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Synthesis of the ABC-ring models of goniodomin A: preference for the unnatural configuration at C11 of the BC-ring in a non-macrocyclic model system

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Abstract

To confirm the natural relative stereochemistry of the ABC-ring of goniodomin A (**1**), the corresponding three stereoisomeric compounds, (2*R*,5*S*,6*S*,7*S*,9*S*,11*R*,15*S*)-, (2*R*,5*S*,6*S*,7*R*,9*R*,11*S*,15*R*)-, and (2*R*,5*S*,6*S*,7*R*,9*R*,11*R*,15*S*)-isomers (**2**, **3**, and **5**, respectively), were stereoselectively synthesized using a Nozaki–Hiyama–Kishi reaction as a key step. It was also found that a (2*R*,5*S*,6*S*,7*R*,9*R*,11*S*,15*S*)-isomer (**4**), corresponding to the absolute configuration of **1** recently proposed by Sasaki, was not detected during the formation of **5** from a common ketodiol substrate under acid-catalyzed spiroacetalization conditions. This would be attributable to the absence of a macrocyclic framework.

Goniodomin A (**1**, Fig. 1) is a unique bioactive metabolite from dinoflagellates *Alexandrium hiranoi* and *monilatium*.[1–3] Its planar structure was elucidated by Murakami's detailed NMR analysis, but its stereochemistry was unknown for a long time.[1] We previously studied the absolute configuration of goniodomin A by model synthesis and NMR comparison between **1** and the models, thereby confirming the natural relative configurations of the A- and F-rings and predicting that of the DE-ring.[4] We then turned our attention to the determination of the configuration of the ABC-ring, and planned to synthesize model compounds **2**–**4** for NMR comparison. During the course of our studies, Sasaki elucidated the absolute configuration of **1** from intensive NMR analysis of the natural product and chemical synthesis of its degradation product.[5] It was also revealed from Sasaki's results that model **4** possessed the natural configuration. In this Letter, we describe the stereoselective synthesis of model compounds **2**, **3**, and **5**, the C11-epimer of **4**, based on the Nozaki–Hiyama–Kishi (NHK) reaction,[6] as well as the notable finding of little production of **4** during the formation of **5** from a common ketodiol substrate under acid-catalyzed spiroacetalization conditions. This would be attributable to the absence of a macrocyclic framework.

Initially, the possible relative configurations of the ABC-ring of **1** were deduced based on our previous results with the A-ring (**6** in Fig. 2) and the NMR data on the BC-ring reported by Murakami.[1] The tentative stereochemistry of the BC-ring (**7**) was derived as follows: (i) the chair conformation of the C-ring with equatorial C16 (R^3) was presumed from a large $J_{H14a–H15}$ (9.1 Hz), showing a trans-diaxial relationship of H14a and H15, even though $J_{H14b–H15}$ had a somewhat puzzling intermediate value (6.7 Hz), which is out of the typical range of an equatorial–axial relationship (2–3 Hz); (ii) the NOE correlation of H7/H15, indicating the close proximity of these protons, implied the double anomeric spirocyclic acetal of the BC-ring; (iii) the NOE enhancement of C9–CH_3/H15 denoted that the methyl group would be at an axial position and *cis* to H7, although it was rather confusing that both

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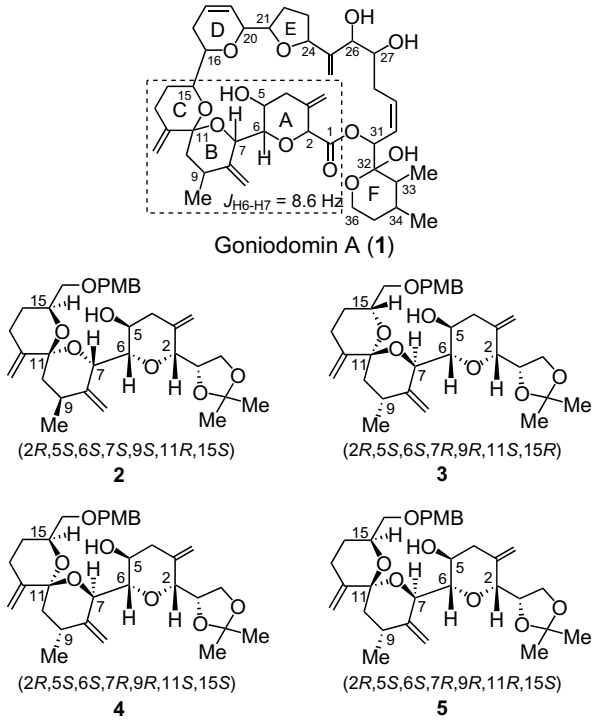


Fig. 1.

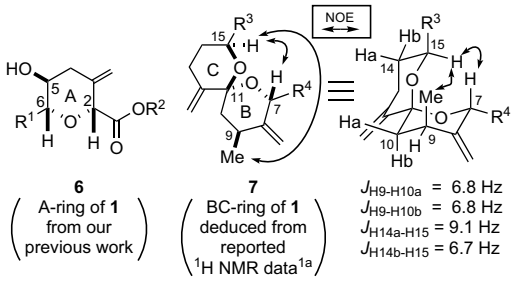
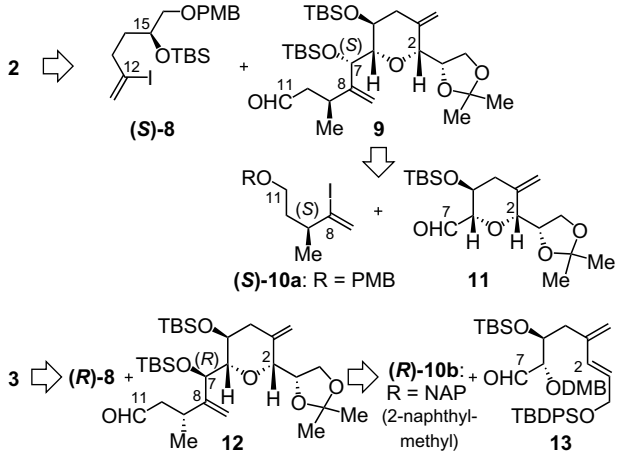


Fig. 2.

$J_{H9-H10a}$ and $J_{H9-H10b}$ showed the same intermediate values (6.8 Hz), which deviated from the normal ^3J values (2–3 Hz) of equatorial–axial or equatorial–equatorial protons. Hence, at this stage, the ABC-ring of **1** was thought to have either (2*R**,5*S**,6*S**,7*S**,9*S**,11*R**,15*S**)-configuration, corresponding to model **2**, or (2*R**,5*S**,6*S**,7*R**,9*R**,11*S**,15*R**)-configuration, corresponding to model **3**.

Next, models **2** and **3** were synthesized to establish the relative stereochemistry of the ABC-ring of **1** by the comparison of the NMR data of **1** and models **2** and **3**. The synthetic routes to **2** and **3** (Scheme 1), established after exhaustive investigations, strongly relied on the following steps: (i) diastereoselective NHK reaction,[6] which created the (7*S*)-configuration of **9** with substrates (***S*)-10a** and **11** and the (7*R*)-configuration of **12** with (***R*)-10b** and **13**, (ii) the second NHK reaction[6] of aldehydes **9** and **12** with

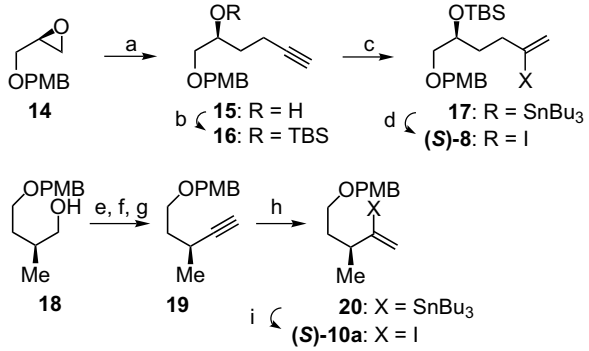


Scheme 1.

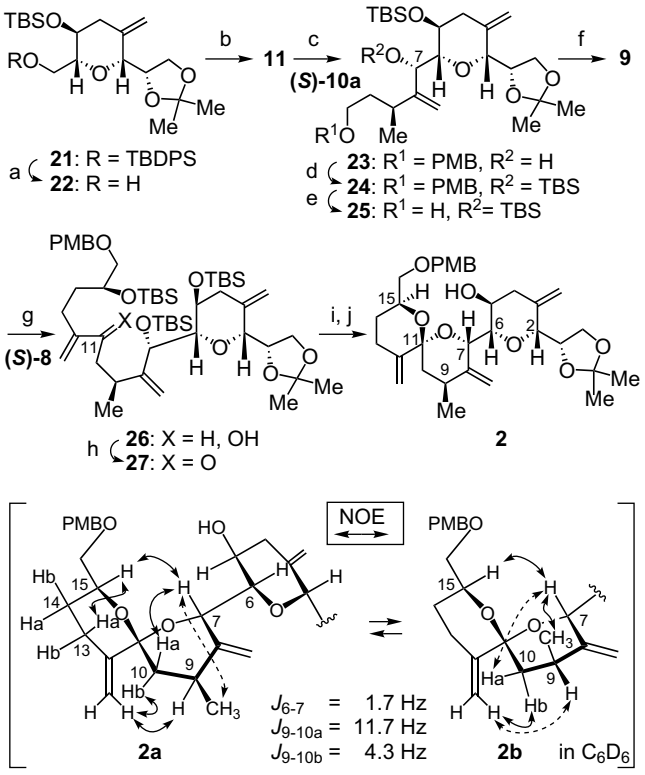
iodide (***S*)-8** or (***R*)-8**, respectively, and (iii) acid-catalyzed stereoselective spiroacetalization. Model **5** was also synthesized from (***S*)-8** and **12** in a similar manner.

Iodide (***S*)-8** was prepared from (*S*)-glycidyl ether **14** by the following four steps: (i) reaction of **14** with propargylmagnesium bromide/CuCN, (ii) TBS protection to form **16**[7] (89%, 2 steps), (iii) regioselective stannylcupration (72%),[8] and (iv) iodination (90%) (Scheme 2). Iodide (***R*)-8** was similarly derived from the (*R*)-enantiomer of **14**. Iodide (***S*)-10a** was synthesized from a known chiral alcohol **18**[9] by a process including Dess–Martin oxidation[10] of **18**, Corey–Fuchs acetylene formation to produce **19** (60%, 3 steps),[11] regioselective stannylation,[8] and iodination (72%, 2 steps). The preparation of (***R*)-10b** was performed in the same way from a NAP ether with (*R*)-configuration corresponding to **19**.[12]

The synthesis of **2** began from known **21**[4a] (Scheme 3). The removal of TBDPS from **21** (52%), followed by TPAP oxidation,[13] produced aldehyde **11**, which was reacted with (***S*)-10a** under NHK conditions[6] to give **23** as a single



Scheme 2. Reagents and conditions: (a) propargylmagnesium bromide, CuCN, Et_2O, −20 °C; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 89% (2 steps); (c) Bu_3SnH, LDA, CuCN, THF, −78 °C, then MeOH, 23 °C, 72%; (d) I_2, THF, 23 °C, 90%; (e) DMPI, CH_2Cl_2, 23 °C; (f) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 71% (2 steps); (g) BuLi, THF, −78 °C, 85%; (h) $Bu_3SnAlEt_2$, CuCN (cat.), THF, −30 °C; (i) I_2, THF, 23 °C, 72% (2 steps).



Scheme 3. Reagents and conditions: (a) 10% NaOH–MeOH (1:1), 23 °C, 52%; (b) TPAP, NMO, CH_2Cl_2, 23 °C; (c) (***S***)-**10a**, $CrCl_2$, $NiCl_2$, DMSO, 23 °C, 81% (2 steps); (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, ~100%; (e) DDQ, CH_2Cl_2–H_2O (10:1), 23 °C, 92%; (f) DMPI, CH_2Cl_2, 23 °C; (g) (***S***)-**8**, $CrCl_2$, $NiCl_2$, DMSO, 23 °C; (h) DMPI, CH_2Cl_2, 23 °C, 67% (3 steps from **25**); (i) TASF, DMF, 23 °C; (j) CSA, CH_2Cl_2, 0 °C, 50% (2 steps).

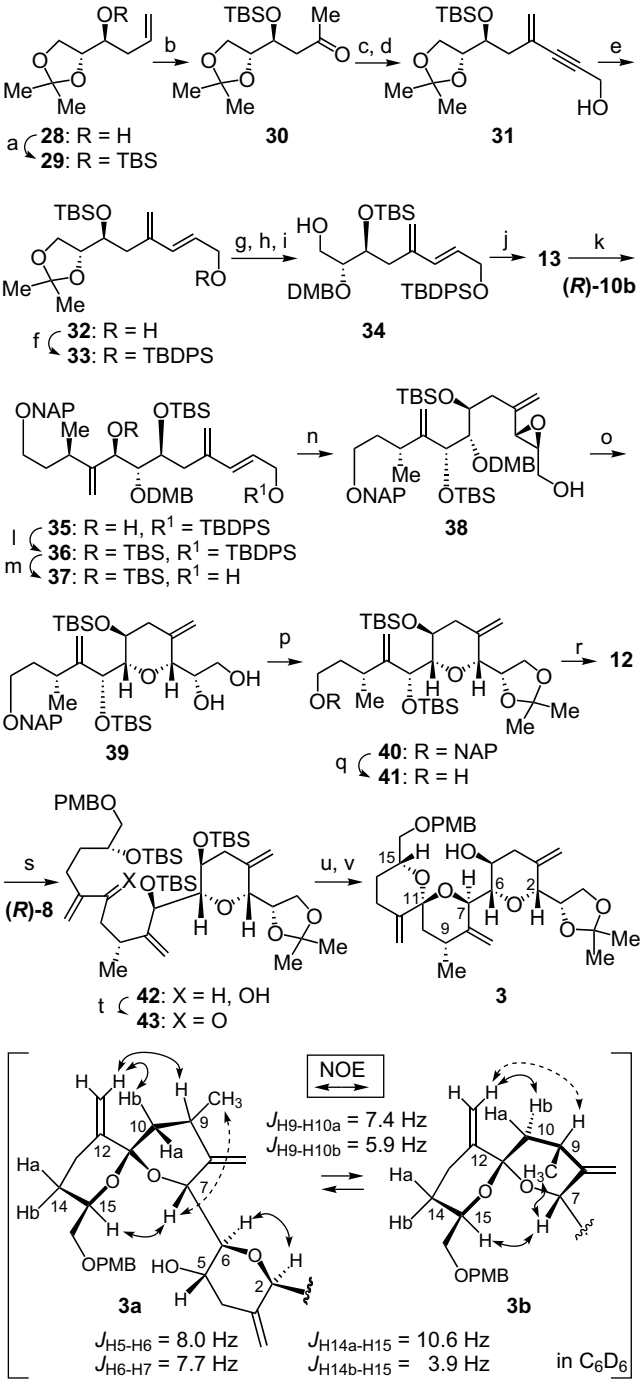
isomer (81%, 2 steps).[14,15] Alcohol **23** was converted to **25** (92%) via protection with TBSOTf and removal of the PMB group. After the oxidation of **25** with DMPI,[10] the resulting **9** was subjected to NHK reaction with (***S***)-**8** to smoothly furnish **26**,[6] which was oxidized to **27** (67% from **25**). The removal of the TBS groups of **27**, followed by treatment with CSA, produced **2** as a single isomer (50%, 2 steps).

The stereochemistry of **2** was confirmed by NMR analysis. The double anomeric spiroacetal structure of the BC-ring with (11*R*)-configuration was determined by the NOE correlations of H7/H15, C12=CH/H10b, and C12=CH/H9. Moreover, the coexistence of NOEs of H7/C9-CH_3 and H7/H10a suggested not only the *cis*-relationship of all of H7, C9-CH_3, and H10a, but also the presence of a conformational equilibrium between the boat and chair forms of the B-ring (**2a** and **2b**, respectively). The deviations of the coupling constants $J_{H9–H10a}$ (11.7 Hz) and $J_{H9–H10b}$ (4.3 Hz) from the normal ^3J values (2–3 Hz) of equatorial–axial or equatorial–equatorial protons in a chair conformer would also be attributed to the chair–boat interconversion equilibrium in the B-ring. The chair conformation of the C-ring of **2** was also confirmed by the NOE correlation of H15/H13a, which indicated a 1,3-diaxial relationship of these protons, though the size of $J_{H14a–H15}$ and $J_{H14b–H15}$ could not be measured due to the chemical shift equivalence of H14a and H14b.

Model **3** was synthesized from known **28**[16] (Scheme 4). The protection of **28** as a TBS ether (99%), followed by modified Wacker oxidation,[17] afforded **30** (93%), which was converted to **31** (87%, 2 steps) through enol triflate formation and the subsequent Sonogashira reaction[18] with propargyl alcohol. Enyne **31** was transformed to **33** (88%, 2 steps) via reduction and protection with TBDPSCl. The removal of the acetonide of **33** (77%) and stepwise selective DMB protection (79%, 2 steps) produced **34**, which was oxidized with TPAP/NMO to afford **13**.[13] NHK coupling of **13** with (***R***)-**10b** efficiently furnished **35** (78%) along with a small amount of its diastereomer (5%).[6] The stereochemistry at C7 of **35** was determined by the NMR analysis of **44** derived from **35**, in which large values of $J_{H5–H6}$ and $J_{H6–H7}$ (both showed 11.2 Hz) and an NOE enhancement between 1,3-diaxial protons H5 and H7 were observed (Fig. 3). Thus, the stereocenter C7 of **35** was successfully constructed by a substrate-control in the NHK reaction step. Alcohol **35** was converted to **38** via TBS protection (85%), TBDPS deprotection (88%),[19] and Katsuki–Sharpless asymmetric epoxidation (96%).[20] The treatment of **38** with $Et_2O{\cdot}BF_3$ successfully constructed the A-ring, and the resulting diol **39** was protected as an isopropylidene acetal to give **40** (80%, 2 steps). After the removal of the NAP group of **40** (98%), the resulting **41** was oxidized to **12**. Iodide (***R***)-**8** was successfully coupled with **12** under NHK conditions[6] to give **42**, which was oxidized to **43** (68% from **41**). The removal of the TBS group from **43** and the subsequent treatment with CSA furnished **3** as a single isomer (94%, 2 steps).

The stereochemistry of **3** was confirmed by NMR analysis. The NOE enhancement of H2/H6, showing the *cis*-relationship of H2 and H6, verified the C2-configuration on the basis of the known C6 stereochemistry. The NOE correlations of H7/H15, C12=CH/H10b, and C12=CH/H9 also established the double anomeric spiroacetal structure of the BC-ring with (11*S*)-configuration. The presence of a chair–boat interconversion equilibrium in the B-ring was suggested from the coexistence of the NOE correlations of C9–Me/H7 and C12=CH/H9, which indicated a 1,3-diaxial relationship of C9–Me and H7 and a close proximity of C12=CH and H9 in a boat conformation, respectively, as well as the deviations of the coupling constants $J_{H9–H10a}$ (7.4 Hz) and $J_{H9–H10b}$ (5.9 Hz) from the normal ^3J values (2–3 Hz) of equatorial–axial or equatorial–equatorial protons. The large $J_{H14a–H15}$ (10.6 Hz) and small $J_{H14b–H15}$ (3.9 Hz) indicated the chair conformation of the C-ring of **3**.

The chemical shifts of **1** significantly deviated from those of both **2** and **3**, partly due to the difference of substituents at C2 and C15 of **1** from those of either model. Therefore, the structural similarity of **1** to **2** or **3** was assessed from the similarity of the NOE correlations and the coupling constants. The reported NOE correlation of H7/H15 in **1** was also observed in each model. Although



Scheme 4. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 99%; (b) $PdCl_2$, $Cu(OAc)_2$, O_2, $AcNMe_2$–H_2O (7:1), 23 °C, 93%; (c) $PhNTf_2$, KHMDS, THF, −78 °C, 87%; (d) propargyl alcohol, $PdCl_2(PPh_3)_2$, CuI, $BuNH_2$, PhMe, 23 °C, ~100%; (e) Red-Al, Et_2O, −20 °C, 90%; (f) TBDPSCl, imidazole, CH_2Cl_2, 23 °C, 98%; (g) AcOH–THF–H_2O (3:1:1), 55 °C, 77%; (h) 3,4-dimethoxybenzaldehyde, CSA, reflux, 90%; (i) DIBAH, Et_2O, −78 °C, 88%; (j) TPAP, NMO, MS4A, CH_2Cl_2, 23 °C; (k) (***R***)-**10b**, $CrCl_2$, $NiCl_2$, DMSO, 23 °C, 78% (2 steps); (l) TBSOTf, 2,6-lutidine, DMAP, CH_2Cl_2, 23 °C, 85%; (m) TBAF, AcOH, THF, 23 °C, 88%; (n) (+)-DET, TBHP, $Ti(iOPr)_4$, MS4A, CH_2Cl_2, −20 °C, 96%; (o) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; (p) 2,2-dimethoxypropane, PTS·H_2O, 0 °C, 80% (2 steps); (q) DDQ, wet CH_2Cl_2, 23 °C, 98%; (r) DMPI, CH_2Cl_2, 23 °C; (s) (***R***)-**8**, $CrCl_2$, $NiCl_2$, DMSO, 23 °C; (t) DMPI, CH_2Cl_2, 23 °C, 68% (3 steps from **41**); (u) TASF, DMF, 23 °C; (v) CSA, CH_2Cl_2, 0 °C, 94% (2 steps).

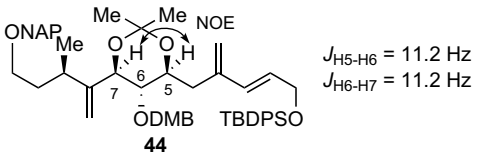
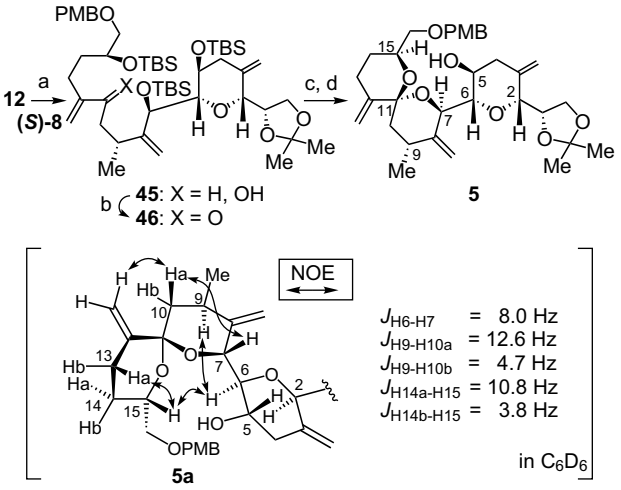


Fig. 3.

the NOE enhancement of H15/C9–CH_3 was absent in both models in contrast to its presence in **1**, the intermediate values of $J_{H9–H10a}$ and $J_{H9–H10b}$ of **1** (both 6.8 Hz) were more similar to those of **3** ($J_{H9–H10a}$ = 7.4 Hz, $J_{H9–H10b}$ = 5.9 Hz) than those of **2** ($J_{H9–H10a}$ = 11.7 Hz, $J_{H9–H10b}$ = 4.3 Hz). The value of $J_{H6–H7}$ of **1** (8.6 Hz, Fig. 1) was also similar to that of **3** (7.7 Hz) and quite different from that of **2** (1.7 Hz). Therefore, the stereochemical relationship between the A- and B-rings of **1** was presumed to be the same as that of **3**.[21] Although the value of $J_{H14a–H15}$ of **1** (9.1 Hz) was similar to that of **3** (10.6 Hz), $J_{H14b–H15}$ of **1** (6.7 Hz) clearly deviated from that of **3** (3.9 Hz). Therefore, it was suspected that the stereochemistry at C15 of **1** was different from that of **3**. Hence, we next attempted to synthesize model **4**, the C15-epimer of **3**, for the confirmation of the above possibility.

Although we applied the above established route to the synthesis of **4**, the produced spiroacetal was **5**, the (11*R*)-epimer of **4** (Scheme 5). Aldehyde **12**, prepared from **41** by Dess–Martin oxidation,[10] was successfully reacted with iodide (***S***)-**8** under NHK conditions[6] to give **45**, which was oxidized to **46** (85% 3 steps from **41**). The removal of the TBS from **46**, followed by the treatment with CSA, furnished **5** as a single isomer (68%, 2 steps).

The stereochemistry of **5** was confirmed by NMR analysis. The chair B-ring with equatorial C9–Me and axial C6 was determined by a large $J_{H9–H10a}$ (12.6 Hz), a small $J_{H9–H10b}$ (4.7 Hz), and the NOE enhancement of H6/H9.



Scheme 5. Reagents and conditions: (a) (***S***)-**8**, $CrCl_2$, $NiCl_2$, DMSO–THF (3:1), 23 °C; (b) DMPI, CH_2Cl_2, 23 °C, 85% (3 steps from **41**); (c) TASF, DMF, 23 °C; (d) CSA, CH_2Cl_2, 0 °C, 68% (2 steps).

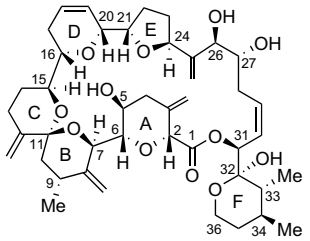


Fig. 4. Absolute configuration of **1** proposed by Sasaki.

The NOE interaction of H7/H10a may suggest distortion of the chair conformer at C7 or some contribution of a boat-conformer with C7 prow and C10 stern due to the 1,3-diaxial repulsion between C6 and an axial oxygen at C11. The chair C-ring was also confirmed by a large $J_{H14a–H15}$ (10.8 Hz), a small $J_{H14b–H15}$ (3.8 Hz), and the NOE enhancement of H13a/H15. The NOE correlations of H6/H15 and C12═CH/H10a established the double anomeric structure of the BC-ring with (11*R*)-configuration. Because these NMR data disagreed with those of **1**,[1] the relative configuration of the BC-ring of **1** must not be 6*S**,7*R**,9*R**,11*R**,15*S**. Interestingly, the $J_{H6–H7}$ value of **5** (8.0 Hz) was quite similar to those of **3** and **1** (7.7 Hz and 8.6 Hz).

We found that model **4** was not detected during the formation of **5** from a common ketodiol substrate, derived from **46**, under acid-catalyzed spiroacetalization conditions. Sasaki, however, proposed the absolute configuration of **1** (Fig. 4),[5] in which the ABC-ring possessed the same stereochemistry as **4**. It is notable that the BC-ring of **1** exists in a form that has been proven to be thermodynamically unstable in a non-macrocyclic system. The presence of the macrocyclic framework of **1** would make the (11*R*)-isomer of the BC-ring (corresponding to **5**) more constrained than the (11*S*)-isomer (corresponding to **4**), and this constraint would invert the relative stability of the (11*R*)- and (11*S*)-isomers. In this study, we could not prove the true stereochemistry of the ABC-ring by model synthesis, but the above finding would be important for designing a synthesis of **1** and suggests that the stereoselective construction of the BC-ring would be successful in the presence of the macrolactone framework.

In conclusion, three stereoisomeric model compounds, (2*R*,5*S*,6*S*,7*S*,9*S*,11*R*,15*S*)-, (2*R*,5*S*,6*S*,7*R*,9*R*,11*S*,15*R*)-, and (2*R*,5*S*,6*S*,7*R*,9*R*,11*R*,15*S*)-isomers (**2**, **3**, and **5**, respectively), for the ABC-ring of **1** were stereoselectively synthesized by using a Nozaki–Hiyama–Kishi reaction as a key step. It was also found that a (2*R*,5*S*,6*S*,7*R*, 9*R*,11*S*,15*S*)-isomer (**4**), corresponding to the absolute configuration of **1** recently proposed by Sasaki, was not detected during the formation of **5** from a common ketodiol substrate under acid-catalyzed spiroacetalization conditions. This would be attributable to the absence of a macrocyclic framework. Further studies toward the total synthesis of **1** are in progress in our laboratory.

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Supplementary data

Supplementary data (spectral data of compounds **2**, **3**, and **5**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.082.

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21. We justified the comparison of macrocyclic **1** to non-macrocyclic models **2** and **3** as follows. If **1** assumes the same stereochemical relationship between the A- and B-rings as **2** with an *anti*-relationship between H6 and H7 in the macrolide framework, the B-ring should transform itself to relieve the severe steric repulsion between C5–OH and C8=CH_2 and show different NMR behavior than the B-rings of non-macrocyclic models **2** and **3**. However, natural compound **1**, in fact, displays quite similar values of $J_{H9–H10a}$ and $J_{H9–H10b}$ to **3**, which suggests the B-ring of **1** does not have a distorted conformation. Therefore, it was thought that **1** possesses the same stereochemical relationship between the A- and B-rings as **3** even within the macrolide framework. This conclusion is now supported by the absolute stereochemistry of **1** proposed by Sasaki.