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A NOVEL ENANTIOSELECTIVE CYCLIZATION OF A CHIRAL EPOXIDE TO A BENZOFURAN SYSTEM

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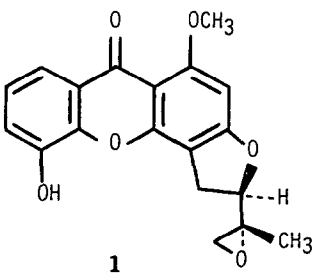
Abstract. A convenient method has been established for the stereoselective construction of a dihydrobenzofuran ring system found in several bioactive natural products. The final step of the synthesis involves the concerted and efficient intramolecular displacement of mesylate **12** to give 2'R,3'R-dihydrobenzofuran a bicyclic analog of **1**. This route was based on a proposed biosynthetic pathway patterned on related rotenoids.

The asymmetric epoxidation[1] of allylic alcohols has emerged as a useful reaction in the chiral synthesis of a large number of complex natural products.[2,3] The stereoselective construction of the epoxydihydrofuran system found in **1** could be applicable to the total synthesis of a variety of natural products with insecticidal[4], fungicidal[5], antimicrobial[6] and antileukemic[7] activity. Our strategy is similar to the zip-type reaction developed by Nicolaou for the stereoselective construction of tetrahydrofurans from chiral oligoepoxides.[2] The practical nature of this approach may allow extension of Crombie's hypothesis for the biosynthesis of rotenoids containing this group.[4]



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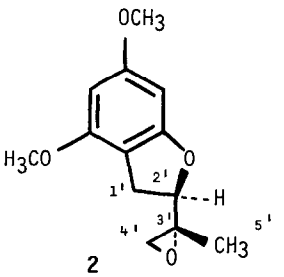

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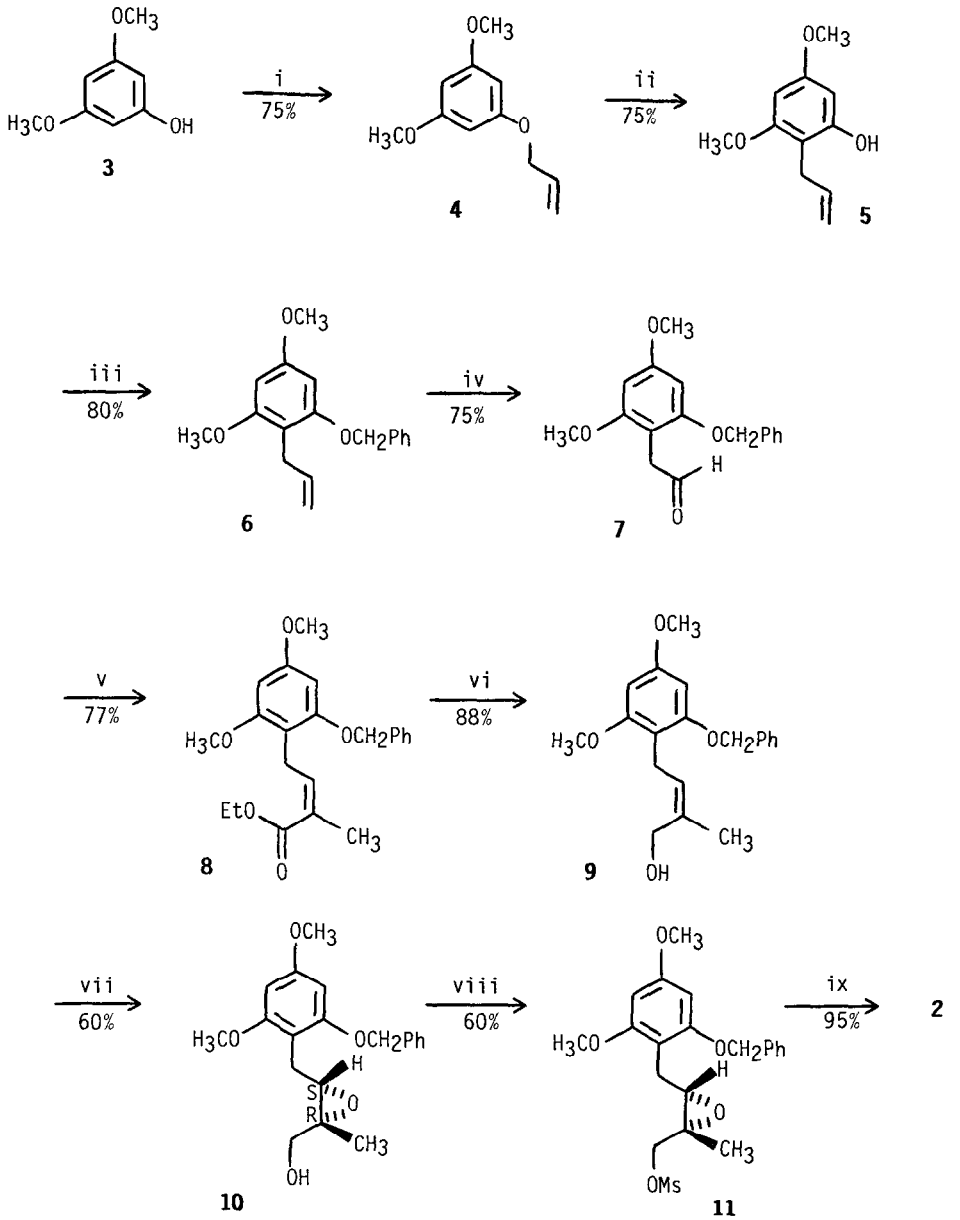
Scheme 1



Reagents: i) Allyl bromide/K_2CO_3/acetone; ii) N,N-dimethylaniline/200°C; iii) *$PhCH_2Br$/NaH/THF*; iv) $OsO_4/NaIO_4$, dioxane-H_2O (3:1); v) $(CF_3CH_2O)_2$ P(O)-$CH(CH_3)COOEt$/ $KN(TMS)_2$/18-crown-6/THF/-85°C/3 hr.; vi) $LiAlH_4$/ether/RT/4 hr; vii) D(-)-DIPT/Ti(O-i-Pr)4/TBHP/CH_2Cl_2/-25°C/3 days; viii) MsCl/pyridine/0°C; ix) 10% Pd-C/$NaHCO_3$/EtOH/1,4-cyclohexadiene/RT/4 hr.

Psorospermin (1) is a plant-derived compound which has significant activity in several animal tumor models. Prior work has established the absolute stereochemistry of 1[8] and concurrently a route to an epimer of 1, O^5-methyl(±)-(2'R,3'S)-psorospermin was developed.[9] An enantioselective route to (-)-(2'R,3'R)-psorospermin (1) requires synthesis of an appropriate Z-allylic alcohol and chiral epoxidation using Sharpless conditions. In developing this approach the bicyclic analog **2** was chosen as a model target.

The route to compound **2** is outlined in Scheme 1. O-Allylation of 3,5-dimethoxyphenol[9] gave the allyl ether **4** as a colorless viscous oil. The allyl ether was heated under pressure in a stainless steel bomb at 200°C for 7 hrs to give phenol **5** via an ortho-Claisen rearrangement. The phenol group was protected[10] as a benzyl derivative (**6**). Compound **6** was then oxidized by osmium tetroxide and cleaved by sodium periodate in a single step[11,12] to give the aldehyde **7** as colorless needles. Compound **7** was reacted with an appropriate phosphonate under modified Horner-Emmons conditions[13,14] to yield the unsaturated ester **8**. After silica gel flash column chromatography, high field ^1H NMR established that **8** was the Z-isomer. Ester **8** was then reduced[15] by lithium aluminum hydride or diisobutyl aluminum hydride in THF to generate the Z-allylic alcohol **9** as a white crystalline solid. Compound **9** was subjected to Sharpless epoxidation [D(-)-diisopropyl tartrate (DIPT)/titanium isopropoxide/t-butyl-hydroperoxide (TBHP)/CH_2Cl_2/-20°C] to give chiral oxirane **10** (ee $\geq$ 95%).[16,17] The epoxy alcohol **10** was reacted with methanesulfonyl chloride in pyridine to give methanesulfonate **11**.[18] In the synthesis of the racemic epimer of 1[9], the deblocking and cyclization were carried out step-wise and produced an overall yield of about 50%. More efficient cyclization of **11** into the target molecule was effected by a one pot procedure involving catalytic transfer hydrogenation[19] under basic conditions to deblock and cyclize to give **2** in 95% yield.[20]

This novel route will be applied to the stereoselective synthesis of 1 and its stereoisomers. The synthesis and biological evaluation of these stereoisomers should aid in establishing structure-antileukemic activity relationships and chiral recognition of small molecule-DNA interactions.

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