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Studies on the Synthesis of Pectenotoxin II: Synthesis of a C(11)–C(26) Fragment Precursor via [3 + 2]-Annulation Reactions of Chiral Allylsilanes

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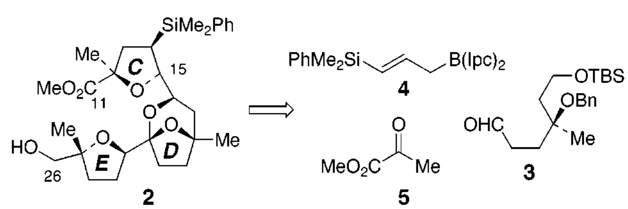
ABSTRACT

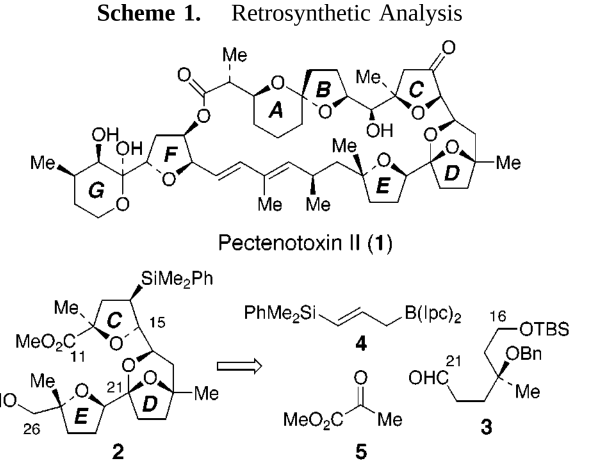


A synthesis of tetracycle 2 corresponding to the C(11)–C(26) fragment of pectenotoxin II is described. The synthesis features two highly stereoselective [3 + 2]-annulation reactions of chiral allylsilanes, generated via allylboration of aldehydes with the chiral γ-silylallylborane 4 or the γ-silylallylboronate 19, for construction of the highly substituted C and E rings.

The pectenotoxins are a family of highly cytotoxic polyether macrolide toxins that are active against human lung (A-549), colon (HT-29), and breast (MCF-7) cancer cell lines.[2,3] Pectenotoxin II (**1**, Scheme 1), produced by the dinoflagellates *Dinophysis fortii* and *D. accuminata*, has also shown selective cytotoxicity against several cell lines representing ovarian, renal, lung, colon, CNS, melanoma, and breast cancer, with differences in LC_{50} values between sensitive and resistant cell lines of 100-fold or more.[3] Pectenotoxin II interacts with the actin cytoskeleton at a unique site and could become an important research tool in the study of basic cellular processes.[4]

Although the pectenotoxins display an array of interesting and potentially significant biological properties, only one study on their synthesis has been reported to date.[5] Pectenotoxin II represents a formidable synthetic challenge, as the structure contains two spiroketals, three tertiary ethers, three substituted tetrahydrofurans, and 19 stereocenters embedded within a 40-carbon chain. The exquisitely complex

Scheme 1. Retrosynthetic Analysis



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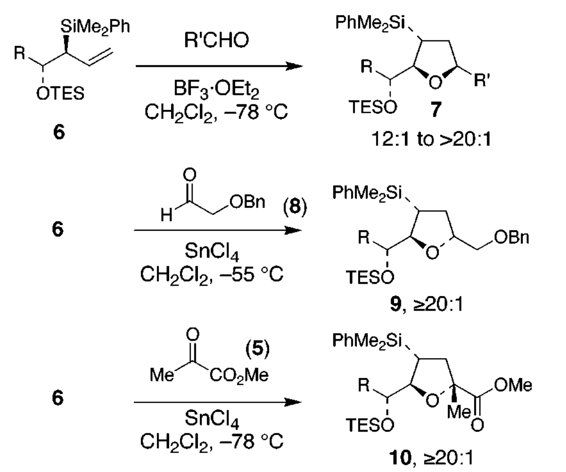
structure of **1** coupled with its interesting biological properties have prompted us to initiate studies targeting the total synthesis of this molecule. We report herein a brief and highly stereocontrolled synthesis of tetracycle **2**, corresponding to the C(11)−C(26) C−D−E fragment of the natural product, by a route that features our convergent three-component coupling sequence for tetrahydrofuran synthesis via chiral allylsilane intermediates.[6]

We recently reported that allylsilanes of general structure **6**, which are readily prepared by allylboration of aldehydes with either chiral allylborane **4**[7] or our first-generation tartrate ester modified γ-silylallylboronates,[8] undergo highly stereoselective [3 + 2] annulation reactions with aldehydes to give 2,3,5-trisubstituted tetrahydrofurans.[6,9] When the reaction is performed by using $BF_3 \cdot Et_2O$ as the (nonchelating) Lewis acid, 2,5-*cis*-tetrahydrofurans **7** are prepared with at least 12:1 and most often with ≥20:1 selectivity. On the other hand, reactions that are performed under chelate control using $SnCl_4$ as the promoter provide 2,5-*trans*-substituted tetrahydrofurans (e.g., **9**) with ≥20:1 selectivity. The chelate-controlled conditions also permit the synthesis of tetrahydrofurans with quaternary centers, as illustrated by the synthesis of **10** in Scheme 2.[6]

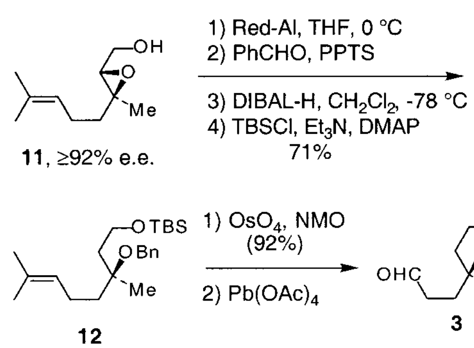
Scheme 2



It was readily apparent that the [3 + 2]-annulation sequence is ideally suited for the synthesis of the E ring of pectenotoxin II via the stepwise three-component coupling of aldehyde **3**, allylborane **4**, and methyl pyruvate (**5**). However, we have not yet learned how to effect a nonchelate controlled [3 + 2]-annulation reaction of allylsilanes **6** and ketones, which would be required for the direct introduction of the 2,5-cis stereochemistry of the C ring of pectenotoxin II. However, recognizing that C(15) of the natural product is adjacent to the C(14)-ketone, it seemed conceivable that the natural configuration at this center could be established at an appropriate point in the synthetic sequence by a base-promoted epimerization reaction. This permitted us to contemplate the synthesis of the C ring unit of **2**, with unnatural C(15) stereochemistry, via a second [3 + 2]-annulation reaction involving **4**, **5**, and the aldehyde generated from deprotection and oxidation of the C(16)-OTBS group of **3**. While we have not yet demonstrated that a C(15) epimerization sequence can be accomplished, we have developed and report herein a remarkably brief synthesis of tetracycle **2** that serves to define the utility of the [3 + 2]-annulation sequence for tetrahydrofuran synthesis in a structurally complex context.

Our synthesis of aldehyde **3** begins with the known geraniol epoxide **11** (≥92% ee) (Scheme 3).[10] Reduction of the epoxy-alcohol (Red-Al, THF)[11] followed by treatment of the 1,3-diol with benzaldehyde (PPTS, PhH, reflux) provided the corresponding benzylidene acetal, which after reductive opening with DIBAL-H (CH_2Cl_2, −78 to 23 °C)[12] and protection of the primary hydroxyl group (TBSCl, Et_3N, DMAP, CH_2Cl_2) afforded the *tert*-butyldimethylsilyl ether **12** in an overall yield of 71% from **11**. The olefin was then oxidatively cleaved by a two-step sequence ((i) OsO_4, NMO, acetone, pH 7 buffer (92%); (ii) $Pb(OAc)_4$, EtOAc) to give the C(21) aldehyde **3** which was used in subsequent chemistry without purification.

Scheme 3



Chiral allylsilane **13**, required for construction of the E ring, was synthesized by the double asymmetric silylallylboration of aldehyde **3** with the γ-silylallylborane **4** (Scheme 4).[7] This reaction provided the desired *anti*-β-hydroxyallylsilane as an inseparable 9−14:1 mixture of diastereomers (77% yield), which was subsequently protected as the corresponding triethylsilyl ether **13** (TESCl, Et_3N, DMAP, CH_2Cl_2, 93%). The yield of allylsilane **13** was 66% for the four-step sequence from olefin **12**. The $SnCl_4$-promoted [3 + 2] annulation of **13** and methyl pyruvate (**5**) then afforded the tetrasubstituted tetrahydrofuran **15** in 66−75% yield (>20:1 ds) accompanied by a small amount of the allylation

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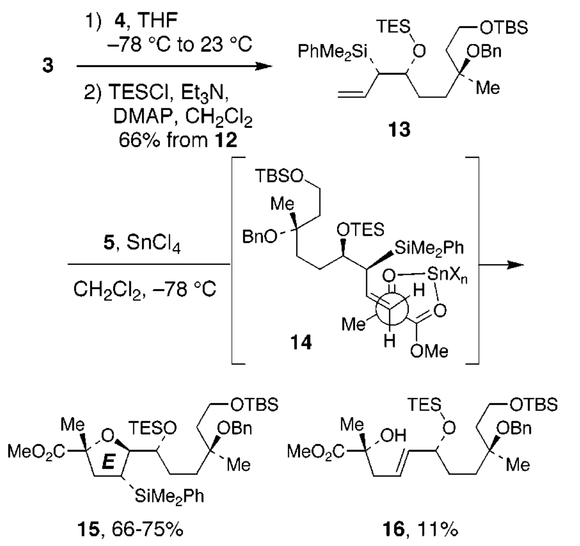
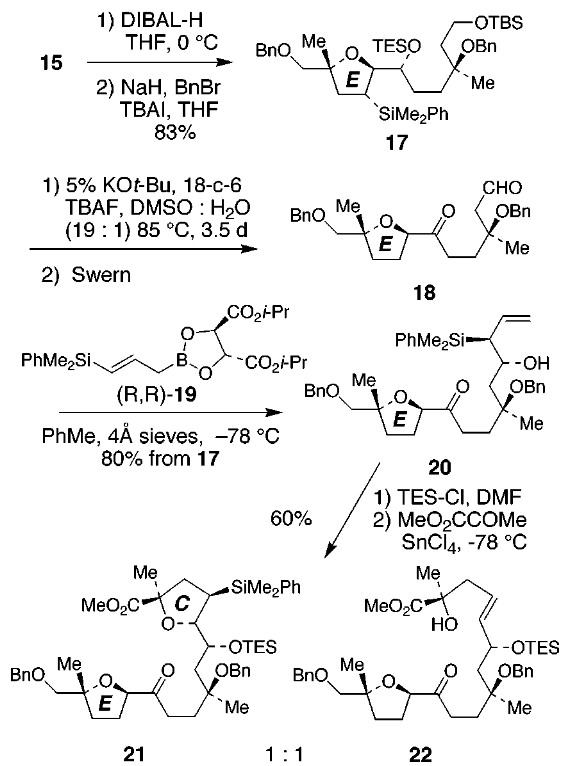
Scheme 4



Scheme 5

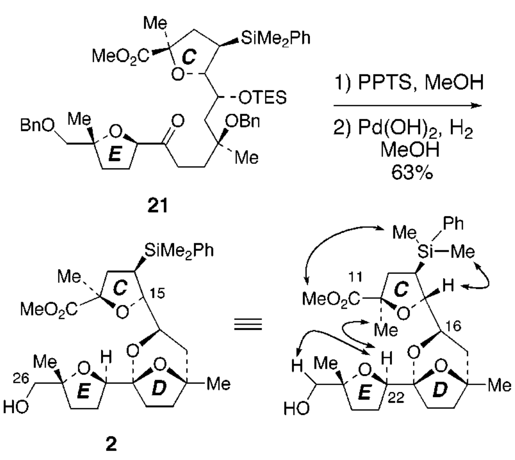


product **16** (11%). The stereochemistry within the tetrahydrofuran ring of **15** was assigned by ^{1}H NOE studies and is consistent with the first step of the [3 + 2]-annulation reaction proceeding by way of the *syn*-synclinal transition state **14**.[13] The stereochemistry of the tertiary alcohol center in **16** is assumed to be the same as that of the quaternary center in **15**, but this has not been assigned rigorously.

Reduction of the methyl ester unit of **15** (DIBAL-H, THF 0 °C) followed by benzylation of the primary alcohol (NaH, BnBr, tetrabutylammonium iodide (TBAI), THF, reflux) afforded **17** in 83% yield (Scheme 5). Global desilylation of **17** by using a modified Hudrlik protiodesilylation protocol[14,15] (5% KO-*t*-Bu, DMSO, H_2O, TBAF, 18-crown-6, 85 °C) afforded the C(16),C(21)-diol in 95% yield. The diol was then oxidized via the standard Swern protocol[16] to give the keto aldehyde **18**, which was used in the subsequent step without purification. Surprisingly, in initial attempts to γ-silylallylate **18** using the allylborane **4**, the aldehyde underwent reduction and allylation products were not obtained. Consequently **18** was treated with our first-generation tartrate ester modified γ-silylallylboronate (*R*,*R*)-**19** (toluene, −78 °C, 4 Å molecular sieves).[8] This reaction provided the allylsilane **20** in 80% yield from **17** with excellent stereo- and regioselectivity; products from allylation of the ketone carbonyl were not observed. Protection of the hydroxyl group of **20** as a TES ether (TES-Cl, DMF, imidazole, 70 °C, 88% yield) then set the stage for introduction of the C ring by a second [3 + 2]-annulation reaction with methyl pyruvate. In the event, treatment of the allylsilane with 3 equiv of the 1:1 complex of methyl pyruvate and $SnCl_4$ in CH_2Cl_2 at −78 °C provided a 1:1 mixture of bis-tetrahydrofuran **21** and an allylated product tentatively assigned the stereochemistry of **22**. The yield of **21** from **20** is thus 30%.

The synthesis of the C−D−E tetracyclic synthon **2** was completed by deprotection of the TES ether (PPTS, MeOH, 77% yield) and then hydrogenolysis of the two benzyl ethers over $Pd(OH)_2$ on carbon in MeOH. Under these conditions, the keto diol spontaneously cyclized to give the targeted tetracycle **2** in 63% overall yield from **21**. The stereochemistry of **2** was confirmed by the ^{1}H NOE data summarized in Scheme 6. Noteworthy are the NOE interactions observed

Scheme 6



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between the C(11)-methoxycarbonyl group and the dimethylphenylsilyl group, as well as that between the dimethylphenylsilyl unit and H(15) which collectively serve to define the stereochemistry within the C ring. Similarly, ^{1}H NOE's observed between H(22) and the C(26)-CH_2OH group confirm the stereochemistry within the trisubstituted E ring. Finally, a long-range ^{1}H NOE was observed between the C(12)-Me and H(22) which is completely consistent with the assigned structure.

In summary, we have developed an expeditious strategy for the synthesis of tetracycle **2**, a synthetic equivalent of the C(11)−C(26) fragment of pectenotoxin II, by a route that employs our recently developed three-component coupling strategy for tetrahydrofuran synthesis. The synthesis of **2** proceeds in 18 steps from geraniol epoxide (**11**) in 4.4% overall yield. Studies currently in progress are focusing on suppressing the allylation pathway that compromised the efficiency of the [3 + 2]-annulation sequence leading to **21** and to defining a strategy for direct introduction of the C ring with correct stereochemistry at C(15). These studies, together with additional progress toward the total synthesis of pectenotoxin II, will be reported in due course.

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Supporting Information Available: Experimental procedures for synthesis of **13**−**21** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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