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CONVENIENT SYNTHESIS OF MAGNOSHININ, AN ANTI-INFLAMMATORY NEOLIGNAN

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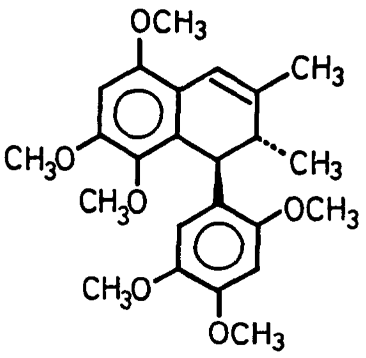
Abstract: Magnoshinin (1) was conveniently synthesized from E-asarone (5) under photochemical conditions. Photochemical conversion of cyclobutane type dimers was also described.

Previously, we reported the isolation and characterization of magnoshinin (1) and magnosalin (2), new neolignans from buds of *Magnolia salicifolia* MAXIM.[1] Recently, both of 1 and 2 were found to show inhibitory effects on adjuvant-induced inflammation in mice.[2] Of these compounds, 1 is particularly interesting, since the anti-inflammatory effect of 1 is fairly strong, being nearly half of that of hydrocortisone acetate when administered orally. We now report a convenient synthesis of 1 utilizing photochemical dimerization of E-asarone (5).[3] A typical synthetic operation is described below.

A degased solution of 5 (0.5 mmol) in acetonitrile (10 ml) containing pyromellitic acid (1 mmol) as an electron acceptor[4] was irradiated with a 300 W high-pressure mercury lamp for 70 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC on Merck Kieselgel 60 PF_{254} with AcOEt-benzene (1:9) to give dimeric products, magnoshinin (1)[5] and magnosalin (2)[6] in 14 and 6 % yields, respectively (Table I). Identities of 1 and 2 were confirmed by comparisons of their spectral data with those of authentic samples. Results employing other electron acceptors are shown in Table I.



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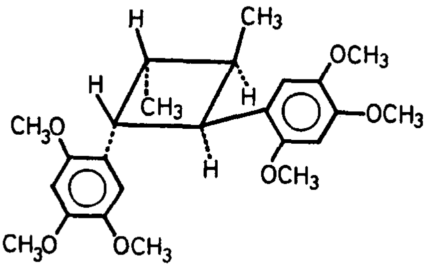

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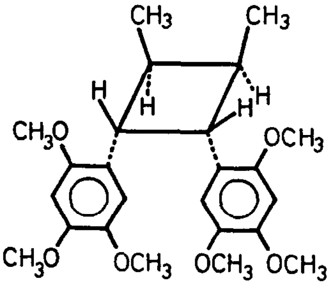

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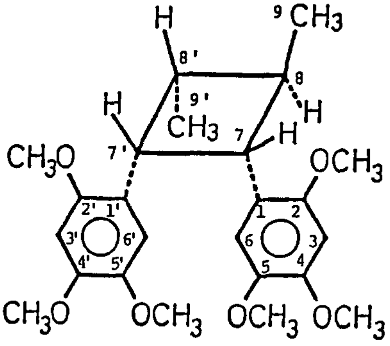
Table I. Photodimerization of E-Asarone

Entry	Electron Acceptor	Yields[a] of Dimeric Products (%)		Recovered Asarone[b] (%)
		1	2	
1	pyromellitic acid	14	6	6.7
2	phthalic acid	13	5	23.1
3	terephthalic acid	5	7	5.3
4	trimesic acid	5	8	22.7

Entries 1-4 were performed under the same condition except for electron acceptor.

a) Isolated yield.

b) This was found to be a mixture of E- and Z-asarone (approximately 1:1) by ^{1}H-NMR analyses.



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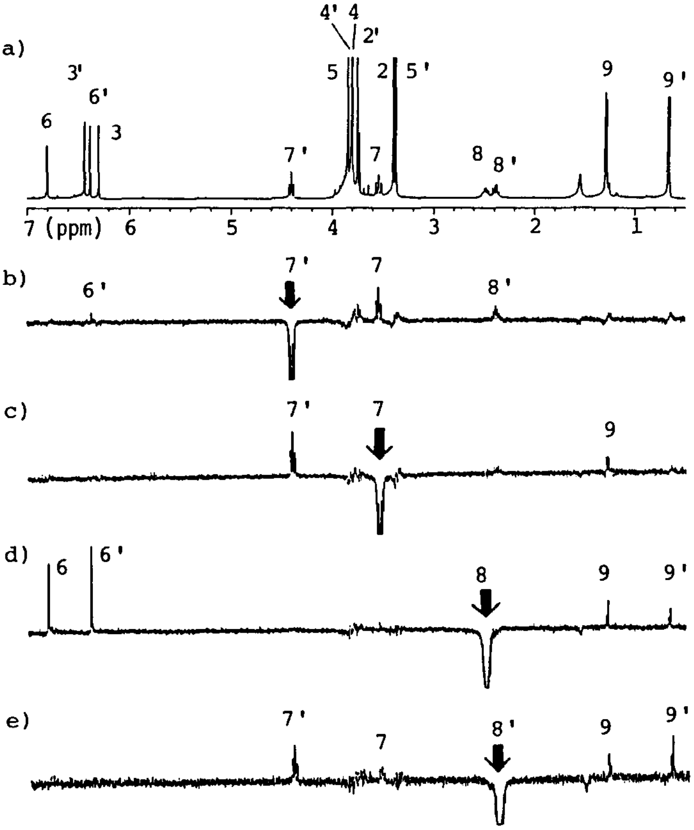


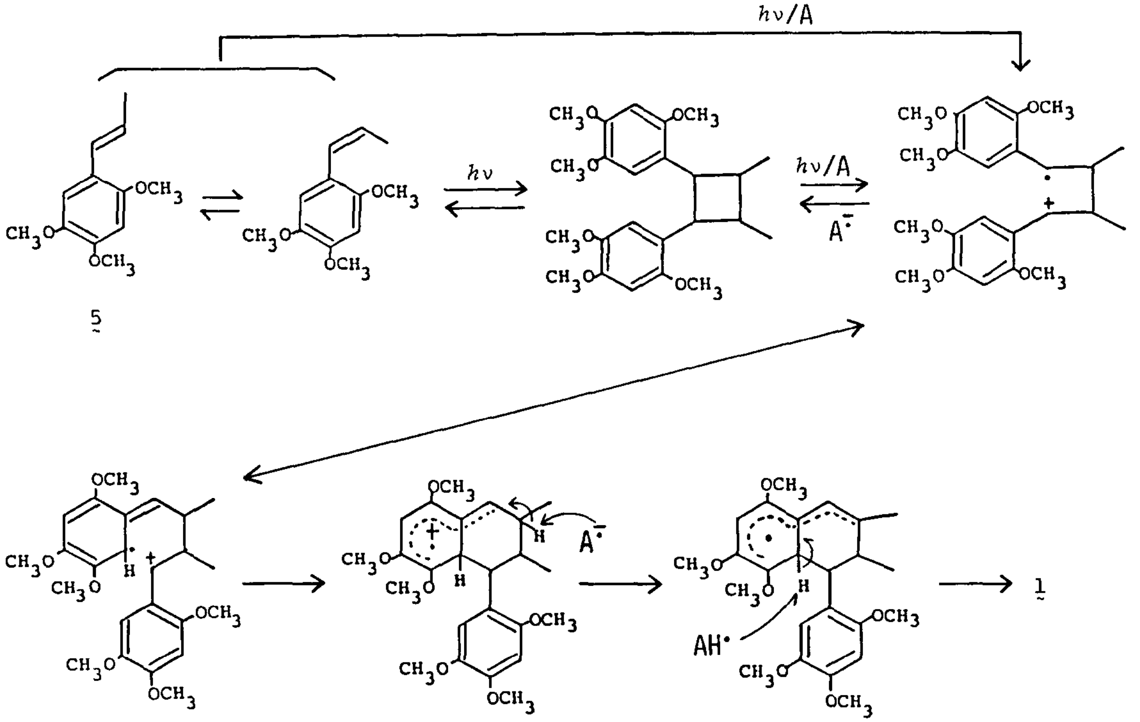
Fig. 1. Normal ^{1}H-NMR and NOE Difference Spectra of 4 in $CDCl_3$ (a - e)

On the other hand, irradiation of a solution of 5 in acetonitrile in the presence of phenanthrene (for 110 h) yielded four dimeric products, magnoshinin (1), magnosalin (2), heterotropan (3),[3,7] and an unknown compound (4)[8] in 2.3, 12.6, 6.6 and 2.0 % yields, respectively, accompanied with a 69 % recovery of a mixture of E- and Z-asarone.

Compound 4, mp 109 - 110°C, had the molecular formula $C_{24}H_{32}O_6$ and its MS[8] was very similar to those of 2 and 3. The ^{1}H-NMR spectrum[8] of 4 showed signals due to two trimethoxyphenyl, two benzylic methine and two $CH-CH_3$ groups, suggesting that it may be a cyclobutane-type dimer with an unsymmetrical structure. Eventually the structure of this product was determined to be 4 based on the detailed NMR studies, especially on the NOE experiments. As shown in Fig. 1, irradiation at the 7'-H and 7-H caused the increase of signal intensity of 6'-, 7- and 8'-protons and 7'- and 9-protons, respectively, and irradiation at the 8-H and 8'-H enhanced the signal intensity of 6-, 6'-, 9- and 9'-protons and 7'-, 7-, 9'- and 9-protons, respectively (Fig. 1. a - e).

In this dimerization, it was observed that the cyclobutane-type products (2, 3 and 4) were formed in early stage of the reaction, while 1 was produced in later stage and accumulated gradually in the reaction mixture. Therefore, these cyclobutane dimers (2, 3 and 4) would be intermediates for the formation of 1. This was verified by the photoreaction of 2 in the presence of phthalic acid, which gave magnoshinin (1) in low yield along with asarone. Similarly heterotropan (3) and 4 produced 1. A possible mechanism for this reaction is shown in Chart 1.

Our present results provided the first example of photochemical synthesis of aryldihydronaphtharene type dimer.



(A: electron acceptor)

Chart 1

References and Notes

1) T. Kikuchi, S. Kadota, K. Yanada, K. Tanaka, K. Watanabe, M. Yoshizaki. T. Yokoi and T. Shingu, *Chem. Pharm. Bull.*, 31, 1112 (1983).
2) M. Kimura, J. Suzuki, T. Yamada, M. Yoshizaki, T. Kikuchi, S. Kadota and S. Matsuda, *Planta Med.*, 291 (1985).
3) Yamamura et al. have reported that photodimerization of E-asarone in hexane solution produced heterotropan (3) as the sole photodimer. See S. Yamamura, M. Niwa, M. Nonoyama and Y. Terada, *Tetrahedron Lett.*, 4891 (1978).
4) Initial attempts at the photochemical dimerization of 5 in the presence of usual electron acceptors, such as m-dicyanobenzene and methyl p-cyanobenzoate, were unsatisfactory. As to the photodimerization leading to the tetralin type products, see M. Yamamoto, H. Yoshikawa, T. Gotoh and Y. Nishijima, *Bull. Chem. Soc. Jpn.*, 56, 2531 (1983), and references cited therein.
5) 1: colorless needles (from isopropyl ether), mp 107 - 109°C, MS m/z: 414 (M^+), 399, 383, 368, 246 and 231; ^{1}H-NMR ($CDCl_3$) δ: 1.053 (3H, d, J = 7.0 Hz, sec-CH_3), 1.727 (3H, d, J = 1.5 Hz, =C-CH_3), 2.212 (1H, qd, J = 7.0, 1.0 Hz, -C$\underline{H}$-CH_3), 3.376, 3.551, 3.838, 3.849, 3.862, 3.911 (each 3H, s, OCH_3 x 6), 6.256, 6.418, 6.514 (each 1H, s, aromatic H) and 6.484 (1H, q, J = 1.5 Hz, -C$\underline{H}$=C-).
6) 2: colorless needles (from isopropyl ether), mp 96 - 98°C, MS m/z: 416 (M^+), 360, 208 and 193; ^{1}H-NMR ($CDCl_3$) δ: 1.183 (6H, diffused d, J = 6.0 Hz, sec-CH_3 x 2), 1.761 (2H, m, C$\underline{H}$-CH_3), 3.259 (2H, m, C$\underline{H}$-Ar), 3.688, 3.850, 3.866 (each 6H, s, OCH_3 x 6), 6.460 and 6.943 (each 2H, s, aromatic H).
7) 3: colorless oil, MS m/z: 416 (M^+), 360, 208 and 193; ^{1}H-NMR (C_6D_6) δ: 1.188 (6H, diffused d, J = 6.5 Hz, sec-CH_3 x 2), 2.791 (2H, m, C$\underline{H}$-CH_3), 3.274, 3.382, 3.520 (each 6H, s, OCH_3 x 6), 4.180 (2H, m, C$\underline{H}$-Ar), 6.215 and 6.794 (each 2H, s, aromatic H).
8) 4: colorless plates (from isopropyl ether), mp 109 - 110°C, MS m/z: 416 (M^+), 360 and 208; ^{1}H-NMR ($CDCl_3$) δ: 0.666 (3H, d, J = 7.0 Hz, 9'-H), 1.288 (3H, d, J = 7.0 Hz, 9-H), 2.387 (1H, m, 8'-H), 2.492 (1H, m, 8-H), 3.369 (3H, s, 5'-OCH_3), 3.393 (3H, s, 2-OCH_3), 3.545 (1H, t, J = 9.0 Hz, 7-H), 3.796 (3H, s, 4-OCH_3), 3.746 (3H, s, 2'-OCH_3), 3.803 (3H, s, 4'-OCH_3), 3.838 (3H, s, 5-OCH_3), 4.402 (1H, t, J = 9.0 Hz, 7'-H), 6.300 (1H, s, 3-H), 6.385 (1H, s, 6'-H), 6.439, (1H, s, 3'-H) and 6.803 (1H, s, 6-H); ^{13}C-NMR ($CDCl_3$) δ: 14.97 (9'-C), 20.03 (9-C), 39.19 (7'-C), 39.50 (8'-C), 41.17 (8-C), 44.11 (7-C), 55.92 (2- and 5'-O$\underline{C}H_3$), 56.09 (4'-O$\underline{C}H_3$), 56.31 (4-O$\underline{C}H_3$), 57.18 (2'- and 5-O$\underline{C}H_3$), 98.14 (3'-C), 98.32 (3-C), 111.77 (6-C), 113.65 (6'-C), 121.04 (1'-C), 122.58 (1-C), 141.80 (5'-C), 143.13 (5-C), 146.52 (4'-C), 147.97 (4-C), 152.02 (2-C) and 152.34 (2'-C). Assignments of ^{1}H- and ^{13}C-NMR signals were accomplished by means of the ^{1}H-decoupling experiments and the ^{1}H-^{13}C and long-range ^{1}H-^{13}C COSY methods.

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