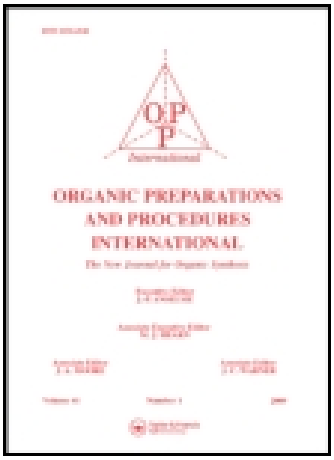

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A Practical Synthesis of α-Asarone via Iodine-catalyzed Isomerization of α/β-Asarone

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

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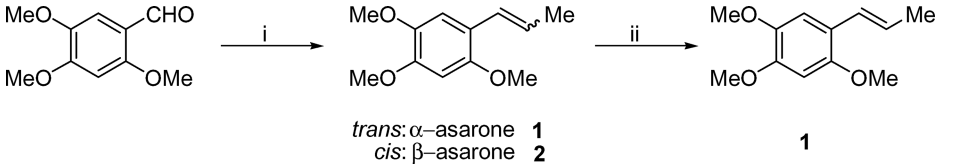
and difficult to recycle. Moreover, traces of palladium are difficult to remove from the product. It would, therefore, be useful to develop a reliable, mild, economical, and environmentally friendly method for the conversion of β-asarone to α-asarone. We present herein a facile synthesis of α-asarone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

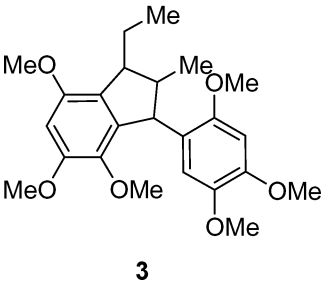


Scheme 1

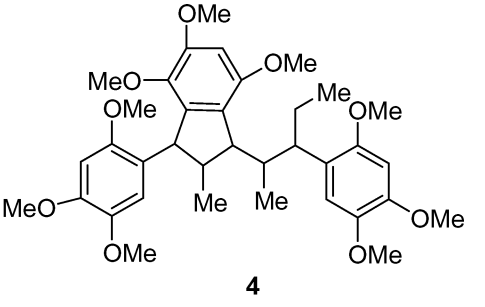
Reagents and conditions: i. $CH_3CH_2\overset{+}{P}Ph_3\ Br^-$, dioxane, K_2CO_3, reflux, 24 hours; ii. 0.1% I_2, EtOAc, rt, 5 hours.

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]



3



4

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% CH_3CN in water; flow rate 1.0 mL/min; detection, 258 nm. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Brucker-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 I_2 (5.29 mmol), and the resulting solution was stirred at room temperature for 5 hours, after which the solution was washed with 1% $Na_2S_2O_3$ 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-trimethoxy phenyl)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). ^{1}H NMR (400MHz, $CDCl_3$): δ 0.58 (t, 3 H, J = 9.6 Hz, CH_3), 0.63 (d, 3 H, J = 9.6 Hz, CH_3), 1.66 (d, 3 H, J = 8.8Hz, CH_3), 1.43 (m, 1 H, CH), 1.73 (m, 2 H, CH_2), 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, OCH_3), 3.61 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.88 (s, 6 H, 2 × OCH_3), 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{36}H_{48}O_9$: C, 69.21; H, 7.74. Found: C, 69.09; H, 7.88.

Acknowledgment

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