ORGANIC LETTERS

2009
Vol. 11, No. 22
5274−5277

Toward the Total Synthesis of Goniodomin A, An Actin-Targeting Marine Polyether Macrolide: Convergent Synthesis of the C15−C36 Segment

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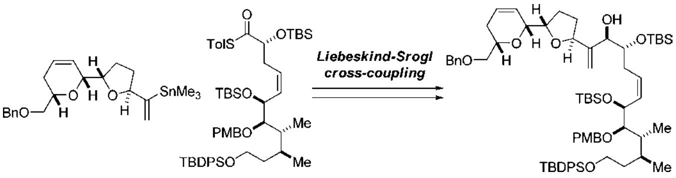
Received September 25, 2009

ABSTRACT



Stereoselective convergent synthesis of the C15−C36 segment of goniodomin A, an actin-targeting marine polyether macrolide natural product, has been achieved. The present synthesis features palladium(0)-catalyzed, copper(I)-mediated Liebeskind−Srogl cross-coupling as the fragment assembly process.

Goniodomin A (**1**, Figure 1) was isolated as a potent antifungal agent by Murakami and co-workers from the dinoflagellate *Alexandrium hiranoi* (formerly *Goniodoma pseudogoniaulax*) collected in a rock pool at Jogashima in Japan in 1988.[1] More recently, it was reported that the dinoflagellate *Alexandrium monilatum* produced goniodomin A.[2] The gross structure of goniodomin A was determined by Murakami and co-workers on the basis of the NMR studies to be a novel polyether macrolide, which is characterized by a spiroacetal ring (B/C-ring), an additional four oxacycles (A-, D-, E-, and F-rings), and 17 stereogenic centers embedded within a 36-carbon chain.[1] We have recently defined the absolute configuration of goniodomin A on the basis of detailed 2D NMR studies and degradation experiments of the natural product, the synthesis of suitable model compounds for NMR spectroscopic comparisons, and by correlation with synthetic reference compounds.[3]

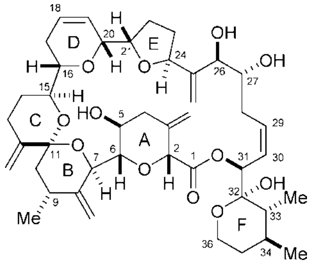


Figure 1. Structure of goniodomin A (**1**).

From a biological perspective, goniodomin A has profound effects on reorganization of the actin cytoskeleton. Goniodomin A has been found to stimulate actomyosin ATPase activity by binding to and altering the conformation of actin.[4,5] It also modulates actomyosin ATPase activity between ventricular and atrial muscles.[6] It has been reported

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[1] Murakami, M.; Makabe, K.; Yamaguchi, K.; Konosu, S.; Walchli, M. R. *Tetrahedron Lett.* **1988**, *29*, 1149–1152.

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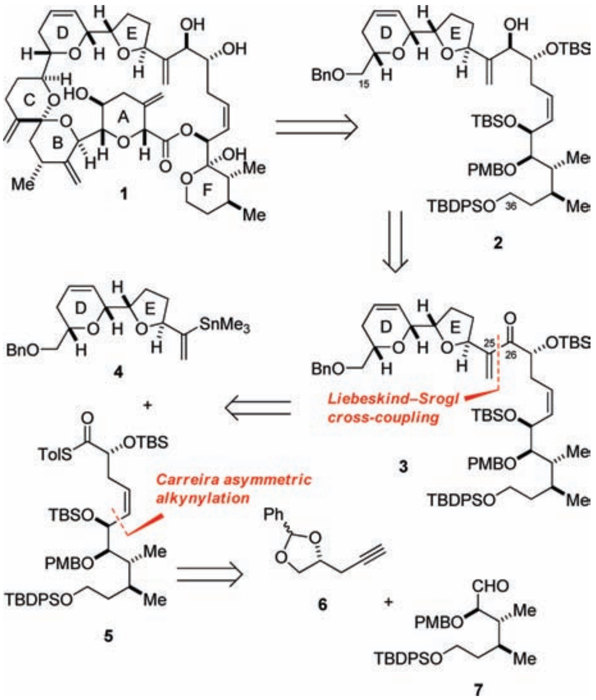
10.1021/ol902217q CCC: $40.75

Scheme 1. Retrosynthetic Analysis



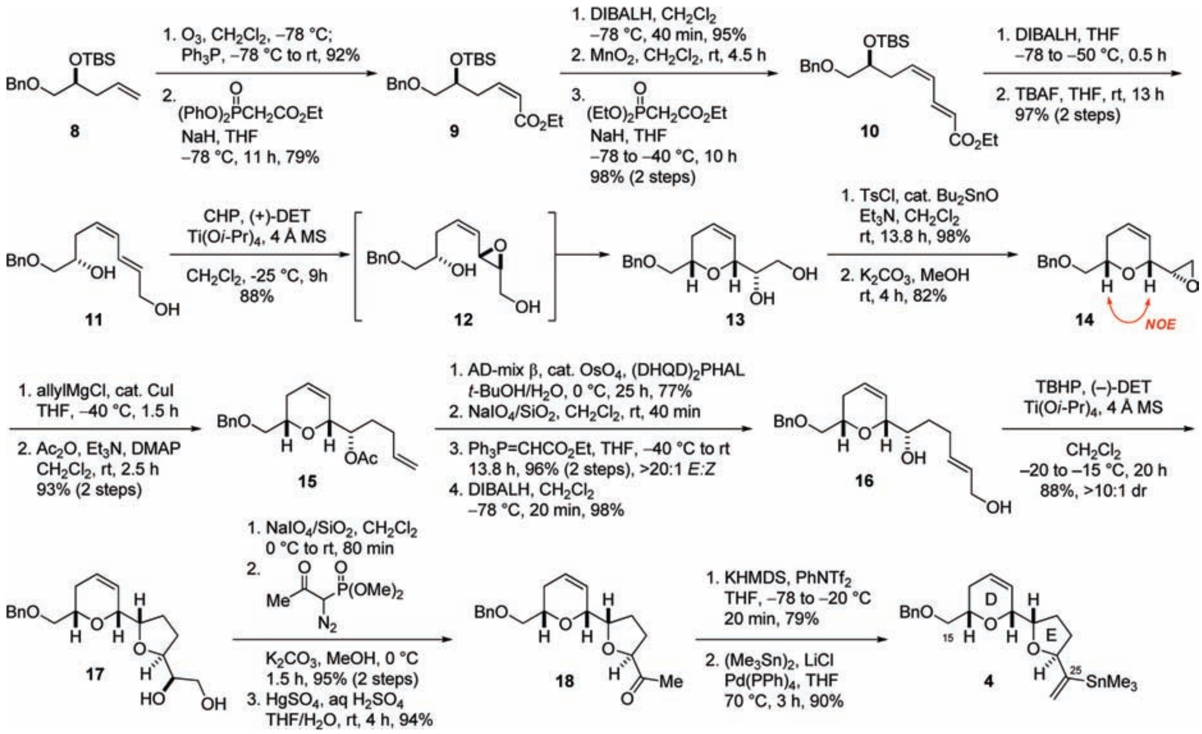
that goniodomin A causes morphological changes in human astrocytoma cells by increasing the filamentous actin content.[7] It also exhibits antiangiogenetic activity via inhibition of actin reorganization in endothelial cells.[8]

The wide-ranging biological properties of goniodomin A, in conjunction with the architecturally complex structure, prompted us to initiate studies on the total synthesis of this natural product.[9] We describe herein a stereoselective construction of the C15−C36 segment **2** of goniodomin A.

Our synthetic strategy toward goniodomin A (**1**) by way of the C15−C36 segment **2** is outlined in Scheme 1. We planned to construct the segment **2** by Liebeskind−Srogl cross-coupling[10−12] between the C15−C25 vinyl stannane **4** and the C26−C36 thiol ester **5** of comparable complexity, followed by stereoselective reduction of the C26 ketone within **3**. We envisioned that two ether rings (D- and E-rings) of **4** would be constructed via 5-exo and 6-exo cyclizations of the respective hydroxy epoxide precursors. Thiol ester **5** could, in turn, arise from the coupling of alkyne **6** and aldehyde **7**[3] by means of a Carreira asymmetric alkynylation protocol.[13]

The synthesis of vinyl stannane **4** started with the known compound **8**,[14] which is available in two steps from (*S*)-benzyl glycidyl ether (Scheme 2). Ozonolysis of the double bond, followed by the Horner−Wadsworth−Emmons (HWE) reaction of the resultant aldehyde under Ando conditions,[15] provided (*Z*)-enoate **9** in 79% yield, along with an 8:1 mixture of the corresponding (*E*)- and (*Z*)-isomers (19%). DIBALH reduction, oxidation with MnO_2, and the HWE reaction gave dienoate **10** in high overall yield. DIBALH reduction was followed by desilylation to afford diol **11** (97%, two steps), which upon Sharpless asymmetric epoxidation using cumyl hydroperoxide (CHP)[16] underwent concomitant 6-exo cyclization of the derived epoxy alcohol

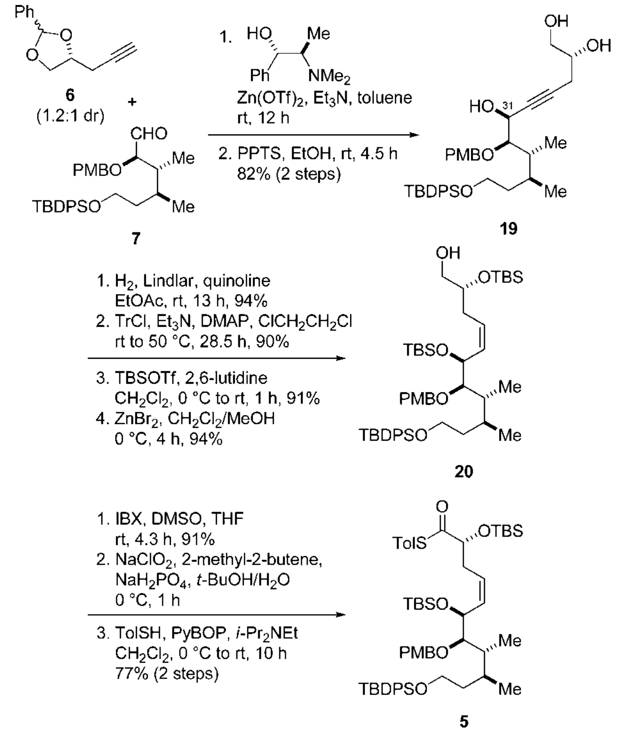
Scheme 2. Synthesis of Vinyl Stannane **4**



12 to provide dihydropyran **13** in 88% yield. The use of *tert*-butylhydroperoxide instead of CHP resulted in a low yield of **13**. Conversion to epoxide **14** was performed by selective tosylation[17] and base treatment (80% yield, two steps). The stereochemistry of **14** was confirmed by an NOE as shown. Subsequent reaction with allylmagnesium chloride and CuI provided, after acylation, acetate **15** in 93% yield (two steps). Chemoselective dihydroxylation of the terminal olefin was best accomplished under the influence of AD-mix β, cat. OsO_4, and $(DHQD)_2PHAL$ (77% after one recycling). Oxidative cleavage of the resultant diol with $NaIO_4/SiO_2$[18] followed by the Wittig reaction produced an enoate (96% for the two steps, >20:1 *E*/*Z*), which was then reduced with DIBALH to afford allylic alcohol **16** (98%). The asymmetric epoxidation/5-exo cyclization sequence proceeded efficiently to give diol **17** in 88% yield (>10:1 dr). The vic-diol moiety of **17** was converted into methyl ketone in a three-step sequence, including $NaIO_4$ oxidation, alkynylation with Ohira−Bestmann reagent,[19] and hydration of the terminal alkyne.[20] Ketone **18** thus obtained was transformed to the corresponding enol triflate (KHMDS, $PhNTf_2$, 79%), which was treated with $(Me_3Sn)_2$, LiCl, and $Pd(PPh_3)_4$ (THF, 70 °C)[21] to furnish the desired vinyl stannane **4** in 90% yield.[22]

The synthesis of thiol ester partner **5** commenced with a fragment coupling of alkyne **6** (a 1.2:1 mixture of epimers)[23] and the previously described aldehyde **7**,[3] which is available in 14 steps from (−)-dimenthyl fumarate. Thus, the reaction of **7** with **6** (2 equiv) under Carreira asymmetric alkynylation conditions ($Zn(OTf)_2$, (+)-*N*-methyl ephedrine, Et_3N, toluene, room temperature)[13] gave the desired alcohol[24] with an approximately 9:1 diastereoselectivity (Scheme 3). Subsequent deprotection of the benzylidene acetal by treatment with PPTS afforded triol **19** in 82% yield for the two steps. At this stage, the undesired diastereomer at C31 could be removed by column chromatography on silica gel. After Lindlar reduction of the triple bond, a three-step sequence of protective group manipulations led to primary alcohol **20** in 72% overall yield. Oxidation of **20** to the corresponding carboxylic acid (IBX, DMSO; then $NaClO_2$) and esterification with *p*-tolylthiol (PyBOP, *i*-Pr_2NEt_2,

Scheme 3. Synthesis of Thiol Ester **5**



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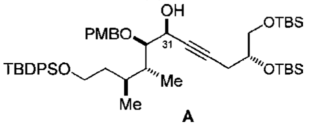
(22) For stereochemical assignment of compound **4**, see Supporting Information.

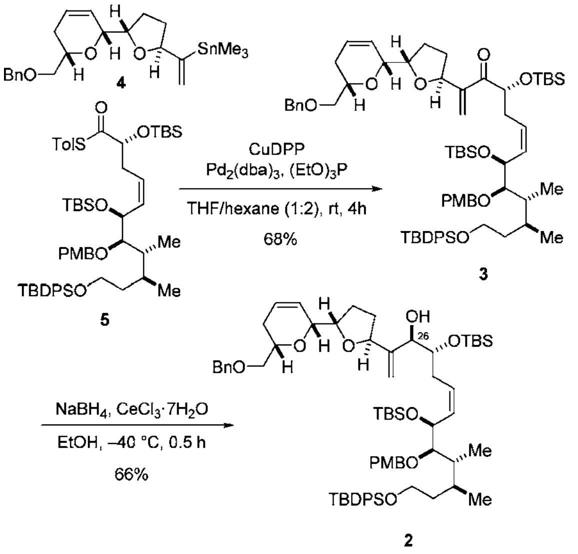
(23) Alkyne **6** was readily available in three steps from (*S*)-glycidol: (1) trimethylsilylacetylene, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 to 0 °C; (2) $PhCH(OMe)_2$, cat. CSA, CH_2Cl_2; (3) K_2CO_3, MeOH, 81% yield for the three steps.

(24) The stereochemistry of the newly generated stereogenic center at C31 was equivocally confirmed by conversion to the known compound **A**[3] by a four-step sequence: (1) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (2) PPTS, EtOH; (3) TBSOTf, 2,6-lutidine, CH_2Cl_2; (4) DIBALH, CH_2Cl_2.

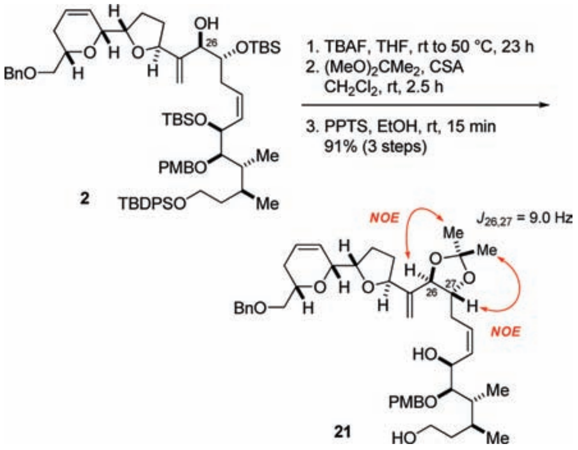


A

Scheme 4. Synthesis of C15−C36 Segment **2**



Scheme 5. Synthesis of Acetonide Derivative **21** for Stereochemical Confirmation



CH_2Cl_2)[25] completed the synthesis of thiol ester **5** in 70% yield for the three steps.

With the requisite fragments in hand, we then turned our attention to the pivotal fragment union. After investigation of several reaction conditions, it was found that a cross-coupling reaction of **5** with **4** (1.1 equiv) could be achieved by treatment with copper(I) diphenylphosphinate (CuDPP, 2.0 equiv), $Pd_2(dba)_3$ (0.1 equiv), and triethylphosphite (0.8 equiv) in THF/hexanes (1:2) at room temperature[10b] (Scheme 4). Thus, the desired cross-coupling product **3** was obtained in 68% yield. In this coupling reaction, small amounts (ca. 10%) of homocoupling product of vinyl stannane **4** were produced. Finally, stereoselective reduction of enone **3** was performed under Luche conditions ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, −40 °C)[26] to furnish the desired alcohol **2** in 66% yield as the only detectable diastereomer. The stereochemistry at C26 was unambiguously confirmed by conversion to the acetonide **21** and NMR analysis as shown in Scheme 5. The stereochemical outcome of this reduction can be rationalized by the Felkin−Ahn model.[27]

In conclusion, we have developed a convergent synthetic route to the C15−C36 segment **2** of goniodomin A. Particularly noteworthy is a Pd(0)-catalyzed, Cu(I)-mediated Liebeskind−Srogl cross-coupling of complex fragments for the critical bond-forming step. Further studies toward the total synthesis of goniodomin A are currently underway in our laboratories and will be reported in due course.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (A) (No. 21241050) from the Japan Society for the Promotion of Science (JSPS) and the Tohoku University Global COE program “International Center of Research & Education for Molecular Complex Chemistry”. T.S. is grateful for a SUNBOR Scholarship.

Supporting Information Available: Experimental procedures, spectroscopic data for new compounds, stereochemical assignment of compound **4**, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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