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A Convergent Synthesis of the C1−C16 Segment of Goniodomin A via Palladium-Catalyzed Organostannane−Thioester Coupling

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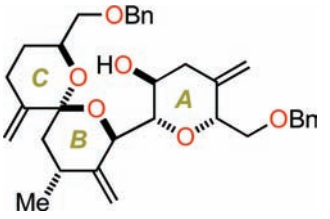
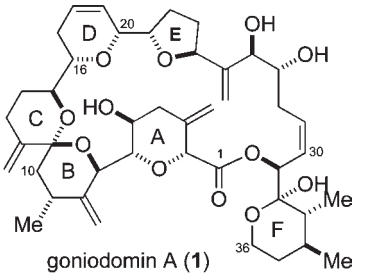
ABSTRACT



A convergent synthesis of the C1−C16 segment of goniodomin A, an actin-targeting marine polyether macrolide natural product, has been achieved via a 2-fold application of palladium-catalyzed organostannane−thioester coupling.

Goniodomin A (**1**, Figure 1) was isolated by Murakami and his colleagues from the dinoflagellate *Alexandrium hiranoi* (formerly known as *Goniodoma pseudogoniaulax*) collected in a rock pool at Jogashima, Japan.[1] Later, this natural product was also identified from the cultured cells of the dinoflagellate *Alexandrium monilatum*.[2] Extensive NMR studies on **1** culminated in the determination of its gross structure, which is characterized by the 32-membered macrocyclic architecture embedded with a 6/6-spiroacetal (BC-ring), three cyclic ethers (A-, D-, and E-rings), and a six-membered cyclic hemiacetal (F-ring). Our group has recently reported the establishment of the complete stereostructure of **1** on the basis of 2D NMR analysis, degradation experiments of the authentic sample, and synthesis and spectroscopic analysis of designed model compounds.[3]

Goniodomin A, originally isolated as an antifungal agent, exhibits intriguing biological activities by targeting actin, such as modulation of the activity of actomyosin ATPase,[4−6] induction of morphological changes in human astrocytoma



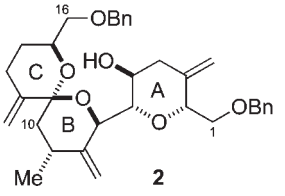


Figure 1. Structures of goniodomin A (**1**) and the C1−C16 segment **2**.

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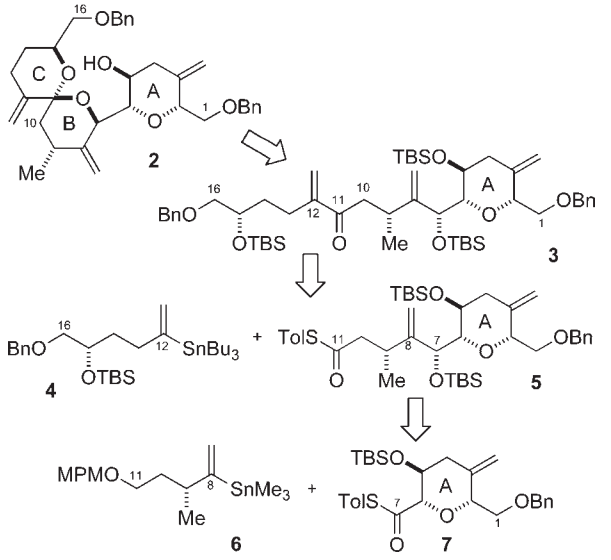
cells by increasing the filamentous actin content,[7] and anti-angiogenic activity via inhibition of actin reorganization in endothelial cells.[8]

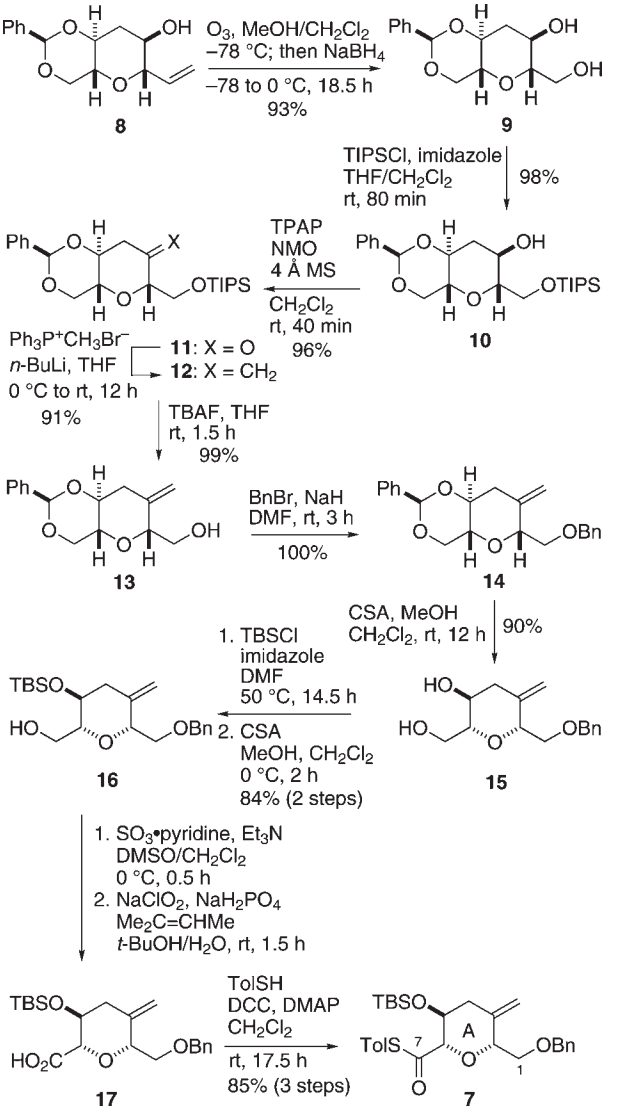
These structural and biological aspects of **1** make it an attractive synthetic target.[9,10] As a part of our efforts toward the total synthesis of **1**, we report herein a convergent synthesis of the A/BC-ring segment **2** (Figure 1) encompassing the C1−C16[11] carbon chain by means of palladium-catalyzed organostannane−thioester coupling.[12,13]

Scheme 1. Synthesis Plan



Our synthesis plan toward the C1−C16 segment **2** is illustrated in Scheme 1 (Tol = *p*-tolyl). We considered that **2** could be constructed from its linear precursor, enone **3**, via spiroacetalization. The enone **3**, in turn, would be synthesized in a convergent manner by a 2-fold use of palladium-catalyzed organostannane−thioester coupling.[12,13] Thus, the C11−C12 bond of **3** could be formed via coupling of vinylstannane **4** and thioester **5**. The latter would be derived from vinylstannane **6** and thioester **7** by forming the C7−C8 bond.

Scheme 2. Synthesis of the A-Ring Thioester **7**



The synthesis of the A-ring thioester **7** commenced with ozonolysis of the known tetrahydropyran **8**[14] followed by reductive workup with $NaBH_4$ to give diol **9** in 93% yield (Scheme 2). Selective silylation of the primary alcohol within **9** (TIPSCl, imidazole) delivered alcohol **10** in 98% yield, which was oxidized with TPAP/NMO[15] to afford ketone **11** in 96% yield. Wittig methylenation of **11** yielded olefin **12** in 91% yield, from which the silyl group was removed with TBAF to give alcohol **13** in 99% yield. Benzylation of the liberated hydroxy group gave benzyl ether **14** quantitatively.

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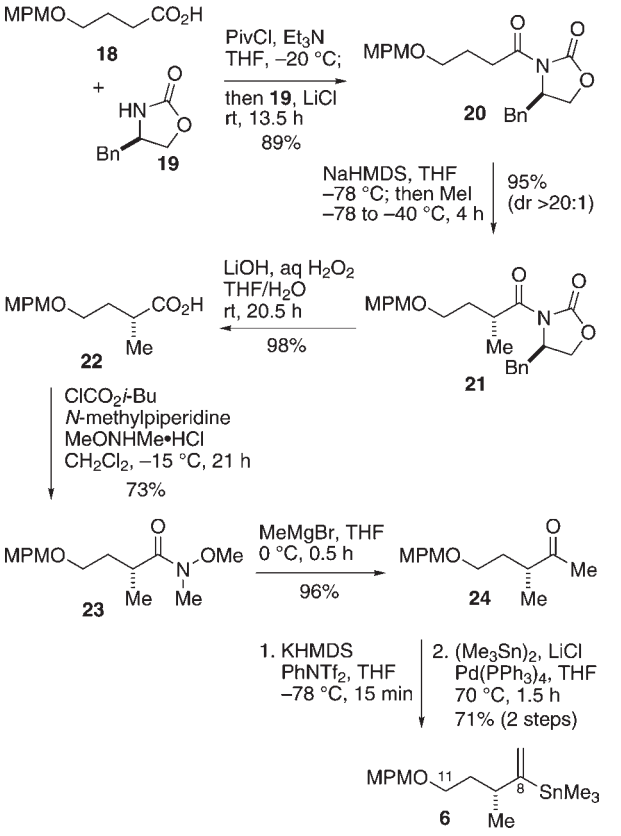
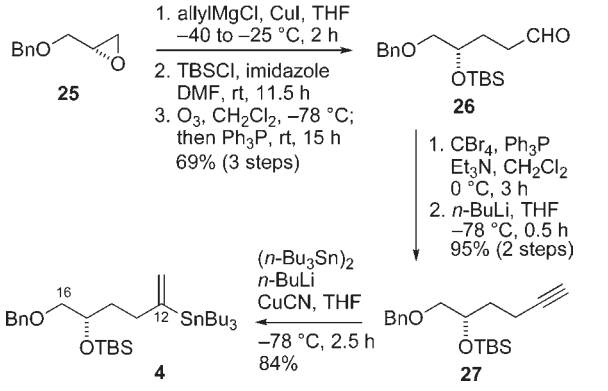
Methanolysis of the benzylidene acetal under acidic conditions provided diol **15** in 90% yield. Bis-silylation of **15** and subsequent acid treatment gave alcohol **16** in 84% yield for the two steps. Oxidation of **16** to carboxylic acid **17** and condensation with *p*-toluenethiol (DCC, DMAP) furnished thioester **7** in 85% yield (three steps).

Scheme 3. Synthesis of Vinylstannane **6**



The vinylstannane **6** was prepared as summarized in Scheme 3. Coupling of the known carboxylic acid **18**[16] with (*R*)-4-benzyloxazolidin-2-one (**19**) (PivCl, Et_3N, THF, −20 °C; then LiCl, **19**, rt)[17] delivered imide **20** in 89% yield. Asymmetric methylation of **20** according to the Evans protocol (NaHMDS, THF, −78 °C; then MeI, −78 to −40 °C)[18] afforded methylated product **21** in 95% yield as a single stereoisomer, as judged by 500 MHz ^{1}H NMR. Removal of the chiral auxiliary by exposure to alkaline peroxide[19] yielded carboxylic acid **22** in 98% yield, which was coupled with *N*,*O*-dimethylhydroxyamine to give Weinreb amide **23** in 73% yield. Treatment of **23** with MeMgBr[20] provided methyl ketone **24** in 96% yield, which was converted to vinylstannane **6** via Stille coupling of the corresponding enol triflate with hexamethylditin under the standard conditions (71%, two steps).[21]

Scheme 4. Synthesis of Vinylstannane **4**



The synthesis of vinylstannane **4** started with copper(I)-catalyzed regioselective allylation of benzyl (*S*)-glycidyl ether (**25**) (Scheme 4). Subsequent silylation and ozonolysis provided aldehyde **26** in 69% overall yield. Aldehyde **26** was transformed to alkyne **27** via a dibromoolefin according to the Corey—Fuchs protocol (95%, two steps).[22] Regioselective hydrostannylation of **27** was performed with $(n\text{-}Bu_3Sn)_2$-$Cu(CN)Li_2$[23] to afford vinylstannane **4** in 84% yield.

Having synthesized the requisite fragments **4**, **6**, and **7**, we proceeded to assemble these fragments toward completion of the synthesis (Scheme 5). Coupling of thioester **7** with vinylstannane **6** was best accomplished under the influence of a $Pd_2(dba)_3/Ph_3As$ catalyst system and copper(I) diphenylphosphinate (CuDPP) in THF at room temperature. Under these conditions, enone **28** was isolated in 96% yield. Chelate-controlled reduction[24] of **28** with $Zn(BH_4)_2$ (Et_2O, −40 °C) gave a chromatographically separable 5:1 mixture of allylic alcohol **29** and its C7 epimer in 63% combined yield. Silylation of **29** and deprotection of the MPM group led to alcohol **30** almost quantitatively. Oxidation of **30** to carboxylic acid **31** followed by coupling with *p*-toluenethiol delivered thioester **5** in 82% yield for the three steps. This was coupled with vinylstannane **4** [$Pd_2(dba)_3/Ph_3As$, CuDPP, THF, room temperature] to afford enone **3** in 86% yield. Removal of the silyl groups with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[25] gave cyclization precursor **32** in 87% yield.

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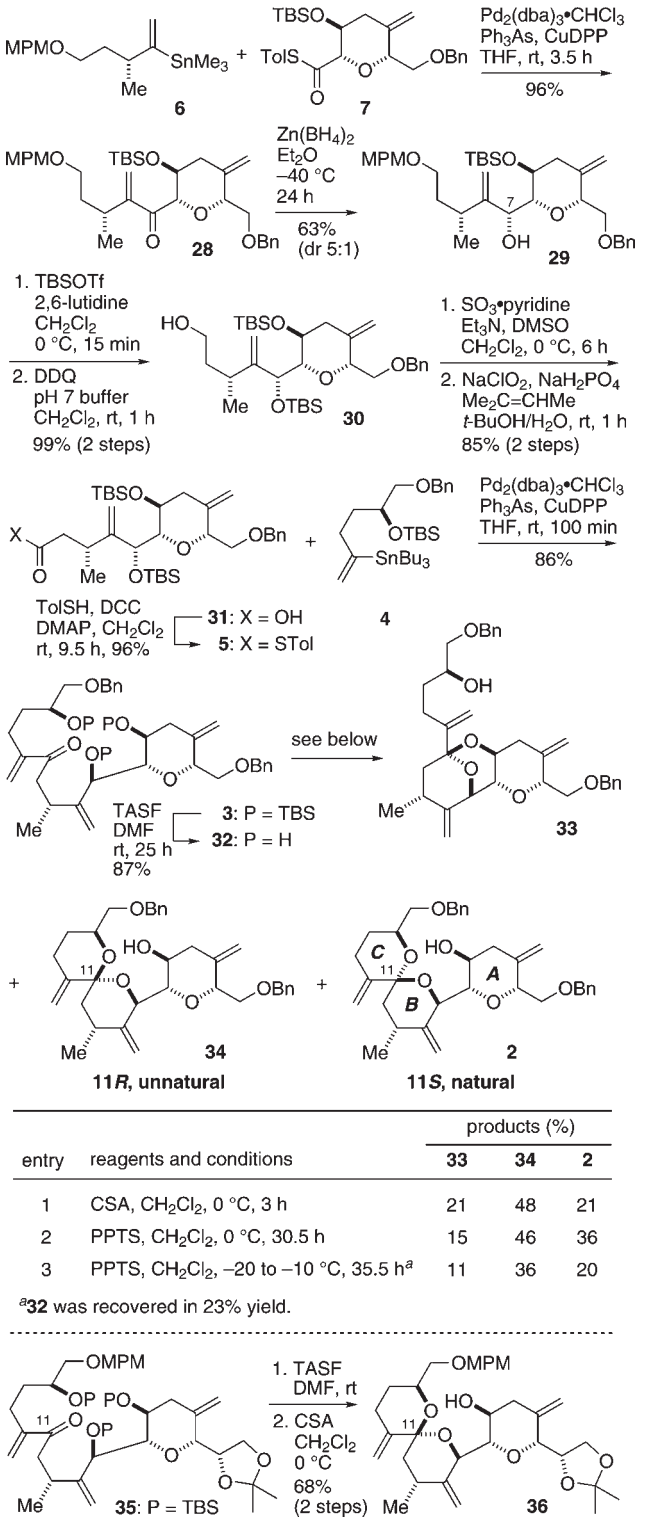
Scheme 5. Synthesis of the C1−C16 Segment **2** via Acid-Catalyzed Acetalization of Ketotriol **32**



entry	reagents and conditions	products (%) 33	34	2
1	CSA, CH_2Cl_2, 0 °C, 3 h	21	48	21
2	PPTS, CH_2Cl_2, 0 °C, 30.5 h	15	46	36
3	PPTS, CH_2Cl_2, –20 to –10 °C, 35.5 h[a]	11	36	20

[a] **32** was recovered in 23% yield.

Finally, we investigated acid-catalyzed cyclization of ketotriol **32** to construct the spiroacetal BC-ring system (see the table in Scheme 5). Treatment of **32** with CSA in CH_2Cl_2 at 0 °C for 3 h gave fused acetal **33** (21%), unnatural (11*R*)-spiroacetal **34** (48%), and natural (11*S*)-spiroacetal **2** (21%) (entry 1). These products were separated by reverse-phase HPLC and structurally characterized by extensive NMR analysis (see the Supporting Information for details). We could improve the yield of the desired **2** by running the cyclization of **32** using PPTS in CH_2Cl_2 at 0 °C for 30.5 h, which afforded **33** (15%), **34** (46%), and **2** (36%) (entry 2). However, spiroacetalization of **32** under low temperature conditions (−20 to −10 °C) was not effective for improving the yield of **2** (entry 3). Careful monitoring of the acetalization indicated that a mixture of **34** and **2** was initially generated but fused acetal **33** increased as the reaction progressed. This observation suggested that **33** might be formed from **34** and/or **2** as a result of thermodynamic equilibration.[26] The predominant formation of unnatural **34** over natural **2** could be reasoned by the double anomeric stabilization effect, whereas the *S* configuration of the C11 stereogenic center of the natural product would be ascribed to the macrocyclic contraint.[3,9c,27] Our result is in sharp contrast to the observation made by Fujiwara and coworkers, who reported that acid-catalyzed cyclization of a closely related ketotriol derived from tris-silyl ether **35** afforded unnatural (11*R*)-spiroacetal **36** as the *sole* product.[9c]

In conclusion, we have developed a convergent synthetic entry to the C1−C16 segment **2** of goniodomin A via a 2-fold use of palladium-catalyzed organostannane−thioester coupling. Further efforts toward the total synthesis of goniodomin A are currently underway and will be reported in due course.

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Supporting Information Available. Detailed experimental procedures, spectroscopic data, stereochemical assignments of selected compounds, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(26) Since individual treatment of **2**, **33**, and **34** with CSA (CH_2Cl_2, 0 °C, 3 h) uniformly gave an approximately 1:2:1 mixture of **2**, **33**, and **34**, formation of these isomers during acid treatment of **32** could be ascribed to thermodynamic equilibration.

(27) In the present study, we could only isolate natural (11*S*)-spiroacetal **2** as a minor product. However, we expect that we would be able to control the C11 stereochemistry in a real system by constructing the macrocyclic framework of **1** prior to spiroacetalization.