A New Approach to the 1-Arylnaphthalene Lignans Utilizing a Tandem Pummerer–Diels–Alder Reaction Sequence

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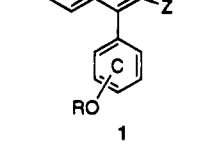
Due to their widespread occurrence in nature and broad range of biological activity, lignans have attracted considerable synthetic attention over the years.[1,2] Much interest has been focused on their effectiveness as antineoplastic agents, and research in this area has revealed several modes of action by which they can regulate the growth of mammalian cells.[3] Over 40 natural arylnaphthalenes, the majority of which are lactones of general type **1**, are known and represent a significant subclass



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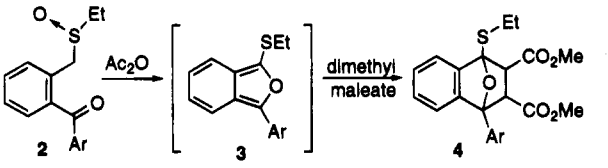
X= H; Y=(C=O); Z=CH_2
X= H; Y=CH_2; Z=(C=O)
X=OH; Y=CH_2; Z=(C=O)

of lignans.[4] Although a wide variety of methods have been utilized for the synthesis of this class of natural products,[5–7] the key step for the construction of the phenyl–naphthyl skeleton can be classified roughly into two methodologies. The first relies on assembling the B-ring of the naphthalene nucleus *via* the annulation of a properly substituted benzene derivative followed by an aromatization process.[8] The second approach is the joining of the pertinent aryl and naphthyl units *via* conjugate addition to a butenolide followed by reaction with an aldehyde.[9] These methods generally require a number of steps for construction of the 1-arylnaphthalene

Scheme 1



skeleton. In this communication we wish to report a short synthesis of several 1-arylnaphthalene lignans based on a new approach involving a *tandem Pummerer–Diels–Alder reaction sequence.*[10]

Pummerer-based transformations[11] are finding widespread applications in carbo-[12] and heterocyclic[13] synthesis. In the realm of carbon–carbon bond formation, most success has been achieved using intramolecular olefinic interception of the Pummerer intermediate.[14] The main features of our strategy are illustrated in Scheme 1. The α-thiocarbocation generated from the Pummerer reaction of an *o*-benzoyl substituted sulfoxide of type **2** is intercepted by the adjacent keto group to produce an α-thioisobenzofuran **3** as a transient intermediate which undergoes a subsequent Diels–Alder cycloaddition with dimethyl maleate. The resulting cycloadduct **4** can be readily converted to representatives of several type of arylnaphthalene lignans.

The versatility of the approach is highlighted through the synthesis of taiwanin C and E and justicidin E, naturally occurring arylnaphthalene lignans which possess all the functionality of podophyllotoxin[1] around a central aromatic ring. The requisite keto sulfoxide **7** was synthesized starting from piperonyl alcohol **5** which was converted to 6-bromopiperonyl bromide **6** (92%).[15] Treatment of **6** with ethanethiol gave the corresponding ethyl sulfide (93%). Transmetalation to the corresponding aryllithium and subsequent treatment with piperonal produced the expected alcohol **7** (90%) which was ultimately oxidized in two separate steps (MnO_2; $NaIO_4$) to give the desired sulfoxide **8** (81% overall). Slow addition of **8** in acetic anhydride to a refluxing solution of dimethyl maleate in acetic anhydride gave cycloadduct **9** in 85% yield (Scheme 2). Further reaction of **9** with *p*-toluenesulfonic acid in CH_2Cl_2 at 25 °C afforded the α-thio-substituted naphthalene **10** in essentially quantitative yield. Desulfurization of **10** with Ra-Ni produced naphthalene **11** (>98%), which on treatment with $KOSiMe_3$,[16] resulted in selective attack on the less hindered ester functionality giving rise to the half acid-ester **12**. The carboxylic acid present in **12** is unusually susceptible to reduction and, on treatment with $LiEt_3BH$, gave taiwanin C[17] (**13**) in 68% isolated yield. When **12** was allowed to react with 2 equiv of NaH followed by reduction with $LiBH_4$, justicidin E (**14**) was isolated as the major product in 51% yield.

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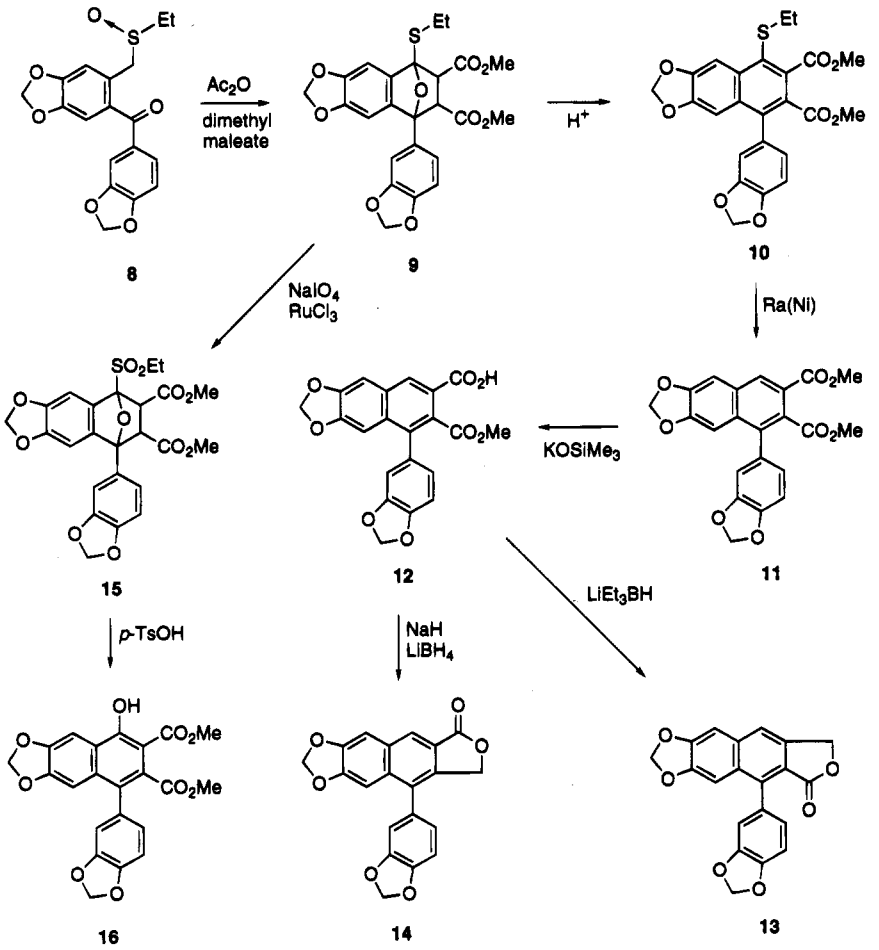
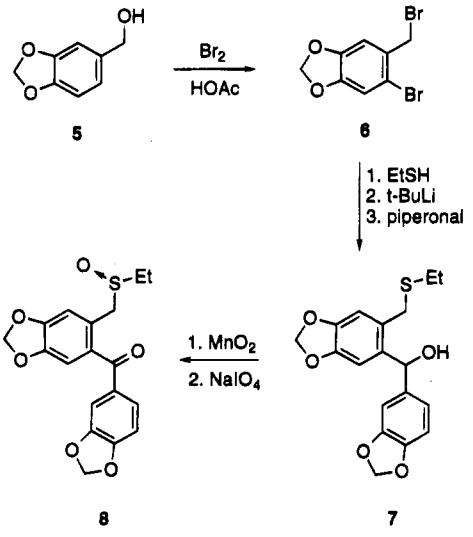
Scheme 2





The above results prompted us to investigate the conversion of cycloadduct **9** into naphthol **16**. Oxidation of **9** with $NaIO_4$ containing a catalytic quantity of $RuCl_3$[18] at 0 °C proceeded in quantitative yield providing sulfone **15**. The selective conversion of cycloadduct **9** to naphthalene **10** is presumably driven by the lone pair of electrons on sulfur which induces regioselective C–O cleavage and the further loss of a molecule of water. The presence of a sulfonyl group on the oxabicyclic ring, on the other hand, promotes the alternate mode of ring cleavage resulting in ejection of ethylsulfinate and ultimately giving naphthol **16**. This compound is easily converted to taiwanin E in high yield.[19]

In conclusion, the method depicted in Scheme 1 appears to be well suited for the preparation of a variety of polycyclic ring systems. We are currently investigating the generality of this process for the construction of azapolycyclic ring systems and its further application in target oriented synthesis.

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Supplementary Material Available: Experimental procedures and characterization data (8 pages).

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