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A scalable process for the synthesis of (*E*)-pterostilbene involving aqueous Wittig olefination chemistry

James McNulty *, David McLeod

Department of Chemistry & Chemical Biology, McMaster University, 1280 Main Street West, Hamilton, Ontario L8S 4M1, Canada

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ABSTRACT

A synthetic approach toward the pharmacologically active (*E*)-stilbene pterostilbene is described using a Wittig reaction conducted under mildly basic, aqueous conditions. A surprising, non-intuitive difference in (*E*)/(*Z*) stereoselectivity was observed comparing the two possible isomeric Wittig routes, allowing for the development of a highly efficient process to access the title stilbene derivative through a one-pot olefination deprotection sequence.

Introduction

Stilbenes and their derivatives constitute important classes of both natural products and synthetic small molecules that are highly valued in areas as diverse as pharmaceuticals,[1] imaging agents,[2] in light emitting diodes and photovoltaic devices (as organic dyes)[3] and also in an expanding array of other applications in the life sciences and materials chemistry.[4] A selection of pharmacologically active stilbenes and derivatives is collected in Figure 1. These include the substituted (*E*)-stilbene resveratrol,[1] the anticancer agent DMU212[5], and pterostilbene **1**,[6] a compound that is associated with a wide range of cardiovascular activities including anti-inflammatory activity and the lowering of plasma lipoprotein and cholesterol levels.[6b] Pterostilbene formulations are currently under clinical evaluation for the treatment of high blood pressure and in reducing oxidative stress.[6c] Several (*Z*)-stilbenes are endowed with potent anticancer activity including combretastatin A4[1e,1f]and the related stilstatins.[7] Clinically approved stilbenes include florbetapir F18, a compound that binds to myelin and is used as a molecular imaging probe in positron emission tomography (PET) in the diagnosis of disorders such as multiple sclerosis,[2] and the anti-asthmatic pharmaceutical singulair.[8] While many synthetic methods are available to access stilbenes,[9] the principal direct methods employed generally involve Wittig and related Horner-type reactions.[9a–d,7] Unfortunately, the classic Wittig olefination approach to stilbenes, including pterostilbene,[10] employing triphenylphosphine-derived semi-stabilized ylides, suffers from notoriously poor (*E*):(*Z*) stereocontrol and the problematic removal of triphenylphosphine oxide. These problems have largely been solved through the use of aqueous Wittig methods employing ylides derived from short chain trialkylphosphines. We have extensively investigated aqueous Wittig olefination reactions over the last few years[11] showing that stabilized and semi-stabilized ylides can be efficiently generated and trapped under increasingly milder chemical conditions delivering olefins with high (*E*)-olefin stereoselectivity,[11a–c] including the stilbenes DMU212 and resveratrol.[11a] Concerning the synthesis of stilbenes specifically, in addition to high (*E*)-olefin sterocontrol,[11a,c] the aqueous Wittig reaction with short-chain trialkylphosphine-derived ylides provides remarkably simplified post-reaction processing in comparison to classic Wittig protocols. Short chain trialkylphosphine oxides such as triethylphosphine oxide and tripropylphosphine oxide are water-soluble and processing is straightforward allowing clean separation and filtration of crystalline stilbene products in most cases.[11a,c] Where the products are oils, the phosphine oxide side products can easily be removed through simple aqueous/organic solvent partition.[11a–d] In view of the current high interest in the development of a pterostilbene based therapeutic[6,10] and the high cost of commercial (*E*)-pterostilbene,[12] we decided to investigate the possibility of a scalable aqueous Wittig approach to (*E*)-pterostilbene from readily available precursors that would benefit from the chemical and processing advantages described above. In this Letter we report the investigation of the two direct Wittig routes to pterostilbene, the discovery of a non-intuitive remote meta-substituent effect on the stereoselectivity of the reaction and the development of a scalable, highly optimized route to this valuable stilbene.

* Corresponding author. Tel.: +1 905 525 9140x27393.
E-mail address: jmcnult@mcmaster.ca (J. McNulty).

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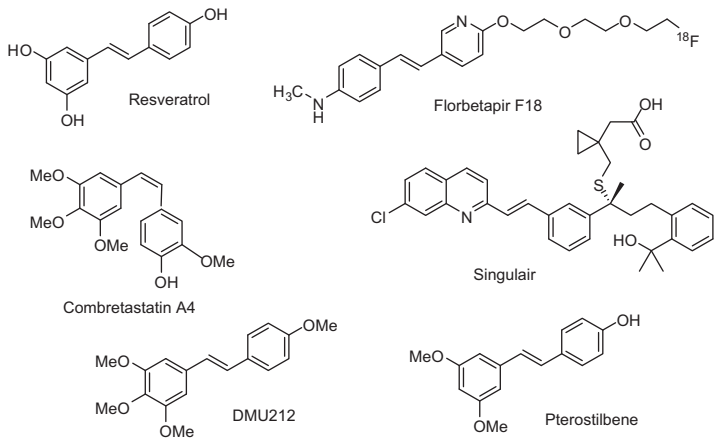
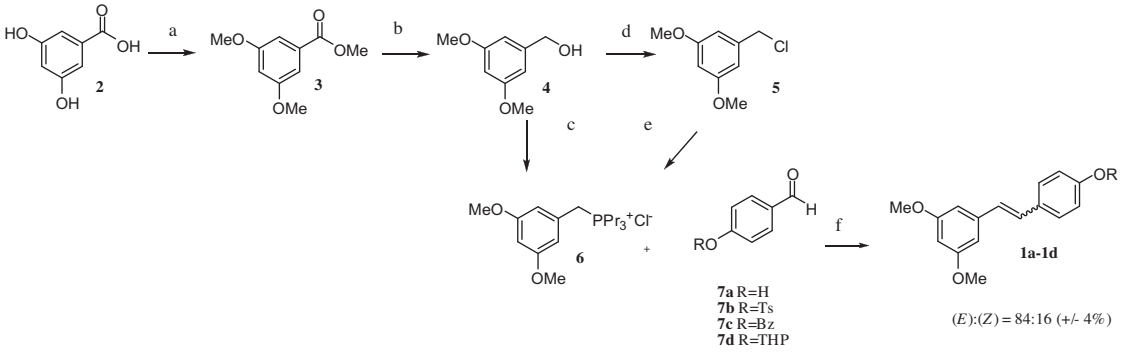


Figure 1. A selection of pharmacologically active stilbenes and analogs.

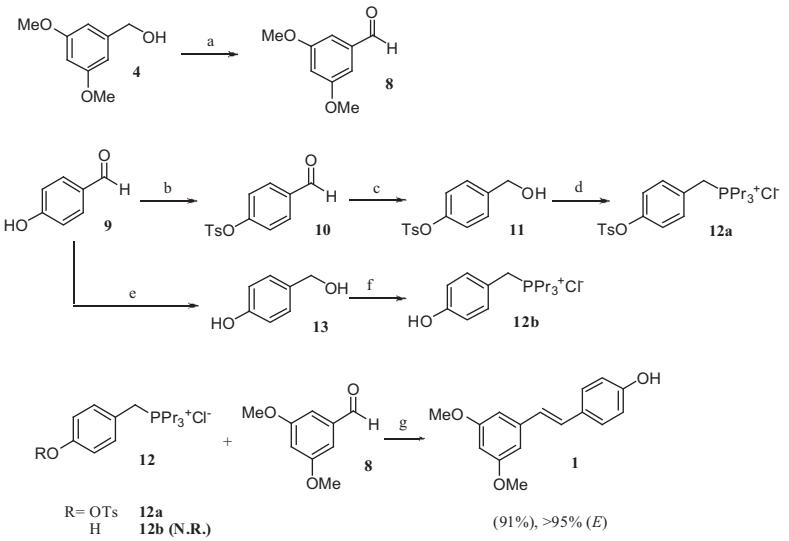
Results and discussion

Two possible Wittig-disconnections can be considered as routes to pterostilbene, A and B (see Graphical abstract). We initially focused on the synthesis of pterostilbene following the route A disconnection (Scheme 1). To this end, the phosphonium salt **6** was prepared from 3,5-dihydroxybenzoic acid **2** using standard chemistry. Notably, the benzyl alcohol **4** was readily converted to the phosphonium salt **6** on heating with tripropylphosphine hydrochloride or via the benzyl chloride **5** allowing batches of phosphonium salt **6** to be made reliably on a 10 g scale. Reaction of this salt was initially attempted on the unprotected 4-hydroxybenzaldehyde **7a** but showed no product formation using a variety of aqueous bases. The phenol **7a** was therefore protected as its THP acetal which reacted successfully to yield the protected pterostilbene. Unfortunately, the (*E*):(*Z*)-stereoselectivity of this reaction was determined to be unsatisfactory in comparison to other stilbenes synthesized employing trialkylbenzylphosphonium salts in aqueous media.[11a–c,i] The reaction of **6** with **7a** and with other protected derivatives (**7b**, **7c**, and **7d**) was investigated under a variety of conditions however changing the phenol protecting group and base afforded no improvement in the stereoselectivity observed and we thus investigated the synthesis following disconnection B.

The required aldehyde **8** was prepared cleanly from the previously synthesized alcohol **4** using the Dess–Martin periodinane. With the aldehyde in hand, work began on the *para*-hydroxy phosphonium salt **12**, as outlined in Scheme 2. We initially decided to attempt the olefination reaction using the protecting group free phosphonium salt **12b**. Reduction of 4-hydroxybenzaldehyde using $NaBH_4$ gave the benzyl alcohol **13** which was directly converted to the tripropylbenzyl phosphonium salt using tripropylphosphine hydrochloride, affording **12b** in good yield as a crystalline solid. Once again, the Wittig reaction of aldehyde **8** using this unprotected salt **12b** failed to produce pterostilbene **1**, however during the course of experimentation on protected alternatives, an interesting discovery was made with use of the tosyl protected phosphonium salt **12a** that allowed for a satisfactory conclusion to the pterostilbene synthesis. The tosyl-protected tripropylphosphonium salt **12a** was prepared in three steps from commercial 4-hydroxybenzaldehyde **9**. Protection of **9** as the tosyl derivative gave aldehyde **10** (95%) which was reduced to the alcohol **11** using a similar route described above for alcohol **4**. The benzyl alcohol **11** was again directly converted to the benzylic phosphonium salt **12** through treatment with tripropylphosphine hydrochloride. Phenolic tosylates are known to slowly saponify under aqueous basic conditions[14] and so there was initially some concern about the aqueous Wittig reaction of salt **12a** with **8**. In the event, the Wittig reaction with aldehyde **8** and phosphonium salt **12a** under our standard aqueous conditions at 100 °C was observed to be rapid (aldehyde disappearance <3 h), but was not clean. The reaction produced both the tosyl derivative of pterostilbene as well as fully deprotected pterostilbene **1**. Simply extending the reaction time to 12 h resulted in a clean, stepwise olefination/deprotection sequence and pterostilbene was isolated in high yield (89%) and, more importantly, with high stereoselectivity (>95:5, (*E*):(*Z*)). Of several bases studied in this reaction, lithium hydroxide provided the highest overall yield and the highest stereoselectivity in favor of the (*E*)-isomer. As described above, as tripropylphosphine oxide



Scheme 1. Synthesis of pterostilbene **1** following Wittig disconnection A. Reagents and conditions: (a) Dimethyl sulfate (2.0 equiv), K_2CO_3, acetone, reflux, 95%; (b) $NaBH_4$, THF–MeOH, reflux, 92%; (c) tripropylphosphine hydrochloride, 100 °C, 24 h, 99%; (d) $SOCl_2$, pyridine, 93%; (e) tripropylphosphine, PhMe, 80 °C, 99%; (f) various conditions, see table (Supplementary data) and text.



Scheme 2. Synthesis of pterostilbene **1** following Wittig disconnection B. Reagents and conditions: (a) DMP, DCM, 91%; (b) TsCl, TEA, DCM, 95%; (c) $NaBH_4$, DCM/MeOH (6:1), SiO_2, 90%; (d) tripropylphosphine hydrochloride, MeCN, 100 °C, overnight, 93%; (e) $NaBH_4$, DCM/MeOH (6:1), SiO_2, 81%; (f) tripropylphosphine hydrochloride, MeCN, 100 °C, overnight, 91%; (g) LiOH (3 equiv), H_2O (1 M), 90 °C, 12 h, 91%.

is fully water soluble, the phosphine oxide was removed through partitioning with water/ethyl acetate and (*E*)-pterostilbene was isolated in 91% yield through filtration through a silica plug and recrystallization.

Lastly, it is interesting to consider the possible origin of the stereochemical differences observed in conducting the two regioisomeric Wittig approaches to pterostilbene. The Wittig reactions of semi-stabilized ylides derived from short-chain trialkylphosphonium salts have been shown to provide higher than expected (*E*)-olefin stereoselection in aqueous, salt-containing media.[11a–c] This result may be either kinetic in origin, that is connected to preference for the planar transition state leading to (*E*)-olefination via a *trans*-oxaphosphetane,[13c] or thermodynamic through oxaphosphetane reversal and/or isomerization of intermediates prior to elimination. In this regard, it is known that the presence of weakly Lewis basic *ortho*-substituents (halogens or methoxy groups) in benzylic phosphonium salts can result in increased (*Z*)-olefin stereocontrol through enhanced kinetic control.[13a,b,d] It is interesting to speculate the involvement of a minor '*meta*'-alkoxy effect contributing to the increased formation of the (*Z*)-stilbene in reactions with aldehyde **6**, although steric factors do not appear favorable to stabilizing the initial oxaphosphetane. The dominant factors determining stereochemistry are the employment of short chain alkyl groups on the intermediate trialkylphosphorane resulting in kinetic preference for the *trans*-oxaphosphetane as well as the potential for equilibration under these aqueous, lithium salt-containing conditions. Strategic considerations toward any Wittig disconnection advocate the use of the structurally simplest phosphonium salt reacting with an aldehyde, where feasible. These results indicate the need to develop versatile synthetic approaches to challenging cases that can allow both regioisomeric variations of the olefination to be investigated.

Conclusion

In conclusion, the two possible regioisomeric Wittig olefination routes toward the synthesis of the pharmacologically active[4] stilbene pterostilbene **1** were investigated under aqueous Wittig conditions. A highly efficient, process-friendly route to pterostilbene was developed involving a high yielding (*E*)-selective stilbene formation, and *in-situ* deprotection leading to **1**. This process takes advantage of many of the green features of the aqueous Wittig reaction that have been disclosed in recent years that involve the intermediacy of stabilized or semi-stabilized ylides.[11] The use of phosphonium salts derived of short-chain trialkylphosphines allows for a high (*E*)-stereoselection as well as simple post reaction processing allowing clean, chromatographically-free removal of these water soluble phosphine oxide side products in many cases. The successful use of water as solvent and weak bases ranging from lithium hydroxide, to potassium carbonate and even weakly basic amines such as L-proline, tosylamide etc. makes this mild olefination chemistry attractive from a green-chemistry perspective. In addition, we wish to highlight the direct conversion of benzylic (or allylic)[11c] alcohols directly (for example Scheme 2, **13**–12**b**) to the corresponding trialkylphosphonium salts through treatment with short-chain trialkylphosphine hydrohalide (HBr or HCl) salts. This process eliminates the requirement for the use of benzylic and allylic halides, which are generally cytotoxic alkylating agents/lachrymators, and removes the requirement for the direct use of pyrophoric trialkylphosphines. Triethyl- and tripropylphoshine hydrohalide and chloride salts are crystalline, air-stable materials and essentially odorless. Although hygroscopic, they can be handled easily in the open laboratory. This direct benzyl/allyl alcohol to phosphonium salt process has now been utilized successfully in a number of useful aqueous Wittig applications.[11c–g] The synthesis of pterostilbene achieved using this chemistry is readily scalable and economic with respect to the number of steps required and the limited purification required throughout the process.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.019.

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