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The first total synthesis of the natural product angoluvarin

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ABSTRACT

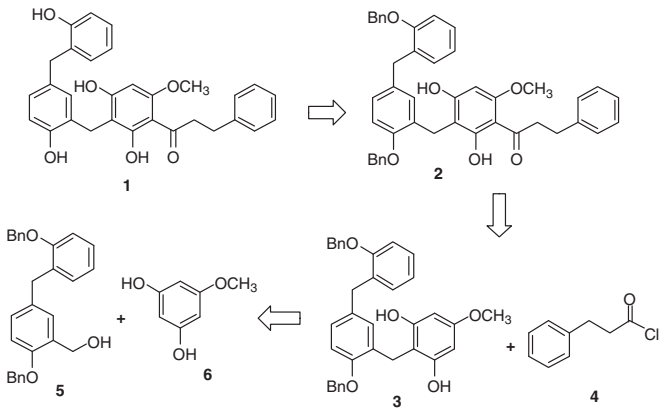
The total synthesis of angoluvarin, a member of the dihydrochalcone family of natural products, is reported. Starting with 2-bromophenol, the synthesis was accomplished in eight steps with an overall yield of 2%. This represents the first reported synthesis of angoluvarin.

A number of C-benzylated dihydrochalcones isolated from the genus *Uvaria*, of the plant family Annonaceae, have displayed a wide variety of biological activity,[1] such as in vivo activity against P-388 lymphocytic leukemia, growth inhibition of human promyelocytic leukemia HL-60 cells, in vitro activity against human carcinoma cells of the nasopharynx, and antibacterial activity against *Staphylococcus aureus, Bacillus subtilis*, *Mycobacterium smegmatis*, *Proteus micabilis*, and *Pseudomonas aeruginosa*. Members of this family and genus have also been extensively used in folk medicine for the treatment of ailments associated with menstruation, dysentery, and snakebites.[2]

In 1987, Hufford and Oguntimein[3] isolated a new dihydrochalcone natural product from *Uvaria angolensis* which they named angoluvarin. Similar to previously isolated dihydrochalcones, angoluvarin also demonstrated antimicrobial activity against *B. subtilis*, *S. aureus*, and *M. smegmatis*. At the time of its isolation, angoluvarin possessed the most complex structure of the known members of this natural product class. In 1993, Achenbach[4] and co-workers reported that angoluvarin can also be isolated from *Uvaria Leptocladon*. In subsequent years even more complex naturally occurring dihydrochalcones were isolated from Annonaceae.[5] Although it has been 23 years since the isolation and structural elucidation of angoluvarin, no reports pertaining to its synthesis have appeared in the literature. We now report the first total synthesis of the natural product angoluvarin.

Our retrosynthetic analysis for the synthesis of angoluvarin is depicted in Scheme 1. We envisioned a three component strategy utilizing two commercially available compounds, 5-methoxyresorcinol (**6**) and hydrocinnamoyl chloride (**4**), as well as alcohol **5**.

Friedel–Crafts alkylation of 5-methoxyresorcinol (**6**) with alcohol **5** could in theory lead to two different regioisomers. Alkylation at C-4/C-6 is statistically favored, but alkylation at C-2, the desired position, is sterically favored. Given the sterically crowded environment of alcohol **5**, as a result of the benzyloxy group situated ortho to the reactive site, it was anticipated that formation of **3**



Scheme 1. Retrosynthetic analysis of angoluvarin.

would be favored over formation of the undesired regioisomer. Subsequent acylation of **3** with hydrocinnamoyl chloride (**4**) was expected to take place in the electron rich resorcinol ring to afford protected angoluvarin **2**. Although there are no regiochemical considerations for C-acylation of the symmetric resorcinol nucleus, O-acylation was considered to be a possible complicating factor. However, it was hoped that reflux conditions would effect a Fries-rearrangement to convert it to desired ketone **2**.

The synthesis of key intermediate **5** began by benzyl-protection of both *o*-bromophenol (**7**) and 3-bromo-4-hydroxybenzaldehyde (**8**) in 90% and 72% yield, respectively (Scheme 2). Halogen-metal exchange of **9** with *sec*-BuLi and subsequent quenching with aldehyde **10** afforded diphenylalcohol **11** in 81% yield. Surprisingly, the presence of the additional bromine in **10** did not pose any major problems due to halogen scrambling with the aryllithium reagent generated from **9**. Presumably the bulky *ortho*-benzyloxy groups present in both reagents prevent close contact between the two reactive sites, thus inhibiting the halogen scrambling. Reduction of **11** with sodium borohydride/trifluoroacetic acid[6] proceeded as expected to provide **12** in 88% yield. Preparation of alcohol **5** can

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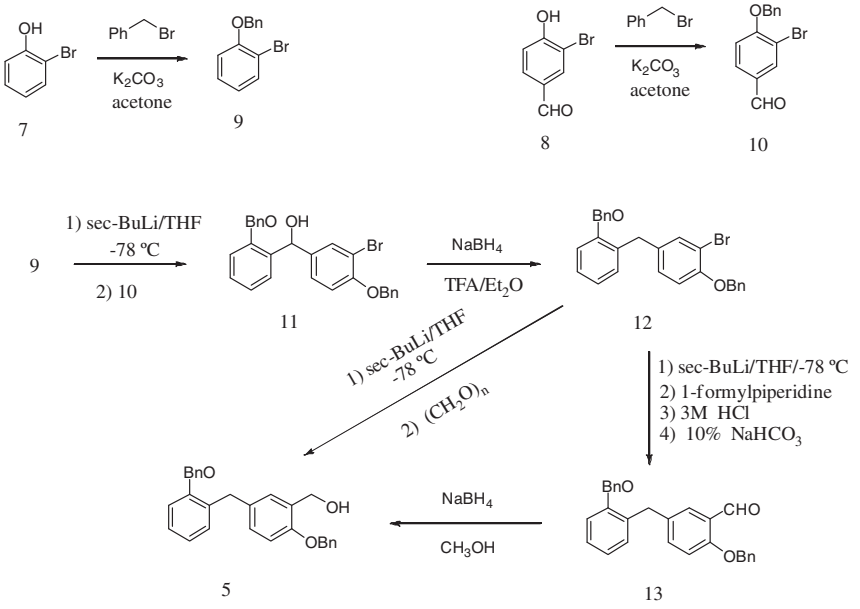

Scheme 2. Synthesis of key intermediate **5.**

be accomplished in two ways from the organolithium reagent derived from **12**: direct conversion by quenching with solid paraformaldehyde or reduction of intermediate aldehyde **13**, which is obtained by utilizing 1-formylpiperidine as the quenching agent. The latter two-step approach proved to be the method of choice, providing **5** in 70% (two-step yield) as opposed to 31% for the one-step process. Attempts to purify aldehyde **13** by flash chromatography were plagued with low yields and decomposition problems, as evidenced by additional spots appearing in the column effluent upon analysis by thin layer chromatography. Furthermore, it was found that a base wash is essential in the workup of this reaction to prevent low yields and complex product mixtures. The workup requires acidification to convert the intermediate piperidinyl alcohol to the aldehyde, but apparently trace amounts of residual acid leads to decomposition of the aldehyde. However, if the required acidification step is immediately followed by a wash with 10% aqueous sodium bicarbonate, and the subsequent reduction is performed without further purification of **13**, the yield and purity of **5** are vastly improved.

With key intermediate **5** in hand, attention was next focused on Friedel–Crafts alkylation with 5-methoxyresorcinol (**6**). It was quickly found that use of strong Lewis acids such as aluminum chloride or ferric bromide led to complex product mixtures; proton NMR indicated that benzyl-deprotection of both phenolic oxygens of **5** had occurred. Two milder Lewis acids were explored, tin(IV) chloride and zinc chloride, with the latter proving to be more efficient, providing **3** in 34% yield. The regiochemistry for the alkylation of 5-methoxyresorcinol (**6**) was determined by proton NMR spectroscopy. The symmetry of the product was evident by the two proton upfield singlet at 5.91 ppm for the hydrogens at C-4/C-6 of the resorcinol ring as well as a two proton singlet at 5.94 ppm representing the two equivalent phenolic hydrogens. The undesired, non-symmetric isomer, which was not evident in any of the column fractions isolated, would have produced two doublets for the non-equivalent ring protons.

Acylation of **3** with hydrocinnamoyl chloride (**4**) also proved to be quite problematic; even relatively mild Lewis acids such as tin(IV) chloride and zinc chloride lead to complete benzyl-deprotection of the phenolic oxygens and very complex product mixtures, as evidenced by TLC and proton NMR spectroscopy. However, it was found that **3** could be slowly acylated by refluxing it in chloroform with a large excess of the acid chloride for 3 days in the absence of a Lewis Acid catalyst, to afford protected angoluvarin **2**. Acylation of the resorcinol ring was supported by the appearance of a highly deshielded proton at 14.88 ppm which is attributed to hydrogen bonding of the phenolic proton ortho to the acyl group. Additionally the proton NMR spectrum now exhibited only a single resorcinol ring proton as opposed to a two proton signal for the resorcinol protons in **3**. It was found that **2** was prone to decomposition on standing for a few days, and all attempts at complete purification were unsuccessful. As a result, **2** was only partially purified by flash chromatography, primarily to separate it from the substantial amount of unreacted hydrocinnamoyl chloride (**4**) present in the reaction product, and then immediately deprotected with boron tribromide in methylene chloride to provide angoluvarin (**1**) in a 14% two-step yield and an overall eight-step yield of 2% from *o*-bromophenol (**7**). Except for the non-hydrogen bonded phenolic hydrogens, which are not completely visible due to peak-broadening, the ^{1}H NMR spectral data are in good agreement with the values reported for the natural product; the ^{13}C NMR spectral data are identical to reported values.

In summary an eight-step synthesis of angoluvarin (**1**) has been accomplished. Although some of the later steps of the synthesis are low yielding, it represents the first reported total synthesis of this natural product that was isolated over 20 years ago. The synthetic strategy developed in this synthesis should be applicable to more complex members of this class of natural products for which total syntheses have also not been reported.

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Supplementary data

General experimental, detailed experimental procedures, and compound characterization data for all new compounds can be found. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.037.

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