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Stereoselective Total Synthesis of (−)-Kumausallene

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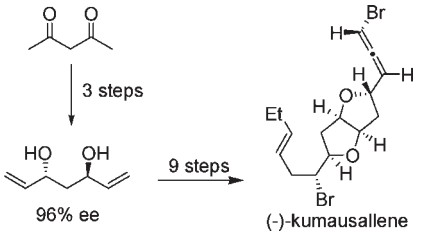
ABSTRACT



A stereoselective total synthesis of (−)-kumausallene was completed in 12 steps from acetylacetone. The hidden symmetry of (−)-kumausallene was recognized, and its skeleton was constructed efficiently from a C_2-symmetric diol by a palladium-catalyzed cascade reaction. High diastereoselectivity was observed for the DMF-promoted biomimetic 1,4-bromocyclization of a conjugated enyne.

(−)-Kumausallene **1**[1] belongs to a family of nonisoprenoid sesquiterpenes with a unique bromoallene moiety (Figure 1).[2,3] The first total synthesis of (±)-kumausallene was accomplished by Overman.[4−6] In this synthesis, the complex dioxabicyclo[3.3.0]octane core was constructed by an elegant ring-expansion annulation strategy[4,5] and the bromoallene moiety was introduced by stereoselective S_N2' displacement of propargylic sulfonate.[7] In the first enantioselective synthesis of (−)-kumausallene by Evans,[8] the 2,5-*cis*-substituted tetrahydrofuran (THF) ring was prepared by an acyl radical cyclization[9] and a very efficient biomimetic strategy was undertaken to forge the bromoallene and the adjacent THF ring simultaneously.[10] Although high stereoselectivity was observed for the formation of

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both THF rings, two diastereomeric bromoallenes were produced in a 1:2.5 ratio favoring the unnatural epimer. We herein describe the first diastereo- and enantioselective total synthesis of (−)-kumausallene employing a desymmetrization strategy for the construction of the 2,5-*cis*-substituted THF ring, which is distinctly different from two previous syntheses.[11] Only one stereoisomeric bromoallene was obtained from the biomimetic 1,4-bromoetherification of the proposed enyne precursor in the biosynthesis.

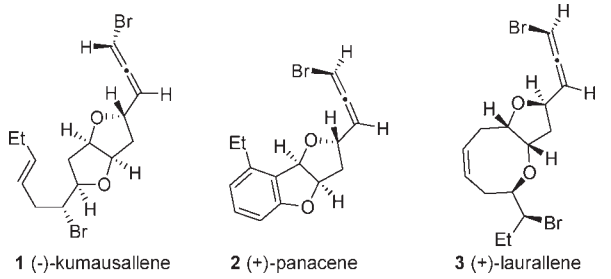
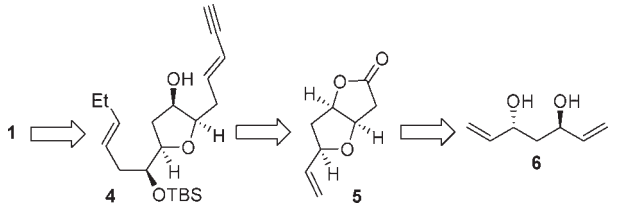


Figure 1. Representative natural products with a bromoallene moiety.

In addition to Evans' approach to (−)-kumausallene, the biomimetic strategy has also been executed in the synthesis of panacene **2**[12,13] and laurallene **3**.[14] Low diastereomeric ratios (1:1 to 1.2:1) were generally observed for the newly generated stereogenic center and the axially chiral allene moiety.[15] However, Canesi observed a dramatic solvent effect for 1,4-bromoetherification of a *trans*-enyne in his synthesis of (±)-panacene. High *syn*-diastereoselectivity was observed in chloroform (dr = 9:1), cyclohexane (dr > 20:1), and benzene (dr > 20:1), while nearly equal amounts of both diastereomers were obtained in acetonitrile or ethyl acetate.[13] Unfortunately, the natural panacene has the *anti*-stereochemistry as shown in Figure 1. Thus, a diastereoselective biomimetic synthesis remains to be developed for this class of halogenated natural products with axial chirality.

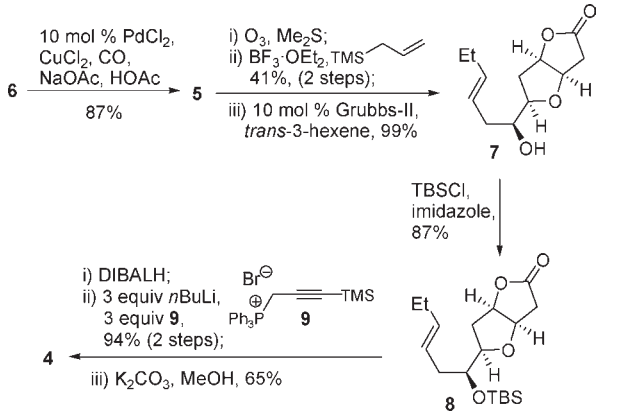
Scheme 1. Retrosynthetic Analysis for (−)-Kumausallene



We recently discovered that the diastereoselectivity of 1,4-bromolactonization of conjugated enynes depended on the choice of catalyst and *syn*-addition was generally favored.[16,17] We envisioned that the stereochemical outcome of the bromoetherification of conjugated enynes could also be catalyst-dependent. If a 1,4-*syn*-bromoetherification of enyne **4** is realized, the synthesis of **1** can be accomplished very efficiently according to the strategy shown in Scheme 1. The upper enyne and lower alkene side chains in tetrahydrofuran **4** will be derived from functionalizations of the vinyl and lactone moieties in compound **5**. This 5-5-*cis*-fused bicyclic system can be prepared from C_2-symmetric diol **6** by adopting a palladium-catalyzed oxycarbonylation−lactonization cascade reaction first described by Semmelhack.[18]

Our synthesis began with the known C_2-symmetric diol **6**,[19] available in three steps and 96% *ee* from acetylacetone.[20] The palladium-catalyzed cascade reaction[18] provided bicyclic lactone **5** in 87% yield as a single stereoisomer (Scheme 2). Ozonolysis, Sakurai allylation,[21] and cross-metathesis with Grubbs II catalyst[22] then furnished alcohol **7** with a complete carbon framework of the lower side chain.[11k] The Sakurai allylation proceeded with a diastereoselectivity of a 4:1 ratio favoring the desired stereoisomer.[23] The minor isomer was easily removed by column chromatography. Protection of the free hydroxyl group in compound **7** and reduction of the lactone to lactol, followed by olefination with commercially available reagent **9**, provided a separable mixture (E/Z = 10:1) of conjugated enynes.[24] Removal of the TMS group in basic methanol smoothly furnished the desired product **4**.

Scheme 2. Stereoselective Synthesis of Trisubstituted THF Ring by Desymetrization of a C_2-Symmetric Diol



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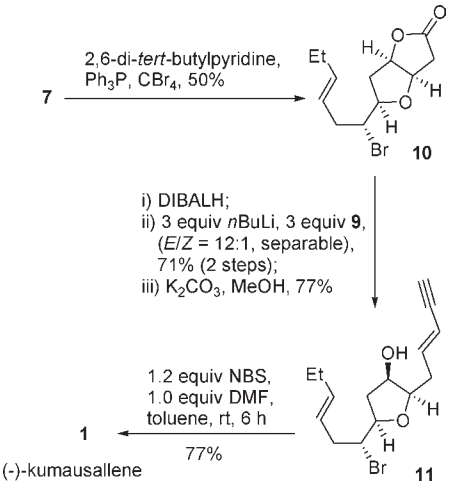
With enyne **4** in hand, we then studied the biomimetic bromoetherification reaction. To our surprise, treatment of enyne **4** with NBS in $CDCl_3$ led to no reaction after 24 h. Switching the solvent from $CDCl_3$ to toluene led to the formation of a complex mixture in 2 h. When we tried the conditions used by Evans in his biomimetic cyclization of a related substrate,[8,25] all olefin signals completely disappeared after 6.5 h and a complex mixture was obtained. No improvement was observed when newly crystallized NBS or freshly prepared TBCD was used. We then explored different additives and solvents for the bromoetherification of enyne **4**. Among the additives that were able to promote the bromolactonization of conjugated enynes in our previous studies,[16,17] only DMF and HMPA could promote the bromoetherification of conjugated enyne **4**. The ratios of bromoallene products to enyne starting material **4** were 4:1 and 1:2 after 24 h for DMF and HMPA respectively. However, the ^{13}C NMR of the crude product showed three characteristic central allene carbons in a ratio of 1:3:1 for DMF and 2:4:1 for HMPA. In both cases, the major product among these three inseparable isomers did not match the desired bromoallene, an intermediate previously reported in Overman's synthesis.[6] We also tried the bromoetherification for the enyne substrate with a free diol derived from compound **4** by removing the TBS protecting group. However, the *trans*-olefin on the lower side chain participated in the halogen mediated reaction and led to unidentifiable products under various conditions.

Since deacetylkumausyne **11** (Scheme 3) was isolated together with kumausallene **1** and was proposed as the precursor for the biosynthesis of the latter,[26] we decided to test the biomimetic cyclization of the former. The conversion of a homoallylic alcohol to the corresponding bromide was known to be problematic and low yielding.[5,6,8] We were able to obtain an ~50% yield of the homoallylic bromide **10** from alcohol **7** if all reagents (2,6-di-*tert*-butylpyridine, Ph_3P, and CBr_4) were carefully purified and dried (Scheme 3). Following the same sequence used previously (**8** to **4**), lactone **10** was converted to enyne **11** in three steps. When we treated compound **11** with NBS and 10 equiv of DMF in deuterated toluene, the biomimetic 1,4-*syn*-bromoetherification of the conjugated enyne occurred smoothly to afford final product **1** without any evidence of other byproducts. In a larger scale reaction, the amount of DMF was lowered to 1.0 equiv and product **1** was isolated in 77% yield. We found the addition of DMF to be critical because, in its absence, the reaction of enyne **11** with NBS led to a complex mixture in 1.5 h without the formation of any bromoallene.

Scheme 3. Completion of (−)-Kumausallene by Biomimetic Cyclization



The spectroscopic data (^1H NMR, ^{13}C NMR, IR) of our synthetic (−)-kumausallene were identical in all respects to values reported in the literature.[23] The stereochemistry of the newly formed tetrahydrofuran ring was further confirmed by the nuclear Overhauser effect (NOE).[23] The observed negative sign of optical rotation ($[\alpha]_D^{20} = -141$ ($c = 0.24$, $CHCl_3$); lit[1] $[\alpha]_D^{20} = -150$ ($c = 1$, $CHCl_3$); lit[8] $[\alpha]_D^{20} = -145$ ($c = 0.4$, $CHCl_3$)) provided further evidence for the absolute stereochemistry of the bromoallene[2,17] based on Lowe's rule.[27]

In summary, we have completed the first diastereo- and enantioselective synthesis of (−)-kumausallene in 12 steps from acetylacetone. We recognized the hidden symmetry of the target and prepared the 2,5-*cis*-substituted THF ring by desymmetrizing a C_2-symmetric diol using a palladium catalyzed cascade reaction. A stereoselective biomimetic cyclization was realized when the 1,4-bromoetherification was conducted on the proposed enyne precursor in biosynthesis.

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Supporting Information Available. ^1H NMR, ^{13}C NMR, IR, HRMS, and optical rotations for intermediates involved in the synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

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