labeled compounds. The specific activities were calculated to be 12.2 Ci/mmol (32.7 μCi/μg) for [^{3}H]tamoxifen and 6.5 Ci/mmol (17.5 μCi/μg) for *cis*-[^{3}H]tamoxifen.

Preparation of [^{3}H]Hydroxytamoxifen and *cis*-[^{3}H]-Hydroxytamoxifen.[16] The procedural details for the preparation of this compound are very similar to those for the preparation of the tritiated tamoxifen isomers. A mixture (11) of bromohydroxytamoxifen and *cis*-bromohydroxytamoxifen was exposed to 25 Ci of carrier-free tritium gas over a palladium on carbon catalyst in DMF for 1 h. Approximately 1803 mCi of tritiated product was produced, and the purification and isomer separation were again effected by silica gel TLC on 20 × 20 cm plates with a layer thickness of 0.25 mm. Up to 46 mCi of the crude product could be applied, and after two developments in benzene/piperidine (9:1), clean separation of the tritiated isomers was observed. In contrast to the tamoxifen case, the *Z* isomer is less mobile than the *E* isomer. The tritiated compounds were separately eluted from the silica gel and were *quickly dissolved in THF containing butylated hydroxytoluene (BHT) to prevent isomerization.*[18]

By this procedure 167 mCi of *cis*-[^{3}H]hydroxytamoxifen and 231 mCi of [^{3}H]hydroxytamoxifen were isolated (63% of the crude material applied), with the radiochemical purities being approximately 99%. The compounds were stored at approximately 1 mCi/mL in THF containing BHT at −25 °C. After storage for 6 months, both isomers showed radiochemical and isomeric purities of >95% and >90%, respectively.

Determination of the Specific Activity of [^{3}H]-Hydroxytamoxifen. Hydroxytamoxifen has an ultraviolet absorbance pattern with maxima at 247 nm (ε 21 300) and 286 (13 200). The UV spectrum of [^{3}H]hydroxytamoxifen was essentially identical with that of the unlabeled compound, and from the absorbance at 286 nm the specific activity was calculated to be 29.5 Ci/mmol (75.7 μCi/μg).

Acknowledgment. Support for this research was provided by a grant from the National Institutes of Health (USPH AM 15556). D.W.R. was supported by fellowships from the University of Illinois and the Lubrizol Corp. The high-resolution mass spectrometry equipment was provided by a grant from the National Cancer Institute (CA 11388). We are grateful to Dr. A. H. Todd (ICI Ltd., Macclesfield, England) and Dr. L. Trench (ICI, U.S.A.) for supplying samples of *cis*-tamoxifen, *trans*-tamoxifen, and *trans*-hydroxytamoxifen for comparison purposes.

Registry No. 1, 10540-29-1; [^{3}H]-1, 81278-36-6; 2, 13002-65-8; [^{3}H]-2, 81278-37-7; [^{3}H]-3, 81278-38-8; *cis*-[^{3}H]-3, 81278-39-9; 4, 100-66-3; 5, 1878-68-8; 6, 67205-73-6; 7, 81278-40-2; 8, 81278-41-3; 9, 81278-42-4; (*E*)-10, 81278-43-5; (*E*)-10·HCl, 81278-44-6; (*Z*)-10, 81278-45-7; (*Z*)-10·HCl, 81278-46-8; (*E*)-11, 81278-47-9; (*Z*)-11, 76579-87-8; 12, 73557-59-2; 13, 81278-48-0; 14, 81278-49-1; 15, 81278-50-4; 16, 81278-51-5; (*E*)-17, 81278-52-6; (*Z*)-17, 81278-53-7; 2-(dimethylamino)ethyl chloride hydrochloride, 4584-46-7; 2-(4-bromophenyl)-1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-hydroxy-1-phenylbutane, 81278-54-8; 4-[(2-tetrahydropyranyl)oxy]phenyl bromide, 36603-49-3; 2-(4-bromophenyl)-1-[4-[2-(dimethylamino)-ethoxy]phenyl]-1-hydroxy-1-(4-hydroxyphenyl)butane, 76579-93-6; 2-phenyl-1,3-dithiane, 5425-44-5; 4-[2-(dimethylamino)ethoxy]phenyl bromide, 2474-07-9; 4-bromophenol, 106-41-2; 1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-hydroxy-1-phenyl-2-(3,4,5-tribromophenyl) butane, 81278-55-9.

An Efficient and Remarkably Regioselective Synthesis of Benzocyclobutenones from Benzynes and 1,1-Dimethoxyethylene

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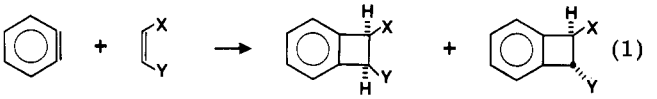
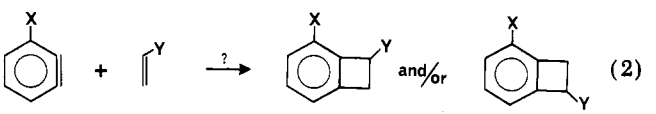
New efficient methodology for the synthesis of substituted benzocyclobutenones is presented that involves the [2 + 2] cycloaddition of various substituted benzynes to 1,1-dimethoxyethylene followed by hydrolysis to the corresponding ketone. In most cases studied a high degree of regioselectivity was observed. These observations are consistent with a nonsynchronous mechanism wherein steric and inductive considerations can be used to account for the products observed.

In recent years benzocyclobutenes have been established as valuable intermediates in organic synthesis.[1] A number of methods have been developed for the synthesis of such systems. Of these, the thermal [2 + 2] cycloaddition of benzynes to olefins is certainly the most direct route.[2] Such cycloadditions involving benzyne and 1,2-disubstituted olefins (eq 1) have been shown to yield mixtures of stereoisomers (stereoretention predominating), thereby establishing mechanistically a stepwise course of reaction.[3] From a purely preparative point of view, the synthesis of





benzocyclobutenes via such [2 + 2] cycloadditions has not been utilized extensively. This can be attributed in part to the modest yields (<50%) usually obtained and to the fact that the regiochemistry of such cycloadditions involving unsymmetric olefin and benzyne partners (eq 2) has received very little attention.[4] In connection with studies aimed at the total synthesis of certain complex

(1) See; (a) Oppolzer, W. *Synthesis* **1978**, 793. (b) Jackson, D. K.; Narasimhan, N. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3989. (c) Kametani, T.; Honda, T.; Fukumoto, K. *Heterocycles* **1980**, *14*, 419. (d) Gould, K. J.; Hacker, N. P.; McOmie, J. F. W.; Perry, D. H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1834. (e) Kametani, T; Fukumoto, K. *Heterocycles*, **1975**, *3*, 29. (f) Arnold, B. J.; Sammes, P. G.; Wallace T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 409, 415.

(2) (a) Klundt, I. L. *Chem. Rev.* **1970**, *70*, 471. (b) Thummel, R. P. *Acc. Chem. Res.* **1980**, *13*, 70. (c) Dhawan, D. L.; Gowland, B. D.; Durst, T. *J. Org. Chem.* **1980**, *45*, 922.

(3) Bowne, A. T.; Christopher, T. A.; Levin, R. H. *Tetrahedron Lett.* **1976**, 4111 and references cited therein.

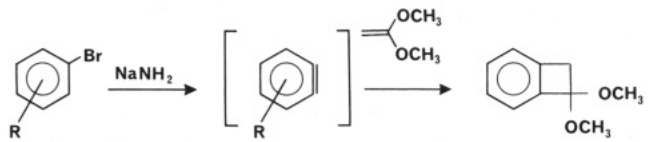
(4) Cyclic enamines and cyclic enolates have been reacted with some substituted benzynes to provide some [2 + 2] adducts: Kametani, T.; Kigasawa, K.; Hayasaka, T.; Kusama, O. *J. Chem. Soc. C* **1971**, 1051. Carre, M. C.; Caubere, P.; Viriot-Villaume, M. L. *Synthesis* **1979**, 48.

0022-3263/82/1947-2393$01.25/0

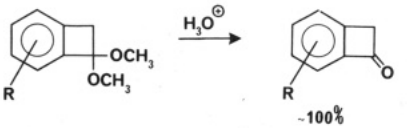
diterpenoids[5] we undertook the present study in order to define further the scope and/or limitations of such unsymmetrical cycloadditions.

We selected 1,1-dimethoxyethylene as the unsymmetrical olefinic partner for several reasons. First, since it is known that benzynes are inherently electrophilic,[6] we felt the choice of a highly electron-rich olefin might afford cycloadducts in greater yield than heretofore realized. Second, the resultant adducts would be readily amendable to a variety of further synthetically useful transformations.[7] Finally, we anticipated that strongly polarized and/or sterically biased olefins might display pronounced regiochemical preferences in their reaction with substituted benzynes insofar as it is known that the orientation of attacking (simple) nucleophiles is influenced by (a) the steric environment near the benzyne bond and (b) substituent-induced polarization of the benzyne bond.[8]

The benzynes were generated from the corresponding bromarenes via sodium amide induced dehydrobromination in refluxing THF or with no solvent.



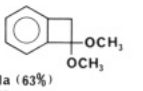
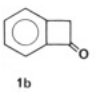
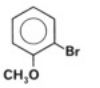
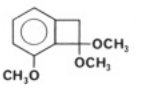
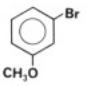
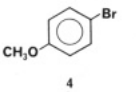
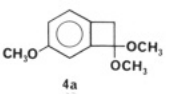
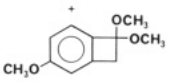
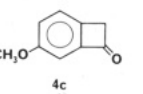
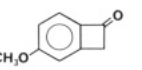
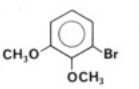
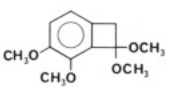
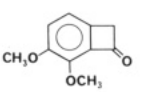
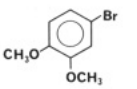
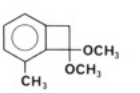
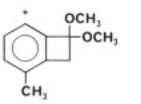
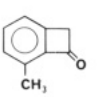
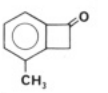
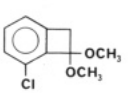
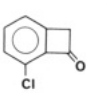
Results of the cycloadditions are summarized in Table I. In a few cases somewhat higher yields of cycloadduct were obtained in the absence of solvent. Depending on the system, reaction was usually complete within 6–12 h. Some variation in reaction time was observed even within multiple runs of the same system. The reasons for this variation are not known. In all cases, an induction period of from 0.5 to several hours was recorded before reaction began. Commercial sodium amide was normally employed in these reactions when it was found that the use of freshly prepared sodium amide or the inclusion of small amounts of sodium amide activating substances such as NaO-*t*-Bu[9] seemed to offer no particular advantage either in terms of duration of reaction or yield.[10] The course of each reaction was monitored conventiently by gas chromatography. After reaction was complete pure benzocyclobutenone, dimethyl ketals were obtained in the yields indicated in Table I by simple distillation. Hydrolysis of each ketal to the corresponding benzocyclobutenone proceeded in essentially quantitative yield at room temperature.



Alternatively, the crude ketal reaction mixture could be hydrolyzed immediately and the resultant benzocyclobutenone purified by sublimation or chromatography. The yields of dimethyl ketal cycloadducts were all good (64–76%) except for the case involving *m*-bromotoluene (**7**) (38%). Nevertheless, cycloadducts **7a** and **7b** were the only volatile materials found in the crude reaction mixture, thus facilitating isolation and purification. In those cases where mixtures of ketal regioisomers were obtained (from bromoarenes **4** and **7**) it was found advantageous to effect separation after hydrolysis to the corresponding ketones since the ketals themselves were labile to various chromatographic conditions.

Cycloaddition proceeded regiospecifically with bromoarenes **2**, **3**, **5**, and **6**. In these cases, none of the regioisomer could be detected by gas chromatography or 200-Mz NMR spectroscopy. Furthermore, the isomeric bromoanisoles **2** and **3** provided the same cycloadduct (**2a**), implicating

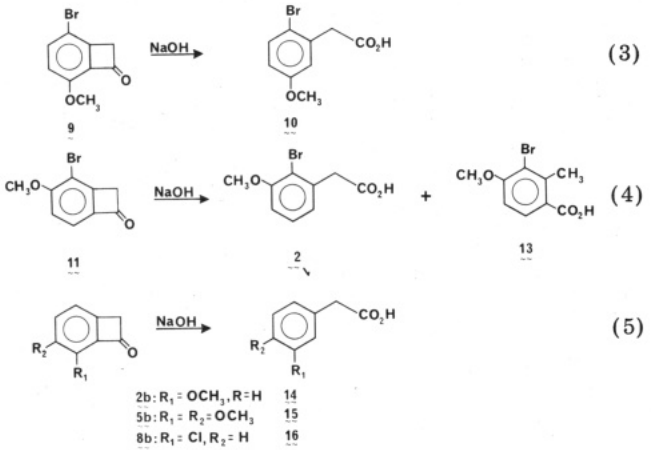
Table I

bromoarene	solvent	cycloadduct, % yield	benzocyclo butenone
 1	none	 1a (63%)	 1b
 2	THF	 2a (70%)	 2b
 3	none	2a (76%)	
 4	THF	 4a +  4b 4a:4b=7:1 (64%)	 4c  4d
 5	THF	 5a (73%)	 5b
 6	THF	5a (69%)	
 7	THF	 7a +  7b 7a:7b=3:1 (38%)	 7c  7d
 8	THF	 8a (76%)	 8b

(5) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 0000.
(6) Rondan, N. G.; Domelsmith, L. N.; Houk, K. N.; Bowne, A. T.; Levin, R. H. *Tetrahedron Lett.* **1979**, 3237.
(7) For selected examples of transformations of benzocyclobutenes see: (a) Bubb, W. A.; Sternhell, S. *Aust. J. Chem.* **1976**, *29*, 1685. (b) Cava, M. P.; Mangold, D.; Muth, K. *J. Org. Chem.* **1964**, *29*, 2947. (c) Cava, M. P.; Mitchell, M. J. *Ibid.* **1962**, *27*, 631. (d) Hart, H.; Hartlage, J. A.; Fish, R. W.; Rafos, R. R. *Ibid.* **1966**, *31*, 2244. (e) Kametani, T.; Katoh, Y.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1712.
(8) Hoffmann, R. W. "Dehydrobenzene and Cycloalkynes"; Academic Press: New York, N.Y., 1967.
(9) Caubere, P. *Acc. Chem. Res.* **1974**, *7*, 301.
(10) The addition of larger amounts of NaO-*t*-Bu (0.25–1.0 equiv based on bromoarene) to the reaction mixture resulted in a very rapid disappearance of starting material, but the yields of cycloadduct were reduced greatly. In these cases, the crude reaction product consisted largely of nonvolatile residues.

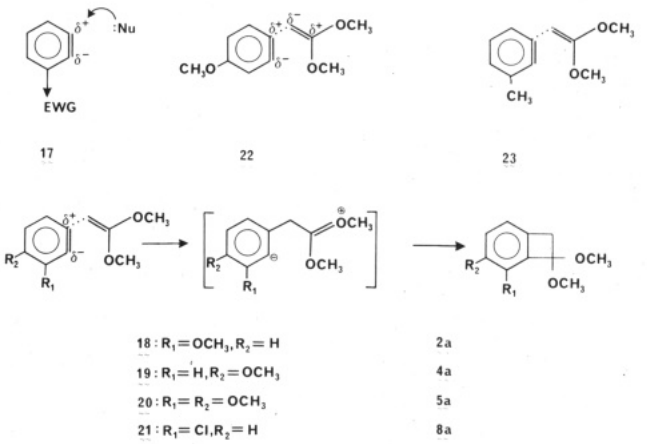
a common benzyne intermediate (vide infra). Similarly, the isomeric bromoveratroles **5** and **6** afforded the adduct (**5a**). The marked preference for bromoarenes such as **3** or **6** to undergo regiospecific dehydrobromination is due to the enhanced acidity of the proton ortho to the two inductively electron-withdrawing groups and has been described previously in some detail.[8] Bromoarenes **4** and **7** yielded a mixture of both regioisomers although even in these cases some selectivity was observed. *m*-Bromochlorobenzene (**8**) underwent dehydrobromination[11] to afford cycloadduct **8a** and a trace (~3%) of an unidentified volatile side-product detected by gas chromatography.

The spectral and physical constants of benzocyclobutenones **1b**, **2b**, **4c**, and **4d** were in agreement with literature values for these compounds.[12] Benzocyclobutenone **7d** has also been reported previously[13] but only its melting point was reported. Benzocyclobutenones **5b**, **7c**, and **8b** appear to be new compounds. A positive distinction between known **7d**[13] (mp 53–54 °C) and its isomer **7c** (mp 68–69 °C) could be made with the use of the Eu(fod)$_3$ shift reagent. Thus, successive addition of small portions of the shift reagent to an NMR sample of the mixture of **7c** and **7d** in $CDCl_3$ caused a significant downfield shift in the methyl resonance of **7c** while leaving the methyl resonance of **7d** relatively unaffected. This behavior is that predicted by assuming coordination of the europium reagent to the carbonyl oxygen of each isomer. In order to establish unambiguously the regiochemistry of **5b** and **8b**, the following experiments were performed. It has been established previously that benzocyclobutenones substituted at the 6-position with an inductively electron-withdrawing substituent (e.g., methoxy) suffer ring fission exclusively to the corresponding phenylacetic acid when treated with alkali (for example, see eq 3).[14] In the



absence of such a substitutent at the 6-position fission occurs to yield both the corresponding phenylacetic and *o*-toluic acids in roughly equal amounts (for example, see eq 4). In the present study, alakli fission of the known benzocyclobutenone **2b** afforded quantitatively (*m*-methoxyphenyl)acetic acid (**14**). Similarly, treatment of **5b** and **8b** with base provided quantitative yields of (3,4-dimethoxyphenyl)acetic acid (**15**) and (*m*-chlorophenyl)acetic acid (**16**), respectively. The alternate regioisomers of benzocyclobutenones **5b** and **8b** would not be expected to afford these results upon fission.

The regioselectivity of the [2 + 2] cycloadditions reported in this investigation parallels that observed in the addition of simple nucleophiles to various substituted benzynes[8] and can be attributed to a combination of steric and inductive effects. Thus, it is known that benzynes flanked by an adjacent electron-withdrawing group are attacked preferentially at the least hindered and most electron-deficient carbon atom of the benzyne bond (cf. 17). In the present study benzyne intermediates **18–21**



[derived from bromoarenes **2** (or **3**), **5** (or **6**), and **8**, respectively] are sterically and inductively polarized in a similar fashion and accept the highly polarized olefinic partner regiospecifically. Cycloaddition of dimethoxyethylene to benzyne **22** is obviously not affected by steric interactions. Nevertheless substantial regioselectivity is still observed and in the direction anticipated on the basis of the inductive effect of the methoxy group. Finally, benzyne **23** (from o-bromotoluene, **7**) is only weakly polarized, and the preferred orientation must rely on steric effects to align the approaching olefin. Accordingly, much lower regioselectivity is observed.

Experimental Section

Infrared spectra were recorded on a Beckman IR 4210 or Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were taken on a Bruker WP-200 spectrometer at 200.133 MHz with tetramethylsilane as internal standard. Mass spectra were determined on a AEI-MS 9 spectrometer. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Gas chromatographic analyses were performed on a Hewlett-Packard 5710A chromatograph equipped with a flame ionization detector and fitted with an 8 ft × $^1/_8$ in. OV-17 on Anakrom ABS 100/110 column. All bromoarenes used in this study with the exception of 3-bromoveratrole were available commercially and were distilled prior to use. All reactions were run under an atmosphere of nitrogen. THF and diethyl ether were distilled before use from sodium–benzophenone.

1,1-Dimethoxyethylene was made from bromoacetaldehyde dimethyl acetal by the method of Corey et al.[15] The bromoacetaldehyde dimethyl acetal (bp 60 °C (30 mm)) was synthesized from vinyl acetate according to a procedure in ref 16 for the corresponding diethyl acetal. The only modifications involved the substution of methanol for ethanol and the use of an addition funnel for the direct addition of reagent grade bromine to the reaction flask.

3-Bromoveratrole (5). To a stirred solution of 20.0 g (0.217 mol) of tetramethylethylenediamine and 150 mL of ether at 0 °C

(11) Dehydrobromination of *m*-bromochlorobenzene with KNH_2 in liquid NH_3 has been reported: Bunnet, J. F.; Kearly, F. J. *J. Org. Chem.* **1971**, *36*, 184.

(12) **1b**: Arnold, B. J.; Sammes, P. *J. Chem. Soc., Perkin Trans. 1* **1974**, 415. **2b**: Kametani, T.; Takeshita, M.; Nemoto, H.; Fukumoto, K. *Chem. Pharm. Bull.* **1978**, *26*, 556. **4c**; see ref **7e**. **4d**: Tomita, M.; Minami, S.; Uyeo, S. *J. Chem. Soc. C* **1969**, 183.

(13) Schiess, P.; Heitzmann, M. *Agnew. Chem.* **1977**, *89*, 485.

(14) Amupitan, J. O.; Stansfield, J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1949.

(15) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

(16) *Org. Synth. Coll. Vol.* **3**, **1955**, 123.

was added 88.7 mL of *n*-butyllithium (2.45 M in hexane). The reaction mixture was stirred at room temp for 1 h, then cooled to −78 °C, and 34.7 g (0.217 mol) of bromine was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 1 h. Water was then added carefully at 0 °C. The ether layer was separated, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and fractional distillation yielded 25.5 g (81%) of 3-bromoveratrole: bp 70 °C (0.5 mm) (lit[17] bp 111–113 °C (9 mm)); NMR ($CHCl_3$) δ 3.86 (s, 3 H), 3.87 (s, 3 H), 6.80–7.12 (m, 3 H).

General Procedure for the Preparation of Benzocyclobutenones. A mixture of 1 equiv of bromoarene, 2 equiv of $NaNH_2$, and 2 equiv of 1,1-dimethoxyethylene in THF (approximately 3 mL/mmol of bromoarene) was stirred at reflux. In those cases where no solvent was used (see Table I), 1 equiv of bromoarene was stirred with 2 equiv of $NaNH_2$ and 4 equiv of 1,1-dimethoxyethylene at 75–80 °C. Typically 0.5–5.0 g of bromoarene was employed in this study. The reaction mixtures gradually turned brown, and the reaction was judged complete when no bromoarene could be observed by gas chromatography. Even within multiple runs employing the same bromarene the reaction time varied widely, necessitating monitoring each reaction by gas chromatography. The reaction mixture was allowed to cool to room temperature and water was added carefully to destroy excess $NaNH_2$. The products were isolated by extraction with ether. The combined ether extracts were then washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent left a brown oil, which was distilled under reduced pressure to provide the pure ketal.

Hydrolysis of the ketal was effected by stirring in THF–water (5:1) containing a trace of HCl for 2 h. Most of the THF was removed in vacuo and the residue extracted with ether. The combined ether extracts were then washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the ether afforded quantitatively the pure benzocyclobutenone.

The mixtures of regioisomers (**4c** and **4d**; **7c** and **7d**) were separated on a column of silica gel (Merck, 70–230 mesh) with ether–hexane as eluant.

Spectral Data for Benzocyclobutenones and Their Dimethyl Ketals.[12] **1a**: IR (neat) 2920, 2819, 1595, 1454, 1330, 1278, 1243, 1206, 1151, 1133, 1113, 1083, 1054, 1033, 850, 754, 720 cm^{-1}; NMR ($CDCl_3$) δ 3.37 (s, 2 H), 3.45 (s, 6 H), 7.20–7.38 (m, 4 H).

2a: IR (neat) 2923, 2820, 1600, 1474, 1438, 1340, 1270, 1234, 1204, 1149, 1131, 1101, 1078, 1030, 940, 868, 843, 768, 735 cm^{-1}; NMR ($CDCl_3$) δ 3.30 (s, 2 H), 3.47 (s, 6 H), 3.85 (s, 3 H), 6.37 (d, J = 8 Hz, 1 H), 6.82 (d, J = 7 Hz, 1 H), 7.29 (dd, J = 7, 8 Hz, 1 H).

5a: IR (neat) 2936, 2832, 1591, 1485, 1433, 1330, 1258, 1234, 1200, 1170, 1133, 1110, 1055, 1026, 991, 856, 830, 800, 744, 709 cm^{-1}; NMR ($CDCl_3$) δ 3.32 (s, 2 H), 3.42 (s, 6 H), 3.84 (s, 3 H), 4.03 (s, 3 H), 6.74 (d, J = 8 Hz, 1 H), 6.88 (d, J = 8 Hz, 1 H).

5b: mp 86–87 °C (petroleum ether); IR ($CHCl_3$) 3030, 3005, 2953, 2837, 1759 (C=O), 1603, 1583, 1490, 1454, 1435, 1410, 1350, 1268, 1258, 1179, 1128, 1066, 1049, 995, 970, 846, 808, 655 cm^{-1}; NMR ($CDCl_3$) δ 3.87 (s, 5 H, OCH_3, CH_2), 4.21 (s, 3 H), 6.94 (d, J = 8 Hz, 1 H), 7.04 (d, J = 8 Hz, 1 H).

7c: mp 68–69 °C (petroleum ether); IR ($CHCl_3$) 3020, 2925, 1759 (C=O), 1610, 1585, 1482, 1336, 1223, 1161, 1148, 1029, 967, 921 cm^{-1}; NMR ($CDCl_3$) δ 2.41 (s, 3 H), 3.93 (s, 2 H), 7.11–7.45 (m, 3 H).

7d: mp 53–54 °C (petroleum ether) (lit[13] mp 53–54 °C); IR ($CHCl_3$) 3007, 2920, 1750 (C=O), 1587, 1482, 1405, 1322, 1254, 1228, 1218, 1201, 1162, 1142, 1006, 971, 698 cm^{-1}; NMR ($CDCl_3$) δ 2.37 (s, 3 H), 391 (s, 2 H), 7.10–7.35 (m, 3 H).

8a: IR ($CHCl_3$) 3004, 2933, 2895, 2830, 1500, 1458, 1302, 1218, 1150, 1130, 1092, 1074, 1038, 946, 912, 837, 815 cm^{-1}; NMR ($CDCl_3$) δ 3.19 (s, 2 H), 3.41 (s, 6 H), 5.91 (s, 2 H, OCH_2O), 6.72 (s, 1 H), 6.79 (s, 1 H).

8b: mp 120–121 °C (petroleum ether); IR ($CHCl_3$) 3030, 3000, 2920, 2892, 1748 and 1757 (C=O), 1590, 1501, 1464, 1288, 1159, 1120, 1033, 948, 901, 858 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (s, 2 H), 6.06 (s, 2 H, OCH_2O), 6.76 (s, 1 H), 6.95 (s, 1 H).

Base-Induced Cleavage of Benzocyclobutenones 2b, 5b, and 8b. The benzocyclobutenone (100 mg) was stirred in 15 mL of 10% aq NaOH at 60 °C for 2 h. The mixture was cooled to room temperature and acidified with concentrated hydrochloric acid. The resultant crystalline product was collected by filtration, rinsed with water, and air dried to afford the corresponding pure phenylacetic acid **14**–**16** in quantitative yield. The spectral and physical properties of each sample were identical with those of commercially available samples.

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Registry No. **1**, 108-86-1; **1a**, 81447-53-2; **1b**, 3469-06-5; **2**, 578-57-4; **2a**, 81447-54-3; **2b**, 66947-60-2; **3**, 2398-37-0; **4**, 104-92-7; **4a**, 81447-55-4; **4b**, 81447-56-5; **4c**, 55171-77-2; **4d**, 22246-27-1; **5**, 5424-43-1; **5a**, 81447-57-6; **5b**, 81447-58-7; **6**, 2859-78-1; **7**, 95-46-5; **7a**, 81447-59-8; **7b**, 81447-60-1; **7c**, 81447-61-2; **7d**, 62708-44-5; **8**, 108-37-2; **8a**, 81447-62-3; **8b**, 81447-63-4; **14**, 1798-09-0; **15**, 93-40-3; **16**, 1878-65-5; 1,1-dimethoxyethylene, 922-69-0.

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Benzocyclobutenones as Synthons for the Synthesis of C-11 Oxygenated Diterpenoids. Application to the Total Synthesis of (±)-Taxodione

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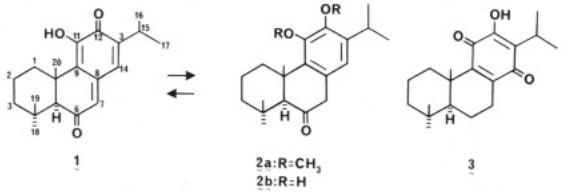
An efficient ten-step total synthesis of racemic taxodione is described. Key steps involve the regiospecific synthesis of benzocyclobutenone **8** via a [2 + 2] cycloaddition (**6** to **8**) and a regioselective base-catalyzed opening of benzocyclobutenol **13** to afford enone **16**.

In 1968 Kupchan et al., reported[1] the isolation of an interesting quinone methide diterpene, taxodione (**1**), from extracts off *Taxodium distichum* Rich (Taxodiaceae). This compound exhibited significant activity in vivo against Walker intramuscular carcinosarcoma 256 in rats and in vitro against cells derived from human carcinoma of the nasopharnyx (KB). In addition, Kupchan reported the conversion of taxodione to the octahydro-



1 **2a**: R = CH_3; **2b**: R = H **3**

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