Asymmetric Total Synthesis of (−)-Isolaurallene

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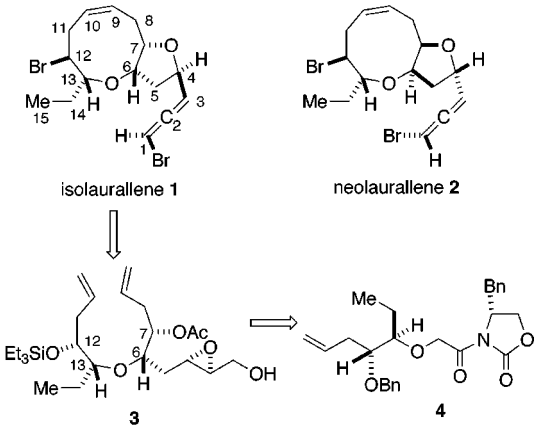
Medium-ring ethers of various structural types have been isolated from marine organisms.[1] While medium-ring ethers such as the ladder ether toxins have important implications with regard to their biological impact, it is the exquisite structures of naturally occurring medium-ring ethers that has provoked the imagination of synthetic chemists. Because eight-membered cyclic ethers are more prevalent, many unique and interesting approaches to their construction have been designed.[2] Nine-membered ethers are perhaps less common, but are present in the ladder toxins brevetoxin A,[3] ciguatoxin,[4] gambieric acid A,[5] the eunicellins,[6] and the simpler metabolites obtusenyne,[7] neolaurallene,[8] and isolaurallene.[9] Synthetic approaches to nine-membered ethers have been limited not only because of their infrequent occurrence, but also because of the challenges associated with their stereoselective assembly.[10] Isolaurallene, which contains a nine-membered cyclic ether, as well as a bromoallene-substituted tetrahydrofuran, was isolated by Kurata from *laurencia nipponica* yamada collected in Izumihama near Hiroo on the Pacific Coast of Hokkaido. The structure of isolaurallene was proposed based on spectroscopic information and later confirmed by a single-crystal X-ray study.[9] The closely related metabolite, neolaurallene, was subsequently isolated and its structure was also elucidated by X-ray crystallography.[8]

As part of our continuing program directed toward the development of flexible strategies for the asymmetric construction of medium-ring ether metabolites,[2] we designed an approach to the synthesis of isolaurallene that focused on construction of the core nine-membered ether through a ring-closing metathesis without the assistance of a cyclic conformational constraint (Scheme 1).[11] A similar asymmetric alkylation−olefin metathesis approach was employed in our recent laurencin synthesis.[12] It was anticipated that diene **3** would undergo rapid closure to the Δ5-oxonene because of the gearing effect created by two synergistic

Scheme 1



gauche effects at C6−C7 and C12−C13.[13] The assembly of diene **3** would be completed by an asymmetric glycolate alkylation[14] of oxazolidinone **4** followed by additional functionalization. The implementation of this plan culminating in the first total synthesis of isolaurallene is the subject of this report.

The oxazolidinone **4** was prepared from the glycolic acid derivative as described for the antipode.[12] Exposure of **4** to NaN(SiMe$_3$)$_2$ and iodide **5**[15] produced the alkylation product **6** in high yield with excellent (97:3) diastereoselectivity (Scheme 2).[14] The auxiliary was reductively removed with sodium borohydride to provide the alcohol **7** in 88% yield.[16] Oxidation of the alcohol **7** under Swern conditions[17] gave the aldehyde **8**, which was immediately exposed to Brown's asymmetric allylation[18] to generate a 96:4 mixture of the two diastereomeric secondary alcohols in 93% yield. The major isomer was subsequently converted to the corresponding acetate **9**. Removal of the benzyl ethers of **9** under oxidative conditions[19] also resulted in oxidation of the allylic alcohol to the aldehyde. The aldehyde was immediately reduced with sodium borohydride to provide diol **10**, which was readily converted to the bis silyl ether **11** upon treatment with Et$_3$SiOTf (67% for 3 steps). The allylic alcohol **12** was prepared by selective removal of the primary silyl ether with catalytic PPTS in ethanol and dichloromethane. Epoxidation of the allylic alcohol **12** under Sharpless conditions[20] led to exclusive formation of the desired epoxyalcohol which was immediately exposed to the Grubbs catalyst [(Cy$_3$P)$_2$Cl$_2$Ru═

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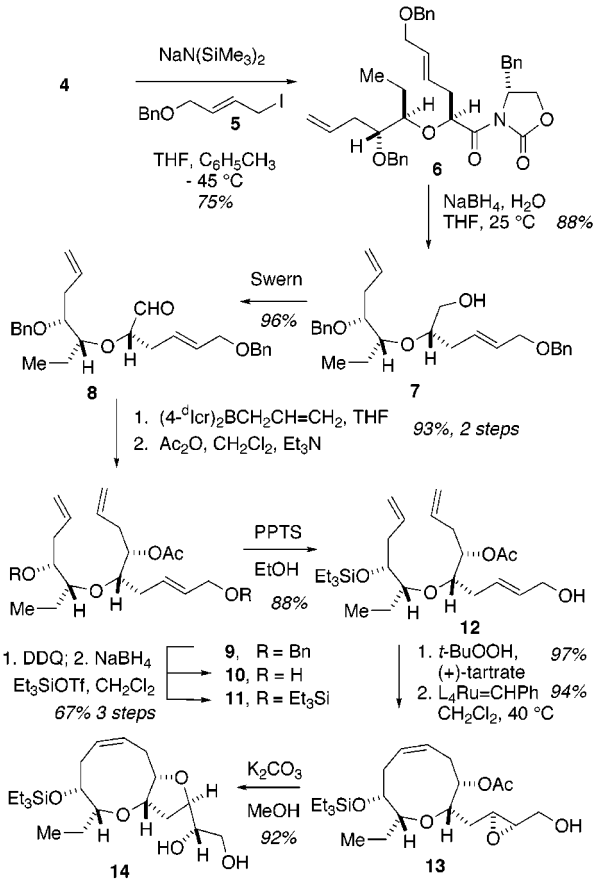
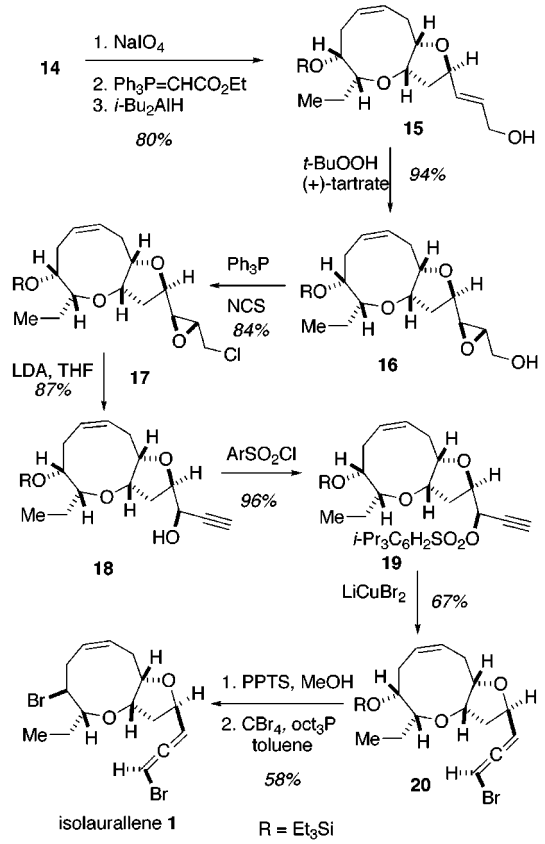
Scheme 2



CHPh, CH_2Cl_2, 40 °C][21] to provide the oxonene **13** in 94% yield in 6 h. The rapid and efficient metathesis formed the nine-membered ring without the aid of a cyclic conformational constraint. Hydrolysis of the acetate **13** with potassium carbonate in methanol resulted in concomitant closure of the tetrahydrofuran ring. The basic skeleton incorporating both the oxonene and the tetrahydrofuran had been completed in just 11 steps from oxazolidinone **4**.

Completion of the synthesis required incorporation of the C12 secondary bromide and stereoselective installation of the bromoallene unit. To this end, diol **14** was converted to the allylic alcohol **15** by oxidative cleavage of the diol to the aldehyde, condensation of the aldehyde with carbethoxy−methylenetriphenylphosphorane, and subsequent reduction of the unsaturated ester with *i*-Bu_2AlH to give the alcohol **15** (Scheme 3). Since a highly stereocontrolled introduction of a propargylic alcohol was required for stereoselective construction of the allene, we once again called on the Sharpless epoxidation[20] to produce the epoxy alcohol **16** with essentially complete control of stereochemistry. Conversion of the epoxy alcohol to the chloride **17** set the stage for the elimination of the chloroepoxide to the propargylic alcohol **18** according to the method of Yadav.[22] The propargylic alcohol **18** was produced in >98:2 diastereoselectivity. In contrast,

Scheme 3



addition of ethynylmagnesium bromide to the aldehyde derived from diol **14** was nonselective. The bromoallene was introduced by conversion of the propargylic alcohol to the trisylate **19** followed by its S_N2' displacement through exposure to $LiCuBr_2$.[23] The desired regioisomer **20** was obtained as an 8:1 mixture of isomeric bromoallenes and was accompanied by 9% of the product from direct S_N2 displacement. Finally, conversion of bromoallene **20** to isolaurallene was achieved by removal of the silyl ether and treatment of the secondary alcohol with CBr_4-trioctylphosphine[24] to give synthetic (−)-isolaurallene in 58% overall yield. The structure of synthetic (−)-isolaurallene was confirmed by comparison of ^{13}C, ^1H NMR, IR, and $[\alpha]_D$ to authentic spectra of the natural product.[9]

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Supporting Information Available: Spectral data and experimental procedures for compounds **1**, **6**−**20** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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