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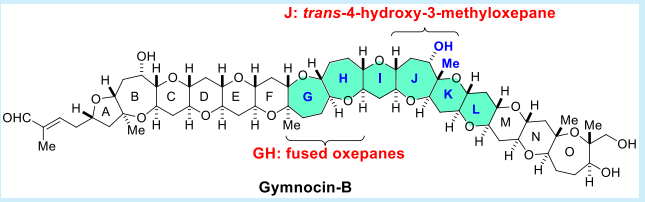
Synthesis of the GHIJKL Fragment of Gymnocin-B

Takeo Sakai,* Hideaki Sakakibara, Yumi Omoto, Marina Tsunekawa, Yoshinori Hadano, Shota Kato, and Yuji Mori*

Faculty of Pharmacy, Meijo University, 150 Yagotoyama, Tempaku-ku, Nagoya 468-8503, Japan

Supporting Information

ABSTRACT: The GHIJKL fragment of gymnocin-B was synthesized using the oxiranyl anion strategy. The first highlight of the synthesis is the bromoketone cyclization reaction on the oxepane ring to construct the fused bisoxepane GH ring. The second key step is the introduction of the *trans*-4-hydroxy-3-methyloxepane J ring via addition of trimethylaluminum to a conjugated oxonium moiety, followed by diastereoselective epoxidation and regioselective reduction.



Red tide is a bloom of algae that seriously damages the fishing industry by causing fish poisoning and massive fish death. Gymnocin-A and -B are naturally occurring polycyclic ethers[1,2] isolated from cultures of a harmful red-tide dinoflagellate, *Karenia mikimotoi*, which have potent cytotoxicities against mouse leukemia cells P388 (IC_{50} 1.4 and 1.7 μg/mL for gymnocin-A and B, respectively, Figure 1).[3,4] The two

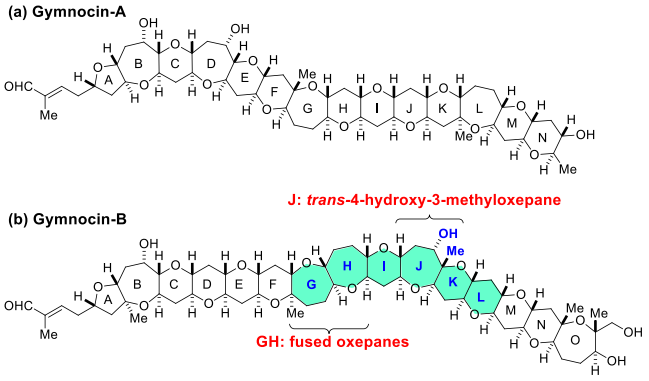


Figure 1. (a) Structure of gymnocin-A. (b) Gymnocin-B and key structural moiety in the GHIJKL system.

gymnocins are structurally similar in terms of the 2-methyl-2-butenal side chains and the ABC ring system, except for the presence of an angular methyl at the AB bridge head in gymnocin-B. Meanwhile, the ring system of the remaining part (D−O) of gymnocin-B is completely different from that of gymnocin-A. Several synthetic studies have been reported thus far for gymnocin-A,[5] and total synthesis of gymnocin-A has been accomplished by two groups including ours.[6] Synthesis of gymnocin-B is more challenging due to its longer and more complex structure. Particularly, a pentadecacyclic system (A−O) is the second longest consecutive cyclic ether skeleton among polycyclic ether natural products, after the octadecacyclic system in brevisulcenal-F.[7] Gymnocin-B involves many characteristic oxepane rings, specifically a bisoxepane system for the GH rings, *trans*-4-hydroxy-3-methyloxepane for the J ring, and 2,7-dimethyloxepane for the O ring. Thus far, a synthetic study of gymnocin-B was reported by Tsukano and Sasaki on the NO ring system.[8] Just recently, the first total synthesis has been published by Sittihan and Jamison.[9] Synthesis of the middle part of gymnocin-B is particularly important because the *trans*-4-hydroxy-3-methyloxepane motif is only present in extremely large polycyclic ethers like gymnocin-B and brevisulcenal-F.[7] Thus, development of an efficient method for the construction of the J ring system is key for the synthesis of gymnocin-B.[10] Therefore, we started our synthetic study of the GHIJKL fragment, which involves the key fused bisoxepane GH and the *trans*-4-hydroxy-3-methyloxepane J systems.

Retrosynthetic analysis of the GHIJKL fragment **1** was carried out using the oxiranyl anion strategy (Scheme 1).[11] The K ring and the JK angular methyl group were planned to be introduced via methyl anion addition to the oxonium cation generated from the α-hydroxy ketone **2** as the last stage of the synthesis, which is a key in the present synthesis. The ketone **2** would be planned to be prepared by coupling between the L-ring epoxy sulfone **3** and the GHI triflate **4** in which the HI system would be constructed by the ring expansion of the six-membered ketone **5** followed by the reductive etherification. Cyclization of bromoketone **6** on an oxepane ring to a *trans*-fused 7−6 system **5** is the next important task in our strategy. The bromoketone **6** would be synthesized from an epoxy sulfone **7** and the G-ring triflate **8**. Based on this strategy, we report herein the synthesis of the GHI and IJK systems and the GHIJKL fragment **1** of gymnocin-B.

The synthesis began with preparation of the seven-membered triflate **8** (Scheme 2). Diol **9**[12] was protected with the di-*tert*-butylsilylene group, and dithioacetalization of the ethyl acetal group provided the dithiane alcohol **10**. Conjugate addition of the alcohol to ethyl propiolate afforded

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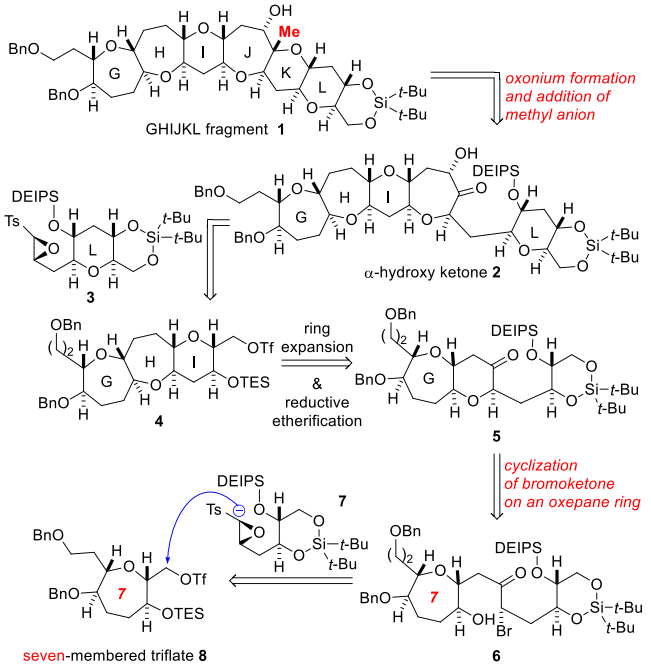
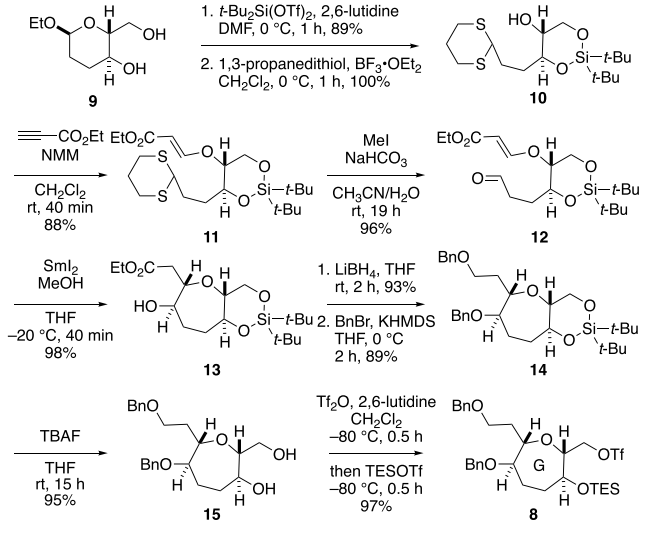
Scheme 1. Retrosynthetic Analysis of the GHIJKL Fragment 1 and Synthetic Key Points



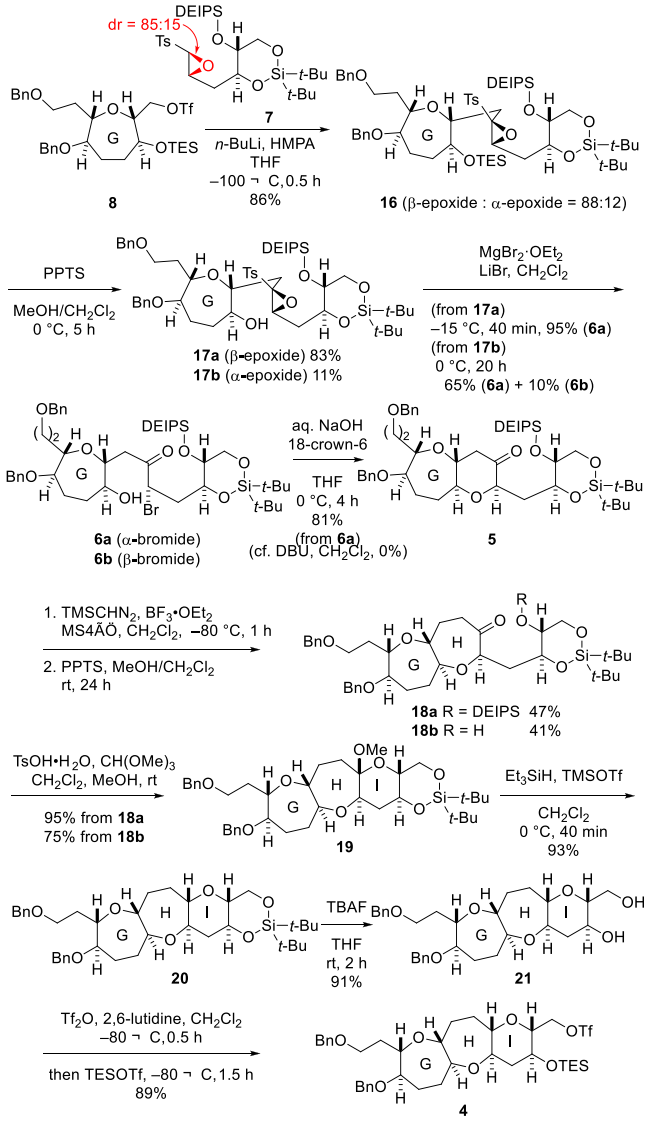
Scheme 2. Synthesis of the Seven-Membered Triflate 8



the unsaturated ester **11**. The dithiane group was removed using methyl iodide to afford aldehyde **12**, which was subjected to ketyl radical cyclization[13] to obtain the seven-membered hydroxy ester **13**. The ester was reduced, and the resulting diol was protected with benzyl bromide to give the dibenzyl ether **14**. The seven-membered triflate **8** was obtained in good yields after demasking the di-*tert*-butylsilylene group and one-pot triflation−triethylsilyl (TES) protection.

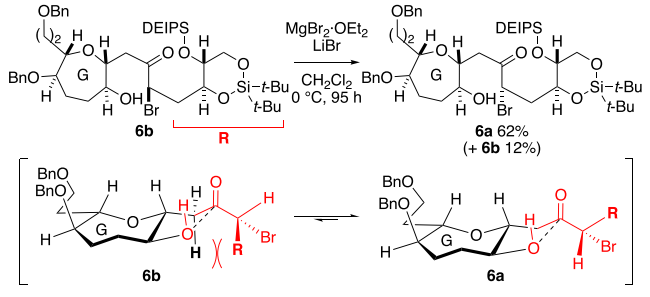
The oxiranyl anion coupling between alkyl triflate **8** and epoxy sulfone **7**[5e] was achieved in good yields, with the diastereomeric ratio of the starting epoxy sulfone retained (Scheme 3). After removal of the TES group of **16** with PPTS, the stereoisomers *β*-epoxide **17a** and *α*-epoxide **17b** were separated. We first examined the $MgBr_2$-mediated bromoketone synthesis from the major *β*-epoxide **17a** to afford bromoketone **6a** in good yields after 40 min at −15 °C.

Scheme 3. Synthesis of the GHI Triflate 4



Interestingly, treatment of the minor *α*-epoxide **17b** with $MgBr_2{\cdot}OEt_2$ also provided the same bromoketone **6a** predominantly after 20 h at 0 °C. The isomeric bromoketone **6b** was obtained in only 10% yield because **6b** underwent the isomerization to the more stable *α*-bromide **6a** by exposure to $MgBr_2{\cdot}OEt_2$ (Scheme 4). Based on a conformational analysis of a model compound of **6a**,[14] a plausibly stable conformation of the major **6a** involves 5-membered coordination between a hydroxy group and a ketone. The dihedral angle between the

Scheme 4. Isomerization from 6b to 6a



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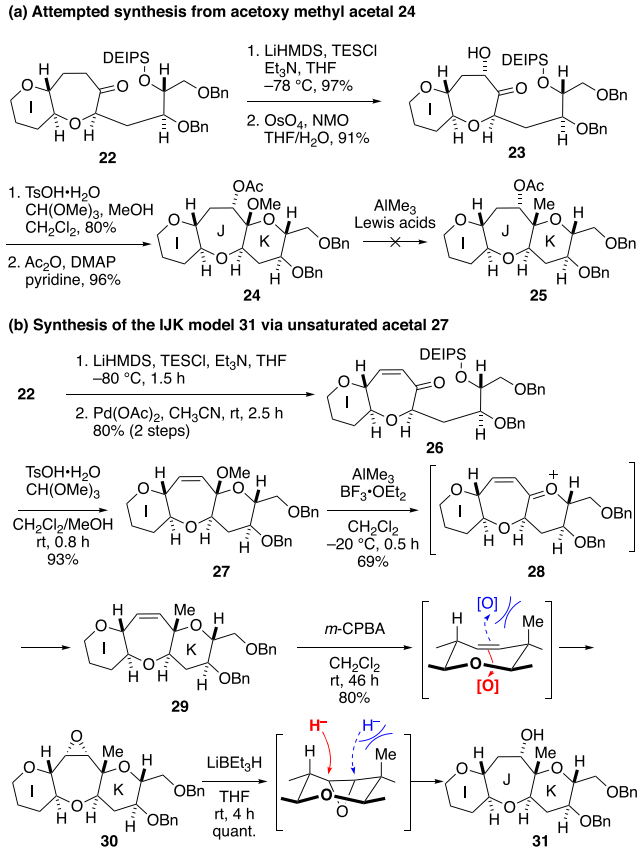
C−Br and the C═O bond is nearly 120 degrees because of the orbital interactions.[15] While the major bromoketone **6a** did not include any major strain in the conformation, the minor **6b** has a severe 1,3-repulsion between a carbonyl α-hydrogen and the group R, i.e., the (1,3,2-dioxasilinan-4-yl)methyl moiety.

Attempting the cyclization of **6a** with DBU in CH_2Cl_2 according to the reported method for the construction of the 6−6 membered ring system[11b] led to a complex mixture with no cyclization product, possibly due to the slow cyclization on the flexible oxepane ring. To our delight, the bromoketone **6a** was cyclized smoothly to the six-membered ketone **5** under aqueous conditions using NaOH and 18-crown-6,[5d] which can be explained by the solvent effect. In water, pK_a values of ketones are slightly higher than those of alcohols (in H_2O, 20 for acetone and 15.5 for methanol), whereas ketones are slightly more acidic than alcohols in aprotic solvents (for example, in DMSO, pK_a for acetone and methanol are 26.5 and 29.0, respectively).[16] We assume that the deprotonation of alcohol occurred before enolization, leading to byproduct formation. The bromoketone epimer **6b** did not cyclize even under aqueous conditions with NaOH, owing to the formation of α-hydroxy ketone (54%) by an intermolecular substitution with an OH anion.[5d] The six-membered ketone **5** was subjected to trimethylsilyldiazomethane ($TMSCHN_2$)-mediated ring expansion[17] to afford the seven-membered α-silyl ketone including a bisoxepane structure of the GH ring. PPTS-mediated desilylation afforded an approximately 1:1 mixture of ketone **18a** and hydroxy ketone **18b**. Both products were subjected to methyl acetalizaton under acidic conditions to afford the methyl acetal **19**. Reductive etherification with TMSOTf and triethylsilane afforded the tricyclic compound **20**. Silylene deprotection with TBAF to the diol **21**, followed by one-pot triflation−TES protection, afforded the GHI triflate **4**.

We next focused on the method for the synthesis of the *trans*-4-hydroxy-3-methyloxepane core in the J ring using a model seven-membered ketone **22** (Scheme 5(a)). First, **22** was subjected to α-oxidation to afford the α-hydroxy ketone **23** diastereoselectively.[6b] Removal of the diethylisopropylsilyl (DEIPS)[18] group provided a hydroxy methyl acetal that was acetylated to form acetoxy methyl acetal **24** in good yield. Introduction of the angular methyl group failed, and the desired product **25** was not obtained at all even after screening of different methyl anion reagents and Lewis acids.[19] $Zn(OTf)_2$-catalyzed thioacetalization[20] of **24** with ethanethiol yielded only a complex mixture.

This failure was attributed to the slow formation of the oxonium intermediate from acetoxy methyl acetal **24**. Thus, methyl addition to a stable conjugated oxonium **28** was examined in the next synthetic plan (Scheme 5(b)). The seven-membered ketone **22** was subjected to Saegusa oxidation[21] to furnish a conjugated ketone **26**. One-pot DEIPS deprotection and methyl acetalization provided the unsaturated methyl acetal **27**, which was then treated with trimethylaluminum in the presence of $BF_3{\cdot}OEt_2$. To our delight, the conjugated oxonium **28** formation followed by the addition of a methyl group advanced efficiently at −20 °C to afford the desired methyl adduct **29** in good yield within 10 min.[22] The alkene functionality in **29** was oxidized using *m*-CPBA to afford the α-epoxide **30** predominantly because the oxidant selectively approached from the α-face, avoiding the steric repulsion of the angular methyl group. The IJK skeleton

Scheme 5. Model Study for Construction of the JK System



31 was completed after superhydride reduction of the epoxide **30** from the less hindered I-ring side.

With the method for the construction of the JK-ring system in hand, we started to assemble the GHIJKL fragment **1** (Scheme 6). Oxiranyl anion coupling with the tricyclic triflate **4** and the L-ring epoxy sulfone **3** gave the coupling product **32** in high yield. The TES group was selectively deprotected by CSA treatment in ethanol, where the DEIPS and di-*tert*-butylsilylene protections remained intact. Bromoketone synthesis and DBU-mediated cyclization afforded the six-membered ketone **35**. Ring expansion furnished the α-silyl ketone **36**, which was subjected to a 1,3-Brook rearrangement[23] to afford TMS enol ether **37**. Enone **38** was obtained in good yield over three steps after Saegusa oxidation[21] of the silyl enol ether. Acid treatment in the presence of trimethyl orthoformate afforded methyl acetal **39**. The conjugated oxonium formation−methyl addition sequence was performed in the presence of trimethylaluminum and TMSOTf to afford **40** in good yield. The reaction with $BF_3{\cdot}OEt_2$ instead of with TMSOTf resulted in low yield, possibly because of the lower Lewis acidity of $BF_3{\cdot}OEt_2$ than TMSOTf for oxonium formation from the large heptacyclic system **39**. The *m*-CPBA oxidation of **40** provided epoxide **41** with exclusive diastereoselectivity. Finally, regioselective reduction of the epoxide completed the synthesis of the GHIJKL fragment **1**.

In conclusion, we have achieved the synthesis of the GHIJKL middle fragment of gymnocin-B using the oxiranyl anion strategy. The key GH bisoxepane structure was effectively constructed; both diastereomeric epoxy sulfones converged to the desirable α-bromide **6a**, which underwent cyclization to afford the six-membered ketone **5**, which is the

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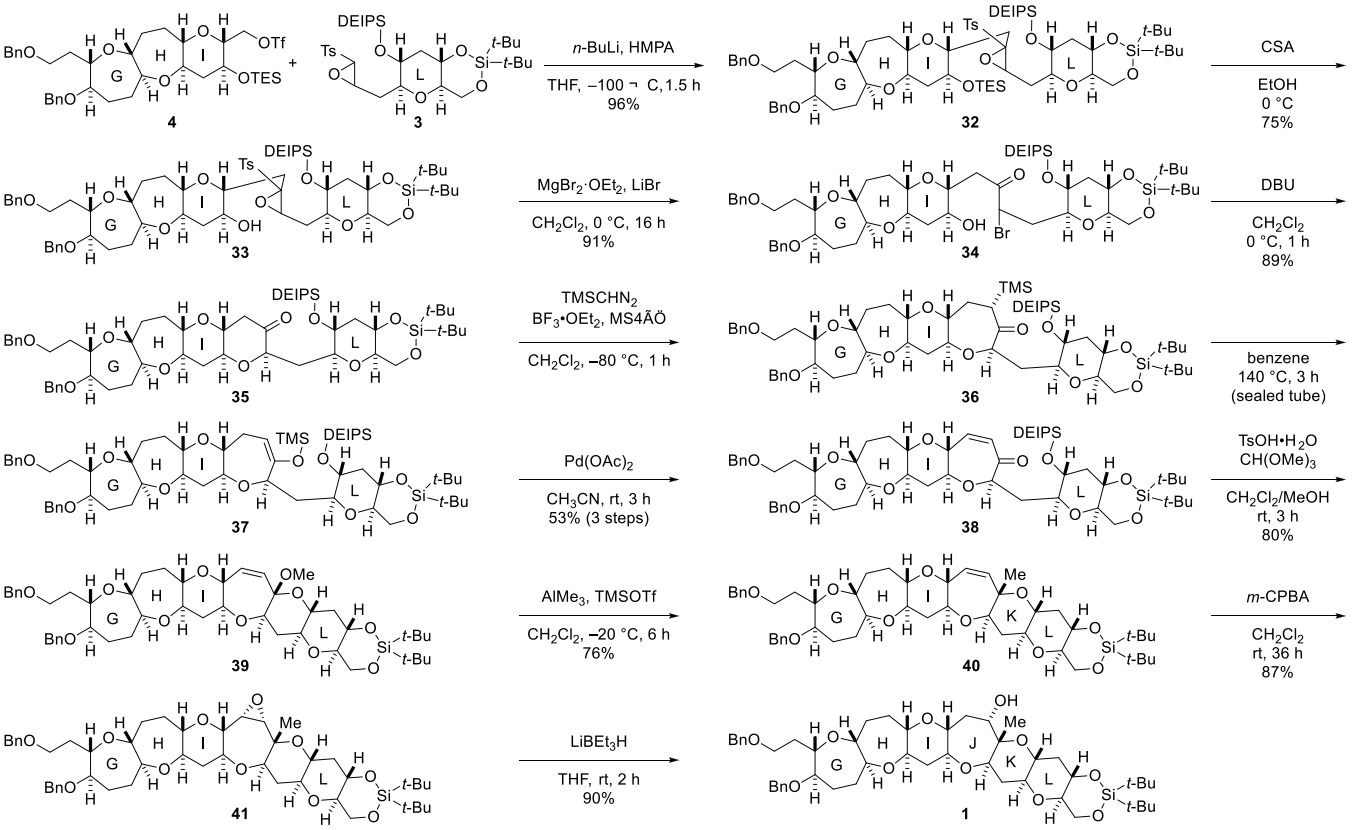
Scheme 6. Synthesis of the GHIJKL Fragment 1



key intermediate for forming the tricyclic GHI triflate **4**. The angular methyl group at the JK bridgehead was introduced via methyl anion addition to the conjugated oxonium generated from the unsaturated methyl acetal **39**. Stereoselective epoxidation and regioselective reduction furnished the *trans*-4-hydroxy-3-methyloxepane J ring system. Further synthetic study toward the total synthesis of gymnocin-B is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02502.

Experimental procedures, preparation of **3** and **22**, spectral data, comparison of ^{1}H and ^{13}C spectra between the GHIJKL fragment **1** and gymnocin-B, and computational conformational analysis for bromoketones **6** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: sakait@meijo-u.ac.jp.
*E-mail: mori@meijo-u.ac.jp.

ORCID

Takeo Sakai: 0000-0002-9006-8249

Notes

The authors declare no competing financial interest.

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