyclization. After conducting a series of experiments designed to elucidate the initiator for the Prins reaction, we concluded that weakly Lewis acidic cerium salts are not completely removed in the aqueous workup and initiate ionization and cyclization upon evaporation of the organic solvent. While this process was quite direct, the yields proved to be irreproducible. A more reliable protocol for this transformation was devised in which the addition of alkylcerium was quenched with aqueous $NaHCO_3$ and a solution of the resulting crude tertiary alcohol in CH_2Cl_2 was subjected to pyridinium triflate and $MgSO_4$ to effect a sequential Peterson olefination and Prins cyclization. This remarkably mild process routinely provided **19** in 75 % yield from **17**. The desiccant and the non-nucleophilic triflate ion were both necessary to promote cyclization without causing protodesilylation of the allylsilane. Although acetal ionization can occur to form two oxocarbenium ions, **18** can proceed through a kinetically facile 6-*endo* pathway while cyclization through the alternative ion would proceed through a less favorable 8-*endo* pathway. Therefore the observed selectivity strongly suggests that cyclization is the product-determining step rather than ionization.[19]

Transposition of the C9 allylic alcohol that was formed in the Prins reaction was required to complete the synthesis of dactylolide (Scheme 4) and was achieved through conversion of the hydroxyl group of **19**



Scheme 3. a) (1) TMSCl, imidazole, DMAP, DMF; (2) **6**, TMSOTf, CH_2Cl_2, −78 °C, 83 %; b) 1) Me_3SiCH_2MgCl, $CeCl_3$, THF, −78 °C→RT; 2) Py·HOTf, $MgSO_4$, CH_2Cl_2, 75 %. TMS = trimethylsilyl, DMAP = 4-dimethylaminopyridine, Tf = trifluoromethanesulfonyl, Py (py) = pyridine, LA = Lewis acid.



Scheme 4. a) (1) PhSeCN, Bu_3P, THF; (2) H_2O_2, py, THF, −30 °C, 62 %; b) (1) $PMBOCH_2Cl$, iPr_2NEt, CH_2Cl_2; (2) HF·Py, py, THF, 80 %; c) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 87 %; d) Diethylphosphonoacetic acid, DCC, DMAP, CH_2Cl_2, 95 %; e) NaHMDS, THF, −78 →0 °C, 73 %; f) DDQ, CH_2Cl_2, buffer (pH 7), 63 % (14 % C7 ketone); g) Dess–Martin periodinane, CH_2Cl_2, 77 %. TEMPO = 2,2,6,6-tetramethylpiperidinyl-1-oxyl, DCC = dicyclohexyl carbodiimide, HMDS = hexamethyldisilazide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

into a selenide with PhSeCN and Bu_3P[20], with no complication from the S_N2' pathway. Oxidation of the crude selenide with H_2O_2 in the presence of pyridine induced a selenium variant[21] of the Mislow–Evans rearrangement[22] to provide allylic alcohol **20** in 62 % yield over the two-step sequence.[23] While the stereochemical outcome of this reaction was not rigorously established, mechanistic analogy[24] strongly suggests that the nascent alcohol is oriented as shown in Scheme 4. Attempts to form the PMB ether of the hydroxyl group at C7 under basic (NaH, PMBCl, NaI) or acidic ($PMBOC(NH)CCl_3$, $BF_3{\cdot}OEt_2$, or TfOH) conditions resulted in low conversions and significant decomposition. Formation of the *p*-methoxybenzyloxymethyl ether[25] ($PMBOCH_2Cl$, iPr_2NEt), however, proceeded much more efficiently. Desilylation of the resulting ether with Py·HF yielded the C3,C19 diol in 80 % yield from **20**. Selective oxidation of the primary allylic C3 alcohol with TEMPO and $PhI(OAc)_2$[26] formed aldehyde **21** in 87 % yield. Macrolactone formation was most conveniently accomplished through an intramolecular Horner–Emmons reaction, a parallel of Smith's approach[3] to this system. Acylation of the hydroxyl group at C19 with diethylphosphonoacetic acid and DCC provided the corresponding phosphonoacetate, which, upon deprotonation with NaHMDS, engaged in an intramolecular condensation reaction to provide macrolactone **22** in 73 % yield from **21**. The synthesis was completed by an oxidative cleavage of both protecting groups with DDQ. This process provided the C7,C20 diol along with variable amounts of the C7 ketone. The allylic oxidation proved to be inconsequential as the following step was a double oxidation of the diol with the Dess–Martin periodinane[27] to provide dactylolide in 77 % yield ($[\alpha]_D = +163°$, $c = 0.29$, MeOH).

In summary, we have reported an efficient total synthesis of dactylolide. Key steps in the sequence include two enantioselective vinylogous Mukaiyama reactions, fragment coupling through acetal formation, a sequential Peterson olefination/Prins cyclization reaction that proceeds under very mild conditions, and a Mislow–Evans rearrangement to effect the transposition of an allylic alcohol. The linear sequence was kept as brief as possible by minimizing carbon–carbon bond-forming reactions and employing a convergent approach. As both antipodes of the catalysts that were used to establish stereogenicity are available, this sequence is also applicable to the synthesis of zampanolide through the use of Hoye's aza-aldol reaction.

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