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SYNTHESIS OF PTEROSTILBENE BY JULIA OLEFINATION

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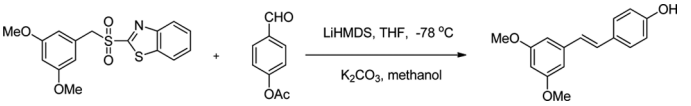
GRAPHICAL ABSTRACT



Abstract *A simple, E-stereoselective route for the synthesis of the biologically active compounds* trans-*pterostilbene and tetramethoxy stilbene from the readily available starting materials 3,5-dimethoxy benzyl alcohol and 4-hydroxy benzaldehyde was developed using Julia olefination as a key reaction.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resources: Full experimental and spectral details.]*

Keywords 3,5-Dimethoxy benzyl alcohol; 4-hydroxy benzaldehyde; Julia olefination; tetramethoxy stilbene; *trans*-pterostilbene

INTRODUCTION

Polyhydroxy stilbenes, such as pterostilbene and resveratrol, have been reported to exhibit a wide range of biological activities including anticancer, induction of peroxisome proliferator activated receptor-α (PPAR-α),[1] antioxidant,[2] anti-inflammatory,[3] antibacterial,[4] antifungal, antiplatelet aggregation, and vasodilator activities and other potential health benefits.[5] Pterostilbene is found in nature in a variety of grapes and berries as well as plants commonly used in traditional folk medicine. Pterostilbene was isolated for the first time from *Pterocarpus santalinus* by Spath and Kromp[6] in 1941. Because of its potential health benefits, significant interest in the synthesis of pterostilbene by using Wittig, Wittig–Horner,[1] Perkin,[7] or transition-metal-catalyzed reactions[8] has been generated in recent years. Herein

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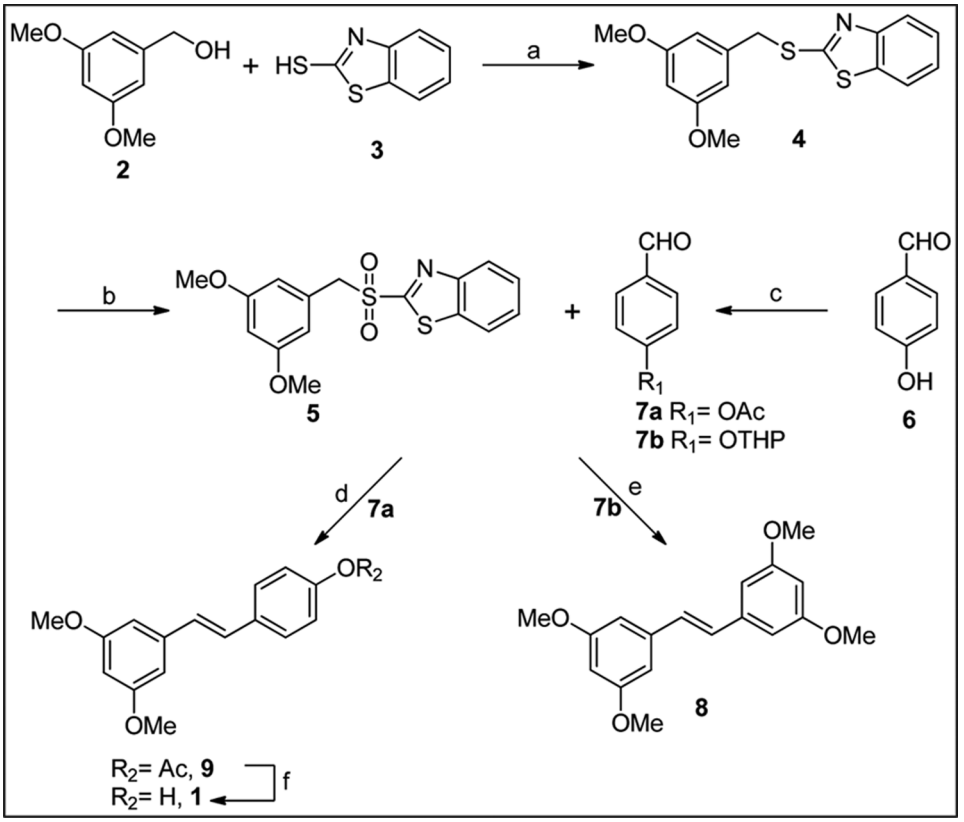
we report a simple, economical alternative method for the gram-scale preparation of pterostilbene using Julia olefination[9] as a key reaction (Figure 1).

Pterostilbene is a naturally occurring dimethyl ether analog of resveratrol. To synthesize these biologically active stilbenes, the majority of the reported patented and unpatented methods have involved Wittig-type olefinations. However, in this particular type of classical method for the synthesis of biologically important stilbenes, several adverse factors such as geometrical isomers[10] (E/Z isomers), harsh conditions, expensive starting materials, and lengthy sequences are often encountered. Alternatively, the Julia or modified Julia olefination reaction is a powerful and versatile synthetic transformation, widely utilized in the construction of complex natural products with excellent control of geometrical isomerism. Herein we report an amenable route for the synthesis of biologically active stilbenes including pterostilbene and tetramethoxy stilbene[11,12] using Julia olefination as a key reaction.

RESULTS AND DISCUSSION

As shown in Scheme 1, readily available and inexpensive 3,5-dimethoxy benzyl alcohol **2** was treated with mercapto benzothiazole under Mitsunobu reaction conditions[13] to give the known sulfide intermediate **4** in excellent yield. Ammonium heptamolybdate–catalyzed oxidation[14] of the sulfide yielded a white, crystalline sulfone **5** with 95% yield. On the other hand, treatment of 4-hydroxy benzaldehyde **6** with acetic anhydride or dihydropyran yielded the corresponding protected benzaldehydes **7a** or **7b**. Treatment ofthe sulfone **5** with lithium hexamethyldisilazide (LiHMDS) at 0 °C, followed by addition of aldehyde **7b**, produced the unexpected compound tetramethoxy stilbene **8** in almost quantitative yield. After conducting several experiments, the exclusive formation of tetramethoxy stilbene was attributed to the unstable and reactive nature of sulfonyl ylide under basic conditions and/or at elevated temperatures. The ylide intermediate underwent self-dimerization with another molecule of **5** to give tetramethoxy stilbene **8**. The sulfone, when treated with LiHMDS in the absence of aldehyde at 0 °C, furnished exclusively compound **8** within 30 min. However, when the sulfone was treated with LiHMDS at −78 °C, a very small amount of **8** (<5%, based on thin-layer chromatography; TLC) was observed after 1.5 h of reaction.

To minimize self-dimerization of sulfone **5**, the reaction was conducted at −78 °C with increased amounts (1.25–1.5 equiv.) of the aldehyde in a modified Julia olefination. Under these conditions with aldehyde **7a**, the expected product, *E*-4-acetylpterostilbene (**9**) was formed in 53% yield along with 19% of deacetylated product (*E*-pterostilbene, **1**) and 12% of *E*-**8**. The noteworthy feature of the current method is the absence of *Z*-isomer of 4-acetylpterostilbene (**9**), stilbene **1**, and tetramethoxy stilbene **8**. Moreover, addition of aldehyde solution to sulfone ylide gave superior yields of 4-acetylpterostilbene (**9**) than the slow, dropwise addition of sulfone to aldehyde. In the case of reverse addition (addition of sulfone ylide to aldehyde), increased amount of side product **8** was observed. When the sulfone ylide was added to 1.25 or 1.50 equivalents of aldehyde, no significant amount of products distribution was observed at −78 °C. Finally, potassium carbonate–mediated saponification of the resulting 4-acetylpterostilbene (**9**) furnished the target pterostilbene (**1**)



Scheme 1. Reagents and conditions: (a) PPh_3, $EtO_2CN{=}NCO_2Et$, THF, 6 h, 0 °C → rt, 90%; (b) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, NaOAc, EtOH–$CHCl_3$ (7:3), rt, 24 h, 95%; (c) Ac_2O, TEA, DMAP, DCM, 0 °C, 1 h, 95% (for **7a**) or DHP, PPTS, DCM, 0 °C–rt, 4 h, 80% (for **7b**); (d) LiHMDS, THF, −78 °C, 4 h, 53%; (e) LiHMDS, THF, 0 °C, 4 h, 90%; (f) K_2CO_3, MeOH, rt, 1 h, 95%.

in 95% yield. Alternatively, the crude product obtained via Julia olefination was subjected to saponification without further purification and furnished 11% of *E*-**8** and 69% of pterostilbene (**1**) with excellent geometrical selectivity.

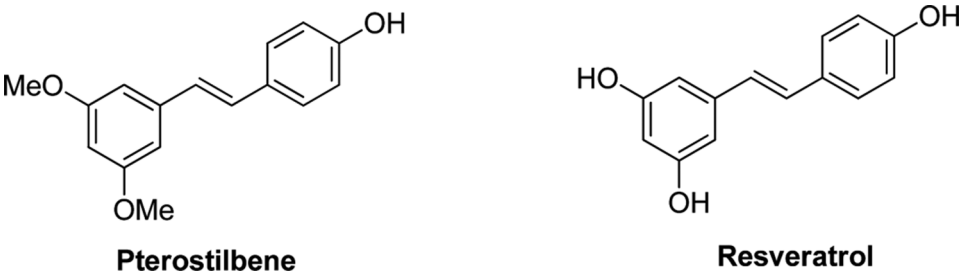


Figure 1. Structures of biologically significant stilbenes.

CONCLUSION

In summary, the synthesis of pterostilbene on a gram scale by Julia olefination has been achieved with good yield from inexpensive and readily available starting materials. In the future, we plan to continue to explore other potential synthetic alternatives including metal-catalyzed reactions to prepare biologically significant stilbenes in a fewer number of steps with improved overall yields.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ on 400 MHz (100 MHz) or 500 MHz (125 MHz) instruments. Chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane (δ) as the internal standard, and coupling constants are reported in hertz (Hz). Assignment of proton resonances was confirmed by correlation spectroscopy. Infrared (IR) spectra were recorded using a universal attenuated total reflection sampling accessory with a diamond ATR (attenuated total reflectance) on an Agilent Cary 630 Fourier transform (FT)–IR spectrometer. The reaction progress was monitored on precoated silica-gel TLC plates. Spots were visualized under 254 nm UV light and/or by dipping the TLC plate into a solution of 2 ml anisaldehyde, 10 ml of glacial acetic acid, and 5 ml of H_2SO_4 in 340 ml MeOH followed by heating with a hot gun. Column chromatography was performed with silica gel (230–400 mesh). All the solvents (hexanes, ethyl acetate, CH_2Cl_2, Et_2O) were distilled prior to use. All reactions were performed under an atmosphere of argon using oven-dried glassware and standard syringe/septa techniques. The solvent tetrahydrofuran (THF) was distilled from sodium benzophenone, and CH_2Cl_2 was dried over P_2O_5. Triethylamine was distilled from CaH_2.

2-((3,5-Dimethoxybenzyl)thio)benzo[d]thiazole (4)

A solution of a mixture of mercapto benzothiazole **3** (6.4 g, 38.6 mmol) and diethyl azodicarboxylate (4.8 mL, 40.2 mmol) in THF (30 mL) was added at 0 °C a solution of 3,5-dimethoxy benzyl alcohol **2** (5.0 g, 29.7 mmol) and triphenylphosphine (10.1 g, 38.5 mmol) in anhydrous THF (30 mL) to and stirred for 6 h at the same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl, extracted with EtOAc (3×50 mL), and evaporated under vacuum, and the resulting residue was purified by silica-gel column chromatography (20% of EtOAc in hexane) to yield sulfide (8.4 g, 90% yield). IR (cm^{-1}) 2934, 2834, 1592, 1423, 1344, 780. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, $J = 8.1$, 1.0 Hz, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.40 (ddd, $J = 8.4$, 7.3, 1.3 Hz, 1H), 7.27 (ddd, $J = 8.3$, 7.3, 1.2 Hz, 1H), 6.61 (d, $J = 2.4$ Hz, 2H), 6.37 (t, $J = 2.3$ Hz, 1H), 4.52 (s, 2H), 3.75 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.37, 160.93, 153.14, 138.35, 135.35, 126.07, 124.29, 121.51, 121.03, 107.10, 99.90, 55.34, 37.92. HRMS-ESI calcd. $C_{16}H_{16}NO_2S_2$ 318.0612; found 318.0606.

2-((3,5-Dimethoxybenzyl)sulfonyl)benzo[d]thiazole (5)

Initially 30% of H_2O_2 (17.8 mL) was added to a solution of sulfide **4** (5.0 g, 15.7 mmol) in ethanol and chloroform (200 mL, 3:1). Ammonium molybdate

$[(NH_4)_6Mo_7O_{24} \cdot 4H_2O]$ (48.5 g, 39.2 mmol) was added portionwise to this mixture. Sodium acetate (11.5 g, 140 mmol) was added to the resulting solution and stirred at room temperature. After 24 h, the mixture was concentrated, diluted with water (100 mL), extracted with EtOAc (3×50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude residue, which was purified by silica-gel column chromatography (20% of EtOAc in hexane) to give white crystalline sulfone **5** 5.2 g) in 95% yield. IR (cm^{-1}) 2963, 2908, 1592, 1430, 1315, 780. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, $J = 8.1$ Hz, 1H), 7.90 (d, $J = 7.9$ Hz, 1H), 7.63–7.58 (m, 1H), 7.56–7.51 (m, 1H), 6.33 (d, $J = 4.1$ Hz, 3H), 4.66 (s, 2H), 3.55 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.19, 161.97, 160.87, 128.08, 127.73, 125.38, 122.33, 108.87, 101.78, 61.30, 55.25. HRMS-ESI calcd. $C_{16}H_{16}NO_4S_2$ 350.0512; found 350.0511.

(*E*)-1,2-Bis(3,5-dimethoxyphenyl)ethane (8)

LiHMDS (5.0 mL of 1.0 M solution in THF) was added to a solution of sulfone **5** (1.75 g, 5.0 mmol) in anhydrous THF (20 mL) at 0 °C and stirred for 30 min at the same temperature, and then a solution of aldehyde **7b** (930 mg, 4.5 mmol) in THF (30 mL) was added. Stirring continued for 3 h at 0 °C. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc, and the solvent was evaporated under reduced pressure to give a crude residue. The residue was purified by silica-gel column chromatography to give compound **8** with 90% yield (1.35 g). IR (cm^{-1}) 2915, 1600, 1515, 1468, 1235, 1185, 960. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 2H), 6.66 (d, $J = 2.3$ Hz, 4H), 6.31 (t, $J = 2.3$ Hz, 2H), 3.82 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.91, 139.07, 129.11, 104.56, 100.05, 55.28. HRMS-ESI calcd. $C_{18}H_{21}O_4$ 301.1440; found 301.1442.

(*E*)-4-(3,5-Dimethoxystyryl)phenol (Pterostilbene) (1)

LiHMDS (17.1 mL of 1.0 M solution in THF, 10.3 mmol) was added to a solution of sulfone **5** (3.0 g, 8.5 mmol) in anhydrous THF (30 mL) at −78 °C and stirred for an additional 30 min at the same temperature. To this cold solution, aldehyde **7a** (1.75 g, 10.63 mmol) in THF (20 mL) was added and stirring continued at −78 °C. After 3 h, the mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc (3×25 mL). The combined organic layers were washed with water and saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product. The residue was purified by silica-gel column chromatography using EtOAc (5–20%) in hexanes to give 4-acetyl pterostilbene (1.35 g, 53% yield) and pterostilbene (0.42 g, 19% yield). Alternatively, the crude product obtained in Julia olefination was subjected to saponification without further purification using K_2CO_3 (18.45 mmol) in methanol (20 mL) at room temperature, followed by purification on silica-gel column chromatography (5–25% EtOAc in hexanes) to yield pure **1** in 69% yield (two steps) (1.52 g). IR (cm^{-1}) 3393, 2989, 2941, 1661, 1581, 1140, 827. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.38 (m, 2H), 7.03 (d, $J = 16.2$ Hz, 1H), 6.89 (dd, $J = 16.4$, 1.6 Hz, 1H), 6.84 (d, $J = 8.7$ Hz, 2H), 6.66 (t, $J = 1.8$ Hz, 2H), 6.41–6.38 (m, 1H), 3.83 (d, $J = 1.6$ Hz, 6H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 160.86, 155.61, 139.72, 129.87, 128.78, 128.03, 126.41, 115.68, 104.40, 99.61, 55.40. HRMS-ESI calcd. $C_{16}H_{17}O_3$ 257.1178; found 257.1178.

SUPPORTING INFORMATION

Supporting information such as general experimental procedures along with spectral data such as IR, ^{1}H NMR, ^{13}C NMR, and HRMS-ESI for the compounds is available via the Supplementary Content section of this article's Web page.

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