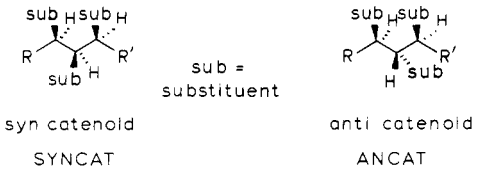
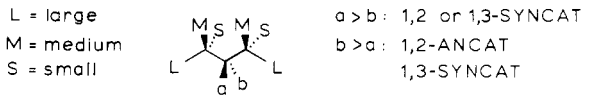
at the same point in the chain, a relative weighting is, of course, required.



A description of this type is commonly required for correlation of results of stereodirected reactions, where acyclic or macrocyclic diastereomers with (more or less) one predominant relative stereochemistry are obtained. It is also useful for correlation of physical and chemical properties of such molecules. To these ends, one is primarily interested in the stereochemical properties of the chain substituents and not in their Cahn–Ingold–Prelog ratings. Thus, such a description of relative stereochemistry should be based on weighting of substituents according to steric volume (large vs. small), as commonly used in conformational analysis. In order to maximize the chemical generalizations derivable from the substituted staggered chain convention, the ends of the chain should be represented by the groups with the largest steric bulk.[15]



(14) A syn vs. anti nomenclature for substituents on a staggered chain was initially proposed by S. Masamune, SK. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew, Chem., Int. Ed. Engl.* **1980**, *19*, 557, footnote 7. If syn and anti refer to the relationships of any named *substituents*, syncat and ancat refer to the relationship of the *substituted centers, based on size of substituents*, as used in conformational analysis. We thank Professor Masamune for providing a manuscript in which a nomenclature of syn or anti is used to express relative stereochemistry of *substituted centers*, derived from *Cahn–Ingold–Prelog priorities of substituents*.

For a rigorous definition, this description can be inferior to the one given at the beginning of this paper (pref–parf) since a choice of relative group size can become ambiguous. (In such cases, it can be used in conjunction with a pref–parf specification.) However, the SYNCAT–ANCAT description will serve organic chemists in the vast majority of cases without ambiguity and, most importantly, it will allow even in verbal discussion an instant recognition of conformation and communality of chemical properties. For instance, in comparison of adjacent centers, those with noninteracting substituents that are ANCAT are always of lower energy than those with SYNCAT stereochemistry. Formation of ANCAT vs. SYNCAT centers also allows direct visualization of the relative transition-state energies leading to such products. This description of relative stereochemistry thus saves all of the useful chemical information that could be derived from the conformational analysis use of erythro vs. threo[5] without the confusion that the diverse uses of those terms have generated and with the added applicability to multiply substituted acyclic and macrocyclic molecules.

Acknowledgment. We thank the Editor, Professor Frederick D. Greene, and the reviewers of earlier versions of this manuscript for their encouragement and suggestions, many of which are included here. In addition, the ideas described have benefited from discussions with several colleagues. Particular thanks are due Professor Gary Newton (University of Georgia) for his help.

(15) At times this may be inconvenient or ambiguous. However, there should be no confusion in any (verbal) description about which groups are the termini of a staggered chain since they will provide the name for the chain and the substituents on the chain will be listed as such by the usual chemical nomenclature.

The syncat–ancat description should be particularly useful for descriptions of multiple-substituted long chains or macrocycles where one can describe the entire stereochemistry by listing the substituent positions along the chain by numbers (a, b, c, etc.) for the majority of substituents on one side: (a, b, c, syncat), the remaining substituents at other positions along the chain are then understood to be relatively ancat derived.

Practical Multigram Syntheses of Benzocyclobutenediones

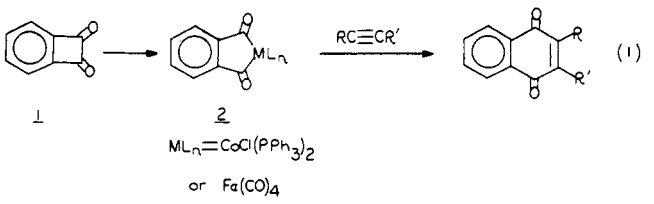
Michael S. South and Lanny S. Liebeskind*

Department of Chemistry, Florida State University, Tallahassee, Florida 32306

Received February 12, 1982

Experimentally simple syntheses of benzocyclobutenedione and substituted benzocyclobutenediones (3-OH; 4-OH; 4-Me; 3-OH, 5-Me) are described which allow the synthesis of these compounds on large scale from inexpensive starting materials. The regiospecific and stereoselective cycloaddition of trimethylsiloxy dienes to 1,4-dichloro-3,3,4-trifluorocyclobutene forms the basis of the synthesis of the substituted benzocyclobutenediones.

We recently described an organo-transition-metal approach to naphthoquinones which required benzocyclobutenedione as a starting material (eq 1).[1] The high-yield preparation of the phthaloylmetal complexes **2**[2] and the subsequent high-yield synthesis of a wide variety of substituted naphthoquinones[3] could make this a method of choice for the synthesis of functionalized naphthoquinones if two criteria can be met. Benzocyclobutenedione and substituted benzocyclobutenediones must be readily available on a multigram scale, and the substituted diones



(1) Liebeskind, L. S.; Baysdon, S. L.; South, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 7397.

(2) Liebeskind, L. S.; Baysdon, S. L.; South, M. S.; Blount, J. F. *J. Organomet. Chem.* **1980**, *202*, C73.

(3) In addition to our naphthoquinone synthesis described in ref 1, we have recently prepared a stable cationic phthaloylcobalt complex which reacts with many functionalized alkynes within 2 h at 80 °C in CH_2Cl_2 to give high isolated yields of substituted naphthoquinones: Baydson, S. L.; Liebeskind, L. S. *Organometallics* **1982**, *1*, 771.

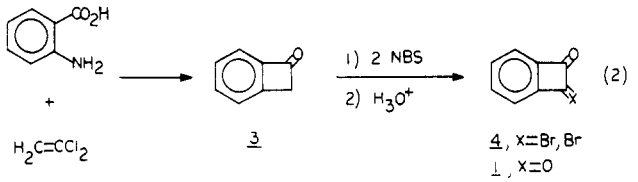
0022-3263/82/1947-3815$01.25/0

must form phthaloylmetal complexes which in turn must react regioselectively (or specifically) with unsymmetrical alkynes. This paper describes a solution to the first problem; our efforts to solve the second problem are underway and will be the subject of a future paper.

The synthesis of benzocyclobutenediones has received some attention in the literature.[4-7] Although McOmie's method for the pyrolysis of phthalazinedione–anthracene adducts gives high yields of some substituted benzocyclobutenediones,[6] the procedure, as described in the literature and in our hands, was convenient only for the preparation of milligram quantities of material. Our need for the large-scale preparation of these compounds prompted a search for a more practical method of synthesis.[8]

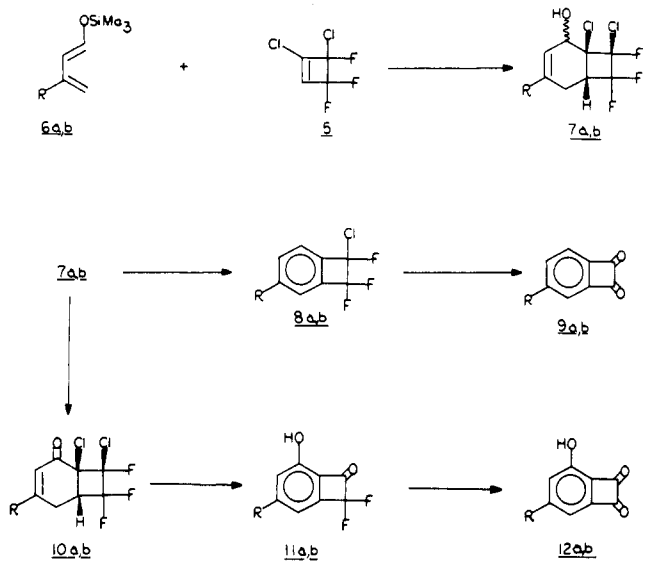
Results

A conversion of anthranilic acid to the parent dione 1 was readily achieved on ≥30-g scale (40% overall yield) by combining two literature observations. In his pioneering studies on benzocyclobutenedione, Cava showed that benzocyclobutenone 3 could be converted into benzocyclobutenedione in high yield by a bromination–hydrolysis sequence (3 → 4 → 1).[9] A recent preparation of benzocyclobutenone from anthranilic acid via benzyne addition to vinylidene chloride[10] provided the means of synthesizing benzocyclobutenedione on large scale from inexpensive materials (eq 2).



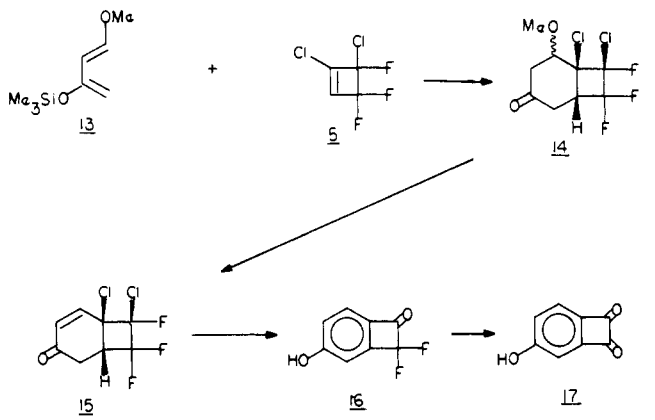
A similar benzyne approach to substituted benzocyclobutenediones did not seem to offer much merit, so we resorted to the Diels–Alder reaction to generate the substituted aromatic ring. After encountering many difficulties in an attempt to use 1-chlorocyclobut-1-ene-3,4-dione[11] as a dienophile for reaction with siloxy dienes,[12] we chose to mask the required carbonyl groups until the aromatic portion of the molecule had been formed. This tactic led us to explore the Diels–Alder chemistry of 1,4-dichloro-3,3,4-trifluorocyclobutene (5).[13] Reaction of cyclobutene 5 with 1-trimethylsiloxy dienes 6a and 6b occurred regiospecifically in the absence of solvent to give cycloadducts 7a and 7b, respectively, in high yield after desilylation (Scheme I). Each adduct existed as a mixture of two epimeric alcohols (vida infra). Aromatization to the tetrahalobenzocyclobutenes 8a and 8b proceeded readily with NaOMe/MeOH at 0 °C and subsequent hydrolysis with 70% H_2SO_4 at 100 °C provided benzocyclobutenedione 9a (1) and 4-methylbenzocyclobutenedione 9b in overall yields of 63% and 72%, respectively. Alternatively, the Diels–Alder adducts 7a and 7b could be oxidized in high yield to enones 10a and 10b. Aromatization again proceeded readily with NaOMe/MeOH; however, a tetrahalobenzocyclobutene did not result. Rather, the geminal chlorofluoro group was specifically converted to a dimethyl ketal, presumably via phenoxide assistance. Instead of isolating the ketal, the NaOMe/MeOH aromatization was followed by a dilute acid hy-

Scheme I[a]



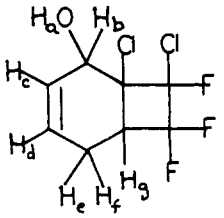
[a] a, R = H; b, R = Me.

Scheme II



(4) Original synthesis: Cava, M. P.; Napier, D. R.; Pohl, R. J. *J. Am. Chem. Soc.* **1963**, *85*, 2076.
(5) Schmidt, A. H.; Ried, W. *Synthesis* **1978**, 869.
(6) Gould, K. J.; Hacker, N. P.; McOmie, J. F. W.; Perry, D. H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1834 and references therein.
(7) Abou-Teim, O.; Jansen, R. B.; McOmie, J. F. W.; Perry, D. H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1841.
(8) Swenton has recently described a pyrolytic method for the synthesis of substituted benzocyclobutenones which is adaptable to large scale (Chenard, B. L.; Slapak, C.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1981**, 179). The products can be converted into benzocyclobutenediones: Anderson, D. K.; Chenard, B. L.; Slapak, C.; Swenton, J. S. 181st National Meeting of the American Chemical Society, Atlanta, GA, Mar 29–Apr 3, 1981; American Chemical Society: Washington, DC, 1981; ORGN 86.
(9) Cava, M. P.; Mangold, D.; Muth, K. *J. Org. Chem.* **1964**, *29*, 2947.
(10) Dürr, H.; Nickels, H.; Pacala, L. A.; Jones, M., Jr. *J. Org. Chem.* **1980**, *45*, 973.
(11) Synthesized from 1-hydroxycyclobut-1-ene-3,4-dione by treatment with $(COCl)_2$–DMF. See: Bellus, D.; Fischer, H.; Greuter, H.; Martin, P. *Helv. Chim. Acta* **1978**, *61*, 1784. Bellus, D. *J. Am. Chem. Soc.* **1978**, *100*, 8026.
(12) The formation of 4,5-dimethylbenzocyclobutenedione from 2,3-dimethylbutadiene and 1-(thiomethyl)cyclobut-1-ene-3,4-dione has been reported (Seitz, G.; Sutrisno, R.; Kämphen, T. *Chem.-Ztg.* **1980**, *104*, 12). In our hands, reaction of the thiobutyl- or chlorocyclobutenedione with 1-(trimethylsiloxy)butadiene or 1-(trimethylsiloxy)-3-methyl-1,3-butadiene or with vinylketene acetals did not result in a controllable Diels–Alder reaction.
(13) Dienophile 5 is readily available in quantity from chlorotrifluoroethylene and vinylidene chloride by a thermal [2 + 2] reaction to 1,1,2-trichloro-2,3,3-trifluorocyclobutane followed by dehydrochlorination with triethylamine in ether as described in: Raasch, M. S.; Miegel, R. E.; Castle, J. E. *J. Am. Chem. Soc.* **1959**, *81*, 2678–2680. Alternatively, 1,1,2-trichloro-2,3,3-trifluorocyclobutane is commercially available from PCR. We wish to emphasize that no rigorous mechanistic information is implied in our use of the terms "Diels–Alder" or "cycloaddition".

Table I. 270-MHz ^{1}H NMR Spectral Data for Alcohol 7a[a]



Chemical Shifts

proton	major isomer	minor isomer
H_a	3.07 (d, J = 9 Hz[b])	2.64 (dd, J = 7, 1.5 Hz[b])
H_b	4.63 (br d, J = 9 Hz)	4.58 (br s)
H_c	5.78 (m)	5.97 (d, J = 11 Hz with 1-Hz allylic couplings)
H_d		5.90 (m)
H_e[c]	2.56 (m)	2.53 (dd, J = 17, 7 Hz)
H_f[c]	2.43 (br d, J = 18 Hz)	2.36 (br dd, J = 17, 8 Hz)
H_g	3.21 (m)	3.28 (15-line m)

Selected Coupling Constants, Hz[d]

proton	major isomer	minor isomer
a,b	9	7
b,c	small	0
b,d		~2
d,e	~2	7
d,f	~0	0
e,f	18	17
e,g	9	0
f,g	~0	8

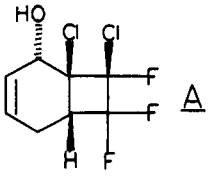
[a] Recorded in $CDCl_3$. [b] Exchanges with D_2O. [c] The lower field absorption of the methylene protons is arbitrarily designated H_e and the higher field absorption H_f. This does not imply that a specific methylene proton will have the same letter designation in both isomers. [d] Either apparent or derived by double-frequency decoupling experiments.

drolysis (1.2 N HCl/MeOH) which gave difluorobenzocyclobutenones **11a** and **11b**. Then, more vigorous hydrolysis produced 3-hydroxybenzocyclobutenedione (**12a**) and 3-hydroxy-5-methylbenzocyclobutenedione (**12b**) in 36% and 63% overall yields, respectively.

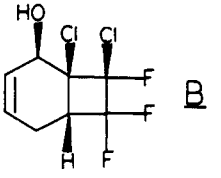
Reaction of Danishefsky's diene, **13**, with 1,4-dichloro-3,3,4-trifluorocyclobutene (**5**) proceeded at 120 °C to give cycloadduct **14** after mild hydrolysis (Scheme II). We found it most convenient to convert this mixture of epimers to crystalline enone **15** (PTSA, benzene, reflux) which on aromatization with NaOMe/MeOH followed by dilute acid hydrolysis gave difluorobenzocyclobutenone **16** in a manner analogous to the formation of **11a** and **11b** (Scheme I). More vigorous hydrolysis of the geminal difluoro group provided 4-hydroxybenzocyclobutenedione (**17**) in 43% overall yield.

Discussion

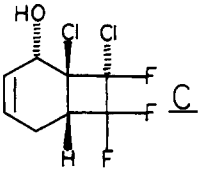
The Diels–Alder reaction of 1,4-dichloro-3,3,4-trifluorocyclobutene (**5**) with any of the dienes used in this work could have proceeded to eight different racemic isomers. There are two regiochemical possibilities: the 1-substituent of the diene and the vinyl chlorine of the dienophile could be "ortho" or "meta" in the cycloadduct. Also, there is the usual stereochemical alternative of an exo vs. an endo transition state (with respect to the cyclobutene ring or with respect to the vinyl chlorine substituent), and, in addition, the dienophile carries a chiral center at the geminal chlorofluoro group so the dienophile can approach from either the "chloro face" or the "fluoro face" of the dienophile. The regio- and stereochemical assignments of Diels–Alder adduct **7a** were determined in the following manner. Analysis of the product of the reaction of diene **6a** with dienophile **5** (after hydrolysis of the trimethylsilyl group) by ^{1}H NMR, GLC, and TLC indicated that only two of the eight possible isomers had formed. Separation of the mixture by medium-pressure liquid chromatography gave primarily one alcohol (less polar) along with smaller amounts of a second alcohol (78:22 ratio). The 270-MHz ^{1}H NMR spectral data of the two alcohols are tabulated in Table I. Assignment of the absorptions to the various protons was straightforward based on chemical shift data. Analysis of the various coupling constants derived from double-resonance decoupling experiments established that for both the major and minor isomers H_b was strongly coupled only to the hydroxylic proton, H_a ($J_{a,b}$ = 9 and 7 Hz, respectively), and did not show any other significant vicinal coupling. Small couplings to the olefinic protons H_c and/or H_d were apparent. In each case the methylene protons H_e and H_f were coupled to each other (18 and 17 Hz, respectively), and in each case, one of the methylene protons showed significant vicinal coupling to an adjacent proton other than the olefinic proton, H_d. In the major isomer H_e was coupled to H_g (9 Hz), and the minor isomer had H_f coupled to H_g (8 Hz). Therefore, the regiochemistry of the cycloaddition was established as exclusively "ortho" for each isomer. Subsequent oxidation of each alcohol of **7a** gave the same enone, **10a**, identical by TLC, GLC, IR, 270-MHz ^{1}H NMR, and mixture melting point. Therefore, the two isomeric alcohols must have been epimeric only at the hydroxyl substituent. Knowing the above results and realizing that the six–four ring fusion must be cis, we were left with two sets of structures that could satisfy the available data for epimeric alcohols **7a**. Structures A and B represent an exo–endo pair of isomers that resulted from



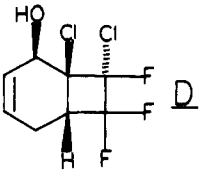
A



B



C



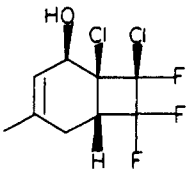
D

cycloaddition at the "fluoro face" of the dienophile, and C and D are the corresponding isomers from attack at the "chloro face". Since $[_\pi 4_s + _\pi 2_s$ cycloaddition to 3,4-substituted cyclobutenes occurs preferentially from the side opposite the substituents,[14] we presumed that the diene would approach dienophile **5** from the less-hindered "fluoro face" and that structures A and B represent the two epimeric alcohols in question. The complexity of the ^{1}H NMR spectra caused by the presence of three fluorine atoms as well as the conformational effects of the fused cyclobutane ring precluded a confident correlation of structures A and B with the corresponding less polar (major) and more polar (minor) alcohol isomers on the

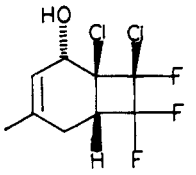
(14) Warrener, R. N.; Johnson, R. P.; Jefford, C. W.; Ralph, D. A. *Tetrahedron Lett.* **1979**, 2939–2942.

basis of chemical shift and coupling constant data. However, reduction of enone **10a** (DIBAL-H, toluene, 0 °C) occurred specifically from only one of the diastereotopic faces of the carbonyl group to give the more polar alcohol isomer in 90% yield. In accord with the general observation of attack of fused ring systems from the less-hindered convex face, reduction of the carbonyl group should occur most readily from the face of the six-membered ring opposite the four-membered ring. This specific reduction allowed us to assign structure A to the minor epimer and structure B to the major epimer of alcohol **7a**. Therefore, if the cycloaddition of diene **6a** to 1,4-dichloro-3,4,4-trifluorocyclobutene (**5**) was a concerted reaction and did not proceed via a stepwise dipolar or electron-transfer mechanism, then cycloaddition has occurred predominantly exo to the cyclobutene ring (endo to the vinyl chlorine), with the minor isomer resulting from an orientation endo to the cyclobutene ring (exo to the vinyl chlorine).

The Diels–Alder reaction of diene **6b** with dienophile **5** proceeded in a similar fashion to give an 84:16 ratio of two epimeric alcohols (**7b**), each which on oxidation produced the same enone, **10b**. Spectroscopic analysis (^{1}H NMR) confirmed the "ortho" regiochemistry and the relative stereochemical assignments follow the arguments outlined above. The major isomer of **7b** was assigned structure E and the minor isomer structure F in analogy



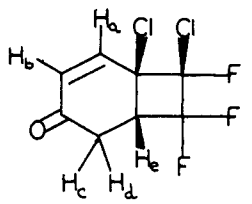
E



F

with the assignments for the epimers of **7a**. The increased isomer selectivity with diene **6b** (84:16) over diene **6a** (78:22) was consistent with formation of the minor isomer via an endo transition state with respect to the cyclobutene ring. In such an endo transition state, the methyl group of diene **6b** would experience greater nonbonded repulsion from the cyclobutene ring substituents than the hydrogen atom of diene **6a**, thereby disfavoring this transition state more for **6b** than for **6a**.

Finally, Danishefsky's diene, **13**, regiospecifically added to dienophile **5**, although in lower yield than the other cycloaddition reactions because of extensive polymerization of the diene. The primary adduct **14** (Scheme II) tended to be contaminated with enone **15** after workup of the Diels–Alder reaction mixture, so crude **14** was directly converted to enone **15**. The regiospecific nature of the cycloaddition was evident from the 60-MHz ^{1}H NMR spectrum of enone **15**. There was some small, long-range



15

coupling ($J \approx 1$ Hz); however, the vinyl hydrogens were each clearly doublets (H_a, δ 6.63, d, J = 10 Hz; H_b, δ 6.15, d, J = 10 Hz), and the methylene hydrogens α to the carbonyl absorbed as an apparent doublet ($H_{c,d}$, δ 2.71, d, J = 4 Hz). The ring-fusion methine, H_e, was a complex multiplet due to proton and fluorine coupling (δ 3.90–3.13). The relative stereochemistry in this series, as with the previous dienes, was presumed to follow from cycloaddition to the "fluoro face" of the dienophile.

Conclusion

The simple reaction conditions and inexpensive reagents described above allow the synthesis of multigram quantities of benzocyclobutenedione and substituted benzocyclobutenediones. The compounds described in this manuscript are now readily available, and other substituted benzocyclobutenediones should be accessible from the appropriate dienes by using the described Diels–Alder methodology.

Experimental Section

General Methods. All melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer, and absorptions are reported in wave numbers. ^{1}H NMR spectra were obtained on a JEOL C60-HL or a Bruker HX-270, and absorptions are expressed in parts per million (δ) with Me_4Si as an internal standard. Gas–liquid chromatograms were obtained with a Varian 3700 instrument equipped with a 6 ft × 0.125 in. stainless-steel column packed with 3% OV-17 on 80/100 Chrom W-HP. Preparative-scale separations were effected by medium-pressure column chromatography with Merck Lobar prepacked silica gel columns or by using traditional gravity columns. Sealed tube reactions were conducted in Fischer–Porter pressure reaction vessels purchased from Lab-Crest Scientific Division. Elemental analyses were performed by Gailbraith Laboratories, Knoxville, TN.

Benzocyclobutenedione (1) from Anthranilic Acid. Benzocyclobutenone was prepared from anthranilic acid according to the procedure of Dürr[10] in the following manner. Anthranilic acid (82.5 g, 0.603 mol) was dissolved in 900 mL of absolute ethanol in a 3-L beaker. After the mixture was cooled in an ice bath, 60 mL of concentrated HCl and then 150 mL of cold isoamyl nitrite (1.022 mol) were added to the magnetically stirred solution. After the mixture was stirred for 10 min in the ice bath, 900 mL of ether was added, and stirring was continued for 5 min. The resulting 2-carboxybenzenediazonium chloride was isolated by suction filtration followed by an ether wash (300 mL); yield 100.5 g (91%). **Caution**: This diazonium salt can be explosive when dry. A 3-L flask fitted with a reflux condenser and nitrogen-inlet tube connected to a gas bubbler was charged with 2-carboxybenzenediazonium chloride (100.5 g, 0.54 mol), propylene oxide (75 mL), freshly distilled 1,1-dichloroethylene (354 mL, 429 g, 4.41 mol), and 1.2 L of 1,2-dichloroethane. After being refluxed for 18 h, the reaction mixture was cooled to room temperature and filtered to remove a tan precipitate. The brown filtrate containing the crude 1,1-dichlorobenzocyclobutene was condensed to an oil on a rotary evaporator and then refluxed for 24 h with 300 mL of 3% aqueous H_2SO_4. After cooling to room temperature, the crude organic product was extracted with ether (4 × 150 mL), and the combined ether layers were washed with 150 mL of saturated $NaHCO_3$ and dried (Na_2SO_4). The ether layer was filtered and condensed on a rotary evaporator, and the crude oil was distilled to give 39.6 g (56%) of benzocyclobutenone, bp 35–37 °C (0.05 mmHg). This product was converted to benzocyclobutenedione by a modification of the original procedure of Cava.[9] To a 3-L round-bottomed flask equipped with a condenser and N_2 inlet were added benzocyclobutenone (39.6 g, 0.336 mol), *N*-bromosuccinimide (149.5 g, 0.84 mol), benzoyl peroxide (4.1 g, 0.017 mol), and 1.75 L of CCl_4. The mixture was refluxed under N_2 for 24 h with monitoring by GLC for disappearance of starting material as well as a transient monobromo compound. After the mixture cooled to room temperature, petroleum ether (1 L) was added, the succinimide was removed by filtration and the filtrate condensed on a rotary evaporator followed by a vacuum pump to give 2,2-dibromobenzocyclobutenone[9] (92.7 g) as a white solid. This material was hydrolyzed in 2-L of 50% aqueous sulfuric acid at reflux for 3 h with monitoring of the reaction mixture by TLC and GLC for loss of starting material. After cooling to room temperature, the reaction mixture was poured onto a large excess

of ice and then diluted with water to a total volume of 4 L. The aqueous layer was extracted with 100-mL portions of CH_2Cl_2 until the extracts were colorless. The combined methylene chloride portions were condensed on a rotary evaporator, and the crude product was passed through a short column of SiO_2 with methylene chloride to give, after evaporation of solvent, 31.7 g of benzocyclobutenedione [yellow solid, mp 132–133 °C (lit.[9] mp 131–132 °C)] in 40% overall yield from anthranilic acid.

Cycloaddition of (*E*)-1-(Trimethylsiloxy)-1,3-butadiene (6a) to 1,4-Dichloro-3,3,4-trifluorocyclobutene (5). (A) Preparation of Alcohols 7a. 1,4-Dichloro-3,3,4-trifluorocyclobutene[13] (11.96 g, 67.6 mmol) and (*E*)-1-(trimethylsiloxy)-1,3-butadiene[15] (14.39 g, 101.4 mmol) were placed in a 3-oz Fischer–Porter pressure vessel equipped with a magnetic stirring bar. After bubbling dry N_2 through the mixture for 5 min, the tube was sealed and placed in an oil bath maintained at 150 °C and stirred for 28 h. After cooling to 25 °C, the tube was opened and the reaction mixture transferred to a 250-mL round-bottomed flask with the aid of a small amount of MeOH. To this mixture was added 100 mL of 1:1 MeOH/1.2 N HCl, and the solution was stirred at room temperature for 3 h. The solution was poured into 200 mL of H_2O and extracted with CH_2Cl_2 (3 × 75 mL), and the combined CH_2Cl_2 fractions were dried over Na_2SO_4. Filtration followed by condensation on a rotary evaporator followed by removal of volatiles with a vacuum pump left 15.4 g of crude alcohols **7a** as a light brown oil. This material is sufficiently pure for use in subsequent reactions; however, the 78:22 mixture of epimers (GLC) can be separated by medium-pressure liquid chromatography (3:2 hexane/CH_2Cl_2) with the major isomer eluting first.

Major isomer: white prisms; mp 69–70 °C (hexane); IR (CH_2Cl_2) 3575; ^1H NMR (270 MHz, $CDCl_3$) δ 5.78 (m, 2 H), 4.63 (br d, J = 9 Hz, 1 H), 3.21 (complex m, 1 H), 3.07 (d, J = 9 Hz, 1 H), 2.56 (m, 1 H), 2.43 (br d, J = 18, 1 H); mass spectrum, m/e (relative intensity) 246 (M^+), 248 (M^+ + 2, 66).

Minor isomer: white needles; mp 95–96 °C (hexane); IR (CH_2Cl_2) 3610; ^1H NMR (270 MHz, $CDCl_3$) δ 5.97 (br d, J = 11 Hz, 1 H), 5.90 (m, 1 H), 4.58 (br s, 1 H), 3.28 (15-line m, 1 H), 2.64 (dd, J = 7, 1.5 Hz, 1 H), 2.53 (dd, J = 17, 7 Hz, 1 H), 2.36 (br dd, J = 17, 8 Hz, 1 H); mass spectrum, m/e (relative intensity) 246 (M^+), 248 (M^+ + 2, 66).

(B) Aromatization of 7a to 1-Chloro-1,2,2-trifluorobenzocyclobutene (8a). A 500-mL round-bottomed flask was charged with crude **7a** from above (5.0 g, 20.2 mmol) and 150 mL of anhydrous MeOH. Dry N_2 was bubbled through the solution for 5 min, and then the flask was equipped with a magnetic stirring bar, pressure-equalizing addition funnel, and a nitrogen-inlet tube. The addition funnel was charged with a solution freshly prepared from sodium (1.86, 81.0 mmol) and MeOH (50 mL), and after the solution of **7a** had been cooled in an ice bath, the NaOMe/MeOH was added dropwise with stirring over 30 min. The reaction mixture was then allowed to warm to room temperature, and stirring was continued for 36 h, at which point 200 mL of 1.2 N HCl was added to the reaction vessel. The reaction mixture was transferred to a separatory funnel containing 300 mL of H_2O, the solution was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic layers were dried over Na_2SO_4. Filtration and removal of solvent on a rotary evaporator followed by a vacuum pump left 3.69 g of crude 1-chloro-1,2,2-trifluorobenzocyclobutene (**8a**) as a light yellow oil. Purification of a separate sample by chromatography (SiO_2, 3:2 hexane/CH_2Cl_2) gave a clear oil: IR (CH_2Cl_2) 1355, 1275; ^1H NMR ($CDCl_3$) δ 7.7–7.2 (m); mass spectrum, m/e (relative intensity) 192 (M^+), 194 (M^+ + 2, 33).

(C) Hydrolysis of 8a to Benzocyclobutenedione (1). An unpurified sample of 1-chloro-1,2,2-trifluorobenzocyclobutene (**8a**, 3.69 g), as prepared above, was stirred at 100 °C for 3.5 h with 200 mL of 70% H_2SO_4. The reaction mixture was poured onto an excess of ice, and after the ice melted it was diluted with H_2O to a total volume of 600 mL. After extraction with CH_2Cl_2 (4 × 75 mL) the combined organic layers were dried (Na_2SO_4) and filtered, and the solution was evaporated to dryness on a rotary evaporator to a yellow solid which was chromatographed on a silcia gel column (3 cm × 1 m; CH_2Cl_2). Evaporation of the solvent gave 1.83 g of benzocyclobutenedione (**1**), identical with the previously prepared sample. The overall yield of **1** from the dienophile **5** was 63% (three steps).

(D) Oxidation of Alcohols 7a to Enone 10a. An unpurified sample of the epimeric alcohol mixture **7a** (15.1 g, ~61.3 mmol) was dissolved in 700 mL of CH_2Cl_2 and stirred for 18 h at room temperature in the presence of pyridinium chlorochromate (36.4 g, 169 mmol). The solution was concentrated to approximately 350 mL on a rotary evaporator and then diluted with an equal volume of Et_2O to precipitate the chromium salts. The solution was filtered through a large pad of Florisil contained in a 350-mL fritted-glass funnel, and the solvents were then removed on a rotary evaporator. The resulting oil was chromatographed (SiO_2, 3:2 hexane/CH_2Cl_2) to yield 10.19 g of enone **10a**: white solid; mp 58–59 °C (hexane); overall yield of 62% (from dienophile **5**, two steps); IR (CH_2Cl_2) 1690, 1635; ^1H NMR (270 MHz, $CDCl_3$) δ 7.05 (dt, J = 10.5, 3.5 Hz, 1 H), 6.22 (dt, J = 10.5, 2.3 Hz, 1 H), 3.48 (m, 1 H), 2.76 (m, 2 H); mass spectrum, m/e (relative intensity) 244 (M^+), 246 (M^+ + 2, 66). Purified samples of the major and minor epimers of alcohol **7a** were oxidized as above to give enone **10a** in 95% and 94% yields, respectively.

(E) Stereoselective Reduction of Enone 10a. Enone **10a** (158 mg, 0.64 mmol) was dissolved in toluene (6 mL) in a round-bottomed flask under an N_2 atmosphere, and the solution was cooled to 0 °C (ice bath). DIBAL-H (1 M in toluene, 645 μL) was added dropwise via syringe and the mixture stirred at 0 °C for 2 h. The reaction was quenched by dropwise addition of H_2O and the mixture then transferred to a separatory funnel which contained CH_2Cl_2 (50 mL) and 1.2 N HCl (50 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated to give 156 mg (98%) of a white solid with a ^1H NMR spectrum essentially identical with that for the minor epimer of alcohol **7a**. Capillary GLC analysis showed <1% of the major alcohol epimer to be present and approximately 9% of a second product which was not identified. Recrystallization of the crude product gave pure minor alcohol, mp 95–96 °C.

(F) Aromatization of Enone 10a to 2,2-Difluoro-6-hydroxybenzocyclobutenone (11a). A solution of enone **10a** (10.19 g, 41.6 mmol) in 300 mL of MeOH was cooled to 0 °C in a 1-L round-bottomed flask, and the solution was saturated with dry N_2 for 5 min. The flask was fitted with a pressure-equalizing addition funnel and a nitrogen-inlet tube, and the addition funnel was charged with a solution freshly prepared from sodium (3.83 g, 166.4 mmol) and MeOH (100 mL). The NaOMe/MeOH solution was added dropwise with stirring over 30 min. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred an additional 3 h. At this stage the reaction product is a dimethyl ketal which can be identified by evaporating a portion of the methanol and partitioning the residue between Et_2O and H_2O. The Et_2O layer, after being dried, provided the crude ketal which showed no carbonyl absorption in the IR and showed the presence of the dimethyl ketal by ^1H NMR (δ 3.05, s). However, it was most convenient to take the NaOMe/MeOH reaction mixture above and hydrolyze the ketal by addition of an equal volume of 1.2 N HCl (400 mL) and refluxing the mixture for 3 h. After cooling to room temperature, the reaction mixture was diluted with 400 mL of H_2O and the product extracted into CH_2Cl_2 (4 × 150 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and evaporated to dryness on a rotary evaporator to give crude **11a** which was filtered through a short plug of silica gel (Et_2O) to give 6.80 g of **11a**: white solid; mp 109–110 °C (CH_2Cl_2/hexane); IR (CH_2Cl_2) 3550, 3500–3000 (br), 1790, 1770 (sh); ^1H NMR (60 MHz, $CDCl_3$) δ 7.80–6.93 (m, 3 H), 6.8–6.6 (br s, 1 H); mass spectrum, m/e 170 (M^+).

(G) Hydrolysis of 11a to 3-Hydroxybenzocyclobutenedione (12a). The sample of difluoro ketone from above (**11a**, 6.80 g) was placed in a 1-L round-bottomed flask and stirred at 100 °C for 4.5 h with 1:1 concentrated H_2SO_4/HOAc (400 mL). The mixture was poured onto an excess of ice and then diluted with H_2O to a total volume of 2 L. The aqueous layer was extracted with 150-mL portions of Et_2O until the extracts were colorless. The combined Et_2O layers were dried (Na_2SO_4), filtered, and evaporated on a rotary evaporator followed by a vacuum pump. The crude product was chromatographed on a silica gel column (3 cm × 1 m; 4:1 Et_2O/petroleum ether) to give 3.6 g of 3-

(15) Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1980; Vol. 8, p 512.

hydroxybenzocyclobutenedione (**12a**): light yellow solid; mp 184–186 °C (EtOAc) (lit.[16] mp 177–178 °C); IR ($CHCl_3$) 3550–3000 (br), 1788, 1765, 1745 (sh); ^1H NMR (60 MHz, acetone-d_6) δ 7.86–7.06 (3 H); 10.6–9.7 (br s, 1 H); mass spectrum, m/e 148 (M^+). The overall yield from dienophile **5** was 36%.

Cycloaddition of (*E*)-1-(Trimethylsiloxy)-3-methyl-1,3-butadiene (6b) to 1,4-Dichloro-3,3,4-trifluorocyclobutene (5). (A) Preparation of (*E*)-1-(Trimethylsiloxy)-3-methyl-1,3-butadiene (6b). The aldehyde required for the synthesis of diene **6b**, 3-methyl-2-butenal, was conveniently prepared on large scale by the chromium(VI) oxidative rearrangement of 2-methyl-3-buten-2-ol.[17] 2-Methyl-3-buten-2-ol (17.6 g, 204.1 mmol) was added dropwise to a magnetically stirred slurry of pyridinium chlorochromate (110 g, 510.3 mmol) in CH_2Cl_2 (1 L) at room temperature. After being stirred for 18 h, the solution was concentrated to a volume of 400 mL, diluted with an equal volume of Et_2O, and then passed through a large pad of Florisil contained in a 350-mL fritted-glass funnel. The filtrate was evaporated to a crude oil and distilled under aspirator vacuum to yield 3-methyl-2-butenal: 11.9 g (70% yield); IR (neat) 1675, 1640; ^1H NMR (60 MHz, $CDCl_3$) δ 9.90 (d, J = 7 Hz, 1 H), 5.76 (br d, J = 7 Hz, 1 H), 2.13 (br s, 3 H), 1.93 (br s, 3 H). The aldehyde was converted to (*E*)-1-(trimethylsiloxy)-3-methyl-1,3-butadiene (**6b**) by a modification of the procedure of Ishida.[18] 3-Methyl-2-butenal (23.3 g, 277 mmol), Et_3N (36.5 g, 361 mmol), chlorotrimethylsilane (39.2 g, 361 mmol), and $ZnCl_2$ (1.87 g, 13.9 mmol) were stirred under N_2 at room temperature in 400 mL of dry, N_2-saturated benzene for 18 h. After the mixture was condensed on a rotary evaporator to ~250 mL, an equal volume of Et_2O was added, and the mixture was filtered, evaporated to a crude oil on the rotary evaporator, and distilled at 0.5 mmHg to give diene **6b**: 35.0 g (81% yield); ^1H NMR (60 MHz, $CDCl_3$) δ 6.43 (d, J = 12 Hz, 1 H), 5.82 (d, J = 12 Hz, 1 H), 4.66 (br s, 2 H), 1.76 (br s, 3 H), 0.20 (s, 9 H); IR (CH_2Cl_2) 1640.

(B) Preparation of Alcohols 7b. 1,4-Dichloro-3,3,4-trifluorocyclobutene (**5**; 10.93 g, 61.7 mmol) and diene **6b** (14.44 g, 92.6 mmol) were placed in a 3-oz Fischer–Porter pressure vessel equipped with a magnetic stirring bar, and then the mixture was saturated with dry N_2 for 5 min. The tube was sealed, placed in an oil bath maintained at 150 °C, and stirred for 10 h. After cooling to 25 °C the tube was opened, and the reaction mixture was transferred to a 250-mL round-bottomed flask with the aid of a small amount of MeOH. To this mixture was added 100 mL of 1:1 MeOH/1.2 N HCl, and the solution was stirred at room temperature for 3 h. The solution was poured into 200 mL of H_2O and extracted with CH_2Cl_2 (3 × 75 mL), and the combined CH_2Cl_2 fractions were dried over Na_2SO_4. Filtration followed by condensation on a rotary evaporator followed by removal of volatiles with a vacuum pump left 15.6 g of crude alcohols **7b** as a light brown oil. Glc analysis indicated an 84:16 ratio of the two epimers of **7b**. A separate sample was chromatographed by medium-pressure liquid chromatography (CH_2Cl_2) with the major isomer eluting first. Major isomer: white solid; mp 46–47 °C (hexane, 0 °C); IR (CH_2Cl_2) 3575; ^1H NMR (60 MHz, $CDCl_3$) δ 5.43 (m, 1 H), 4.55 (br d, J = 9 Hz, 1 H), 3.63–2.80 (complex m, 1 H), 2.98 (d, J = 9 Hz, 1 H), 2.43–2.13 (m, 2 H), 1.75 (d, J = 1 Hz, 3 H); mass spectrum, m/e (relative intensity) 260 (M^+), 262 (M^+ + 2, 66). Minor isomer: white solid; mp 78–79 °C (petroleum ether); IR (CH_2Cl_2) 3610; ^1H NMR (60 MHz, $CDCl_3$) δ 5.58 (m, 1 H), 4.40 (m, 1 H), 3.70–2.80 (complex m underlying an absorption at 3.2, 1 H), 3.20 (br s, 1 H), 2.55 (m, 2 H), 1.81 (br s, 3 H); mass spectrum, m/e (relative intensity) 260 (M^+), 262 (M^+ + 2, 66). However, rather than purifying and separating the individual epimers of **7b**, the crude mixture from above was sufficiently pure for subsequent reactions.

(C) Aromatization of 7b to 1-Chloro-1,2,2-trifluoro-4-methylbenzocyclobutene (8b). A sample of crude **7b** from above (5.0 g, 19.2 mmol) was dissolved in 150 mL of absolute MeOH in a 500-mL round-bottomed flask, and the solution was saturated with nitrogen for 5 min. The flask was equipped with a pressure-equalizing dropping funnel. The funnel was charged with a solution freshly prepared from sodium (1.76 g, 76.6 mmol) and MeOH (50 mL), and a nitrogen-inlet tube was attached. The round-bottomed flask was cooled in an ice bath, and the NaOMe/MeOH was added dropwise over 30 min to the stirred solution of **7b**. The reaction mixture was then allowed to warm to room temperature, and stirring was continued an additional 48 h. The reaction mixture was quenched with 200 mL of 1.2 N HCl and then transferred to a separatory funnel containing 300 mL of H_2O. The solution was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and condensed with a rotary evaporator and then with a vacuum pump to leave 3.75 g of crude 1-chloro-1,2,2-trifluoro-4-methylbenzocyclobutene (**8b**) as a yellow oil. A small sample from another reaction was purified by chromatography (SiO_2, 3:2 hexane/CH_2Cl_2) to give a clear oil: IR (CH_2Cl_2) 1330, 1290, 1270, 1130; ^1H NMR (60 MHz, $CDCl_3$) δ 7.56–7.13 (m, 3 H), 2.36 (s, 3 H); mass spectrum, m/e (relative intensity) 206 (M^+), 208 (M^+ + 2, 33).

(D) Hydrolysis of 8b to 4-Methylbenzocyclobutenedione (9b). The unpurified sample of **8b** from above (3.75 g) was stirred at 100 °C for 3.5 h with 200 mL of 70% H_2SO_4. The reaction mixture was poured onto an excess of ice, and after the ice melted it was diluted to a total volume of 600 mL. After extraction with CH_2Cl_2 (4 × 75 mL), the combined organic layers were dried (Na_2SO_4) and filtered, and the solution was evaporated to dryness on a rotary evaporator to give a yellow solid which was chromatographed on a silica gel column (3 cm × 1 m; CH_2Cl_2). Evaporation gave 2.08 g of 4-methylbenzocyclobutenedione (**9b**) as light yellow crystals in 72% overall yield from dienophile **5**: mp 103–104 °C (hexane); IR (CH_2Cl_2) 1787, 1763; ^1H NMR (60 MHz, $CDCl_3$) δ 7.96–7.45 (m, 3 H), 2.58 (s, 3 H). Anal. Calcd for $C_9H_6O_2$: C, 73.96; H, 4.14. Found: C, 73.98; H, 4.40.

(E) Oxidation of Alcohols 7b to Enone 10b. An unpurified sample of the epimeric alcohol mixture **7b** (15.6 g, ~59.8 mmol) was dissolved in 700 mL of CH_2Cl_2 and stirred for 18 h at room temperature in the presence of pyridinium chlorochromate (26.6 g, 123.5 mmol). The solution was concentrated to approximately 350 mL on a rotary evaporator and then diluted with an equal volume of Et_2O to precipitate the chromium salts. The solution was filtered through a large pad of Florisil contained in a 350-mL fritted-glass funnel, and the solvents were then removed on a rotary evaporator. The resulting oil was chromatographed (SiO_2, 3:2 hexane/CH_2Cl_2) to yield enone **10b**: white solid; mp 64–65 °C (hexane); 14.0 g (overall yield of 88% from dienophile **5**); IR (CH_2Cl_2) 1675, 1638; ^1H NMR (60 MHz, $CDCl_3$) δ 6.02 (br s, 1 H), 3.83–3.00 (complex m, 1 H), 2.91–2.50 (m, 2 H), 2.05 (d, J = 1 Hz, 3 H); mass spectrum, m/e (relative intensity) 258 (M^+), 260 (M^+ + 2, 66). Purified samples of the major epimer and minor epimer of alcohol **7b** were independently oxidized as above to give enone **10b** in 99% and 94% yields, respectively.

(F) Aromatization of Enone 10b to 2,2-Difluoro-4-methyl-6-hydroxybenzocyclobutenedione (11b). A solution of enone **10b** (14.0 g, 54.1 mmol) in 350 mL of MeOH was cooled to 0 °C in a 2-L round-bottomed flask, and the solution was saturated with dry N_2 for 5 min. The flask was fitted with a pressure-equalizing addition funnel and a nitrogen-inlet tube, and the addition funnel was charged with a solution freshly prepared from sodium (4.97 g, 216.2 mmol) and MeOH (150 mL). The NaOMe/MeOH solution was added dropwise with stirring over 30 min, and after the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred an additional 3 h. An equal volume of 1.2 N HCl (500 mL) was then added, and the mixture was refluxed for 3 h to hydrolyze the intermediate ketal. After cooling to room temperature, the reaction mixture was diluted with 500 mL of H_2O and the product extracted into CH_2Cl_2 (4 × 150 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and evaporated to dryness on a rotary evaporator followed by a vacuum pump to give 9.46 g (95%) of **11b** as a light yellow solid: mp 155–156 °C (CH_2Cl_2/hexane); IR (CH_2Cl_2) 3600–3000, 3540, 1788; ^1H NMR (60 MHz, acetone-d_6) δ 8.26 (br s, 1 H), 7.03 (s, 1 H), 6.86 (br s, 1 H), 2.43 (s, 3 H); mass spectrum, m/e 184 (M^+).

(G) Hydrolysis of 11b to 3-Hydroxy-5-methylbenzocyclobutenedione (12b). The sample of **11b** prepared above (9.46 g, 51.1 mmol) was dissolved in 500 mL of 70% H_2SO_4 and stirred

(16) Jung, M. E.; Lowe, J. A. *J. Org. Chem.* **1977**, *42*, 2371–2373.
(17) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685. Sundararaman, P.; Herz, W. *J. Org. Chem.* **1977**, *42*, 813–819.
(18) Ishida, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1161–1168.

under N_2 for 3.5 h in an oil bath maintained at 100 °C. The reaction mixture was poured onto an excess of ice, and after the ice had melted H_2O was added to bring the total volume to 1500 mL. The solution was extracted with CH_2Cl_2 (5 × 100 mL), and the combined organic layers were extracted with saturated $NaHCO_3$ until the extracts were colorless. The combined $NaHCO_3$ extracts were back-washed with CH_2Cl_2 (100 mL) and then acidified to pH 1 with 12 M HCl. The product was extracted into CH_2Cl_2 (5 × 100 mL), the organic layer was dried (Na_2SO_4) and filtered, and solvent was removed on a rotary evaporator followed by a vacuum pump to yield 6.3 g of 3-hydroxy-5-methylbenzocyclobutenedione in 63% overall yield from dienophile **5**: light yellow crystals; mp 191–193 °C (EtOAc); IR (CH_2Cl_2) 3540, 1789, 1755; ^1H NMR (60 MHz, acetone-d_6) δ 7.29 (s, 1 H), 6.95 (s, 1 H), 2.46 (s, 3 H). Anal. Calcd for $C_9H_6O_3$: C, 66.66; H, 3.73. Found: C, 66.56; H, 3.90.

Cycloaddition of 1-Methoxy-3-(trimethylsiloxy)-1,3-butadiene (13) to 1,4-Dichloro-3,3,4-trifluorocyclobutene (5). (A) Preparation of Enone 15. 1,4-Dichloro-3,3,4-trifluorocyclobutene (**5**; 3.08 g, 17.4 mmol) and Danishefsky's diene (**13**; 4.50 g, 26.1 mmol) were placed in a 3-oz Fischer–Porter pressure vessel equipped with a magnetic stirring bar, and the mixture was saturated with dry N_2 for 5 min. The tube was sealed, placed in an oil bath maintained at 120 °C, and stirred for 3.5 h. After cooling to 25 °C, the tube was opened, and the contents were transferred to a 100-mL round-bottomed flask with the aid of a small amount of MeOH. To this mixture was added 100 mL of 1:1 MeOH/1.2 N HCl, and the solution was stirred at room temperature for 2 h. The dark solution was poured into a separatory funnel, diluted with 200 mL of H_2O, and extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and condensed on a rotary evaporator to yield 3.11 g of crude **14** as a dark oil. The compound is contaminated with diene decomposition products as well as some enone **15**, but the following spectroscopic absorptions of **14** are apparent: IR (CH_2Cl_2) 1720; ^1H NMR (60 MHz, $CDCl_3$) δ 4.72 (t, J = 5 Hz, ~1 H), 3.30 (s, ~3 H), 2.6–2.7 (m, ~4 H). Without purification, crude **14** (3.11 g) was placed in a 250-mL round-bottomed flask and dissoved in dry benzene (175 mL). After addition of *p*-toluenesulfonic acid (166 mg, 0.87 mmol), the mixture was refluxed under N_2 for 27 h, cooled to room temperature, transferred to a separatory funnel, washed with saturated $NaHCO_3$ (2 × 25 mL), dried (Na_2SO_4), filtered, and condensed on a rotary evaporator, and the residue was chromatographed on silica gel (3 cm × 0.75 m; 3:2 hexane/CH_2Cl_2) to yield enone **15**: 2.25 g (53% yield from dienophile **5**); white needles; mp 44–45 °C (sublimed); IR (CH_2Cl_2) 1695; ^1H NMR (60 MHz, $CDCl_3$) δ 6.63 (d, J = 10 Hz, 1 H with smaller splittings), 6.15 (d, J = 10 Hz, 1 H with smaller splittings), 3.90–3.13 (m, 1 H), 2.71 (apparent d, J = 4 Hz, 2 H); mass spectrum, m/e (relative intensity) 244 (M^+), 246 (M^+ + 2, 66).

(B) Aromatization of Enone 15 to 2,2-Difluoro-4-hydroxybenzocyclobutenone (16). A solution of enone **15** (2.25 g, 9.2 mmol) in 60 mL of MeOH was cooled to 0 °C in a 250-mL round-bottomed flask and the solution was saturated with dry N_2 for 5 min. The flask was fitted with a pressure equalizing addition funnel and a nitrogen inlet tube and the addition funnel was charged with a solution freshly prepared from sodium (0.846 g, 36.8 mmol) and MeOH (30 mL). The NaOMe/MeOH solution was added dropwise with stirring over 30 min, and after the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred an additional 3 h. An equal volume of 1.2 N HCl (90 mL) was added, and the mixture was refluxed for 3 h to hydrolyze the intermediate ketal. After cooling to room temperature, the reaction mixture was diluted with 200 mL of H_2O and the product extracted into CH_2Cl_2 (3 × 75 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and evaporated to dryness on a rotary evaporator followed by a vacuum pump to give **16**: 1.5 g (96%); white crystals; mp 163–164 °C (EtOAc/hexane); IR (CH_2Cl_2) 3570, 1795, 1770; ^1H NMR (60 MHz, acetone-d_6) δ 9.8 (br s, 1 H), 7.70–7.16 (m, 3 H); mass spectrum, m/e 170 (M^+).

(C) Hydrolysis of 16 to 4-Hydroxybenzocyclobutenedione (17). The sample of **16** prepared above (1.50 g, 8.82 mmol) was placed in a 250-mL round-bottomed flask with 1:1 concentrated H_2SO_4/HOAc (90 mL) and stirred at 90 °C under N_2 for 3 h. The reaction mixture was poured onto an excess of ice and diluted with H_2O to a total volume of 350 mL. The solution was extracted with Et_2O (3 × 100 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and condensed to a crude solid on a rotary evaporator. This material was chromatographed on a silica gel column (3 cm × 1 m; Et_2O) to yield 4-hydroxybenzocyclobutenedione: 1.10 g (84% yield, 43% overall from dienophile **5**); light yellow crystals; mp 174.5–175 °C (EtOAc) (lit.[7] mp 167–170 °C); IR ($CHCl_3$) 3600–3000 (br), 3575, 1808 (sh), 1790, 1769, 1755 (sh); ^1H NMR (60 MHz, CD_3CN) δ 7.81 (d, J = 8 Hz, 1 H), 7.36–7.06 (m, 2 H), 6.23 (br s, 1 H); mass spectrum, m/e 148 (M^+).

Acknowledgment is made to the National Cancer Institute, DHEW (Grant No. CA 26374), for support of this work.

Registry No. **1**, 6383-11-5; **3**, 3469-06-5; **4**, 82431-14-9; **5**, 2927-72-2; **6a**, 63383-46-0; **6b**, 73912-36-4; **7a** (isomer 1), 82431-15-0; **7a** (isomer 2), 82468-19-7; **7b** (isomer 1), 82431-19-4; **7b** (isomer 2), 82468-20-0; **8a**, 82431-16-1; **8b**, 82444-39-1; **9b**, 82431-20-7; **10a**, 82431-17-2; **10b**, 82431-21-8; **11a**, 82431-18-3; **11b**, 82431-22-9; **12a**, 62416-21-1; **12b**, 82431-23-0; **13**, 59414-23-2; **15**, 82431-24-1; **16**, 82431-25-2; **17**, 75833-48-6; anthranilic acid, 118-92-3; 2-carboxybenzenediazonium chloride, 4661-46-5; 1,1-dichloroethylene, 75-35-4; 1,1-dichlorobenzocyclobutene, 68913-13-3; 3-methyl-2-butenal, 107-86-8; 2-methyl-3-buten-2-ol, 115-18-4.

Deperoxidation of Ethers. A Novel Application of Self-Indicating Molecular Sieves

David R. Burfield

Department of Chemistry, University of Malaya, Kuala Lumpur 22-11, West Malaysia

Received January 18, 1982

The removal of peroxides from contaminated ethers by treatment with self-indicating molecular sieves (IMS) is proposed as a safe and facile method of ether purification. Quantitative analysis of peroxide content before and after treatment with IMS show that ethers such as THF, diethyl ether, and diisopropyl ether can be readily decontaminated by an ambient-temperature or reflux process. The deperoxidation process is enhanced under nitrogen and has been safely carried out on a bulk scale and with initial peroxide contents as high as 0.5 M. IMS, in common with most other chemical reducing agents used for ether deperoxidation, are, however, ineffective for the decomposition of unreactive species such as dialkyl peroxides.

Aliphatic ethers, with their characteristic solvation abilities, excel as inert reaction media in numerous synthetic procedures. However, in practice this usefulness is often tempered by an unfortunate proclivity to facile air oxidation at ambient temperatures which leads to peroxide formation.[1] The presence of peroxides is not only po-

0022-3263/82/1947-3821$01.25/0