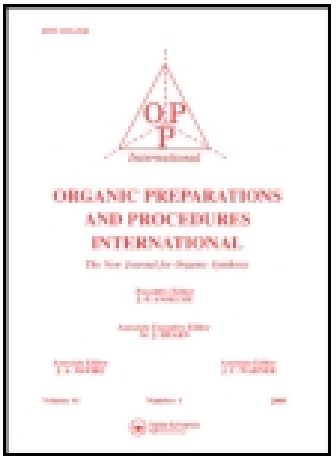

Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

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Published online: 24 Sep 2012.

To cite this article: Elvia V. Cabrera, Kelly P. Marrugo, José G. Ortega, Ajoy K. Banerjee & Jennifer L. Sanchez (2012) Total Synthesis of α-Asarone, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 44:5, 455-459, DOI: 10.1080/00304948.2012.715061

To link to this article: http://dx.doi.org/10.1080/00304948.2012.715061

Organic Preparations and Procedures International, 44:455–459, 2012

ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2012.715061

OPPI BRIEFS

Total Synthesis of α-Asarone

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α-Asarone (**6**), a substance of potent hypolipidemic activity[1] is mainly found in wild ginger (*Asarum europaeumL-Aristolochiceae*)[2] and guatteria (*Guatteria gaumeri-Annonacea*),[3] the plant growing in Southwestern Mexico. In addition, α-asarone is known to have sedating, neuroleptic, spasmolytic, antiulcerogenic and antiatherogenic activity.[4] The potent biological activities coupled with its low availability from natural source have given the origin of a plethora of publications[5,6] dealing with the studies directed towards the synthesis of α-asarone. However α-asarone (*trans*-isomer, **6**), obtained in the most published methods[6,7] is contaminated with undesired *toxic* β-asarone (*cis*-isomer, **7**) whose separation by column chromatography is difficult due to the similarities in R_f values of the two isomers. Therefore isomerization method was sought for the conversion of β-asarone to α-asarone. The Pd(II) catalysed [$(MeCN)_2$ $PdCl_2$] isomerization of a mixture of α- and β-asarone, attempted by Xu and collaborators,[8] improved the yield of α-asarone (71%) but also produced two dimers of α-asarone. However, the cost of the catalyst does not recommend the use of this method for large scale preparations. Moreover traces of palladium are difficult to remove from the product. Although the iodine-catalyzed isomerization of a mixture of α- and β-asarone has been reported[6] to yield α-asarone in high yield (81%) and high purity, β-asarone, a dimer and a trimer were present (less than 0.5%). The knowledge gained from a study of these approaches[6] encouraged us to develop a concise and convenient route which would only afford α-asarone.

We selected a suitable starting material whose transformation to α-asarone could be realized without using the Wittig,[6,8] Friedel-Crafts[9] and Grignard[10] reactions respectively and thus the formation of β-asarone (**7**) as well the process of isomerization could be avoided. The synthetic route is outlined in *Scheme 1*. Reduction of commercially available

Received March 9, 2012
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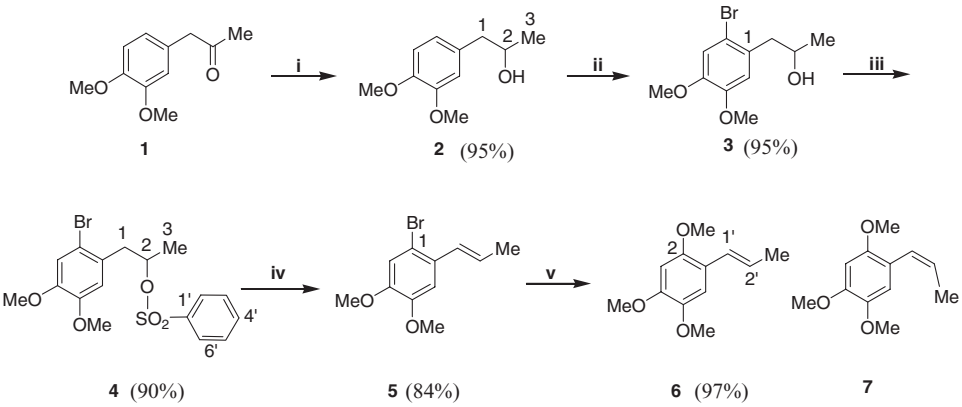

Reagents and conditions: (i) $NaBH_4$, EtOH, rt, 30 min; (ii) NH_4Br, H_2O_2, AcOH, rt, 4 h; (iii) $PhSO_2Cl$, Pyridine, rt, 24 h; (iv) NaH, DMF (anhyd), rt, 24 h; (v) Cu(I)Br, MeONa, DMF, reflux, 18 h.

Scheme 1

3,4-dimethoxyphenylacetone (**1**) with sodium borohydride produced the known alcohol **2** in 95% yield.[11] Bromination[12] of **2** with ammonium bromide and hydrogen peroxide (32%) in acetic acid yielded bromide **3** in 95% yield. Considerable difficulty was encountered in finding the proper conditions to effect the direct conversion of **3** to **5**. Although this transformation appeared straight forward, in practice none of an extensive list of typical dehydrating reagents (*p*-toluenesulfonic acid in toluene at reflux, sulfuric acid and SiO_2 in toluene at room temperature, thionyl chloride and pyridine, anhydrous sodium acetate and acetic anhydride at reflux temperature) were successful. Finally the dehydration of benezenesulfonyl derivative **4** effected with sodium hydride in dimethylformamide (DMF) at room temperature furnished the desired product **5** in 84% yield.

The benzenesulfonyl derivative **4** was obtained in 90% yield by stirring the alcohol **3** in pyridine with benzenesulfonyl chloride ($PhSO_2Cl$) at room temperature. Dehydration of **2** followed by bromination to obtain **5** was not attempted to avoid the possibility of the bromination of the double bond. With the synthesis of the compound **5**, we were ready to address the repeated attempts using published methods[7,13] met with limited success. Finally following the method of Aalten and coworkers[14] with minor modifications, compound **5** was heated with a saturated solution of sodium methoxide, DMF and copper(I) bromide to afford α-asarone **6** in 97% yield which was homogeneous on TLC in different system. Its mp. was identical with that of the published report.[10] The ^{1}H NMR and ^{13}C NMR data agreed with the reported data[15] of α-asarone indicating α-configuration of the resulting asarone. No trace of the oily β-asarone (**7**) was detected.

In conclusion, a concise approach to the synthesis of α-asarone as the sole product in high overall yield (66%) has been developed. The unwanted toxic β-asarone (**7**) detected in most of the published papers was not formed.[5,8]

Experimental Section

Unless otherwise stated all meting points are uncorrected and were determined on an Electrothermal melting point apparatus. Infrared (IR) spectra were recorded on a Nicolet-Fourier

(FT) Instrument and NMR (^{1}H and ^{13}C) spectra were determined on a Brucker AM-300 spectrometer in $CDCl_3$. Chemical shifts (δ) are expressed in ppm. The form of signals is expressed as s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Mass spectra (MS) were determined on a Dupont 21-492B. Column chromatography was carried on silica gel 60 (Merck). Thin layer chromatography (TLC) plates were coated with silica gel and the spots were visualized using ultraviolet light. All organic extracts were dried over anhydrous $MgSO_4$ and solvents were evaporated *in vacuo*. Elemental analyses were performed on a Carlo-Erba 1108 Elemental Analyser.

1-(3,4-Dimethoxyphenyl)propan-2-ol (2)

To a solution of ketone **1** (2.01 g, 10.30 mmol) in EtOH (14 ml) was added a solution of sodium borohydride (510 mg, 13.50 mmol) in EtOH (15 ml) and stirred for 30 min at room temperature. The solvent was partially evaporated and the residue was extracted with CH_2Cl_2. The organic extract was washed with a diluted solution of HCl (35 ml, 10%), brine (40 ml), dried and evaporated. The resulting oil was chromatographed (hexane:Et_2O 1:1) to obtain the alcohol **2** (1.92 g, 95%), R_f 0.19 (hexane:Et_2O 1:1), mp 42–44°C (from hexane) (*lit.*[9] 43–44°C); IR (cm^{-1}): 3399 (OH); MS (*m/z*): 179 $(M^{+1}\text{-}H_2O)^+$; ^{1}H NMR: δ 6.78 (d, 1H, J = 8.58 Hz) (ArH at C-5), 6.71 (m, 2H) (ArH at C-2 and C-6), 4.00-3.90 (m, 1H) (H at C-2), 3.84 (s, 3H, OMe), 3.82 (s, 3H, OMe), 2.70 (dd, 1H, J = 4.68 Hz and J = 13.57 Hz) (H at C-1), 2.57 (dd, 1H, J = 8.07 Hz and J = 13.57 Hz) (H at C-1), 1.68 (br s, 1H, OH), 1.20 (d, 3H, J = 6 Hz) (H at C-3); ^{13}C NMR: δ 149.00 (ArC-3), 147.76 (ArC-4), 131.07 (ArC-1), 121.29 (ArC-6), 112.67 (ArC-2), 111.48 (ArC-5), 68.79 (C-2), 55.89 (OMe), 55.81(OMe), (45.30 (C-1), 22.67 (C-3).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.53; H, 8.36.

1-(2-Bromo-4,5-dimethoxyphenyl)propan-2-ol (3)

To a solution of the alcohol **2** (508 mg, 2.59 mmol) in glacial acetic acid (9.3 ml) was added ammonium bromide (410 mg, 5.13 mmol) and dropwise hydrogen peroxide (2 ml, 5 mmol) of 35% and the contents were allowed to stirred at room temperature for 4 h. The progress of the reaction was monitored by thin layer chromatography (TLC). The resulting yellow solution was treated with a saturated solution (10 ml) of $NaHCO_3$ and extracted with Et_2O. The organic extracts were washed with brine, dried and evaporated to give the bromide **3** (677 mg, 95%) as white solid, R_f 0.17 (hexane:Et_2O 1:1), mp 82–83°C (from ether); IR (cm^{-1}): 3412 (OH); MS (*m/z*): 257 (M^+ -H_2O), 178 (M^{+1}-H_2O-Br); ^{1}H NMR: δ 7.01 (s, 1H) 6.74 (s, 1H) (ArH-3, ArH-6), 4.13-4.03 (m, 1H, H-2), 3.83 (s, 6H) (4-OMe, 6-OMe), 2.87 (dd, 1H, J = 4.62, J = 13.66 Hz) (H at C-1), 2.72 (dd, 1H, J = 8.13, J = 13.66 Hz) (H at C-1), 1.25 (d, 3H, J = 6 Hz) (H at C-3); ^{13}C NMR: δ 148.36 (ArC-3, ArC-4), 130.07 (ArC-1), 115.82 (ArC-2), 114.62 (ArC-6), 114.32 (ArC-5), 67.78 (C-2), 56.17 (OMe), 56.10 (OMe), 45.20 (C- 1), 22.93 (C-3).

Anal. Calcd for $C_{11}H_{15}BrO_3$: C, 48.01; H, 5.45. Found: C, 48.24; H, 5.61.

Benzenesulfonic Acid 2-(2-Bromo-4,5-dimethoxyphenyl-1-methylethyl Ester (4)

To a solution of the bromide **3** (545 mg, 1.98 mmol) in dry pyridine (20 ml) was added dropwise benzenesulfonyl chloride 957 mg (5.47 mmol) and stirred for 20 h at room

temperature. The reaction mixture was treated with ice-water and extracted with Et_2O (100 ml). The ether extracts were washed successively with a diluted solution of HCl (20 ml, 5%), a solution of $NaHCO_3$ (25 ml, 5%), brine, dried and evaporated. The resulting solid on chromatographic purification (hexane:Et_2O 8:2) furnished the sulphonyl derivative **4** (740 mg, 90%), R_f 0.33 (hexane:Et_2O 1:1), mp 75–76°C (from ether); IR (cm^{-1}): 1342, 1168; MS (*m/z*): 259 (M^{+1} -$C_6H_5O_3S$); ^{1}H NMR: δ 7.63 (dd, 2H, $J = 1.25$ Hz, $J = 8.28$ Hz) (H at C-2′ and H at C-6′), 7.49 (dt, 1H, $J = 1.15$ Hz, $J = 7.50$ Hz) (H at C-4′), 7.35 (t, 2H, $J = 7.83$ Hz) (H at C-3′ and H at C-5′), 6.76 (s, 1H, ArH-5), 6.51 (s, 1H, ArH-2), 4.81-4.87 (m, 1H, H-2), 3.80 (s, 3H, OMe), 3.73 (s, 3H, OMe), 2.88 (dd, 1H, $J = 4.95$ Hz, $J = 14.28$ Hz) (H at C-1), 2.84 (dd, 1H, $J = 8.25$ Hz, 14.25 Hz, H-1), 1.43 (d, 3H, $J = 6$ Hz) (H at C-3); ^{13}C NMR: δ 148.46 (ArC-4),148.09 (ArC-3), 136.84 (C-1′), 133.07 (C-4′), 128.81 (C-2′ and C-6′), 127.79 (ArC-1), 127.44 (C-3′ and C-5′), 115.41 (ArC-2), 114.42 (ArC-5), 114.29 (ArC-6), 79.80 (C-2), 56.07 (OMe), 55.95 (OMe), 42.46 (C-1), 21.29 (C-3).

Anal. Calcd for C_{17} $H_{19}BrO_5S$: C, 49.15; H, 4.57. Found: C, 49.43; H, 4.76.

1-Bromo-4,5-dimethoxy-2-propenylbenzene (5)

To a suspension of sodium hydride (60% dispersion in mineral oil) (338 mg, 14 mmol) in dry DMF (6 ml) was added a solution of sulfonyl derivative **4** (604 mg, 1.46 mmol) in dry DMF (4 ml) under nitrogen. The reaction mixture was stirred for 24 h at room temperature, diluted with cold water and extracted with $CHCl_3$. The organic extract was washed with a diluted solution of HCl (20 ml, 5%), saturated solution of $NaHCO_3$, distilled water, dried and evaporated. The resulting product was chromatographed (hexane:Et_2O 9:1) to obtain the olefine **5** (316 mg, 84%), R_f 0.36 (hexane:Et_2O 9:1), mp 43–44°C (from hexane); IR (cm^{-1}): 3088, 3034, 3000, 1650, 1600; MS (*m/z*): 257 (M^+), 178 (M^{+1} -Br); ^{1}H NMR: δ 6.96 (s, 1H, ArH-6), 6.95 (s,1H, ArH-3), 6.62 (dq, 1H, $J = 1.70$ Hz, $J = 15.63$ Hz) (H at C-1), 6.06 (dq, 1H, $J = 6.65$ Hz, $J = 15.56$ Hz) (H at C-2), 3.86 (s, 3H, OMe), 3.84 (s, 3H, OMe), 1.89 (dd, 3H, $J = 1.70$, $J = 6.65$ Hz) (H at C-3); ^{13}C NMR: δ 148.74 (ArC-4), 148.58 (ArC-5), 129.99 (ArC-1), 129.63 (C-1), 126.88 (C-2), 115.40 (ArC-6), 113.33 (C-2), 109.15 (ArC-3), 56.16 (OMe), 56.01 (OMe), 18.49 (C-3).

Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.36; H, 5.05. Found: C, 51.57; H, 5.17.

(E)-1-(2,4,5-Trimethoxyphenyl)-1-propene (α-Asarone) (6)

To a saturated solution of sodium methoxide, prepared by dissolving sodium (700 mg) and dry methanol (4 ml), was added dry DMF (2 ml) and heated under reflux followed by the addition of copper(I) bromide (114 mg, 0.79 mmol). Heating was continued for an additional 30 min and to the suspension was added dropwise a solution of the olefin **5** (202 mg, 0.78 mmol) in dry DMF (4 ml). The resulting mixture was heated under reflux for 18 h. The reaction was cooled, filtered, diluted with water and extracted with $CHCl_3$.The organic extract was washed with a saturated solution of $NaHCO_3$, brine, dried and evaporated to afford an oil which was chromatographed (hexane:Et_2O 9:1) to obtain α-asarone **6** (158 mg, 97%), R_f 0.21 (hexane:Et_2O 9:1), as crystalline white solid, mp 43–44°C (from exane) (*lit.*[5,13] 44–45°C); IR(cm^{-1}): 3036, 2997 and 1609; MS (*m/z*): 209 (M^{+1}), 178 (M^{+1} –OMe); δ 6.92 (s, 1H) (H at C-6), 6.63 (dq, 1H, $J = 1.7$ Hz and

$J = 15.9$ Hz) (H at 1′), 6.46 (s, 1H) (H at C-3), 6.08 (dq, 1H, $J = 6.6$ Hz and $J = 15.8$ Hz) (H at C-2′), 3.86 (s, 1H), 3.84 (s, 1H), 3.80 (s, 3H) (OMe at C-2, C-4 and C-5), 1.87 (dd, 3H, $J = 1.74$ Hz and $J = 6.63$ Hz) (H at C-3′); ^{13}C NMR: δ 150.69 (C-2), 148.78 (C-4), 143.43 (C-5), 125.07 (C-2′), 124.35 (C-1′), 119.11 (C-1), 109.92 (C-6), 98.09 (C-3), 56.74 (OMe), 56.51 (OMe), 56.13 (C-2), 18.76 (C-3′).

Anal. Calcd for C_{12} H_{16} O_3: C, 69.21; H, 7.74. Found: C, 69.33; H, 7.82.

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