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Guangyu Xu^a; Chang Liu^a; Wei Zhang^b; Gaolei Zuo^a

^a College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha, PR, China ^b College of Medicine, Hunan Normal University, Changsha, PR, China

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A Practical Synthesis of α -Asarone via Iodine-catalyzed Isomerization of α/β -Asarone

Guangyu Xu,¹ Chang Liu,¹ Wei Zhang,² and Gaolei Zuo¹

¹College of Chemistry and Chemical Engineering, Hunan Normal University,
Changsha, P. R. China

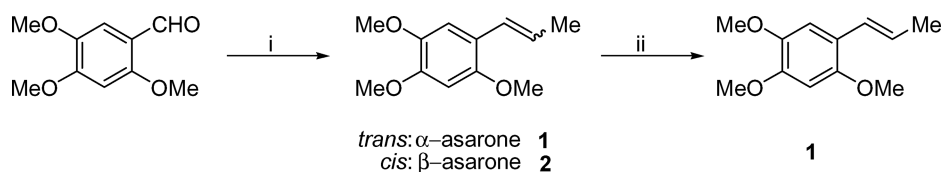
²College of Medicine, Hunan Normal University, Changsha, P. R. China

α -Asarone (**1**), isolated from the *Guatteria guameri* plant growing in southeast Mexico, is reported to be an anti-platelet and hypolipidemic agent.^{1,2} In addition, it is known to have sedating, neuroleptic, spasmolytic, anti-ulcerogenic and anti-atherogenic activity.^{3,4} Due to its low availability from natural sources, several synthetic approaches have been developed for α -asarone (*trans*-isomer, **1**), which involve Grignard, Wittig, Aldol-Grob, Friedel-Crafts reactions.^{5–9} However, in the above methods, some of the unwanted toxic β -asarone (*cis*-isomer, **2**) was always formed, along with the desired α -asarone, which is difficult to separate by column chromatography due to similarities in R_f values. β -Asarone can be converted to α -asarone by fusion with KOH in good yield.¹⁰ However, this reaction requires an excess amount of KOH (37 equiv.) and high temperature (200–220°C). Selenium dioxide, which can effectively convert β -asarone to α -asarone,¹⁰ is not a good choice due to its toxicity. A recently developed palladium (II) catalyzed isomerization of *cis*-arylalkenes can also be applied to the preparation of α -asarone,^{11,12} however, industrial applications of this reaction on synthesis of α -asarone are challenging because the catalyst is expensive,

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Address correspondence to Guangyu Xu, Hunan Normal University, College of Chemistry and Chemical Engineering, Changsha 410081, P. R. China. E-mail: gyxu@hunnu.edu.cn

and difficult to recycle. Moreover, traces of palladium are difficult to remove from the product. It would, therefore, be useful to develop a reliable, mild, economical, and environmentally friendly method for the conversion of β -asarone to α -asarone. We present herein a facile synthesis of α -asarone *via* iodine-catalyzed isomerization of α/β -asarone mixture (Scheme 1).

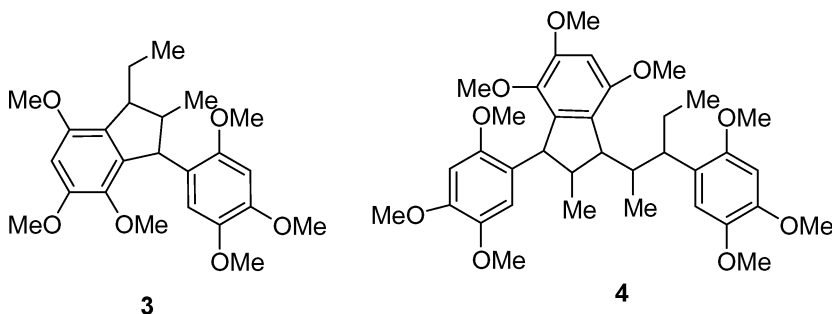


Scheme 1

Reagents and conditions: i. $\text{CH}_3\text{CH}_2\text{PPh}_3^+ \text{Br}^-$, dioxane, K_2CO_3 , reflux, 24 hours; ii. 0.1% I_2 , EtOAc, rt, 5 hours.

Although the iodine catalyzed isomerization of *cis*-stilbenes to *trans*-stilbenes has been reported,^{13–15} to the best of our knowledge, the successful iodine catalyzed inversion of β -asarone has not been described. We thus investigated the effect of solvent and the amount of iodine on the isomerization of a 43:57 mixture of α - and β -asarone obtained as previously described.¹²

It was found that the use of solvents such as toluene, chloroform, dioxane, ethyl acetate, and benzene all led to good selectivity (97/3 mixture) in 1 hour or less using 2 mol% iodine at room temperature; the best yields (79%) were obtained in toluene and ethyl acetate. The use of 0.1 mol% of iodine in ethyl acetate at room temperature for 5 hours gave the best results (97/3 [by GC] and 92% yield [based the total amount of the two isomers]). The fact that the isomerization may be performed in the dark (7 hours) makes it suitable for large scale production. The two by-products formed in the isomerization reaction were isolated by silicon gel column chromatography using hexane/ethyl acetate (4/1) as eluent, and identified by NMR and MS as dimer **3** and trimer **4**. By-product **3** had been reported previously.¹²



In summary, a simple and practical catalytic process for the preparation of pure α -asarone has been demonstrated. The mild conditions, operational simplicity, low toxicity, and low loading of catalyst make this process a more useful and practical alternative to the conventional methods for the acquisition of α -asarone from abundantly available but toxic β -asarone in nature.

Experimental Section

All reagents and solvents were obtained from commercial suppliers and used without further purification. Mps were determined on a Büchi 510 melting point apparatus and are uncorrected. GC was performed on an Agilent 6890N with a capillary column (0.32 mm × 32 m) immobile with liquid SE-30 (column flow rate 1.3 mL/min, vaporizer temperature 240°C, column temperature 170°C, detector temperature 250°C). The purity of product was determined by HPLC: column, SB-C18 column, 250 mm × 4.6 mm, 5 μ; mobile phase, 10% CH₃CN in water; flow rate 1.0 mL/min; detection, 258 nm. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ on a Bruker-400 NMR spectrometer. EIMS were determined with a HP5989B mass spectrometer.

Preparation of α-Asarone

In a 10-L glass vessel, a solution of α/β-asarone mixture (1.10 kg, 5.29 mol, 97.1% purity) in 5.5 L of ethyl acetate was added 1.34g of I₂ (5.29 mmol), and the resulting solution was stirred at room temperature for 5 hours, after which the solution was washed with 1% Na₂S₂O₃ solution (2 × 500 ml) to destroy the remaining iodine. The organic phase was washed with water and concentrated to give a pale yellow oil. The residue was dissolved in 1.5 L of hot aq. EtOH solution (7:3 EtOH-water) then cooled to 0°C to afford 0.87 kg (81%) of 99.1% pure (HPLC) of α-asarone as a white solid, mp. 61.5–62.1°C, *lit.*⁵ 62–63°C. β-Asarone and other impurities were present in less than 0.5%.

2,3-Dihydro-4,5,7-trimethoxy-3-(2,4,5-trimethoxyphenyl)-1-(3-(2,4,5-trimethoxyphenyl)pentan-2-yl)-2-methyl-1H-indene (4)

White solid (from EtOH), mp. 132.0–135.2°C, isolated by chromatography on silica gel (4:1 hexane-ethyl acetate). ¹H NMR (400MHz, CDCl₃): δ 0.58 (t, 3 H, *J* = 9.6 Hz, CH₃), 0.63 (d, 3 H, *J* = 9.6 Hz, CH₃), 1.66 (d, 3 H, *J* = 8.8Hz, CH₃), 1.43 (m, 1 H, CH), 1.73 (m, 2 H, CH₂), 2.21 (m, 1 H, CH), 2.83 (dd, 1 H, *J* = 5.6, 7.2 Hz, CH), 3.20 (m, 1 H, CH), 3.44 (s, 3 H, OCH₃), 3.61 (s, 3 H, OCH₃), 3.73 (s, 3 H, OCH₃), 3.77 (s, 3 H, OCH₃), 3.79 (s, 3 H, OCH₃), 3.86 (s, 3 H, OCH₃), 3.86 (s, 3 H, OCH₃), 3.88 (s, 6 H, 2 × OCH₃), 4.21 (d, 1 H, *J* = 5.2 Hz, CH), 6.40 (s, 1 H, ArH), 6.43 (s, 1 H, ArH), 6.48 (s, 1 H, ArH), 6.55 (s, 1 H, ArH), 6.59 (s, 1 H, ArH). ¹³C NMR (100 MHz, CDCl₃): δ 12.4, 14.9, 21.0, 26.2, 42.1, 49.3, 49.6, 53.1, 55.1, 56.0, 56.2, 56.4, 56.5, 56.5, 56.6, 56.7, 60.0, 96.5, 97.7, 97.9, 113.0, 125.2, 126.7, 127.0, 139.7, 139.9, 142.5, 142.8, 147.0, 147.5, 151.2, 151.8, 152.4, 152.8; MS (ESI): [M+Na]⁺ 647.3.

Anal. Calcd. for C₃₆H₄₈O₉: C, 69.21; H, 7.74. Found: C, 69.09; H, 7.88.

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