Oxidation of *o*-Methoxyphenols with a Hypervalent Iodine Reagent: Improved Synthesis of Asatone and Demethoxyasatone

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Oxidation of the 2-methoxyphenols **1c–f** with phenyliodonium(III) diacetate (PIDA) in methanol resulted in the formation of the cyclohexa-2,4-dienones **4c–f**, which dimerized spontaneously to a single product (**5c–f**) in each case. Using this method the synthesis of asatone (**5a**) and its demethoxy analogue (**5b**) was also accomplished starting from the readily available phenol derivatives **1a** and **1b**, respectively.

Introduction

In the last two decades hypervalent iodine reagents, such as phenyliodonium(III) diacetate (PIDA) and phenyliodonium(III) bis(trifluoroacetate) (PIFA) have become very popular in organic synthesis owing to their versatility and lack of environmental effects.[1][2] Recently, the use of hypervalent iodine reagents has also gained popularity in the field of flavonoid chemistry.[3−9] These reagents have also been found to be very efficient oxidants for the preparation of 4-alkyl-4-methoxy- and 4,4-dimethoxycyclohexa-2,5-dienones from the corresponding *p*-substituted phenols in methanol.[10−12] Based on the dearomatization of 2,3-isopropylidenepyrogallol with different phenyliodonium(III) reagents, which leads to 6,6-disubstituted-cyclohexa-2,4-dienones, we have recently demonstrated that these processes involve phenoxenium ion intermediates.[13]

In a continuation of this work we intended to study the scope and limitations of the oxidation of 2-alkoxyphenol derivatives in order to elaborate a simple route for the synthesis of neolignanes such as asatone (**5a**) and its 5-demethoxy derivative (**5b**), which possess antileukemic activity (Scheme 1).[14] Therefore, as models, we oxidized guajacol (**1c**) and dimethylacetal of the vanillins **1d−f** with PIDA in methanol, since authentic samples of the 1,4,4a,8a-tetrahydro-1,4-ethanonaphthalene-6,10(4H)-dione derivatives **5c−f** (formed by the spontaneous dimerization of the expected dearomatization products **4c−f**) were in our hands as we have already reported their preparation from the corresponding phenols **1c−f** with thallium(III) nitrate (TTN) in methanol.[15]

Results and Discussion

Oxidation of guajacol (**1c**) with one equivalent of PIDA in methanol takes place very smoothly at room temperature to give, quantitatively, a single product, as evidenced by TLC monitoring. This product could not be isolated as, even under mild conditions, it transformed rapidly into another substance of m.p. 181−183°C (isolated in 76% yield). This compound turned out to be **5c** (TLC, NMR spectroscopy), which is also available in good yield (59%) by oxidation with TTN in methanol. Our product was identical with a compound obtained by Andersson and Berntsson[16] by the oxidation of **1c** with periodic acid in methanol. Oxidation of **1d−f** (prepared by transacetalization of the corresponding vanillin with trimethyl orthoformate) with PIDA in methanol at room temperature also resulted in the smooth formation of **5d−f** via the intermediates **4d−f**. Yields of the crystalline dimers **5d−f** were almost the same (**5d**: 46%, **5e**: 22%, **5f**: 30%) as with TTN oxidations.[15] It should be noted that, besides **5d−f**, no other defined product could be detected in the reaction mixture by TLC. Our findings clearly indicate that the phenoxenium ions **2d−f** are formed from the reaction of **1d−f** with PIDA in methanol, are stabilized in their mesomeric form **3d−f**, and then undergo a nucleophilic attack by methanol directed in each case at the carbon atom carrying the methoxy group, as shown in Scheme 1. The fact that on oxidation of **1f** no 2,5-cyclohexadien-1-one derivative was formed at all, but exclusively **4f**, which rapidly dimerized to **5f**, prompted us to attempt the synthesis of asatone (**5a**) by oxidation of **1a** with PIDA in methanol.

Asatone was isolated from *Asarum taitonense* Hayata by Yamamura et al.[17] in 1972, and structure **6** was proposed for it based mainly on ^{1}H NMR spectroscopic data. This structure was later revised[18] to **5a** on the basis of a chemical correlation with isoasatone (**7**) isolated from the same plant (Scheme 2), the structure of which had been elucidated by X-ray crystallography.[19]

Furthermore, it was shown that asatone (**5a**) possessed remarkable antileukemic activity in mice.[14] Yamamura and co-workers[20][21] also accomplished the biomimetic synthesis of asatone in very poor yield (1−4%) by anodic oxidation of **1a** and they suggested that this transformation may have occurred via the orthoquinone monoacetal **4a**.

As shown by TLC monitoring, the oxidation of **1a** with PIDA in methanol proceeded very smoothly at room tem-

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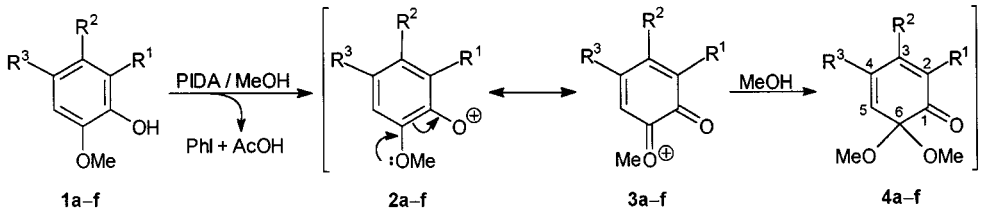
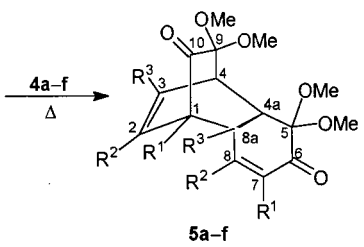
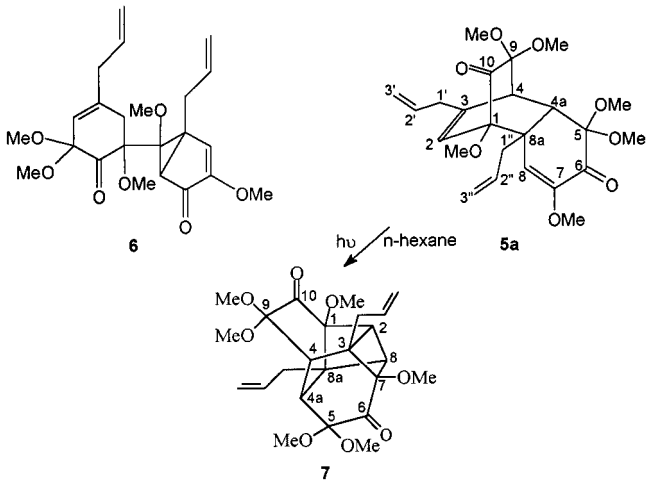




1–5	R^1	R^2	R^3
a	OMe	H	allyl
b	H	H	allyl
c	H	H	H
d	$CH(OMe)_2$	H	H
e	H	$CH(OMe)_2$	H
f	H	H	$CH(OMe)_2$

Scheme 1. Synthetic route to asatone (**5a**) and related compounds (**5b**−**f**)



Scheme 2. Chemical correlation of asatone (**5a**) with isoasatone (**7**)

perature and gave a single product (in all probability **4a**). The latter, however, could not be isolated in pure form, because it rapidly became contaminated by dimer **5a** (see Experimental Section). Dimerization by a Diels−Alder reaction proceeded spontaneously even at room temperature and only asatone (**5a**) could be detected by TLC in the syrupy crude product. This crystallized on treatment with a mixture of *n*-hexane and benzene and the product (m.p. 101−102°C, 22%) was found to be identical with the natural product (mixed m.p., ^{1}H and ^{13}C NMR spectroscopy, see Table 1.). Full ^{1}H- and ^{13}C-NMR spectroscopic assignments were obtained from ^{1}H, ^{1}H-COSY, gradient-enhanced ^{1}H, ^{13}C-HSQC and HMBC NMR experiments (Figure 1). The small value of $^3J_{H\text{-}4,H\text{-}4a}$ (Table 1) is compatible with the *gauche* relationship of the respective hydrogens in the cycloadducts. Furthermore, 7-OMe gives rise to a strong NOE cross peak to H-2 in the 2D NOESY map of **4a**, indicative of the *endo* stereochemistry of the product.

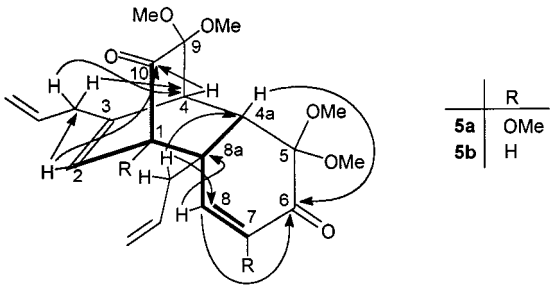


Figure 1. Important HMBC correlations for **5a** and **5b**

In full accordance with the results of Mitchell and Russel,[12] the oxidation of eugenol **1b** with PIDA in methanol also gave a single product **4b** (by TLC), dimerization of which resulted in 5-demethoxyasatone **(5b)** in 41% yield. As expected, the dimerization of **4b** to **5b** proceeded with the same stereo- and regioselectivity as found for the monomers **4c**−**f**. ^{1}H and ^{13}C NMR spectroscopic data for **5b** are given in Table 1.

It should be noted that Yamamura and co-workers[20] also observed the different reactivity of eugenol (**1b**) and 2,6-dimethoxy-4-allylphenol (**1a**) under the conditions of anodic oxidation. Namely, oxidation of **1b** resulted in **5b** in much higher yield (22%) than that of **1a** (1%). This is in accordance with our own experience, that TTN oxidation of **1a** does not yield a detectable amount of asatone.

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Table 1. ^{1}H and ^{13}C NMR spectroscopic data for **5a** and **5b**

Atom no.	δ ^{1}H (ppm)		δ ^{13}C (ppm)	
	5a	**5b**	**5a**	**5b**
1	–	2.98	90.05	56.77
1-OMe	3.43	–	54.72	–
2	5.50	5.38	121.66	121.27
3	–	–	144.93	146.28
4	2.83	2.84	43.78	44.48
4a	2.85	2.80	44.42	45.44
5	–	–	93.14	94.61
5-OMe	3.37, 3.26	3.25, 3.35	50.10, 50.24	50.34, 50.17
6	–	–	188.66	193.37
7	–	6.26	150.48	150.48
7-OMe	3.55	–	55.55	–
8	5.33	5.91	116.52	127.01
8a	–	–	49.68	47.61
9	–	–	98.64	98.32
9-OMe	3.33, 3.02	3.01, 3.34	49.05, 50.22	49.90, 48.75
10	–	–	201.42	201.66
1′	2.79	2.73	38.92	38.87
1″	2.12, 2.70	2.28, 2.49	41.23	43.76
2′	5.62	5.60	133.37	133.59
2″	5.89	5.85	135.16	132.59
3′	5.08 5.05	5.00	118.23	117.77
3″	5.01 4.98	5.08 5.11	116.88	119.41

^{1}H Coupling constants (Hz)		
	5a	**5b**
$^3J_{1,2}$	–	6.6
$^3J_{4,4a}$	<1.5	1.5
$^3J_{7,8}$	–	10.5

Experimental Section

General: Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. NMR experiments were carried out on a Bruker Avance DRX 500 or AM-360 spectrometer in $CDCl_3$ (0.4 mL) at 298 K. Chemical shifts are referenced to tetramethylsilane (^{1}H, δ = 0) or to the residual solvent signal (^{13}C, δ = 77.00). Gradient enhanced COSY[22] and NOESY measurements (500 MHz) were performed with standard Bruker software. ^{13}C, ^{1}H correlations through one-bond vs. long-range couplings were obtained from sensitivity-enhanced[23] gradient HSQC[24] and gradient HMBC[25] experiments, respectively. Pre-coated silica gel plates (Kieselgel 60 F 2540 0.25 mm, Merck) were used for analytical TLC. For workup the solutions were dried ($MgSO_4$) and concentrated in vacuo. Yields are given for the isolated compounds after crystallization.

General Procedure for the Preparation of Dimethyl Acetals 1d–f: 7.51 mmol of the corresponding aldehyde was dissolved in a mixture of absolute methanol (8 mL) and methyl orthoformate (5 mL) in the presence of NH_4NO_3 (200 mg) and the reaction mixture refluxed for 1 h. It was then quenched with piperidine (0.2 mL), filtered and the solvent evaporated in vacuo. The residue was used directly in the oxidations.

General Procedure for the Oxidation of Phenols 1a–f: 7.4 mmol of the phenol was dissolved in absolute methanol (10 mL). A methanolic solution (35 mL) of PIDA (7.4 mmol, 2.38 g) was then added dropwise within 20 min. at room temperature. The progress of the reaction was monitored by TLC (toluene/acetone = 4:1). After 2 h the solution was filtered through basic aluminum oxide and the product eluted with methanol, purified by flash chromatography on silica gel and finally crystallized from a mixture of *n*-hexane and benzene (2:1).

4,4a-Dihydro-1,5,5,7,9,9-hexamethoxy-3,8a-bis(2-propenyl)-1,4-ethanonaphthalene-6,10(4*H*)-dione, Asatone (5a): M.p. 100–102°C; 365 mg (22%). M.p.[17] 101–102°C. ^{1}H- and ^{13}C-NMR spectroscopic data are given in Table 1.

1,4,4a,8a-Tetrahydro-5,5,9,9-tetramethoxy-3,8a-bis(2-propenyl)-1,4-ethanonaphthalene-6,10(4*H*)-dione, Demethoxyasatone (5b): M.p. 73–74°C; 588 mg (41%). M.p.[20] 77–78°C. ^{1}H- and ^{13}C-NMR spectroscopic data are given in Table 1.

1,4,4a,8a-Tetrahydro-5,5,9,9-tetramethoxy-1,4-ethanonaphthalene-6,10(4*H*)-dione (5c): M.p. 181–183°C (dec.); 866 mg (76%). M.p.[16] 191–193°C.

1,7-Bis(dimethoxymethyl)-1,4,4a,8a-tetrahydro-5,5,9,9-tetramethoxy-1,4-ethanonaphthalene-6,10(4*H*)-dione (5d): M.p. 134–136°C; 775 mg (46%). M.p.[15] 134–135°C.

2,8-Bis(dimethoxymethyl)-1,4,4a,8a-tetrahydro-5,5,9,9-tetramethoxy-1,4-ethanonanaphthalene-6,10(4*H*)-dione (5e): M.p. 128–129°C; 370 mg (22%). M.p.[15] 129–130°C.

3,8a-Bis(dimethoxymethyl)-1,4,4a,8a-tetrahydro-5,5,9,9-tetramethoxy-1,4-ethanonaphthalene-6,10(4*H*)-dione (5f): M.p. 97–100°C; 506 mg (30%). M.p.[15] 94–95°C.

[1] E. Varvoglis, *Tetrahedron* **1997**, *53*, 1179–1255.
[2] T. Kitamura, Y. Fujiwara, *Org. Prep. Proc.* **1997**, *29*, 409–458.
[3] R. M. Moriarty, O. Prakash, *J. Org. Chem.* **1984**, *50*, 151–153.
[4] O. Prakash, S. Pahuja, S. N. Sawhny, *Indian J. Chem. Sect. B.* **1991**, *30B*, 1023–1072.
[5] O. Prakash, S. Goyal, S. Pahuja, S. P. Shir, *Synth. Commun.* **1990**, *20*, 1409–1415.
[6] O. Prakash, S. Pahuja, M. P. Tanwar, *Indian J. Chem. Sect. B.* **1994**, *33B*, 272–273.
[7] Gy. Litkei, K. Gulácsi, S. Antus, G. Blaskó, *Liebigs Ann. Chem.* **1995**, 1711–1715.
[8] O. Prakash, M. P. Tanwar, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1168–1171.
[9] K. Gulácsi, Gy. Litkei, S. Antus, T. E. Gunda, *Tetrahedron* **1998**, *54*, 13867–13876.
[10] A. McKillop, L. McLaren, R. J. Taylor, *J. Chem. Soc., Perkin Trans. 1* **1994**, 2047–2048.
[11] A. Pelter, S. M. A. Elgendy, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1891–1895.
[12] A. S. Mitchell, R. A. Russel, *Tetrahedron* **1997**, *53*, 4387–4410.
[13] L. Kürti, P. Herczegh, J. Visy, M. Simonyi, S. Antus, A. Pelter, *J. Chem. Soc. Perkin Trans. 1* **1999**, 379–380.
[14] K. Sasaki, Y. Hirata, S. Yamamura, Y. P. Chen, M. H. Hong, H. Y. Hsu, *Tetrahedron Lett.* **1973**, *49*, 4881–4884.
[15] S. Antus, M. Nógrádi, E. Baitz-Gács, L. Radics, H. -D. Becker, B. Karlsson, H. H. Pilotti, *Tetrahedron* **1978**, *34*, 2573–2577.
[16] G. Andersson, P. Berntsson, *Acta. Chem. Scand. B.* **1975**, *29*, 948–952.
[17] Y. P. Chen, M. Hong, H. Y. Hsu, S. Yamamura, Y. Hirata, *Tetrahedron Lett.* **1972**, *16*, 1607–1610.
[18] S. Yamamura, Y. Terada, Y. P. Chen, H. Y. Hsu, Y. Hiruta, *Tetrahedron Lett.* **1975**, *24*, 1903–1904.
[19] Y. Takeda, S. Yamamura, *Chem. Lett.* **1978**, 553–554.
[20] M. Iguchi, A. Nishiyama, Y. Terada, S. Yamamura, *Tetrahedron Lett.* **1977**, *51*, 4511–4514.
[21] A. Nishiyama, H. Eto, Y. Terada, M. Iguchi, S. Yamamura, *Chem. Pharm. Bull.* **1983**, *31*, 2820–2833.
[22] I. M. Brereton, S. Crozier, J. Field, D. M. Doddrell, *J. Magn. Reson.* **1991**, *93*, 54.
[23] A. G. Palmer III, J. Cavanagh, P. E. Wright, M. Rance, *J. Magn. Reson.* **1991**, *93*, 151.
[24] L. E. Kay, P. Keifer, T. Saarinen, *J. Am. Chem. Soc.* **1992**, *114*, 10663.
[25] R. E. Hurd, B. K. John, *J. Magn. Reson.* **1991**, *91*, 648.

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