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First Total Synthesis and Structural Reassignment of (−)-Aplysiallene

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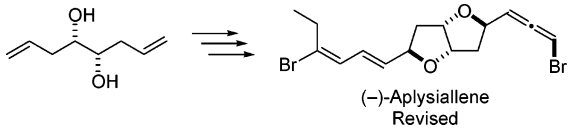
ABSTRACT

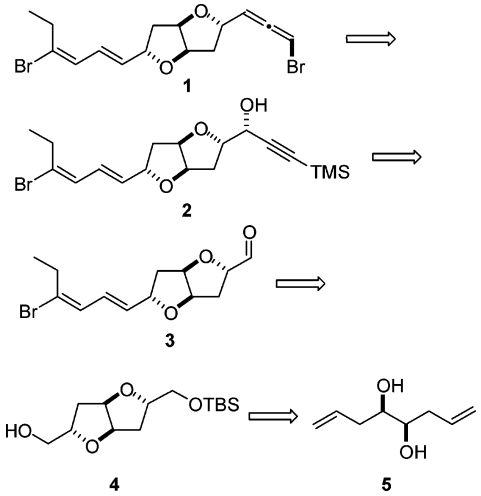


The first total synthesis of (−)-aplysiallene has been completed in 16 steps and features a key sequential Mukaiyama aerobic oxidative cyclization to prepare the fused bis-THF core. The original stereochemical assignment has been revised as shown.

Aplysiallene **1** was first isolated in 1985 from the red alga *Laurencia okamurai Yamada* by Suzuki and Kurosawa.[1] Its intriguing structural features include (1) a unique *cis*-fused 2,6-dioxabicyclo[3,3,0]octane skeleton consisting of two *trans*-tetrahydrofuran rings, (2) an unusual (*E*,*E*)-bromodiene side chain, and (3) an *R*-bromoallene[2] appendage. The absolute stereochemistry of **1** was assigned according to its strong negative optical rotation (due to the allene[3]), and the relative stereochemistry was assigned by NOE correlations and comparison with kumausallene.[4] In 2001, Okamoto also reported the isolation of **1** from the sea hare *Aplysia kurodai* and found it functions as a Na^+/K^+ ATPase inhibitor with $IC_{50} = 0.7\ \mu M$.[5] In this communication, we report the first asymmetric total synthesis of aplysiallene and provide evidence for its structural revision.[6]

It was envisaged that the *R*-bromoallene substituent could be prepared from the corresponding *R*-propargyl alcohol **2a**, which in turn should be accessible by an *anti*-selective alkynylation between aldehyde **3** and trimethylsilylacetylene.[7] Although we are unaware of precedence for the direct introduction of the bromodiene subunit, a plausible derivation could be from alcohol **4**, which would be stereoselectively prepared by sequential oxidative cyclization[8] of the known (*R*,*R*)-diol **5** (Scheme 1).

Scheme 1. Retrosynthetic Analysis of (−)-Aplysiallene



The synthesis began with reaction of (*S*,*S*)-diepoxybutane **6** with vinyl magnesium bromide in the presence of CuBr to give the (*S*,*S*)-diol *ent*-**5** in 72% yield (Scheme 2). Note that the stereochemistry of *ent*-**5** is opposite to that required

(1) Suzuki, M.; Kurosawa, E. *Phytochemistry* **1985**, *24*, 1999−2002.
(2) For a review on bromoallene natural products, see: Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196−1216.
(3) Lowe, G. *J. Chem. Soc., Chem. Commun.* **1965**, 411.
(4) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1643−1644.
(5) (a) Okamoto, Y.; Nitanda, N.; Ojika, M.; Sakagami, Y. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 474−476. (b) Okamoto, Y.; Nitanda, N.; Ojika, M.; Sakagami, Y. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 460.
(6) For a review on reassignment of natural products, see: Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012−1044.

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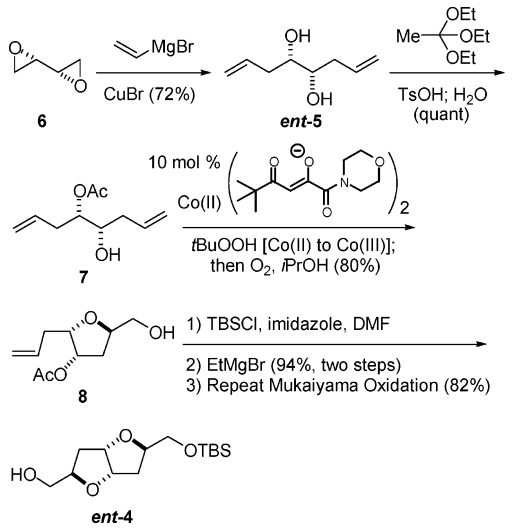
Scheme 2. Synthesis of the bis-THF Core



for the reported natural product, so this should in principle lead to a synthesis of *ent*-**1**. The diol *ent*-**5** was then quantitatively desymmetrized by acylation via the intermediate ortho ester,[9] and the resulting material was subjected to a slightly modified[10a] Mukaiyama cobalt-catalyzed aerobic oxidative cyclization to afford mono-THF **8** as a single diastereomer. Protection of the primary hydroxyl group as its TBS ether and deprotection of the acetate with EtMgBr set the stage for the second oxidative cyclization which afforded the key intermediate *ent*-**4**. The Mukaiyama oxidation has recently emerged as a useful tool for the stereoselective construction of *trans*-THFs,[10] and the power of this methodology is illustrated here by the straightforward and efficient synthesis of *ent*-**4** in 62% yield over five steps.[11]

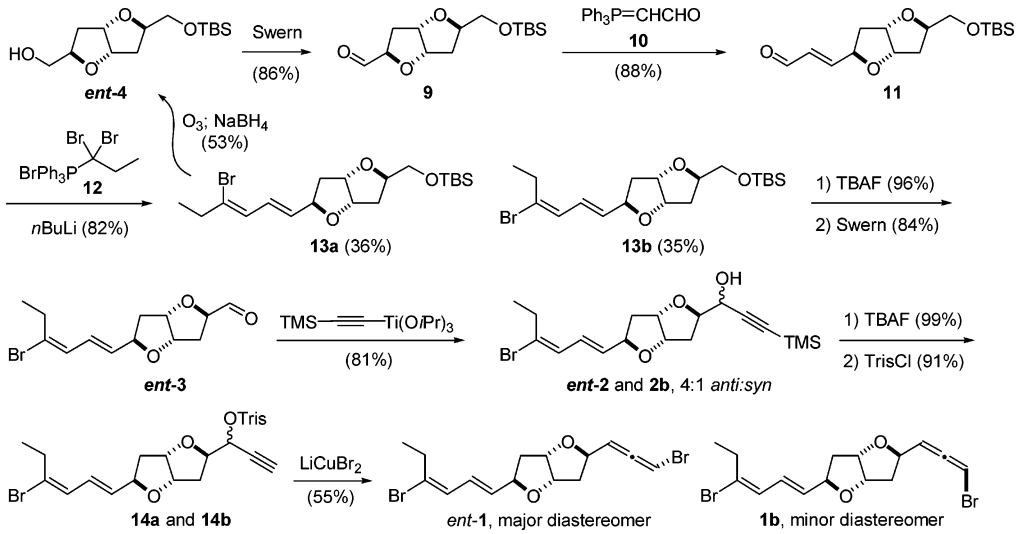
The regiospecific and stereospecific introduction of the bromodiene moiety poses a significant synthetic challenge. In particular, the presence of the vinyl bromide functionality largely precluded the use of olefin coupling strategies,[12] and after having examined several methods,[13] the best approach that emerged was based on Wittig chemistry. Thus, Swern oxidation of *ent*-**4** gave sensitive aldehyde **9**, which was immediately treated with Wittig reagent **10** to give **11** (76%, two steps). Introduction of the bromoolefin was accomplished nonselectively by reaction with the Smithers reagent[14] **12** to give dienes **13a** and **13b** (82% combined yield, **13a**/**13b** = 1.1:1).

Although the isolated yield of **13b** was only 35%, the dienes **13a** and **13b** were separable by flash chromatography on the gram scale, and unwanted **13a** can be recycled by ozonolysis followed by a $NaBH_4$ workup to give alcohol *ent*-**4** in 53% yield. In contrast, attempted conversion of **13a** directly into **9** by ozonolysis with a PPh_3 workup resulted in complete decomposition of **13a**.

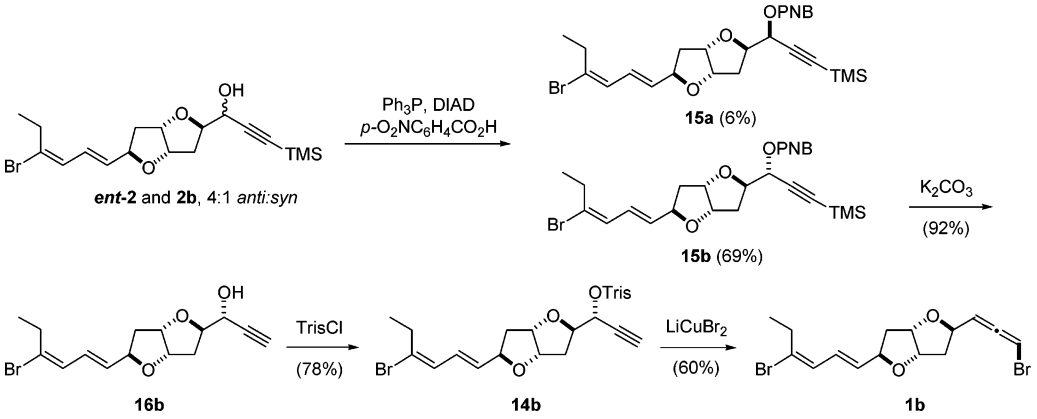
With the bromodiene side chain at hand, deprotection of the silyl ether **13b** by treatment with TBAF followed by Swern oxidation afforded the highly labile aldehyde *ent*-**3** (81%, two steps), which was used immediately in the following addition step. As expected, alkynylation of *ent*-**3** with the titanium acetylide of trimethylsilylacetylene (generated in situ with *n*-BuLi and $ClTi(OiPr)_3$) gave *ent*-**2** and **2b** as an inseparable 4:1 *anti*/*syn* mixture in 81% combined yield.[7,10a,15] The mixture of isomers was treated with TBAF to give the corresponding propargyl alcohols, which were converted to trisylates **14a** and **14b** (90%, two steps). In the final step, the trisylates displaced with $LiCuBr_2$ gave allene *ent*-**1** and a trace of diastereomer **1b** (Scheme 3).[16]

However, a comparison of the ^1H and ^{13}C NMR of *ent*-**1** with the data reported for the natural product revealed several inconsistencies (Table 1). Specifically, in the ^{13}C NMR, carbons C2, C3, and C4 (Figure 1) were off by ±0.3 ppm, and in the ^1H NMR, the two allene protons were off by ±0.02 ppm. The absolute *S* configuration of the allene in *ent*-**1** was confirmed by the strong positive optical rotation[3] ($[\alpha]_D$ = +166°, $CHCl_3$). Taken together, these data suggested that

Scheme 3. Synthesis of the Proposed Structure of (+)-Aplysiallene



Scheme 4. Synthesis of Revised (−)-Aplysiallene



the reported structure must be incorrect. In this regard, examination of the ^{1}H and ^{13}C NMR from minor isomer **1b** appeared to be a match,[17] so efforts were undertaken to prepare **1b** as the major isomer.

Table 1. Summary of ^{13}C NMR Data

^{13}C	isolation	*ent*-**1**	**1b**
1[a]	73.8	73.9	73.8
2	201.8	201.5	201.8
3	101.0	101.4	101.0
4	76.6	76.2	76.6
5	40.6	40.8	40.6
6	83.7	83.6	83.7
7	84.0	84.2	84.0
8	41.3	41.3	41.3
9	79.7	79.7	79.7
10	133.1	133.1	133.1
11	125.9	126.0	125.9
12	130.4	130.3	130.3
13	132.1	132.1	132.1
14	29.7	29.7	29.7
15	13.3	13.3	13.3

[a] Carbon atom numbering begins at the bromoallene.

The most direct approach to prepare **2b**, the *syn* epimer of *ent*-**2**, would be a *syn*-alkynylation of aldehyde *ent*-**3**. However, we found that Carreira alkynylation[11b,18] of a model THF-2-carbaldehyde with trimethylsilylacetylene gave consistently low yields despite optimization efforts. Attempts to form the propargyl trisylate **14b** directly from *ent*-**2** with inversion of stereochemistry under Mitsunobu conditions were unsuccessful,[19] although Kim and co-workers recently reported a similar reaction.[20] Ultimately, the desired *syn*

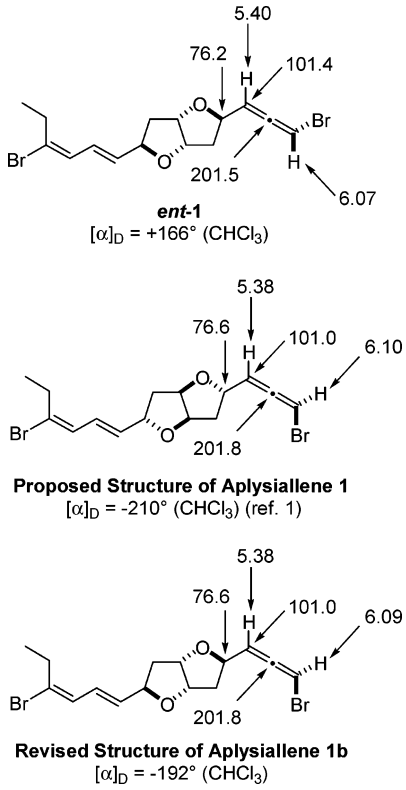


Figure 1. Structural revision of aplysiallene.

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(8) Inoki, S.; Mukaiyama, T. *Chem. Lett.* **1990**, 67−70.
(9) Hanessian, S.; Roy, R. *Can. J. Chem.* **1985**, *63*, 163−172.
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(11) For the synthesis of related fused bis-THF systems, see ref 7 and: (a) Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 3175−3177. (b) Boukouvalas, J.; Pouliot, M.; Robichaud, J.; MacNeil, S.; Snieckus, V. *Org. Lett.* **2006**, *8*, 3597−3599. (c) Feldman, K. S.; Mechem, C. C.; Nader, L. *J. Am. Chem. Soc.* **1982**, *104*, 4011−4012.
(12) For a related example using olefin coupling, see: Qian, M.; Huang, Z.; Negishi, E. *Org. Lett.* **2004**, *6*, 1531−1534. In our case, such a strategy was initially pursued but abandoned after the failure to prepare (*E*)-1-iodo-2-bromobutene, despite a report on the successful preparation of a similar haloolefin, (*E*)-1-iodo-2-bromohexene: Barluenga, J.; Rodriguez, M. A.; Campos, P. J. *J. Org. Chem.* **1990**, *55*, 3104−3106.

diastereomer was secured by subjecting *ent*-**2** and **2b** to classic Mitsunobu conditions that afforded propargyl *p*-nitrobenzoates **15a** and **15b**, which were separable by flash chromatography (Scheme 4). Treatment of **15b** with K_2CO_3 in MeOH resulted in global deprotection to the isomerically pure propargyl alcohol **16b**. Finally, **1b** was obtained after trisylation and subsequent reaction with $LiCuBr_2$ (47%, two steps). The ^1H and ^{13}C NMR spectra, optical rotation, and mass spectrum fragmentation pattern of **1b** were an exact match to the reported data for the natural product.

In summary, the total synthesis of (−)-aplysiallene has been completed in 16 steps in 2.3% overall yield. Synthetic highlights include the first application of a Mukaiyama aerobic oxidative cyclization to form the *cis*-fused 2,6-dioxabicyclo-[3,3,0]octane skeleton and the use of the Smithers reagent to secure the bromodiene side chain. Moreover, the stereochemistry of aplysiallene is unambiguously reassigned to **1b**.

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Supporting Information Available: General experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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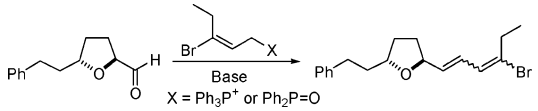
(13) Initial efforts were undertaken to furnish the bromodiene side chain on a model system by a one-step olefination strategy, but such reactions under various conditions consistently gave low (20∼30%) yields consisting of mixtures of all four olefin isomers.



(14) (a) Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 2833−2838. (b) In our case, addition of DMSO gave negligible improvement on *E*/*Z* selectivity. Gao, L.; Murai, A. *Heterocycles* **1996**, *42*, 745−774.

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(17) For spectral comparison between kumausallene and 1-*epi*-kumausallene, see ref 7.

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