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Pectenotoxin-2 Synthetic Studies. 2. Construction and Conjoining of ABC and DE Eastern Hemisphere Subtargets

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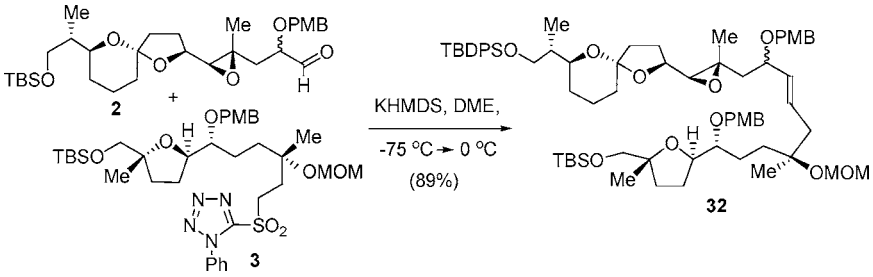
ABSTRACT



Practical asymmetric synthesis of aldehyde 2 and tetrazolyl sulfone 3 has allowed for their coupling via Julia olefination to generate 32 as a single product. This substance possesses the entire carbon backbone of the A–E substructure of pectenotoxin-2.

The pectenotoxins comprise a small unique family of complex marine natural products.[1] As a result of their nanomolar cytotoxic properties[2] and fascinating structural features, a unified, highly convergent route to the most potent member, pectenotoxin-2 (**1**), has been undertaken at Ohio State[3] and leading laboratories elsewhere.[4,5] The considerable progress made in devising a route to the western FG sector has been detailed in our earlier report.[3] In continuation of this theme, we detail herein the assembly of subunits ABC (**2**) and DE (**3**) (Scheme 1). Taken together, these building blocks constitute the entire C1−C26 eastern two-thirds of the target compound.

From among several possible options for constructing **2**, we came to favor a strategy wherein convergency would be realized via coupling to a Weinreb amide, with spiroacetal generation following soon thereafter. The pathway originated by aldol condensation involving chiral auxiliary **4**[6] and the known aldehyde **5**[7] in the presence of dibutylboron triflate, which resulted in the stereocontrolled generation of **6**[8] (Scheme 2). Here we were able to protect the hydroxyl group as the PMB ether via trichloroacetimidate technology[9] in advance of reductive cleavage of the oxazolidinone ring with $LiAlH_4$[10] and formation of the *tert*-butyldiphenylsilyl ether[11] as in **8**. The latter was subjected to hydrogenolysis over W-2

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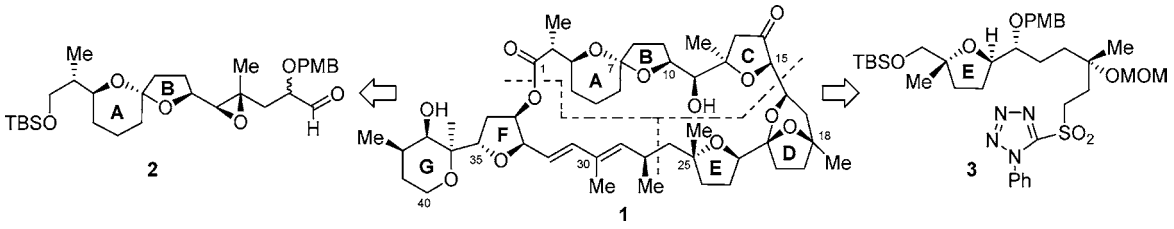
Scheme 1



Raney nickel,[12] which catalyst was instrumental in removing the benzyl group selectively in the presence of the OPMB ether. Following the conversion of **9** into iodide **10** in a conventional manner,[13] we proceeded to effect its lithiation with *tert*-butyllithium[14] in advance of the addition of **11**, prepared from L-glutamic acid as outlined in Scheme 3.[15−17] Since the chromatographic purification of the precursor to **11** on silica gel often resulted in reversion to the lactone,[18] immediate conversion to the PMB derivative was always undertaken.

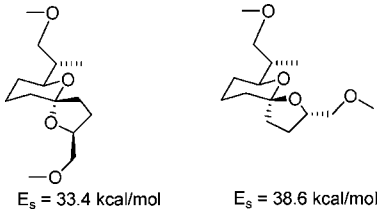
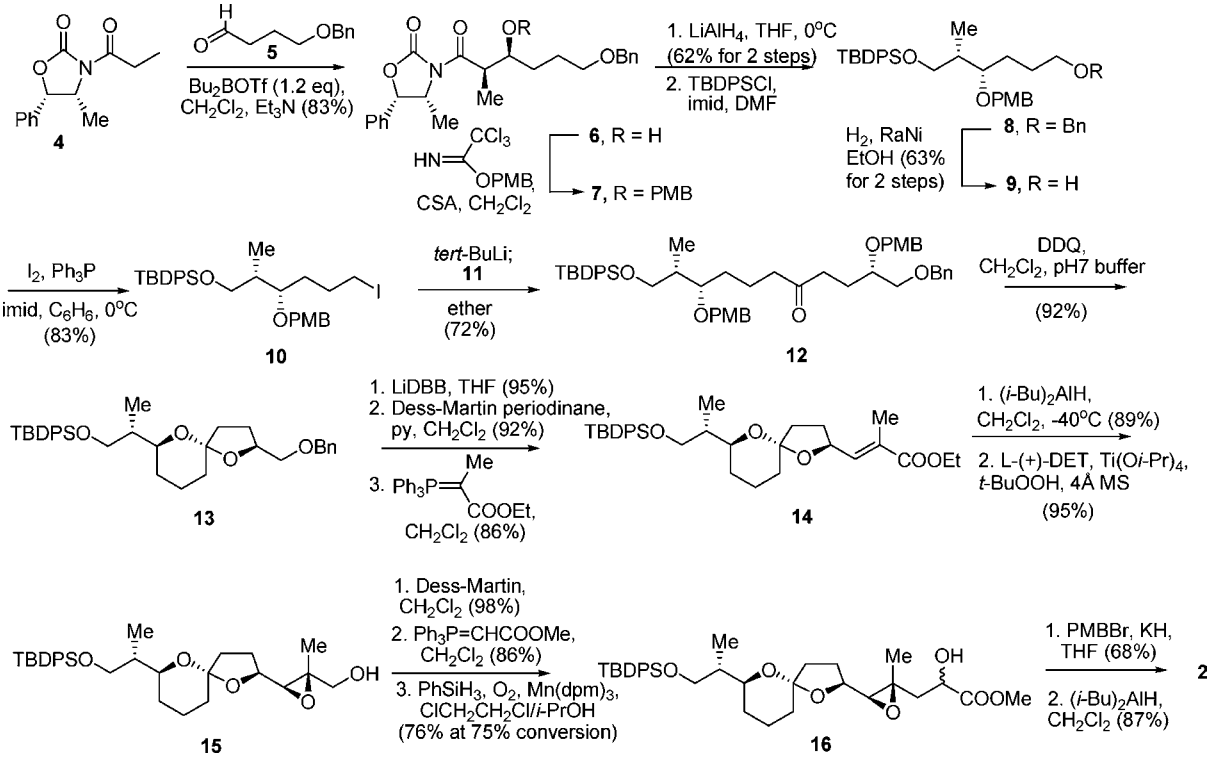


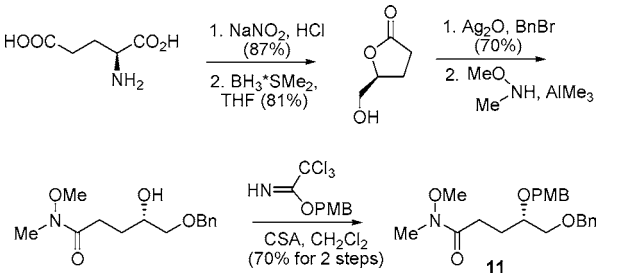
Figure 1. MM3 calculations of the two possible stereoisomers of **13** as the dimethoxy derivative.

Ketone **12** was integrated within the synthetic pathway by reaction with DDQ in the presence of moist CH_2Cl_2.[12] This 2-fold deprotection step resulted in cyclization to give predominantly that spiroacetal assumed to be the diastereomer stabilized by the anomeric effect (Figure 1). The first of two chain extensions was suitably addressed by reductive cleavage of the benzyl ether with lithium di-*tert*-butylbiphenyl,[19] oxidation with the Dess−Martin periodinane,[20] and a Wittig reaction. This sequence of steps delivered **14** efficiently, and made possible the acquisition of **15** by subsequent Dibal-H reduction and asymmetric epoxidation with L-(+)-diethyl tartrate.[21] Incorporation of the requisite two additional carbons was accomplished in a comparable way with the

Scheme 2. Synthesis of **2**



Scheme 3. Preparation of **11**



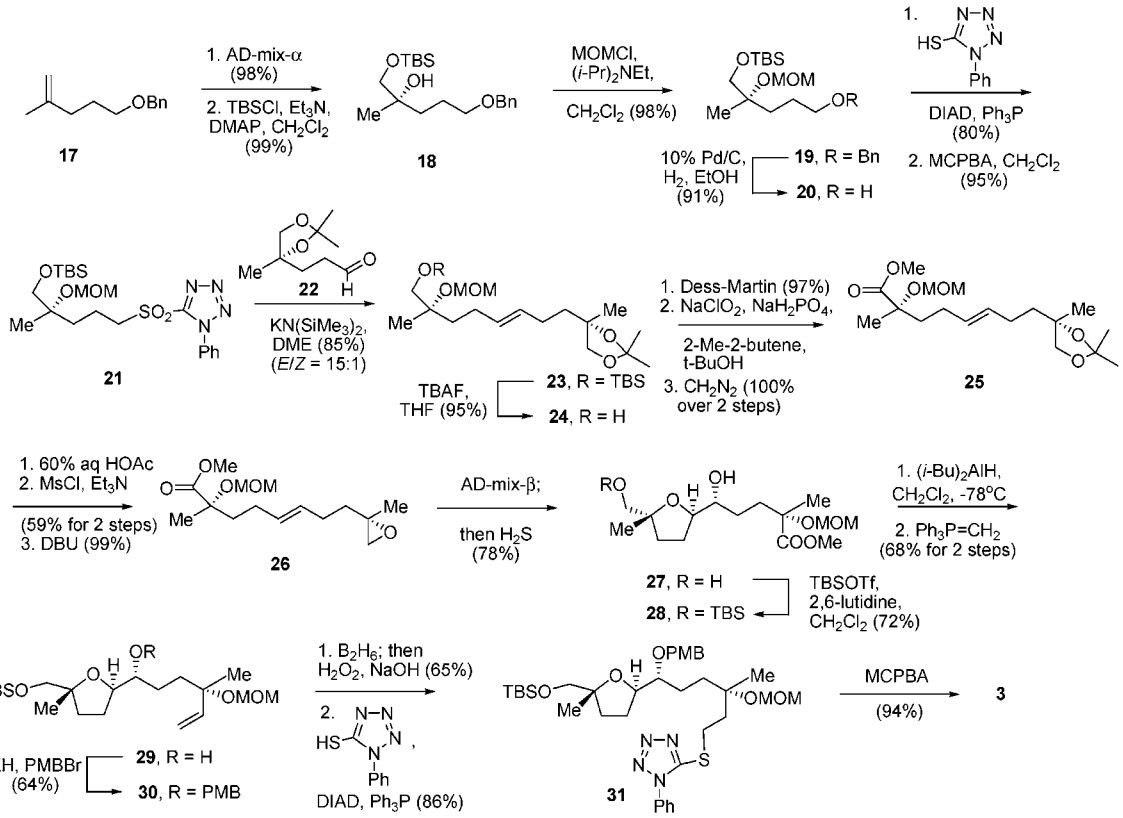
lower ylide. The final steps in the pursuit of **2** involved the formation of **16** by oxidation catalyzed with bis(dipivaloylmethanato)manganese(III) complex,[22] protection as the PMB derivative, and controlled reduction of the ester group.

To position ourselves to produce **3**, benzyl ether **17**[23] was subjected to asymmetric dihydroxylation[24] with AD-mix-α[25] and selective silylation of the primary carbinol as in **18** (Scheme 4). After proper modification of the hydroxyl protecting groups, the 1-phenyl-1*H*-tetrazol-5-yl sulfone **21** was synthesized according to the Kocienski protocol.[26] Concurrently, access to **22** was likewise gained from **17** by sequential Sharpless dihydroxylation, conversion to the acetonide, hydrogenolytic cleavage of the benzyl ether, and periodinane oxidation. The Julia−Lythgoe coupling of **21** to **22** proceeded as planned to provide **23** as a 15:1 *E*/*Z* mixture. The subsequent three-step conversion of **23** to ester **25** was notably efficient, thereby setting the stage for establishing the feasibility of selective acetonide hydrolysis in the presence of a tertiary MOM ether. In practice, we turned to 60% acetic acid at 0 °C. Acceptable yields of the targeted diol were realized, however, only if reaction was allowed to proceed for approximately 5 h. In view of the limited solubility of **25** in the reaction medium, its selective extraction into hexane allowed for the convenient isolation of the diol and its stereocontrolled conversion to epoxide **26**. The reaction of this intermediate with AD-mix-*β* was next studied and several products were observed under standard conditions. Ultimately, treatment with H_2S in place of a standard workup procedure promoted acid-catalyzed cyclization and afforded uniquely tetrahydrofuran **27**, whose structural formulation rests convincingly on the results of detailed COSY and NOESY experiments.

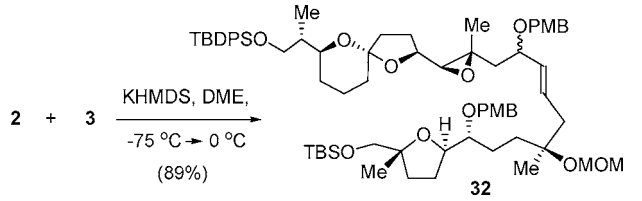
The sequel to this concise routing consisted of selective primary hydroxyl protection as the TBS ether in advance of reduction to the lactol and ring-opening Wittig olefination. Subsequent formation of the PMB ether made possible terminal functionalization of the chain via hydroboration and formation of the tetrazolyl sulfone **3**.

Once **2** and **3** became available, they were conjoined by means of the Julia protocol to afford **32** as a single product in 89% yield (Scheme 5). The *E* nature of the

Scheme 4. Synthetic Route to **3**



Scheme 5. Conjoining of **2** and **3**



interconnective double bond so generated was apparent from the coupling constant of 15.7 Hz for the olefinic protons.

In summary, the entire carbon backbone of the A−E subsector of pectenotoxin-2 has been assembled through total synthesis. Ongoing work is targeting the more advanced oxygenation of **32** and its proper attachment to the western FG building block whose construction we have previously reported.[3]

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Note Added after ASAP Publication. Reference 4d was missing from the version published on April 6, 2005; the corrected version was published on April 11, 2005.

Supporting Information Available: Experimental details and ^{1}H NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Prepared by heating methallyl alcohol with triethyl orthoacetate in the presence of pivalic acid followed by $LiAlH_4$ reduction and *O*-benzylation of the Claisen rearrangement product.

(24) The enantiomeric purity of the resulting diol of $[\alpha]^{23}_D$ −2.5 (*c* 0.67, $CHCl_3$) was shown to be > 95% ee by hplc analysis on a chiral OD column and by hydrogenolysis to give the triol whose $[\alpha]^{21}_D$ −1.1 (*c* 2.5, CH_3OH) compared closely to the value, $[\alpha]^{23}_D$ −1.2 (*c* 1.7, CH_3OH), reported by Mori [Mori, K. *Tetrahedron* **1975**, 31, 1381] for 100% pure material.

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