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Stereoselective Construction of 2,7-Disubstituted *fused*-Bis Tetrahydrofuran Skeletons: Biomimetic-Type Synthesis and Biological Evaluation of (±)- and (−)-Aplysiallene and Their Derivatives

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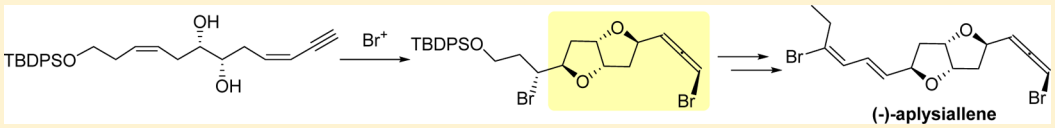
Supporting Information



ABSTRACT: A series of *trans*/*trans* and *cis*/*cis fused*-bis tetrahydrofuran compounds have been obtained stereoselectively in high yields via a one-pot operation involving the intramolecular haloetherification of (*Z*,*Z*)-diene diol **19a** and (*E*,*E*)-diene disilylether **19d**, respectively. This method was subsequently applied to the biomimetic-type synthesis of (±)- and (−)-aplysiallene. The inhibitory activities of these compounds and their bromodiene isomers toward Na^+/K^+ ATPase were determined in vitro, and gave IC_{50} values of approximately 15 μM in all cases.

INTRODUCTION

The bicyclic structure of the 2,7-disubstituted-1,8-dioxabicyclo[3.3.0]octane (*fused*-bis THF) scaffold can exist as one of three different stereoisomers, the *trans*/*trans*, *cis*/*trans*, and *cis*/*cis* isomers **1**−**3**. This structural motif can be found in various natural products, such as (−)-aplysiallene,[1] (−)-kumausallene,[2] and laurenidificin[3] (Figure 1). All of these

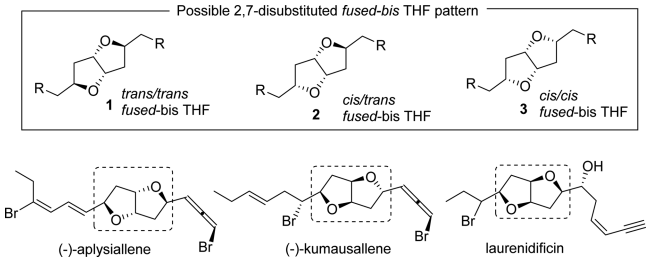


Figure 1. Possible 2,7-disubsutituted *fused*-bis THF structures, including the natural products (−)-aplysiallene, (−)-kumausallene, and laurenidificin.

compounds have *cis*-fused [3.3.0]bicyclic ring systems. Although *trans*-fused ones are nominally possible, they are much higher in energy and none have been reported.

Considerable research efforts have been directed toward the biosynthesis of bromine-containing cyclic ether compounds derived from red algae. These compounds are generally believed to be synthesized via intramolecular bromoetherification of the virtual precursor laurediol, and numerous studies have been conducted to develop a deeper understanding of the biosynthesis of these compounds using enzymes.[4] It has also been suggested that cyclic ethers such as (−)-kumausallene are biosynthesized by the double bromoetherification of laurediol, based on the isolation of *trans*-deacetylkumausyne from *Laurencia nipponica* (Scheme 1).[2b]

Although the pathway responsible for the biosynthesis of (−)-aplysiallene remains unknown, the structure of this compound is very similar to that of (−)-kumausallene. On the basis of the similarity in structure of these two compounds, it seems plausible that (−)-aplysiallene could also be biosynthesized through a similar pathway via the double bromoetherification of a suitable diene-yne diol.

Several synthetic studies toward the construction of natural products containing a *fused*-bis THF skeleton have been performed.[5] However, many of these strategies involve generating the required bis-THF framework via sequential (or tandem) ring-closing reactions of 1,2-diols bearing pendant functional groups, such as alkenes, epoxides, and alcohols. There are no reports pertaining to the total synthesis of *fused*-bis THF-containing systems via direct double bromoetherification of a suitable diene-yne diol precursor.[5] Wolfe et al. and Pagencopf et al. succeeded in the step-by-step stereoselective synthesis of *trans*/*trans fused*-bis THFs.[5a,b] For the stereoselective synthesis of *cis*/*trans fused*-bis THF compounds, many studies have appeared associated with the preparation of kumausallene.[5c−e] It is noteworthy that these methods involve initial formation of a mono-THF ring, followed by the

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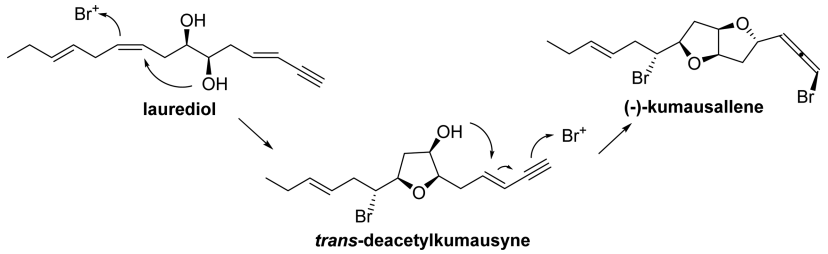
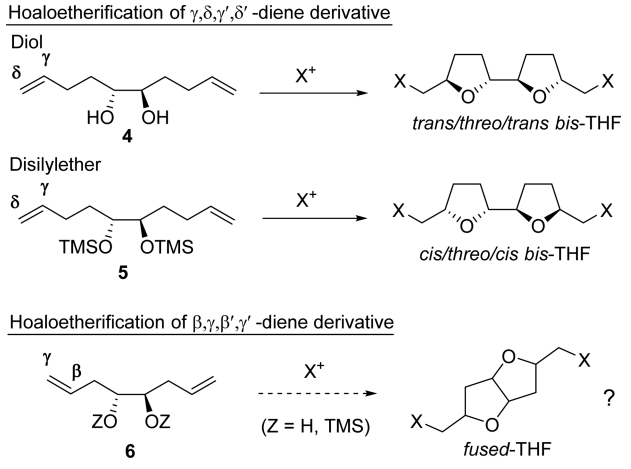
Scheme 1. Postulated Biosynthesis of Cyclic Bromoether Compounds



construction of a second THF ring in a separate step, to give the *fused*-bis THF skeleton, and usually require multiple steps. Lee et al. report a one-step synthesis of *cis*/*cis fused*-bis THF skeletons,[5f] and Martin et al. describe a method for the one-pot construction of *trans*/*trans* and *cis*/*trans fused*-bis THF compounds.[5g] However, the former method involves radical cyclization, and the bis-THF product must undergo many subsequent steps for the transformation of the side chains, and the latter method gives low stereoselectivity.

It is well-known that the double haloetherification of (5*R*,6*R*)-1,9-decadiene-5,6-diol **4**, whose olefins are located at the *γ*,*δ*,*γ*′,*δ*′-positions relative to the two hydroxyl functions, leads to the selective formation of the *trans*/*threo*/*trans* bis-THF skeleton because of the repulsion between the substituents at the 2- and 5-positions of the THF ring.[6] In contrast, we found that the bissilylether **5** gave the *cis*/*threo*/*cis* bis-THF skeleton selectively because of the repulsion between the silyl groups at the 2- and 5-positions.[7a] On the basis of this result, it was envisaged that 1,7-octadiene-4,5-diol **6**, which has olefin moieties at the *β*,*γ*,*β*′,*γ*′-positions relative to its hydroxyl groups, would give a *fused*-bis THF skeleton. These results demonstrate that unprotected diene diol gives the *trans*/*trans*-isomer of the *fused*-bis THF skeleton, whereas protected diene diol affords the corresponding *cis*/*cis*-isomer (Scheme 2).[8]

Scheme 2. Double Haloetherification of *γ*,*δ*,*γ*′,*δ*′-Dienediol 4 and Its Silylether 5, and Postulated Outcome of the Haloetherification of the *β*,*γ*,*β*′,*γ*′-Dienediol Derivative 6



In this manuscript, we report the stereoselective synthesis of a *fused*-bis THF skeleton by the double haloetherification of a diene diol substrate and a related derivative, as part of our ongoing research toward the stereoselective synthesis of bioactive natural products containing a 2,5-disubstituted *bis*-THF ring,[7] and the highly stereoselective formation of *trans*/*trans* and *cis*/*cis fused*-bis THF compounds in high yields using a one-pot procedure (Scheme 3).

This method was subsequently applied to the biomimetic-type synthesis of (±)- and (−)-aplysiallene, involving the double bromoetherification of diene diol derivative **7** as a key step (Scheme 4). The inhibitory activities of (±)- and (−)-aplysiallene, as well as their bromodiene isomers, were subsequently evaluated toward Na^+/K^+ ATPase.

RESULT AND DISCUSSION

Stereoselective Construction of *fused*-Bis THF Rings. Our initial work toward assessing the validity of this approach was conducted using 1,7-octadiene-4,5-diol (**6a**) and its derivatives **6b** and **6c** as model substrates, as they all contain two terminal olefins (Table 1). The reaction of **6a** with NIS (3.0 equiv) in CH_2Cl_2 gave two *fused*-bis THF compounds, including the *trans*/*trans* **9** and *trans*/*cis* **10** isomers, in total good yields but with poor selectivity. *cis*/*cis* isomer **11** was not observed (Table 1, entry 1). In contrast, reaction of the bistrimethylsilyl ether **6b** under the same conditions gave a 2:1 mixture of the *cis*/*trans* and *cis*/*cis fused*-bis THF compounds **10** and **11** in excellent total yield, but with poor selectivity (Table 1, entry 2). The use of **6c** as a substrate, bearing two bulkier triethylsilyl groups instead of the trimethylsilyl groups in **6b**, led to the same ratio of the *cis*/*trans* isomer **10** to *cis*/*cis* isomer **11** in a poor yield, with the mono-THF compound being obtained as the major product (Table 1, entry 3). In theses two cases, *trans*/*trans* isomer **9** was not observed. The stereochemistry of the products were determined by ^{1}H NMR analyses. Compounds **9** and **11** showed symmetrical ^{1}H NMR spectra, whereas compound **10** showed an asymmetrical one. Furthermore, compound **11** exhibited an NOE between the two protons on the carbons bearing the oxygen atoms (see Supporting Information).

The results in Table 1 show that the use of unprotected diol **6a** led to the formation of the *trans*/*trans*-isomer **9** as the major product, whereas protected diols **6b** and **6c** gave the formation of the *cis*/*cis*-isomer **11**. However, the selectivities observed in all three cases were poor. In these reactions, *fused*-bis THF rings **9**−**11** were formed from the diene compounds **6a**−**c** in a stepwise manner in one pot. These reactions would initially undergo a single iodoetherification reaction to give a mono-THF ring, which would subsequently undergo a second iodoetherification to give *fused*-bis THF rings **9**−**11**. Scheme 5 shows the case for the reaction of **6a**. TLC analysis of the reaction mixture revealed the presence of two mono-THF compounds, whose structures were determined by ^{1}H NMR and IR. The second cyclization reaction would proceed in a *trans*-fashion through intermediates **ii** and **iv**, avoiding the unfavorable endo transition states in intermediates **i** and **iii**. This therefore suggests that the first iodocyclization step lacks

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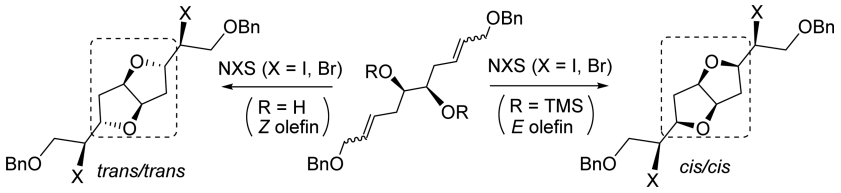
Scheme 3. Stereoselective Synthesis of *trans*/*trans* and *cis*/*cis fused*-Bis THF Compounds



Scheme 4. Biomimetic-Type Synthesis of (±)- and (−)-Aplysiallene via the Double Bromoetherification of Diene Diol 7

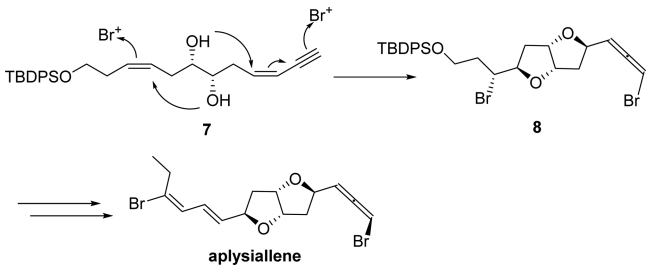
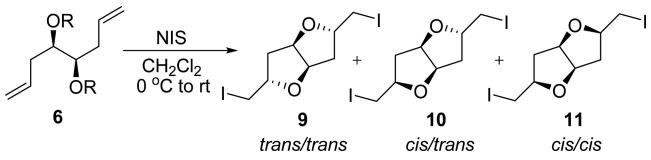


Table 1. Double Iodoetherification of 1,7-Octadiene-4,5-diol and Its Derivatives



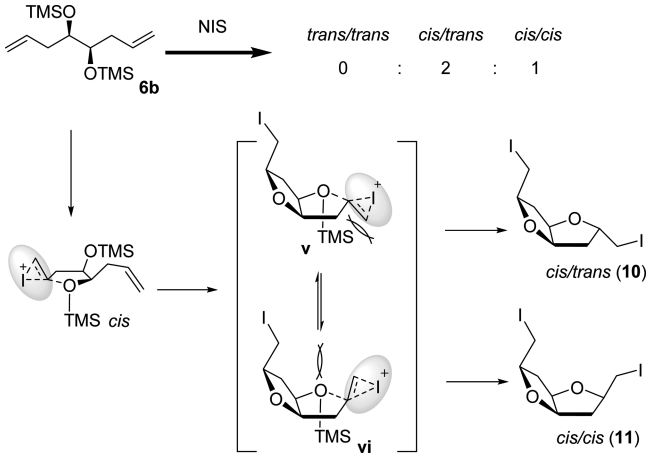
entry	6	R	ratio[a] 9:10:11	yield (%)[b]
1	**6a**	H	7:4:NO[d]	73
2	**6b**	TMS	NO:2:1	100
3[c]	**6c**	TES	NO:2:1	25

[a]Determined by ^{1}H NMR. [b]Combined isolated yield. [c]Mono-THF (*cis*) 57%, overall yield 82%. [d]NO means "not observed".

stereocontrol and that the level of repulsion in the *cis*-intermediate is not sufficiently large to favor the exclusive formation of the *trans*/*trans*-isomer (Scheme 5).

Scheme 6 shows the mechanism for the double iodoetherification of **6b**. TLC analysis of this reaction mixture revealed

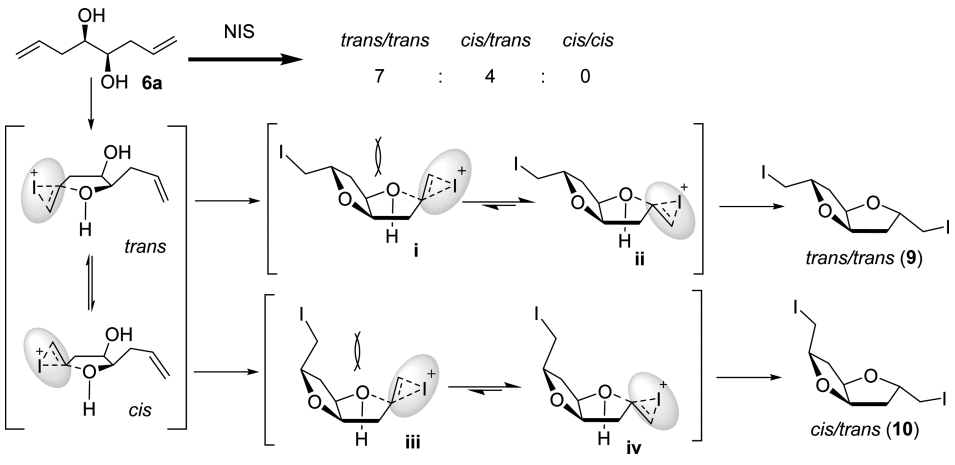
Scheme 6. Mechanistic Considerations for the Double Iodoetherification of the Disilylether 6b



the presence of only one mono THF compound, which suggests that the first step in this reaction was a stereoselective *cis*-iodocyclization. This implies that the second cyclization lacked stereocontrol, which was attributed to competition from transition state **v**, which would experience repulsion between the trimethylsilyl group and the side chain, and transition state **vi**, which would experience repulsion between the bis-THF rings and endo orientation of the side chain.

It was subsequently envisaged that the iodoetherification of substrates bearing internal olefin moieties instead of terminal olefin moieties would proceed more selectively (Scheme 7). In the case of a diene diol, the first cyclization would be more important than the second one, because the second cyclization would proceed in a *trans*-fashion, as shown in Scheme 5. The extent of the repulsion between the substituents following the first cyclization would therefore force the equilibrium between

Scheme 5. Mechanistic Considerations for the Double Iodoetherification of 1,7-Octadiene-4,5-diol (6a)



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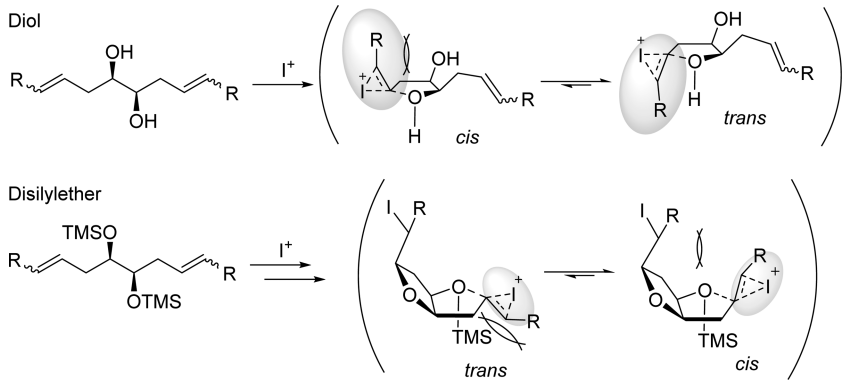
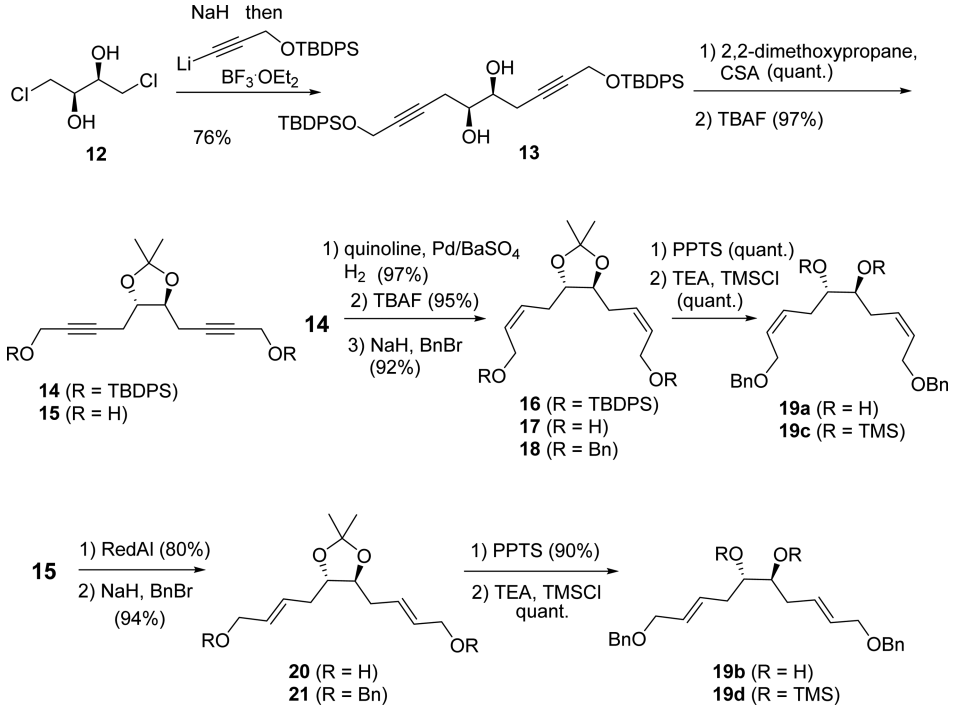
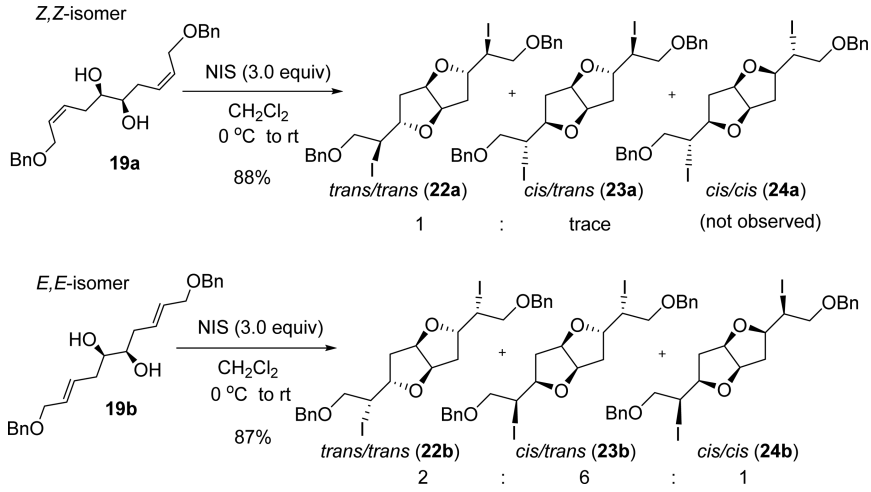
Scheme 7. Mechanistic Considerations for the First Cyclization during the Iodoetherification of Internal Olefin Compounds



Scheme 8. Syntheses of Diene Diols 19a,b and Their TMS-Ethers 19c,d



Scheme 9. Iodoetherification of the Internal Diene Diols 19a,b



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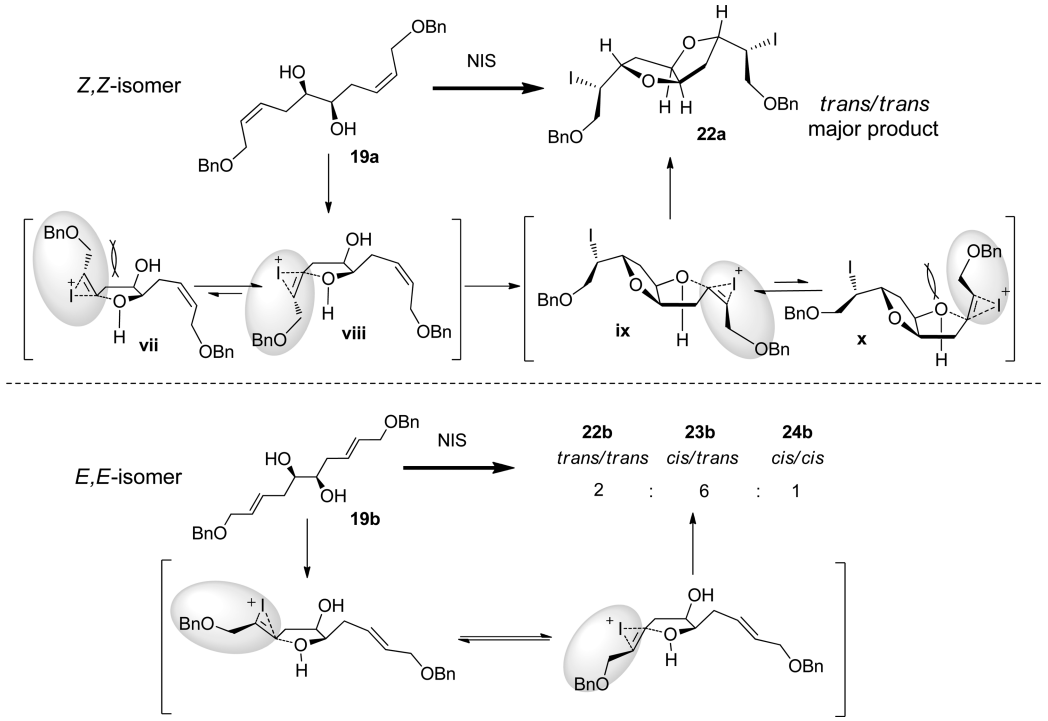
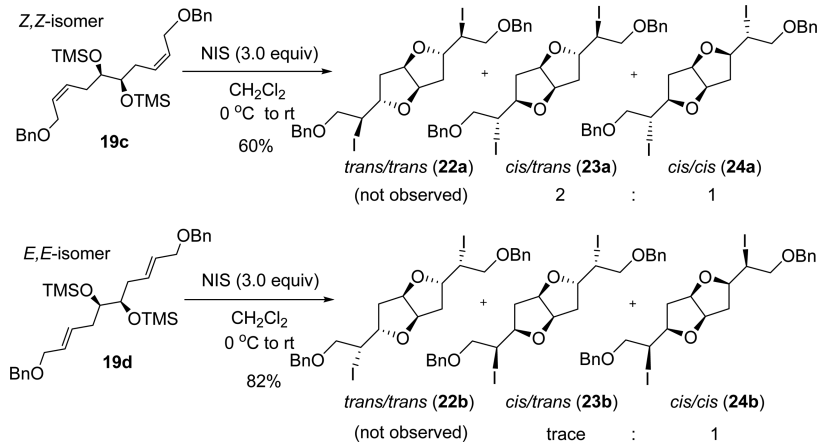
Scheme 10. Rationalization of the Stereochemistry of the Products from Diene Diols 19a and 19b



Scheme 11. Iodoetherification Reactions of the Internal Diene Disilylethers 19c and 19d



the two transition states (i.e., *cis* and *trans*) in the mono-THF compound to favor the *trans*-transition state, giving the *trans*/*trans fused*-bis THF compound selectively. In contrast, for the silylether protected diol, the repulsion between the trimethylsilyl group and the side chain, following the formation of the *fused*-bis THF compound, would force the equilibrium toward the *trans*-transition state. Although the repulsion between the bis-THF rings and the endo orientation of the side chain could lead to the *cis*-transition state, it was envisaged that controlling the geometrical isomer of the substrate would reduce the population of this transition states to a minimum, and favor the formation of the *cis*/*cis fused*-bis THF compound as the major product.

We then planned to investigate the iodoetherification of (*Z*,*Z*)- and (*E*,*E*)-diene diols **19a** and **19b** and their silylethers **19c** and **19d**. Compounds **19a**−**d** were synthesized in racemic forms as shown in Scheme 8.

Commercially available **12** was treated with NaH to give a bis-epoxide, which was treated with lithium acetylide (prepared by the reaction of *tert*-butyldiphenyl(prop-2-yn-1-yloxy)silane and *n*-BuLi) and $BF_3{\cdot}OEt_2$ to give **13** in 76% yield. Reaction of **13** with 2,2-dimethoxypropane in the presence of a catalytic amount of CSA afforded acetonide **14** in quantitative yield. Desilylation of **14** with TBAF gave the acetonide diol **15** in 97% yield. Hydrogenation of **14** under Lindlar's conditions afforded (*Z*,*Z*)-diene compound **16** in 97% yield, which was desilylated with TBAF to give (*Z*,*Z*)-diene diol **17** in 95% yield. Benzylation of **17** with NaH and BnBr afforded bis-benzyl ether **18**, and subsequent acidic hydrolysis with PPTS gave (*Z*,*Z*)-diene diol **19a** in quantitative yield. Trimethylsilylation of **19a** with Et_3N and TMSCl afforded (*Z*,*Z*)-diene disilylether **19c** in quantitative yield. (*E*,*E*)-Diene diol **19b** and its silylether **19d** were synthesized from compound **15**. Reduction of **15** with Red-Al gave (*E*,*E*)-diene product **20** in 80% yield, and (*E*,*E*)-

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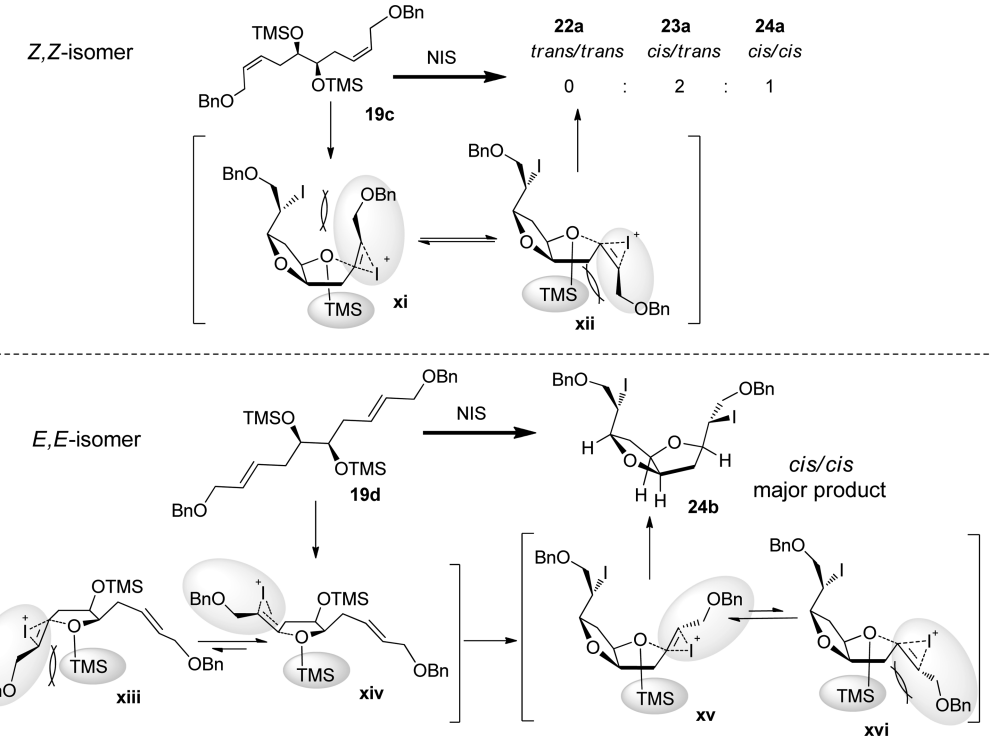
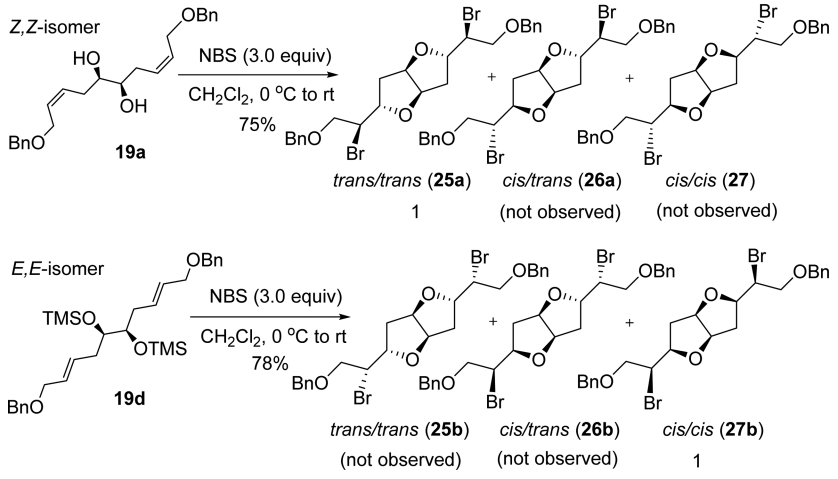
Scheme 12. Rationalization of the Stereochemistry of the Products Formed from Protected Diene Diols 19c and 19d



Scheme 13. Bromoetherification of the Internal (*Z*,*Z*)-Diene Diol 19a and (*E*,*E*)-Diene Disilylether 19d



diene diol **19b** and its silylether **19d** were afforded in 85% yield using the same procedures for **19a** and **19d**, respectively.

The results for the iodoetherification of the (*Z*,*Z*)- and (*E*,*E*)-diene diols **19a** and **19b** are shown in Scheme 9. As expected, (*Z*,*Z*)-diene diol **19a** gave the *trans*/*trans*-isomer **22a** selectively, whereas the (*E*,*E*)-isomer **19b** afforded poor selectivity.

The results shown in Scheme 9 can be rationalized according to the mechanistic consideration shown in Scheme 10. In the case of the (*Z*,*Z*)-diene diol **19a**, transition state **vii** would experience much greater repulsion than transition state **viii**. The first cyclization in **19a** would therefore proceed via transition state **viii**, followed by the second cyclization via transition state **ix**, avoiding the unfavorable endo transition state **x**, giving the *trans*/*trans*-isomer **22a** selectively. In contrast, the (*E*,*E*)-diene diol **19b** would give three isomers (**22b**, **23b**, and **24b**) with low selectivity. The lack of selectivity from this substrate can be attributed to the lack of stereocontrol during the first cyclization. This is owing to the lack of significant repulsive forces between the different substituents and the benzyloxymethyl group, which would be directed away from the THF ring.

We proceeded to examine the reactions of diene disilylethers **19c** and **19d** (Scheme 11). In the case of the (*Z*,*Z*)-diene disilylether **19c**, whose parent diol **19a** showed high selectivity, the *cis*/*trans* and *cis*/*cis fused*-bis THF compounds **23a** and **24a** were formed as a 2:1 mixture. However, the corresponding (*E*,*E*)-diene disilylether **19d** afforded the *cis*/*cis fused*-bis THF **24b** with high selectivity.

The results in Scheme 11 can be rationalized according to the mechanistic considerations shown in Scheme 12. The (*Z*,*Z*)-diene silylether **19c** afforded a 2:1 mixture of the *cis*/

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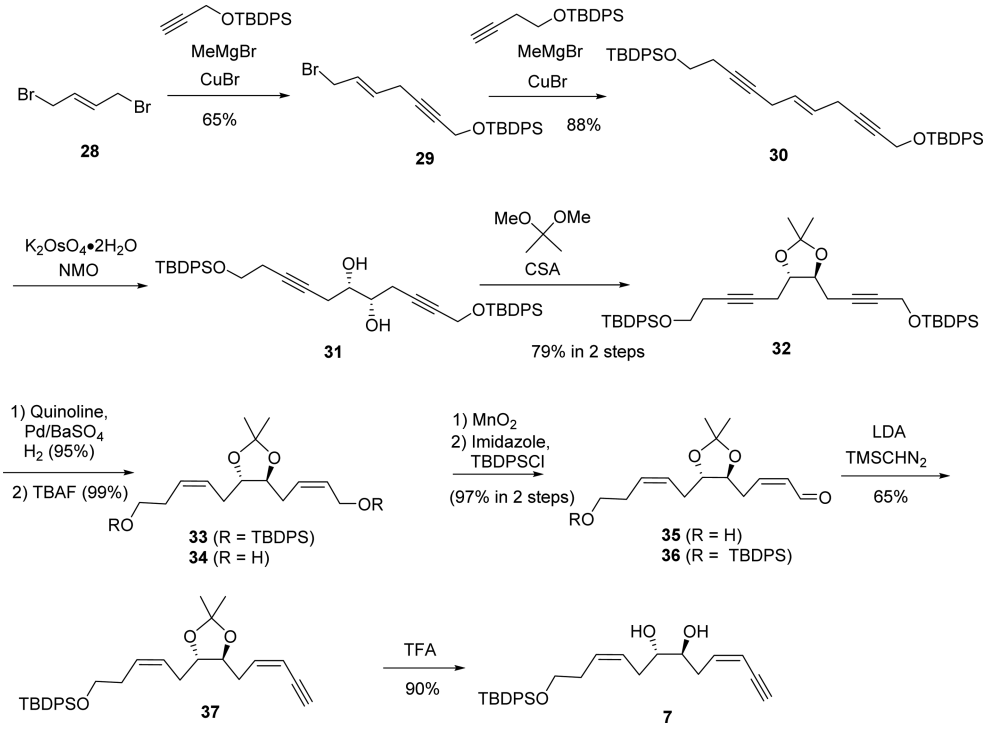
J. Org. Chem. 2015, 80, 10261−10277

Scheme 14. Synthesis of *Z*-Diene-yne Diol 7



trans- and *cis*/*cis*-isomers **23a** and **24a**, respectively. TLC analysis of the reaction mixture for **19c** revealed that the initial cyclization reaction to give the mono-THF product occurred in a selective manner to give the *cis*-isomer, whereas the second cyclization lacked any form of selectivity. The lack of selectivity in the second cyclization was attributed to competition between transition state **xi**, with repulsion between the bis-THF rings and endo orientation of the side chain, and transition sate **xii**, with repulsion between the trimethylsilyl group and the side chain. In contrast, the *E*-olefin silylether **19d** reacted selectively under the same conditions to give the *cis*/*cis*-isomer **24b** as the major product. In this case, the initial cyclization reaction occurred in a stereoselective manner to give the *cis*-mono THF compound via transition state **xiv**, which would be much more stable than the alternative transition state **xiii** because of repulsion between the trimethylsilyl group and the side chain. The second cyclization would then proceed via transition state **xv** for the same reason to give **24b** selectively.

Given that the natural products with a *fused*-bis THF skeleton shown in Figure 1 contain bromine rather than iodine atoms, we proceeded to investigate the double bromoetherification of the diene diol substrates (Scheme 13). The bromoetherification of **19a** and **19d** with NBS proceeded in similar fashions to the corresponding iodoetherification reactions with NIS, which are shown in Schemes 9 and 11, respectively. Thus, the (*Z*,*Z*)-diene diol **19a** afforded the *trans*/*trans fused*-bis THF product **25a** selectively, and the (*E*,*E*)-diene disilylether **19d** afforded the *cis*/*cis*-isomer **27b** selectively.

Synthetic Work and Bioactive Study of Aplysiallene. (−)-Aplysiallene (**1**) was first isolated in 1985 from the red alga *Laurencia okamurai* Yamada, and its structure was determined to comprise a *cis*-fused 2,6-dioxabicyclo[3,3,0]octane skeleton with two *trans*-THF rings.[1a] This compound was also isolated from the sea hare *Aplysia kurodai* in 2001 and was reported to exhibit inhibitory activity toward Na^+/K^+ ATPase with an IC_{50} value of 0.7 mM.[1b] The first asymmetric total synthesis of (−)-aplysiallene was achieved by Pagenkopf and Wang in 2007,[5b] which resulted in the reassignment of the stereochemistry of the bromoallene side chain and the absolute configuration of the natural product, as shown in Figure 1. The synthetic strategy reported in this work involved the stepwise construction of the *trans*/*trans fused*-bis THF skeleton. Pagenkopf and Wang also mentioned in the introduction of their manuscript that (−)-aplysiallene (**1**) inhibited Na^+/K^+ ATPase activity with an IC_{50} value of 0.7 μM, although several other studies have reported large variations in its activity.[1a,5b]

As described in the previous section, *fused*-bis THF compounds can be constructed in a stereoselective manner from internal olefins, meaning that the side chain conversion process would be much more efficient. Furthermore, it was envisaged that the bromoallene unit could be installed by bromoetherification of an ene-yne moiety, as (a) formation of the bromoallene unit of kumausallene is thought to be via bromoetherification of ene-yne moiety in its biogenesis,[2b] and (b) the formation of a bromoallene unit is already reported via bromoetherification of an ene-yne moiety.[5d,9]

Racemic Synthesis. Scheme 14 shows the synthesis of the precurser for bromoetherification, (*Z*,*Z*)-diene-yne diol **7**, which would be used for the construction of the *fused*-bis THF skeleton, from commercially available (*E*)-1,4-dibromo-2-butene (**28**). The reaction of **28** with a Grignard reagent prepared by the treatment of the propargyl alcohol derivative with methylmagnesium bromide and copper bromide gave **29**, which was reacted with another Grignard reagent to afford ene-diyne **30** in 57% yield over the two steps.[10] Oxidation of **30** with OsO_4 gave diyne-diol **31**, which was protected with 2,2-dimethoxypropane to afford acetonide **32** in 79% yield over the two steps. Subsequent reduction of **32** with Lindlar's catalyst afforded (*Z*,*Z*)-diolefin **33** in 95% yield, and treatment of **33**

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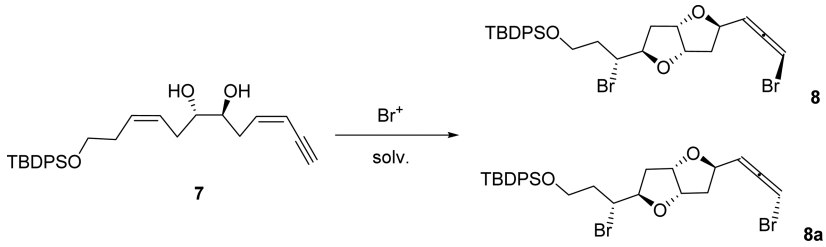
J. Org. Chem. 2015, 80, 10261−10277

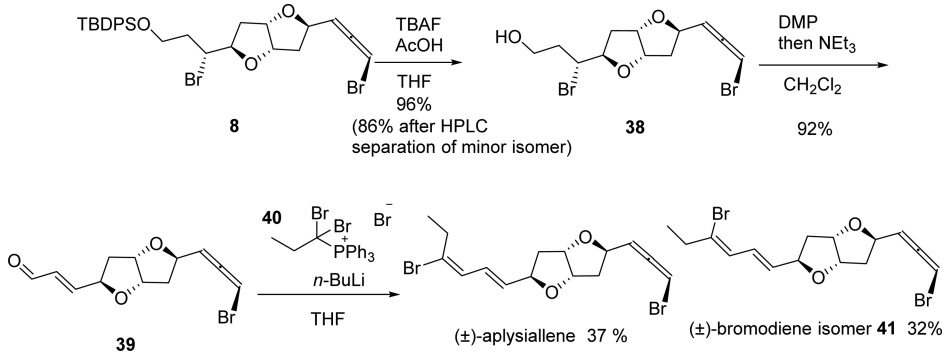
Table 2. Bromoetherification of 7



entry	Br^+	solv.	yield	ratio (**8**:**8a**)[a]
1	NBS	CH_2Cl_2	74%	9:1
2	NBS	CH_3CN	48%	1:1
3	TBCO	CH_2Cl_2	91%	9:1
4	TBCO	CH_3CN	54%	1:1
5	TBCO	cyclohexane	78%	4:1
6	TBCO	toluene	80%	5:1

[a]Determined by ^1H NMR.

Scheme 15. Completion of the Total Synthesis of (±)-Aplysiallene



with TBAF resulted in the deprotection of the TBDPS ether to give **34** in 99% yield. The resulting allyl alcohol **34** was selectively oxidized with MnO_2 followed by the protection of the remaining alcohol moiety as a TBDPS ether to afford unsaturated aldehyde **36** in 97% yield over the two steps. The subsequent conversion of aldehyde **36** to alkyne **37** was achieved in 65% yield.[11] TFA deprotection of the acetonide in **37** afforded the desired (*Z*,*Z*)-diene-yne diol **7** in 90% yield.

The results of our experiments toward the double bromoetherification of **7** are shown in Table 2. Treatment of **7** with NBS (5.0 equiv) in CH_2Cl_2 afforded *fused*-bis THF bromoallene **8** in 74% yield together with its bromoallene isomer **8a** in a 9:1 ratio (Table 2, entry 1). The stereochemistry of the *fused*-bis THF ring was deduced from the results of our former experiments shown in Schemes 9 and 13, and the stereochemistry of the bromoallene moiety was assigned based on results presented in ref 5b. These assignments were subsequently confirmed by the conversion of **8** to natural aplysiallene (vide infra). Given that NBS is poorly soluble in CH_2Cl_2, we decided to investigate the use of CH_3CN as the reaction solvent, but this resulted in a decrease in the stereoselectivity of the reaction toward the bromoallene unit (1:1 ratio, Table 2, entry 2). In contrast, the use of 2,4,4,6-tetrabromo-1,4-cyclohexadienone (TBCO), instead of NBS, in CH_2Cl_2 led to a significant improvement in the yield, with the bromoallene unit being formed as a 9:1 mixture of **8** and **8a** (Table 2, entry 3). The use of TBCO in CH_3CN led to a decrease in the stereoselectivity of the reaction toward the bromoallene unit (1:1 ratio, Table 2, entry 4). Cyclohexane and toluene were also investigated, and gave the desired product **5** in good yields with moderate selectivity (Table 2, entries 5 and 6). On the basis of these results, the use of TBCO in CH_2Cl_2 was identified as optimal in terms of yield and selectivity. This observation, where the configuration of a bromoallene depends on the reaction solvent, has already been reported.[9c]

Compounds **8** and **8a** were inseparable at this stage. Treatment of **8**, contaminated with a small amount of **8a**, with TBAF in THF in the presence of AcOH gave alcohol **38** in 96% yield (Scheme 15). In the absence of AcOH, the yield of **38** was poor (58%). At this point, compound **38** could be purified from its bromoallene isomer by HPLC separation (Reversed CEL: Mightysil RP-18 GP 250-10) using a 1:1 (v/v) mixture of MeOH and H_2O as the mobile phase. Dess-Martin oxidation[12] of **38**, followed by Et_3N treatment, gave the unsaturated aldehyde **39** in 92% yield. Subsequent Wittig reaction of **39** with the dibromophosphonium reagent **40**[13] gave (±)-aplysiallene in 37% yield, together with the stereoisomer of aplysiallene **41**. The spectroscopic data (^1H and ^{13}C NMR) of the synthesized aplysiallene agreed with those reported in the literature.

Asymmetric Synthesis. Having successfully accomplished the synthesis of racemic aplysiallene, we proceeded to investigate the synthesis of optically pure aplysiallene. We initially planned to carry out an enantioselective Sharpless dihydroxylation of **30**,[14] but could only obtain the diyne diol **31** with low yield (51%) and low ee (60% ee). Further examination with several substrate analogs such as allyl halides

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J. Org. Chem. 2015, 80, 10261−10277

29 and **42** (Figure 2) improved the ee (~80% ee) but yield was still low (~60%).

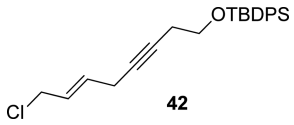


Figure 2. Structure of **42**.

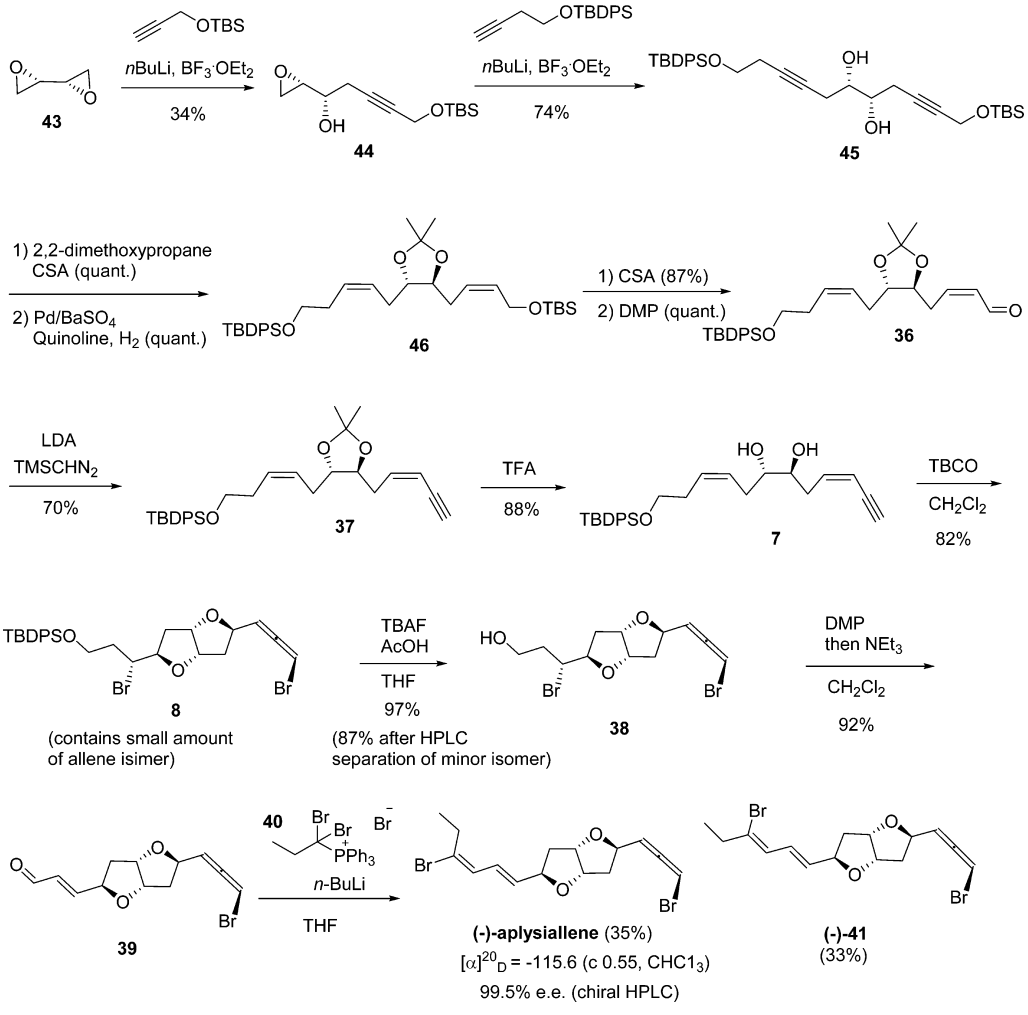
We then decided to use optically pure (*S,S*)-diepoxide **43**[15] as a starting substrate (Scheme 16). The reaction of **43** with the ate complex prepared by the treatment of Li acetylide with BF_3·Et_2O gave the monoalkynylated epoxide **44** in 34% yield,[16] and this was reacted with another ate complex to give diol **45** in 74% yield. The subsequent protection of diol **45**, followed by reduction of the alkynes with Lindlar's catalyst, gave **46** in quantitative yield. Treatment of **46** with CSA led to the selective deprotection of the TBS ether, and the resulting alcohol was oxidized with DMP to afford unsaturated aldehyde **36** in 87% yield over the two steps. The subsequent steps to synthesize (−)-aplysiallene were the same as those described above for the synthesis of the racemic material. The enantiomeric excess of the synthesized (−)-aplysiallene was determined by HPLC analysis. Although the optical rotation of our synthesized aplysiallene ($[\alpha]^{20}_D$ − 115.6 (*c* = 0.55, $CHCl_3$)) is different from the reported values ($[\alpha]^{23}_D$ − 213 (*c* = 0.985, $CHCl_3$)[1a] and $[\alpha]_D$ − 192 (*c* = 0.002, $CHCl_3$)[5b]), its optical purity (99.5% ee) was determined by HPLC (see Supporting Information).

Bioactive Evaluation of Aplysiallene and Its Derivatives. We tested the inhibitory activities of aplysiallene and its derivatives toward purified Na^+/K^+ ATPase from rat brain. The Na^+/K^+ ATPase activity decreased in a dose-dependent manner in the presence of (−)- and (±)-aplysiallene, as well as their derivatives, although the (−)-aplysiallene precursor **38** did not show any inhibitory activity (Figure 3). The IC_{50} values of (−)-aplysiallene, bromodiene isomer (−)-**41**, (±)-aplysiallene, and (±)-**41** were determined to be 15.0, 13.8, 12.9, and 16.5 μM, respectively. The IC_{50} value of the same enzyme for Na^+/K^+ ATPase specific inhibitor, ouabain, was 0.4 μM (data not shown), suggesting that Na^+/K^+ ATPase inhibition activity of (−)-aplysiallene and its derivatives is about one-fortieth that of ouabain.

CONCLUSION

We have developed a highly stereoselective strategy for the formation of *trans/trans* and *cis/cis fused*-bis THF compounds in high yields using a one-pot procedure, which has allowed us to accomplish the total synthesis of (±)- and (−)-aplysiallene.

Scheme 16. Asymmetric Total Synthesis of (−)-Aplysiallene



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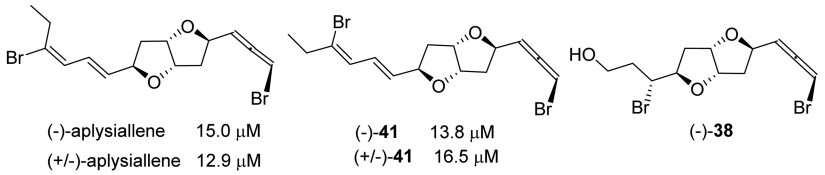
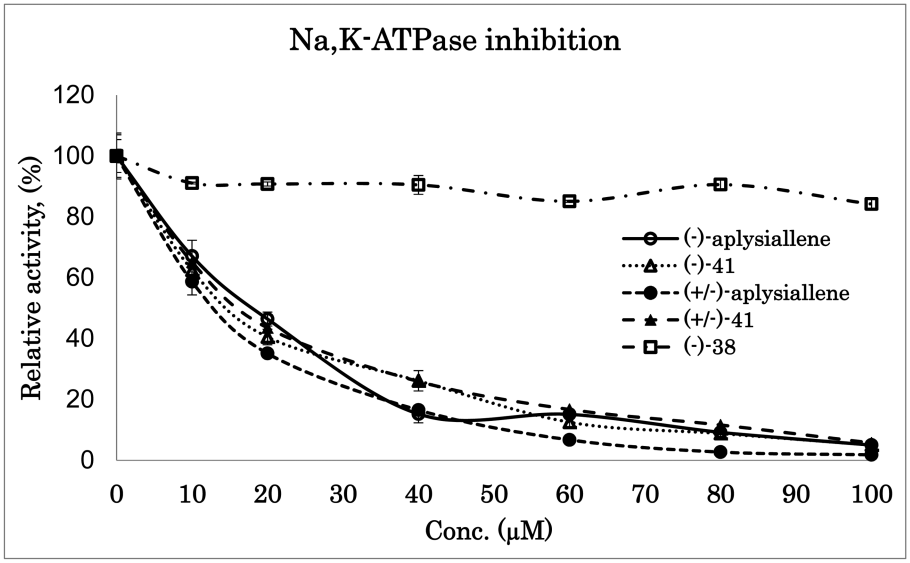
J. Org. Chem. 2015, 80, 10261−10277





conc. μM	(−)-aplysiallene	SD	(−)−41	SD	(+/−)-aplysiallene	SD	(+/−)−41	SD	(−)−38	SD
0	100	7.57	100	6.99	100	5.41	100	7.59	100	2.24
10	67.1	5.22	62.5	2.43	58.7	4.38	65.1	3.66	91.1	0.3
20	46.4	2.29	40.5	2.54	35.1	0.78	43.5	4.28	90.8	0.66
40	15.2	2.87	26.1	3.34	16.5	0.14	25.9	3.01	90.5	3.1
60	15.1	0.67	12.5	1.64	6.7	0.49	16.7	1.02	85.1	0.3
80	9.2	1.54	8.8	0.39	2.7	0.5	11.6	0.48	90.6	1.58
100	5	0.88	5	0.47	1.8	0.28	5.7	0.63	84.2	1.66

Figure 3. Na^+/K^+ ATPase inhibition activity of (−)-aplysiallene and its derivatives.

Our synthesis represents the first reported biomimetic-type synthesis based on the direct intramolecular double bromoetherification of diene-yne diols for the construction of *fused*-bis THF skeletons bearing an adjacent *R*-bromoallene unit. The desired compounds were obtained in a stereoselective manner in a one-pot operation. Furthermore, the biological evaluation of (±)- and (−)-aplysiallene, and their bromodiene isomers, revealed that they possess similar Na^+/K^+ ATPase inhibitory activities, with IC_{50} values of approximately 15 μM. This study represents the first reported biological evaluation of synthesized aplysiallene and its derivatives.[17]

EXPERIMENTAL SECTION

Genaral Protocols. All reagents were purchased from commercial sources and used without further purification. Reactions were performed under a nitrogen or an argon atmosphere using purchased anhydrous solvent. All reactions were monitored by thin-layer chromatography using silica plate. The products were purified by column chromatography over silica gel (70−230 mesh ASTM or 40−50 μm, spherical neutral). ^{1}H NMR and ^{13}C NMR were recorded at 25 °C on 300 and 75, 400 and 100, 500 and 125, or 600 and 150 MHz, respectively, and the chemical shifts are reported relative to internal TMS (^{1}H, δ = 0.00) and $CDCl_3$ (^{13}C, δ = 77.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (integration, multiplicity, coupling constant (Hz)). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra (KBr) were recorded in frequency of absorption (cm^{-1}). High-resolution mass spectra were performed by a mass spectrometer using an orbitrap analyzer. Optical rotations were measured on a polarimeter. Enantiomeric excess (ee) was determined by chiral HPLC analysis using UV detector.

Synthesis of Substrates and Experimental Details for Table 1. *(4R*,5R*)-Octa-1,7-diene-4,5-diol (**6a**).* This is a known compound.[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.93−5.79 (2H, m), 5.18 (2H, d, J = 6.9 Hz), 5.13 (2H, s), 3.57−3.54 (2H, m), 2.38−2.21 (4H, m), 2.14 (2H, br s) ppm.

(4R,5R*)-4,5-Diallyl-2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane (**6b**).* To a dry round-bottom flask flushed with argon were added **6a** (300 mg, 2.11 mmol) and dry CH_2Cl_2 (20 mL). TMSCl (0.8 mL, 6.33 mmol) and imidazole (575 mg, 8.44 mmol) were added to the solution, and the resulting mixture was stirred at 0 °C. After 1 h, it was quenched with H_2O. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (10:1) as an eluent to give **6b** (586.8 mg, 97%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.81 (2H, ddt, J = 16.5, 10.5, 7.1 Hz), 5.10−5.00 (4H, m), 3.61−3.55 (2H, m), 2.41−2.33 (2H, m), 2.12−2.07 (2H, m), 0.11 (18H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.3, 116.4, 75.2, 36.1, 0.5 ppm. IR (KBr): 2956, 1642, 1261, 1099 cm^{-1}; HRMS

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(MALDI) m/z 309.1672 (calcd for $C_{14}H_{30}O_2NaSi_2$ $[M + Na]^+$, 309.1677).

(5R,6R*)-5,6-Diallyl-3,3,8,8-tetraethyl-4,7-dioxa-3,8-disiladecane (**6c**).* To a dry round-bottom flask flushed with argon were added **6a** (150 mg, 1.06 mmol) and dry CH_2Cl_2 (5 mL). TESCl (0.53 mL, 3.17 mmol) and imidazole (290 mg, 4.22 mmol) were added to the solution, and the resulting mixture was stirred at 0 °C. After 1 h, it was quenched with H_2O. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (10:1) as an eluent to give **6c** (574 mg, quant.) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.85 (2H, ddt, J = 15.0, 12.0, 7.2 Hz), 5.09−4.98 (4H, m), 3.62 (2H, dt, J = 6.5, 4.2 Hz), 2.47−2.39 (2H, m), 2.09−1.99 (2H, m), 0.95 (18H, t, J = 7.9 Hz), 0.59 (12H, q, J = 7.9 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.8, 116.2, 75.3, 35.4, 6.9, 5.1 ppm. IR (KBr): 2859, 1453, 1362, 1106 cm^{-1}; HRMS (FAB) m/z 393.2630 (calcd for $C_{20}H_{42}O_2NaSi_2$ $[M + Na]^+$, 393.2621).

Entry 1. To a round-bottom flask flushed with argon were added **6a** (50 mg, 0.35 mmol) and dry CH_2Cl_2 (3.6 mL). NIS (238 mg, 1.06 mmol) was added to the solution at 0 °C, and the resulting mixture was allowed to warm to rt for 2 h by stirring before it was quenched with $Na_2S_2O_3$ aq. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (4:1) as an eluent to give **9** (64.3 mg, 46%) and **10** (36.7 mg, 27%) as a yellow oil.

Entry 2. To a round-bottom flask flushed with argon were added **6b** (50 mg, 0.18 mmol) and dry CH_2Cl_2 (1.8 mL). NIS (237 mg, 1.05 mmol) was added to the solution at 0 °C, and the resulting mixture was allowed to warm to rt and stirred for 20 h before it was quenched with $Na_2S_2O_3$ aq. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (4:1) as an eluent to give **10** (46.6 mg, 67%) and **11** (23.3 mg, 33%) as a yellow oil.

(2S,3aR*,5S*,6aR*)-2,5-Bis(iodomethyl)hexahydrofuro[3,2-b]furan (**9**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.82 (2H, d, J = 3.7 Hz), 4.14−4.02 (2H, m), 3.26−3.25 (4H, m), 2.32 (2H, dd, J = 13.5, 5.3 Hz), 1.78−1.69 (2H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 84.9, 78.6, 41.4, 10.1 ppm. IR (KBr): 2938, 1430, 1356, 1312, 1259, 1132, 1051 cm^{-1}; HRMS (FAB) m/z 394.9001 (calcd for $C_8H_{12}I_2O_2$ $[M + H]^+$, 394.9005).

(2R,3aR*,5S*,6aR*)-2,5-Bis(iodomethyl)hexahydrofuro[3,2-b]furan (**10**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.85−4.84 (1H, m), 4.60 (1H, t, J = 4.3 Hz), 4.18−4.12 (1H, m), 3.97−3.91 (1H, m), 3.33−3.28 (4H, m), 2.39−2.31 (2H, m), 1.85 (1H, ddd, J = 13.5, 7.4, 2.3 Hz), 1.69 (1H, ddd, J = 13.0, 9.0, 4.3 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 85.2, 84.7, 79.2, 77.3, 40.0, 40.0, 9.7, 9.0 ppm. IR (KBr): 2932, 1428, 1359, 1201, 1173, 1135, 1057 cm^{-1}; HRMS (MALDI) m/z 416.8820 (calcd for $C_8H_{12}O_2NaI_2$ $[M + Na]^+$, 416.8819).

(2R,3aR*,5R*,6aR*)-2,5-Bis(iodomethyl)hexahydrofuro[3,2-b]furan (**11**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.62 (2H, d, J = 4.6 Hz), 4.18−4.13 (2H, m), 3.36 (4H, d, J = 6.9 Hz), 2.35−2.30 (2H, m), 2.03 (2H, dd, J = 13.5, 6.0 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 85.6, 80.8, 39.0, 9.6 ppm. IR (KBr): 2912, 1174, 1097, 1058 cm^{-1}; HRMS (MALDI) m/z 416.8824 (calcd for $C_8H_{12}O_2NaI_2$ $[M + Na]^+$, 416.8819).

Synthesis of Substrates and Experimental Details for Schemes 9, 11, and 13. *Syntheses of Substrates **19a−d**.*

(9S,10S*)-2,2,17,17-Tetramethyl-3,3,16,16-tetraphenyl-4,15-dioxa-3,16-disilaoctadeca-6,12-diyne-9,10-diol (**13**).* To a dry round-bottom, three-neck flask flushed with argon were added commercially available **12** (4.77 g, 30.0 mmol) and dry THF (200 mL). NaH (2.9 g, 72.5 mmol) was added to the solution at 0 °C, and the resulting mixture was stirred at the same temperature. To another dry round-bottom, three-neck flask flushed with argon were added *tert*-butyldiphenyl(prop-2-yn-1-yloxy)silane (22.1 g, 75.0 mmol) and dry THF (150 mL). A 1.64 M *n*-BuLi solution in THF (43.9 mL, 72.0 mmol) was added to the solution at −78 °C, and the resulting mixture was stirred at the same temperature. After 1 h, addition of $BF_3{\cdot}OEt_2$ (11.3 mL, 90.0 mmol) was followed by the cannulation of the latter solution to the former solution at −78 °C, and the resulting mixture was stirred for 18 h at −78 °C. It was quenched with saturated NH_4Cl aq. The organic layer was separated, washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (3:1) as an eluent to give **13** (14.7 g, 76%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72−7.69 (8H, m), 7.46−7.3 (12H, m), 4.32 (4H, t, J = 2.1 Hz), 3.58 (2H, t, J = 5.2 Hz), 2.40 (4H, m), 1.04 (18H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.6, 133.1, 133.1, 129.8, 127.7, 81.3, 81.1, 70.8, 52.8, 26.6, 24.2, 19.1 ppm. IR (KBr): 3381, 2932, 2859, 1428, 1113, 1107, 1072 cm^{-1}; HRMS (MALDI) m/z 697.3134 (calcd for $C_{42}H_{50}O_4NaSi_2$ $[M + Na]^+$, 697.3140).

((((4S,5S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(but-2-yne-4,1-diyl))bis(oxy))bis(tert-butyldiphenylsilane) (**14**).* To a round-bottom flask flushed with argon were added **13** (206 mg, 0.31 mmol) and dry CH_2Cl_2 (0.3 mL). 2,2-Dimethoxypropane (56 μL, 0.46 mmol) and CSA (4 mg, 0.017 mmol) were added to the solution, and the resulting mixture was stirred at rt. After 30 min, the mixture was concentrated in vacuo, and the crude residue was purified using silica gel column chromatography using *n*-hexane/EtOAc (10:1) as an eluent to give **14** (217.5 mg, quant.) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (8H, m), 7.41−7.37 (12H, m), 4.30 (4H, t, J = 1.9 Hz), 3.84 (2H, t, J = 3.3 Hz), 2.54 (4H, m), 1.39 (6H, s), 1.04 (18H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.6, 133.1, 129.7, 127.7, 108.9, 80.7, 80.6, 77.8, 52.8, 27.2, 26.7, 23.0, 19.1 ppm. IR (KBr): 2932, 2859, 1428, 1219, 1113, 1070 cm^{-1}; HRMS (MALDI) m/z 737.3461 (calcd for $C_{45}H_{54}O_4NaSi_2$ $[M + Na]^+$, 737.3453).

4,4′-((4S,5S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(but-2-yn-1-ol) (**15**).* To a round-bottom flask flushed with argon were added **14** (831.6 mg, 1.16 mmol) and dry THF (5.8 mL). A 1 M TBAF solution in THF (4.2 mL, 4.12 mmol) was added to the solution at 0 °C, and the resulting mixture was stirred at rt. After 30 min, the mixture was concentrated in vacuo and charged on silica gel column chromatography and purified using *n*-hexane/EtOAc (1:2 → 0:1) as eluents to give **15** (270.7 mg, 97%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.27 (4H, t, J = 2.1 Hz), 3.97 (2H, m), 2.63 (4H, m), 1.70 (2H, br s), 1.43 (6H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 109.3, 81.3, 80.9, 78.1, 51.2, 27.3, 23.2 ppm. IR (KBr): 3368, 2989, 2936, 1730, 1374, 1219, 1069 cm^{-1}; HRMS (MALDI) m/z 261.1098 (calcd for $C_{13}H_{18}O_4Na$ $[M + Na]^+$, 261.1097).

(((2Z,2′Z)-((4S,5S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(but-2-ene-4,1-diyl))bis(oxy))bis(tert-butyldiphenylsilane) (**16**).* To a dry round-bottom flask were added **14** (978 mg, 1.37 mmol) and dry EtOAc (7 mL). $Pd/BaSO_4$ (15 mg) and quinolline (0.33 mL, 2.78 mmol) were added to the solution, and the resulting mixture was stirred at rt. After 30 min, the atmosphere in a reaction vessel was replaced with H_2 and the resulting mixture was stirred for further 2 h at the same temperature. The mixture was filtered through short Celite column with EtOAc, and the filtrate was concentrated under reduced pressure. The crude reside was purified by silica gel column chromatography using *n*-hexane/EtOAc (10:1) as an eluent to give **16** (950 mg, 97%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68−7.65 (8H, m), 7.41−7.35 (12H, m), 5.72−5.64 (2H, m), 5.43−5.34 (2H, m), 4.20 (4H, d, J = 5.5 Hz), 3.52−3.46 (2H, m), 2.06 (4H, t, J = 5.5 Hz), 1.27 (6H, s), 1.03 (18H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.6, 133.7, 133.7, 131.7, 129.6, 127.6, 125.3, 108.0, 79.6, 60.3, 27.1, 26.8, 19.1 ppm. IR (KBr): 2931, 2858, 1428, 1112 cm^{-1}; HRMS (MALDI) m/z 741.3764 (calcd for $C_{45}H_{58}O_4NaSi_2$ $[M + Na]^+$, 741.3766).

(2Z,2′Z)-4,4′-((4S,5S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(but-2-en-1-ol) (**17**).* To a round-bottom flask flushed with argon were added **16** (922.4 mg, 1.28 mmol) and dry THF (6.4 mL). A 1 M TBAF solution in THF (4.6 mL, 4.6 mmol) was added to the solution at 0 °C, and the resulting mixture was stirred at rt. After 30 min, the mixture was concentrated in vacuo and charged on silica gel column chromatography and purified using *n*-hexane/EtOAc (1:2 → 0:1) as eluents to give **17** (290 mg, 95%) as a colorless oil. ^{1}H NMR (300

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MHz, $CDCl_3$) δ: 5.92−5.83 (2H, m), 5.65 (2H, dt, J = 10.5, 7.9 Hz), 4.22−4.07 (4H, m), 3.72−3.70 (2H, m), 2.42−2.38 (4H, m), 2.05 (2H, br, s), 1.39 (6H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 131.6, 127.7, 108.4, 79.2, 57.7, 30.1, 27.0 ppm. IR (KBr): 3353, 2986, 2872, 1371, 1219, 1032 cm^{-1}; HRMS (MALDI) m/z 265.1403 (calcd for $C_{13}H_{22}O_4Na$ [M + Na]$^+$, 265.1410).

(4S,5S*)-4,5-Bis((Z)-4-(benzyloxy)but-2-en-1-yl)-2,2-dimethyl-1,3-dioxolane (**18**).* To a dry round-bottom flask flushed with argon were added **17** (298.9 mg, 1.23 mmol), dry THF (1 mL) and dry DMF (0.25 mL). NaH (129 mg, 3.21 mmol) was added to the solution at 0 °C, and the resulting mixture was stirred at the same temperature. After 15 min, BnBr (0.33 mL, 2.72 mmol) was added, and the reaction mixture was stirred for further 2 h at rt before it was quenched with MeOH and water. The mixture was diluted with Et_2O. The organic layer was separated, washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (10:1) as an eluent to give **18** (476.4 mg, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33−7.29 (10H, m), 5.74 (2H, dt, J = 12.0, 5.6 Hz), 5.64 (2H, dt, J = 12.0, 6.1 Hz), 4.50 (4H, s), 4.06 (4H, d, J = 6.1 Hz), 3.66 (2H, t, J = 3.6 Hz), 2.32 (4H, m), 1.36 (6H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.2, 128.8, 128.4, 128.1, 127.8, 127.6, 108.2, 79.6, 72.2, 65.7, 30.8, 27.1 ppm. IR (KBr): 2860, 1454, 1370, 1092 cm^{-1}; HRMS (MALDI) m/z 445.2348 (calcd for $C_{27}H_{34}O_4Na$ [M + Na]$^+$, 445.2349).

(2Z,8Z)-(5S,6S*)-1,10-Bis(benzyloxy)deca-2,8-diene-5,6-diol (**19a**).* To a dry round-bottom flask flushed with argon were added **18** (476.4 mg, 1.13 mmol) and 95% EtOH aq. (11 mL). PPTS (142 mg, 0.56 mmol) was added to the solution, and the resulting mixture was refluxed for 2 h at 85 °C before it was quenched with K_2CO_3. The mixture was dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (3:1) as an eluent to give **19a** (426.9 mg, quant.) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38−7.29 (10H, m), 5.80 (2H, dt, J = 11.4, 6.4 Hz), 5.687 (2H, dt, J = 11.4, 7.6 Hz), 4.52 (4H, s), 4.05 (4H, d, J = 6.4 Hz), 3.49−3.45 (2H, m), 3.47 (2H, t, J = 5.5 Hz), 2.31 (4H, t, J = 6.9 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.8, 130.4, 128.4, 128.3, 127.9, 127.8, 72.6, 72.3, 65.3, 32.2 ppm. IR (KBr): 3416, 3028, 2862, 1454, 1088, 1072 cm^{-1}; HRMS (MALDI) m/z 405.2032 (calcd for $C_{24}H_{30}O_4Na$ [M + Na]$^+$, 405.2036).

(4S,5S*)-4,5-Bis((Z)-4-(benzyloxy)but-2-en-1-yl)-2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane (**19c**).* To a dry round-bottom flask flushed with argon were added **19a** (59.7 mg, 0.156 mmol) and dry CH_2Cl_2 (1.6 mL). TMSCl (60 μL, 0.47 mmol) and TEA (0.13 mL, 0.94 mmol) were added to the solution, and the resulting mixture was stirred at 0 °C. After 1 h, it was quenched with H_2O. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (10:1) as an eluent to give **19c** (81.5 mg, quant.) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27−7.19 (10H, m), 5.61−5.53 (4H, m), 4.43 (4H, s), 4.04−3.97 (4H, m), 3.46 (2H, d, J = 8.6 Hz), 2.28−2.24 (2H, m), 2.02−1.96 (2H, m), 0.00 (18H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.3, 130.6, 128.3, 127.8, 127.8, 127.5, 75.2, 72.1, 65.9, 29.3, 0.5 ppm. IR (KBr): 2956, 2859, 1454, 1251, 1095 cm^{-1}; HRMS (MALDI) m/z 549.2831 (calcd for $C_{30}H_{46}O_4NaSi_2$ [M + Na]$^+$, 549.2827).

(2E,2′E)-4,4′-((4S,5S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(but-2-en-1-ol) (**20**).* To a round-bottom flask flushed with argon were added **15** (209 mg, 0.88 mmol) and dry THF (1.75 mL). A 60 wt % RedAl solution in toluene (1.4 mL, 4.39 mmol) was added to the solution at 0 °C, and the resulting mixture was allowed to warm to rt with stirring. After 20 h, the reaction mixture was diluted with Et_2O and quenched with 1 N NaOH aq to precipitate white solid. The precipitation was filtered through short Celite column with EtOAc and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (1:2 → 0:1) as eluents to give **20** (169.7 mg, 80%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.73 (2H, dt, J = 15.2, 6.9 Hz), 5.61 (2H, dt, J = 15.2, 5.0 Hz), 3.92 (4H, dd, J = 5.0, 1.2 Hz), 3.77−3.75 (2H, m), 2.34−2.29 (4H, m), 1.50 (6H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 131.9, 127.4, 108.3, 79.7, 63.3, 35.7, 27.2 ppm. IR (KBr): 3321, 2986, 2865, 1372, 1220, 1076 cm^{-1}; HRMS (MALDI) m/z 265.1412 (calcd for $C_{13}H_{22}O_4Na$ [M + Na]$^+$, 265.1410).

(4S,5S*)-4,5-Bis((E)-4-(benzyloxy)but-2-en-1-yl)-2,2-dimethyl-1,3-dioxolane (**21**).* To a dry round-bottom flask flushed with argon were added **20** (169.7 mg, 0.70 mmol), dry THF (0.5 mL) and dry DMF (0.2 mL). NaH (73 mg, 1.82 mmol) was added to the solution at 0 °C and the resulting mixture was allowed to warm to rt with stirring. After 30 min, BnBr (0.19 mL, 1.54 mmol) was added and the reaction mixture was stirred for further 2 h at rt before it was quenched with MeOH and water. The mixture was diluted with Et_2O. The organic layer was separated, washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (10:1) as an eluent to give **21** (277.7 mg, 94%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36−7.31 (10H, m), 5.75 (2H, dt, J = 15.4, 5.7 Hz), 5.67 (2H, dt, J = 15.4, 4.7 Hz), 4.50 (4H, s), 3.99 (4H, d, J = 4.7 Hz), 3.76−3.68 (2H, m), 2.37−2.31 (4H, m), 1.38 (6H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.3, 129.3, 128.4, 127.8, 127.6, 108.3, 79.6, 72.1, 70.6, 35.5, 27.2 ppm. IR (KBr): 2854, 1454, 1370, 1218, 1090, 1058 cm^{-1}; HRMS (MALDI) m/z 445.2346 (calcd for $C_{27}H_{34}O_4Na$ [M + Na]$^+$, 445.2349).

(2E,8E)-(5S,6S*)-1,10-Bis(benzyloxy)deca-2,8-diene-5,6-diol (**19b**).* To a dry round-bottom flask flushed with argon were added **21** (184.7 mg, 0.44 mmol) and 95% EtOH aq. (4.4 mL). PPTS (65.7 mg, 0.26 mmol) was added to the solution, and the resulting mixture was refluxed for 2 h at 85 °C before it was quenched with K_2CO_3. The mixture was dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (3:1 → 0:1) as eluents to give **19b** (151 mg, 90%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35−7.30 (10H, m), 5.79−5.71 (4H, m), 4.51 (4H, s), 4.00 (4H, d, J = 4.1 Hz), 3.53 (2H, t, J = 4.3 Hz), 2.38−2.25 (4H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.2, 129.8, 129.8, 128.3, 127.7, 127.6, 72.8, 72.2, 70.5, 36.8 ppm. IR (KBr): 4213, 3425, 3016, 2856, 1454, 1218 cm^{-1}; HRMS (MALDI) m/z 405.2037 (calcd for $C_{24}H_{30}O_4Na$ [M + Na]$^+$, 405.2036).

(4S,5S*)-4,5-Bis((E)-4-(benzyloxy)but-2-en-1-yl)-2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane (**19d**).* To a dry round-bottom flask flushed with argon were added **19b** (109.6 mg, 0.287 mmol) and dry CH_2Cl_2 (1 mL). TMSCl (0.2 mL, 1.72 mmol) and TEA (0.4 mL, 2.87 mmol) were added to the solution, and the resulting mixture was stirred at 0 °C. After 1 h, it was quenched with H_2O. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (10:1) as an eluent to give **19d** (150.5 mg, quant.) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34−7.27 (10H, m), 5.73 (2H, dt, J = 15.0, 7.1 Hz), 5.65 (2H, dt, J = 15.0, 5.7 Hz), 4.50 (4H, s), 3.99 (4H, d, J = 5.7 Hz), 3.59−3.57 (2H, m), 2.38 (2H, dd, J = 15.0, 6.5, 2.5 Hz), 2.12 (2H, dt, J = 15.0, 7.2 Hz), 0.10 (18H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.4, 131.8, 128.4, 128.3, 127.7, 127.5, 75.1, 71.9, 70.9, 34.6, 0.5 ppm. IR (KBr): 2956, 2853, 1362, 1251, 1097 cm^{-1}; HRMS (MALDI) m/z 549.2832 (calcd for $C_{30}H_{46}O_4NaSi_2$ [M + Na]$^+$, 549.2827).

Iodoetherification and Bromoetherification of 19a and 19d. *General Procedure of Haloetherification of Diol.* To a round-bottom flask flushed with argon were added **19a** (36 mg, 0.094 mmol) and dry CH_2Cl_2 (1.0 mL). NIS (63.6 mg, 0.282 mmol) was added to the solution at 0 °C, and the resulting mixture was allowed to warm to rt for 2 h by stirring before it was quenched with $Na_2S_2O_3$ aq. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (4:1) as an eluent to give **22a** (52.1 mg, 88%) as a yellow oil. **22a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33−7.29 (10H, m), 4.79 (2H, d, J = 4.5 Hz), 4.57 (4H, s), 4.25−4.19 (2H, m), 3.85−3.80 (6H, m), 2.25 (2H, dd, J = 13.6, 5.8 Hz), 1.89 (2H, ddd, J = 13.6, 9.8, 4.5 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.7, 128.4, 127.8, 127.7, 84.6, 78.6, 73.5, 73.1, 41.2, 38.4

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ppm; IR (KBr): 2919, 2859, 1453, 1099, 1063 cm^{-1}. HRMS (MALDI) m/z 656.9986 (calcd for $C_{24}H_{28}O_4NaI_2$ $[M + Na]^+$, 656.9969).

General Procedure of Haloetherification of TMS Ether. To a round-bottom flask flushed with argon were added **19d** (34 mg, 0.065 mmol) and dry CH_2Cl_2 (0.7 mL). NIS (44.2 mg, 0.194 mmol) was added to the solution at 0 °C, and the resulting mixture was allowed to warm to rt for 24 h by stirring before it was quenched with $Na_2S_2O_3$ aq. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (4:1) as an eluent to give **24b** (33.0 mg, 82%) as a yellow oil. **24b**: ^1H NMR (500 MHz, $CDCl_3$) δ: 7.36−7.27 (10H, m), 4.62 (2H, d, J = 12.0), 4.57 (2H, d, J = 12.0), 4.52 (2H, d, J = 5.2 Hz), 4.30 (2H, dt, J = 7.9, 4.9 Hz), 4.23 (2H, td, J = 7.9, 6.1 Hz), 3.81−3.80 (4H, m) 2.32−2.26 (2H, m), 2.19 (2H, dd, J = 14.1, 6.3 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.8, 128.4, 127.7, 127.6, 84.9, 81.5, 73.0, 72.5, 39.1, 36.5 ppm. IR (KBr): 2903, 2862, 1453, 1103, 1073 cm^{-1}; HRMS (MALDI) m/z 656.9961 (calcd for $C_{24}H_{28}O_4NaI_2$ $[M + Na]^+$, 656.9969).

(2S,3aR*,5S*,6aR*)-2,5-Bis((S*)-2-(benzyloxy)-1-bromoethyl)-hexahydrofuro[3,2-b]furan (**25a**).* **25a** (35.3 mg, 75%) was obtained from **19a** (33.3 mg, 0.087 mmol) and NBS (46.5 mg, 0.26 mmol). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.31−7.28 (10H, m), 4.76 (2H, d, J = 4.1 Hz), 4.56 (4H, s), 4.34 (2H, ddd, J = 12.0, 5.8, 3.3 Hz), 4.06 (2H, td, J = 6.7, 3.2 Hz), 3.87−3.76 (4H, m), 2.21 (2H, dd, J = 13.4, 6.0 Hz), 2.01 (2H, ddd, J = 13.4, 9.3, 4.1 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.7, 128.5, 127.8, 127.7, 84.8, 78.6, 73.3, 72.0, 55.8, 38.8 ppm. IR (KBr): 2933, 2859, 1453, 1362, 1106, 1072 cm^{-1}; HRMS (MALDI) m/z 561.0248 (calcd for $C_{24}H_{28}O_4NaBr_2$ $[M + Na]^+$, 561.0247).

(2R,3aR*,5R*,6aR*)-2,5-Bis((S*)-2-(benzyloxy)-1-bromoethyl)-hexahydrofuro[3,2-b]furan (**27b**).* **27b** (9.8 mg, 78%) was obtained from **19d** (12.3 mg, 0.023 mmol) and NBS (12.5 mg, 0.070 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35−7.26 (10H, m), 4.62 (2H, d, J = 12.4), 4.57 (2H, d, J = 12.4), 4.52 (2H, d, J = 5.5 Hz), 4.30 (2H, dt, J = 9.8, 4.0 Hz), 4.23 (2H, td, J = 7.7, 6.8 Hz), 3.81−3.80 (4H, m), 2.29 (2H, ddd, J = 14.0, 7.8, 6.0 Hz), 2.19 (2H, dd, J = 14.3, 6.3 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.8, 128.4, 127.7, 127.6, 85.0, 80.7, 73.2, 71.4, 55.0, 37.1 ppm. IR (KBr): 2940, 2861, 1453, 1106 cm^{-1}; HRMS (MALDI) m/z 561.0238 (calcd for $C_{24}H_{28}O_4NaBr_2$ $[M + Na]^+$, 561.0247).

Experimental Details for Total Synthesis of (±)-Aplysiallene. *(E)-((7-Bromohept-5-en-2-yn-1-yl)oxy)(tert-Butyl)diphenyl Silane (**29**).* To a dry round-bottom, three-neck flask flushed with argon were added *tert*-butyldiphenyl(prop-2-ynyloxy)silane (1.5 g, 5.09 mmol) and dry THF (10 mL). A 0.92 M MeMgBr solution in THF (6.6 mL, 6.09 mmol) was added to the solution at rt, and the resulting mixture was warmed to 65 °C and stirred for 2 h. To the another dry round-bottom, three-neck flask flushed with argon were added CuBr (73 mg, 0.51 mmol), 1,4-*trans*-dibromo-2-butene (**28**) (2.18 g, 10.19 mmol), and dry THF (12 mL). The former resulting solution was cannulated to the latter solution at 65 °C. The reaction mixture was stirred for further 9 h at the same temperature before it was quenched with saturated NH_4Cl aq. The mixture was diluted with EtOAc. The organic layer was separated, washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/CH_2Cl_2 (6:1 → 3:1) as an eluent to give **29** (1416 mg, 65%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.72−7.69 (4H, m), 7.46−7.36 (6H, m), 5.97−5.86 (1H, m), 5.68 (1H, dt, J = 15.0, 5.3 Hz), 4.34 (2H, t, J = 2.1 Hz), 3.94 (2H, d, J = 7.6 Hz), 2.99−2.93 (2H, m), 1.06 (9H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.6, 135.6, 133.2, 129.9, 129.7, 129.7, 127.8, 127.6, 81.5, 81.1, 77.2, 52.8, 32.2, 26.37, 21.6, 19.1 ppm. IR (KBr): 2959, 2930, 2857, 1427, 1111, 1074 cm^{-1}; HRMS (MALDI) m/z 449.0909 (calcd for $C_{23}H_{27}ONaSiBr$ $[M + Na]^+$, 449.0907).

*(E)-2,2,18,18-Tetramethyl-3,3,17,17-tetraphenyl-4,16-dioxa-3,17-disilanonadeca-9-en-6,12-diyne (**30**).* To a dry round-bottom, three-neck flask flushed with argon were added (but-3-yn-1-yloxy)(*tert*-butyl)diphenylsilane[19] (1228 mg, 3.98 mmol) and dry THF (4 mL). A 0.92 M MeMgBr solution in THF (4.4 mL, 3.98 mmol) was added to the solution at rt, and the resulting mixture was a warmed to 65 °C. After 2 h of stirring, CuBr (76 mg, 0.53 mmol) was added to the mixture and then **29** (1135 mg, 2.66 mmol) in dry THF (4 mL) was cannulated. The reaction mixture was stirred for further 3 h at 65 °C before it was quenched with saturated NH_4Cl aq. The mixture was diluted with EtOAc. The organic layer was separated, washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/CH_2Cl_2 (6:1 → 3:1) as eluents to give **30** (1538 mg, 88%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.73−7.66 (8H, m), 7.44−7.35 (12H, m), 5.61 (2H, t, J = 2.6 Hz), 4.32 (2H, t, J = 1.5 Hz), 3.76 (2H, t, J = 7.1 Hz), 2.91−2.85 (4H, m), 2.46−2.43 (2H, m), 1.05 (18H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.6, 135.6, 133.3, 129.7, 129.6, 127.6, 126.4, 125.4, 80.4, 62.8, 61.7, 52.9, 26.8, 26.7, 22.9, 21.7, 21.7, 19.2, 7.0 ppm. IR (KBr): 2959, 2932, 2858, 1428, 1113 cm^{-1}; HRMS (MALDI) m/z 677.32420 (calcd for $C_{43}H_{50}O_2NaSi_2$ $[M + Na]^+$, 677.32416).

tert-Butyl((5-((4S,5S*)-5-(4-((tert-butyldiphenylsilyl)oxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-yn-1-yl)oxy)-diphenylsilane ((±)-**32**).* To a round-bottom flask were added **30** (1310 mg, 2.00 mmol), acetone (1 mL) and H_2O (1 mL). A 4.8 M 4-methylmorpholine *N*-oxide solution in H_2O (1.0 mL, 5.0 mmol) and $K_2OsO_4{\cdot}2H_2O$ (74 mg, 0.20 mmol) were added to the mixture at 0 °C, and the resulting mixture was allowed to warm to rt and stirred for 3 h before it was quenched with saturated $Na_2S_2O_3$ aq. The mixture was diluted with EtOAc. The organic layer was separated, washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (3:1) as an eluent to give crude (±)-**31** including some minor product (1087 mg) as a yellow oil. To a round-bottom flask flushed with argon were added crude (±)-**31** (1087 mg) and dry CH_2Cl_2 (5 mL). 2,2-Dimethoxypropane (3 mL, 24.5 mmol) and CSA (39 mg, 0.17 mmol) were added to the solution successively, and the resulting mixture was stirred at rt. After 30 min, the mixture was concentrated in vacuo, and the crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (3:1) as an eluent to give (±)-**32** (1151 mg, 79% in 2 steps) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.69−7.66 (8H, m), 7.44−7.33 (12H, m), 4.28 (2H, t, J = 2.1 Hz), 3.86−3.82 (2H, m), 3.73 (2H, t, J = 7.2 Hz), 2.55−2.47 (4H, m), 2.43 (2H, td, J = 7.2, 2.0 Hz), 1.38 (6H, s), 1.04 (18H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.6, 135.5, 133.6, 133.1, 129.7, 129.6, 127.6, 108.8, 80.7, 80.6, 79.4, 78.0, 77.7, 76.4, 62.6, 52.8, 27.1, 26.7, 26.6, 23.0, 22.9, 22.9, 19.1, 19.1 ppm. IR (KBr):4213, 3018, 2930, 2860, 2400, 1429, 1218 cm^{-1}; HRMS (MALDI) m/z 751.3611 (calcd for $C_{46}H_{56}O_4NaSi_2$ $[M + Na]^+$, 751.3609).

tert-Butyl(((Z)-5-((4S,5S*)-5-((Z)-4-((tert-butyldiphenylsilyl)oxy)-but-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-en-1-yl)oxy)-diphenylsilane ((±)-**33**).* To a dry round-bottom flask were added (±)-**32** (576.7 mg, 0.79 mmol) and dry EtOAc (8 mL). Quinolline (0.19 mL, 1.58 mmol) and Pd/$BaSO_4$ (10 mg) were added to the solution successively, and the resulting mixture was stirred at rt. After 30 min, the atmosphere in a reaction vessel was replaced with H_2 and the resulting mixture was stirred for further 2 h at the same temperature. The mixture was filtered through short Celite column with EtOAc and the filtrate was concentrated under reduced pressure. The crude reside was purified by silica gel column chromatography using *n*-hexane/EtOAc (6:1) as an eluent to give (±)-**33** (550 mg, 95%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.68−7.65 (8H, m), 7.44−7.33 (12H, m), 5.78−5.69 (1H, m), 5.50−5.36 (3H, m), 4.23 (2H, d, J = 5.8 Hz), 3.62 (2H, t, J = 6.9 Hz), 3.55 (2H, m), 2.29−2.18 (4H, m), 2.12−2.09 (2H, m), 1.33 (3H, s), 1.30 (3H, s), 1.04 (18H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.5, 133.9, 133.7, 131.7, 129.6, 129.6, 128.4, 127.6, 127.6, 126.1, 125.5, 108.0, 79.8, 79.8, 63.4, 60.3, 31.0, 30.8, 30.6, 27.2, 27.1, 26.8, 26.8, 19.2, 19.1 ppm. IR (KBr): 2958, 2932, 2858, 1428, 1112, 1089 cm^{-1}; HRMS (MALDI) m/z 755.3928 (calcd for $C_{46}H_{60}O_4NaSi_2$ $[M + Na]^+$, 755.3922).

(Z)-5-((4S,5S*)-5-((Z)-4-Hydroxybut-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-en-1-ol ((±)-**34**).* To a round-bottom flask flushed with argon were added (±)-**33** (998.3 mg, 1.39 mmol) and

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dry THF (2.7 mL). A 1 M TBAF solution in THF (4 mL, 4.00 mmol) was added to the solution at 0 °C, and the resulting mixture was stirred at rt. After 30 min, the mixture was concentrated in vacuo and charged on silica gel column chromatography and purified using *n*-hexane/EtOAc (1:2 → 0:1) as eluents to give (±)-**34** (351 mg, 99%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.92−5.84 (1H, m), 5.66−5.56 (3H, m), 4.19−4.11 (2H, m), 3.72−3.67 (4H, m), 1.40 (3H, s), 1.39 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 131.6, 128.6, 127.7, 127.6, 108.4, 99.9, 79.7, 79.3, 61.8, 57.8, 30.8, 30.2, 30.1, 27.0 ppm. IR (KBr): 3364, 2933, 2873, 1371, 1241, 1057 cm^{-1}; HRMS (MALDI) *m*/*z* 279.1565 (calcd for $C_{14}H_{24}O_4Na$ [M + Na]$^+$, 279.1567).

(Z)-4-((4S,5S*)-5-((Z)-5-((tert-Butyldiphenylsilyl)oxy)pent-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enal ((±)-**36**).* To a dry round-bottom flask flushed with argon were added (±)-**34** (351 mg, 1.37 mmol) and dry CH_2Cl_2 (14 mL). MnO_2 (1200 mg, 13.7 mmol) was added to the solution at rt, and the resulting mixture was stirred at rt. After 12 h, the reaction mixture was filtered through short Celite column with Et_2O and the filtrate concentrated under reduced pressure. No further purification was necessary. (±)-**35** is unstable and should be used in the next step immediately. Under argon, to a solution of (±)-**35** in dry CH_2Cl_2 (3.5 mL) was added imidazole (126 mg, 2.46 mmol) at 0 °C. The resulting suspension was stirred for 20 min at 0 °C, followed by dropwise addition of TBDPSCl (0.53 mL, 0.19 mmol). The reaction mixture was allowed to warm to rt and stirred for further 2 h before it was quenched by addition of water. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (6:1 → 4:1) as eluents to give (±)-**36** (654.7 mg, 97% in 2steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.00 (1H, d, *J* = 7.7 Hz), 7.69−7.65 (4H, m), 7.46−7.35 (6H, m), 6.63 (1H, dt, *J* = 12.0, 7.8 Hz), 6.06 (1H, ddt, *J* = 12.0, 7.7, 1.5 Hz), 5.62−5.44 (2H, m), 3.76−3.70 (2H, m), 3.67 (2H, t, *J* = 6.9 Hz), 2.80 (2H, ddd, *J* = 7.7, 4.7, 1.5 Hz), 2.36−2.28 (4H, m), 1.38 (3H, s), 1.37 (3H, s), 1.04 (9H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.8, 147.2, 135.5, 133.8, 131.6, 129.6, 129.1, 127.6, 125.5, 108.6, 79.4, 79.0, 63.3, 31.0, 31.0, 30.4, 27.2, 27.1, 26.8, 19.2 ppm. IR (KBr): 2933, 2858, 1684, 1428, 1112, 1091 cm^{-1}; HRMS (MALDI) *m*/*z* 517.2747 (calcd for $C_{30}H_{42}O_4NaSi$ [M + Na]$^+$, 517.2745).

tert-Butyl(((Z)-5-((4S,5S*)-2,2-dimethyl-5-((Z)-pent-2-en-4-yn-1-yl)-1,3-dioxolan-4-yl)pent-3-en-1-yl)oxy)diphenylsilane ((±)-**37**).* To a dry round-bottom, three-neck flask flushed with argon were added diisopropylamine (0.3 mL, 2.2 mmol) and dry THF (4.4 mL). A 1.6 M *n*-BuLi solution in THF (1.4 mL, 2.2 mmol) was added to the solution at −78 °C, and the resulting mixture was stirred at 0 °C. After 15 min, 2 M $TMSCHN_2$ solution in THF (1.1 mL, 2.2 mmol) was added at −78 °C to give the reaction mixture. After 1 h, 7.2 mL of the reaction mixture was add to (±)-**36** (140.4 mg, 0.29 mmol) in dry THF in another flask under argon at −78 °C, and the resulting solution was stirred for further 1 h at −30 °C before it was quenched with saturated NH_4Cl aq. The mixture was diluted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (10:1) as an eluent to give (±)-**37** (89.9 mg, 65%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69−7.65 (4H, m), 7.46−7.35 (6H, m), 6.09 (1H, dtd, *J* = 12.0, 7.4, 1.2 Hz), 5.59−5.48 (3H, m), 3.72−3.70 (2H, m), 3.67 (2H, t, *J* = 7.1 Hz), 3.07 (1H, d, *J* = 1.2 Hz), 2.69−2.50 (2H, m), 2.34−2.32 (4H, m), 1.38 (6H, s), 1.05 (9H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.5, 135.5, 133.8, 129.6, 128.4,127.6, 126.1, 110.5, 108.2, 82.2, 80.1, 79.7, 79.3, 63.4, 33.1, 31.0, 30.4, 27.2, 27.1, 26.8, 19.2 ppm. IR (KBr): 2931, 2859, 1428, 1112, 1089 cm^{-1}; HRMS (MALDI) *m*/*z* 511.2638 (calcd for $C_{31}H_{40}O_3NaSi$ [M + Na]$^+$, 511.2639).

(3Z,9Z)-(6S,7S*)-12-((tert-Butyldiphenylsilyl)oxy)dodeca-3,9-dien-1-yne-6,7-diol ((±)-**7**).* To a dry round-bottom flask flushed with argon were added (±)-**37** (60 mg, 0.13 mmol) and dry CH_2Cl_2 (3.2 mL). Mixed TFA/CH_2Cl_2/H_2O (4:4:1, v/v/v, 0.158 mL) was added to the solution at 0 °C, and the resulting mixture was allowed to warm to rt and stirred for 30 min before it was neutralized with K_2CO_3. The mixture was dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (3:1) as an eluent to give (±)-7 (49.2 mg, 90%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68−7.66 (4H, m), 7.46−7.35 (6H, m), 6.13 (1H, dtd, *J* = 12.0, 7.6, 1.5 Hz), 5.66−5.48 (3H, m), 3.68 (2H, t, *J* = 6.5 Hz), 3.56 (1H, dd, *J* = 11.5, 5.7 Hz), 3.47 (1H, dd, *J* = 11.5, 5.7 Hz), 3.11 (1H, d, *J* = 1.5 Hz), 2.59−2.56 (2H, m), 2.45−2.22 (4H, m), 1.04 (9H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.3, 135.6, 133.7, 130.0, 129.6, 127.6, 126.5, 110.5, 82.1, 80.2, 73.1, 72.9, 63.5, 34.6, 31.5, 30.8, 26.8, 19.2 ppm. IR (KBr): 3309, 2931, 2858, 1428, 1112, 1090 cm^{-1}; HRMS (MALDI) *m*/*z* 471.2327 (calcd for $C_{28}H_{36}O_3NaSi$ [M + Na]$^+$, 471.2326).

((R)-3-Bromo-3-((2R*,3aS*,5R*,6aS*)-5-((R*)-3-bromopropa-1,2-dien-1-yl)hexahydrofuro[3,2-b]furan-2-yl)propoxy) (tert-Butyl)-diphenylsilane ((±)-**8**) and ((S*)-3-Bromo-3-((2R*,3aS*,5R*,6aS*)-5-((R*)-3-bromopropa-1,2-dien-1-yl)hexahydrofuro[3,2-b]furan-2-yl)propoxy) (tert-Butyl)diphenylsilane ((±)-**8a**).* To a round-bottom flask flushed with argon were added (±)-7 (40 mg, 0.092 mmol) and dry CH_2Cl_2 (0.9 mL). TBCO (113 mg, 0.276 mmol) was added to the solution, and the resulting mixture was stirred for 1 h at 0 °C before it was quenched with saturated $Na_2S_2O_3$ aq. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with 1 N NaOH aq and saturated brine, and concentrated in vacuo. The crude residue was diluted with *n*-hexane and washed with 1 N NaOH aq and saturated brine, and dried over $NaSO_4$. The solution was concentrated in vacuo, and the obtained residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (10:1) as an eluent to give (±)-**8** containing (±)-**8a** (50.6 mg, 91%, (±)-**8**/(±)-**8a** = 9:1) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.68−7.64 (4H, m), 7.43−7.40 (6H, m), 6.10 (9/10 H, dd, *J* = 5.9, 1.1 Hz), 6.08 (1/10 H, dd, *J* = 6.0, 1.7 Hz), 5.41 (1/10 H, t, *J* = 6.0 Hz), 5.39 (9/10 H, t, *J* = 5.9 Hz), 4.84−4.83 (1H, m), 4.78−4.76 (1H, m), 4.70−4.66 (1H, m), 4.28 (1H, dt, *J* = 10.0, 4.0 Hz), 4.20 (1H, dt, *J* = 10.0, 4.9 Hz), 3.89 (1H, ddd, *J* = 15.0, 9.4, 4.3 Hz), 3.836−3.813 (1H, m), 2.33 (1H, dd, *J* = 13.5, 5.7 Hz), 2.24 (1H, dd, *J* = 13.5, 5.4 Hz), 2.11−2.09 (1H, m), 2.05−1.95 (2H, m), 1.91 (1H, ddd, *J* = 13.5, 8.9, 4.9 Hz), 1.05 (9H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.8, 135.6, 135.5, 133.5, 133.4, 129.7, 127.7, 100.9, 84.4, 84.0, 76.3, 73.8, 61.2, 55.6, 40.7, 38.9, 26.8, 19.2 ppm. IR (KBr): 2931, 2858, 1428, 1112, 1091 cm^{-1}; HRMS (MALDI) *m*/*z* 627.0539 (calcd for $C_{28}H_{34}O_3NaSiBr_2$ [M + Na]$^+$, 627.0536).

(R)-3-Bromo-3-((2R*,3aS*,5R*,6aS*)-5-((R*)-3-bromopropa-1,2-dien-1-yl)hexahydrofuro[3,2-b]furan-2-yl)propan-1-ol ((±)-**38**).* To a dry round-bottom flask flushed with argon were added (±)-**8** containing (±)-**8a** (71.6 mg, 0.11 mmol) and dry THF (3.3 mL). AcOH (66 μL, 0.11 mmol) and 1 M TBAF solution in THF (0.66 mL, 0.66 mmol) were added to the solution at 0 °C, and the resulting mixture was stirred for 14 h at 0 °C to rt before it was quenched with saturated $NaHCO_3$ aq. The mixture was diluted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (2:1 → 1:2) as eluents to give (±)-**38** containing its bromallene isomer (41.2 mg, 96%) as a yellow oil. Further purification by HPLC (Mightysil RP-18 GP 250−10 (5 μm), H_2O/MeOH = 50/50) gave (±)-**38** (36.7 mg, 86%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.09 (1H, dd, *J* = 5.8, 1.1 Hz), 5.38 (1H, t, *J* = 5.8 Hz), 4.86−4.84 (1H, m), 4.78−4.76 (1H, m), 4.72−4.68 (1H, m), 4.24−4.22 (2H, m), 3.92−3.89 (1H, m), 3.84−3.81 (1H, m), 2.34 (1H, dd, *J* = 13.8, 5.7 Hz), 2.26 (1H, dd, *J* = 13.8, 5.7), 2.15−2.08 (2H, m), 2.03 (1H, ddd, *J* = 13.8, 8.9, 4.9 Hz), 1.92 (1H, ddd, *J* = 13.8, 8.7, 5.1 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.8, 100.8, 84.7, 83.8, 82.1, 76.3, 73.9, 60.0, 55.7, 40.6, 38.7, 38.3 ppm. IR (KBr): 3449, 2949, 2930, 1076, 1051 cm^{-1}; HRMS (MALDI) *m*/*z* 388.93576 (calcd for $C_{12}H_{16}O_3NaBr_2$ [M + Na]$^+$, 388.93584).

(E)-3-((2R,3aS*,5R*,6aS*)-5-((R*)-3-Bromopropa-1,2-dien-1-yl)-hexahydrofuro[3,2-b]furan-2-yl)acrylaldehyde ((±)-**39**).* To a dry round-bottom flask flushed with argon were added (±)-**38** (43.7 mg, 0.12 mmol) and dry CH_2Cl_2 (1.2 mL). DMP (76 mg, 0.27 mmol) was added to the solution at 0 °C and the resulting mixture was allowed to

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J. Org. Chem. 2015, 80, 10261−10277

warm to rt. After 1.5 h of stirring, TEA (115 μL, 0.83 mmol) was added to the reaction mixture and the resulting solution was stirred for further 30 min at rt before it was quenched with saturated $Na_2S_2O_3$ aq. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with saturated NH_4Cl aq and saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (4:1 → 2:1) as eluents to give (±)-**39** (31.2 mg, 92%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.57 (1H, d, *J* = 7.9 Hz), 6.77 (1H, dd, *J* = 15.7, 5.0 Hz), 6.30 (1H, ddd, *J* = 15.7, 7.9, 1.5 Hz), 6.11 (1H, dd, *J* = 5.8, 1.5 Hz), 5.39 (1H, t, *J* = 5.8 Hz), 4.89−4.86 (1H, m), 4.78−4.74 (3H, m), 2.40 (1H, dd, *J* = 13.4, 5.4 Hz), 2.33 (1H, dd, *J* = 13.8, 5.4 Hz), 2.00 (1H, ddd, *J* = 13.8, 8.3, 5.4 Hz), 1.81 (1H, ddd, *J* = 13.4, 10.6, 4.7 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.8, 193.3, 155.0, 131.1, 100.8, 84.3, 83.6, 77.9, 76.6, 74.0, 40.6, 40.3 ppm. IR (KBr): 2927, 1691, 1072 cm^{-1}; HRMS (MALDI) *m*/*z* 306.9941 (calcd for $C_{12}H_{13}O_3NaBr$ [M + Na]$^+$, 306.9940).

*(±)-Aplysiallene and (±)-**41**.* To a dry round-bottom, three-neck flask flushed with argon were added (±)-**40** (104 mg, 0.19 mmol) and dry THF (2 mL). A 1.55 M *n*-BuLi solution in THF (0.11 mL, 0.16 mmol) was added to the solution at −40 °C, and the resulting mixture was stirred at the same temperature. After 30 min, the solution was cannulated to (±)-**39** (31.3 mg, 0.11 mmol) in dry THF (1 mL) in another flask under argon at −78 °C and the resulting mixture was stirred at −40 °C. After 1 h, it was quenched with saturated $NaHCO_3$ aq. The mixture was diluted with Et_2O. The organic layer was separated, washed with $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (10:1) as an eluent to give (±)-**aplysiallene** (15.7 mg, 37%) as a yellow oil. Further purification for biological study by HPLC (Mightysil RP-18 GP 250-10 (5 μm), H_2O/MeOH = 20/80) gave aplysiallene diastereomer (±)-**41** (13.8 mg, 32%) as a yellow oil. (±)-**aplysiallene**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.42 (1H, d, *J* = 11.0 Hz), 6.33 (1H, ddd, *J* = 14.1, 11.0, 0.9 Hz), 6.10 (1H, dd, *J* = 5.7, 1.5 Hz), 5.61 (1H, dd, *J* = 14.1, 6.9 Hz), 5.38 (1H, t, *J* = 6.0 Hz), 4.81 (1H, t, *J* = 4.8 Hz), 4.76−4.69 (2H, m), 4.55−4.48 (1H, m), 2.57 (2H, q, *J* = 7.3 Hz), 2.30 (2H, dd, *J* = 13.8, 5.8 Hz), 2.26 (2H, dd, *J* = 12.7, 5.2 Hz), 1.96 (1H, ddd, *J* = 13.2, 8.5, 5.2 Hz), 1.75 (1H, ddd, *J* = 13.2, 10.3, 4.8 Hz), 1.13 (3H, t, *J* = 7.4 Hz) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ: 201.8, 133.0, 132.2, 130.3, 126.0, 100.9, 84.0, 83.7, 79.7, 76.6, 73.9, 41.3, 40.6, 29.7, 13.3 ppm. IR (KBr): 2974, 2936, 1075 cm^{-1}; HRMS (MALDI) *m*/*z* 410.9570 (calcd for $C_{15}H_{18}O_2NaBr_2$ [M + Na]$^+$, 410.9566). (±)-**41**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.54 (1H, dd, *J* = 15.2, 9.9 Hz), 6.25 (1H, d, *J* = 9.9 Hz), 6.10 (1H, dd, *J* = 5.9, 1.7 Hz), 5.72 (1H, dd, *J* = 15.2, 7.1 Hz), 5.39 (1H, t, *J* = 5.9 Hz), 4.82−4.80 (1H, m), 4.75−4.71 (2H, m), 4.58−4.54 (1H, m), 2.51 (2H, q, *J* = 7.2 Hz), 2.30 (1H, dd, *J* = 13.5, 6.0), 2.26 (1H, dd, *J* = 13.5, 5.5),, 1.96 (1H, ddd, *J* = 13.5, 8.5, 5.3 Hz), 1.75 (1H, ddd, *J* = 13.5, 10.3, 5.0 Hz), 1.13 (3H, t, *J* = 7.2 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.8, 134.1, 132.2, 129.7, 125.6, 101.0, 84.1, 83.6, 79.8, 76.6, 73.8, 41.3, 40.6, 35.3, 13.4 ppm. IR (KBr): 2971, 2933, 1076 cm^{-1}; HRMS (MALDI) *m*/*z* 410.95660 (calcd for $C_{15}H_{18}O_2NaBr_2$ [M + Na]$^+$, 410.95658).

Experimental Details for Total Synthesis of (−)-Aplysiallene.

*(S)-5-((tert-Butyldimethylsilyl)oxy)-1-((S)-oxiran-2-yl)pent-3-yn-1-ol (**44**).* To a dry round-bottom, three-neck flask flushed with argon were added *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (700 mg, 4.09 mmol) and dry Et_2O (35 mL). A 1.55 M *n*-BuLi solution in THF (2.9 mL, 4.50 mmol) was added to the solution at −78 °C, and the resulting mixture was stirred at the same temperature. After 30 min, **43** (352 mg, 4.09 mmol) in dry Et_2O (10 mL) and BF_3·OEt_2 (1.1 mL, 4.09 mmol) were added successively to the mixture at −78 °C, and the resulting solution was stirred for 30 min at the same temperature. After 1 h, it was quenched with saturated $NaHCO_3$ aq. The mixture was diluted with Et_2O. The organic layer was separated, washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (4:1 → 2:1) then CH_2Cl_2/Et_2O (20:1 → 10:1 → 5:1) as eluents to give **44** (360 mg, 34%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.31 (2H, t, *J* = 2.2 Hz), 3.68 (1H, m), 3.16 (1H, td, *J* = 4.4, 2.8 Hz), 2.84 (1H, t, *J* = 4.4 Hz), 2.78 (1H, dd, *J* = 5.2, 2.8 Hz), 2.65−2.48 (2H, m), 2.15 (1H, d, *J* = 6.5 Hz), 0.90 (9H, s), 0.11 (6H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 81.5, 80.1, 69.4, 54.0, 51.8, 44.9, 25.8, 25.1, 18.3, −5.2 ppm. IR (KBr): 3418, 2930, 2858, 1473, 1255, 1141, 1078 cm^{-1}; HRMS (MALDI) *m*/*z* 279.1382 (calcd for $C_{13}H_{24}O_3NaSi$ [M + Na]$^+$, 279.1387). $[\alpha]^{18}_D$ = +12.5 (*c* 0.228, $CHC1_3$).

*(9S,10S)-2,2,3,3,18,18-Hexamethyl-17,17-diphenyl-4,16-dioxa-3,17-disilanonadeca-6,12-diyne-9,10-diol (**45**).* To a dry round-bottom, three-neck flask flushed with argon were added (but-3-yn-1-yloxy)(*tert*-butyl)diphenylsilane (620 mg, 4.09 mmol), dry THF (4 mL) and **44** (100 mg, 0.39 mmol). A 1.55 M *n*-BuLi solution in THF (1.6 mL, 2.53 mmol) was added to the solution at −78 °C, and the resulting mixture was stirred at the same temperature. After 30 min, BF_3·OEt_2 (0.48 mL, 1.75 mmol) was added to the solution at −78 °C and the resulting solution was stirred for 30 min at the same temperature. After 1 h, it was quenched with saturated $NaHCO_3$ aq. The mixture was diluted with Et_2O. The organic layer was separated, washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (10:1 → 6:1 → 3:1) as eluents to give **45** (164 mg, 74%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70−7.66 (4H, m), 7.43−7.39 (6H, m), 4.29 (2H, t, *J* = 2.1 Hz), 3.767−3.721 (4H, m), 2.50 (2H, dt, *J* = 2.1, 2.7 Hz), 2.44−2.43 (4H, m), 1.051 (9H, s), 0.90 (9H, s), 0.10 (6H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.5, 133.6, 129.7, 127.7, 80.9, 77.2, 76.6, 71.1, 71.0, 62.6, 51.9, 26.7, 25.8, 24.3, 24.3, 22.9, 19.2, 18.3, −5.2 ppm. IR (KBr): 3278, 2930, 2858, 1428, 1254, 1112, 1082 cm^{-1}; HRMS (MALDI) *m*/*z* 587.2978 (calcd for $C_{33}H_{48}O_4NaSi_2$ [M + Na]$^+$, 587.2983); mp = 48 °C; $[\alpha]^{20}_D$ = +6.51 (*c* 0.126, $CHC1_3$).

*tert-Butyl(((Z)-5-((4S,5S)-5-((Z)-4-((tert-butyldimethylsilyl)oxy)-but-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-en-1-yl)oxy)-diphenylsilane (**46**).* To a round-bottom flask flushed with argon were added **45** (326.9 mg, 0.58 mmol) and dry CH_2Cl_2 (1.2 mL). 2,2-Dimethoxypropane (1.4 mL, 11.6 mmol) and CSA (13.4 mg, 0.058 mmol) were successively added to the solution and the resulting mixture was stirred at rt. After 30 min, TEA (2 mL) was added to the mixture, which was concentrated in vacuo. The crude reside was purified by silica gel column chromatography using *n*-hexane/EtOAc (6:1) as an eluent to give corresponding **acetonide** (352.3 mg, quant.) as a colorless oil. To a dry round-bottom flask were added **acetonide** (348 mg, 0.58 mmol) and dry EtOAc (5.8 mL). Quinolline (0.2 mL, 1.73 mmol) and Pd/$BaSO_4$ (42 mg) were added to the solution successively. After 30 min, the atmosphere in a reaction vessel was replaced with H_2 and the resulting mixture was stirred for further 2 h at the same temperature. The mixture was filtered through short Celite column with EtOAc and the filtrate was concentrated under reduced pressure. The crude reside was purified by silica gel column chromatography using *n*-hexane/EtOAc (6:1) as an eluent to give **46** (355.5 mg, quant.) as a colorless oil. **Acetonide**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.682−7.651 (4H, m), 7.46−7.35 (6H, m), 4.28 (2H, t, *J* = 2.2 Hz), 3.90−3.87 (2H, m), 3.74 (2H, t, *J* = 7.2 Hz), 2.58−2.57 (2H, m), 2.53−2.51 (2H, m), 2.43 (2H, tt, *J* = 7.2, 2.2 Hz), 1.40 (3H, s), 1.38 (3H, s), 1.04 (9H, s), 0.89 (9H, s), 0.10 (6H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.5, 133.6, 129.6, 127.7, 108.9, 80.3, 78.1, 77.9, 76.3, 62.7, 51.9, 27.2, 27.1, 26.8, 25.8, 23.1, 23.0, 22.9, 19.2, 18.3, −5.2 ppm. IR (KBr): 2930, 2859, 1252, 1112, 1072 cm^{-1}; HRMS (MALDI) *m*/*z* 627.3298 (calcd for $C_{36}H_{52}O_4NaSi_2$ [M + Na]$^+$, 627.3296). $[\alpha]^{23}_D$ = +15.9 (*c* 0.127, $CHC1_3$). **46**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72−7.64 (4H, m), 7.46−7.36 (6H, m), 5.67 (1H, dt, *J* = 11.6, 5.6 Hz), 5.56−5.51 (3H, m), 4.24 (2H, d, *J* = 5.6 Hz), 3.68 (4H, t, *J* = 6.7 Hz), 2.37−2.29 (6H, m), 1.39 (6H, s), 1.06 (9H, s), 0.91 (9H, s), 0.08 (6H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.5, 133.8, 132.1, 129.6, 128.4, 127.6, 126.1, 125.3, 108.0, 79.8, 63.3, 59.4, 31.0, 30.9, 30.6, 27.2, 26.8, 25.9, 19.2, 18.3, −5.1, −5.2 ppm. IR (KBr): 2930, 2859, 1252, 1083 cm^{-1}; HRMS (MALDI) *m*/*z* 631.3610 (calcd for $C_{36}H_{56}O_4NaSi_2$ [M + Na]$^+$, 631.3609). $[\alpha]^{26}_D$ = −2.92 (*c* 0.201, $CHC1_3$).

*(Z)-4-((4S,5S)-5-((Z)-5-((tert-Butyldiphenylsilyl)oxy)pent-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enal ((−)-**36**).* To a dry

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J. Org. Chem. 2015, 80, 10261−10277

round-bottom flask flushed with argon were added **46** (465 mg, 0.77 mmol), dry CH_2Cl_2 (7.5 mL) and dry MeOH (2.5 mL). CSA (169 mg, 0.73 mmol) was added to the solution, and the resulting mixture was stirred for 15 min at 0 °C before it was quenched with saturated $NaHCO_3$ aq. The mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using *n*-hexane/EtOAc (3:1) as an eluent to give corresponding TBDMS deprotected **alcohol** (329.1 mg, 87%) as a yellow oil. **Alcohol**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68−7.61 (4H, m), 7.45−7.35 (6H, m), 5.87 (1H, dt, J = 11.1, 5.4 Hz), 5.65−5.46 (3H, m), 4.17 (1H, dd, J = 12.7, 7.2 Hz), 4.04 (1H, dd, J = 12.6, 6.7 Hz), 3.72−3.59 (4H, m), 2.32 (6H, q, J = 6.7 Hz), 1.38 (3H, s), 1.37 (3H, s), 1.05 (9H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.6, 133.8, 131.6, 129.6, 128.7, 128.1, 127.6, 125.8, 108.2, 79.6, 79.3, 63.3, 57.7, 31.0, 30.3, 30.2, 27.2, 27.0, 26.8 ppm. IR (KBr): 3474, 2958, 2859, 1428, 1111, 1090 cm^{-1}; HRMS (MALDI) m/z 517.2747 (calcd for $C_{30}H_{42}O_4NaSi$ $[M + Na]^+$, 517.2745). $[\alpha]^{24}_D$ = −14.2 (c 0.290, $CHC1_3$). To a round-bottom flask flushed with argon were added **alcohol** (34.1 mg, 0.069 mmol) and dry CH_2Cl_2 (2 mL). DMP (38.5 mg, 0.086 mmol) was added to the solution at 0 °C, and the resulting mixture was allowed to warm to rt and stirred for 1 h. The solution was diluted with *n*-Hexane (1.5 mL). The crude was purified by silica gel column chromatography using *n*-hexane/EtOAc (8:1) as an eluent to give **36** (33.9 mg, quant.) as a colorless oil. Spector Data (^{1}H NMR and ^{13}C NMR) of chiral compound **36** were identical with those of (±)-**36**. **Chiral 36** $[\alpha]^{23}_D$ = −18.8 (c 0.229, $CHC1_3$).

The following routes to synthesize (−)-aplysiallene were the same as those of racemic one.

*tert-Butyl(((Z)-5-((4S,5S)-2,2-dimethyl-5-((Z)-pent-2-en-4-yn-1-yl)-1,3-dioxolan-4-yl)pent-3-en-1-yl)oxy)diphenylsilane ((−)-**37**).* According to the same procedure for (±)-**37**, (−)-**37** (192 mg) was obtained from (−)-**36** (284 mg) in 70% yield. (−)-**37** $[\alpha]^{22}_D$ = −33.6 (c 0.077, $CHC1_3$).

*(3Z,9Z)-(6S,7S)-12-((tert-Butyldiphenylsilyl)oxy)dodeca-3,9-dien-1-yne-6,7-diol ((+)-**7**).* According to the same procedure for (±)-7, (+)-7 (155.2 mg) was obtained from (−)-**37** (192 mg) in 88% yield. (+)-7 $[\alpha]^{23}_D$ = +69.1 (c 0.131, $CHC1_3$).

*((R)-3-Bromo-3-((2R,3aS,5R,6aS)-5-((R)-3-bromopropa-1,2-dien-1-yl)hexahydrofuro[3,2-b]furan-2-yl)propoxy) (tert-Butyl)-diphenylsilane (Chiral-**8**) and ((S)-3-Bromo-3-((2R,3aS,5R,6aS)-5-((R)-3-bromopropa-1,2-dien-1-yl)hexahydrofuro[3,2-b]furan-2-yl)-propoxy) (tert-Butyl)diphenylsilane (Chiral-**8a**).* According to the same procedure for (±)-**8** containing (±)-**8a**, chiral-**8** containing chiral-**8a** (159.8 mg) was obtained from (+)-7 (139.2 mg) in 82%.

*(R)-3-Bromo-3-((2R,3aS,5R,6aS)-5-((R)-3-bromopropa-1,2-dien-1-yl)hexahydrofuro[3,2-b]furan-2-yl)propan-1-ol ((−)-**38**).* According to the same procedure for (±)-**38**, (−)-**38** containing its isomer (33.6 mg) was obtained from chiral-**5** containing chiral-**5a** (33.6 mg) in 97% yield. (−)-**38** (30 mg) was separated by HPLC (Mightysil RP-18 GP 250-10 (5 μm), H_2O/MeOH = 50/50). $[\alpha]^{18}_D$ = −23.0 (c 0.075, $CHC1_3$).

*(E)-3-((2R,3aS,5R,6aS)-5-((R)-3-Bromopropa-1,2-dien-1-yl)-hexahydrofuro[3,2-b]furan-2-yl)acrylaldehyde ((−)-**39**).* According to the same procedure for (±)-**39**, (−)-**39** (21.4 mg) was obtained from (−)-**38** (35 mg) in 92% yield. $[\alpha]^{23}_D$ = −147.1 (c 0.60, $CHC1_3$).

*(−)-Aplysiallene and (−)-**41**.* According to the same procedure for (±)-**aplysiallene**, (−)-**aplysiallene** (12 mg, 35%) and (−)-**41** (11.4 mg, 33%) were obtained from (−)-**39** (83.2 mg). (−)-**aplysiallene** $[\alpha]^{20}_D$ = −115.6 (c 0.55, $CHC1_3$) and (−)-**41** $[\alpha]^{22}_D$ = −174.1 (c 0.36, $CHC1_3$).

Experimental Procedures for Bioactive Study of Aplysiallene and Its Derivatives. *Preparation of Na,K-ATPase from Rat Brain.* The whole rat brain was homogenized and centrifuged at 7500 rpm for 15 min. The supernatant was then centrifuged at 15 000 rpm for 45 min. The obtained sediment was defined as the microsome fraction. Na,K-ATPase was purified according to Jφrgensen's method.[20] The membrane compartment was solubilized using sodium dodecyl sulfate of 0.55 mg/mg of the amount of the protein, then put on the density gradient of the glycerol according to the methods of Post et al., and centrifuged at 15 000 rpm for 15 h. The fraction with high Na,K-ATPase activity was centrifuged at 35 000 rpm for 1 h and recovered as purified Na,K-ATPase.[21]

Assay of Na,K-ATPase Activity. Na,K-ATPase activity was determined in a standard incubation medium (300 μL), containing 1 μL of the enzyme, 25 mM sucrose, 0.1 mM ethylenediaminetetraacetic acid (EDTA), 50 mM Tris-HCl at pH 7.4, 160 mM NaCl, 16 mM KCl, 5 mM $MgCl_2$ and 5 mM ATP with or without 1 mM ouabain, in the presence or absence (control) of each concentration of (−)-aplysiallene, (±)-aplysiallene, bromodiene (−)-**41**, bromodiene racemic (±)-**41**, and (−)-aplysiallene precursor (−)-**38**. Reaction mixtures were preincubated for 30 min at 37 °C. The reaction was started by the addition of ATP and allowed to proceed for 30 min; then the reaction was stopped by the addition of 0.3 mL of 12% SDS. The released inorganic phosphate was detected by the method of Chifflet et al.[22] Briefly, 0.6 mL of the solution containing 3% ascorbic acid, 0.5 N HCl and 0.5% ammonium molybdate was added to the 0.6 mL reaction mixture with SDS, which was left for 3−10 min at room temperature. Then, 0.9 mL of a solution containing 2% sodium citrate, 2% sodium metaarsenite and 2% acetic acid was added to the mixture, which was then incubated for 10 min at 37 °C. The developed color was read at 850 nm spectrophotometrically. The results are expressed as the mean percentage of enzyme activity relative to the corresponding control value, from experiments performed in triplicate.[23]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01882.

^{1}H and ^{13}C NMR spectra of new compounds, and copies of HPLC chromatograms of (±)- and (−)-aplysiallene and (±)- and (−)-**41**. (PDF)

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Notes

The authors declare no competing financial interest.

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