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Synthesis of the C21–C28 segment of pectenotoxin-4

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Abstract—The synthesis of the C21–C28 segment of pectenotoxin-4 as the C21 Weinreb amide is described. Feasibility studies for the union of a related Weinreb amide and a functionalized alkyne are also reported.

We were attracted to the synthetic challenges posed by macrolide pectenotoxin-4 (**1**, Fig. 1) and its impressive, albeit only partially documented, biological profile.[1] The pectenotoxins are a small but structurally imposing class of substances from isolates collected off the coast of Japan. These natural products were thought to originate from the pecten scallops. Subsequent investigations revealed that dinoflagellates, in this case *Dinophysis fortii*, within the shellfish are the source of these metabolites. Highlights of the biological profile include potent actin depolymerization activity[2] and tumor cell repression[3] in P53 deficient cells.[4]

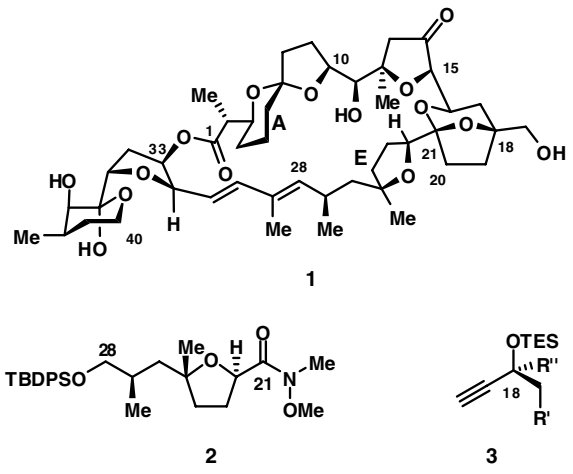

Figure 1. Pectenotoxin-4.

Several routes toward the pectenotoxins have appeared, highlighted by the elegant total synthesis by Evans, et al.[5] Ignoring for the present discussion the important issue of exact timing, we focused on an approach to the endgame that set as the goal the late-stage formation of the C20–C21 junction. A Weinreb amide–alkynylide coupling seems an attractive solution, owing to the anticipated reliability of such a union. To test the feasibility of this proposal, the coupling of a suitable C21–C28 fragment (**2**) with complex model alkynes of general structure **3** was examined (Fig. 1). Although any serious synthetic venture would have to coordinate creation of the 19 stereocenters, the C_{40} backbone, and formation of the eight oxygen heterocycles either ancillary to or subsumed within the 34-membered macrolide, we report here the synthesis of segment **2** and preliminary investigations related to a planned C1–C20/C21–C40 coupling.

The synthesis of **2**, summarized in Schemes 1–3, commenced with the preparation of aldehyde **7**. Implementation of the Jacobsen hydrolytic kinetic resolution of glycidol **4**,[6] followed by selective protection of the primary alcohol with pivaloyl chloride (→**5**), gave a single product, as assessed by Mosher ester analysis (>95% ee).[7] Protection of **5** using *p*-methoxybenzyl imidate[8] gave **6** in an overall yield of 68%. Removal of the pivolate followed by Swern oxidation[9] provided differentially protected L-glyceraldehyde **7**. This five-step sequence from commercial reagents proceeded in 52% overall yield.[10]

Alkyne **10** was prepared by alkylation of **8** with commercially available (TMS) propargyl bromide **9** (dr 9:1, 63%).[11] Cleavage of the oxazolidinone with lithium

Keywords: Pectenotoxin; Tetrahydrofuran synthesis; Weinreb amide; Marshall cyclization.
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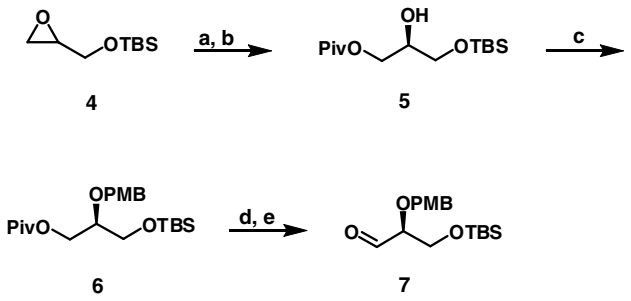
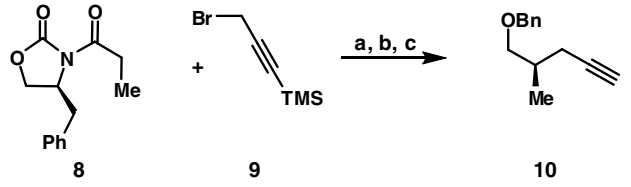


Scheme 1. Reagents and conditions:[19] (a) (*R*,*R*)-salen-Co(III)-OAc (0.49 equiv), H_2O, Et_2O, rt, 18 h, 47%; (b) Piv-Cl (1 equiv), pyr (5 equiv), CH_2Cl_2, 0 °C–rt, 4 h, 94%; (c) PMBOC(=NH)CCl_3 (1.2 equiv), TfOH (0.01 mol %), Et_2O, rt, 0.5 h, 77%; (d) DiBAl-H (1.5 equiv), hexanes, 0 °C–rt, 4 h, 85%; (e) DMSO (4 equiv), $(COCl)_2$ (2.2 equiv), *i*-Pr_2EtN (4.0 equiv), −78 °C, 90%.



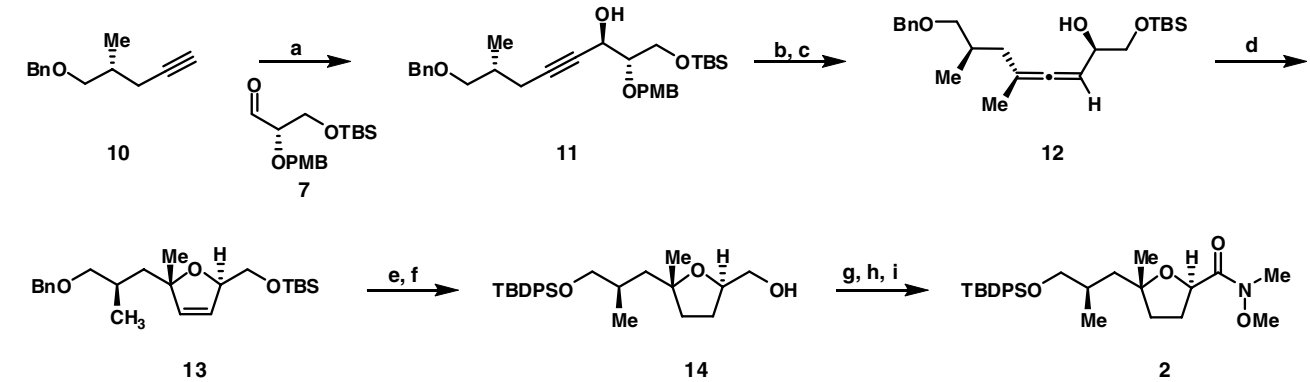
Scheme 2. Reagents and conditions:[19] (a) LiHMDS (1.2 equiv), THF, −78 °C–rt, 4 h, 9:1 dr, 63%; (b) $LiBH_4$ (2.5 equiv), THF, 0 °C, 84%; (c) BnOC(=NH)CCl_3 (1.5 equiv), TfOH; (0.01 mol %), Et_2O, rt, 1 h then MeOH, K_2O_3 excess, 1 h, 86%.

borohydride followed by protection of the primary alcohol with benzyl imidate[9] and then in situ cleavage of the TMS group with MeOH and potassium carbonate provided **10**. The yield of **10** from this three-step sequence was 46% overall.

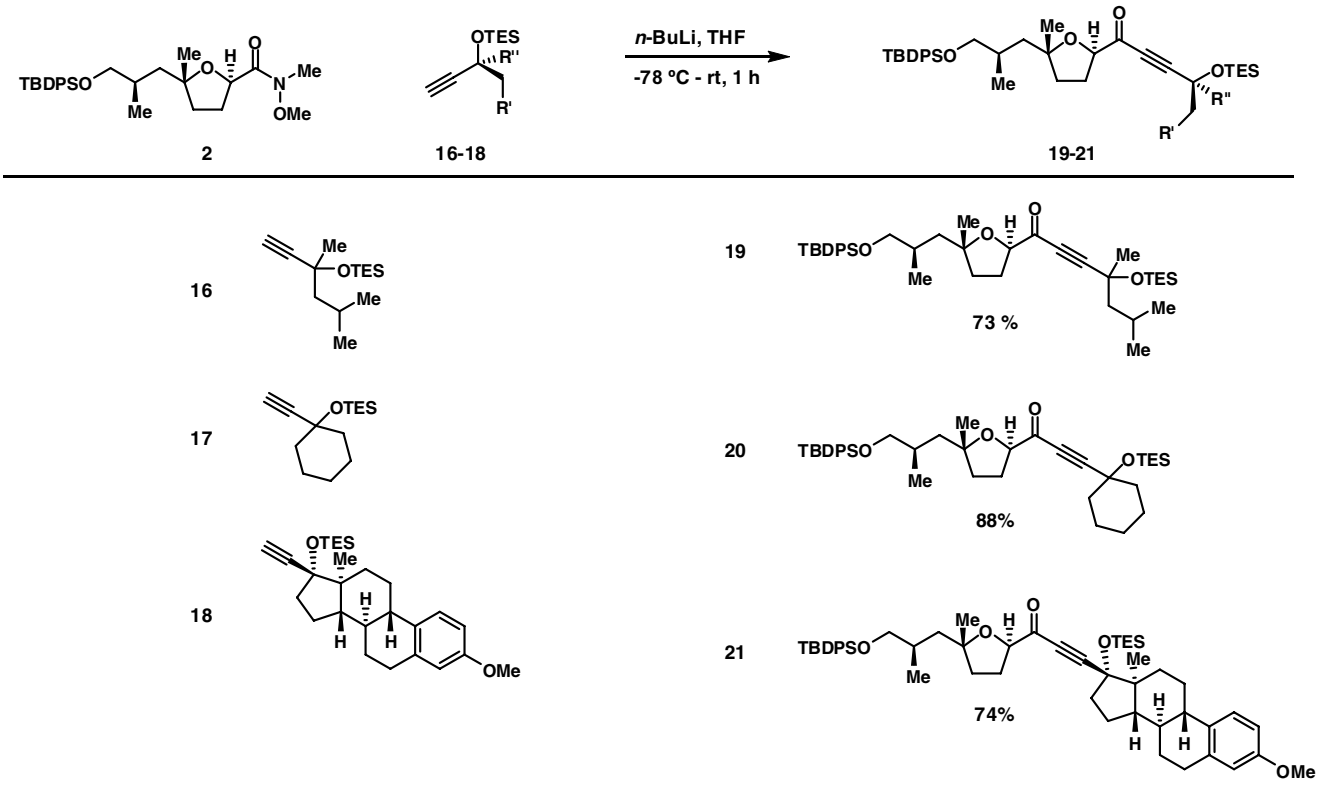
The synthetic sequence to **2** from **7** and **10** is shown in Scheme 3. Initial evaluation of a Felkin–Anh type[12] union of the titaniumisopropoxide alkynylide[13] derived from **10** with aldehyde **7** provided **11** in 1.5:1 dr and 53% yield.[14] Use of the lithium alkynylide in THF and in the presence of 5 equiv of HMPA[15] offered only a modest improvement (dr 2:1, 62% yield). Carreira alkynylation of **7** with **10**, however, proved significantly more efficient and selective (85%, dr 4:1).[16a] The so-called matched amino alcohol ligand of the Carreira reaction has been shown to enhance selectivity of anti-Felkin–Anh addition to α-siloxy aldehydes. Furthermore, and consistent with formation of **11**, the antipodal amino alcohol ligand has been shown to override intrinsic selectivity and give Felkin–Ahn addition as the major product.[16b]

Addition of mesyl chloride and then excess methyl cuprate effected the single-flask conversion of **11** to allene **12** in an efficient (95%) and convenient procedure. Cleavage of the PMB ether with DDQ (88%) and then subjection of the resultant allenol to Marshall cyclization conditions provided dihydrofuran **13** in 93% yield.[17] Hydrogenation with concomitant hydrogenolysis of **13** (93%), protection of the primary alcohol with TBDPSCl, and then removal of the TBS group in the same flask gave **14** in 82% yield. Sequential oxidation of **14** to the carboxylic acid and then amidation gave **2**. [Compound **2** characterization data. ^1H NMR, 500 MHz ($CDCl_3$) given as δ (multiplicity, *J* in Hz; integration): 7.67 (d, 7.9; 4H), 7.40 (m; 6H), 4.73 (br s; 1H), 3.69 (s; 3H) 3.46 (dq, 6.6; 2H) 3.19 (s; 3H), 2.13 (br s; 2H), 1.83 (m; 1H), 1.76 (q, 8.0; 2H), 1.67 (dd, 6.9; 1H) 1.33 (m; 1H), 1.29 (s; 3H), 1.06 (s; 9H), 1.01 (d, 6.6; 3H); ^{13}C NMR, 100 MHz, ($CDCl_3$) δ 173.9, 135.8, 134.5, 129.7, 127.7, 85.6, 75.1, 69.8, 61.6, 44.1, 37.5, 32.8, 32.3, 29.0, 27.1, 26.4, 19.4, 18.9; ESI/MS calculated for $NaC_{28}H_{41}NO_4Si$ (M+23) 506.28, found 506.3.]

Weinreb amide alkynylation has proven a reliable and convergent approach to establish new carbon connectiv-



Scheme 3. Reagents and conditions:[19] (a) **10** (1.2 equiv), TEA (1.2 equiv), $Zn(OTf)_2$ (1.1 equiv), (−)-*N*-methylephedrine (1.2 equiv), tol., rt, 85%, dr 4:1; (b) TEA (1.5 equiv), MsCl (1.5 equiv), Et_2O, −78 °C–rt, 1 h, then, Cu(Me)CNLi (5.0 equiv) in Et_2O, −78 °C–rt, 0.5 h, 95%; (c) DDQ (1.2 equiv), 1:1 CH_2Cl_2–PBS 7.8 pH, 88%; (d) $AgNO_3$ (1.1 equiv), $CaCO_3$ (2.0 equiv), 4:1 acetone–H_2O, 93%; (e) 10 wt % Pd/C (0.05 equiv), EtOAc, 24 h, 93%; (f) (i) TEA (1.3 equiv), DMAP (0.1 equiv), TBDPSCl (1.5 equiv), CH_2Cl_2, 0 °C, (ii) solvent removal in vacuo then TFA–AcOH–H_2O 4:1:1 (v/v), 0 °C, 1 h, 82%; (g) TPAP (0.1 equiv), NMO (2.0 equiv), CH_2Cl_2, rt, 1 h; (h) $NaClO_2$ (10 equiv), NaH_2PO_4 (20 equiv), 2-methyl-2-butene 2.0 M in THF (50 equiv), THF–*t*-BuOH–H_2O 4:1:4 (v/v) 89% (two steps). (i) IBCF (2.0 equiv), *i*-Pr_2EtN (2.0 equiv), DMAP (0.1 equiv), THF, 0 °C, 0.5 h, then *i*-Pr_2EtN (2.0 equiv), HCl·$HN(CH_3)OCH_3$ (3.0 equiv), 1 h, 89%.



Scheme 4.

ity in the assembly of ynones late in a synthesis.[18] We chose to evaluate in a model the viability of a Weinreb amide/alkyne coupling for the late-stage union of a C1–C20 fragment with a C21–C40 fragment (Scheme 4). Weinreb amide **2** served to model the C21–C40 pectenotoxin fragment and alkynes **16**–**18** served to model the C1–C20 fragment. The coupling was found to be effective (73–88%), even on small scale (5 mg). In each instance, the alkyne (THF, 0.2 M) was treated with base (1.0 equiv of 1.6 M *n*-BuLi in hexanes) at −78 °C and the mixture was allowed to warm to 0 °C. The alkynylide was then added dropwise to the Weinreb amide (0.2 M), at −78 °C. The final ratio of alkyne to amide in this study was 2:1. The mixture was allowed to warm to room temperature over the course of 45 min and stirred until TLC analysis showed complete consumption of **2** (1 h). [Compound **21** characterization data. ^{1}H NMR, 500 MHz ($CDCl_3$) given as δ (multiplicity, J in Hz): 7.65 (d, 7.5; 4H), 7.39 (m, 6H), 7.20 (d, 8.8; 1H), 6.71 (dd, 8.2; 1H), 6.63 (d, 8.6; 1H), 4.39 (t, 8.1; 1H), 3.78 (s, 3H), 3.43 (m, 3H), 2.33 (m, 2H), 2.23 (m, 2H), 2.11 (m, 1H), 2.00 (t, 12.0H; 1H), 1.86 (m, 2.00), 1.78 (m, 5), 1.67 (m, 3), 1.46 (m, 4H), 1.36 (m, 1), 1.28 (s, 3H), 1.05 (s, 9H), 0.98 (m, 12H), 0.87 (s, 3H), 0.69 (m, 6H); ^{13}C NMR, 100 MHz, ($CDCl_3$) δ, 188.7, 157.7, 138.3, 135.8, 134.2, 132.8, 129.7, 127.8, 126.6, 114.0, 111.7, 99.7, 86.3, 84.5, 81.0, 69.7, 55.4, 49.4, 48.9, 43.8, 40.5, 40.4, 37.5, 32.9, 32.5, 30.9, 29.6, 27.5, 27.1, 26.6, 26.4, 23.4, 19.5, 19.0, 13.8, 7.2, 6.2 ESI/MS calcd for $C_{53}H_{74}O_5Si_2$ (M+23) 869.5, found 869.4.] The high isolated yields of **19**–**21** augur well for C1–C20/C21–C40 coupling *en route* to the pectenotoxins.[18]

Acknowledgments

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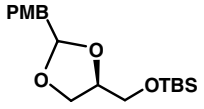

A

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19. Acronyms and abbreviations: DDQ = dichloro dicyano quinone, DiBAl-H = diisobutylaluminum hydride, DMAP = 4-(*N*,*N*-Dimethylamino)pyridine, DMSO = dimethyl sulfoxide, EtOAc = ethyl acetate, LiHMDS = lithium hexamethyldisilazane, MeOH = methanol, MsCl = mesyl chloride, PivCl = pivaloyl chloride, TBDPSCl = *tert*-butyldiphenylsilyl chloride, TEA = triethylamine, TfOH = triflic acid, THF = tetrahydrofuran, TPAP = tetrapropylammonium perruthenate.