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A Modular Approach to Marine Macrolide Construction. 4. Assembly of C36–C51 and C29–C44 Building Blocks and Evaluation of Key Coupling Reactions Targeting Spongistatin 1 (Altohyrtin A)

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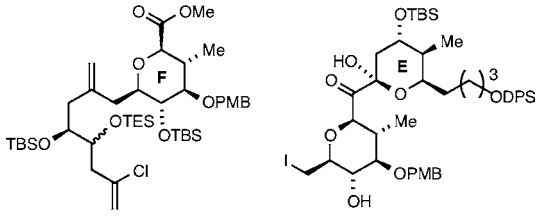
ABSTRACT



C36-C52 subunit C29-C44 subunit

Routes have been developed for the stereocontrolled elaboration of two highly functionalized sectors of spongistatin 1. The approach to ring F takes advantage of *B*-alkyl Suzuki–Miyaura coupling to install the C44–C45 bond. The E-ring pyran moiety was generated by acylation of an α-sulfonyl carbanion, the stereogenic centers of which were incorporated by sequential asymmetric aldol reactions.

More than 10 years have elapsed since the spongipyran marine macrolides have been characterized[1−3] and their extraordinary inhibitory capacity against many human cancer cell lines defined.[4] The outstanding potency of these structurally unique macrolides has generated substantial interest in the total synthesis of spongistatin 1 (**1**, X = Cl) and 2 (**1**, X = H),[5] as well as their AB and CD spiroketal sectors, and the constituent E and F rings. Our own efforts in this area have consisted of the development of an expeditious enantioselective route to C1−C28 (see framed sector of **1**),[6] with the intent of conjoining this major eastern fragment to a properly functionalized C29−C51 subunit. An early vision of this merger involved deployment of the *B*-alkyl Suzuki−Miyaura cross-coupling reaction[7] as a means for convenient installation of the C44−C45 bond that links the vinyl chloride side chain to ring F. In recent years, this protocol has gained increasing acceptance in natural product synthesis[8] but has

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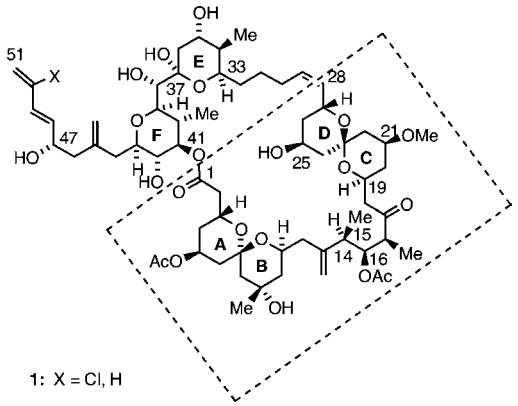
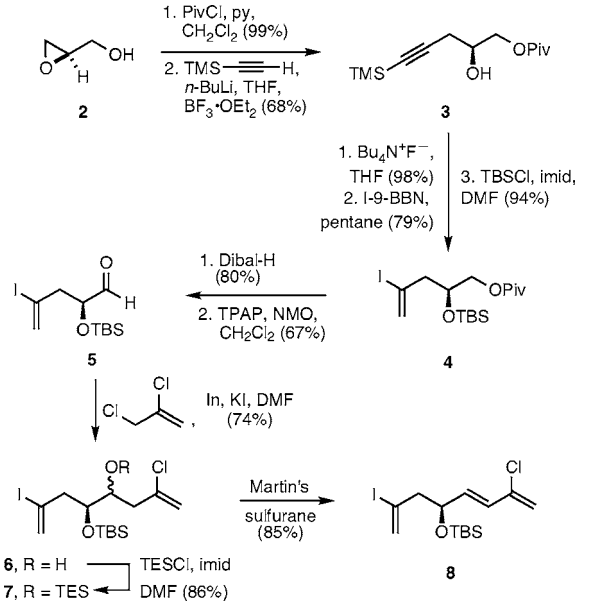
not yet been utilized in pursuit of the spongistatins. In this report, we show that reaction occurs smoothly and efficiently between an alkylborane residing in a fully functionalized F-ring setting and a vinyl iodide consisting of the partially polyunsaturated side chain.



Our advance on vinyl iodides **7** and **8** began with ring cleavage of (*R*)-glycidol (**2**) by reaction of its pivalate ester with lithium trimethylsilylacetylide as earlier described[9] (Scheme 1). Following liberation of the terminal alkyne, conversion to the 2-iodo-1-alkene was conveniently accomplished with 9-iodo-9-BBN.[10] Hydroxyl protection as the TBS derivative and reduction of the pivalate ester then set the stage for oxidation to aldehyde **5** and three-carbon chain extension involving 2,3-dichloropropene and indium powder in DMF.[11] The availability of **7** in this manner was

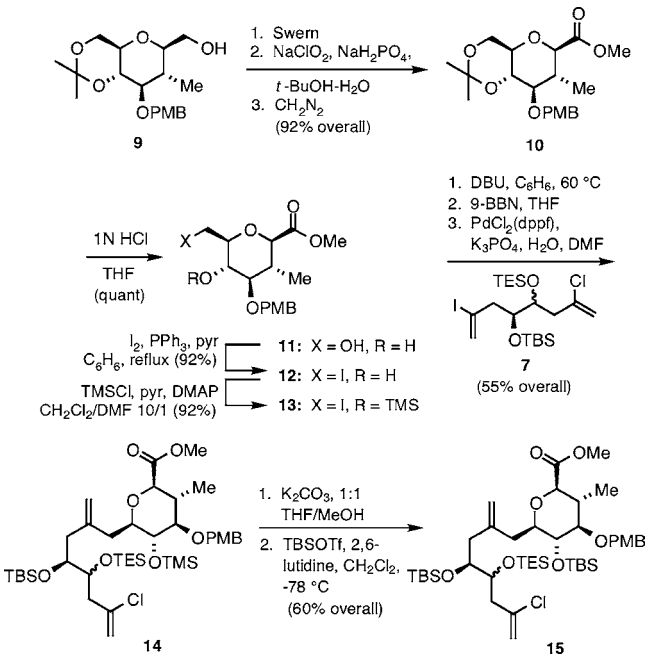
Scheme 1. Vinyl Iodide Syntheses



anticipated to provide more advanced intermediates having a C44−C51 side chain less sensitive to degradation than its trienyl counterpart. In this connection, the dehydration of **6** to give **8** proved uneventful when performed with the Martin sulfurane reagent.[12]

The elaboration of ring F involved preliminary conversion of carbinol **9**[13] to its methyl ester **10**. We came to favor the three-step sequence shown in Scheme 2 because it delivered **10** efficiently without complications attributable to epimerization. The critical particulars surrounding generation of the *exo*-olefin consisted of sequential mild acidic hydrolysis to

Scheme 2. Crafting of the F Ring



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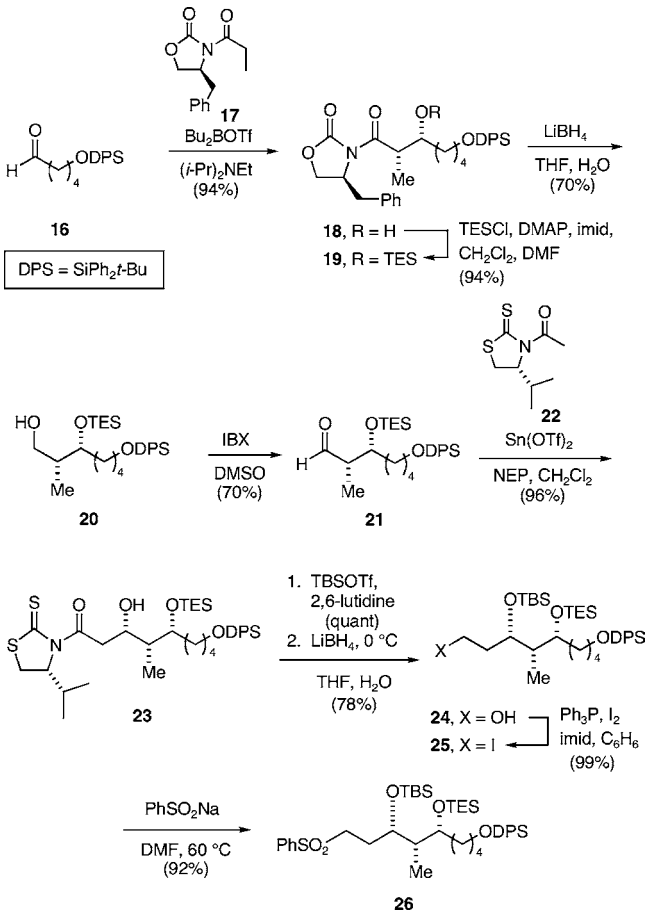
produce diol **11**, regiocontrolled formation of primary iodide **12**,[14] silyl protection of the remaining hydroxyl group,[18] and dehydroiodination with DBU in C_6H_6 at 60 °C.[15] The borane reagent was in turn generated by the action of 9-BBN−H on the *exo*-methylene intermediate.[16] At this point, recourse was made to the combined capabilities of $PdCl_2$(dppf) and K_3PO_4 to deliver in 55% overall yield a product identifiable by spectroscopic means as **14**. The coupling constant of 9.3 Hz observed between H42 and H43 was especially diagnostic of their trans-diaxial relationship. During subsequent scrutiny of further chemical manipulations, we became aware of the lability of **14** and congeners thereof. These complications were resolved by replacement of the labile OTMS group in **14** by the more robust OTBS group as in **15** before proceeding forward.

Our complementary thrust began with the operational proposition that the E-ring pyran subunit could be correlated to a terminal sulfone defined by **26**, the stereogenic centers in which were to be installed by means of asymmetric aldol reactions (Scheme 3). Following the generation of aldehyde

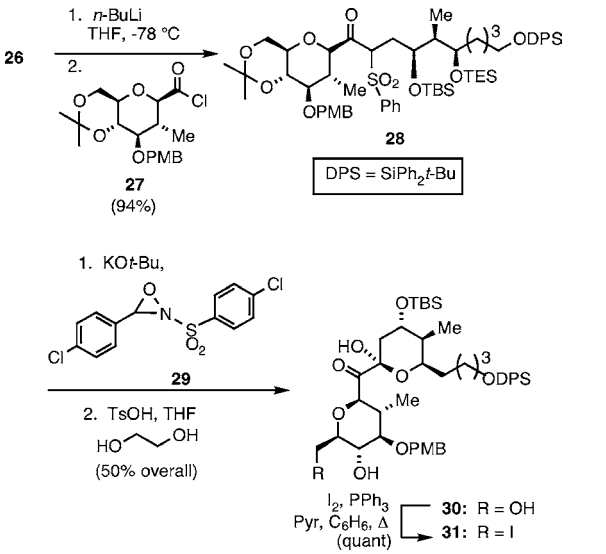
Scheme 3. Elaboration of Sulfone **26**



16 from 1,5-pentanediol, its exposure to the dibutylboron enolate of **17**[17,18] gave rise in a 94% combined yield to a 70:30 mixture of aldols rich in the syn isomer. Chromatographic purification followed protection as the TES ether. Sequential lithium borohydride reduction to the primary alcohol **20** and oxidation with IBX[19] led to aldehyde **21**. At this point, we made recourse to the tin(II) enolate of thiazolidinethione **22** for the purpose of generating **23**. The involvement of a highly chelated transition state in this instance requires that the absolute configuration of **22** be opposite to that of **17**. Indeed, the Fujita−Nagao protocol[20] functioned very effectively to furnish **23** as the sole product in 96% yield. Reductive removal of the chiral auxiliary and subsequent generation of iodide **25** made possible the ultimate acquisition of sulfone **26**.

Construction of the required building block began by acylating the carbanion of sulfone **26** with acid chloride **27**, as generated from **10** via saponification and subsequent exposure to 1-chloro-*N*,*N*-2-trimethylpropenylamine.[21] Oxidation of the resulting **28** with the reactive dichlorinated oxaziridine **29** introduced by Williams[22] gave rise to the α-diketone (Scheme 4). The latter was treated directly with

Scheme 4. Synthesis of the Completely Assembled Bispyran **31**



p-toluenesulfonic acid to bring about chemoselective removal of the TES group. Acetonide hydrolysis in a solvent system of THF and ethylene glycol followed to induce cyclization

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to lactol **30**. Our ability to preserve the integrity of the labile OTBS group at C34 in this manner is notable. When formation of the methyl glycoside was found to be precluded because of the proximal ketone carbonyl, generation of primary iodide **31** followed immediately.

The lessons learned in this study are expected to be useful in our continuing studies aimed at developing a synthetic entry to spongistatin 1. Applications toward this goal are currently being pursued.

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Supporting Information Available: Detailed experimental procedures and spectral characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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