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Synthetic Studies on Gambieric Acids, Potent Antifungal Polycyclic Ether Natural Products: Reassignment of the Absolute Configuration of the Nonacyclic Polyether Core by NMR Analysis of Model Compounds

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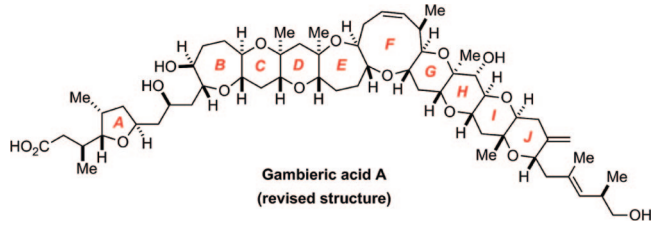

A highly stereocontrolled, convergent synthesis of the A/B-ring fragment of gambieric acids (GAs) has been developed on the basis of (i) a Suzuki−Miyaura coupling of the C1−C6 alkylborate and the C7−C17 vinyl iodide and (ii) a diastereoselective haloetherification for the construction of the A-ring tetrahydrofuran as key steps. Inspection of the ^{1}H and ^{13}C NMR chemical shifts of the synthesized A/B-ring model compounds led to a stereochemical reassignment of the absolute configuration of the polycyclic ether core of GAs. This structure revision was further supported by a synthesis of the A/BC-ring model compound of gambieric acid B and a comparison of its ^{1}H and ^{13}C NMR data with those of the natural product.

Introduction

Since the structure elucidation of brevetoxin B by Nakanishi and co-workers more than two decades ago, the synthetically challenging molecular architectures and the potent and diverse biological activities of marine polycyclic ether natural products have continued to stimulate the interests of chemists and biologists.[1,2] Gambieric acids A−D (GAA−GAD, Figure 1), secondary metabolites of the ciguatera causative dinoflagellate *Gambierdiscus toxicus*, represent formidable synthetic targets due to the enormous molecular architecture comprised of the B−J-ring nonacyclic polyether core arranged with a complex side chain containing the A-ring tetrahydrofuran. The gross structure, including the relative stereochemistry of the polycyclic ether domain, was established by Nagai, Yasumoto, and co-workers based on extensive 2D-NMR analysis.[3] Subsequently, the relative stereochemistry of the unassigned portions and the absolute configuration were determined by using the modified Mosher's method, conformational analysis based on $^{3}J_{H,H}$ values and NOE correlations, and chiral fluorimetric HPLC analysis.[4] It has been reported that gambieric acids exhibit extraordinary antifungal activity against *Aspergillus niger*, which is approximately 2000 times more potent than that of amphotericin B, with minimal toxicity against mammals.[5] Additionally, a possible role of GAA as an endogenous growth regulator of *G. toxicus* has been reported on the basis of the observation that GAA enhances the cell concentration of the dinoflagellate in a

(1) For reviews of marine polycyclic ether natural products, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909. (b) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3–18. (c) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, 293−314. (d) Yasumoto, T. *Chem. Rec.* **2001**, *1*, 228–242.

(2) For recent reviews of the synthesis of polycyclic ethers, see: (a) Marmsäter, F. P.; West, F. G. *Chem.−Eur. J.* **2002**, *8*, 4346–4353. (b) Evans, P. A.; Delouvrie, B. *Curr. Opin. Drug Discov. Dev.* **2002**, *5*, 986–999. (c) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379–4405. (d) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314–4347. (e) Fuwa, H.; Sasaki, M. *Curr. Opin. Drug Discov. Dev.* **2007**, *10*, 784–806. (f) Sasaki, M.; Fuwa, H. *Nat. Prod. Rep.* **2008**, *25*, 401–426. (g) Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7182–7225.

(3) (a) Nagai, H.; Torigoe, K.; Satake, M.; Murata, M.; Yasumoto, T.; Hirota, H. *J. Am. Chem. Soc.* **1992**, *114*, 1102–1103. (b) Nagai, H.; Murata, M.; Torigoe, K.; Satake, M.; Yasumoto, T. *J. Org. Chem.* **1992**, *57*, 5448–5453.

(4) Morohashi, A.; Satake, M.; Nagai, H.; Oshima, Y.; Yasumoto, T. *Tetrahedron* **2000**, *56*, 8995–9001.

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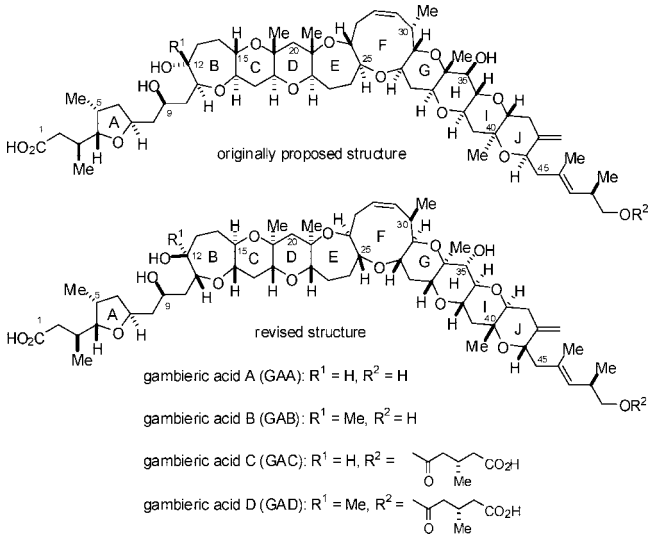


FIGURE 1. Proposed and revised structures of gambieric acids.

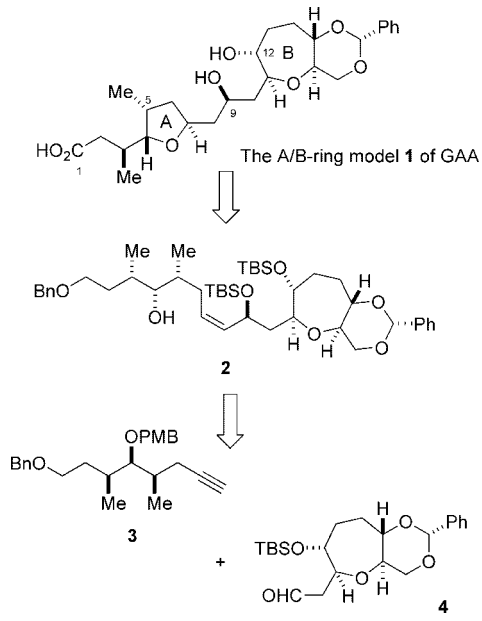
dose dependent manner with inhibition at higher concentrations.[6] Inoue et al. reported that GAA competitively inhibits the binding of the tritiated dihydrobrevetoxin B [^{3}H]PbTx-3 to site 5 of the voltage-sensitive sodium channels of excitable membranes, although the affinity is substantially weaker than that of brevetoxins and ciguatoxins.[7] These intriguing biological activities coupled with their synthetically formidable molecular architecture have engendered significant interests of the synthetic community.[8−12] Herein, we describe our first- and second-generation approaches toward the stereocontrolled synthesis of the A/B-ring fragment of GAs, along with the structure analyses of the synthetic fragments based on NMR spectroscopy, which culminated in a stereochemical reassignment of the absolute configuration of the nonacyclic polyether domain of GAs.[13]

Results and Discussion

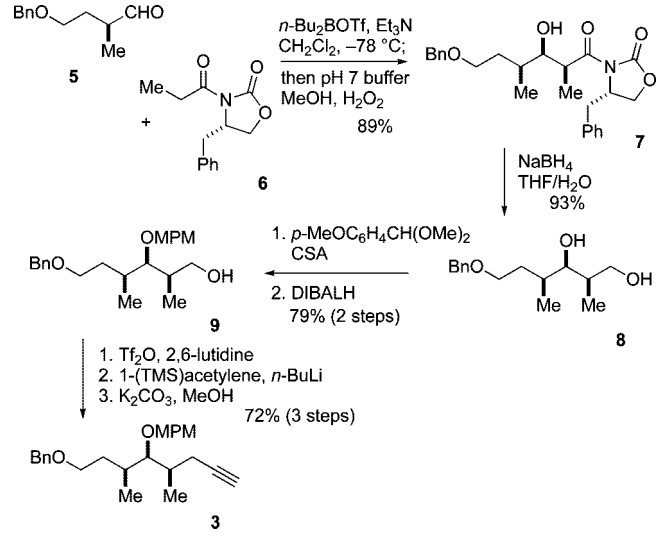
Initial Approach toward the A/B-Ring Fragment of GAA Based on an Acetylide/Aldehyde Coupling. We initially envisioned the synthesis of the A/B-ring model compound **1** of GAA as summarized in Scheme 1. In this plan, the A-ring tetrahydrofuran of **1** was retrosynthetically dissected to hydroxy alkene **2** on the basis of a diastereoselective bromoetherification. The hydroxy alkene **2** was, in turn, planned to be synthesized by coupling of a lithium acetylide derived from alkyne **3** and aldehyde **4**.

The synthesis of alkyne **3** commenced with a *syn*-aldol reaction of aldehyde **5**,[14] readily prepared from (*R*)-Roche ester,

SCHEME 1. Initial Synthesis Plan for the A/B-Ring Model Compound 1 of GAA



SCHEME 2. Synthesis of Alkyne 3



with *N*-propionyl-(*S*)-benzyl-2-oxazolidinone (**6**) under the Evans conditions,[15] giving alcohol **7** in 89% yield as a single stereoisomer, as judged by 500 MHz ^{1}H NMR (Scheme 2). Removal of the chiral auxiliary of **7** using sodium borohydride in aqueous THF[16] led to diol **8** in 93% yield. After protection of **8** as its *p*-methoxybenzylidene acetal, its regioselective cleavage using DIBALH cleanly afforded alcohol **9** in 79% yield for the two steps. Triflation followed by displacement with a lithium acetylide derived from 1-(trimethylsilyl)acetylene and *n*-BuLi, and subsequent removal of the trimethylsilyl group gave alkyne **3** in 72% yield for the three steps.

The synthesis of aldehyde **4** started with reduction of the known lactone **10**[17] using lithium aluminum hydride followed

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(7) Inoue, M.; Hirama, M.; Satake, M.; Sugiyama, K.; Yasumoto, T. *Toxicon* **2003**, *41*, 469–474.
(8) (a) Kadota, I.; Oguro, N.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 3645–3647. (b) Kadota, I.; Takamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 3649–3651.
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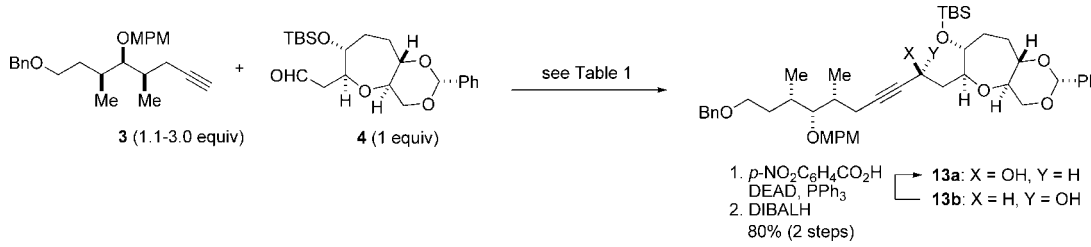
(16) Prashad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067–7070.
(17) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983–14992.

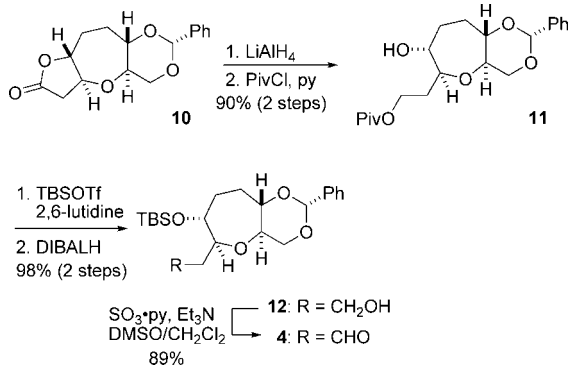
TABLE 1. Acetylide/Aldehyde Coupling for the Assembly of 3 and 4[a]



				yields[c] (%)		
entry	base[b]	**3** (equiv)	conditions	**13a**	**13b**	recovered **4**
1	*n*-BuLi	1.1	THF, −78 to 0 °C	28	16	0
2	*n*-BuLi	2.0	THF, −78 °C	38	20	25
3	*n*-BuLi	3.0	THF, −78 °C	44	29	13
4	*n*-BuLi	1.1	THF/HMPA, −78 °C	decomposed		
5	EtMgBr	1.1	THF, −60 °C to rt	no reaction		
6	*n*-BuLi/$CeCl_3$	2.0	THF, −78 °C	22	12	45

[a] All reactions were carried out by first treating **3** with base for 30 min at the indicated conditions followed by addition of **4**. [b] 0.9 equiv of base relative to **3** was used. [c] Isolated yields after purification by flash column chromatography on silica gel.

SCHEME 3. Synthesis of Aldehyde 4



by selective protection of the primary alcohol of the derived diol, giving pivalate **11** in 90% yield for the two steps (Scheme 3). Protection of the remaining secondary alcohol as the *tert*-butyldimethylsilyl (TBS) ether followed by reductive cleavage of the pivalate with DIBALH led to alcohol **12** in 98% yield for the two steps. Oxidation of the alcohol **12** afforded aldehyde **4** in 89% yield.

With the requisite fragments in hand, we then focused our attention on their assembly and the construction of the A-ring. We examined the coupling of a lithium acetylide derived from alkyne **3** and aldehyde **4** in detail (Table 1). By using 1.1 equiv of alkyne **3** and *n*-BuLi in THF at −78 to 0 °C, a mixture of diastereomers **13a** and **13b** was obtained in moderate yield (28% and 16% yields, respectively, entry 1). These diastereomers were separated by flash chromatography on silica gel. Since it was observed that the remainder of aldehyde **4** underwent decomposition upon warming the reaction mixture to 0 °C, the following experiments were performed at −78 °C. When the molar amounts of alkyne **3** and *n*-BuLi were increased to 2 equiv, a slight improvement of the yields of **13a**,**b** was observed (entry 2). Finally, we found that the use of 3 equiv of alkyne **3** and *n*-BuLi was optimal for the present coupling reaction, giving **13a** and **13b** in 44% and 29% yields, respectively (entry 3). The excess alkyne **3** employed in the reaction could be recovered after flash column chromatography on silica gel. Our further attempts including the use of HMPA as a cosolvent or the use of an alkynylcerium reagent or an alkynylmagnesium reagent prepared from alkyne **3** were ineffective for the present case (entries 4−6). Application of the modified Mosher's method[18] to determine the C9[19] stereochemistry of the propargyl alcohol **13a** revealed that the major diastereomer **13a** possessed the desired stereochemistry at C9. The undesired, minor diastereomer **13b** could be converted to the desired **13a** by Mitsunobu inversion[20] followed by reduction of the resultant benzoate (80% yield for the two steps).

Half-reduction of the alkyne of **13a** (H_2, Lindlar catalyst), protection of the C9 hydroxy group as the TBS ether, and cleavage of the *p*-methoxybenzyl (MPM) group afforded hydroxy alkene **2** in 81% yield for three steps (Scheme 4). Upon treatment of **2** with NBS in acetonitrile at room temperature, diastereoselective cyclization of the A-ring[21] was smoothly accomplished via a bromonium cation intermediate, giving rise to bromide **14**, which was immediately reduced under radical conditions to deliver tricyclic compound **15** in 87% yield with a diastereomer ratio of 4:1. The undesired C7 epimer was readily separated by flash column chromatography on silica gel. The stereochemical outcome of the bromoetherification can be explained as illustrated in Figure 2. The major diastereomer **15** would be derived from the transition state A (**TS-A**) after radical reduction, whereas **TS-B** would lead to the corresponding C7 epimer. **TS-A** would be energetically more stable than **TS-B**, since **TS-B** suffers from an unfavorable steric repulsion between the C51 methyl group and the C7−C9 moiety. Hydrogenolysis of the benzyl ether and the benzylidene acetal of **15** followed by reprotection of the 1,3-diol moiety gave alcohol **16** (84% yield for the two steps). A two-stage oxidation of alcohol **16** and subsequent esterification of the derived carboxylic acid delivered methyl ester **17** in 72% yield for the three steps. Finally, deprotection of the silyl groups (TASF, DMF, 84%

(18) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
(19) The numbering of carbon atoms of all compounds in this paper corresponds to that of the natural product.
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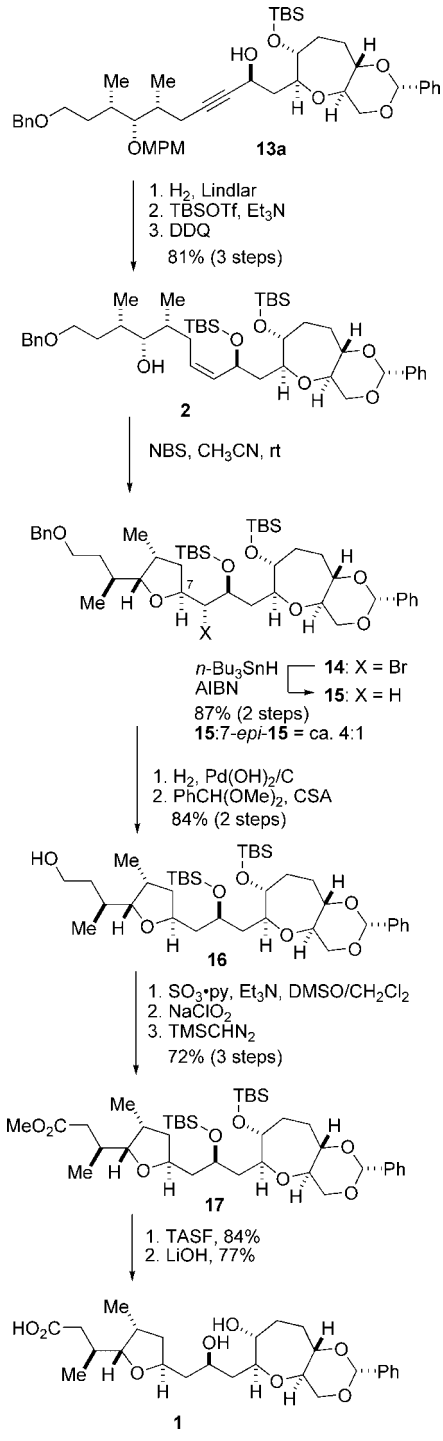
SCHEME 4. Synthesis of an A/B-Ring Model Compound 1 of GAA



yield)[22] and saponification (LiOH, THF/MeOH/H_2O, 77% yield) completed the synthesis of the A/B-ring fragment **1** of GAA.

Unexpectedly, the ^1H and ^{13}C NMR chemical shifts of the synthetic fragment **1** did not match those of the corresponding domain of natural GAA (Table 2). Clearly, the ^1H and ^{13}C NMR data of the C8−C11 moiety of synthetic **1** deviated significantly from those of the parent natural product, which suggested that

(22) (a) Barrett, A. G. M.; Peña, M.; Willardsen, J. A. *J. Org. Chem.* **1996**, *61*, 1082–1100. (b) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436–6437.

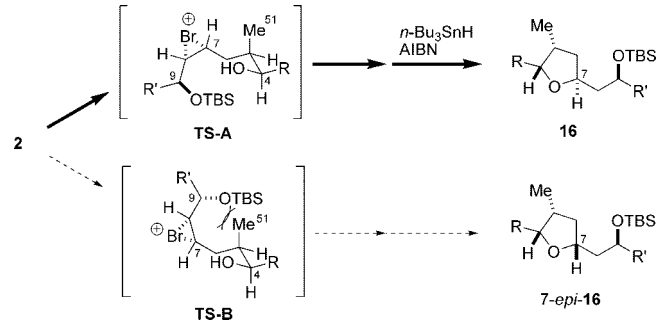


FIGURE 2. Plausible explanation for the stereochemical outcome of the bromoetherification of **2**.

TABLE 2. Deviation of ^1H and ^{13}C NMR Chemical Shifts between Natural GAA and Synthetic Model Compound 1 (1:1 CD_3OD/Pyridine-d_5)[a]

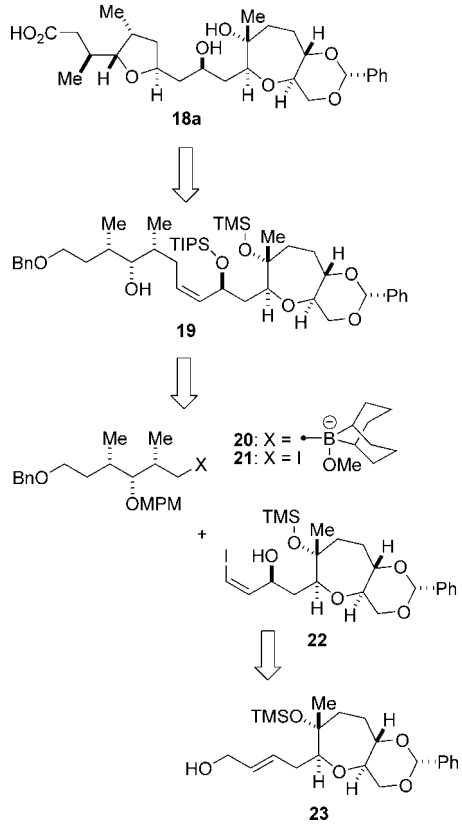
position	^1H NMR [$\Delta(\delta_N-\delta_S)$]	^{13}C NMR [$\Delta(\delta_N-\delta_S)$]
2	0.03	0.6
	−0.01	
3	−0.02	0.1
4	0.01	0.2
5	0.01	0.1
6	0.00	0.0
	0.00	
7	0.02	−0.3
8	−0.06	−1.3
	0.09	
9	0.00	1.3
10	0.20	−0.2
	0.04	
11	−0.26	1.2
12	0.02	−0.3
13	−0.04	0.1
	−0.06	
50	0.03	0.2
51	0.01	0.1

[a] ^1H and ^{13}C NMR spectra of natural GAA and compound **1** were recorded at 400 MHz (100 MHz) and 600 MHz (150 MHz), respectively. Chemical shifts are reported in ppm relative to the internal residual solvent (^1H NMR, CD_2HOD 3.31 ppm; ^{13}C NMR, CD_3OD 49.8 ppm). δ_N and δ_S are chemical shifts of the natural product and synthetic model compound **1**, respectively.

the originally proposed structure of GAA should be reexamined. However, structure analysis of the natural product was prohibited due to the unavailability of the authentic sample as well as its complex NMR spectroscopic data. Since Satake and co-workers have assigned the relative stereochemistry of the A/B-ring moiety and the absolute configuration of the C9 hydroxy group using natural GAB and its derivatives, we turned our attention to the synthesis of an A/B-ring fragment of GAB for further detailed investigation.

Improved Approach toward the A/B-Ring Fragment of GAB Based on a Suzuki−Miyaura Coupling. Our initial synthesis of the A/B-ring fragment **1** of GAA utilized the coupling of a lithium acetylide derived from alkyne **3** and aldehyde **4** as a key fragment assembly process (see Table 1). However, it was necessary to employ a large excess of alkyne **3** to attain an acceptable level of conversion yield. Moreover, the diastereoselectivity of the acetylide/aldehyde coupling was moderate, giving an approximately 1.5:1 mixture of the desired isomer and its epimer. It was necessary to separate these diastereomers by careful flash column chromatography on silica gel and convert the undesired isomer to the desired one by the Mitsunobu inversion/reduction sequence. These impractical

SCHEME 5. Synthesis Plan for an A/B-Ring Model Compound 18a of GAB via Suzuki−Miyaura Coupling



aspects of the fragment assembly process were significant drawbacks for material throughput, which prompted us to devise a more efficient synthetic approach toward the A/B-ring fragment of GAB.

We envisioned that hydroxy alkene **19**, a key precursor for the diastereoselective bromoetherification, could be synthesized from alkylborate **20** (prepared from iodide **21**) and vinyl iodide **22** by Suzuki−Miyaura coupling[23] (Scheme 5). The vinyl iodide **22** was easily traced back to allylic alcohol **23** with introduction of the C9 stereogenic center by utilizing Sharpless asymmetric epoxidation.

The synthesis of vinyl iodide **22** started with mesylation of the known alcohol **24**[17] followed by displacement with NaCN to give nitrile **25** in 98% yield for the two steps (Scheme 6). Exposure of **25** to MeLi (Et_2O, −78 to 0 °C) smoothly afforded methyl ketone **26** in 85% yield after acidic workup. Desilylation of **26** followed by hetero-Michael reaction of the derived alcohol using methyl propiolate and *N*-methylmorpholine (NMM) provided *β*-alkoxy acrylate **27**. According to the Nakata protocol,[24] treatment of **27** with SmI_2 in the presence of methanol in THF at room temperature cleanly furnished lactone **28** in 74% yield as a single isomer, whose stereochemistry was unambiguously confirmed by NOE experiments as shown. Reduction of the lactone of **28** with DIBALH followed by Wittig homologation, and subsequent silylation of the resultant tertiary alcohol led to enoate **29** in 89% yield for the three steps. After reducing **29** with DIBALH to give allylic alcohol **23** quantitatively, Sharpless asymmetric epoxidation of **23** using (+)-DET as a chiral auxiliary led to hydroxy epoxide **30** in 83% yield as a single stereoisomer, as judged by 500 MHz ^{1}H NMR. Chlorination of **30** with PPh_3 in CCl_4 in the presence of $NaHCO_3$ gave chloro epoxide **31** in 85% yield. According to the Takano protocol,[25] exposure of **31** to excess LDA in THF at −40 °C smoothly furnished propargylic alcohol **32** in 92% yield. After iodination of **32** (NIS, $AgNO_3$, 93% yield), the resultant iodoalkyne **33** was reduced with diimide generated in situ from *o*-nitrobenzenesulfonyl hydrazide (NBSH) and Et_3N,[26] giving rise to vinyl iodide **22** in 96% yield. Thus, the C9 stereogenic center was successfully established with complete stereocontrol by means of Sharpless asymmetric epoxidation. The stereochemistry of the C9 position was unambiguously confirmed by derivatization of alcohol **32** into the Mosher esters **35a**,**b** as shown in Scheme 7.

Assembly of the key intermediates and completion of the synthesis are illustrated in Scheme 8. Iodide **21**, prepared from alcohol **9** by iodination under standard conditions, was treated with *t*-BuLi in the presence of *B*-MeO-9-BBN[27] to generate alkylborate **20**, which was in situ reacted with vinyl iodide **22** under the influence of a $PdCl_2$(dppf)/Ph_3As catalyst system and Cs_2CO_3 in aqueous THF/DMF at 50 °C, leading to the desired *cis*-olefin **36** in 75% yield. Protection of the hydroxy group of **36** as its TBS ether was followed by removal of the MPM group, giving hydroxy alkene **19** in 80% yield for the two steps. Diastereoselective bromoetherification of **19** by its treatment with NBS in acetonitrile at room temperature and the ensuing reduction under radical conditions (*n*-Bu_3SnH, AIBN) delivered tricyclic compound **37** in 69% yield for the two steps. In contrast to the case of **2**, the bromoetherification of **19** proceeded with complete stereocontrol, as judged by 500 MHz ^{1}H NMR of the crude reaction mixture.[28] The stereochemistries of the C4, C5, and C7 positions were unambiguously established by NOESY experiments on compounds **37** and **18a**. Elaboration of **37** into the A/B-ring fragment **18a** of GAB was efficiently accomplished through the previously described seven-step sequence. Not surprisingly, the ^{1}H and ^{13}C NMR spectroscopic data of the synthetic model compound **18a** did not match those of the corresponding moiety of the natural GAB (Table 3). As in the case of GAA, the ^{1}H and ^{13}C NMR chemical shifts of the C7−C11 moiety clearly differed from those of the natural product.[29]

The spectroscopic discrepancies between the synthetic fragments **1**/**18a** and natural products led us to reexamine the originally proposed structure of GAB. Since the ^{1}H and ^{13}C NMR chemical shifts of the C2−C7 moiety of **1** and **18a** were in good agreement with those of the respective natural products,

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(24) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron* **2002**, *58*, 1853–1864.

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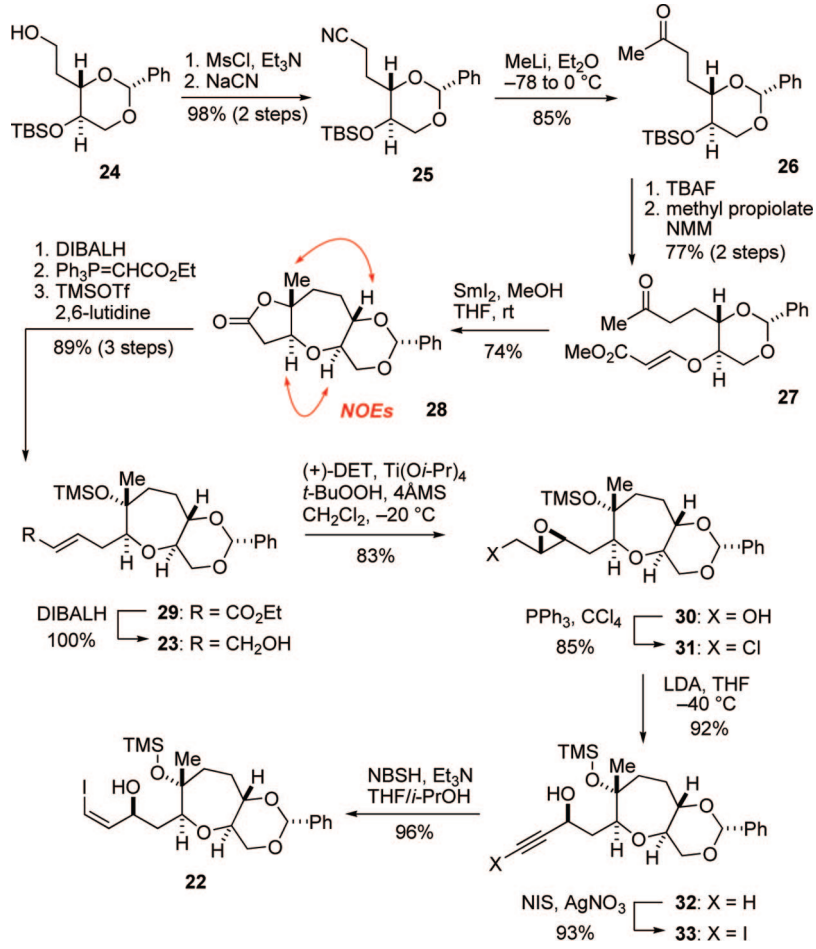
(27) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885–7892.

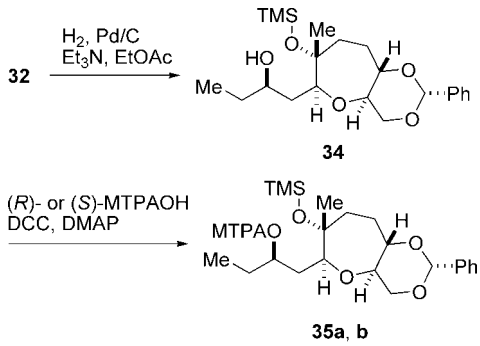
(28) It is interesting that the difference of the C12 position between hydroxy alkenes **2** and **19** affected the apparent diastereoselectivity of their respective bromoetherifications. However, we notice that the net yield of tricyclic compound **15** was 70% from hydroxy alkene **2**, which is comparable to that of tricyclic compound **37** (69% yield from hydroxy alkene **19**). Although the reason for this result is not clear, we speculate that the undesired mode of cyclization (i.e., Figure 2, **TS-B**) of **19** would result in decomposition of the substrate. Similarly, bromoetherification/reduction of hydroxy alkene **48** proceeded with a seemingly better diastereoselectivity (dr = 3.5:1) than that of hydroxy alkene **63** (dr = 2:1), but the net yield of the desired tricyclic compound **49** (47%) was almost the same as that of **65** (49%) (vide infra).

(29) Similarly, the ^{1}H and ^{13}C NMR chemical shifts of the C7−C11 moiety of **18a** in C_5D_5N differed from those of GAB in C_5D_5N. See the Supporting Information for details.

SCHEME 6. Synthesis of Vinyl Iodide 22



SCHEME 7. Synthesis of Mosher Esters 35a,b

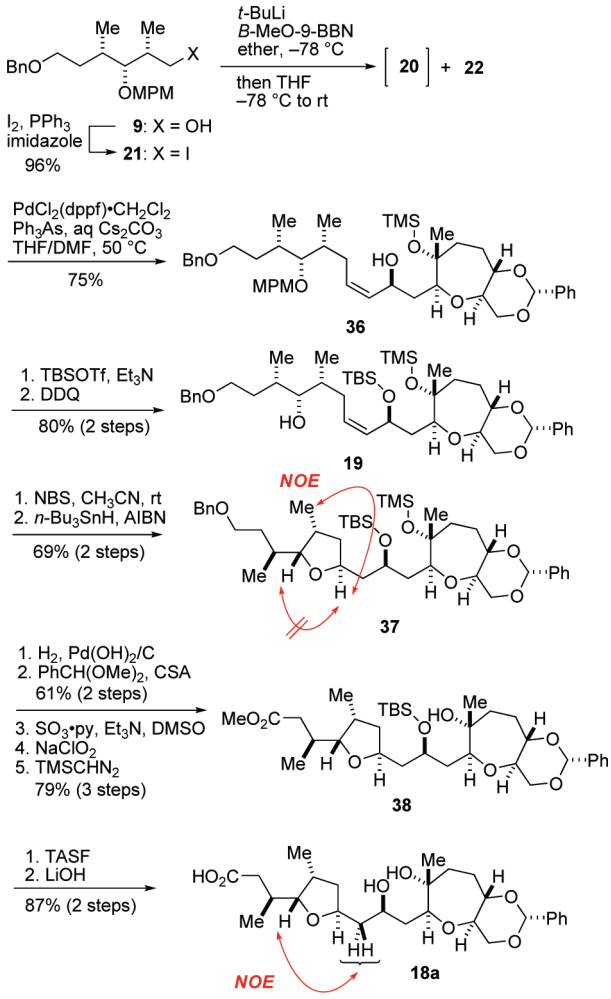


we focused our attention on the relative stereochemistry of the C7−C11 moiety. Satake and co-workers assigned the relative correlations between C7/C9 and C9/C11 mainly based on $^3J_{H,H}$ analysis and NOE data, while the C9 stereogenic center was established by the modified Mosher's method.[4] Since unambiguous assignment of the relative configuration of the C7−C11 stereochemical triad was deemed necessary, we decided to synthesize three possible diastereomers **18b-d** as potential candidates for the A/B-ring substructure of GAB (Figure 3).

The synthesis of model compounds **18b−d** is outlined in Scheme 9 (see the Supporting Information for details). The convergence of our second-generation approach enabled us to prepare and assemble the requisite fragments in an efficient manner. Thus, iodide ***ent*-21** was readily prepared from (*S*)-Roche ester **39** in the same way as described for the synthesis of **21**. On the other hand, vinyl iodide **42**, the C9 epimer of **22**, was synthesized from allylic alcohol **23** simply by tuning the chiral auxiliary used in the Sharpless asymmetric epoxidation, yielding an approximately 7:3 mixture of diastereomers as judged by 500 MHz ^{1}H NMR. The undesired minor diastereomer could be removed by flash column chromatography on silica gel after the ensuing chlorination step. Coupling of the requisite fragments was efficiently achieved under the optimized Suzuki−Miyaura conditions [$PdCl_2$(dppf)/Ph_3As, Cs_2CO_3, aqueous THF/DMF, 50 °C], giving rise to *cis*-olefins **43**, **47**, and **51** in high yields. Bromoetherification of hydroxy alkenes **44** and **52** using NBS in acetonitrile at room temperature proceeded smoothly to provide, after radical reduction (*n*-Bu_3SnH, AIBN), tricyclic compounds **46** and **53** as a single stereoisomer, respectively. On the other hand, under the identical conditions, hydroxy alkene **48** gave tricyclic compound **49** in rather moderate yield with low diastereoselectivity (dr = 3.5:1). The undesired C7 epimer could be separated by flash column chromatography on silica gel. The tricyclic compounds **46**, **49**, and **53** thus prepared were elaborated to model compounds **18b-d** in seven steps as described before. For each of the model compounds, the stereochemistries of the C4, C5, and C7 stereogenic centers were established by NOESY experiments as shown.

Table 3 summarizes the deviations of the ^{1}H and ^{13}C NMR chemical shifts of the synthetic model compounds **18a−d** (δ_S) from those of the natural GAB (δ_N). It is clear that the ^{1}H and ^{13}C NMR chemical shifts of the diastereomer **18c** are in close

SCHEME 8. Synthesis of an A/B-Ring Model Compound 18a of GAB



agreement with those of the natural product, while the other diastereomers showed different spectroscopic properties. Conformational analysis of **18c** based on $^3J_{H,H}$ values ($J_{7,\ 8b} = 10.2$ Hz, $J_{8a,\ 8b} = 13.2$ Hz, $J_{8a,\ 9} = 9.4$ Hz, $J_{9,\ 10a} = 8.4$ Hz, $J_{10a,\ 10b} = 13.6$ Hz, $J_{10b,\ 11} = 9.0$ Hz) and NOESY and HMBC spectra in pyridine-d_5 revealed that **18c** reproduces not only the relative stereochemistry but also the conformation of the C7−C11 moiety of the natural GAB (Figure 4). Since the absolute configuration of the C9 stereogenic center of **18c** is opposite to that of the natural product, as was determined unambiguously by the modified Mosher's method, **18c** represents an enantiomer of the A/B-ring substructure of GAB. Thus, the configuration of the polycyclic ether region of GAB should be corrected such that it is opposite to the original assignment.

Second-Generation Synthesis and Structure Analysis of the A/B-Ring Fragment of GAA. The successful stereochemical reassignment of the originally proposed structure of GAB encouraged us to reexamine the structure of GAA as well. In view of biosynthesis, the structures of other natural congeners of GAs should also be revised in a similar manner. Thus, we embarked on the synthesis of model compound **54** based on our second-generation strategy (Scheme 10). Reduction of lactone **10** with DIBALH followed by Wittig homologation using $Ph_3P{=}CHCO_2Et$, and subsequent silylation of the remaining alcohol gave enoate **55** in 63% yield (three steps). The enoate **55** was elaborated to vinyl iodide **61** in a manner similar

TABLE 3. Deviation of ^{1}H and ^{13}C NMR Chemical Shifts between Natural GAB and the Diastereomeric A/B-Ring Model Compounds 18a−d (in 1:1 CD_3OD/Pyridine-d_5)[a]

	^{1}H NMR [$\Delta(\delta_N-\delta_S)$]				^{13}C NMR [$\Delta(\delta_N-\delta_S)$]			
position	**18a**	**18b**	**18c**	**18d**	**18a**	**18b**	**18c**	**18d**
2	0.06	0.06	0.10	0.09	0.6	0.6	0.6	0.7
	0.00	0.01	0.02	0.02				
3	0.00	0.01	0.01	0.02	0.0	0.2	0.1	0.2
4	0.02	0.01	0.08	0.00	0.3	0.0	0.3	0.0
5	0.04	0.05	0.08	0.06	0.1	0.3	0.1	0.2
6	−0.02	−0.01	0.02	−0.03	0.1	0.4	0.3	0.5
	−0.02	−0.09	0.02	−0.11				
7	0.06	0.16	0.02	0.11	−0.5	−2.3	−0.2	−2.4
8	−0.15	−0.09	−0.04	−0.29	−1.7	−1.0	0.0	0.6
	0.12	−0.02	−0.04	0.00				
9	0.08	0.18	0.04	0.19	1.4	0.4	0.1	−1.3
10	0.09	0.12	−0.11	−0.09	0.5	0.8	0.3	0.4
	0.10	0.01	−0.11	−0.11				
11	−0.39	−0.38	−0.06	−0.08	1.4	1.7	0.1	0.3
12					0.3	0.3	0.2	0.2
13	−0.05	−0.05	−0.06	−0.01	0.3	0.3	0.6	1.2
	−0.10	−0.11	−0.05	−0.06				
50	0.10	0.12	0.05	0.12	0.3	0.3	0.1	0.4
51	0.03	0.02	0.05	0.03	0.1	0.0	0.1	0.1
12Me	−0.02	−0.03	−0.01	−0.01	0.5	0.5	0.7	0.8

[a] ^{1}H and ^{13}C NMR spectra of natural GAB and model compounds **18a−d** were recorded at 400 MHz (100 MHz) and 600 MHz (150 MHz), respectively. Chemical shifts are reported in ppm relative to the internal residual solvent (^{1}H NMR, CD_2HOD 3.31 ppm; ^{13}C NMR, CD_3OD 49.8 ppm). δ_N and δ_S are chemical shifts of the natural product and synthetic model compounds **18a−d**, respectively.

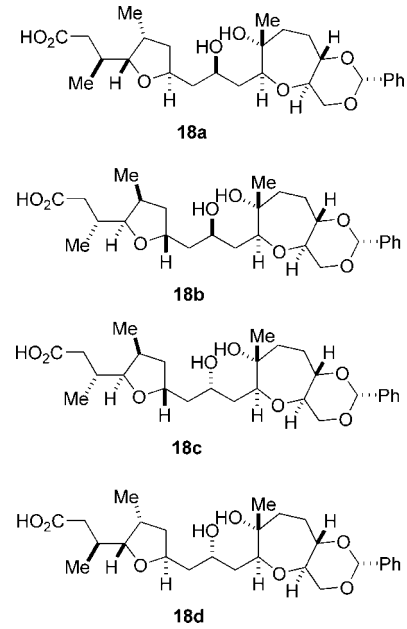
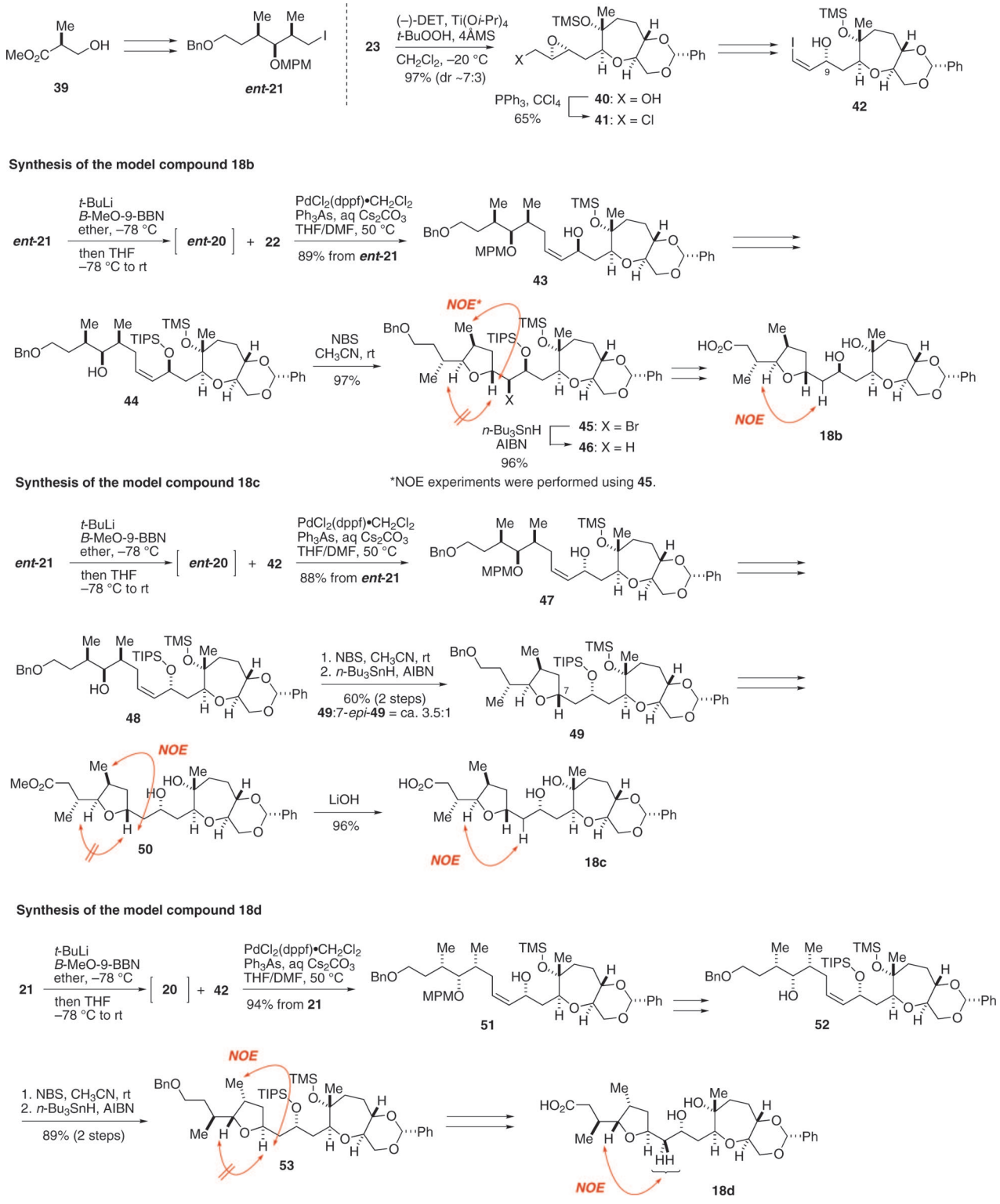


FIGURE 3. Structures of possible diastereomers **18a−d**.

to that described for the synthesis of **22**. Suzuki−Miyaura coupling of **61** with alkylborate ***ent*-20** generated in situ from the corresponding iodide ***ent*-21** under the optimized conditions [$PdCl_2$(dppf)/Ph_3As, Cs_2CO_3, aqueous THF/DMF] furnished *cis*-olefin **62** (87% yield), which was converted to hydroxy alkene **63** by the standard protective group manipulations. Exposure of **63** to NBS in acetonitrile at room temperature effected diastereoselective bromoetherification to afford, after reduction of the derived bromide under radical conditions, an approximately 2:1 mixture of tricyclic compound **65** and its C7-epimer, which was separated by flash column chromatography

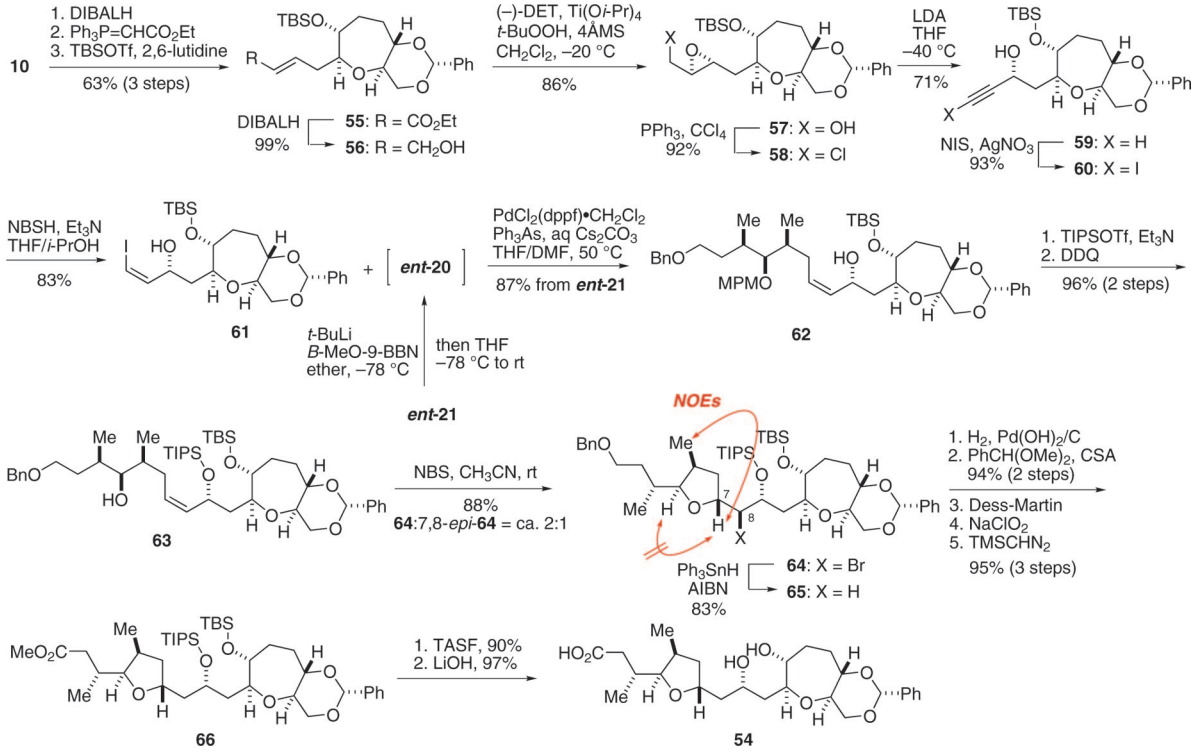
SCHEME 9. Synthesis of the Three Diastereomeric Model Compounds 18b–d



on silica gel. Elaboration of **65** into the model compound **54** was achieved in seven steps as described previously. As expected, the ^{1}H and ^{13}C NMR spectroscopic data of the synthetic model compound **54** matched those of the natural GAA (Table 4). Thus, the absolute configuration of the polycyclic ether region of GAA should be corrected to be opposite to that of the original assignment. Overall, we have successfully revised the structures of all members of the GA family, as represented in Figure 1.

Synthesis and Structure Analysis of an A/BC-Ring Fragment of GAB. Having successfully revised the original stereochemical assignment of the polycyclic ether region of GAs, we embarked on the synthesis of the A/BC-ring fragment **67** of GAB in order to establish a reliable route readily applicable to a total synthesis and the stereochemical confirmation of the revised structure by NMR analysis. Our synthesis plan for the A/BC-ring fragment **67** is summarized in Scheme 11. It was envisaged that the A-ring tetrahydrofuran of **67** would be

SCHEME 10. Synthesis of the A/B-Ring Model Compound 54 of GAA



constructed by a diastereoselective bromoetherification, although this transformation has proven to be inefficient for the synthesis of model compounds with the desired stereochemistry (i.e., **18c** and **54**). Hydroxy alkene **68** would be synthesized through a Suzuki−Miyaura coupling of an alkylborate generated from iodide ***ent*-21** and vinyl iodide **69**. Vinyl iodide **69** would be prepared from tricyclic lactone **70**, which would be accessible from the known tetrahydropyran **71** corresponding to the C-ring.

The synthesis of vinyl iodide **69** commenced with silylation of the known alcohol **71**,[30] giving TIPS ether **72** in 94% yield (Scheme 12). Deprotection of the benzylidene acetal of **72** under acidic conditions gave diol **73** in 90% yield, which was protected (MOMCl, *i*-Pr_2NEt) to provide bis-MOM ether **74** in 96% yield. Hydroboration of **74** using disiamylborane delivered alcohol **75** in a nearly quantitative yield, which was transformed to nitrile **76** via a mesylate in 94% yield (two steps). Treatment of **76** with MeMgBr in Et_2O gave methyl ketone **77** in 63% yield along with recovered **76** (27%). After desilylation of **77** with

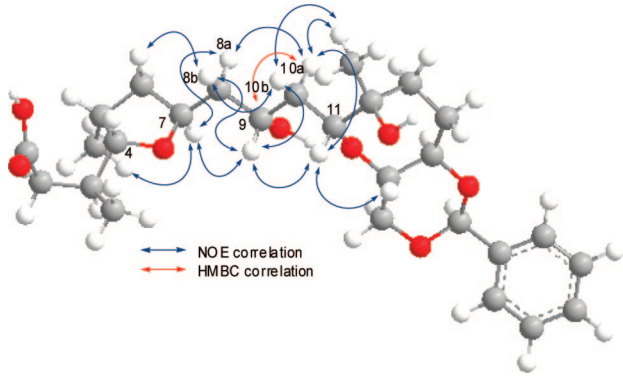


FIGURE 4. Selected NOESY and HMBC correlations of compound **18c** (600 MHz, pyridine-d_5). Blue arrows denote NOESY correlations. Red arrows denote HMBC correlations.

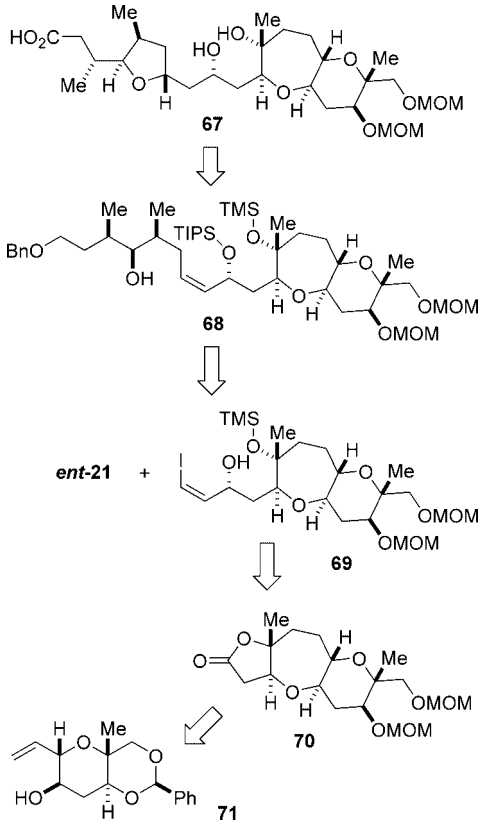
TABLE 4. Deviation of ^1H and ^{13}C NMR Chemical Shifts between Natural GAA and the A/B-Ring Model Compound 54 (in 1:1 CD_3OD/Pyridine-d_5)[a]

position	^1H NMR [$\Delta(\delta_N-\delta_S)$]	^{13}C NMR [$\Delta(\delta_N-\delta_S)$]
2	0.01	0.6
	0.04	
3	−0.01	0.1
4	0.04	0.2
5	0.01	0.0
6	0.01	0.1
	0.01	
7	−0.01	−0.1
8	0.00	0.0
	0.01	
9	0.01	0.3
10	0.00	0.1
	0.00	
11	−0.07	0.1
12	−0.03	0.1
13	−0.04	0.8
	−0.03	
50	0.02	0.1
51	0.01	0.1

[a] ^1H and ^{13}C NMR spectra of natural GAA and compound **54** were recorded at 400 MHz (100 MHz) and 600 MHz (150 MHz), respectively. Chemical shifts are reported in ppm relative to the internal residual solvent (^1H NMR, CD_2HOD 3.31 ppm; ^{13}C NMR, CD_3OD 49.8 ppm). δ_N and δ_S are chemical shifts of the natural product and synthetic model compound **54**, respectively.

TBAF (98% yield), the resultant alcohol was reacted with methyl propiolate in the presence of NMM to afford β alkoxy acrylate **78** in 98% yield. Exposure of **78** to SmI_2 in the presence of methanol in THF at room temperature cleanly furnished tricyclic lactone **70** in 92% yield as a single stereoisomer. The stereochemistry of **70** was established by NOE experiments as shown. DIBALH reduction of **70** followed by Wittig reaction using $Ph_3P{=}CHCO_2Et$, and subsequent silylation with trimethylsilylimidazole delivered TMS ether **79** in 75% yield (three

SCHEME 11. Synthesis Plan for the A/BC-Ring Fragment 67 of GAB



steps), which was reduced with DIBALH to give allylic alcohol **80** almost quantitatively. Sharpless asymmetric epoxidation using (−)-DET as a chiral auxiliary afforded hydroxy epoxide **81** in 94% yield as an approximately 9:1 mixture of diastereomers (judged by 500 MHz ^{1}H NMR). Treatment of **81** with Ph_3P in the presence of $NaHCO_3$ in refluxing CCl_4 gave chloro epoxide **82** (89% yield). Exposure of **82** to excess LDA smoothly afforded propargylic alcohol **83** in 86% yield. Iodination (NIS, $AgNO_3$, 91% yield) followed by diimide reduction of the resultant iodoalkyne **84** furnished vinyl iodide **69** in 91% yield.

With the requisite fragment in hand, the fragment coupling and the construction of the A-ring tetrahydrofuran were investigated (Scheme 13). An alkylborate generated from iodide ***ent*-21** by treating with *t*-BuLi and *B*-MeO-9-BBN was coupled with vinyl iodide **69** in the presence of a $PdCl_2$(dppf)/Ph_3As catalyst system and Cs_2CO_3 as a base in aqueous THF/DMF at 50 °C, giving rise to *cis*-olefin **85** in 88% yield. After protection of **85** as the TIPS ether, the MPM group was cleaved to give hydroxy alkene **68** in 77% yield for the two steps.

However, diastereoselective haloetherification of **68** was found to be quite challenging (Table 5). Treatment of **68** with NBS in acetonitrile at room temperature gave an approximately 2.3:1 mixture of **86a**, **b** in 43% combined yield (entry 1). The rather low diastereoselectivity coupled with the unacceptable yield led us to screen reaction conditions. An attempt to improve the diastereoselectivity by performing the reaction at 0 °C proved to be unfruitful (entry 2). Exposure of **68** to NIS in acetonitrile at room temperature gave a 1:1 mixture of **86a**,**b** in 46% combined yield along with 33% of the starting material (entry 4). A highly reactive reagent bis(*sym*-collidine)$I^+PF_6^-$,[31] generated in situ from iodine and bis(*sym*-collidine)$Ag^+PF_6^-$, smoothly facilitated iodoetherification to provide a 1:1 mixture of **86a**,**b** in 79% yield (entry 5). The use of bis(*sym*-collidine)$Br^+PF_6^-$ was ineffective in the present case (entry 6).

The observed low diastereoselectivity of the haloetherification of **68** could be explained by considering two possible transition states of the reaction (Figure 5). The transition state C (**TS-C**) would give the desired diastereomer **86a**, while **TS-D** would lead to the undesired isomer **86b**. **TS-C** suffers from a steric repulsion between the C4 hydrogen and the C9 siloxy group (P═TIPS), while **TS-D** involves an unfavorable interaction between the C51 methyl group and the C7−C9 moiety. The unsatisfactory results of the haloetherification of **68** may be attributable to these steric interactions present in possible transition states. Based on these mechanistic considerations, we thought that **TS-C** would become energetically more favored than **TS-D** by removal of the bulky TIPS group of the C9 alcohol. Eventually, hydroxy alkene **87**, prepared from **68** by desilylation (TBAF, 100% yield), was treated with bis(*sym*-collidine)$I^+PF_6^-$ in CH_2Cl_2 at room temperature (Scheme 14). As expected, we were pleased to find that the diastereoselective iodoetherification proceeded cleanly to furnish iodide **88** in 83% yield as a single stereoisomer (judged by 500 MHz ^{1}H NMR). At this stage, the stereochemistries of the C4, C5, and C7 stereogenic centers were confirmed by NOE experiments as shown.

Completion of the synthesis of the A/BC-ring fragment **67** of GAB is depicted in Scheme 15. Protection of the hydroxy group of **88** (Ac_2O, Et_3N, DMAP) gave acetate **89** in 100% yield. Removal of the iodine atom of **89** was best achieved using Ph_3SnH and AIBN in refluxing THF, leading to tricyclic compound **90** in 96% yield after hydrogenolysis of the benzyl group. A two-stage oxidation (Dess−Martin periodinane; then $NaClO_2$) and subsequent esterification provided methyl ester **91** in 52% overall yield from **90** after purification by flash column chromatography on silica gel. Finally, saponification cleanly furnished the A/BC-ring fragment **67** in 93% yield. The ^{1}H and ^{13}C NMR chemical shifts of the synthesized **67** are in excellent accordance with those of the natural GAB (Table 6). Thus, our revised structure of GAB was confirmed by the synthesis and structure analysis of the tricyclic model compound **67**.

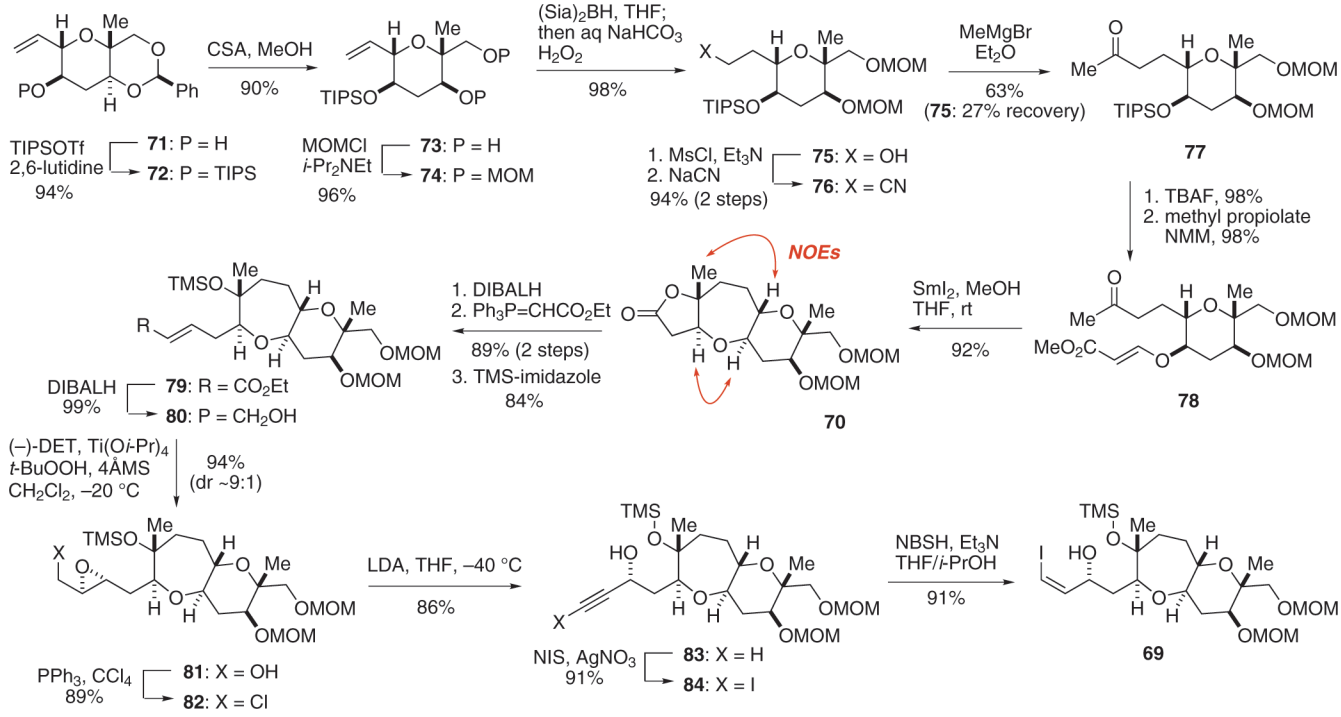
Conclusion

We have developed two strategies for the synthesis of the A/B-ring fragments of GAs. The first-generation synthesis employed an acetylide/aldehyde coupling as the fragment assembly process. However, the low diastereoselectivity at the C9 stereocenter and the necessity of employing large excess amounts of the alkyne component were serious drawbacks in terms of the material throughput, which made this approach less attractive. In the second-generation approach, the C9 stereogenic center was introduced by Sharpless asymmetric epoxidation and the fragment assembly was efficiently achieved by Suzuki−Miyaura coupling. The construction of the A-ring tetrahydrofuran was achieved by diastereoselective bromoetherification.

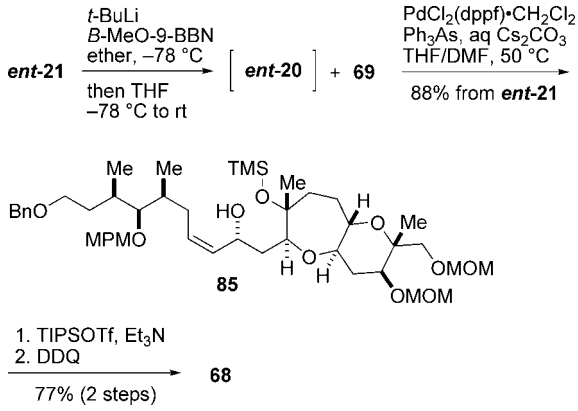
Surprisingly, the ^{1}H and ^{13}C NMR spectroscopic data of the synthesized fragments of GAA and GAB (**1** and **18a**,

(30) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517–4552.

SCHEME 12. Synthesis of Vinyl Iodide 69

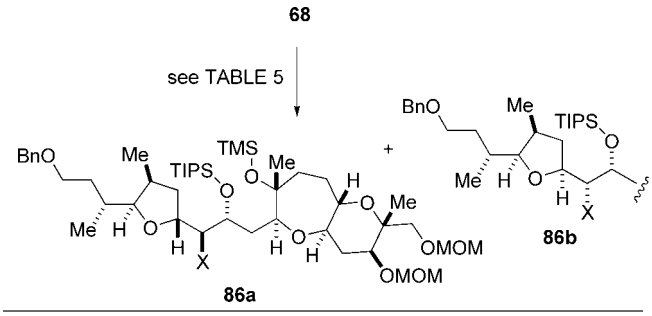


SCHEME 13. Synthesis of Hydroxy Alkene 68



respectively) did not match those of the corresponding moiety of the respective natural products. In particular, substantial deviation of the chemical shifts of the C8−C11 moiety was observed. These spectroscopic discrepancies led us to reexamine the originally proposed structure of GAB. According to Satake and co-workers, the relative stereochemical correlations between C7/C9 and C9/C11 were determined mainly based on $^{3}J_{H,H}$ analysis and NOE experiments, while the C9 stereogenic center was established by the modified Mosher's method. Therefore, it was necessary to ascertain the relative configuration of the C7−C11 stereochemical triad in an unambiguous manner. Eventually, we synthesized three possible diastereomers **18b-d** and found that the ^{1}H and ^{13}C NMR spectroscopic data of **18c** were in excellent agreement with those of the natural GAB. Thus, the absolute configuration of the polycyclic ether region of GAB should be revised such that it is opposite to the original assignment. The structure of GAA was similarly revised due to the fact that the ^{1}H and ^{13}C NMR chemical shifts of the tricyclic model compound **54** matched those of the natural GAA.

TABLE 5. Unfruitful Attempts at Haloetherification of Hydroxy Alkene 68



entry	reagents and conditions	X	yield (%) (**86a/86b**)[a]
1	NBS, CH_3CN, rt	Br	43 (2.3:1)
2	NBS, CH_3CN, 0 °C	Br	24 (2.4:1)
3	NIS, CH_3CN, −40 to 0 °C	I	26 (0.5:1)[b]
4	NIS, CH_3CN, rt	I	46 (1.0:1)[c]
5	I_2, bis(*sym*-collidine)$AgPF_6$, CH_2Cl_2, rt	I	79 (1.0:1)
6	Br_2, bis(*sym*-collidine)$AgPF_6$, CH_2Cl_2, rt	Br	13 (1.0:1)

[a] Diastereomer ratio was determined by ^{1}H NMR (500 MHz). [b] **68** was recovered in 68% yield. [c] **68** was recovered in 33% yield.

In addition, the applicability of our developed strategy for the construction of the A/B-ring moiety in a more complex situation was investigated through the synthesis of an A/BC-ring fragment of GAB. Unfortunately, the haloetherification of hydroxy alkene **68** suffered from low diastereoselectivity. After detailed mechanistic considerations on the possible transition state models, we found that iodoetherification of the C9 unprotected hydroxy alkene **87** proceeded cleanly to afford iodide **88** in excellent yield as a single stereoisomer. The ^{1}H and ^{13}C NMR spectroscopic data of the A/BC-ring fragment **67** were in excellent agreement with those of the corresponding moiety of the natural GAB. Thus, our revised

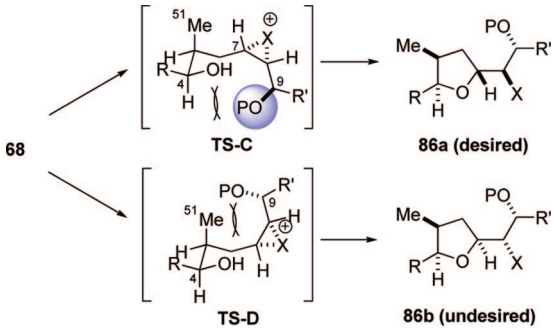
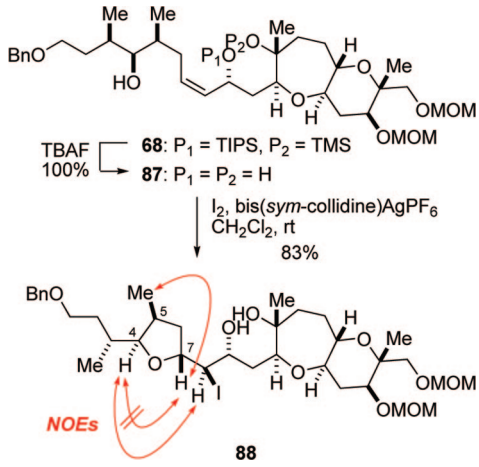
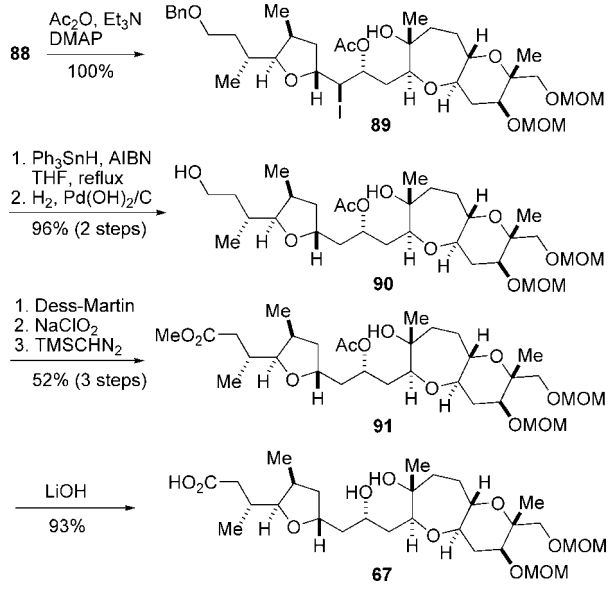


FIGURE 5. Mechanistic considerations on haloetherification of hydroxy alkene **68**.

SCHEME 14. Highly Diastereoselective Iodoetherification of 87



SCHEME 15. Synthesis of the A/BC-Ring Model Compound 67 of GAB



structures of GAs were further supported. The present study underscores the important role of organic synthesis in the structure elucidation of architecturally complex natural products.[32] However, an unambiguous confirmation of our revised structures of GAs will have to be done through total synthesis. Further studies toward the total synthesis of GAs are currently underway and will be reported in due course.

TABLE 6. Deviation of ^{1}H and ^{13}C NMR Chemical Shifts between Natural GAB and the A/BC-Ring Model Compound 67 (in 1:1 CD_3OD/Pyridine-d_5)[a]

position	^{1}H NMR [$\Delta(\delta_N-\delta_S)$]	^{13}C NMR [$\Delta(\delta_N-\delta_S)$]
2	0.07	0.5
	0.02	
3	0.00	0.1
4	0.09	0.3
5	0.08	0.1
6	−0.01	0.2
	0.03	
7	0.03	−0.2
8	−0.05	−0.4
	−0.03	
9	0.05	−0.3
10	−0.10	−0.3
	−0.05	
11	0.02	0.7
12		0.1
13	0.01	0.3
	−0.01	
50	0.02	−0.1
51	0.04	0.0
12Me	−0.01	0.2

[a] ^{1}H and ^{13}C NMR spectra of natural GAB and compound **67** were recorded at 400 MHz (100 MHz) and 600 MHz (150 MHz), respectively. Chemical shifts are reported in ppm relative to the internal residual solvent (^{1}H NMR, CD_2HOD 3.31 ppm; ^{13}C NMR, CD_3OD 49.8 ppm). δ_N and δ_S are chemical shifts of the natural product and synthetic model compound **67**, respectively.

Experimental Section

Triisopropylsilyl Ether 72. To a solution of alcohol **71** (6.87 g, 24.9 mmol) in CH_2Cl_2 (170 mL) at 0 °C were added 2,6-lutidine (5.8 mL, 49.8 mmol) and TIPSOTf (10 mL, 37.3 mmol). After being stirred at 0 °C for 1.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 2% EtOAc/hexanes) to give triisopropylsilyl ether **72** (10.2 g, 94%) as a colorless oil: $[\alpha]^{19}_D$ −62.8 (*c* 1.00, $CHCl_3$); IR (film) 2944, 2867, 1463, 1383, 1092, 1007, 924, 882, 819, 749, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 7.38−7.32 (m, 3H), 5.92 (ddd, J = 17.0, 10.5, 6.0 Hz, 1H), 5.55 (s, 1H), 5.36 (m, 1H), 5.22 (m, 1H), 3.99−3.92 (m, 2H), 3.69−3.65 (m, 2H), 3.60 (dd, J = 13.0, 4.0 Hz, 1H), 2.26 (ddd, J = 12.0, 3.5, 3.5 Hz, 1H), 1.88 (ddd, J = 12.0, 12.0, 11.0 Hz, 1H), 1.53 (s, 3H), 1.03 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.5, 136.4, 129.2, 128.4 (×2), 126.3 (×2), 117.6, 102.9, 78.8, 76.6, 76.2, 71.7, 68.9, 34.6, 18.2 (×3), 18.1 (×3), 14.8, 12.6 (×3); HRMS (FAB) calcd for $C_{25}H_{41}O_4Si$ [(M + H)$^+$] 433.2769, found 433.2776.

Diol 73. To a solution of triisopropylsilyl ether **72** (10.2 g, 23.5 mmol) in CH_2Cl_2/MeOH (1:1, v/v, 160 mL) was added CSA (1.64 g, 23.5 mmol). After being stirred at room temperature for 4.5 h, the reaction mixture was quenched with Et_3N and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10−40% EtOAc/hexanes) to give diol **73** (7.23 g, 90%) as a colorless oil: $[\alpha]^{21}_D$ −66.2 (*c* 1.00, $CHCl_3$); IR (film) 3427, 2944, 2868, 2359, 1463, 1120, 1057, 882, 824, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (ddd, J = 17.0, 10.5, 6.0 Hz, 1H), 5.30 (m, 1H), 5.18 (m, 1H), 3.86 (m, 1H), 3.74

(31) (a) Brunel, Y.; Rousseau, G. *J. Org. Chem.* **1996**, *61*, 5793–5800. (b) Gao, X.; Snider, B. B. *J. Org. Chem.* **2004**, *69*, 5517–5527.

(32) For a review, see: Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012–1044.

(dd, $J = 9.0, 5.5$ Hz, 1H), 3.64−3.74 (m, 3H), 2.24−2.20 (m, 2H), 2.15 (br, 1H), 1.69 (ddd, $J = 12.0, 11.5, 11.5$ Hz, 1H), 1.18 (s, 3H), 1.03 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.5, 117.1, 76.3, 75.8, 71.1, 68.5, 67.2, 38.1, 18.1 (×6), 13.0, 12.6 (×3); HRMS (FAB) calcd for $C_{18}H_{37}O_4Si$ [$(M + H)^+$] 345.2456, found 345.2469.

Bis-methoxymethyl Ether 74. To a solution of diol **73** (7.23 g, 21.1 mmol) in CH_2Cl_2 (150 mL) at 0 °C were added *i*-Pr_2NEt (73 mL, 423 mmol) and MOMCl (16 mL, 211 mmol). After being stirred at 40 °C overnight, the solution was cooled to room temperature. The reaction mixture was diluted with EtOAc, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 8% EtOAc/hexanes) gave bis-methoxymethyl ether **74** (8.59 g, 96%) as a colorless oil: $[\alpha]^{21}_D$ −49.5 (*c* 1.00, $CHCl_3$); IR (film) 2945, 2868, 2359, 1463, 1102, 1037, 920, 882, 681 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.93 (ddd, $J = 16.9, 10.8, 6.0$, 1H), 5.24 (m, 1H), 5.14 (m, 1H), 4.68−4.62 (m, 4H), 3.77−3.71 (m, 2H), 3.55−3.46 (m, 3H), 3.35 (s, 3H), 3.34 (s, 3H), 2.33 (ddd, $J = 12.0, 4.2, 4.2$ Hz, 1H), 1.70 (ddd, $J = 12.0, 11.4, 11.4$ Hz, 1H), 1.17 (s, 3H), 1.03 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.7, 116.7, 96.9, 96.1, 76.3, 75.9, 72.7, 72.1, 70.9, 55.4, 55.3, 36.4, 18.1 (×6), 13.3, 12.6 (×3); HRMS (FAB) calcd for $C_{22}H_{45}O_6Si$ [$(M + H)^+$] 433.2980, found 433.2991.

Alcohol 75. To a solution of 2-methyl-2-butene in THF (80 mL) at 0 °C was added borane dimethylsulfide complex (1.9 M solution in THF, 16.0 mL, 30.4 mmol). After being stirred at 0 °C for 1 h, a solution of bis-methoxymethyl ether **74** (8.59 g, 20.2 mmol) in THF (30 mL + 2 × 5.0 mL rinse) was added. After being stirred at 0 °C for 1 h, the reaction mixture was treated sequentially with saturated aqueous $NaHCO_3$ and 30% aqueous H_2O_2. The resultant mixture was stirred at 0 °C for 10 min and then at room temperature for 1 h. The mixture was diluted with EtOAc, washed with H_2O, saturated aqueous Na_2SO_3, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20% EtOAc/hexanes) gave alcohol **75** (8.73 g, 98%) as a colorless oil: $[\alpha]^{20}_D$ −40.4 (*c* 1.00, $CHCl_3$); IR (film) 2945, 2868, 2360, 1463, 1384, 1101, 1046, 919, 882, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63−4.59 (m, 4H), 3.80−3.73 (m, 2H), 3.62 (dd, $J = 4.5, 4.5$ Hz, 1H), 3.55−3.53 (m, 2H), 3.46 (m, 2H), 3.33 (s, 6H), 3.20 (dd, $J = 7.5, 3.0$ Hz, 1H), 2.31 (ddd, $J = 12.0, 4.0, 4.0$ Hz, 1H), 2.05 (m, 1H), 1.70−1.64 (m, 2H), 1.21 (s, 3H), 1.04 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 96.8, 96.0, 76.7, 76.2, 73.1, 72.6, 70.3, 62.0, 55.5, 55.3, 35.9, 33.6, 18.1 (×6), 13.3, 12,6 (×3); HRMS (FAB) calcd for $C_{22}H_{47}O_7Si$ [$(M + H)^+$] 451.3086, found 451.3105.

Nitrile 76. To a solution of alcohol **75** (8.49 g, 19.2 mmol) in CH_2Cl_2 (125 mL) at 0 °C were added Et_3N (5.50 mL, 39.4 mmol) and MsCl (2.29 mL, 29.6 mmol). After being stirred at 0 °C for 1 h, the reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mesylate was used in the next reaction without purification.

To a solution of the above crude mesylate in DMSO (125 mL) was added NaCN (4.73 g, 95.8 mmol). After being stirred at 60 °C for 2 h, the reaction mixture was cooled to room temperature. The mixture was diluted with diethyl ether, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 8−20% EtOAc/hexanes) gave nitrile **76** (8.11 g, 94%) as a colorless oil: $[\alpha]^{20}_D$ −63.9 (*c* 1.00, $CHCl_3$); IR (film) 2945, 2360, 1463, 1102, 1038, 919, 882, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64−4.61 (m, 4H), 3.72 (dd, $J = 12.0, 5.0$ Hz, 1H), 3.51−3.42 (m, 3H), 3.36 (m, 1H), 3.37 (s, 6H), 2.45−2.41 (m, 2H), 2.32 (ddd, $J = 11.5, 4.0, 4.0$ Hz, 1H), 2.22 (m, 1H), 1.70−1.59 (m, 2H), 1.14 (s, 3H), 1.04 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.7, 96.9, 96.1, 76.5, 73.0, 72.6, 71.9, 70.0, 55.4, 55.2, 36.2, 28.0, 18.2 (×3), 18.1 (×3), 13.6, 13.5, 12.6 (×3); HRMS (FAB) calcd for $C_{23}H_{45}O_6NSiNa$ [$(M + Na)^+$] 482.2908, found 482.2923.

Methyl Ketone 77. To a solution of nitrile **76** (571.7 mg, 1.219 mmol) in diethyl ether (13.0 mL) at 0 °C was added MeMgBr (3.0 M solution in diethyl ether, 3.60 mL, 10.8 mmol) dropwise. After being stirred at room temperature overnight, the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 °C. The mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−10% ether/benzene) gave methyl ketone **77** (358.9 mg, 63%) as a colorless oil, along with recovered **76** (151.8 mg, 27%). Data for **77**: $[\alpha]^{19}_D$ −55.6 (*c* 1.00, $CHCl_3$); IR (film) 2945, 2868, 1719, 1464, 1149, 1101, 1040, 919, 882, 823, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64−4.60 (m, 4H), 3.68 (dd, $J = 12.5, 5.0$ Hz, 1H), 3.48−3.40 (m, 3H), 3.33 (s, 6H), 3.20 (td, $J = 1.5, 10.0$ Hz, 1H), 2.50 (m, 1H), 2.42 (m, 1H), 2.30 (ddd, $J = 12.0, 4.5, 4,5$ Hz, 1H), 2.21−2.15 (m, 1H), 2.11 (s, 3H), 1.66−1.51 (m, 2H), 1.09 (s, 3H), 1.04 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 96.9, 96.1, 76.1, 74.3, 72.8, 72.0, 70.9, 55.4, 55.2, 40.1, 36.3, 29.9, 26.5, 18.2 (×3), 18.1 (×3), 13.5, 12.6 (×3); HRMS (FAB) calcd for $C_{24}H_{49}O_7Si$ [$(M + H)^+$] 477.3242, found 477.3251.

***β*-Alkoxy Acrylate 78.** To a solution of methyl ketone **77** (5.51 g, 11.7 mmol) in THF (80 mL) at 0 °C was added TBAF (1.0 M solution in THF, 35.2 mL, 35.2 mmol). After being stirred at room temperature for 30 min, the reaction mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20−80% EtOAc/hexanes) gave crude alcohol, which was used in the next reaction without further purification.

To a solution of the above crude alcohol in CH_2Cl_2 (80 mL) were added methyl propiolate (2.90 mL, 34.7 mmol) and NMM (1.90 mL, 17.3 mmol), and the resultant solution was stirred at room temperature overnight. Concentration under reduced pressure followed by purification by flash column chromatography (silica gel, 15−70% EtOAc/hexanes) gave *β*-alkoxy acrylate **78** (4.52 g, 98% for the two steps) as a colorless oil: $[\alpha]^{21}_D$ −43.6 (*c* 1.00, $CHCl_3$); IR (film) 2950, 1713, 1642, 1439, 1359, 1288, 1202, 1146, 1110, 1041, 918 cm^{-1};^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, $J =$ 6.6 Hz, 1H), 5.28 (d, $J = 12.6$ Hz, 1H), 4.63−4.60 (m, 4H), 3.76 (dd, $J = 12.0, 4.8$ Hz, 1H), 3.67 (s, 3H), 3.58 (m, 1H), 3.49−3.42 (m, 3H), 3.33 (s, 6H), 2.54 (m, 1H), 2.46−2.37 (m, 2H), 2.11 (s, 3H), 1.99 (m, 1H), 1.67 (m, 1H), 1.54 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.4, 168.0, 161.1 (×2), 98.1, 96.8, 96.1, 80.1, 76.6, 72.2, 71.6, 70.8, 55.3, 51.2, 39.3, 31.9, 29.9, 25.9, 13.3; HRMS (FAB) calcd for $C_{19}H_{33}O_9$ [$(M + H)^+$] 405.2119, found 405.2133.

Lactone 70. To a solution of *β*-alkoxy acrylate **78** (4.52 g, 11.3 mmol) in THF (75 mL) were added MeOH (1.4 mL, 34 mmol) and SmI_2 (0.1 M solution in THF, 400 mL, 40 mmol). After being stirred at room temperature for 1 h, the reaction mixture was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The resultant mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure to remove the bulk of THF. The residue was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, saturated aqueous $Na_2S_2O_3$, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 40−60% EtOAc/hexanes) gave lactone **70** (3.82 g, 92%) as a colorless oil: $[\alpha]^{22}_D$ −37.9 (*c* 1.00, $CHCl_3$); IR (film) 2946, 1784, 1453, 1384, 1253, 1211, 1145, 1110, 1038, 970, 941, 916 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.64−4.62 (m, 4H), 4.19 (dd, $J = 10.8, 9.0$ Hz, 1H), 3.71 (dd, $J = 12.0, 4.8$ Hz, 1H), 3.48−3.42 (m, 3H), 3.33 (s, 6H), 3.18 (m, 1H), 2.71−2.63 (m, 2H), 2.34 (ddd, $J = 12.0, 4.8, 4.8$ Hz, 1H), 2.08 (m, 1H), 2.00 (m, 1H), 1.96−1.90 (m, 2H), 1.67 (m, 1H), 1.38 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 96.8, 96.0, 87.0, 81.2, 77.4, 76.4, 72.9, 71.8, 71.3, 55.6, 55.3, 34.3, 33.2, 32.5, 30.1, 24.3, 13.2; HRMS (FAB) calcd for $C_{18}H_{31}O_8$ [$(M + H)^+$] 375.2013, found 375.2018.

Enoate 79. To a solution of lactone **70** (2.95 g, 7.89 mmol) in CH_2Cl_2 (80 mL) at −78 °C was added DIBALH (1.02 M solution in hexane, 9.3 mL, 9.49 mmol). After being stirred at −78 °C for 30 min, the reaction mixture was quenched with MeOH and treated with saturated aqueous potassium sodium tartrate. The mixture was diluted with EtOAc and vigorously stirred at room temperature until the layers became clear. The organic layer was separated and washed with brine. The aqueous layers were combined and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude lactol was used in the next reaction without purification.

To a solution of the above crude lactol in toluene (80 mL) was added $Ph_3P{=}CHCO_2Et$ (3.30 g, 9.47 mmol). The resultant mixture was stirred at 80 °C for 30 min. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 50% EtOAc/hexanes) to give alcohol (3.07 g, 89% for the two steps) as a colorless oil: $[\alpha]^{19}_D$ −32.1 (*c* 1.00, $CHCl_3$); IR (film) 3480, 2937, 1719, 1654, 1458, 1371, 1320, 1267, 1148, 980, 918 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (dt, J = 15.5, 7.5 Hz, 1H), 5.88 (d, J = 15.5 Hz, 1H), 4.64−4.59 (m, 4H), 4.17 (q, J = 7.0 Hz, 2H), 3.69 (dd, J = 11.5, 4.5 Hz, 1H), 3.48 (s, 2H), 3.37 (dd, J = 10.0, 2.0 Hz, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 3.21 (m, 1H), 3.06 (m, 1H), 2.46 (dd, J = 14.5, 8.0 Hz, 1H), 2.27−2.20 (m, 2H), 1.83 (m, 1H), 1.79−1.74 (m, 3H), 1.64−1.57 (m, 2H), 1.27 (t, J = 7.0 Hz, 3H), 1.15 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 146.3, 123.3, 96.8, 95.8, 86.8, 82.3, 76.7, 75.5, 74.8, 73.3, 72.0, 60.2, 55.5, 55.3, 39.7, 33.6, 33.3, 27.4, 24.1, 14.2, 13.7; HRMS (FAB) calcd for $C_{22}H_{39}O_9$ [$(M + H)^+$] 447.2589, found 447.2590.

To a solution of the above alcohol (1.85 g, 4.14 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added trimethylsilylimidazole (0.91 mL, 6.21 mmol). After being stirred at room temperature overnight, the reaction mixture was quenched with MeOH. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc/hexanes) to give enoate **79** (1.85 g, 84%) as a colorless oil: $[\alpha]^{21}_D$ −23.5 (*c* 1.00, $CHCl_3$); IR (film) 2930, 2857, 1721, 1656, 1462, 1368, 1259, 1174, 1101, 1053, 976, 836, 775, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (m, 1H), 5.84 (m, 1H), 4.65−4.58 (m, 4H), 4.16 (q, J = 7.5 Hz, 2H), 3.68 (dd, J = 12.0, 5.0 Hz, 1H), 3.47 (s, 2H), 3.37−3.32 (m, 7H), 3.19 (td, J = 9.0, 4.5 Hz, 1H), 3.03 (td, J = 12.0, 4.0 Hz, 1H), 2.41 (dd, J = 14.5, 7.0 Hz, 1H), 2.21−2.15 (m, 2H), 1.92 (dd, J = 13.5, 7.5 Hz, 1H), 1.80−1.55 (m, 4H), 1.26 (t, J = 7.5 Hz, 3H), 1.11 (s, 6H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 147.0, 122.8, 96.8, 95.8, 87.7, 82.2, 77.7, 76.7, 75.6, 73.4, 72.1, 60.1, 55.5, 55.3, 38.7, 33.6, 33.4, 27.4, 24.4, 14.2, 13.7, 2.4 (×3); HRMS (FAB) calcd for $C_{25}H_{46}O_9SiNa$ [$(M + Na)^+$] 541.2803, found 541.2811.

Allylic Alcohol 80. To a solution of enoate **79** (2.54 g, 4.90 mmol) in CH_2Cl_2 (45 mL) at −78 °C was added DIBALH (1.02 M solution in hexane, 12.0 mL, 12.2 mmol). After being stirred at −78 °C for 30 min, the reaction mixture was quenched with MeOH, and saturated aqueous potassium sodium tartrate was added. The mixture was diluted with EtOAc and vigorously stirred at room temperature until the layers became clear. The organic layer was separated and washed with brine. The aqueous layers were combined and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 50% EtOAc/hexanes) gave allylic alcohol **80** (2.30 g, 99%) as a colorless oil: $[\alpha]^{21}_D$ −26.6 (*c* 1.00, $CHCl_3$); IR (film) 3542, 2947, 2361, 1376, 1251, 1148, 1102, 1039, 919, 840, 754 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.76−5.65 (m, 2H), 4.66 (d, J = 6.0 Hz, 1H), 4.61 (d, J = 6.5 Hz, 1H), 4.51 (d, J = 6.5 Hz, 1H), 4.49 (d, J = 6.5 Hz, 1H), 3.95−3.90 (m, 3H), 3.62 (d, J = 10.5 Hz, 1H), 3.59 (d, J = 10.5 Hz, 1H), 3.35 (m, 1H), 3.30 (td, J = 9.5, 4.0 Hz, 1H), 3.22 (s, 3H), 3.14 (s, 3H), 3.10 (m, 1H), 2.53 (ddd, J = 12.0, 4.5, 4.5 Hz, 1H), 2.37 (m, 1H), 2.14 (m, 1H), 1.97−1.75 (m, 4H), 1.61 (dd, J = 14.5, 11.0 Hz, 1H), 1.21 (s, 3H), 1.11 (s, 3H), 0.91 (brs, 1H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 132.0, 129.8, 97.1, 96.0, 88.8, 82.9, 78.3, 77.1, 76.5, 73.8, 72.4, 63.6, 55.2, 55.0, 39.4, 34.1, 33.8, 28.1, 24.8, 14.0, 2.6 (×3); HRMS (FAB) calcd for $C_{23}H_{44}O_8SiNa$ [$(M + Na)^+$] 499.2698, found 499.2708.

Hydroxy Epoxide 81. To a solution of allylic alcohol **80** (118.3 mg, 0.228 mmol) in CH_2Cl_2 (3 mL) were added 4 Å molecular sieves (59.0 mg) and (−)-diethyl tartrate (0.04 M solution in CH_2Cl_2, 1.3 mL, 0.052 mmol). The mixture was cooled to −20 °C, and $Ti(O^iPr)_4$ (0.015 mL, 0.046 mmol) was added. The resultant mixture was stirred at −20 °C for 30 min. To this mixture was added *t*-BuOOH (3.7 M solution in isooctane, 0.12 mL, 0.44 mmol). After being stirred at −20 °C overnight, the reaction mixture was treated with wet Na_2SO_4, allowed to warm to room temperature, and filtered through a plug of Celite. The filtrate was diluted with EtOAc and washed with water and brine. The aqueous layers were combined and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 30−70% EtOAc/hexanes) to give hydroxy epoxide **81** (105.9 mg, 94%) as a colorless oil: $[\alpha]^{20}_D$ −19.3 (*c* 1.00, $CHCl_3$); IR (film) 2948, 1452, 1378, 1252, 1149, 1104, 1040, 919, 840, 754 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 4.66 (d, J = 6.5 Hz, 1H), 4.62 (d, J = 6.5 Hz, 1H), 4.55 (d, J = 6.5 Hz, 1H), 4.52 (d, J = 6.5 Hz, 1H), 4.10 (dd, J = 11.5, 5.0 Hz, 1H), 3.63 (dd, J = 11.0, 5.0 Hz, 2H), 3.46 (dd, J = 10.5, 2.5 Hz, 1H), 3.31 (m, 1H), 3.26−3.21 (m, 4H), 3.15 (s, 3H), 3.07 (dd, J = 11.5, 5.5 Hz, 1H), 2.94 (dd, J = 11.5, 5.5 Hz, 1H), 2.87 (m, 1H), 2.73 (td, J = 5.5, 1.5 Hz, 1H), 2.56 (ddd, J = 11.5, 4.5, 4.5 Hz, 1H), 1.95−1.75 (m, 6H), 1.64−1.52 (m, 2H), 1.22 (s, 3H), 1.02 (s, 3H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 96.9, 95.8, 97.0, 82.2, 77.5, 76.7, 75.6, 73.5, 72.2, 57.9, 56.5, 55.6, 55.4, 44.7, 38.4, 33.6, 32.5, 27.4, 24.6, 13.8, 2.5 (×3); HRMS (FAB) calcd for $C_{23}H_{44}O_9SiNa$ [$(M + Na)^+$] 515.2647, found 515.2650.

Chloro Epoxide 82. To a solution of hydroxy epoxide **81** (105.9 mg, 0.215 mmol) in CCl_4 (4.0 mL) were added PPh_3 (155.8 mg, 0.592 mmol) and $NaHCO_3$ (13.3 mg, 0.158 mmol). After being refluxed for 1 day, the reaction mixture was concentrated under reduced pressure. Purification of residue by flash column chromatography (silica gel, 10−15% EtOAc/hexanes) gave chloro epoxide **82** (98.2 mg, 89%) as a colorless oil: $[\alpha]^{21}_D$ −32.8 (*c* 1.00, $CHCl_3$); IR (film) 2949, 1456, 1377, 1252, 1149, 1104, 1077, 1046, 919, 840, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.66−4.52 (m, 4H), 3.70 (dd, J = 11.0, 4.5 Hz, 1H), 3.65 (dd, J = 11.5, 5.0 Hz, 1H), 3.48−3.45 (m, 3H), 3.41 (dd, J = 10.5, 2.0 Hz, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 3.22 (td, J = 9.5, 4.5 Hz, 1H), 3.14 (m, 1H), 3.30 (m, 2H), 2.32 (ddd, J = 12.0, 4.5, 4.5 Hz, 1H), 1.92 (m, 1H), 1.84−1.60 (m, 6H), 1.13 (s, 3H), 1.10 (s, 3H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 96.9, 95.9, 87.0, 82.2, 77.5, 76.7, 75.6, 73.5, 72.2, 57.9, 56.5, 55.6, 55.4, 44.7, 38.4, 33.6, 32.5, 27.4, 24.6, 13.8, 2.5 (×3); HRMS (FAB) calcd for $C_{23}H_{43}ClO_8SiNa$ [$(M + Na)^+$] 533.2308, found 533.2321.

Propargylic Alcohol 83. To a freshly prepared solution of LDA [prepared from diisopropylamine (0.140 mL, 0.977 mmol) and *n*-BuLi (1.65 M solution in hexane, 0.540 mL, 0.891 mmol)] in THF (0.5 mL) at −40 °C was added a solution of chloro epoxide **82** (98.2 mg, 0.192 mmol) in THF (1.0 mL + 2 × 0.4 mL rinse). After being stirred at −40 °C for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl, diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 30−40% EtOAc/hexanes) to give propargylic alcohol **83** (78.0 mg, 86%) as a yellow oil: $[\alpha]^{20}_D$ −41.4 (*c* 1.00, $CHCl_3$); IR (film) 3455, 2947, 1377, 1252, 1218, 1148, 1104, 1039, 919, 840, 755, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.70−4.63 (m, 4H), 4.56 (m, 1H), 3.74 (dd, J = 12.0, 5.0 Hz, 1H), 3.60 (dd, J = 9.0, 2.5 Hz, 1H), 3.51 (s, 2H), 3.38 (s, 3H), 3.37 (s, 3H), 3.33 (m, 2H), 2.93 (brs, 1H), 2.52 (d, J = 2.0 Hz, 1H), 2.31 (ddd, J = 11.5, 4.5, 4.5 Hz, 1H), 2.03−1.62 (m,

7H), 1.17 (s, 3H), 1.16 (s, 3H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 96.9, 95.9, 87.1, 84.5, 81.9, 77.6, 76.7, 75.4, 73.4, 73.1, 72.1, 61.6, 55.6, 55.3, 38.4 (×2), 33.7, 27.4, 24.7, 13.7, 2.4 (×3); HRMS (FAB) calcd for $C_{23}H_{42}O_8SiNa$ [(M + Na)$^+$] 497.2541, found 497.2552.

Iodoalkyne 84. To a solution of propargylic alcohol **83** (149.6 mg, 0.290 mmol) in acetone (3.0 mL) at 0 °C were added NIS (78.3 mg, 0.348 mmol) and $AgNO_3$ (29.6 mg, 0.174 mmol). After being stirred at 0 °C for 1 h, the reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 25% EtOAc/hexanes) to give iodoalkyne **84** (173.0 mg, 91%) as a colorless oil: $[\alpha]^{20}_D$ −53.7 (*c* 0.51, $CHCl_3$); IR (film) 3429, 2946, 2889, 2824, 1531, 1350, 1251, 1142, 1104, 1079, 1038, 919, 840 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 4.70−4.64 (m, 3H), 4.51 (s, 2H), 3.91 (dd, J = 11.5, 5.0 Hz, 1H), 3.60 (dd, J = 19.0, 11.0 Hz, 2H), 3.53 (dd, J = 7.5, 2.0 Hz, 1H), 3.28−3.24 (m, 4H), 3.19 (m, 1H), 3.15 (s, 3H), 2.45 (ddd, J = 11.5, 4.5, 4.5 Hz, 1H), 2.39 (brs, 1H), 2.06 (ddd, J = 13.5, 7.0, 2.5 Hz, 1H), 1.97−1.77 (m, 3H), 1.75−1.69 (m, 2H), 1.50 (m, 1H), 1.21 (s, 3H), 0.99 (s, 3H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 97.1, 96.5, 95.9, 87.0, 82.1, 78.0, 77.1, 75.6, 73.6, 72.5, 63.4, 55.3, 55.0, 39.2, 38.8, 34.2, 28.1, 24.6, 13.9, 2.5 (×3), 1.8; HRMS (FAB) calcd for $C_{23}H_{41}IO_8SiNa$ [(M + Na)$^+$] 623.1508, found 623.1516.

Vinyl Iodide 69. To a solution of iodoalkyne **84** (169.3 mg, 0.282 mmol) in THF/*i*-PrOH (1:1, v/v, 5.0 mL) at 0 °C were added *o*-nitrobenzenesulfonyl hydrazide (286 mg, 1.32 mmol) and Et_3N (0.180 mL, 1.32 mmol). After being stirred at room temperature for 5 h, the reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% acetone/hexanes) to give vinyl iodide **69** (154.9 mg, 91%) as a colorless oil: $[\alpha]^{20}_D$ −13.5 (*c* 1.00, $CHCl_3$); IR (film) 3458, 2948, 1455, 1376, 1251, 1216, 1139, 1103, 1038, 919, 840, 753, 728, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (m, 1H), 6.25 (m, 1H), 4.66−4.59 (m, 4H), 4.55 (m, 1H), 3.70 (dd, J = 10.5, 5.5 Hz, 1H), 3.48 (s, 2H), 3.45 (dd, J = 10.5, 2.5 Hz, 1H), 3.35 (s, 3H), 3.23 (s, 3H), 3.23−3.18 (m, 2H), 2.38 (ddd, J = 11.5, 4.0, 4.0 Hz, 1H), 1.92 (m, 1H), 1.84 (ddd, J = 14.0, 5.0, 2.5 Hz, 1H), 1.80−1.70 (m, 2H), 1.68−1.59 (m, 3H), 1.14 (s, 3H), 1.13 (s, 3H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 96.8, 95.6, 87.9, 82.6, 81.8, 77.6, 76.6, 75.2, 74.2, 73.3, 72.1, 55.5, 55.3, 38.3, 36.2, 33.7, 27.3, 24.5, 13.6, 2.5 (×3); HRMS (FAB) calcd for $C_{23}H_{43}IO_8SiNa$ [(M + Na)$^+$] 625.1664, found 625.1665.

***cis*-Olefin 85.** To a solution of iodide ***ent*-21** (111.7 mg, 0.232 mmol) in diethyl ether (2.3 mL) was added *B*-MeO-9-BBN (1.0 M solution in hexane, 0.60 mL, 0.60 mmol). The resulting mixture was cooled to −78 °C and treated with *t*-BuLi (1.58 M solution in pentane, 0.51 mL, 0.81 mmol) at once. The mixture was stirred at −78 °C for 5 min before THF (2.3 mL) was added. The resultant mixture was allowed to warm to room temperature and stirred for 1 h. In a separate flask, vinyl iodide **69** (104.2 mg, 0.173 mmol) was dissolved in DMF (1.7 mL), to which $PdCl_2(dppf)\cdot CH_2Cl_2$ (14 mg, 0.017 mmol), Ph_3As (21.2 mg, 0.069 mmol), and 3 M aqueous Cs_2CO_3 (0.17 mL, 0.51 mmol) were added sequentially. The ethereal solution of alkylborate was then cannulated into the DMF solution, and the resulting mixture was stirred at 50 °C overnight. The reaction mixture was diluted with H_2O and extracted three times with diethyl ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography of the residue (silica gel, 10−50% EtOAc/hexanes) gave *cis*-olefin **85** (127.2 mg, 88%) as a colorless oil: $[\alpha]^{18}_D$ −7.4 (*c* 1.00, $CHCl_3$); IR (film) 2936, 1514, 1455, 1375, 1249, 1038, 840, 749, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.23 (m, 7H), 6.85−6.83 (m, 2H), 5.53−5.43 (m, 2H), 4.66−4.57 (m, 5H), 4.51−4.44 (m, 4H), 3.77 (s, 3H), 3.67 (dd, J = 11.5, 5.0 Hz, 1H), 3.53−3.40 (m, 5H), 3.34 (s, 3H), 3.31 (s, 3H), 3.22 (m, 1H), 3.16−3.08 (m, 2H), 2.29 (m, 1H), 2.22−2.09 (m, 2H), 1.94−1.84 (m, 3H), 1.80−1.71 (m, 3H), 1.68−1.49 (m, 5H), 1.13 (s, 3H), 1.12 (s, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 138.4, 133.9, 131.3, 129.2, 128.9 (×2), 128.8, 128.4 (×2), 127.8 (×2), 127.6, 113.7 (×2), 96.9, 95.9, 88.3, 86.3, 81.6, 77.7, 76.6, 74.5, 73.5, 72.9, 72.1, 68.2, 67.1, 55.6, 55.3 (×2), 38.3, 37.6, 35.9, 34.4, 33.8, 32.1, 31.8, 27.4, 24.6, 15.8, 14.0, 13.7, 2.5 (×3); HRMS (FAB) calcd for $C_{46}H_{74}O_{11}SiNa$ [(M + Na)$^+$] 853.4893, found 853.4902.

Hydroxy Alkene 68. To a solution of *cis*-olefin **85** (53.0 mg, 0.064 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C were added Et_3N (0.02 mL, 0.128 mmol) and TIPSOTf (0.025 mL, 0.096 mmol). After being stirred at 0 °C for 4 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10−30% EtOAc/hexanes) to give triisopropylsilyl ether (50.6 mg, 80%) as a colorless oil: $[\alpha]^{18}_D$ −6.5 (*c* 1.00, $CHCl_3$); IR (film) 2942, 2865, 1249, 1148, 1084, 1038, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.25 (m, 7H), 6.88−6.85 (m, 2H), 5.53 (m, 1H), 5.31 (m, 1H), 4.71 (m, 1H), 4.65−4.57 (m, 4H), 4.51−4.44 (m, 4H), 3.77 (s, 3H), 3.62 (dd, J = 11.5, 5.0 Hz, 1H), 3.54−3.45 (m, 5H), 3.33 (s, 3H), 3.31 (s, 3H), 3.20 (m, 1H), 3.13−3.08 (m, 2H), 2.34 (ddd, J = 11.0, 3.5, 3.5 Hz, 1H), 2.12−2.01 (m, 2H), 1.91−1.59 (m, 10H), 1.49 (m, 1H), 1.13 (s, 3H), 1.08 (s, 3H), 1.06 (m, 21H), 0.96−0.93 (m, 6H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 138.6, 135.9, 131.3, 129.0 (×2), 128.3 (×2), 127.6 (×2), 127.5, 126.6, 113.7 (×2), 96.8, 96.1, 86.2, 84.2, 81.5, 77.5, 76.7, 75.9, 74.3 (×2), 72.9, 72.3, 68.7, 66.6, 55.4, 55.3, 55.2, 39.2, 38.7, 36.2, 34.0, 33.9, 32.9, 32.5, 27.5, 24.7, 18.2 (×6), 15.3, 15.0, 13.7, 12.4 (×3), 2.5 (×3); HRMS (FAB) calcd for $C_{55}H_{94}O_{11}Si_2Na$ [(M + Na)$^+$] 1009.6227, found 1009.6240.

To a solution of the above triisopropylsilyl ether (113.8 mg, 0.115 mmol) in CH_2Cl_2/pH 7 phosphate buffer (10:1, v/v, 3.3 mL) at 0 °C was added DDQ (28.5 mg, 0.127 mmol). After being stirred at room temperature for 1 h, the reaction mixture was cooled to 0 °C and treated with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5−20% EtOAc/hexanes) gave hydroxy alkene **68** (96.0 mg, 96%) as a colorless oil: $[\alpha]^{18}_D$ −11.3 (*c* 1.00, $CHCl_3$); IR (film) 3522, 2940, 2866, 1464, 1251, 1102, 1038, 839, 734, 683, 504, 445 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 5.39−5.31 (m, 2H), 4.98−4.58 (m, 5H), 4.51 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 3.67 (dd, J = 11.5, 5.0 Hz, 1H), 3.55−3.44 (m, 4H), 3.35 (s, 3H), 3.33 (s, 3H), 3.22 (m, 1H), 3.15−3.13 (m, 2H), 3.10 (brs, 1H), 3.03 (m, 1H), 2.34−2.25 (m, 2H), 1.97 (m, 1H), 1.87 (m, 1H), 1.79−1.58 (m, 9H), 1.31 (m, 1H), 1.12 (s, 3H), 1.09 (s, 3H), 1.05 (m, 21H), 0.93 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 134.8, 128.9, 128.4 (×2), 127.6 (×2), 127.5, 96.9, 95.4, 85.3, 81.6, 78.6, 77.5, 76.5, 75.6, 73.4, 72.9, 72.2, 68.4, 66.6, 55.5, 55.3, 39.9, 38.7, 35.5, 34.0, 33.4, 33.3, 32.9, 27.5, 24.5, 18.2 (×6), 15.7, 13.7, 12.4 (×3), 12.1, 2.5 (×3); HRMS (FAB) calcd for $C_{47}H_{86}O_{10}Si_2Na$ [(M + Na)$^+$] 889.5652, found 889.5662.

Hydroxy Alkene 87. To a solution of hydroxy alkene **68** (50.6 mg, 0.058 mmol) in THF (1.0 mL) at 0 °C was added TBAF (1.0 M solution in THF, 0.15 mL, 0.15 mmol). After being stirred at room temperature for 2.5 h, the reaction mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 70−90% EtOAc/hexanes) gave hydroxy alkene **87** (37.3 mg, 100%) as a colorless oil: $[\alpha]^{20}_D$ −14.3 (*c* 0.65, CH_3OH); IR (film) 3445, 2934, 2878, 1456, 1375, 1217, 1147, 1099, 1076, 1037, 916, 740, 699 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.35−7.33 (m, 4H),

7.27 (m, 1H), 5.50 (m, 1H), 5.41 (m, 1H), 4.70 (d, J = 7.0 Hz, 1H), 4.64−4.57 (m, 4H), 4.52 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 3.75 (dd, J = 11.5, 5.0 Hz, 1H), 3.58−3.49 (m, 4H), 3.46 (d, J = 10.5 Hz, 1H), 3.43 (d, J = 10.5 Hz, 1H), 3.37−3.35 (m, 2H), 3.34 (s, 3H), 3.28 (s, 3H), 3.25−3.21 (m, 2H), 3.06 (m, 1H), 2.34 (ddd, J = 12.0, 4.0, 4.0 Hz, 1H), 2.27 (m, 1H), 2.12 (m, 1H), 1.87−1.57 (m, 10H), 1.41 (m, 1H), 1.11 (s, 3H), 1.07 (s, 3H), 0.95 (d, J = 6.0 Hz, 3H), 0.93 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 140.0, 135.4, 130.3, 129.1 (×2), 128.4 (×2), 128.1, 97.4, 96.3, 86.6, 82.2, 77.8, 77.4, 76.7, 74.3, 74.1, 73.2, 72.8, 68.9, 66.3, 55.6, 55.2, 40.0, 39.7, 36.4, 34.5, 34.4, 33.7, 33.1, 28.4, 24.8, 15.0, 14.3, 14.0; HRMS (FAB) calcd for $C_{35}H_{58}O_{10}Na$ [(M + Na)$^+$] 661.3922, found 661.3928.

Iodide 88. To a solution of bis(*sym*-collidine)$AgPF_6$ (13.7 mg, 0.028 mmol) in CH_2Cl_2 (0.5 mL) was added I_2 (5.7 mg, 0.022 mmol). After being stirred at room temperature for 5 min, a solution of hydroxy alkene **87** (11.9 mg, 0.019 mmol) in CH_2Cl_2 (0.8 mL + 2 × 0.4 mL rinse) was added. After being stirred at room temperature for 30 min, the reaction mixture was filtered through a plug of Celite. The filtrate was diluted with EtOAc and washed with 10% aqueous $Na_2S_2O_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 60% diethyl ether/benzene) to give iodide **88** (11.6 mg, 83%) as a colorless oil: $[\alpha]^{19}_D$ −7.2 (*c* 1.00, MeOH); IR (film) 3434, 2935, 2876, 1595, 1453, 1236, 1075, 1043, 968, 838, 739, 699, 616 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.35−7.34 (m, 4H), 7.28−7.25 (m, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.62 (d, J = 7.0 Hz, 1H), 4.61−4.58 (m, 2H), 4.52 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.33 (dd, J = 6.0, 3.0 Hz, 1H), 4.08 (d, J = 4.0 Hz, 1H), 3.93 (ddd, J = 9.0, 6.5, 2.5 Hz, 1H), 3.77 (dd, J = 12.0, 4.0 Hz, 2H), 3.75−3.69 (m, 3H), 3.65−3.52 (m, 2H), 3.46 (d, J = 10.5 Hz, 1H), 3.43 (d, J = 10.5 Hz, 1H), 3.31 (s, 3H), 3.29−3.28 (m, 5H), 2.41−2.36 (m, 2H), 2.29 (ddd, J = 12.0, 8.0, 4.0 Hz, 1H), 1.96−1.61 (m, 10H), 1.23 (m, 1H), 1.12 (s, 3H), 1.10 (s, 3H), 1.01 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 140.0, 129.0 (×2), 128.2 (×2), 128.1, 97.4, 96.4, 88.1, 88.0, 82.4, 77.4, 76.2, 75.9, 74.7, 74.6, 73.9, 73.2, 72.7, 68.4, 55.6, 55.2, 53.6, 42.2, 39.8, 38.1, 35.7, 34.5, 33.6, 31.9, 28.3, 24.6, 17.4, 14.7, 13.9; HRMS (FAB) calcd for $C_{35}H_{58}IO_{10}$ [(M + H)$^+$] 765.3069, found 765.3080.

Acetate 89. To a solution of iodide **88** (41.0 mg, 0.054 mmol) in THF (3.0 mL) at 0 °C were added Et_3N (0.04 mL, 0.273 mmol), DMAP (0.70 mg, 0.005 mmol), and Ac_2O (0.02 mL, 0.219 mmol). After being stirred at room temperature overnight, the reaction mixture was cooled to 0 °C and quenched with MeOH. The mixture was diluted with EtOAc, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 70% EtOAc/hexanes) to give acetate **89** (42.7 mg, 100%) as a colorless oil: $[\alpha]^{19}_D$ −10.0 (*c* 1.00, CH_3OH); IR (film) 3462, 2932, 1734, 1373, 1237, 1097, 1038, 968, 698 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.35−7.32 (m, 4H), 7.28−7.25 (m, 1H), 4.81 (m, 1H), 4.65 (d, J = 6.5 Hz, 1H), 4.63 (d, J = 6.5 Hz, 1H), 4.60 (d, J = 6.5 Hz, 1H), 4.58 (d, J = 6.5 Hz, 1H), 4.53−4.45 (m, 3H), 3.85 (ddd, J = 10.0, 6.5, 4.0 Hz, 1H), 3.75−3.69 (m, 2H), 3.60−3.51 (m, 4H), 3.44 (dd, J = 11.0, 7.0 Hz, 2H), 3.33 (s, 3H), 3.28 (s, 3H), 3.23 (m, 1H), 3.09 (m, 1H), 2.40 (m, 1H), 2.34−2.25 (m, 2H), 2.07 (s, 3H), 1.92−1.84 (m, 3H), 1.79−1.55 (m, 6H), 1.29−1.16 (m, 2H), 1.10 (s, 3H), 1.09 (s, 3H), 1.02 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 170.3, 140.1, 129.0 (×2), 128.2 (×2), 128.1, 97.4, 96.6, 87.7, 86.6, 82.7, 77.4, 76.7, 76.6, 75.7, 74.7, 74.3, 73.3, 72.7, 68.4, 55.6, 55.2, 48.7, 41.8, 40.3, 35.9, 35.7, 34.7, 33.6, 31.9, 28.4, 24.4, 21.3, 17.4, 14.6, 14.0; HRMS (FAB) calcd for $C_{37}H_{59}IO_{11}Na$ [(M + Na)$^+$] 829.2994, found 829.3004.

Tricyclic Compound 90. To a solution of acetate **89** (26.0 mg, 0.033 mmol) in THF (5.0 mL) was added Ph_3SnH (0.6 M solution in THF, 1.0 mL, 0.60 mmol). To the resultant mixture heated at 80 °C was added a solution of AIBN (4.9 mg, 0.030 mmol) in THF (1.0 mL) via cannula. After being refluxed for 1.5 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 15−90% EtOAc/hexanes) to give crude material, which was used in the next reaction without further purification.

To a solution of the above crude material in MeOH (4.0 mL) was added 20% $Pd(OH)_2$/C (26.8 mg). After the reaction mixture was stirred at room temperature for 30 min under an atmosphere of hydrogen, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% MeOH/$CHCl_3$) to give tricyclic compound **90** (26.5 mg, 96% for the two steps) as a colorless oil: $[\alpha]^{28}_D$ −25.6 (*c* 1.00, $CHCl_3$); IR (film) 3477, 3414, 2935, 1244, 1148, 1096, 1043, 834 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 5.18 (m, 1H), 4.66 (d, J = 6.5 Hz, 1H), 4.61 (d, J = 6.5 Hz, 1H), 4.60 (s, 2H), 4.09 (ddd, J = 16.0, 9.0, 4.0 Hz, 1H), 3.75 (dd, J = 11.5, 4.5 Hz, 1H), 3.65 (m, 2H), 3.60−3.55 (m, 2H), 3.47−3.42 (m, 4H), 3.32 (s, 3H), 3.29 (s, 3H), 3.22 (ddd, J = 9.5, 9.5, 4.0 Hz, 1H), 3.09 (m, 1H), 2.35 (ddd, J = 9.0, 4.0, 4.0 Hz, 1H), 2.27 (m, 1H), 1.99 (s, 3H), 1.96−1.82 (m, 3H), 1.80−1.74 (m, 3H), 1.73−1.55 (m, 7H), 1.19−1.12 (m, 1H), 1.11 (s, 3H), 1.04 (s, 3H), 1.02 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 170.4, 129.1, 97.4, 96.4, 86.0, 85.5, 82.8, 77.4, 76.9, 74.4, 74.1, 73.6, 72.8, 71.8, 55.6, 55.2, 42.0, 41.7, 40.2, 37.0, 36.6, 35.9, 34.5, 31.4, 28.4, 24.4, 21.4, 17.7, 14.2, 14.1; HRMS (FAB) calcd for $C_{30}H_{55}O_{11}$ [(M + H)$^+$] 591.3739, found 591.3739.

Ester 91. To a solution of tricyclic compound **90** (16.7 mg, 0.027 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added Dess−Martin periodinane (23 mg, 0.054 mmol). After being stirred at room temperature, the reaction mixture was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3. The resultant mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 70% EtOAc/hexanes) gave crude aldehyde.

To a solution of the above aldehyde in THF/H_2O (5:1, v/v, 1.8 mL) were added 2-methyl-2-butene (0.016 mL, 0.153 mmol) and NaH_2PO_4 (2.8 mg, 0.023 mmol). The reaction mixture was cooled to 0 °C and treated with $NaClO_2$ (4.8 mg, 0.054 mmol). After being stirred at room temperature for 1 h, the reaction mixture was diluted with H_2O and acidified with 0.5 M aqueous HCl. The mixture was extracted two times with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% MeOH/$CHCl_3$) to give crude carboxylic acid, which was used in the next reaction without purification.

To a solution of the above carboxylic acid in MeOH/benzene (1:1, v/v, 3.0 mL) was added $TMSCHN_2$ (2.0 M solution in hexane, 0.023 mL, 0.046 mmol). After being stirred at room temperature for 30 min, the resultant mixture was concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 70−100% EtOAc/hexanes) gave ester **91** (8.5 mg, 52% for the three steps) as a colorless oil: $[\alpha]^{28}_D$ −16.7 (*c* 1.00, $CHCl_3$); IR (film) 3464, 2935, 2360, 1736, 1438, 1375, 1242, 1148, 1095, 1038, 917 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 5.17 (m, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.62−4.58 (m, 3H), 4.12 (m, 1H), 3.75 (dd, J = 11.5, 4.5 Hz, 1H) 3.63 (s, 3H), 3.59 (s, 1H), 3.50 (dd, J = 9.0, 4.0 Hz, 1H), 3.47−3.41 (m, 3H), 3.32 (s, 3H), 3.29 (s, 3H), 3.22 (ddd, J = 9.5, 9.5, 4.0 Hz, 1H), 3.08 (ddd, J = 13.0, 9.5, 4.0 Hz, 1H), 2.37−2.33 (m, 2H), 2.28 (m, 1H), 2.01−1.91 (m, 5H), 1.89−1.76 (m, 5H), 1.73−1.55 (m, 6H), 1.11 (s, 3H), 1.05 (d, J = 4.5 Hz, 3H), 1.05 (s, 3H), 0.90 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 173.2, 170.4, 129.1, 97.4, 96.4, 85.5, 84.9, 82.8, 77.4, 76.9, 74.4, 74.0, 72.8, 71.7, 55.6, 55.2, 51.6, 42.0, 41.6,

40.2, 38.6, 36.6, 35.8, 34.5, 32.4, 28.4, 24.4, 21.4, 18.2, 14.1 (×2); HRMS (FAB) calcd for $C_{31}H_{54}O_{12}Na$ [$(M + Na)^+$] 641.3508, found 641.3514.

A/BC-Ring Model Compound 67. To a solution of ester **91** (6.0 mg, 0.010 mmol) in MeOH/THF/H_2O (1:1:1, v/v/v, 1.5 mL) at 0 °C was added LiOH·H_2O (2.2 mg, 0.049 mmol). After being stirred at room temperature for 5.5 h, the reaction mixture was cooled to 0 °C and acidified with 0.25 M aqueous HCl. The mixture was extracted five times with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20% MeOH/$CHCl_3$) gave the A/BC ring model compound **67** (5.1 mg, 93%) as colorless oil: $[\alpha]^{27}_D$ −11.3 (*c* 0.45, MeOH); IR (film) 3420, 2934, 1716, 1378, 1148, 1043, 918 cm^{-1}; ^1H NMR (600 MHz, 1:1 C_5D_5N/CD_3OD) δ 4.62 (d, J = 6.6 Hz, 1H), 4.60 (d, J = 6.6 Hz, 1H), 4.57 (d, J = 6.6 Hz, 1H), 4.55 (d, J = 6.6 Hz, 1H), 4.43 (m, 1H), 4.17 (m, 1H), 3.84 (dd, J = 11.4, 4.8 Hz, 1H), 3.58 (m, 1H), 3.49 (d, J = 10.8 Hz, 1H), 3.45 (d, J = 10.8 Hz, 1H), 3.40 (dd, J = 9.6, 4.6 Hz, 1H), 3.28−3.19 (m, 8H), 2.40 (ddd, J = 11.4, 4.2, 4.2 Hz, 1H), 2.34 (d, J = 15.0, 3.0 Hz, 1H), 2.13−2.09 (m, 2H), 2.03−1.92 (m, 4H), 1.80−1.59 (m, 7H), 1.50 (ddd, J = 13.8, 9.6, 2.4 Hz, 1H), 1.19 (d, J = 6.6 Hz, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 0.81 (d, J = 7.2 Hz, 3H), (three protons missing due to the H/D exchange); ^{13}C NMR (150 MHz, 1:1 C_5D_5N/CD_3OD) δ 176.8, 151.0, 130.1, 98.5, 97.5, 87.6, 86.2, 84.2, 78.5, 78.1, 75.2, 73.9, 69.2, 56.6, 56.4, 46.0, 42.7, 41.4, 41.2, 40.3, 36.8, 35.7, 33.4, 29.4, 25.6, 19.6, 15.2, 15.1; HRMS (FAB) calcd for $C_{28}H_{51}O_{11}$ [$(M + H)^+$] 563.3426, found 563.3439.

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Supporting Information Available: Detailed synthetic schemes for compounds **18b−d**, experimental details for compounds not described in Experimental Section, 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.

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