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Total synthesis of (+)-brasilenyne *via* concise construction of an oxonane framework containing a 1,3-*cis*,*cis*-diene†

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The enantioselective total synthesis of (+)-brasilenyne has been accomplished. The key features of the synthesis include the convergent preparation of a highly functionalized endocyclization precursor *via* selective epoxide opening, the construction of an oxonene skeleton through perfect regioselective Pd(0)-catalyzed endocyclization, and the installation of a 1,3-*cis*,*cis*-diene unit *via* a decarboxylative photophenylselenylation and site-selective selenoxide elimination sequence.

Medium-sized cyclic ether metabolites have been continuously isolated from *Laurencia* red algae and marine organisms that feed on *Laurencia* species.[1] These *Laurencia* oxacycles have attracted considerable attention of synthetic chemists[2] because of their unique structural features including various ring sizes, diverse stereogenic centers, one or more halogen atoms, and terminal enyne or allene units.[1] In particular, marine natural products consisting of oxonane, a nine-membered cyclic ether, have been continuously reported, although synthetic studies on the oxonanes are less than the oxocanes, eight-membered cyclic ethers.[2]

(+)-Brasilenyne (**1**), one of the *Laurencia* oxacycles that contains an α,α′-*trans*-substituted oxonane skeleton (Fig. 1), was isolated from *Aplysia brasiliana* and reported to show antifeedant activity.[3] This secondary metabolite has only been synthesized *via* an elegant intramolecular silicon-assisted cross-coupling of two vinyl groups by the Denmark[4] group partly due to the difficulty in the installation of the 1,3-*cis*,*cis*-diene unit in the oxonane framework by other approaches including ring closing metathesis.[5] We herein report the total synthesis of **1** *via* concise construction of an oxonane framework containing a 1,3-*cis*,*cis*-diene.

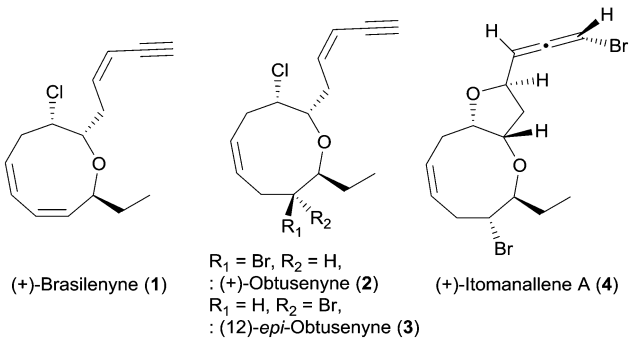

Fig. 1 (+)-Brasilenyne (**1**) and the related oxonane natural product from the *Laurencia* family.

Our retrosynthetic plan is outlined in Scheme 1. The labile enyne moiety was planned to be introduced into **5** by Julia olefination[6] at the final stage. The C7-chloride would be directly introduced *via* halide displacement of the C7-hydroxy group. The important 1,3-*cis*,*cis*-diene would be constructed by a regioselective selenoxide elimination of selenide **6** with the preexisting ring olefin intact. The oxonane intermediate **6**, which possesses appropriate substituents to be converted to **1**, can be derived from **7** by desulfonylation and concise conversion of ester to phenylselenide.[7] The key α,α′-*trans*-substituted oxonene **7** was anticipated to be effectively prepared by selective Pd(0)-catalyzed endocyclization, which was previously studied by Hoffmann[8] and our group,[9] of allylic carbonate **8**. The endocyclization precursor **8** was considered to be quite appropriate for the concise construction of the oxonene core **5**. As the construction of the 1,3-*cis*,*cis*-diene unit in the oxonane system could not be efficiently accomplished from the cyclization precursors reported by Hoffmann[8] and our group,[9] we optimized the nucleophilic part with benzenesulfonyl acetate.[10] The benzenesulfonyl acetate moiety was anticipated to be effectively transformed into phenylselenide *via* a radical chain reaction. The cyclization precursor **8** could be convergently prepared by the diastereoselective epoxide ring opening of **9** with allylic alcohol **10** and with the assistance of copper triflate.[11]

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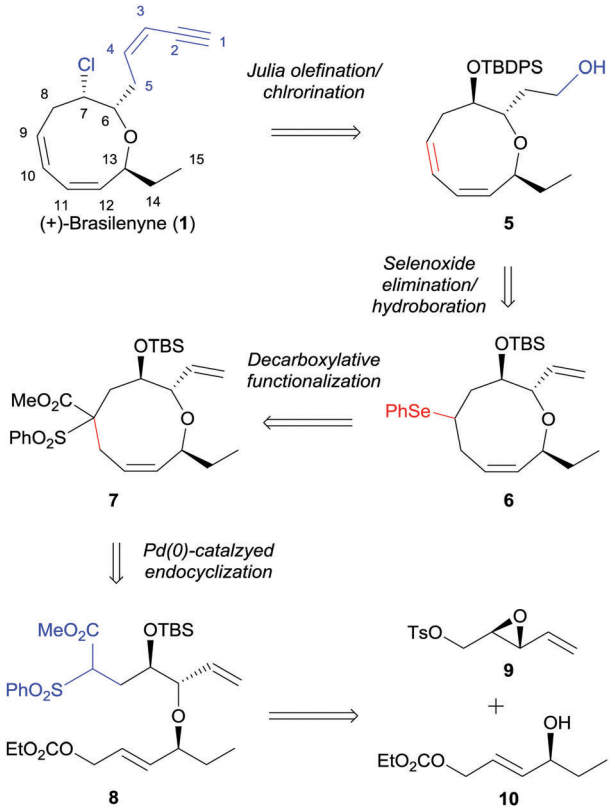
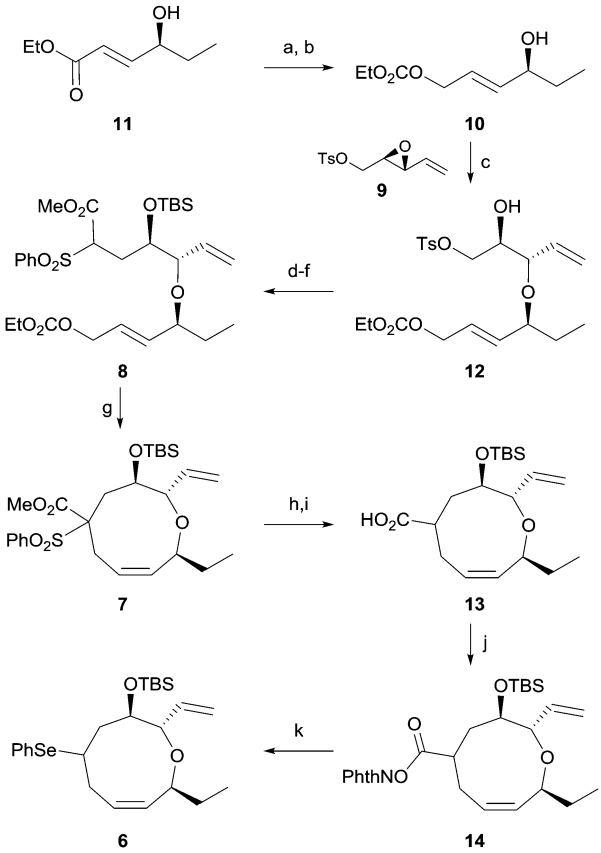


Scheme 1 Strategy for the asymmetric total synthesis of (+)-brasilenyne (**1**). TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, Ph = phenyl, Ts = *p*-toluenesulfonyl.



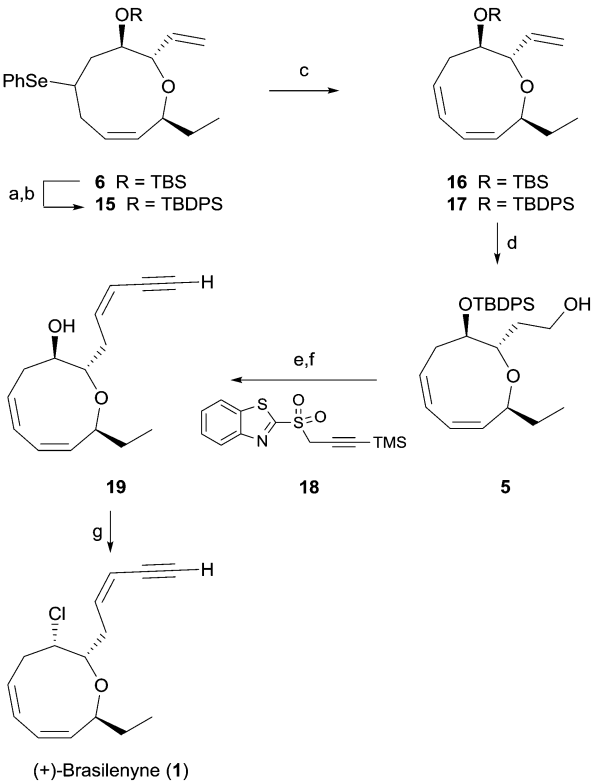
Scheme 2 Synthesis of the oxonene intermediate. (a) DIBAL-H, THF, −78 °C, 30 min, 81%; (b) $ClCO_2Et$, 2,6-lutidine, MeCN, −20 °C, 2 h, 84%; (c) $Cu(OTf)_2$, CH_2Cl_2, 0 °C, 1 h, 59%; (d) NaI, acetone, reflux, 12 h; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 86% for 2 steps; (f) $PhSO_2CH_2CO_2Me$, NaH, DMF, 80 °C, 20 h, 71%; (g) $Pd(dppe)_2$, DMSO, 60 °C, 2 h, 75%; (h) SmI_2, THF, −78 °C, 30 min; (i) $LiOH{\cdot}H_2O$, THF/H_2O/MeOH (1 : 1 : 1), 8 h, 90% for 2 steps; (j) *N*-hydroxyl phthalimide, DCC, DMAP, THF, 4 h, 91%; (k) blue LEDs, $(PhSe)_2$, $Ru(bpy)_3Cl_2{\cdot}6H_2O$, BNAH, THF/$H_2O$ (2 : 1), 2 h, 79%. dppe = 1,2-bis(diphenylphosphino)ethane, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, BNAH = 1-benzyl-1,4-dihydronicotinamide, bpy = 2,2′-bipyridyl.

The synthesis of **1** was commenced by preparing the cyclization precursor **8** as shown in Scheme 2. DIBAL reduction of the known ester **11**[12] and ethoxycarbonylation of the resulting alcohol afforded allylic carbonate **10** in 68% yield for two steps. Diastereoselective epoxide opening[11] of **9**, which is prepared from divinylcarbinol *via* a three-step sequence,[13] in the presence of copper triflate produced ether **12** in 59% yield. Unfortunately, the regioisomeric ether was consistently produced in 29% yield despite our continuous efforts. Iodide displacement of tosylate **12** and TBS protection of alcohol followed by reaction with the benzenesulfonyl acetate anion produced the cyclization precursor **8** in 61% yield for three steps.

With the cyclization precursor in hand, we initially confirmed the feasibility of the key endocyclization through intensive cyclization studies including different solvents and temperatures. Treatment of allylic carbonate **8** with $Pd(dppe)_2$ in DMSO at 60 °C for 2 h produced the desired nine-membered cyclic ether **7** in 75% yield. The regioisomeric seven-membered cyclic ether was not observed. The excellent regioselectivity of the endocyclization is likely due to the preferred attack of the highly bulky benzenesulfonyl acetate anion at the sterically less hindered terminal carbon of the π-allyl palladium complex.[14] In addition, production of the isomeric 6,13-*cis* cyclic ether *via* epimerization at C13 through the cleavage of ether linkage,[8b,8c] of which we were concerned, was not observed.

We next focused on efficient installation of the diene moiety in the oxonene skeleton. Initial attempts at decarboxylation of oxonene **7** followed by direct elimination[15] of the benzenesulfonyl group to obtain a diene system were not successful. Thus, removal of the benzenesulfonyl group of **7** with samarium iodide followed by ester hydrolysis afforded acid **13** in 90% yield for two steps. We tried to directly transform the acid to the corresponding halide[16] or selenide[7a] *via* the Hunsdiecker type reaction, which proved to be ineffective. In addition, efforts to directly eliminate the acid[17] were also unsuccessful. Therefore, we finally decided to utilize decarboxylative photo-phenylselenylation. Reaction of acid **13** with *N*-hydroxyphthalimide in the presence of DCC produced ester **14**, which was transformed into phenylseleno oxonene **6** in 72% yield for two steps *via* treatment with diphenyl diselenide and BNAH in the presence of a ruthenium catalyst.[7b] To the best of our knowledge, few synthetic applications of decarboxylative phenylselenylation using photoredox catalysis have been reported.[18]

As shown in Scheme 3, facile regioselective elimination of **6** delightfully proceeded upon hydrogen peroxide treatment to afford the corresponding diene **16** in 67% yield along with a



Scheme 3 Completion of (+)-brasilenyne (**1**) synthesis. (a) TBAF, THF, 0 °C, 3 h; (b) TBDPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 4 h, 83% for 2 steps; (c) H_2O_2, 2-methyl-2-butene, pyridine, CH_2Cl_2, 0 °C, 12 h, 67% for **16**, 90% for **17**; (d) (9-BBN) $_2$, THF, 8 h then, 2N NaOH, H_2O_2, 0 °C, 1 h, 72%; (e) DMP, $NaHCO_3$, CH_2Cl_2, 1 h then, **18**, DBU, CH_2Cl_2, −55 °C, 2 h, 83%; (f) TBAF, THF, 6 h, 99%; (g) CCl_4, *n*-Oct_3P, toluene, 60 °C, 12 h, 93%. TBAF = tetrabutylammonium fluoride, BBN = 9-borabicyclo[3,3,1]nonane, DMP = Dess–Martin periodinane, DBU = 1,8-diazabicyclo[5,4,0]undec-7-ene.

small amount of the regioisomeric triene and the *trans*-olefinic isomer. However, replacing the TBS protecting group of selenide with a TBDPS protecting group produced the triene **17** in 90% isolated yield with only a small amount of the regioisomeric triene. Formation of the favorable conformation for the excellent regioselective *syn*-elimination of the selenoxide produced from **15** is likely induced by a steric effect of the bulky TBDPS group.[19]

Triene **17** was reacted with 9-BBN to give alcohol **5** in 72% yield. For completion of the synthesis, geometrically selective formation of the enyne moiety was extensively examined. The reaction[6] of the aldehyde obtained from the Dess–Martin periodinane oxidation of **5** with benzothiazolyl sulfone **18** in the presence of DBU produced the *cis*-enyne product ($Z/E > 20:1$) in 83% isolated yield, which is superior in terms of yield and geometric selectivity to the Peterson type olefination used in previous synthesis.[4] Global deprotection of the TBDPS and TMS groups with TBAF afforded the hydroxy enyne **19** in 99% yield. Finally, reaction of alcohol **19** with carbon tetrachloride and trioctylphophine[4] produced **1** in 93% yield. Synthetic **1** was identical in all respects to natural **1**.[3]

In summary, we accomplished the asymmetric total synthesis of (+)-brasilenyne (**1**) in 18 steps from the known ester **11** (21 steps from the commercially available starting materials). The key features of our synthesis include stereoselective installation of the stereocenters at the α,α′-positions of the ether linkage and the C7-stereocenter *via* a selective epoxide ring-opening reaction, concise construction of the oxonane framework by perfectly regioselective endocyclization, effective elaboration of the 1,3-*cis*,*cis*-diene unit *via* a sequence of decarboxylative photophenylselenylation followed by selenoxide elimination, and geometrically selective introduction of the *cis*-enyne side chain *via* the one-pot process of oxidation/Julia olefination of alcohol **5**. This versatile synthetic approach is expected to be widely utilized for the syntheses of the *Laurencia* oxonane natural products.

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Conflicts of interest

There are no conflicts to declare.

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