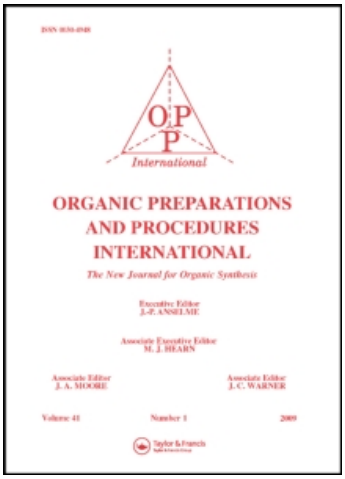



**Organic Preparations and Procedures International**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

# AN EFFICIENT SYNTHESIS OF α-ASARONE

Francisco Díaz[a]; Leticia Contreras[a]; Rosa Flores[a]; Joaquín Tamariz[a]; Fernando Labarrios[a]; Germán Chamorro[b]; Héber Muñoz[a]
[a] Department of Chemistry, Escuela Nacional de Ciencias Biológicas, I.P.N. Prol. Carpio y Plan de Ayala, México, DF, Mexico [b] Department of Pharmacology, Escuela Nacional de Ciencias Biológicas, I.P.N. Prol. Carpio y Plan de Ayala, México, DF, Mexico

**To cite this Article** Díaz, Francisco , Contreras, Leticia , Flores, Rosa , Tamariz, Joaquín , Labarrios, Fernando , Chamorro, Germán and Muñoz, Héber(1991) 'AN EFFICIENT SYNTHESIS OF α-ASARONE', Organic Preparations and Procedures International, 23: 2, 133 — 138
**To link to this Article: DOI:** 10.1080/00304949109458299
**URL:** http://dx.doi.org/10.1080/00304949109458299

ORGANIC PREPARATIONS AND PROCEDURES INT., 23 ( 2), 133-138 (1991)

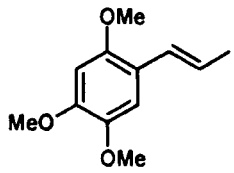
# AN EFFICIENT SYNTHESIS OF α-ASARONE

Francisco Díaz,[a] Leticia Contreras,[a] Rosa Flores,[a] Joaquín Tamariz,[a] Fernando Labarrios,[a] Germán Chamorro[b] and Héber Muñoz*[a]

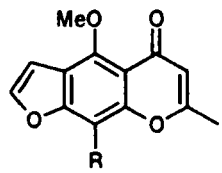
[a]Department of Chemistry and [b]Department of Pharmacology, Escuela Nacional de Ciencias Biológicas, I.P.N. Prol. Carpio y Plan de Ayala Apartado Postal 23175, C.P. 16000 México, D.F., MEXICO



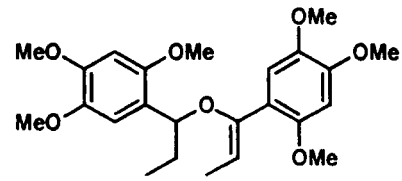
Much effort has been recently devoted to development of drugs which lower blood cholesterol level,[1] recognized as a predictor of risk of cardiovascular disease, particularly atherosclerosis.[2] Recently, Chamorro and his group[3] reported the hypocholesterolemic and cholelytiasic activity of α-asarone (**1**). On this basis and considering its structural analogy with khellin (**2a**) and visnagin (**2b**), two members of furochromones isolated from *Ammi visnaga L.* which have been found to possess desirable lipid-altering activity,[4] we decided to continue further pharmacologic studies. The scarcity of natural α-asarone (from *Guatteria gaumeri*, found in Yucatán, México) persuaded us to attempt its synthesis.




**1**



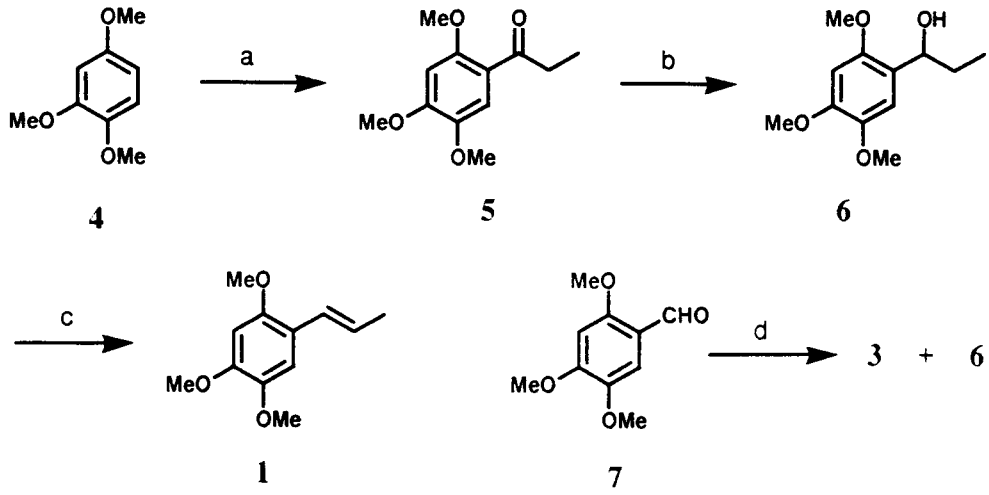

**2a**, R = OMe
**2b**, R = H




**3**

The difficulties encountered with a number of reported approaches,[5] led us to base our synthesis on an acylation method described by Dominguez *et al.*[6] 1,2,4-Trimethoxybenzene (**4**),[7] when heated with propionic anhydride in the presence of catalytic amounts of iodine produced more than 85% yield of 2,4,5-trimethoxypropiophenone (**5**) (Scheme). In contrast, propionylation

using strong acidic catalyst[8] led at best to 20-25% yield of the desired product and very tedious purification procedures were required.




[a]Propionic anhydride, $I_2$; [b]$NaBH_4$, EtOH;
[c]$Ac_2O$, AcONa, reflux; [d]EtMgI, ether



Reduction of phenone **5** with sodium borohydride in ethanol gave a quantitative yield of the corresponding alcohol **6**, which proved difficult to dehydrate employing *p*-toluenesulfonic acid in toluene,[9a] thionyl choride with or without pyridine,[9b] triphenylphosphine in carbon tetrachloride,[9c] aluminum oxide,[5g] or phosphorus oxychloride.[5f] The desired α-asarone (**1**) was finally obtained by treatment of **6** with acetic anhydride and sodium acetate under reflux for several hours in nearly quantitative yield (Scheme).

Preparation of **6** as a non-isolated intermediate during the synthesis of α-asarone has also been described by Sharma and Dandiya[5f] by reaction of asaraldehyde (**7**) and ethylmagnesium iodide. In our hands this procedure gave only poor results (30% isolated yield) even with an excess of the Grignard reagent;[10] after acidic treatment of the crude reaction mixture, we isolated a second solid product, **3**, having chromatographic properties very close to **1** but with different spectral characteristics. The IR spectrum of solid **3** does not show the characteristic signal for the benzylic hydroxide function of compound **6**. Other bands correspond to a 1,2,4,5-tetrasubstituted aromatic pattern (860 $cm^{-1}$) and a trisubstituted double bond (835 $cm^{-1}$). Its $^1H$ NMR

spectrum shows signals at δ 0.92 (t, 3H) and 1.67 (br s, 3H) corresponding to two methyl groups, attached to a methylene and to a double bond respectively. Besides, integration gives 18 protons assigned to six aromatic methoxy groups and one methine hydrogen between δ 3.7 and 4.0 ppm. Others signals are consistent with four aromatic protons, possibly in a relative *para* position, and one vinylic proton. The $^{13}C$ NMR spectrum confirms the existence of the methyl attached to a methylene group at 12.5 ppm (q, $^{1}J_{C,H}$ = 125.0 Hz) and a second vinylic methyl at 17.4 ppm (q, $^{1}J_{C,H}$ = 122.1 Hz). There are also six aromatic methoxy groups between 56.1 and 56.9 ppm and a total of twenty four carbon signals. These data, the elemental analysis and the mass spectrum [m/e 431 ($M^{+}$- 1, 0.2)] have allowed us to tentatively assign structure **3** for this coumpound, which could be formed through a Cannizzaro-type reaction between the magnesium salt of **6** and asaraldehyde (**7**) to give ketone **5**, necessary to the formation of **3**. However, we are continuing experiments in order to confirm this structure, test the mechanism and determine if this type of reaction is general for polymethoxy substituted aromatic aldehydes.

The pharmacological results of the synthetic α-asarone (**1**) will be published elsewhere.



## EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover melting-point apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer 599B spectrophotometer. $^{1}H$ NMR spectra were recorded on a Varian EM-390 spectrometer. $^{13}C$ NMR spectra were recorded on a Jeol FX-90Q (22.49 MHz) spectrometer. The mass spectra (MS) were taken on a Hewlett-Packard 5985-A spectrometer. Starting materials and reagents were purchased from Aldrich Chemical Co. and were used without any further purification. Anhydrous ethyl ether (J. T. Baker) was always recently distilled from sodium.

**2,4,5-Trimethoxypropiophenone** (**5**). To a solution of 168.0 g (1.0 mol) of 1,2,4-trimethoxybenzene (**4**) in 130.0 g (128 mL, 1.0 mol) of propionic anhydride, was added 2.54 g ( 0.01 mol) of iodine and the mixture was heated on a water bath (70° ± 3°) for 6 h. After cooling to room temperature, the product was collected and recrystallized from hexane to yield **5** (212.8 g, 95%) as a white crystalline solid, mp. 105-106° (Rf = 0.5, Si-Gel, hexane/EtOAc, 8:2). IR(KBr): 2960-2930, 1645, 1600, 1510, 1290, 1240, 850 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$): δ 1.13 (t, J = 7.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.02 (q, J = 7.0 Hz, 2H, $CH_3\underline{CH_2}$), 3.88 (s, 3H, -OMe), 3.91 (s, 3H, -OMe), 3.97 (s, 3H, -

OMe), 6.51 (s, 1H, ArH), 7.45 (s, 1H, ArH). MS(70 eV): 224 ($M^+$, 16), 195 (100), 180 (6), 165 (2), 137 (8).
Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.12; H, 7.25

**1-(2,4,5-Trimethoxyphenyl)propan-1-ol (6).** To a solution of 112.0 g (0.5 mol) of propiophenone **5** in approximately 2.0 L of anhydrous ethyl alcohol was carefully added 18.9 g (0.5 mol) of powdered sodium borohydride; the mixture was stirred at RT for 1 h. The solution obtained was evaporated to dryness. The crude solid was washed with water (3 x 200 mL), and the residual solid collected and recrystallized from hexane to give a quantitative yield of **6** as a white solid, mp. 69-70°, lit.[5g] 69-70° (Rf = 0.33, Si-Gel, hexane/EtOAc, 8:2). IR(KBr): 3400, 2970, 1520, 1240, 1060 $cm^{-1}$. $^1H$ NMR($CDCl_3$): δ 0.95 (t, J = 7.5 Hz, 3H, $\underline{CH_3}CH_2$), 1.72 (m, 2H,.$CH_3\underline{CH_2}$), 3.86 (s, 3H, -OMe), 3.93 (s, 3H, -OMe), 3.96 (s, 3H, -OMe), 4.38 (t, J = 6.5 Hz, 1H, -$\underline{CH}$(OH)$CH_2CH_3$), 6.56 (s, 1H, ArH), 6.93 (s, 1H, ArH). MS(70 eV): 226 ($M^+$, 14), 208 (18), 197 (100), 167 (21), 138 (33).
Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.69; H, 8.01. Found: C, 63.48; H, 8.12

**Grignard Reaction of Asaraldehyde (7).** Five mL (5.0 mmol) of a 1.0 M solution of ethylmagnesium iodide was prepared in anhydrous ether from magnesium powder (223 mg, 5.5 mmol), freshly distilled ethyl iodide (780 mg, 5.0 mmol) and a small crystal of iodine. To this Grignard reagent, a saturated solution of **7** (980 mg, 5.0 mmol) in anhydrous ether (~2.0 mL) was added dropwise mantaining a gentle reflux, which was maintained an additional for 30 min; the reaction was then quenched with a 5% methanolic solution of sulfuric acid (5.0 mL). The ethereal solution was washed with water, dried and evaporated to dryness. The crude oil was chromatographed on a Si-Gel column (hexane/EtOAc, 9:1) to give first 450 mg (20% yield) of **3** as a white solid product, mp. 93-94° (Rf = 0.53, Si-Gel, hexane/EtOAc, 8:2) and then 340 mg (30%) of the desired alcohol **6**, mp. 69-70°. Spectral data of **3** are as follows: IR(KBr): 3000-2840, 1600, 1505, 1465, 1400, 1220, 1055, 860, 835 $cm^{-1}$. $^1H$ NMR($CDCl_3$): δ 0.92 (t, J = 7.5 Hz, 3H, $\underline{CH_3}CH_2$), 1.67 (br s, 3H, $\underline{CH_3}CH$=), 1.6-2.15 (m, 2H, $CH_3\underline{CH_2}$), 3.7-4.0 (m, 19H, 6-OMe, $\underline{CH}$(OR)$CH_2CH_3$), 6.46 (br s, 1H, Me$\underline{CH}$=), 6.65 (br s, 2H, ArH, Ar$\underline{CH}$=), 6.75 (s, 1H, ArH), 6.85 (s, 1H, ArH). $^{13}C$ NMR($CDCl_3$): 152.2 (m), 151.7 (m), 148.2 (m), 147.7 (m), 143.2 (m), 142.6 (m), 139.9 (m), 124.5 (m), 119.8 (d, $^3J_{C,H}$= 4.9 Hz), 119.8 (d, $^1J_{C,H}$= 154.3 Hz), 114.7 (d, $^1J_{C,H}$= 157.2 Hz),

112.0 (d, $^1J_{C,H}$= 154.3 Hz, 2C), 98.2 (d, $^1J_{C,H}$= 154.2 Hz), 56.9 (q, $^1J_{C,H}$= 143.5 Hz), 56.7 (q, $^1J_{C,H}$= 143.5 Hz), 56.6 (d, $^1J_{C,H}$= 144.5 Hz, 2C), 56.1 (q, $^1J_{C,H}$= 145.5 Hz, 2C), 47.0 (d, $^1J_{C,H}$= 128.1 Hz), 26.4 (t, $^1J_{C,H}$= 123.1 Hz), 12.5 (q, $^1J_{C,H}$= 125.0 Hz). MS(70 eV): 431 ($M^+$-1, 0.2), 417 (11), 416 (39), 221 (18), 220 (12), 219 (100).
Anal. Calcd. for $C_{24}H_{32}O_7$: C, 66.66; H, 7.40. Found: C, 66.80; H, 7.35

**α-Asarone (1).** Alcohol **6** (113.0 g, 0.5 mol) and 20.5 g (0.25 mol) of anhydrous sodium acetate were dissolved in 450 mL of acetic anhydride and heated under reflux for 3 h. The reaction mixture was evaporated to dryness under vacuum and the oily residue was redissolved in warm hexane, filtered and cooled to give a solid, which was recrystallized from hexane. The total amount recovered was 93.6-98.0 (90-95%) of **1** as a white crystalline solid, mp. 62-63°, lit.[5g] 62-63°. IR(KBr): 3020, 2940, 1600, 1520, 1470, 1225, 1060, 900 $cm^{-1}$. $^1H$ NMR($CDCl_3$): δ 1.86 (dd, J = 1.5, 6.5 Hz, 3H, $CH_3CH$=), 3.83 (s, 3H, -OMe), 3.86 (s, 3H, -OMe), 3.90 (s, 3H, -OMe), 5.85-6.30 (m, 1H, $CH_3CH$=), 6.52 (s, 1H, ArH), 6.65 (d, J = 16.5 Hz, ArCH=), 6.93 (s, 1H, ArH). MS(70 eV): 208 ($M^+$, 17), 193 (6), 165 (7), 40 (100).

Acknowledgments.- We thank Dr. H. Salgado for reviewing the manuscript. We also thank Miss. A. Acosta, Miss. S. Mendoza, Dra. R. Contreras and Dr. H. Gómez for determining some of the spectra. This work was supported in part by COSNET (grant number 869767), México.



## REFERENCES

1. See for example: M. N. Cayen, *Progr. Drug Metab.*, **7**, 173 (1983) and references cited therein; C. R. Sirtori and L.Tosi, *Atheroscler. Rev.*, **3**, 183 (1978); V. G. Vries, S. A. Schaffer, E. E. Largis, M. D. Dutia, C. H. Wang, J. D. Bloom and A. S. Katocks, Jr., *J. Med. Chem.*, **26**, 1411 (1983); P. J. Woorstad, J. M. Chapman, G. H. Cocolas, S. D. Wyrich and H. I. Hall, *ibid.*, **28**, 1591 (1985); T. Moriya, M. Seki, S. Takebe, K. Matsumoto, K. Tokadrina, T. Mori, A. Odawara and S. Takayama, *ibid.*, **31**, 1197 (1988) and references cited therein.
2. A. M. Gotto, Jr., *Atheroscler. Rev.*, **4**, 17 (1979).
3. C. Gómez, G. Chamorro, M. A. Chávez, G. Martínez, M. Salazar and N. Pages, *Plantes Med. et Phytother.*, XXI, 279 (1987).

4. R. I. Levy, *Arteriosclerosis* (Dallas) **1**, 313 (1981); R. B. Gammill, C. E. Day and P. E. Schurs, *J. Med. Chem.*, **26**, 1672 (1983); A. J. Yamashita, *J. Am. Chem. Soc.*, **107**, 5823 (1985).
5. a) K. Gatterman and J. Eggers, *Ber.*, **32**, 289 (1889). b) R. Bert, *Compt. Rend.*, **213**, 879 (1941). c) C. N. Rao, T. R. Seshadri and T. R. Thirivengadam, *Proc. Indian Acad. Sci.*, **30A**, 114 (1949). d) T. R. Seshadri, F. A. So and T. R. Thirivengadam, *ibid.*, **32A**, 110 (1950). e) F. Sánchez-Viesca, *Ciencia* (Mex.) **26**, 113 (1966). f) P. K. Sharma and P. C. Dandiya, *Indian J. Appl. Chem.*, **32**, 236 (1969). g) E. A. Shirokova, G. M. Segal and J. V. Torgov, *Bioorg. Khim.*, **11**, 270 (1985).
6. X. A. Dominguez, C. Gómez, J. Slim, D. Griesecke and B. E. Ureta, *J. Am. Chem. Soc.*, **76**, 5150 (1954).
7. G. Bargellino and E. Martegiani, *Gazz. Chim. Ital.*, **41**(II), 448 (1911).
8. H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.*, **68**, 2639 (1946); H. D. Hartough and A. I. Kosak, *ibid.*, **69**, 1012 (1947); H. D. Hartough and A. I. Kosak, *ibid.*, **69**, 3098 (1947); S. R. Sandler and W. Karo ed. "Organic Functional Group Preparations", Academic Press, New York, 1968, vol. 1, pp. 176-186; see also ref. 5g.
9. a) W. S. Johnson and V. J. Bauer, *J. Am. Chem. Soc.*, **83**, 606 (1961). b) J. S. Lomas, *Tetrahedron Lett.*, 599 (1971). c) E. J. Snyder, *J. Org. Chem.*, **37**, 1466 (1972).
10. We performed several experiments to determine the effect of increasing the amount of the Grignard reagent to 6:1 ratio, without any improvement in the yield of alcohol **6**; in every case, **3** was isolated as a by-product even when air was eliminated from the reaction medium in order to avoid possible oxidation . Similar results were obtained with commercial 2.0 M ethylmagnesium chloride (Aldrich).

**(Received May 22, 1990; in revised form December 17, 1990)**