remaining parts were fitted with a quartz plate for UV irradiation and a deposition plate for admitting the sample and matrix gas. For UV experiments, a sapphire cold window and quartz window were used. The temperature of the matrix was controlled by an Iwatani TCCl controller (gold vs Chromel thermocouple).

Argon (Seitetsu Chemicals, 99.999%), oxygen (Seitetsu Chemicals, 99.9995%), $^{18}O_2$ (Isotech, 97% isotopic purity), carbon monoxide (Seitetsu Chemicals, >99.9%) and volatile organic compounds were mixed in a gas handling system by standard manometric techniques. Less volatile compounds were directly sublimed on the cold window while a large excess of the host gas was deposited simultaneously.

Irradiations were carried out using a Wacom 500 W xenon high pressure arc lamp or a Ushio 500-W mercury high pressure arc lamp. For broad-band irradiation, Toshiba cut-off filters were used (50% transmittance at the wavelength specified).

Materials. Dimethyl (α-diazobenzyl)phosphonate (**1**)[7] and dimethyl α-(diazophenacyl)phosphonate (**4**)[8] were synthesized according to the literature procedures. Benzoyl phosphate **8**[10] was prepared by the reaction of 1,3-diethoxy-3-(dimethylphosphenyl)prop-2-en-1-one with benzoic acid. Dimethyl (phenoxycarbonyl)phosphonate (**9**) was obtained by treating phenyl chloroformate with $P(OMe)_3$ followed by distillation: bp 104 °C/0.5 Torr; ^1H NMR (CCl_4) δ 3.94 (d, J = 12.0 Hz, 6 H), 7.02-7.44 (m, 5 H); IR (KBr) 1735, 1480, 1272, 1028, 797, 735 cm^{-1}. Benzoylphosphonate **5**[7] was prepared by reaction of benzoyl chloride with $P(OMe)_3$. All other chemicals were used as received or distilled before use as specified.

Acknowledgment. The present work was supported by a Grant-in-Aid for Scientific Rearch from Minitry of Education, Science and Culture of Japan.

Stereoselective Photocyclization of Some Phenolic, Highly Congested Benzophenones and Benzaldehydes. Use of *cis*-2-Arylbenzocyclobutenol Methyl Ethers for the Synthesis of Lignans

Gloria Coll, Antoni Costa, Pere M. Deyà, Francina Flexas, Carmen Rotger, and José M. Saá*

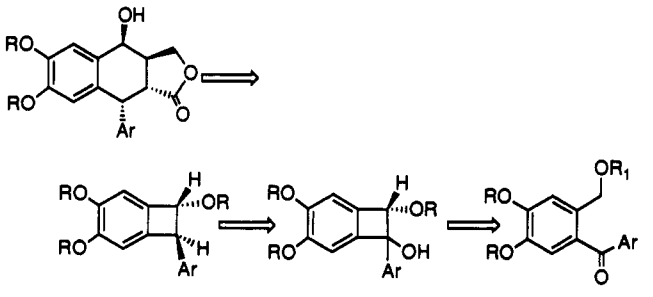
Departament de Química, Universitat de les Illes Balears, E-07071 Palma de Mallorca, Spain

Received May 12, 1992

Irradiation of some highly congested, phenolic 2-(methoxymethyl)benzophenones provides a rapid, efficient and stereoselective entry to the corresponding 1-aryl-1-hydroxy-2-methoxybenzocyclobutenes in high chemical yield. The analogous photocyclization reaction of phenolic benzaldehydes appears to be more limited in scope. According to semiempirical (AM1) calculations on the thermal ring opening of a large number of benzocyclobutene derivatives, α,α'-dioxygenated *o*-quinodimethanes are significantly more stable (5-7 kcal/mol) than the corresponding benzocyclobutene derivatives, thereby suggesting that 1-hydroxy-2-alkoxybenzocyclobutenes are unlikely to be thermally derived from the corresponding *o*-QDM's during photolysis of *o*-(methoxymethyl)benzophenones. Hydrogenolysis (H_2, Pd/C) of either the cis or trans isomers of 1-aryl-1-hydroxy-2-methoxybenzocyclobutenes gives rise to cis-trans mixtures of 1-methoxy-2-arylbenzocyclobutenes enriched in the cis isomer. These enriched mixtures undergo thermal isomerization to the desired trans 1-methoxy-2-arylbenzocyclobutenes. The cis-enriched mixture directly derived from the hydrogenolysis step can be used as a precursor of the required (*E,E*)-α-aryl-α'-methoxy-*o*-quinodimethane for the synthesis of lignanes via the intermolecular Diels-Alder approach.

The antitumor properties[1] shown by synthetically derived podophyllotoxin glycosides etoposide and teniposide (in clinical use[2]) have spurred a great deal of synthetic effort toward the naturally occurring lignan podophyllotoxin[3] and related analogs.[4] Among the recently developed synthetic approaches,[5] that of Durst and Macdonald[6] is notable because the stereochemical control of the four contiguous chiral centers was achieved in a single operation. The authors' tactic was to utilize an intramolecular Diels-Alder cycloaddition between an in situ generated *o*-quinodimethane[7] and the appropriate dienophile appended in the side chain.

Scheme I



(1) For a recent discussion of the antitumor activity of different podophyllotoxin derivatives, see: Thurston, L. S.; Imakura, Y.; Haruna, M.; Li, D.-H.; Liu, Z.-C.; Liu, S.-Y.; Cheng, Y.-C.; Lee, K. H. *J. Med. Chem.* **1989**, *32*, 604.

(2) Jardine, I. In Anticancer Agents Based on Natural Products Models; Cassady, J. M., Douras, J. D., Eds.; Medicinal Chemistry Monographs; Wiley: New York, 1980; Vol. 16, 319.

(3) Gensler, W. J.; Gatsonis, C. D. *J. Am. Chem. Soc.* **1962**, *84*, 1748. Rajapaksa, D.; Rodrigo, R. *J. Am. Chem. Soc.* **1981**, *103*, 6208. Kende, A. S.; King, M. L.; Curran, D. P. *J. Org. Chem.* **1981**, *46*, 2826. Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082. Van der Eyken, J.; De Clerq, P.; Vandewalle, M. *Tetrahedron. Lett.* **1985**, *26*, 3871. Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7854. Kaneko, T.; Wong, H. *Tetrahedron Lett.* **1987**, *28*, 517. Vyas, D. M.; Skonezky, P. M.; Jenks, T. A.; Doyle, T. W. *Tetrahedron Lett.* **1986**, *27*, 3099. Jones, D. W.; Thompson, A. M. *J. Chem. Soc., Chem. Commun.* **1987**, 1797. Forsey, S. P.; Rajapaksa, D., Taylor, N. J.; R. Rodrigo, R. *J. Org. Chem.* **1989**, *54*, 4280. Jones, D. W.; Thompson, A. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1370. See also ref 5.

(4) Pearce, H. L.; Bach, N. J.; Cramer, T. L. *Tetrahedron Lett.* **1989**, *30*, 907. Van der Eyken, J.; Bosmans, J.-P.; Van Haver, D.; Vandewalle, M.; Hulkenberg, A.; Veerman, W.; Nieuwenhuizen. *Tetrahedron Lett.* **1989**, *29*, 3873. Bosmans, J.-P.; Van der Eyken, J.; Vandewalle, M.; Hulkenberg, A.; Van Hes, R.; Veerman, W. *Tetrahedron Lett.* **1989**, *29*, 3877. Tomioka, K.; Kubota, Y.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1622. See also ref 5.

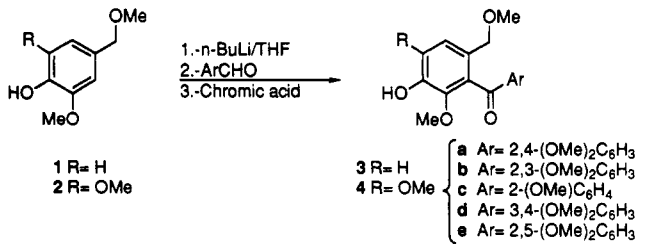
(5) Choy, W. *Tetrahedron* **1990**, *40*, 2281. Jung, M. E.; Lam, P. Y.-S.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087 and references cited therein. See also refs 6 and 10.

(6) MacDonald, D. I.; Durst, T. *J. Org. Chem.* **1986**, *51*, 4749. Macdonald, D. I.; Durst, T. *J. Org. Chem.* **1988**, *53*, 3663.

(7) Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873. Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3. Kametani, T. *Pure Appl. Chem.* **1980**, *51*, 747. Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. Oppolzer, W. *Heterocycles* **1980**, *14*, 1615. Oppolzer, W. *Synthesis* **1978**, 793.

0022-3263/92/1957-6222$03.00/0

Scheme II



The potential general interest of this approach for the preparation of podophyllotoxin analogues is, however, limited in scope due to the scarcity of synthetic methodology for the preparation of the required *trans*-1-hydroxy-2-arylbenzocyclobutenes.[8] These key compounds, by virtue of torquoselectivity control,[9] give rise via thermal conrotatory ring opening to the E,E-α-hydroxy-α'-aryl-o-quinodimethanes needed for the cycloaddition step. Since the benzocyclobutenol and dienophile units need to be linked together immediately prior to the cycloaddition step,[6] an additional important issue which poses severe limitations for a practical synthesis of these compounds has to be taken into consideration, namely the extreme lability of benzocyclobutenols toward acids or bases.[10] Obviously, if these two units were linked in a "safer" step the scope of Durst's approach would be much wider.[11] Accordingly, we decided to search for a novel approach toward 1-alkoxy-2-arylbenzocyclobutenes in which the alkoxy group could carry the appropriate dienophile moiety.[6]

Photoenolization[12] of highly congested, phenolic 2-(alkoxymethyl)benzophenones can render 1-hydroxy-2-alkoxybenzocyclobutene derivatives easily available.[13] For this to take place efficiently, we hypothesize, substituents in positions 2 and 6 of the phenolic ring should be bulky enough to force this ring to an (almost) orthogonal position,[14] thereby impeding the normal transmission[15] of the electronic influence[16] of the –OR groups to the carbonyl. Actually, this plan was based on the well-known, highly efficient Norrish type II[17] photochemical conversion of sterically congested 2,6-disubstituted benzophenones into the corresponding benzocyclobutenols initially reported by Matsuura and Kitaura.[18]

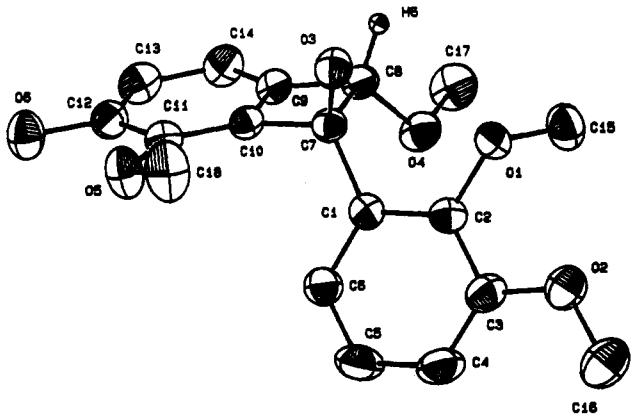


Figure 1. ORTEP plot of **6b**.

The resulting 1-aryl-1-hydroxy-2-alkoxybenzocyclobutenes were envisioned as suitable precursors of the target *trans*-1-alkoxy-2-arylbenzocyclobutenes provided that a stereocontrolled reductive removal of the tertiary alcohol could be achieved (Scheme I). To test the plan we chose to study first the photochemically-based approach on model compounds,[19] namely 1-methoxy-2-arylbenzocyclobutenes, and check their Diels–Alder reactivity. We describe herein our efforts towards these goals.

Phenolic Benzocyclobutenediol Derivatives from Photocyclization of Phenolic *o*-Methoxymethylbenzophenones and -benzaldehydes. Phenolic benzophenones **3** and **4** were prepared in a straightforward manner, in ca. 50–60% overall yield, by the recently developed regioselective lithiation of unprotected 4-(methoxymethyl)phenols **1** and **2**,[20] followed by quenching with the appropriate benzaldehyde and rapid chromic acid oxidation of the resulting phenolic diaryl methanols (Scheme II). When chromic acid oxidations were scaled up to 5 mmol (or higher), substantially reduced yields of the desired benzophenones were obtained. Oxidation with PCC, MnO_2, DEAD, NiO_2, DMSO/TFA, and CrO_3/Py led to intractable tars. Moreover, all attempts at reaching the desired benzophenones by direct acylation of the lithiated intermediate uniformly failed. Using *N*-methoxybenzamide as the acylating agent,[21] the desired product could be obtained, however, in an unacceptable low conversion (<10%). No C-acylation was observed when either benzonitrile or benzoyl chloride was employed.

Preparative irradiations of benzophenones **3** and **4** were typically carried out using a Pyrex-filtered 400-W Hanovia mercury lamp in tetrahydrofuran and, occasionally, in benzene or toluene solutions (3–6 mM). Photocyclization was fast and highly efficient in THF, and no photoreduction was observed. Slower reactions were observed in benzene or toluene. Irradiation in methanol under otherwise identical conditions gave back unchanged starting material. Irradiation of benzophenones contaminated with their benzhydrol precursor was found to be very inefficient. Careful degassing was mandatory in order to avoid for-

(8) Klundt, I. *Chem. Rev.* **1970**, *70*, 473 and references cited therein. Charlton, J. L.; Alauddin, M. M.; Penner, G. H. *Can. J. Chem.* **1986**, *64*, 793. Glinski, M. B.; Durst, T. *Can. J. Chem.* **1983**, *61*, 573. Khan, Z.; Durst, T. *Can. J. Chem.* **1987**, *65*, 482.

(9) Jefford, C. W.; Bernardinelli, G.; Wang, Y.; Spellmeyer, D. C.; Buda, A.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1157 and references cited therein.

(10) Macdonald, D. I.; Durst, T. *J. Org. Chem.* **1988**, *53*, 3663. Macdonald, D. I.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 2235. Choy, W.; Yang, H. *J. Org. Chem.* **1988**, *53*, 5796.

(11) This strategy has been recently been employed by Kraus and Chen for the synthesis of pleurotin and deoxyaklavinone. See: Kraus, G. A.; Chen, L. *Synlett.* **1991**, 89. Kraus, G. A.; Chen, L. *Synlett* **1991**, 51.

(12) For a review on photoenolization, see: Sammes, P. G. *Tetrahedron* **1976**, *32*, 405.

(13) Steric congestion favors cyclobutenol formation. See: refs 12 and 18.

(14) Pinkus, A. G.; Custard, H. C., Jr. *J. Chem. Phys.* **1970**, *74*, 1042. Liebfritz, D. *Chem. Ber.* **1975**, *108*, 3014.

(15) For a conceptually similar approach to aflatoxins, see: Kraus, G. A.; Thomas, P. J.; Schwiden, M. D. *Tetrahedron Lett.* **1990**, *31*, 1819.

(16) Quantum yields for hydrogen atom abstraction are dramatically affected by electron-donating groups. See: Wagner, P. J.; Siebert, J. *J. Am. Chem. Soc.* **1981**, *103*, 7329. Wagner, P. J.; Kempainen, A. E.; Schott, M. N. *J. Am. Chem. Soc.* **1973**, *95*, 5604. Wagner, P. J. *Acc. Chem. Res.* **1982**, *22*, 83.

(17) Wagner, P. J. *Acc. Chem. Res.* **1983**, *16*, 461. Wagner, P. J. *Top. Curr. Chem.* **1976**, *66*, 1. Wagner, P. J. *Acc. Chem. Res.* **1971**, *4*, 168.

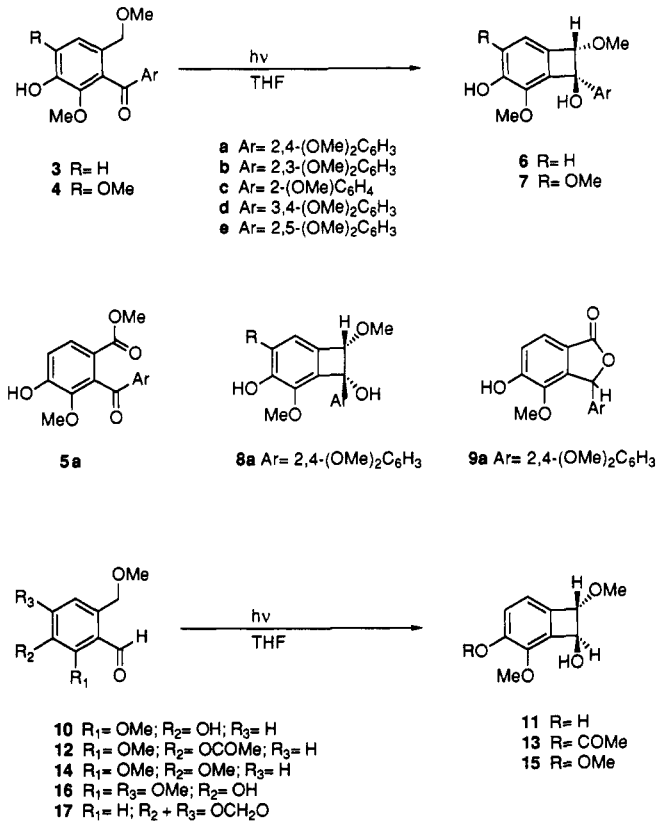
(18) Ito, Y.; Matsuura, T. *J. Am. Chem. Soc.* **1983**, *105*, 5237. Ito, Y.; Nishimura, H.; Umehara, Y.; Yamada, Y.; Tone, M.; Matsuura, T. *J. Am. Chem. Soc.* **1983**, *105*, 1590. Ito, Y.; Umehara, Y.; Hijiya, T.; Yamada, Y.; Matsuura, T. *J. Am. Chem. Soc.* **1980**, *102*, 5919. Ito, Y.; Umehara, Y.; Nakamura, K.; Yamada, Y.; Matsuura, T. *J. Org. Chem.* **1981**, *46*, 4359. Kitaura, Y.; Matsuura, T. *Tetrahedron* **1971**, *27*, 1597. Matsuura, T.; Kitaura, Y. *Tetrahedron* **1969**, *25*, 4487. Matsuura, T.; Kitaura, Y. *Tetrahedron Lett.* **1967**, *8*, 3309.

(19) A preliminary communication has appeared in print: Coll, G.; Costa, A.; Deyá, P. M.; Saá, J. M. *Tetrahedron Lett.* **1991**, *32*, 263.

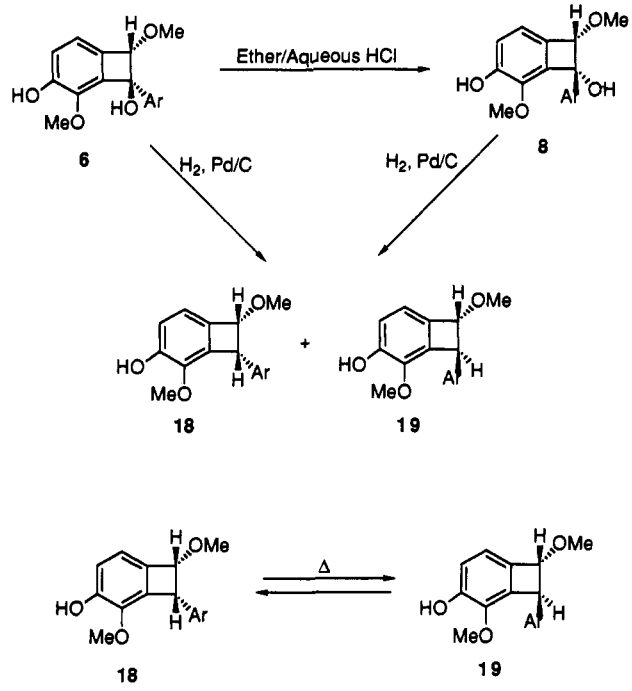
(20) Saá, J. M.; Llobera, A.; García-Raso, A.; Costa, A.; Deyá, P. M. *J. Org. Chem.* **1988**, *53*, 4263. Saá, J. M.; Morey, J.; Costa, A. *Tetrahedron Lett.* **1986**, *27*, 5215.

(21) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Scheme III



Scheme IV



mation of keto ester **5**, a well-known byproduct derived from oxygen trapping of the intermediate biradicals.[22]

Crude material from irradiation (1–2 h; ^{1}H monitoring) was shown to be only one (>90% pure) diastereoisomeric pair of the benzocyclobutenediol derivatives **6** and **7** and was obtained in quantitative conversion. For the case of **3e** photolysis was accompanied by the simultaneous destruction of the corresponding benzocyclobutenediol **6e**, as shown by NMR. All attempts to further purify the crude oily products **6** and **7** by chromatography or distillation led to large material losses. Crystallization was achieved for the case of **6b**. The presence of a high-field aliphatic methoxyl at 3.25–3.28 ppm in the ^{1}H NMR spectra of **6** and **7** suggested a cis relationship with the adjacent aromatic group in C-1. Unfortunately, NOE difference and COSY spectra were inconclusive in demonstrating the proposed stereochemistry. Eventually, an X ray analysis carried out on suitable crystals of **6b** fully confirmed the initial assignment (Figure 1).[53]

Irradiation of highly congested phenolic *o*-(methoxymethyl)benzophenones **3** and **4** is a highly efficient, diastereoselective reaction[23] which yields the less stable (see below) *trans*-1-aryl-1-hydroxy-2-methoxybenzocyclobutene derivatives **6** and **7** in good yield (Scheme III). Interestingly, simultaneous with our work,[19] Wagner et al. reported that irradiation of a variety of acetophenones and benzophenones having a prochiral ortho CH_2 yielded the corresponding benzocyclobutenol derivatives in a highly stereoselective manner.[24] According to AM1 semiempirical studies of the thermal ring opening of benzocyclobutenes (see below for discussion), the outstanding stereochemical control of our reaction cannot be accounted for by assuming that dienols (photoenols) are the primary photoproducts since α,α'-dioxygenated *o*-quinodimethanes (*o*-QDM) are 5–7 kcal/mol more stable than the corresponding 1,2-dioxygenated benzocyclobutenes.

Occasionally, during irradiation of **3a**, we noticed the formation of two secondary products. Eventually, it was found that this happened when aliquots removed for ^{1}H NMR monitoring were returned to the irradiation flask as chloroform solutions. The structure of the first byproduct was easily recognized from the ^{1}H NMR as the cis stereoisomer **8a**. Its formation is assumed to be a consequence of the acid-promoted (from photodecomposition of chloroform[25]) isomerization of the tertiary alcohol **6a** to the more stable isomer **8a**.[26] Accordingly, irradiation of **3a** in the presence of solid potassium carbonate yielded stereoisomer **6a** only. Moreover, treatment of an ethereal solution of **6a** with 6 N HCl at room temperature for several hours yielded a 3:1 equilibrium mixture of **8a** and **6a**, respectively, as shown by ^{1}H NMR (Scheme IV). Chromatographic separation of this mixture allowed us to isolate a pure sample of **8a** which exhibits a low-field NMR signal (3.60 ppm) corresponding to a "regular" aliphatic methoxyl, i.e., not under the influence of the local magnetic field of the vicinal aryl group. In other words, methoxy and aryl groups in **8a** are trans to each other. According to AM1 calculations **8c** is 2 kcal/mol more stable than **6c** presumably as a consequence of the additional hydrogen bond involving the aliphatic –OH and –OMe groups in **8c**.

(22) Yang, N. C.; Rivas, C. *J. Am. Chem. Soc.* **1961**, *83*, 2213. Heindel, N. D.; Sarver, E. W.; Pfau, M. A. *Tetrahedron Lett.* **1968**, *9*, 3579. Porter, F.; Tchir, M. F. *J. Chem. Soc. A* **1971**, 3772. Pfau, M.; Sarver, E. W.; Heindel, N. D. *Bull. Soc. Chim. Fr.* **1973**, 183.

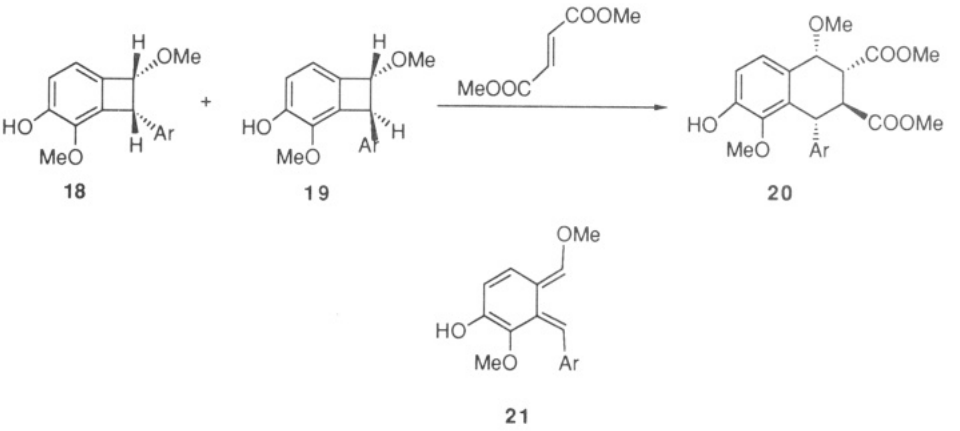
(23) Wagner, P. J.; Park, B. S. *Tetrahedron Lett.* **1991**, *32*, 165. Wagner, P. J.; Kelso, P. A.; Kempainen, A. E.; McGrath, J. M.; Schott, H. N.; Zepp, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 7506. Wagner, P. J. *Acc. Chem. Res.* **1989**, *22*, 83. Wagner, P. J.; Meador, M. A.; Giri, B. P.; Scaiano, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 1087. Wagner, P. J.; Chin, C. *J. Am. Chem. Soc.* **1979**, *101*, 7134. Wagner, P. J.; Zepp, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 4958. Pappas, S. P.; Alexander, J. E., Jr.; Zehr, R. D. *J. Am. Chem. Soc.* **1974**, *96*, 6928.

(24) Wagner, P. J.; Subrahmanyan, D.; Park B.-S. *J. Am. Chem. Soc.* **1991**, *113*, 709.

(25) Hydrogen chloride (from the photochemical decomposition of methylene chloride) has been shown to play a key role in the photochemically driven oxidation of benzylic alcohols with DDQ. See: Pira, O.; Amongag, A.; Pete, J.-P. *Tetrahedron Lett.* **1991**, *32*, 3993.

(26) Benzocyclobutenols and derivatives (methyl ethers) undergo solvolysis in strong acid solution. See: Hart, H.; Hartlage, J. A. *J. Am. Chem. Soc.* **1967**, *89*, 6672. Blomquist, A. T.; Bottomley, C. G. *J. Am. Chem. Soc.* **1965**, *87*, 86. See also ref 7 for further examples.

Scheme V



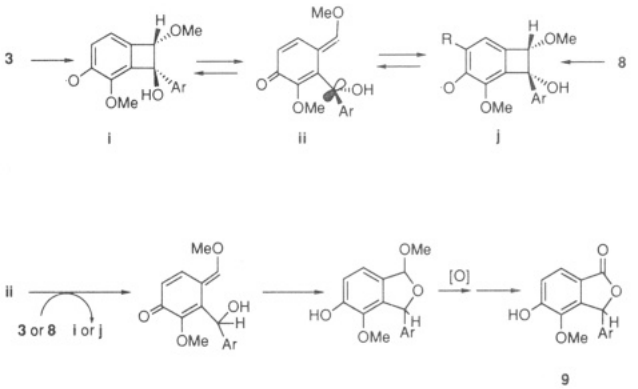
A second minor byproduct also observed during irradiation of **3a**[27] was identified as the phtalide **9a** (Scheme III) on the basis of its spectral properties.

Interestingly, even the highly congested benzaldehyde **10** or its derivatives **12** and **14** undergo efficient photocyclization to benzocyclobutenediol derivatives **11**, **13**, and **15** (Scheme III). The reaction appears, however, to be much more sensitive to substituent effects as revealed by the fact that simple analogues such as **16** or **17** yielded complex mixtures on irradiation, the expected benzocyclobutenediol derivatives not being detected by ^{1}H NMR.[28]

Hydrogenolysis[29] (H_2, Pd/C) of **6a** took place in a highly stereoselective[30] manner furnishing the less stable *cis*-benzocyclobutene derivative **18a** in 70% yield, contaminated with a small amount (ca. 5%) of the trans isomer **19a**. An analytical sample of **18a** was obtained by chromatography on TLC plates. Both the presence of a high-field aliphatic methoxyl at 3.10 ppm and two coupled hydrogens (J = 4.3 Hz) at 5.02 ppm and 5.35 ppm in the ^{1}H NMR spectrum of **18a** are consistent with a cis relationship between the –OMe and Ar groupings. Hydrogenolysis of **6b** and **6c** took place regioselectively with apparent overall retention of configuration, thus yielding the *cis*-2-aryl-1-methoxybenzocyclobutenes **18b** and **18c** as the major isomers. Actually, hydrogenolysis of **6b** yielded a 75:25 mixture of **18b**:**19b** whereas **6c** gave rise, under otherwise identical conditions, to a 60:40 mixture of **18c**:**19c**. Except for the **6a** → **18a** + **19a** transformation, these mixtures were not separated into their components because, as shown below, a simple protocol was eventually found for their conversion into highly enriched mixtures of the desired trans isomers and also because these mixtures can be used as precursors of the desired (*E*,*E*)-α-methoxy-α'-aryl-*o*-quinodimethanes in Diels–Alder reactions with appropriate dienophiles (vide infra).

Surprisingly, hydrogenolysis of a sample of **6a** + **8a**, enriched in the cis isomer **8a** (20:80, respectively), yielded also benzocyclobutene derivative **18a**, i.e., with apparent inversion of configuration. These contradictory results

Scheme VI



may be rationalized, however, by assuming that **6a** equilibrates to the more stable **8a** during the reaction (water is produced). We argue that **8a** undergoes hydrogenolysis much faster than **6a** because the S_N2-like attack by palladium[31] on the alcohol bearing carbon is clearly favored for **8a**, on simple steric grounds.

The thermodynamically more stable *trans*-1-aryl-2-methoxybenzocyclobutenes **19** were easily available in good yield and purity (>75%) from the above **18** + **19** mixtures by simply refluxing the mixture in toluene (5–6 h). No clear-cut explanation for this, not totally unexpected,[32] interconversion, which violates the Woodward and Hoffman rules, is available yet.[33] Notwithstanding the actual reaction mechanism, we speculate that this is a radical reaction initiated by oxidation of the phenol moiety by trace amounts of adventitious oxygen.[27] The *trans*-1-aryl-2-methoxybenzocyclobutenes **19** thus obtained were found to be somewhat unstable compounds as shown by the fact that on attempted chromatography an important loss of material was noticed. Nevertheless, they can be stored in the refrigerator, under argon, without noticeable destruction, for months.[34]

In accordance with the above observations, we have tried to use the crude (cis-enriched) cis–trans mixtures **18** + **19**

(27) As a working hypothesis, formation of **9a** can be assumed to involve the intermediacy of a phenoxy radical derived from oxidation by adventitious oxygen. As illustrated below, radical formation may induce cleavage of the four-membered ring (and reformation). Hydrogen abstraction by the resulting carbon radical species, followed by internal trapping of the resulting *o*-quinodimethane by the alcohol moiety, oxidation, and hydrolysis might eventually lead to **9a** (see Scheme VI).

(28) Charlton, J. L.; Koh, K. *Tetrahedron Lett.* **1988**, *29*, 5596.

(29) In most cases, hydrogenolysis promoted by palladium proceed with inversion of configuration. See: Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985 and references cited therein. See, however, ref 30 for noticeable exceptions.

(30) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093.

(31) Benzylic halides undergo S_{N2}-like oxidative addition by Pd(0) with inversion of configuration. See: Lau, K. S. Y.; Wong, P. K.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 5832.

(32) 1,2-Diiodo- and 1,2-diphenylsubstituted benzocyclobutenes have been shown to undergo cis–trans isomerization. See: Jensen, F. R.; Coleman, W. E. *J. Org. Chem.* **1958**, *23*, 869. Carpino, L. *J. Am. Chem. Soc.* **1962**, *84*, 2196. For other closely related examples, see: Kündig, E. P.; Bernardinelli, G.; Leresche, J.; Romanesns, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 407. Chapman, O. L.; Chang, C. C.; Rosenquist, N. R. *J. Am. Chem. Soc.* **1976**, *98*, 261.

(33) Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed. Eng.* **1969**, *8*, 781.

(34) No apreciable change has been observed (^{1}H NMR monitoring) on a 5:1 mixture of 6a:5a after seven months at 5 °C.

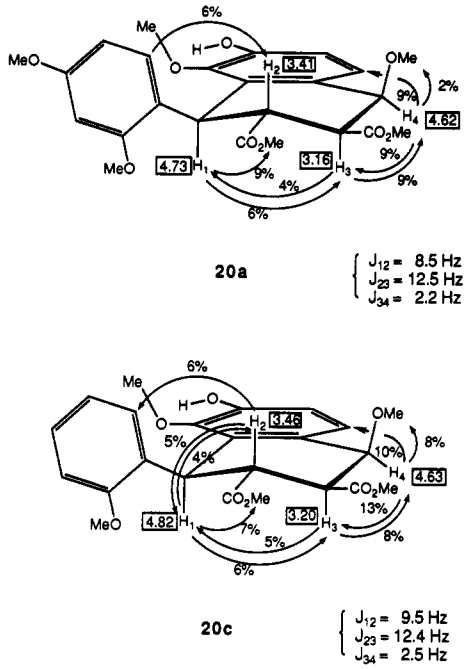


Figure 2.

directly derived from the hydrogenolysis step as precursors of the corresponding trans isomers for Diels–Alder cycloaddition reactions. By carrying this thermal transformation in the presence of a dienophile, we expected that trapping of the (*E,E*)-*o*-quinodimethane (resulting from the trans benzocyclobutene) should occur predominantly, since cycloaddition reactions of the corresponding *Z,E*-*o*-quinodimethane (from the *cis*-benzocyclobutene) are known to be much slower.[35] We have implemented this plan by reacting **18a**:**19a** (95:5) or **18c**:**19c** (60:40) with an external dienophile of well-known behavior such as dimethyl fumarate. The expected Diels–Alder adducts **20**, from reaction of (*E,E*)-*o*-quinodimethane **21a** or **21c**, were obtained in ca. 40% yield (Scheme V). The structure of the adducts was fully confirmed by careful analysis of their ^{1}H NMR data, NOE difference spectra[36] and comparison with the reported data for closely related compounds.[37]

In summary, the photolysis of phenolic 2-(methoxymethyl)benzophenones stereoselectively provides benzocyclobutenediols monomethyl ethers which can be put to good use for the synthesis of lignans.

Stereoselectivity of the Photocyclization. Semiempiric AM1 Calculations. To account for the highly stereoselective nature of our photolysis, we initially surmised that a conformational bias was already present in the ground-state benzophenones as demonstrated for other 2,6-disubstituted analogues.[38] However, examination of the ^{1}H NMR spectrum of **3a** down to −60 °C did not show evidence of restricted rotation around the Ar–CO bonds.

We next examined whether or not Wagner's generalized mechanism was applicable to our phenolic 2,6-disubstituted benzophenones.[24] In contrast with Wagner's observations, we found that irradiation for 20 min of benzophenone **3a** (ca. 0.03 M) in THF-d_8 in the presence of *p*-toluenesulfonic acid (2 mg/mL), yields benzocyclobutenediol derivative **6a** in almost quantitative yield, thus suggesting that the dienols are either not formed as reaction intermediates in our reactions or, if formed, cyclization must be faster than protonation.[39] Furthermore, irradiation of either a THF-d_8 solution (0.03 M) of **3a** containing CD_3OD (0.9 M) or a THF-d_8 solution (ca. 0.012 M) of **3a** containing TFA-d_1 (ca. 0.03 M) yielded benzocyclobutenediol derivative **6a**. No trace of benzylic deuteration on the starting benzophenone or the final benzocyclobutenol was detected in either case (^{1}H NMR monitoring). Furthermore, no appreciable rate deceleration was noticed when operating under these conditions. If we assume that protonation is likely to be a much faster reaction than electrocyclization, we are forced to conclude that our phenolic benzocyclobutenediol derivatives do not originate from the corresponding dienols[40] and, accordingly, that dienols cannot be the primary photoproducts of our photolysis.[24]

In order to gain a deeper understanding of the thermal processes presumably operating during photolysis, we have carried out a semiempirical AM1 study[41,46] on the thermal electrocyclic ring opening of benzocyclobutenes.

Thermal electrocyclic reactions have been thoroughly studied in recent years. Both experimental[43] and theoretical results[44] support the additivity[45] of substituent effects for disubstituted cyclobutenes, the strong tendency of –OR groups to move outward (even when a bulky substituent is on the same carbon atom) thus being elegantly explained.[44] However, since the additivity rule breaks down for geminal disubstitution,[46] its direct application to trisubstituted cyclobutenes was considered not to be a trivial task.

The benzocyclobutene → *o*-quinodimethane interconversion, for which ab initio and experimental[47] (ΔH = +13 kcal/mol[47c] or +10.6 kcal/mol;[47d] E_a = +39.9 kcal/mol)

(35) Arnold, B. J.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 415. See also refs 7, 8, and 12.

(36) Selected data of NOE difference spectra of compounds **20a** and **20c** (see Figure 2).

(37) Charlton, J. L.; Durst, T. *Tetrahedron Lett.* **1984**, *25*, 5287. Durst, T.; Kozma, E. C.; Charlton, J. L. *J. Org. Chem.* **1985** *50*, 4829.

(38) See: ref 18 and Bonini, B. F.; Grossi, L.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* **1986**, *51*, 517. Weissensteiner, W.; Scharf, J.; Schlog, K. *J. Org. Chem.* **1987**, *52*, 1210.

(39) For the protonation of photogenerated dienols see: (a) Haag, R.; Wirz, J.; Wagner, P. J. *Helv. Chim. Acta* **1977**, *60*, 2595. (b) Das, P. K.; Encinas, M. V.; Small, R. D., Jr.; Scaiano, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 6965. (c) Porter, G.; Tchir, M. F. *J. Chem. Soc. A* **1973**, 3772. (d) Findley, D. M.; Tchir, M. F. *J. Chem. Soc., Faraday Trans. 1* **1976**, 72, 1096.

(40) For base-catalyzed photoinduced deuterations see: Hopf, H.; Zander, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 432 and ref 39a.

(41) For semiempirical calculations on Norrish type II reactions see: Gritsan, N. P.; Khmelinski, I. V.; Usov, O. M. *J. Am. Chem. Soc.* **1991**, *113*, 9615. Boer, F. F.; Shannon, T. W.; McLafferty, F. W. *J. Am. Chem. Soc.* **1968**, *90*, 7239. Dewar, M. J. S.; Doubleday, C. *J. Am. Chem. Soc.* **1977**, *99*, 4935. Dougherty, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 5780. Hydrogen abstraction in Norrish type II reactions has been studied by ab initio methods. See: Dorigo, A. E.; McCarrick, M. A.; Loncharich R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 7508.

(42) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(43) Piers, E.; Lu, Y.-F. *J. Org. Chem.* **1989**, *54*, 2267. Moss, R. J.; White, R. O.; Rickborn, B. *J. Org. Chem.* **1985**, *50*, 5132. Jefford, C. W.; Boschung, A. F.; Rimbault, C. G. *Tetrahedron Lett.* **1974**, *15*, 3387. Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Bailey, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 1871. Dolbier, W. R., Jr.; Koroniak, H.; Burton, D. J.; Heinze, P. *Tetrahedron Lett.* **1986**, *27*, 4387. See also refs 43a,c, and d for additional experimental observations.

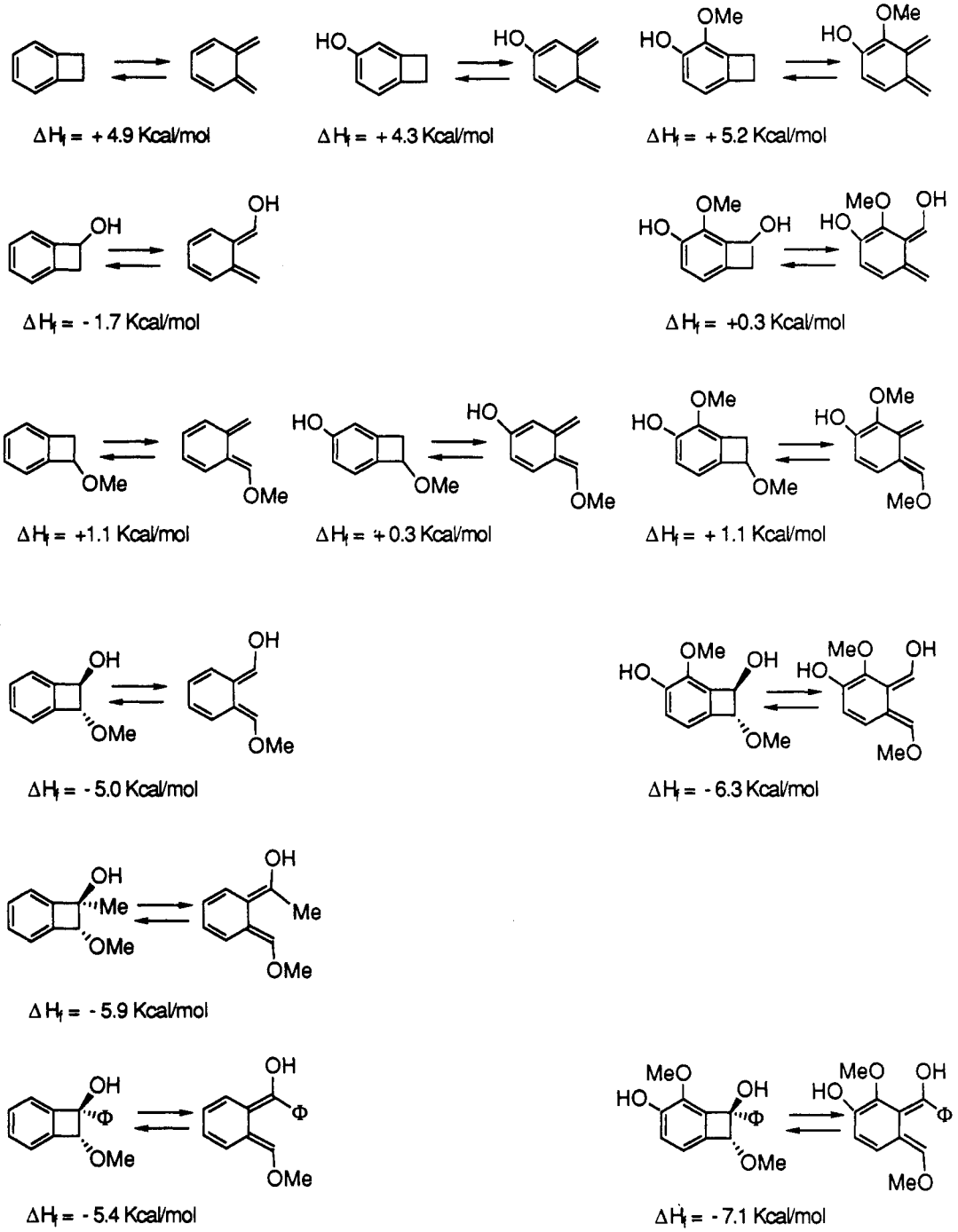
(44) (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989. (b) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (c) Rudolf, K.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 3708. (d) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault, C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2125. (e) Buda, A. B.; Wang, Y.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 2264.

(45) Frey, H. M.; Pope, B. M.; Skinner, R. F. *Trans. Faraday Soc.* **1967**, *63*, 1166. Frey, H. M.; Solly, R. K. *Trans. Faraday Soc.* **1969**, *65*, 448.

(46) Kallel, E. A.; Wang, Y.; Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 6795 and references cited therein.

(47) (a) Roth, W. R.; Biermann, M.; Dekker, H.; Jochems, R.; Mosselman, C.; Hermann, H. *Chem. Ber.* **1979**, *111*, 3892. (b) Roth, W. R.; Scholz, B. P. *Chem. Ber.* **1981**, *114*, 3741. (c) Münzel, N.; Schweig, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 471. (d) Skancke, A.; Skancke, P. N. *Acta Chem. Scand.* **1988**, *A42*, 428.

Table I. AM1 Calculated Enthalpies of Reaction



data were available, was first tested for the sake of comparison. In spite of a recent claim on the contrary,[9] Prof. Houk[48] now agrees on the fact that AM1 correctly predicts that this reaction is endothermic (ΔH = +4.9 kcal/mol), the transition state being product-like (ΔH^* = +43.74 kcal/mol), in reasonably good agreement with experiment.

As illustrated in Table I, calculations reveal that 1-monoxygenated benzocyclobutenes are, in general, more stable than the corresponding ring-opened α-oxygenated *o*-quinodimethanes. Contrarywise, 1,2-dioxygenated benzocyclobutenes are significantly less stable than the corresponding α,α'-dioxy-substituted *o*-quinodimethanes (ΔH_f = −5 to −7 kcal/mol). In other words, AM1 does not support a mechanism for the photocyclization of *o*-(methoxymethyl)benzophenones and -acetophenones in which dienols are the thermal precursors of benzocyclobutenols. Since 1,2-benzocyclobutenediol derivatives are 5–7 kcal/mol less stable than the corresponding *o*-quinodimethanes we propose that the former but not the latter are the primary photoproducts in our reactions.

Since diastereoselectivity appears not to be created during cyclization (the less stable product forms) it must be due to nonbonded interactions preexisting in the biradical species, as pointed out by Lewis.[49] In this regard, the recently described reaction-induced isc phenomena appear to be of interest for explaining the abnormal photophysical and photochemical properties associated with the photochemistry of sterically congested benzo-

(48) The reported[9] ΔH = −5.1 kcal/mol (AM1) for the benzocyclobutene → *o*-quinodimethane interconversion is in error. Personal communication by Prof. K. N. Houk.

(49) Lewis, F. D.; Hilliard, T. A. *J. Am. Chem. Soc.* **1972** *94*, 3852.

phenones.[50] Further work still needs to be done to resolve these mechanistic issues.

Summarizing, we have demonstrated the following: (1) irradiation of some highly congested, phenolic 2-(methoxymethyl)benzophenones provides a rapid, efficient, and stereoselective entry to the corresponding phenolic 1-aryl-1-hydroxy-2-methoxybenzocyclobutenes in high chemical yield, the analogous reaction on phenolic benzaldehydes being more limited in scope, (2) hydrogenolysis (H_2, Pd/C) of this class of compounds gives rise to (cis enriched) cis–trans mixtures of 1-methoxy-2-arylbenzocyclobutenes which undergo thermal isomerization to the desired *trans*-1-methoxy-2-aryl benzocyclobutenes, and (3) the cis-enriched mixtures undergo intermolecular Diels–Alder reaction with dienophiles thereby giving rise to the cycloadducts expected from reaction of the trans isomers! According to semiempirical (AM1) calculations on the thermal ring opening of a large number of benzocyclobutene derivatives, α,α'-dioxygenated *o*-quinodimethanes are significantly more stable (5–7 kcal/mol) than the corresponding benzocyclobutene derivatives, thereby suggesting that 1-hydroxy-2-alkoxybenzocyclobutenes are unlikely to be thermally derived from the corresponding *o*-QDM's during photolysis of *o*-(methoxymethyl)benzophenones.

Experimental Section

General Methods. All melting points are uncorrected and were taken on a capillary melting point apparatus. The boiling points given refer to those observed on bulb-to-bulb distillation (Büchi GKR-50 apparatus). Proton and carbon NMR spectra were obtained on Varian FT-80A, Bruker WP 200SY, or Bruker AMX 300 instruments, in $CDCl_3$, using Me_4Si as internal standard, unless otherwise noted. Electron-impact mass spectra were recorded on a Hewlett-Packard 5988A GC/MS spectrometer, operating at 70 eV ionizing energy. Infrared spectra were recorded on a Hitachi 260-10 infrared spectrophotometer. Elemental analyses were obtained at the Servei de Microanalisi del CSIC (Barcelona). High-resolution mass spectra (HRMS) were obtained on a Kratos MS-50 (Santiago de Compostela), VG Micromass ZAB-2F (La Laguna, Tenerife), or Kratos MS80RFA (Sevilla) spectrometers. Metalations were carried out under strict exclusion of air. The solvents used were thoroughly dried prior to use. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Organolithium reagents (Fluka) were used as received, once titrated. Irradiations were carried out with a 400-W Hanovia mercury lamp.

The standard workup procedure employed throughout involved extraction of the aqueous solution with three to five 25-mL portions of CH_2Cl_2 or Et_2O, followed by drying the organic extracts over anhydrous sodium sulfate and evaporation in vacuo. The residue was usually flash chromatographed on silica gel prior to bulb-to-bulb distillation or crystallization. Packing material for column chromatography was Merck silica gel 60 (70–230 mesh) unless otherwise noted.

Preparation of Benzophenones 3 and 4. General Procedure. A 100-mL, three-necked flask was charged with a THF solution (25 mL) of phenolic benzyl methyl ether 1 or 2 (10 mmol) and cooled to 0 °C. Commercial nBuLi (25 mmol) in hexanes (1.6 M) was added dropwise, under argon atmosphere. Stirring was continued for an additional 4 h at room temperature. By this time the solution was generally yellowish-brown and some precipitate had formed. The mixture was cooled to −78 °C, and a THF solution of the appropriate aryl aldehyde (15 mmol) added slowly. After 2 h at −78 °C the bath was removed and the mixture left to reach room temperature. Water was then added, followed by extraction with hexane, (discarded). The aqueous solution was brought to pH 6 by careful addition of 1 M HCl and extracted with ether (4 × 25 mL). The extracts were washed with brine and water, dried over anhydrous sodium sulfate, and evaporated to dryness. The resulting crude diarylmethanol was submitted to oxidation without further purification.

To a THF solution of the crude alcohol (2.5 mmol), cooled to 0 °C, was added recently prepared chromic acid solution (10 mmol) dropwise with stirring. After 10 min sodium dithionite was added, followed by a saturated solution of sodium bicarbonate. The mixture was filtered and the resulting solution extracted with hexane. The extracts were dried with anhydrous sodium sulfate and evaporated to dryness. The crude yellowish oil residue was purified by column chromatography on silica gel using methylene chloride/methanol (98:2) as eluant, thus furnishing phenolic benzophenones 3 or 4, analytical samples of which were obtained either by bulb-to-bulb distillation or crystallization.

3-Hydroxy-6-(methoxymethyl)-2,2′,4′-trimethoxybenzophenone (3a). Obtained in 56% overall yield as an oil, bp 170–2 °C (0.05 mmHg). ^{1}H-NMR δ: 7.66 (dd, J = 1.4, 7.8 Hz, 1 H), 7.05 (d, J = 8.0 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 6.48 (dd, J = 1.4, 7.8 Hz, 1 H), 6.44 (s, 1 H), 4.23 (s, 2 H), 3.85 (s, 3 H), 3.69 (s, 3 H), 3.66 (s, 3 H), 3.15 (s, 3 H) ppm. ^{13}C-NMR δ: 193.41, 164.91, 161.49, 148.12, 143.48, 135.73, 134.32, 127.25, 124.44, 120.84, 115.70, 104.85, 98.50, 71.34, 61.69, 57.55, 55.47, 55.23 ppm. IR (CCl_4): 3540, 1660, 1595, 1275, 1210, 1160, 1120, 1030 cm^{-1}. EIMS, m/e (relative abundance): 332 (M^+, 10), 301 (70), 286 (20), 285 (20), 270 (20), 179 (100), 165 (40), 151 (30). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.06. Found: C, 64.61; H, 6.43.

3-Hydroxy-6-(methoxymethyl)-2,2′,3′-trimethoxybenzophenone (3b). Obtained in 50% overall yield as a crystalline, white solid mp 99–100 °C (methylene chloride/hexane). ^{1}H-NMR δ: 7.32–6.90 (m, 5 H), 4.28 (s, 2 H), 3.85 (s, 3 H), 3.67 (s, 3 H), 3.57 (s, 3 H), 3.20 (s, 3 H) ppm. IR (CCl_4): 3260, 1660, 1300, 1260, 1200 cm^{-1}. EIMS m/e (relative abundance): 332 (M^+, 41), 301 (100), 285 (66), 270 (20), 255 (19), 178 (85), 165 (19), 151 (26). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.06. Found: C, 64.91; H, 6.00.

3-Hydroxy-6-(methoxymethyl)-2,2′-dimethoxybenzophenone (3c). The title compound was obtained in 60% overall yield as a crystalline solid mp 130–2 °C. ^{1}H NMR δ: 7.69–6.89 (m, 6 H), 5.64 (s, 1 H), 4.25 (s, 2 H), 3.71 (s, 3 H), 3.67 (s, 3 H), 3.15 (s, 3 H) ppm. IR (CCl_4): 3330, 1650, 1275, 1250 cm^{-1}. EIMS, m/e (relative abundance): 302 (M^+, 41), 271 (100), 255 (35), 240 (28), 225 (12), 179 (48), 135 (53), 81 (39). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.55; H: 5.96. Found: C, 67.51; H: 5.99.

3-Hydroxy-6-(methoxymethyl)-2,3′,4′-trimethoxybenzophenone (3d). The title compound was obtained in 49% as an oily substance bp 180 °C (0.05 mmHg). ^{1}H NMR δ: 7.59 (d, J = 1.8 Hz, 1 H), 7.25 (dd, J = 10.3, 1.8 Hz, 1 H), 7.12 (d, J = 8.3 Hz, 1 H), 6.98 (d, J = 10.3 Hz, 1 H), 6.82 (d, J = 8.3 Hz, 1 H), 5.86 (s, 1 H), 4.24 (s, 2 H), 3.93 (s, 6 H), 3.68 (s, 3 H), 3.14 (s, 3 H) ppm. IR (CCl_4): 3540, 2920, 1660, 1300, 1270, 1200 cm^{-1}. EIMS m/e (relative abundance): 332 (M^+, 80), 301 (100), 285 (95), 270 (45), 255 (27), 179 (98), 151 (26). Anal. Calcd for $C_{18}H_{20}C_6$: C, 65.05; H, 6.06. Found: C, 65.26; H: 6.15.

3-Hydroxy-6-(methoxymethyl)-2,2′,5′-trimethoxybenzophenone (3e). Obtained in 40% yield as a crystalline solid mp 79–80 °C (methylene chloride/hexane). ^{1}H NMR δ: 7.30–6.81 (m, 5 H), 5.73 (s, 1 H), 4.24 (s, 2 H), 3.77 (s, 3 H), 3.66 (s, 3 H), 3.58 (s, 3 H), 3.16 (s, 3 H) ppm. IR (CCl_4): 3540, 2490, 1650, 1600, 1490, 1275, 1220 cm^{-1}. EIMS, m/e (relative abundance): 332 (M^+, 21), 302 (19), 301 (100), 300 (17), 285 (15), 279 (26), 255 (44), 179 (26), 167 (17), 165 (15). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.06. Found: C, 65.01; H, 6.07.

3-Hydroxy-6-(methoxymethyl)-2,4,2′,3′-tetramethoxybenzophenone (4b). Obtained in 49% yield as an oil, bp 185–190 °C (10^{-3} mmHg). ^{1}H NMR δ: 7.15–6.99 (m, 3 H), 6.83 (s, 1 H), 5.59 (s, 1 H), 4.38 (s, 2 H), 3.93 (s, 3 H), 3.86 (s, 3 H), 3.63 (s, 3 H), 3.60 (s, 3 H), 3.29 (s, 3 H) ppm. IR (CCl_4): 3460, 2920, 1665, 1610, 1310, 1260 cm^{-1}. EIMS m/e (relative abundance): 362 (M^+, 9), 331 (100), 315 (9), 301 (21), 300 (87), 285 (36), 209 (13), 197 (10), 165 (17). Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.96; H, 6.12. Found: C, 62.91; H, 6.11.

Preparation of 3-Hydroxy-2-methoxy-6-(methoxymethyl)benzaldehyde (10). The title compound, mp 92–5 °C, was prepared following the described procedure.[20]

3-Acetoxy-2-methoxy-6-(methoxymethyl)benzaldehyde (12). The title compound was prepared by overnight treatment of 10 (204 mg) with acetic anhydride (5 mL) in pyridine. Standard workup provided crude 12 which was bulb-to-bulb distilled (122–5

(50) Wagner, P. J.; Meador, M. A.; Zhou, B.; Park, B. S. *J. Am. Chem. Soc.* **1991**, *113*, 9630.

°C (0.04 mmHg)). On cooling it solidified, mp 61–2 °C. ^{1}H NMR δ: 10.49 (s, 1 H), 7.47 (d, J = 8.4 Hz, 1 H), 7.28 (d, J = 8.4 Hz, 1 H), 4.79 (s, 2 H), 3.93 (s, 3 H), 2.37 (s, 3 H) ppm. IR (KBr): 1770, 1695, 1550, 1495, 1400, 1265, 1200 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found C, 60.52; H, 5.65.

2,3-Dimethoxy-6-(methoxymethyl)benzaldehyde (14). The title compound was prepared in 90% yield by treatment of a suspension of **10** (200 mg) and cesium carbonate (600 mg) in dry DMF (5 mL) with methyl iodide (260 mg), under stirring for 24 h at room temperature. Standard workup afforded **14** as a white solid, mp 68–9 °C (cyclohexane). ^{1}H NMR δ: 10.53 (s, 1 H), 7.33 (d, J = 8.4 Hz, 1 H), 7.12 (d, J = 8.4 Hz, 1 H), 4.74 (s, 2 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.48 (s, 3 H) ppm. IR (KBr): 1695, 1590, 1495, 1295, 1180, 1140 cm^{-1}. EIMS, m/e (relative abundance): 210 (M$^+$, 38), 196 (31), 195 (63), 181 (50), 180 (31), 178 (29), 163 (54), 149 (88), 137 (57), 135 (57), 94 (58). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.65; H, 6.72.

Preparation of 3-Hydroxy-2,4-dimethoxy-6-(methoxymethyl)benzaldehyde (16). The title compound was prepared in 40% yield following the described procedure for **10**. The crude product was bulb-to-bulb distilled (170 °C (0.005 mmHg), thereby obtaining pure **10** which solidified on standing, mp 106–7 °C (hexane–ether). ^{1}H NMR (THF-d_8) δ: 10.45 (s, 1 H), 8.28 (s, 1 H), 7.18 (s, 1 H), 4.83 (s, 2 H), 4.06 (s, 3 H), 4.03 (s, 3 H), 3.54 (s, 3 H) ppm. IR (KBr): 3540, 1680, 1620, 1595, 1220, 1170 cm^{-1}. EIMS, m/e (relative abundance): 226 (M$^+$, 70), 211 (100), 193 (45), 179 (49), 165 (39), 151 (42), 136 (30). Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.34; H, 6.19. Found: C, 58.29; H, 6.36.

Irradiation of Benzophenones 3 and 4 and Benzaldehydes 10–17. General Procedure. Preparation of Benzocyclobutenediol Derivatives 6, 7, 11, 13, and 15. A THF solution of benzophenones or benzaldehydes, thoroughly deoxygenated with argon, at room temperature was irradiated, in a Pyrex vessel, with a medium-pressure Hanovia mercury lamp until complete disappearance of the starting material was observed by ^{1}H NMR. A gentle argon stream was maintained throughout the whole operation. The solvent was then removed under reduced pressure taking care the bath temperature did not exceed 40 °C in order to avoid the conversion back to starting material. Crude 1-hydroxy-2-methoxydihydrobenzocyclobutenes were obtained in quantitative yield with >90% purity (see the text for exceptions), as determined by NMR analysis. Products decomposed on attempted bulb-to-bulb distillation. Regular crystallization at the solvent's boiling point induced variable amounts of isomerization back to the corresponding benzophenone. Crystallization at room temperature worked in the case of **6b** only. Analytically pure samples were obtained by chromatography on silica gel plates using methylene chloride/methanol (98:2) as eluant.

Benzene or toluene can be used as the solvent for irradiation, instead of tetrahydrofuran, the overall rate of reaction being somewhat reduced. Irradiation in methanol gives the starting compounds completely unchanged.

***trans*-1,5-Dihydroxy-2,6-dimethoxy-1-(2′,4′-dimethoxyphenyl)dihydrobenzocyclobutene (6a).** The title compound was obtained in quantitative yield (>90% pure) as an oil. ^{1}H NMR δ: 7.00 (d, J = 7.7 Hz, 1 H), 6.86 (dd, J = 7.7, 0.75 Hz, 1 H), 6.76 (d, J = 8.4 Hz, 1 H), 6.57 (d, J = 2.3 Hz, 1 H), 6.40 (dd, J = 8.4, 2.3 Hz, 1 H), 5.7 (s, 1 H), 5.3 (s, 1 H), 4.83 (d, J = 0.75 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 3.80 (s, 3 H), 3.27 (s, 3 H) ppm. ^{13}C NMR δ: 160.15, 158.27, 146.23, 142.33, 134.46, 130.54, 126.75, 121.55, 117.56, 117.36, 104.26, 99.13, 89.79, 86.42, 59.15, 57.22, 55.52, 55.22 ppm. IR (CCl_4): 3560, 2920, 1615, 1490, 1280, 1240, 1210 cm^{-1}. EIMS m/e (relative abundance): 332 (M$^+$, 2), 316 (85), 301 (85), 285 (75), 257 (27), 227 (15), 209 (18), 165 (100), 122 (78), 101 (20). Exact mass calcd for $C_{18}H_{20}O_6$: 332.1260. Found: 332.1260.

***trans*-1,5-Dihydroxy-2,6-dimethoxy-1-(2′,3′-dimethoxyphenyl)dihydrobenzocyclobutene (6b).** Obtained in 70% yield as a solid, mp 141–2 °C (methylene chloride/hexane). ^{1}H NMR δ: 6.99 (d, J = 7.7 Hz, 1 H), 6.97 (dd, J = 7.7, 8.2 Hz, 1 H), 6.90 (dd, J = 8.2, 1.4 Hz, 1 H), 6.88 (d, J = 7.7 Hz, 1 H), 6.49 (dd, J = 7.7, 1.4 Hz, 1 H), 5.8 (bs, 1 H), 5.6 (bs, 1 H), 4.87 (s, 1 H), 4.06 (s, 3 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.28 (s, 3 H) ppm. IR (KBr): 3560, 2940, 1480, 1280, 1270, 1230 cm^{-1}. EIMS m/e (relative abundance): 332 (M$^+$, 3), 302 (10), 301 (46), 285 (15), 271 (18), 270 (40), 255 (23), 179 (17), 167 (15), 165 (14), 137 (18), 125 (18), 111 (25). Anal. Calcd for $C_{18}H_{20}C_6$: C, 65.05; H, 6.06. Found: C, 65.00; H, 6.06.

***trans*-1,5-Dihydroxy-2,6-dimethoxy-1-(2′-methoxyphenyl)dihydrobenzocyclobutene (6c).** The title compound was obtained as an unstable oil in quantitative yield (>90% pure) as determined by ^{1}H NMR. ^{1}H NMR δ: 7.31 (ddd, J = 2.4, 6.8, 8.1 Hz, 1 H), 7.00 (d, J = 7.8 Hz, 1 H), 6.99 (dd, J = 8.1, 2.4 Hz, 1 H), 6.91 (dd, J = 2.5, 8.4, 1 H), 6.89 (ddd, J = 2.4, 6.8, 8.1 Hz, 1 H), 6.87 (d, J = 7.7 Hz, 1 H), 5.8 (s, 1 H), 5.4 (s, 1 H), 4.87 (s, 1 H), 4.00 (s, 3 H), 3.94 (s, 3 H), 3.25 (s, 3 H) ppm. ^{13}C NMR δ: 157.48, 146.45, 142.53, 130.11, 128.67, 125.58, 120.79, 117.77, 117.63, 110.96 ppm. IR ($CDCl_3$): 3540, 2940, 1490, 1260 cm^{-1}. EIMS m/e (relative abundance): 302 (M$^+$, 6), 272 (18), 271 (100), 270 (39), 256 (18), 255 (34), 240 (31), 225 (15), 179 (29), 135 (18). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.55; H, 5.96. Found: C, 67.78; H, 5.58.

***trans*-1,5-Dihydroxy-2,4,6-trimethoxy-1-(2′,3′-dimethoxyphenyl)dihydrobenzocyclobutene (7b).** The title compound was obtained in quantitative yield and >80% purity, as determined by NMR. ^{1}H NMR δ: 6.92 (m, 2 H), 6.60 (s, 1 H), 6.51 (dd, J = 7.8, 1.3 Hz, 1 H), 5.78 (s, 1 H), 5.67 (s, 1 H), 4.89 (s, 1 H), 4.05 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.26 (s, 3 H), ppm. EIMS m/e (relative abundance): 362 (M$^+$, 4), 332 (10), 331 (44), 301 (10), 300 (41), 286 (10), 285 (25), 269 (11), 236 (12), 209 (11), 193 (11), 182 (24), 168 (12), 167 (47), 165 (44), 149 (23), 137 (19). Exact mass calcd for $C_{18}H_{19}O_6$: 331.1181. Found: 331.1198. Exact mass for molecular ion at 362 (M$^+$, 4) could not be obtained.

***trans*-1,5-Dihydroxy-2,6-dimethoxydihydrobenzocyclobutene (11).** The title compound was obtained as an oil (>90% pure). ^{1}H NMR δ: 6.93 (d, J = 7.7 Hz, 1 H), 6.82 (d, J = 7.7 Hz, 1 H), 5.55 (s, 1 H), 5.10 (s, 1 H), 4.59 (s, 1 H), 4.08 (s, 3 H), 3.54 (s, 3 H) ppm. ^{13}C NMR δ: 146.02, 142.27, 133.48, 126.45, 117.42, 116.85, 86.70, 75.74, 58.14, 56.79 ppm. IR ($CDCl_3$): 3550, 2950, 1480, 1440, 1280, 1240 cm^{-1}. EIMS, m/e (relative abundance): 196 (M$^+$, 44), 181 (48), 165 (31), 164 (32), 163 (38), 149 (100), 135 (30), 121 (41). Exact mass calcd for $C_{10}H_{12}O_4$: 196.0735. Found: 196.0734.

***trans*-5-Acetoxy-1-hydroxy-2,6-dimethoxydihydrobenzocyclobutene (13).** The title compound was obtained as an oil (>75% pure). ^{1}H NMR δ: 7.00 (d, J = 7.6 Hz, 1 H), 6.91 (d, J = 7.6 Hz, 1 H), 5.07 (s, 1 H), 4.58 (s, 1 H), 4.03 (s, 3 H), 3.55 (s, 3 H), 2.29 (s, 3 H) ppm. IR ($CDCl_3$): 3590, 2940, 1765, 1485, 1370, 1275, 1205 cm^{-1}. EIMS, m/e (relative abundance): 238 (M$^+$, 15), 210 (18), 196 (36), 195 (21), 181 (76), 179 (40), 164 (49), 163 (53), 152 (19), 149 (100), 135 (40). Exact mass calcd for $C_{12}H_{14}O_5$: 238.0841. Found: 238.0842.

***trans*-1-Hydroxy-2,5,6-trimethoxydihydrobenzocyclobutene (15).** The title compound was obtained as an oil (>80% pure). ^{1}H NMR δ: 6.90 (m, 2 H), 5.11 (s, 1 H), 4.60 (s, 1 H), 4.10 (s, 3 H), 3.85 (s, 3 H), 3.56 (s, 3 H) ppm. IR ($CDCl_3$): 3595, 2940, 1605, 1580, 1495, 1275, 1240, 1200, 1040 cm^{-1}. EIMS, m/e (percent, relative abundance): 210 (M$^+$, 38), 195 (100), 180 (40), 179 (27), 178 (34), 163 (74), 151 (22), 135 (51), 120 (31). Exact mass calcd for $C_{11}H_{14}O_4$: 210.0892. Found: 210.0893.

Preparation of Methyl 4-Hydroxy-6-(2′,4′-dimethoxybenzoyl)-5-methoxybenzoate (5a). Irradiation of a toluene (30-mL) solution of benzophenone **3a** (30 mg) was carried out as shown in the general procedure, except that no exclusion of air was done prior to irradiation. The starting material disappeared after irradiation for 1 h. Toluene was removed and the residue chromatographed on silica gel using ether/hexane (6:4) as eluant. Benzoate **5a** was obtained as an oil in 41% isolated yield, bp 190 °C (5×10^{-3} mmHg). ^{1}H NMR δ: 7.85 (d, J = 8.8 Hz, 1 H), 7.71 (d, J = 8.8 Hz, 1 H), 6.95 (d, J = 8.5 Hz, 1 H), 6.52 (dd, J = 8.5, 2.3 Hz, 1 H), 6.38 (d, J = 2.3 Hz, 1 H), 3.83 (s, 3 H), 3.68 (s, 3 H), 3.64 (s, 3 H), 3.59 (s, 3 H) ppm. ^{13}C-NMR δ: 179.9, 165.8, 165.0, 153.3, 143.0, 140.1, 133.5, 127.5, 120.3, 118.8, 115.1, 105.3, 98.6, 62.1, 55.5, 55.3, 51.6 ppm. IR (CCl_4): 3540, 2940, 1725, 1640, 1290, 1270, 1210 cm^{-1}. EIMS m/e (relative abundance): 346 (M$^+$, 31), 316 (10), 315 (16), 287 (20), 283 (22), 269 (9), 209 (18), 195 (17), 177 (12), 165 (100). Exact mass calcd for $C_{18}H_{18}O_7$: 346.10525. Found: 346.10513.

Preparation of 5-Hydroxy-4-methoxy-3-(2′,4′-dimethoxyphenyl)-1,3-dihydroisobenzofuran-1-one (9a). The title compound was isolated as a byproduct (30% yield) of the irradiation

of **4a** in tetrahydrofuran containing ca. 0.5 mL of chloroform. Crystalline solid (methylene chloride/hexane), mp 156–7 °C. ^{1}H NMR δ: 7.61 (d, J = 8.2 Hz, 1 H), 7.13 (d, J = 8.2 Hz, 1 H), 6.90 (s, 1 H), 6.74 (d, J = 8.5 Hz, 1 H), 6.51 (d, J = 2.4 Hz, 1 H), 6.40 (dd, J = 8.5, 2.4 Hz, 1 H), 6.12 (s, 1 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.67 (s, 3 H) ppm. ^{13}C NMR δ: 170.20, 161.94, 158.83, 153.51, 140.88, 139.11, 129.44, 121.56, 119.66, 117.54, 116.12, 104.77, 98.78, 75.60, 59.75, 55.62, 55.21 ppm. IR (KBr): 3140, 1730, 1610, 1315, 1300, 1275, 1265, 1205 cm^{-1}. EM m/e (relative abundance): 316 (M^+, 100), 301 (26), 285 (13), 257 (30), 242 (24), 241 (26), 212 (9), 165 (9), 122 (7). Anal. Calcd for $C_{17}H_{16}O_6$: C, 64.53; H, 5.10. Found: C, 64.56; H, 5.09.

***cis*-1,5-Dihydroxy-2,6-dimethoxy-1-(2′,4′-dimethoxyphenyl)dihydrobenzocyclobutene (8a).** A stirred solution of **6a** (500 mg) in ether was treated with 6 N HCl for 1 h at room temperature. The solution was neutralized with NaOH and extracted with ether. The organic phase was dried and evaporated to dryness. The crude product was shown by ^{1}H NMR to be a 1:3 mixture of **6a** and **8a**, respectively. A sample of **8a** was obtained by chromatography on silica gel plates, as an unstable oil, in 15% yield. ^{1}H NMR δ: 7.15 (s, 1 H), 6.92 (d, J = 6.7 Hz, 1 H), 6.85 (d, J = 6.7 Hz, 1 H), 6.47 (m, 2 H), 4.75 (s, 1 H), 3.90 (s, 3 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.60 (s, 3 H) ppm. IR (CCl_4): 3550, 2950, 2850, 1600, 1480, 1280, 1220 cm^{-1}. EM m/e (relative abundance): 332 (M^+, 3), 301 (45), 285 (12), 270 (13), 225 (8), 180 (11), 179 (100), 165 (13), 151 (12). Exact mass calcd for $C_{18}H_{20}O_6$: 332.1260. Found: 332.1240.

Hydrogenolysis of 6 and 7. Preparation of *cis*- and *trans*-2-Aryl-1-methoxydihydrobenzocyclobutenes 18 and 19. General Procedure. A methanolic solution of crude **6** (from irradiation of benzophenones **4**) was hydrogenolized (H_2, 33 psig) in the presence of 10% Pd/C during 5 h. The catalyst was filtered off and washed with methanol and the combined solution evaporated to dryness under reduced pressure. Crude material (70–80% yield) was found to be a mixture of *cis*- and *trans*-**18** and -**19** in variable proportions depending on the structure. Attempted purification by chromatography on silica gel plates resulted in substantial decomposition.

***cis*-4-Hydroxy-1,3-dimethoxy-2-(2′,4′-dimethoxyphenyl)-dihydrobenzocyclobutene (18a).** Hydrogenolysis of **6a**, as illustrated in the general procedure, furnished (70% yield) crude **18a** shown to be (^{1}H NMR) higher than 90% pure, the minor impurity being **19a** (see below for its solution and spectral properties). Alternatively, hydrogenolysis of a crude 1:3 mixture of **6a** and **8a**, obtained by acid-catalyzed epimerization of **6a** as illustrated above, also furnished (70% yield) crude **18a** of the same purity (90%).

A pure sample of **18a** was obtained by chromatography as a yellowish oil which decomposed on attempted bulb-to-bulb distillation. ^{1}H NMR δ: 6.90 (d, J = 8.3 Hz, 1 H), 6.89 (d, J = 7.7 Hz), 6.84 (d, J = 7.7 Hz, 1 H), 6.47 (d, J = 2.4 Hz, 1 H), 6.43 (dd, J = 8.3, 2.4 Hz, 1 H), 5.53 (s, 1 H), 5.35 (d, J = 4.3 Hz, 1 H), 5.02 (d, J = 4.3 Hz, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.67 (s, 3 H), 3.10 (s, 3 H) ppm. IR (CCl_4): 3560, 2940, 1260, 1250, 1230, 1210 cm^{-1}. EIMS m/e (relative abundance): 316 (M^+, 4), 286 (35), 285 (100), 271 (14), 270 (30), 269 (18), 255 (17), 151 (15), 135 (11). Exact mass calcd for $C_{18}H_{20}O_5$: 316.1305. Found: 316.1309.

***cis*- and *trans*-4-Hydroxy-1,3-dimethoxy-2-(2′,3′-dimethoxyphenyl)dihydrobenzocyclobutene (18b and 19b).** Hydrogenolysis of **6b** as illustrated in the general procedure furnished a 1:1 unseparable mixture of **18b** and **19b** in 70% yield. ^{1}H NMR δ: 6.99–660 (m, 10 H), 5.43 (d, J = 4.5 Hz, 1 H, **18b**), 5.06 (d, J = 4.5 Hz, 1 H, **18b**), 4.97 (d, J = 1.3 Hz, 1 H, **19b**), 4.57 (d, J = 1.3 Hz, 1 H, **19b**), 3.88 (s, 6 H), 3.86 (s, 6 H), 3.80 (s, 3 H, **19b**), 3.65 (s, 3 H), 3.61 (s, 3 H), 3.15 (s, 3 H, **18b**) ppm. IR (CCl_4): 3550, 2930, 1480, 1440, 1270, 1220 cm^{-1}. EIMS m/e (relative abundance): 316 (M^+, 16), 288 (22), 286 (27), 285 (100), 284 (65), 270 (31), 269 (35), 255 (58), 254 (57), 253 (18), 241 (17), 239 (63), 225 (37), 137 (42), 135 (18). Exact mass calcd for $C_{18}H_{20}O_5$: 316.1305. Found: 316.1309.

***cis*- and *trans*-4-Hydroxy-1,3-dimethoxy-2-(2′-methoxyphenyl)dihydrobenzocyclobutene (18c and 19c).** Hydrogenolysis of **6c** as illustrated in the general procedure furnished an unseparable 3:1 mixture of **18c** and **19c**, respectively, in 60% yield. ^{1}H NMR δ: 7.21–6.77 (m, 12 H), 5.45 (d, J = 4.3 Hz, 1 H, **18c**), 5.07 (d, J = 4.3 Hz, 1 H, **18c**), 4.97 (d, J = 1.2 Hz, 1 H, **19c**), 4.50 (d, J = 1.2 Hz, 1 H, **19c**), 3.89 (s, 3 H, **18c**), 3.87 (s, 3 H, **19c**), 3.63 (s, 3 H, **18c**), 3.61 (s, 3 H, **19c**), 3.51 (s, 3 H, **19c**), 3.09 (s, 3 H, **18c**) ppm. IR (CCl_4): 3550, 2910, 1480, 1460, 1440, 1280, 1220. EIMS m/e (relative abundance): 286 (M^+, 7), 258 (10), 256 (19), 255 (100), 254 (15), 240 (17), 239 (32), 255 (18), 223 (12), 211 (19), 195 (39), 137 (15). 121 (12), 120 (12). Exact mass calcd for $C_{17}H_{18}O_4$: 286.1200. Found: 286.1205.

Cis–Trans Isomerization of 4-Hydroxy-1,3-dimethoxy-2-(2′,4′-dimethoxyphenyl)dihydrobenzocyclobutene (18a → 19a). A 0.01 M solution of *cis*-benzocyclobutene **18a** in toluene (10 mL) was heated to reflux temperature. After 5 h an (1:9) equilibrium mixture of **18a** and **19a** was obtained, as shown by integration of the ^{1}H NMR signals corresponding to H_1 (5.35, d, J = 4.3 Hz) in **18a** and H_1 (4.46, d, J = 2.4 Hz) in **19a**. A sample of **19a** could be isolated by chromatography on silica gel plates, albeit with high loss of material.

Compound **19a** impurified with **18a** was isolated as an oily substance which decomposed on attempted bulb-to-bulb distillation. ^{1}H NMR δ: 6.94–6.35 (m, 5 H), 5.54 (s, 1 H), 4.88 (d, J = 2.4 Hz, 1 H), 4.46 (d, J = 2.4 Hz, 1 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.62 (s, 3 H), 3.50 (s, 3 H) ppm. EIMS m/e (relative abundance): 316 (M^+, 5), 286 (23), 285 (65), 270 (27), 255 (16), 253 (14), 241 (11), 149 (17), 135 (12). Exact mass calcd for $C_{18}H_{20}O_5$: 316.1305. Found: 316.1308.

Diels–Alder Reaction of Cis–Trans Benzocyclobutenes 18a–19a with Dimethyl Fumarate. Preparation of Dimethyl 6-Hydroxy-1-(1,2-*cis*),5-dimethoxy-4-(3,4-*trans*)-(2′,4′-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2,3-*trans*-dicarboxylate (20a). A 50-mL toluene solution of 180 mg (0.57 mmol) of a 95:5 cis–trans mixture of benzocyclobutenes **18a** and **19a**, respectively, and dimethyl fumarate (160 mg, 1.1 mmol) was heated to reflux under an argon atmosphere. After 6 h the solvent and excess fumarate were removed under reduced pressure. The viscous, yellowish residue was chromatographed twice on a silica gel column using methylene chloride as eluant. Compound **20a** (110 mg, 42% yield) was obtained as a colorless oil which decomposes on attempted bulb-to-bulb distillation. ^{1}H NMR δ: 6.98 (d, J = 8.2 Hz, 1 H), 6.86 (d, J = 8.2 Hz, 1 H), 6.78 (d, J = 8.2 Hz, 1 H), 6.45 (d, J = 2.4 Hz, 1 H), 6.33 (dd, J = 8.2, 2.4 Hz, 1 H), 4.73 (d, J = 8.5 Hz, 1 H), 4.62 (d, J = 2.2 Hz, 1 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.62 (s, 3 H), 3.44 (s, 3 H), 3.41 (dd, J = 8.5, 12.5 Hz, 1 H), 3.35 (s, 3 H), 3.16 (dd, J = 12.5, 2.2 Hz, 1 H) ppm. ^{13}C NMR δ: 176.12, 172.16, 158.91, 157.34, 150.00, 145.31, 133.19, 128.69, 126.93, 125.90, 113.54, 113.39, 104.60, 97.47, 77.44, 59.68, 59.42, 56.08, 55.34, 55.11, 51.64, 48.02, 45.20, 45.03. IR ($CDCl_3$): 3540, 2940, 1730, 1600, 1460, 1430, 1290, 1260, 1200, 1180 cm^{-1}. EIMS m/e (relative abundance): 460 (M^+, 7), 428 (10), 369 (23), 368 (84), 338 (12), 327 (44), 322 (22), 316 (24), 301 (13), 300 (17), 290 (17), 285 (32), 277 (11), 263 (11), 257 (12), 255 (11), 241 (12), 240 (14), 238 (20), 231 (11), 223 (17) 222 (100), 181 (17), 165 (28), 161 (12), 151 (25), 139 (11), 138 (10), 135 (14), 121 (16), 115 (10). Exact mass calcd for $C_{24}H_{28}O_9$: 460.1733. Found: 460. 1720.

Diels–Alder Reaction of Cis–Trans Benzocyclobutenes 18c–19c with Dimethyl Fumarate. Preparation of Dimethyl 6-Hydroxy-1-(1,2-*cis*),5-dimethoxy-4-(3,4-*trans*)-(2′-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2,3-*trans*-dicarboxylate (20c). Dimethyl fumarate (40 mg, 0.28 mmol) was added to a solution of 20 mg (0.07 mmol) of a 7:3 mixture of *cis*- and *trans*-benzocyclobutene derivatives **18c** and **19c**, respectively, in toluene (15 mL). The mixture was heated to reflux under an argon atmosphere during 5 h. The solvent and excess fumarate were the removed under reduced pressure. The viscous, yellowish residue was chromatographed on silica gel plates using methylene chloride as eluant. The title compound **12c** was obtained in 40% yield (12 mg) as an oil which decomposes on attempted distillation. ^{1}H NMR δ: 7.15 (m, 1 H), 6.98 (d, J = 8.1 Hz, 1 H), 6.84 (m, 4 H), 4.82 (d, J = 9.5 Hz, 1 H), 4.63 (d, J = 2.4 Hz, 1 H), 3.85 (s, 3 H), 3.74 (s, 3 H), 3.61 (s, 3 H), 3.40 (s, 3 H), 3.46 (dd, J = 9.5, 12.4 Hz, 1 H), 3.36 (s, 3 H), 3.20 (dd, J = 12.4, 2.4 Hz, 1 H) ppm. IR ($CDCl_3$): 3500, 2930, 1720, 1600, 1460, 1430, 1280, 1240 cm^{-1}. EIMS m/e (relative abundance): 430 (M^+, 10), 398 (26), 339 (25), 338 (88), 308 (16), 307 (69), 292 (37), 277 (15), 275 (10), 263 (11), 259 (11), 249 (10), 247 (13), 240 (14), 239 (16), 238 (100), 237 (18), 221 (10) 207 (10). Exact mass calcd for $C_{23}H_{26}O_8$: 430.1627. Found: 430.1613.

Calculations. Theoretical calculations were carried out at the restricted Hatree–Fock (RHF) level using AM1 semiempirical SCF-MO method as implemented in a modified version[51] of the MOPAC program.[52]

Acknowledgment. Financial support by the DGICYT (PB87/0019) is gratefully acknowledged. Thanks are also due to Prof. J.D. Martin (U. de La Laguna) and Dr. G. Tojo (U. de Santiago de Compostela) for carrying out our HRMS. Time allocation for calculations, performed with a VAX 8820 computer, was generously provided by the Centre de Càlcul de la Universitat de les Illes Balears.

Note Added in Proof. A total synthesis of racemic podophyllotoxin based on the above grounds (tandem photolysis/intramolecular Diels–Alder) has been recently reported: Kraus, G.; Wu, Y. *J. Org. Chem.* **1992**, *57*, 2922.

Supplementary Material Available: ^{1}H NMR spectra for compounds **5a**, **6a**, **7b**, **8a**, **11**, **13**, **15**, **18a**, **19a**, **18b** + **19b**, **18c** + **19c**, **20a**, and **20c** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(51) (a) Olivella, S. QCPE Program No. 486. (b) Olivella, S.; Vilarrasa, J. *J. Heterocycl. Chem.* **1981**, *18*, 1189.
(52) VAX Version: Stewart, J. J. P. *QCPE Bull.* **1983**, *3*, 101.
(53) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Influence of Microwaves on the Rate of Esterification of 2,4,6-Trimethylbenzoic Acid with 2-Propanol

Kevin D. Raner* and Christopher R. Strauss

CSIRO Division of Chemical and Polymers, Private Bag 10, Clayton, Victoria 3168, Australia

Received June 15, 1992

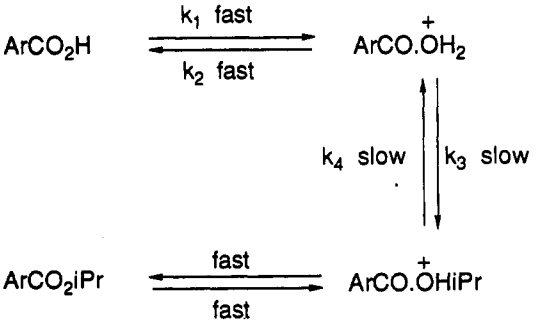
The influence of microwave irradiation on the reaction kinetics of the acid-catalyzed esterification of 2,4,6-trimethylbenzoic acid in *i*-PrOH was investigated. The rate constants for the reaction at various temperatures were measured in experiments conducted in an oil bath and the Arrhenius parameters were calculated. Reactions were carried out under microwave irradiation with different temperature profiles and the final ester concentrations were determined. The measured ester concentrations were in agreement with those calculated by computer modeling of the reaction using the Arrhenius parameters obtained from the oil bath experiments. The rate constant at 150 °C was directly determined in a recently developed microwave reactor and was consistent with the measured Arrhenius parameters. The rate of the esterification was concluded to be the same in both the microwave reactor and in the oil bath experiments.

It is well documented that microwave irradiation can be employed to accelerate chemical reactions[1–3] and rate enhancements of up to a 1000-fold over conventional conditions have been reported.[1]

An explanation for the fact that reaction rates are increased under microwave irradiation could be simply that the radiation leads to an increase in the reaction temperature. There have been suggestions however, of the existence of an additional "microwave effect" which can accelerate a reaction to a rate faster than would be expected on the basis of the measured reaction temperature.[4–6] Others have rejected this proposal.[7,8] Jahngen et al.[4] initially reported an effect in the hydrolysis of ATP. When they were able to take full account of the temperature gradients in the system, however, they concluded that the rate of hydrolysis was not influenced by microwave radiation.[7]

Two main experimental difficulties are largely responsible for the inconsistencies in the above literature. In order to perform kinetics studies the temperature must be known and the reaction solution must be either thermally homogeneous or have thermal gradients that are known or are capable of being modeled.

Scheme I



Domestic microwave ovens operate by alternating from maximum power output to zero power; this arrangement is unsatisfactory for precise control of temperature. For this reason we recently developed a microwave reactor which was more suitable for studying chemical kinetics.[9] The system consisted of a domestic microwave oven which was modified to allow operation at constant power output. The unit also possessed a facility for magnetic stirring. The internal temperature and pressure of the PFA/PTFE reaction vessel could be monitored and the temperature history could be recorded on a computer.

(1) Gedye, R. N.; Smith, F. E.; Westaway, K. C. *Can. J. Chem.* **1988**, *66*, 17.
(2) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1.
(3) Abramovitch, R. A. *Org. Prep. Proc. Int.* **1991**, *23*, 683.
(4) Sun, W. C.; Guy, P. M.; Jahngen, J. H.; Rossomando, E. F.; Jahngen, E. G. E. *J. Org. Chem.* **1988**, *53*, 4414.
(5) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles* **1990**, *30*, 741.
(6) Berlan, J.; Giboreau, P.; Lefeuvre, S.; Marchand, C. *Tetrahedron Lett.* **1991**, *32*, 2363.
(7) Jahngen, E. G. E.; Lentz, R. R.; Pesheck, P. S.; Sackett, P. H. *J. Org. Chem.* **1990**, *55*, 3406.
(8) Pollington, S. D.; Bond, G.; Moyes, R. B.; Whan, D. A.; Candlin, J. P.; Jennings, J. R. *J. Org. Chem.* **1991**, *56*, 1313.
(9) Constable, D.; Raner, K. D.; Somlo, P.; Strauss, C. R. Submitted for publication.

0022-3263/92/1957-6231$03.00/0