and turn into an isotropic liquid without showing any mesophase. When this liquid was cooled at the same rate, the crystal slowly appeared, but formation of mesophase was still not observed.

Optical properties of the material were observed with a Laborlux12POLS polarizing microscope. Photographs were taken with a Leica camera (MPS28). The imaging plate apparatus Rigaku RU 200 equipped with a Marresearch 2D detector was used for the X-ray analysis (the radiation was $Cu_{K\alpha}$; $\lambda = 1.542$ Å).

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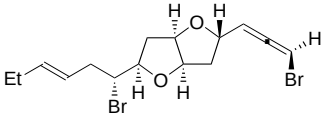
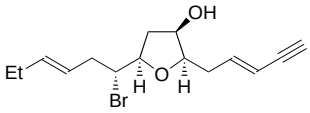
Enantioselective Total Synthesis of the Nonisoprenoid Sesquiterpene (−)-Kumausallene**

P. Andrew Evans,* V. Srinivasa Murthy, Jamie D. Roseman, and Arnold L. Rheingold

(−)-Kumausallene (**1**) was isolated by Kurosawa and co-workers in 1983 from the red algae *Laurencia Nipponica* Yamada[1] indigenous to the coast of Hokkaido in Japan, and is a member of a class of halogenated nonisoprenoid sesquiterpenes that contain a *cis*-2,5-disubstituted tetrahydrofuran unit halogenated or oxygenated at C3.[2–4] In a program directed towards the construction of *cis*-2,5-disubstituted tetrahydrofuran-3-ones using acyl radical cyclizations,[5–7] we decided to apply this methodology to the enantioselective total synthesis of kumausallene (**1**) and thus confirm the



(–)-Kumausallene **1**



(+)-*trans*-Deacetylkumausyne **2**

absolute configuration of the bromoallene moiety, which had previously been assigned on the basis of optical rotation data (Lowe's rule).[1, 8] Furthermore, the proposal that kumausallene (**1**) is biomimetically related to (+)-*trans*-deacetylkumausyne (**2**)[9] through an electrophilic cyclization of the C3 hydroxy group onto the enyl side chain[10] provided an additional incentive to incorporate this feature into the synthetic sequence and determine the suitability of the bromoallene to multistep synthesis. Herein, we describe the first enantioselective synthesis of (−)-kumausallene (**1**) by a

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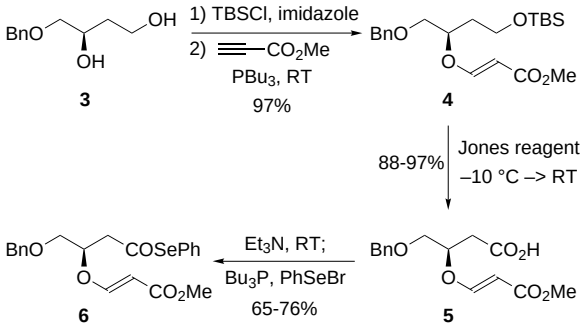
strategy that can, in principle, be adapted to facilitate the synthesis of related metabolites[4] and that unequivocally establishes the absolute configuration of the bromoallene.

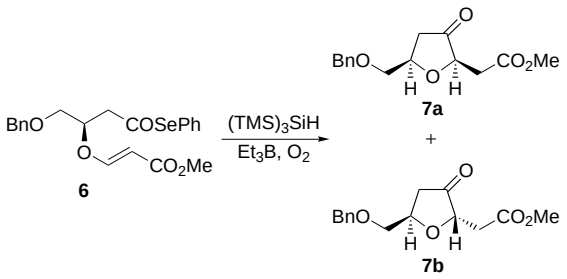
The synthesis of **1** was initiated with the preparation of the acyl selenide **6** by the four-step sequence outlined in Scheme 1. The enantiomerically enriched 1,3-butanediol **3** (92% *ee*), prepared by the method reported by Sharpless



Scheme 1. Preparation of the acyl selenide **6**. Bn = benzyl, RT = room temperature.

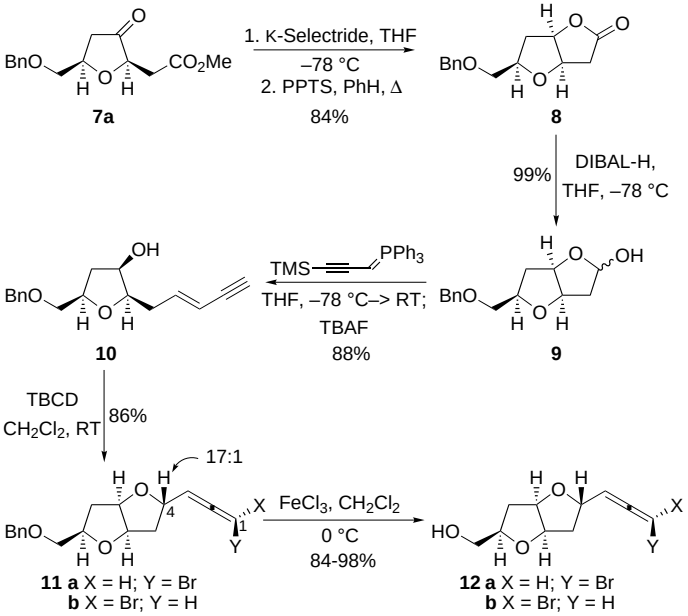
et al.,[11] was selectively protected as its primary *tert*-butyldimethylsilyl (TBS) ether, and the remaining secondary alcohol was allowed to react with tributylphosphane and methyl propiolate,[12] giving the vinylogous carbonate **4** in 97% overall yield. Oxidation of the *tert*-butyldimethylsilyl ether **4** with Jones reagent gave the carboxylic acid **5** (88–97%),[13] which was transformed to the acyl selenide **6** (65–76%) by the Crich protocol.[14]

The acyl radical cyclization of **6** using tris(trimethylsilyl)silane and triethylborane at $-78\,^{\circ}C$, in the presence of air, furnished the cyclic ethers **7a** and **7b** (92%) in a 32:1 mixture of diastereoisomers (by HPLC), favoring **7a** (Scheme 2). The analogous reaction at room temperature furnished **7a** and **7b** with only modest diastereoselectivity (8:1), illustrating the role that entropy plays in this type of free radical cyclization.[15, 16]



Scheme 2. Intramolecular acyl radical cyclization. TMS = trimethylsilyl.

The introduction of the bromoallene at this early juncture in the synthetic sequence offers the advantage of avoiding additional protection/deprotection steps and the possibility of evaluating the biomimetic electrophilic-type cyclization of **10** to give **11** (Scheme 3). Earlier studies suggested that the bromoallene is particularly labile, hence this reaction sequence was expected to determine the stability of the bromoallene, and thus required an orthogonally protected



Scheme 3. Introduction of the bromoallene by means of an electrophilic biomimetic-type cyclization.

primary hydroxy group. Treatment of the cyclic ketone **7a** with K-Selectride at $-78\,^{\circ}C$, followed by pyridinium *p*-toluenesulfonate (PPTS) in refluxing benzene, furnished the bicyclic lactone **8** in 84% overall yield. Hence, the strategic lactone **8** required for preparing related metabolites[4] containing the *cis*-2,5-disubstituted tetrahydrofuran moiety was prepared in 55% overall yield from the 1,3-butanediol **3**. Reduction of the lactone **8** with diisobutylaluminum hydride (DIBAL-H) occurred smoothly to furnish the lactol **9** in nearly quantitative yield. Wittig homologation of **9** using two equivalents of (3-trimethylsilyl-2-propynyl)triphenylphosphorane[17] led to the formation of the predominantly *trans*-enyne, which was desilylated in situ with tetra-*N*-butylammonium fluoride (TBAF) to furnish the isomeric enynes **10** ($E/Z \approx 10{:}1$) in 88% overall yield. Treatment of **10** with freshly prepared 2,4,4,6-tetrabromocyclohexadienone (TBCD)[18, 19] gave the bromoallenes **11a** and **11b** (86%) as a 2.5:1 mixture favoring the unnatural C1 epimer, **11b** (kumausallene numbering). Bromoallenes **11a** and **11b** were debenzylated with ferric chloride[20] to liberate the primary alcohols **12a** and **12b** (84–98%).

It is gratifying that although the diastereoselectivity in favor of **12a** could not be significantly improved, the undesired diastereoisomer **12b** could be separated by preparative HPLC and recycled by means of the reaction sequence outlined in Scheme 4. Treatment of the bromoallene **12b** with samarium(II) diiodide furnished the enynes **13** (99%) as an almost equal mixture of geometrical isomers ($E{:}Z = 1{:}1.25$).[21] The enynes **13** were then resubjected to the biomimetic electrophilic cyclization, with the primary hydroxy group unmasked, to furnish the bromoallenes **12a** and **12b** (85–96%) as a 1:1 mixture of C1 epimers. The epimers were separated, and the undesired isomer **12b** resubjected to the reaction sequence to furnish **12a** in 78% overall yield after recycling two times.[22]

The (*E*)-pentenyl appendage was then introduced in a manner analogous to that employed by Overman et al.,[2] by

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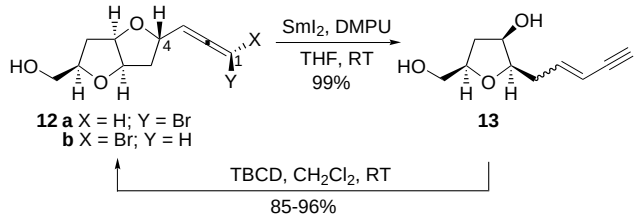
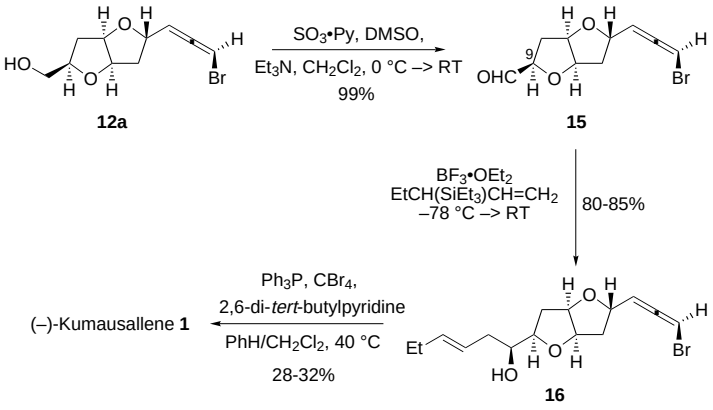


Scheme 4. Recycling protocol for the conversion of the epimeric bromoallene. DMPU = 1,3-dimethyl-2-oxohexahydropyrimidine.

using the Sakurai reaction,[23] albeit in the presence of the relatively labile bromoallene moiety (Scheme 5). Oxidation of alcohol **12a** with sulfur trioxide/pyridine (Py) furnished the



Scheme 5. Completion of the total synthesis of (−)-kumausallene (**1**).

aldehyde **15** with evidence for some equilibration (11:1 by NMR). Treatment of **15** with 3-triethylsilyl-1-pentene[24] in the presence of boron trifluoride etherate furnished the secondary alcohol **16** (80–85%) as a 14:1 mixture of diastereoisomers. The C10 epimers of **16** were separated by preparative HPLC and the major epimer was converted into (−)-kumausallene (**1**) as outlined in Scheme 5. The spectroscopic data and optical rotation of synthetic kumausallene (**1**) were identical in all respects to the values reported for the natural substance [^{1}H/^{13}C NMR and IR, $[\alpha]_D^{16} = -145$ ($c = 0.4$ in $CHCl_3$); lit.[1] $[\alpha]_D^{20} = -150$ ($c = 1$ in $CHCl_3$)].

The enantioselective synthesis of the nonisoprenoid sesquiterpene (−)-kumausallene (**1**) was accomplished in 14 steps through the intermediacy of a bicyclic lactone prepared from the optically enriched 1,3-butanediol **3** (92% *ee*). The synthesis demonstrates that the bromoallene is compatible with multiple synthetic operations and provides the unambiguous assignment of the absolute configuration of the bromoallene.

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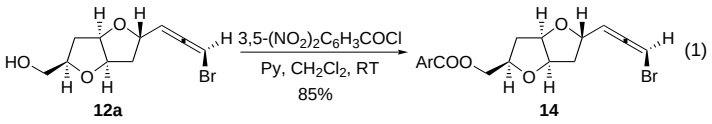

the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-12260. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033: e-mail: deposit@cccd.cam.ac.uk).
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