A Mild and Convenient Procedure for the Conversion of Toxic β-Asarone into Rare Phenylpropanoids: 2,4,5-Trimethoxycinnamaldehyde and γ-Asarone†

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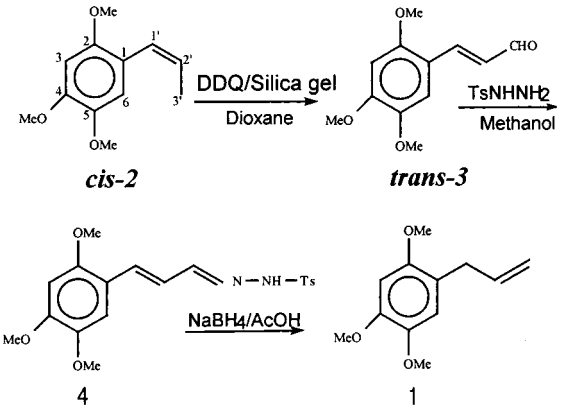
Oxidation of β-asarone (**2**) with DDQ gave *trans*-2,4,5-trimethoxycinnamaldehyde (**3**), which on treatment with *p*-toluenesulfonyl hydrazine provided corresponding α,β-unsaturated hydrazone derivative (**4**). Reduction of **4** with sodium borohydride in acetic acid afforded γ-asarone (**1**) in 43% yield.

In nature asarones[1] exist in three isomeric forms, namely, α-, β-, and γ-asarone (*trans*-2,4,5-trimethoxy-1-propenylbenzene, *cis*-2,4,5-trimethoxy-1-propenylbenzene, and 1-allyl-2,4,5-trimethoxybenzene, respectively). γ-Asarone (**1**) is a rare phenylpropanoid[2] first isolated from *Caesulia axillaries*[3] and later detected as a biologically active[4] constituent of various essential oil bearing plants.[5] However, no simple method is available for separation and isolation of asarones (α, β, and γ) in single isomeric form due to their similar physical properties. Separation of less abundant **1** via column chromatography of asarones-rich essential oil is particularly difficult. A few methods for the synthesis of **1** are found in the literature,[2,6] but protocols either involve multiple steps starting from dimethoxyphenol[6a,c] with overall poor yield or require careful handling of sodium perchlorate during electrolysis of methyl eugenol.[2,6b] Herein we report a simple synthesis of **1** from toxic β-asarone[7] (**2**) via formation of a key intermediate, 2,4,5-trimethoxycinnamaldehyde (**3**), as outlined in Scheme 1; compound **3** is itself a rare phenylpropanoid found in traces in *C. axillaries*[8] and *Alpinia flabella*.[9]

β-Asarone (**2**) is found in several plants[1] including *Acorus calamus*[10] (family Araceae). The high percentage of toxic **2** (varying from 70 to 90% in tetraploid and hexaploid strains[11] distributed extensively in India, Pakistan, Bangladesh, Japan, and China) restricts the market potential[12] of calamus oil. Therefore, as a part of our continuing efforts to generate value-added products,[13] compound **2** has been converted into rarer phenylpropanoids **3** and **1**. Treatment of **2** (*cis*-isomer) with DDQ[14] in wet dioxane afforded **3** in 41% yield, whereas the addition of a catalytic amount of silica gel (60−120 mesh size) improved the yield of **3** up to 62%. ^{1}H NMR clearly indicated the formation of **3** as *trans* α,β-unsaturated aldehyde in which the olefinic proton appeared at δ 7.81 (J = 15.8 Hz) rather than the expected *cis*-isomer.[15] Alternatively, the above oxidation was repeated starting with *trans*-asarone, which produced an 84% yield of expected *trans*-cinnamaldehyde (**3**), identified by mixed melting point and comparison of its spectral data with an authentic sample.[8,13c] These results clearly indicated formation of the thermodynamically more stable *trans* isomeric form of cinnamaldehyde (**3**) whether starting from *cis*- or *trans*-asarone; however, *trans*-asarone provided higher yields. Compound **3** has been isolated, so far, from two plants,[8,9] but only in trace amounts. Treatment of a methanolic solution of **3** with *p*-toluenesulfonylhydrazine[16] (1.2 equiv) afforded the corresponding α,β-unsaturated tosylhydrazone derivative (**4**) in 79% yield. To obtain the product **1**, the reduction and double-bond migration[17] of tosylhydrazone derivative **4** proceeded smoothly and in good yield (43%) with acetic acid−sodium borohydride, but yields were lower using sodium cyanoborohydride−sulfolane. The R_f value (0.39 in 4% ethyl acetate in hexane) of **1** was exactly the same as that for **2**; however, spectral data of **1** were found consistent with those in the literature.[1,6c] Finally, we conclude that the synthesis of **3** and **1** from **2** is convenient and efficient in comparison to reported[2,6,8] methods.

Scheme 1



Experimental Section

General Experimental Procedures. Melting points were determined with a Metler FP80 micromelting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ using TMS as an internal standard and EIMS on a JEOL JMS-HX 300 mass spectrometer, respectively. DDQ and α-asarone were purchased from Merck and Sigma Chemical Co., respectively.

Plant Material and Isolation of β-Asarone (2). The rhizomes of *Acorus calamus* were collected from Palampur (1300 m altitude) in May−June 1997, and the plant specimen was compared against a voucher specimen (no.1066) in the herbarium of the IHBT, Palampur, India. The steam distillation of rhizomes gave calamus oil (1.7% w/w), which after column chromatography on a silica gel column with hexane/ethyl acetate (99:1 to 90:10) provided **1** (82% w/w) as pale yellow liquid (R_f 0.39 on silica gel TLC plate in 4% ethyl acetate in hexane), and its spectral data agreed well with reported[1,13] literature values.

Preparation of 2,4,5-Trimethoxycinnamaldehyde (3) from β-Asarone (2). A mixture of **2** (2.08 g, 0.01 mol) and DDQ (4.54 g, 0.02 mol) in wet dioxane (40 mL) was stirred for 15 min. A catalytic amount of silica gel (0.2−0.3 g) was added

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to the above mixture with constant stirring at room temperature overnight. The precipitated hydroquinone ($DDQH_2$) was filtered and further washed with dioxane. The filtrate and washings were concentrated to dryness, resuspended in $CHCl_3$ (25 mL), washed with H_2O (2 × 10 mL), $NaHCO_3$ (10%, 2 × 10 mL), and brine (2 × 10 mL), and dried over anhydrous Na_2SO_4. The residue obtained on evaporation of the solvents was column chromatographed on silica gel containing some neutral alumina at the top. The column was eluted with hexanes−ethyl acetate (9:1 to 3:2). The fractions were monitored on a TLC plate, and the desired fractions were combined and solvent removed under vacuum to afford **3** (1.38 g) in 62% yield as a yellow solid with R_f 0.67 (25% ethyl acetate in hexane): mp 139 °C (lit.[8] 140 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.65 (1H, d, J = 7.8 Hz, H-3′), 7.81 (1H, d, J = 15.8 Hz, H-1′), 7.03 (1H, s, H-6), 6.64 (1H, dd, J = 15.8 Hz, J = 7.8 Hz, H-2′), 6.51 (1H, s, H-3), 3.95 (s, 3H, 2-OCH_3), 3.91 (s, 3H, 4-OCH_3), 3.87 (s, 3H, 5-OCH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 194.1 (C-3′), 154.1 (C-1′), 153.2 (C-2), 147.6 (C-4), 143.3 (C-5), 126.4 (C-2′), 114.5 (C-1), 110.5 (C-6), 96.5 (C-3), 56.4 (5-OCH_3), 56.2 (2-OCH_3), 56.0 (4-OCH_3); EIMS m/z 222 $[M]^+$ (44), 207 (18), 191 (100), 179 (14), 171 (27), 151 (14), 147 (7), 69 (58), 58 (80).

Preparation of 2,4,5-Trimethoxycinnamyltosylhydrazone (4). The cinnamaldehyde **3** (1.11 g, 0.005 mol) was dissolved in boiling MeOH (40 mL), and the solution was cooled to room temperature. *p*-Toluenesulfonylhydrazine (1.12 g, 0.006 mol) was added and the solution stirred at room temperature overnight. The red viscous material obtained on evaporation of solvents was chromatographed on a silica gel column with hexanes−ethyl acetate (9:1 to 3:7) as the eluent. The fractions containing **4** were pooled on the basis of TLC. Evaporation of solvent gave yellow crystals (1.54 g) of tosylhydrazone (**4**) in 79% yield with R_f 0.32 (25% ethyl acetate in hexane): mp 155−168 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (2H, d, Ts-H), 7.62 (1H, d, H-3′), 7.32 (2H, d, Ts-H), 7.02 (1H, d, H-1′), 6.98 (1H, s, H-6), 6.69 (1H, dd, H-2′), 6.49 (1H, s, H-3), 3.96 (3H, s, 2-OCH_3), 3.93 (3H, s, 4-OCH_3), 3.86 (3H, s, 5-OCH_3), and 2.43 (3H, s, Ts-CH_3).

Preparation of γ-Asarone (1). A solution of tosylhydrazone **4** (0.78 g, 0.002 mol) in glacial acetic acid (8 mL) was added dropwise to a precooled solution of sodium borohydride (0.38 g, 0.01 mol) and acetic acid (3 mL) under nitrogen atmosphere. The reaction mixture was stirred initially at 5−10 °C for 1 h and finally at 90−120 °C for 12 h. The mixture was poured on to ice-cooled H_2O and extracted with CH_2Cl_2 (20 mL × 3). The organic layers were combined, washed with dilute sodium hydroxide and saturated brine, and dried over anhydrous Na_2SO_4. The crude product was chromatographed on silica gel (hexanes−ethyl acetate from 99:1 to 90:10) to obtain 0.18 g (43%) of **1** as a viscous liquid with R_f 0.39 (4% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) at δ 6.70 (1H, s, H-6), 6.53 (1H, s, H-3), 5.95 (1H, m, H-2′), 5.04 (2H, m, H-3′), 3.88 (3H, s, 2-OCH_3) 3.83 (3H, s, 4-OCH_3), 3.80 (3H, s, 5-OCH_3), and 3.32 (2H, d, J = 6.6 Hz, H-1′); ^{13}C NMR ($CDCl_3$) δ 151.72 (C-2), 148.30 (C-4), 143.40 (C-5), 137.04 (C-2′), 120.42 (C-1), 115.58 (C-3′), 114.38 (C-6), 98.41 (C-3), 56.99 (4-OCH_3 & 5-OCH_3), 56.62 (2-OCH_3), and 34.05 (C-1′); EIMS m/z 208 $[M]^+$ (100), 193 (60), 165 (40), 134 (10), 77 (18), 69 (34). On the basis of the above spectral data and comparing with reported literature,[1,6c] the liquid was identified as **1**.

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References and Notes

(1) Patra, A.; Mitra, A. K. *J. Nat. Prod.* **1981**, *44*, 668−669.
(2) Vargas, R. R.; Pardini, V. L.; Viertler, H. *Tetrahedron Lett.* **1989**, *30*, 4037−4040.
(3) Devgan, O. N.; Bokadia, M. M. *Aust. J. Chem.* **1968**, *21*, 2001.
(4) Masuda, T.; Inazumi, A.; Yamada, Y.; Padolina, W. G.; Kikuzaki, H.; Nakatani, N. *Phytochemistry* **1991**, *30*, 3227−3228.
(5) Avella, E.; Diaz, P. P.; Diaz, A. M. P. de; De-Diaz, A. M. P. *Planta Med.* **1994**, *60*, 195.
(6) (a) Shulgin, A. T. *Can. J. Chem.* **1965**, *43*, 3437. (b) Shaopeng, W.; John, S. S. *Tetrahedron Lett.* **1990**, *31*, 1513−1516. (c) Marina, D. G.; Pietro, M.; Antonino, P.; Lucio, P. *Phytochemistry* **1992**, *31*, 4119−4123.
(7) (a) Taylor, J. M.; Jones, W. I.; Hogan, E. C.; Gross, M. A.; David, D. A.; Cook, E. L. *Toxicol. Appl. Pharmacol.* **1967**, *10*, 405. (b) Keller, K.; Odenthal, K. P.; Leng, P. E. *Planta Med.* **1985**, *1*, 6−9. (c) Abel, G. *Planta Med.* **1987**, *53*, 251−253.
(8) Kulkarni, M. M.; Sohoni, J.; Rojatkar, S. R.; Nagasampagi, B. A. *Ind. J. Chem. Sect. B* **1986**, 25*B*, 981−982.
(9) Kikuzaki, H.; Tesaki, S.; Yonemori, S.; Nakatani, N. *Phytochemistry* **2001**, *56*, 109−114.
(10) Motley, T. J. *Econ. Bot.* **1994**, *48*, 397−412.
(11) Mazza, G. *J. Chromatogr.* **1985**, *328*, 179−206.
(12) Harborne, J. B.; Baxter, H. In *Phytochemical Dictionary, A Handbook of Bioactive Compounds from Plants;* Taylor & Francis Ltd: Washington, DC, 1993; p 474.
(13) (a) Sinha, A. K. US Patent No. 09-652376 filed on August 31, 2000. (b) Sinha, A. K; Joshi, B. P.; Dogra, R. *Nat. Prod. Lett.* **2001**, *15*, 439−444. (c) Sinha, A. K.; Dogra, R.; Joshi, B. P. *Indian J. Chem.* **2002**, *41B*, in press.
(14) Tomrny, I.; Shiming, L.; Knut, L. *Tetrahedron Lett.* **1998**, *39*, 2413−2416.
(15) Saxena, D. B. *Phytochemistry* **1986**, *25*, 553−555.
(16) Goffredo, R.; Alessandro, M. *Synthesis* **1976**, 530−532.
(17) (a) Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923−926. (b) Hutchins, R. O.; Nicholas, R. N. *J. Org. Chem.* **1978**, *43*, 2299−2301.

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