

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

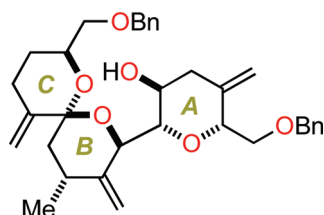
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ABSTRACT



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

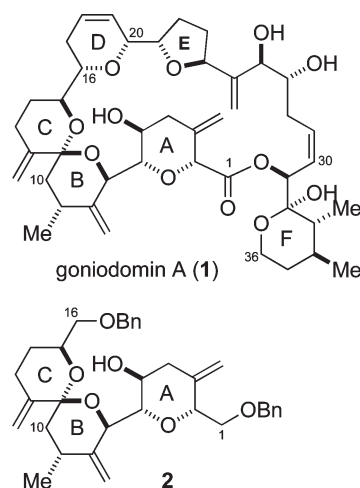


Figure 1. Structures of goniodomin A (**1**) and the C1–C16 segment **2**.

as modulation of the activity of actomyosin ATPase,^{4–6} induction of morphological changes in human astrocytoma

(1) Murakami, M.; Makabe, K.; Yamaguchi, K.; Konosu, S.; Walchli, M. R. *Tetrahedron Lett.* **1988**, 29, 1149.

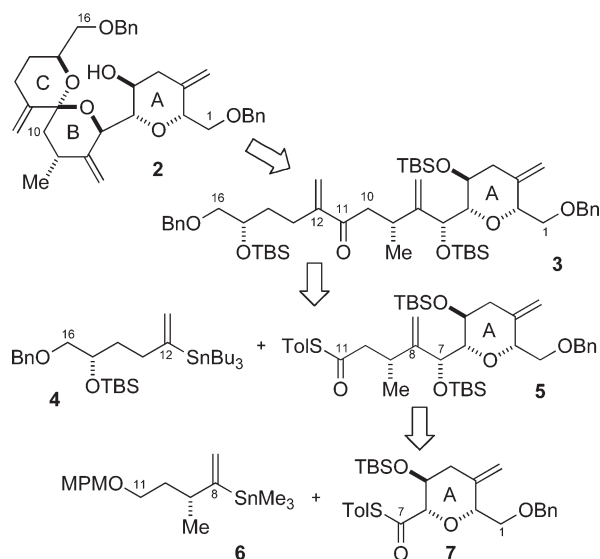
(2) Hsia, M. H.; Morton, S. L.; Smith, L. L.; Beauchesne, K. R.; Huncik, K. M.; Moeller, P. D. R. *Harmful Algae* **2006**, 5, 290.

(3) Takeda, Y.; Shi, J.; Oikawa, M.; Sasaki, M. *Org. Lett.* **2008**, 10, 1013.

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–C16¹¹ 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**.

(4) Furukawa, K.-I.; Sakai, K.; Watanabe, S.; Maruyama, K.; Murakami, M.; Yamaguchi, K.; Ohizumi, Y. *J. Biol. Chem.* **1993**, 268, 26026.

(5) Matsunaga, K.; Nakatani, K.; Murakami, M.; Yamaguchi, K.; Ohizumi, Y. *J. Pharmacol. Exp. Ther.* **1999**, 291, 1121.

(6) Yasuda, M.; Nakatani, K.; Matsunaga, K.; Murakami, M.; Momose, K.; Ohizumi, Y. *Eur. J. Pharmacol.* **1998**, 346, 119.

(7) Mizuno, K.; Nakataha, N.; Ito, E.; Murakami, M.; Yamaguchi, K.; Ohizumi, Y. *J. Pharm. Pharmacol.* **1998**, 50, 645.

(8) Abe, M.; Inoue, D.; Matsunaga, K.; Ohizumi, Y.; Ueda, H.; Asano, T.; Murakami, M.; Sato, Y. *J. Cell. Physiol.* **2002**, 190, 109.

(9) (a) Fujiwara, K.; Naka, J.; Katagiri, T.; Sato, D.; Kawai, H.; Suzuki, T. *Bull. Chem. Soc. Jpn.* **2007**, 80, 1173. (b) Katagiri, T.; Fujiwara, K.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2008**, 49, 233. (c) Katagiri, T.; Fujiwara, K.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2008**, 49, 3242.

(10) (a) Saito, T.; Fuwa, H.; Sasaki, M. *Org. Lett.* **2009**, 11, 5274. (b) Saito, T.; Fuwa, H.; Sasaki, M. *Tetrahedron* **2011**, 67, 429.

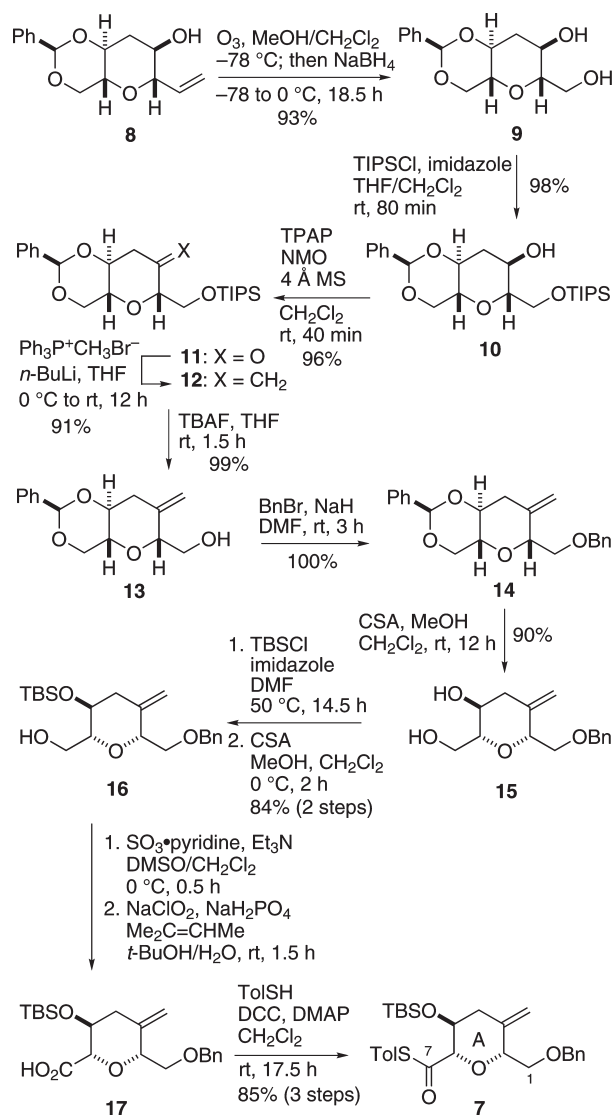
(11) The carbon numbering corresponds to that of the natural product.

(12) (a) Wittenberg, R.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2003**, 5, 3033. (b) Li, H.; Yang, H.; Liebeskind, L. S. *Org. Lett.* **2008**, 10, 4375.

(13) For a review, see: Prokopcová, H.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, 48, 2276.

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**



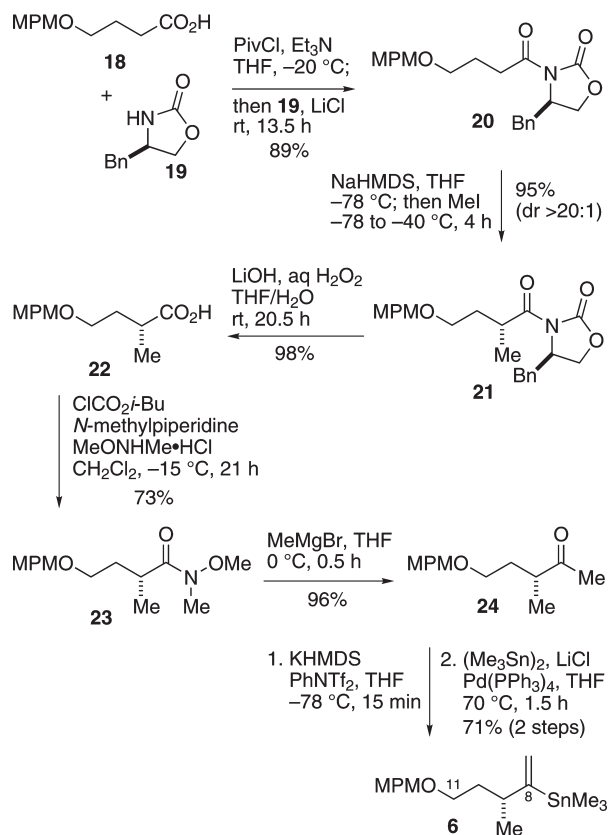
The synthesis of the A-ring thioester **7** commenced with ozonolysis of the known tetrahydropyran **8**¹⁴ followed by reductive workup with NaBH₄ to give diol **9** in 93% yield (Scheme 2). Selective silylation of the primary alcohol within **9** (TIPSCl, imidazole) delivered alcohol **10** in 98% yield, which was oxidized with TPAP/NMO¹⁵ 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.

(14) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, 57, 3019.

(15) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

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).

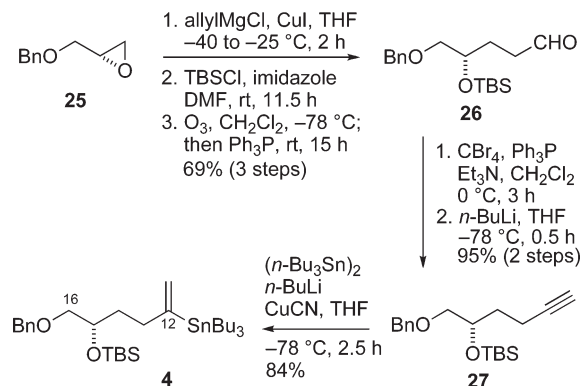
Scheme 3. Synthesis of Vinylstannane **6**



The vinylstannane **6** was prepared as summarized in Scheme 3. Coupling of the known carboxylic acid **18**¹⁶ with (*R*)-4-benzyl-2-oxazolidinone (**19**) (PivCl, Et₃N, 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 ¹H NMR. Removal of the chiral auxiliary by exposure to alkaline peroxide¹⁹ yielded carboxylic acid **22** in 98% yield, which was coupled with *N,O*-dimethylhydroxylamine to give Weinreb amide **23** in 73% yield. Treatment of

23 with MeMgBr²⁰ 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*-Bu₃Sn)₂-Cu(CN)Li²³ 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 Pd₂(dba)₃/Ph₃As catalyst system and copper(I) diphenylphosphinate (CuDPP) in THF at room temperature. Under these conditions, enone **28** was isolated in 96% yield. Chelate-controlled reduction²⁴ of **28** with Zn(BH₄)₂ (Et₂O, -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** [Pd₂(dba)₃/Ph₃As, 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.

(16) Hirai, K.; Ooi, H.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 857.

(17) Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 7775.

(18) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(19) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(20) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(21) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277.

(22) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(23) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1989**, *54*, 5064.

(24) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338.

(25) (a) Noyori, R.; Nishida, I.; Sataka, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223. (b) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.

[illegible]

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

1. TASF
DMF, rt
 2. CSA
CH₂Cl₂
0 °C
 68%
(2 steps)

35: P = TBS

36

(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 constraint.^{3,9c,27} Our result is in sharp contrast to the observation made by Fujiwara and co-workers, 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.