AN EFFICIENT ROUTE TO CHIRAL BENZOOXABICYCLO[3.2.1]OCTANE RING SYSTEM— THE FIRST ENANTIOCONTROLLED TOTAL SYNTHESIS OF (-)-FILIFORMIN

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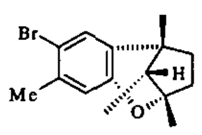
Abstract--The first enantiocontrolled total synthesis of (-)-filiformin (**1**) was achieved by the cyclization of phenolic allyl alcohol (**5**) to give benzooxabicyclo[3.2.1]octane (**6**) as a key process.

(-)-Filiformin (1) having the benzooxabicyclo[3.2.1]octane ring system is a marine sesquiterpene isolated[1] from the alga, *Laurencia filiformis* and these types of compounds have also been reported to display significant biological activity[2] (Scheme 1).



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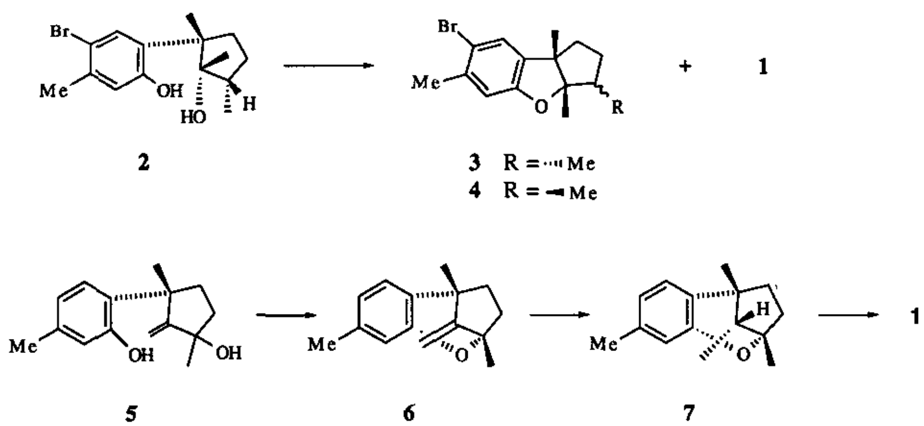
Scheme 1

Although the trichothecenes,[3] the well-known group of sesquiterpene antibiotics having oxabicyclo[3.2.1]octane unit, have arisen great synthetic interest[4] for many years, the few efforts have been made at development of the ring system leading to synthesis of **1**[5] and the lack of regioselectivity for the cyclization of the phenolic alcohol (**2**) *via* carbocation intermediate have been encountered[5b] to give the mixture of aplysin (**3**), epi-aplysin (**4**) and (**1**). Now, we wish to report the facile construction of the chiral benzooxabicyclo[3.2.1]octane system (**6**) based on the regiocontrolled cyclization of the phenolic allyl cation generated from the chiral phenolic allyl alcohol (**5**) leading to the first enantiocontrolled total synthesis of (-)-filiformin (**1**) *via* **7** (Scheme 2).



Scheme 2

During our study[6] directed toward the enantioselective construction of cyclobutanones and application to the synthesis of biologically desirable compounds, we have developed a highly enantioselective preparation of the phenolic allyl alcohol (**5**).[7] Thus,[†] the phenolic allyl alcohol (**5**) was treated with pyridinium *p*-toluenesulfonate in refluxing benzene for 3 h to give **6** {$[\alpha]_D^{20}$ -13.0° ($CHCl_3$)} as the only isolated compound in 95% yield which on hydrogenation in the presence of palladium carbon as a catalyst afforded **7** {$[\alpha]_D^{20}$ -36.1° ($CHCl_3$)} stereoselectively in 70% yield. This stereochemical outcome could be due to the effective size of the π system making the aromatic region of **6** to be the more encumbered one.[5a] Although the stereochemistry of **7** was determined unequivocally by converting **7** into filformin (**1**), a *syn* relationship of the apical methyl group and the aromatic ring was evidenced at this stage by the high field signal (0.77 ppm) of this methyl group in the ^{1}H-nmr spectrum of **7**. Finally, bromination of **7** with bromine in the presence of sodium bicarbonate in $CHCl_3$ furnished (-)-filiformin (**1**) {$[\alpha]_D^{20}$ -16.4° ($CHCl_3$), lit.,[1a] $[\alpha]_D^{20}$ -20.0° ($CHCl_3$)} in 80% yield. The sample thus obtained was identical with the authentic compound[1a] in its ^{1}H-nmr (300 MHz, $CDCl_3$) spectral comparison. Thus we could achieve the first enantiocontrolled total synthesis of (-)-filiformin (**1**).

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