Exploiting Pseudo C_2-Symmetry for an Efficient Synthesis of the F-Ring of the Spongistatins
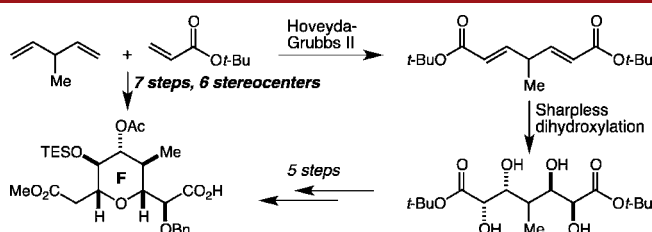
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ABSTRACT

A concise and efficient synthesis of the F-ring fragment of the potent antimitotic marine macrolide spongistatin 1 has been developed. The key sequence involves double cross-metathesis/Sharpless asymmetric dihydroxylation reactions to establish four stereocenters in a pseudo C_2-symmetric array, followed by a selective protection reaction that breaks the pseudosymmetry, establishes a fifth stereocenter, and effectively differentiates the ester termini. Overall, the six contiguous stereocenters in the C(37)−C(45) F-ring fragment are established in just seven steps.

The spongistatins, structurally complex marine macrolides possessed of extraordinarily potent antimitotic activity, have elicited a great deal of attention from synthetic chemists since their isolation in 1993[1−3] resulting in seven groups reporting syntheses of spongistatin 1 and/or 2.[4−10] We are pursuing the design, synthesis, and evaluation of a series of analogs of spongistatin 1, with the CD spiroketal region as the main focus of those efforts.[11] In order to synthesize the completed CD spiroketal-modified analogs of spongistatin 1, we will of course require a supply of the C(29)−C(51) EF fragment[12] (Figure 1A), and our initial explorations into the development of an efficient,

step-economical, and scalable synthesis of that fragment are the subject of this report.

We set as our initial goal the development of an efficient synthesis of pentasubstituted tetrahydropyran F-ring fragment **1** with an ester at C(45) from which to construct the chlorodiene side chain and a methyl ketone at C(37) for introduction of the E-ring by way of an aldol reaction according to the Paterson precedent[7c] (Figure 1B). Within **1** there may be found a latent element of pseudo C_2-symmetry, and we became intrigued by the possibility

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of employing a two-directional chain synthesis strategy.[13] To this end, we envisioned that the C(43) stereocenter might arise from reduction of a lactol and, in the first iteration of our retrosynthesis, that the C(37) methyl ketone might arise from decarboxylation of the corresponding β-ketoester. These operations lead retrosynthetically to lactol **2**, and in turn to tetraol **3**, revealing the pseudo C_2-symmetry. We were optimistic that spontaneous lactol formation from a tetraol such as **3** would prove an effective and straightforward method for termini differentiation, as lactol **2** should be favored over the alternative, lactol **4**, in which the C(40) methyl group would be axially disposed. Double Sharpless asymmetric dihydroxylation (AD)[14,15] leads retrosynthetically to **5**, which we hoped might be accessible by double cross-metathesis (CM)[16] with vinyl ketone **6** and 3-methyl-1,4-pentadiene **7**. The possibility that we might access **2** in just two steps from **6** and **7** provided all the impetus we needed to initiate this investigation.

Initial attempts to accomplish the double CM reaction of diene **7** with **6a** (R = Me) resulted only in dimerization of **6a** (Scheme 1). Various protected/masked versions of **6a**
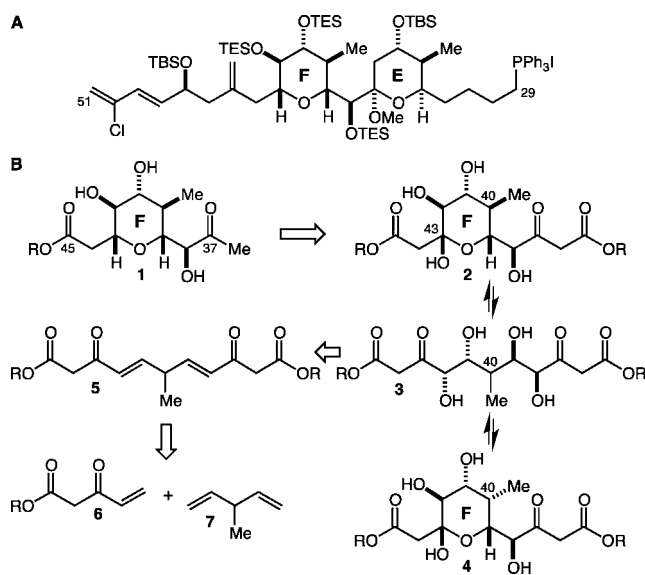

Figure 1. (A) The C(29)−C(51) EF fragment of spongistatin 1. (B) Retrosynthetic analysis of the C(37)−C(45) F-ring fragment reveals pseudo C_2-symmetry.

(among them alcohol **8** and dioxolane **9**) also failed to provide any of the desired CM products. We turned next to the use of simple acrylate esters (methyl and *tert*-butyl) and were delighted to find not only that the double cross metathesis reaction worked well with 10 mol % of the second generation Hoveyda-Grubbs catalyst (HG-II)[17] but also that the products, **10a** and **10b**, were stable to standard workup and purification procedures. Initial attempts to establish the feasibility of the double Sharpless AD reaction using AD-Mix-β revealed that while no tetraol product could be isolated from the reaction of **10a**, tetraol **11** could indeed be isolated, albeit in low yield, from the reaction of **10b**. The *tert*-butyl ester was therefore selected for optimization, and in the case of the CM reaction, the primary goal was a significantly reduced HG-II catalyst loading. By adding the catalyst portionwise over 7 days it proved possible to achieve an 80% yield of **10b** with a catalyst loading of 2.25 mol %. While this is a quite low catalyst loading, especially for a double CM reaction, and while this procedure proved reliable on multigram scale (22 g of **10b** were produced in a single run), the inconveniently long reaction time motivated us to optimize further. Using *tert*-butyl acrylate as the solvent, we found that a total loading of 0.69 mol % of the HG-II catalyst added portionwise (3 × 0.23 mol %) over a total reaction time of just 5 h allowed the isolation of **10b** in 58% yield, also on multigram scale. Despite the lower yield, this protocol is a significant improvement in terms of the amount of product produced per unit of HG-II catalyst. For the double AD reaction, the low yield was the primary problem, and this was addressed by increasing the loading

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of both the osmium source ($K_2OsO_4 \cdot 2 H_2O$) and the chiral ligand (($(DHQD)_2PHAL$). Using 4 and 5 mol %, respectively, tetraol **11** could be isolated as the major product of a 4.5:1 mixture of diastereomers[18] in 62% yield. Importantly, this reaction proved reliable on multigram scale as well and was used to prepare 16.4 g of **11** in a single run.

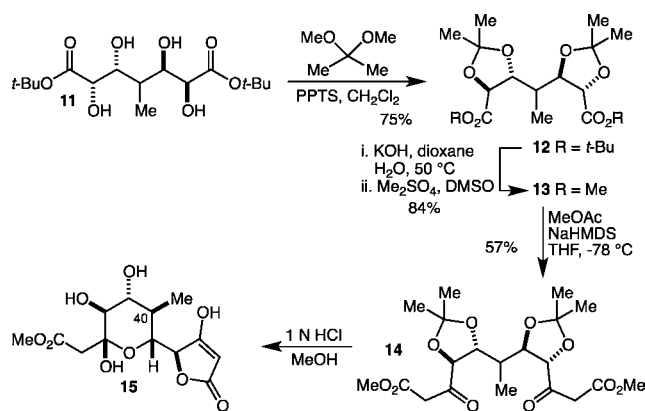**Scheme 1.** Development of a Scalable Two-Step Synthesis of Pseudo C_2-Symmetric Tetraol **11**
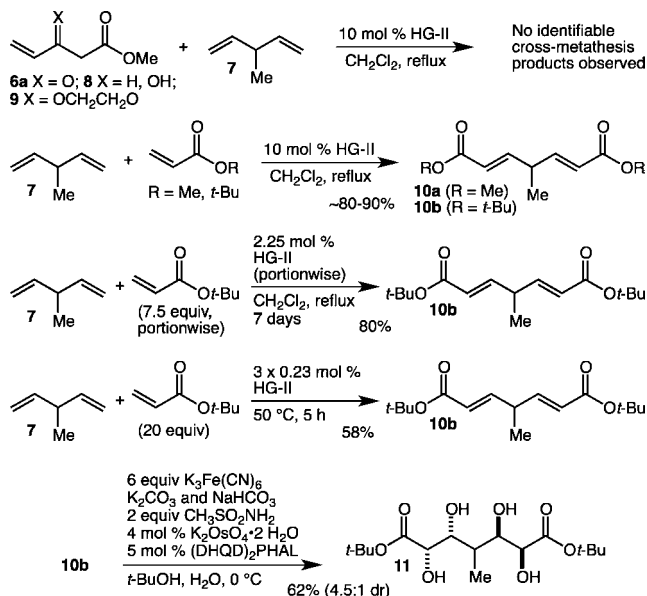
With efficient access to large quantities of **11** in just two steps secured, we turned our attention to its elaboration into a compound such as **3** so as to be able to investigate the effectiveness of the pseudo symmetry-breaking cyclization reaction. To that end, tetraol **11** was protected in the form of bis-acetonide **12** in 75% yield (Scheme 2). Saponification and alkylation provided bis-methyl ester **13** in 84% overall yield. Double Claisen condensation of **13** with methyl acetate then delivered bis-β-ketoester **14** in 57% yield. Hydrolysis/methanolysis of the acetonides with 1 N HCl in methanol led to the relatively clean production of a compound that we have assigned as **15**. There was some irreproducibility in this transformation, and the product was difficult to work with, but we were able to characterize **15** by ^{1}H NMR spectroscopy including a NOESY experiment which supported the stereochemical assignment at the methyl-bearing C(40) stereocenter. Though this route was abandoned due to the difficulties in doing anything productive with **15**, we were delighted to secure this evidence that the C(40) stereocenter could indeed be controlled in this fashion.

Scheme 2. Demonstration of Termini Differentiation by Way of a Selective Lactolization Reaction


Further experimentation revealed other transformations of tetraol **11** were possible, such as its completely selective conversion to orthoester **16** in 72% yield[19] (Scheme 3). Although the fact that the C(40) methyl group is equatorial in **16** and axial in **17** provides a simple rationalization for this selectivity, the A-value of a methyl group in the 5-position of a 2-methyl-1,3-dioxane is only 0.97 kcal/mol,[20] and it thus appears that other less obvious interactions are relevant as well. Benzylation of the remaining alcohol provided fully protected tetraol **18** in 78% yield. Prior to replacing the *tert*-butyl esters with methyl esters in anticipation of attempting a double Claisen condensation (cf. **13** to **14**), we decided to see if **18** itself was a viable substrate. Interestingly, while **18** did undergo a Claisen condensation, only the C(43) ester was reactive under these conditions. Upon optimization, this reaction provided **19** in 80% yield. Treatment of **19** with pyridinium *p*-toluene sulfonate (PPTS) in MeOH/H_2O resulted in smooth and selective partial hydrolysis of the orthoester and cyclization to give lactol **20** in 98% yield. With access to **20** secured, we were finally in a position to examine the lactol reduction[21] to set the final stereocenter of the F-ring. Initial attempts using Et_3SiH and $BF_3 \cdot OEt_2$ proved messy and inefficient, while the use of triethylsilyl triflate (TESOTf) as the Lewis acid led to partial *t*-Bu ester cleavage in addition to the desired reduction. Rather than attempting to avoid this cleavage, we decided to drive it to completion by using excess TESOTf and letting the reaction mixture warm to 0 °C. A triethylamine quench further resulted in alcohol silylation, and when this process was optimized, it led to the isolation of **21** in 72% yield.

We turned our attention next to the transformation of **21** into a compound that was appropriately functionalized for attachment of the E-ring and the chlorodiene side chain. As discussed above, this meant transformation of the carboxylic acid into a methyl ketone, while we envisioned

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(18) We have been unable to isolate a pure sample of the minor diastereomer, but the ^{1}H NMR spectrum of the mixture is consistent with it being, as expected, one of the two possible *meso* tetraol diastereomers.

(19) The starting material (**11**) used in this experiment was the 4.5:1 mixture of diastereomers produced in the double AD reaction (Scheme 1). No evidence for the formation of a second orthoester was observed, suggesting that the minor tetraol diastereomer does not successfully cyclize to an orthoester.

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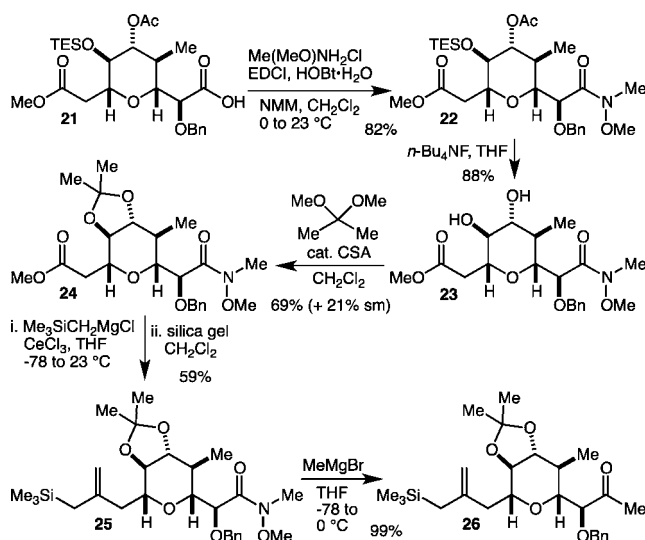(21) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.

Scheme 3. Termini Differentiation by Selective Protection and F-Ring Completion

Scheme 4. Elaboration of the F-Ring for Installment of the E-Ring and the Chlorodiene Side Chain
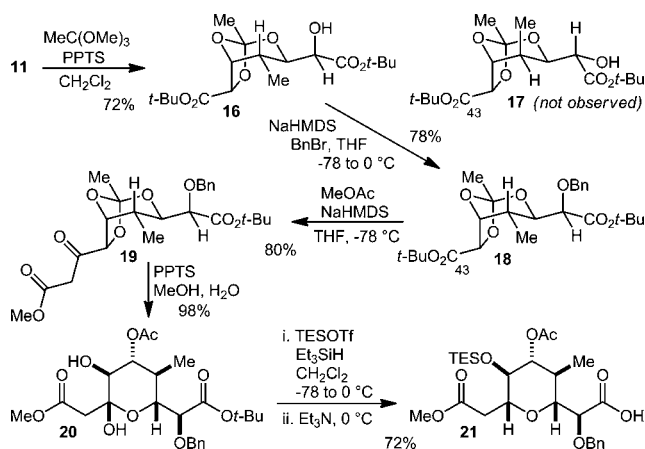
that an allylsilane might prove a versatile functionality with which to install the chlorodiene side chain. Thus, acid **21** was transformed into Weinreb amide[22] **22**[23] in 82% yield (Scheme 4). Attempts to transform the methyl ester into an allylsilane using Bunnelle's method[24] at this stage were completely unsuccessful, a failure we attributed to severe steric hindrance around the ester, mainly due to the TES ether. Cleavage of the TES ether and the acetate could be carried out with n-Bu$_4$NF to give an 88% yield of diol **23**, which was transformed into acetonide **24** in 69% yield. We recovered 21% of **23** from this latter reaction, whose reluctance to go to completion is attributable to ring strain in the *trans*-fused acetonide. Gratifyingly, conversion of less sterically encumbered ester **24** to allylsilane **25** using Bunnelle's procedure could be carried out at this stage, albeit with moderate efficiency (59% yield). Finally, addition of MeMgBr to the Weinreb amide delivered **26**, ready for coupling at both ends to install the E-ring and the chlorodiene side chain.

We have described an efficient synthesis of the F-ring of the spongistatins. A previously unrecognized latent element of pseudo C_2-symmetry was identified and exploited by way of a double CM and double Sharpless AD sequence that quickly established four carbinol stereocenters in just two steps. Diastereoselective protection of the tetraol broke the pseudo C_2-symmetry and established the C(40)

methyl-bearing stereocenter, and effectively differentiated the ester termini. Just four additional steps delivered completed F-ring fragment **21**, which contains 6 of the 11 stereocenters found in the EF fragment of the spongistatins, in seven steps and 16% overall yield from commercially available starting materials. Five additional steps produced a fully elaborated F-ring fragment appropriately functionalized and protected for installation of the E-ring and the chlorodiene side chain. Efforts to refine and streamline this sequence, especially with respect to minimizing functional group and protecting group manipulations, for use in an efficient, step-economical, and scalable synthesis of the EF fragment of the spongistatins are ongoing.

Supporting Information Available. Experimental procedures, characterization data, and stereochemical proofs as well as X-ray crystallographic data for compound **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Compound **22** proved crystalline, and an X-ray structural analysis was carried out which confirmed its assigned stereostructure. See the Supporting Information for details.

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The authors declare no competing financial interest.