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Synthesis of Natural Products Possessing a Benzo[*b*]furan Skeleton

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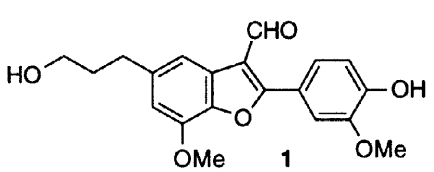
Abstract

A related synthetic strategy has been used to prepare two natural products (XH-14 and ailanthoidol) which possess a benzo[*b*]furan skeleton. The synthesis of XH-14 involved the use of a palladium-catalyzed cyclization with concomitant carbonylation via insertion of carbon monoxide to introduce regioselectively a formyl group in the 3-position.

Keywords: benzo[b]furan, Ailanthoidol, XH-14

As part of our ongoing research on the development of adenosine antagonists [1], we became interested in recent reports concerning the isolation and biological activity of molecules with a benzofuran skeleton. XH-14 (**1**) was isolated from the plant, *Salvia miltiorrhiza* and found to be a potent antagonist of the A_1 adenosine receptor [2,3]. A structurally related compound called ailanthoidol (**2**) was isolated from the tree, *Zanthoxylum ailanthoides* [4]. While there have been no reports on this compound's action at the adenosine receptor, extracts of the bark and leaves of this tree have been used in folk medicine.



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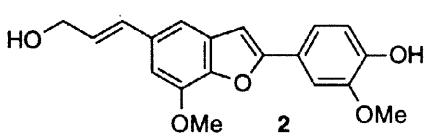

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Yang and coworkers devised a total synthesis of XH-14 starting from vanillin which involved eight steps [3]. The key steps involved the coupling of an appropriately substituted *ortho*-bromophenol with a cuprous acetylide to form the benzofuran skeleton and the regioselective introduction of the 3-formyl group via a modified Gattermann-Adams reaction. We subsequently developed a shorter synthesis (six steps from eugenol) [5] which retained these key steps and introduced the 2-substituent later in the synthesis, facilitating a

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structure-activity evaluation of the importance of this group in A_1 adenosine receptor binding [6]. Unfortunately, the scope of this approach is limited by the Gattermann-Adams reaction which proved to be unreliable in our synthesis of XH-14 [5] and unsatisfactory for the synthesis of other 2-substituted analogs [6]. Another synthesis of XH-14 has been reported which involved an interesting oxidative dimerisation of methyl ferulate (methyl 3-methoxy-4-hydroxycinnamate) to form the benzofuran skeleton [7]. This reaction proceeded in low yield (34%) and offers little flexibility for the synthesis of analogs. We now report a new and improved synthetic approach which has been used to prepare XH-14 (**1**) and the related natural product, ailanthoidol (**2**).

Our synthesis of ailanthoidol started with the construction of the benzofuran nucleus by coupling the *ortho*-halophenol **3** with the alkyne **4** with concommitant cyclisation (Scheme 1). While originally a Stevens-Castro coupling was employed, the reactions using stoichiometric amounts of copper proved difficult to scale up. It was found that performing the reaction under Sonogashira conditions [8] gave a better and more reproducable yield (Table 1). $PdCl_2(PPh_3)_2$ proved to be a more effective catalyst than $Pd(PPh_3)_4$. A further improvement was achieved by using the iodophenol **3b**. The resultant benzofuran **5** was then transformed into ailanthoidol in two steps. Briefly, this involved removal of the benzyl protecting group with titanium tetrachloride followed by DIBAL reduction of the ester using sodium sulfate decahydrate to decompose excess reagent (77% yield over two steps). This order of events afforded the highest yield. Ailanthoidol was obtained as a white solid after recrystallization from aqueous methanol.

Scheme 1

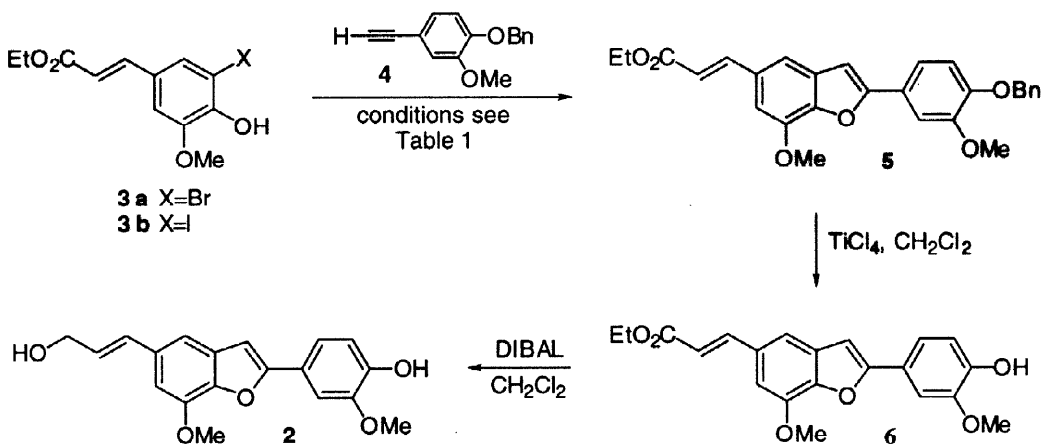
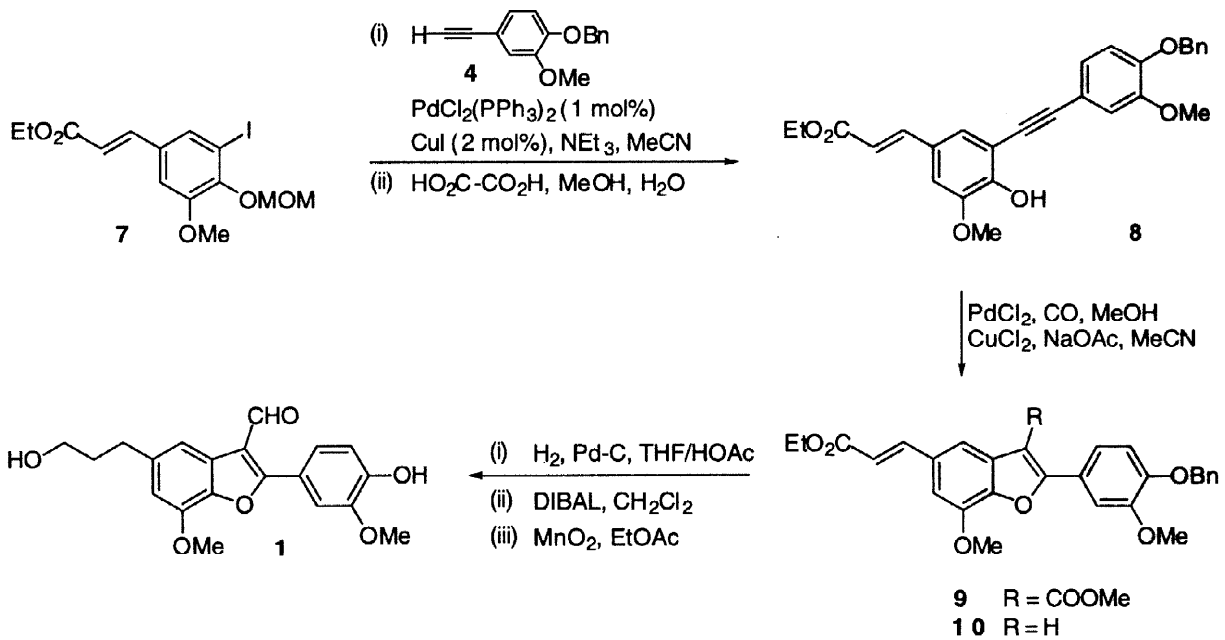


Table 1

Entry	Substrate	Conditions	Yield, %
1	**3a**	Cu-acetylide of **4**, Py, reflux	65
2	**3a**	Cu_2O, Py, reflux	62
3	**3a**	$PdCl_2(PPh_3)_2$, CuI, NEt_3, MeCN	69
4	**3a**	$Pd(PPh_3)_4$, CuI, NEt_3, MeCN	52
5	**3b**	$PdCl_2(PPh_3)_2$, CuI, NEt_3, MeCN	88

The synthesis of XH-14 was achieved using a closely related strategy which utilised the Sonogashira coupling conditions described above. However, in this case the intermediate *ortho*-hydroxytolan was isolated prior to cyclisation and a palladium catalysed carbonylative cyclisation reaction was used to form the benzofuran ring system with concomitant acylation of the 3-position. The conditions used for this reaction were based on those developed by Kondo *et al.* for the synthesis of a range of indole-3-carboxylates and benzofuran-3-carboxylates [9]. In this case, ethyl 3-methoxy-4-hydroxy-5-iodocinnamate (**3b**) was protected as a MOM ether and coupled with the appropriately substituted alkyne to afford the corresponding MOM protected *ortho*-hydroxytolan in a 92% yield (Scheme 2). Removal of the MOM protecting group using oxalic acid in aqueous methanol gave a quantitative yield of the *ortho*-hydroxytolan **8**. Addition of a catalytic amount of palladium chloride to a stirred solution of **8** and sodium acetate in methanol under an atmosphere of carbon monoxide was found to induce cyclisation to a vinyl-palladium(II) species which after insertion of carbon monoxide and reaction with methanol yielded the substituted benzofuran **9** in a 68% isolated yield [10]. The resulting palladium(0) species was reoxidised by copper(II)chloride allowing the use of a substoichiometric amount of palladium. The choice of base proved to be important as **8** showed a pronounced tendency to undergo uncatalyzed autocyclization under basic conditions. Thus, the unfunctionalized benzofuran **10** was formed exclusively when potassium carbonate was used instead of sodium acetate. Transformation of **9** into the final product **1** was then accomplished via straightforward methodology. Catalytic hydrogenation effected simultaneous debenzylation and reduction of the alkene in 81% yield. DIBAL reduction of both esters followed by workup with sodium sulfate decahydrate gave the corresponding diol in 61% yield which was then chemoselectively oxidised using manganese dioxide (87% yield) to give **1**.

Scheme 2



Thus, a new synthesis of XH-14 (**1**) has been developed which gives exclusively the 3-formylated isomer. This synthesis is high yielding and easily modified to give access to a variety of different 2-substituted analogs. The preparation of these compounds is currently underway and their biological activities will be reported elsewhere in due course.

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References and Notes

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[10] The *ortho*-hydroxytolan **8** (430 mg, 0.94 mmol), palladium acetate (22 mg, 10 mol%), $CuCl_2$. $2H_2O$ (340 mg, 1.99 mmol) and sodium acetate (165 mg, 2.01 mmol) were stirred in methanol under an atmosphere of carbon monoxide for five hours. Normal workup followed by purification by column chromatography (hexanes-chloroform-ethyl acetate 5:5:1) afforded the benzofuran **9** (332 mg, 0.64 mmol, 68%). The unfunctionalized benzofuran **10** (140 mg) was obtained as a by-product.