Registry No. **1a**, 374-01-6; **1b**, 118334-94-4; **1c**, 6189-13-5; **1d**, 421-47-6; **1e**, 421-46-5; **1f**, 118334-95-5; **2a**, 920-66-1; **2b**, 118334-96-6; **2c**, 67674-48-0; **2d**, 431-87-8; **2e**, 2252-79-1; **2f**, 4141-91-7; **3**, 677-21-4; **4**, 375-17-7; $C_4F_9SO_2F$, 375-72-4; toluenesulfonyl chloride, 98-59-9.

Synthesis of Substituted Benzocyclobutenediones

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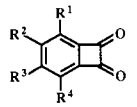
Introduction

Benzocyclobutenediones **1** are proving to be useful intermediates for the controlled synthesis of complex organics.[2] Although a number of methods describing synthetic approaches to substituted and unsubstituted benzocyclobutenediones have been published,[2a,3] none to date allow the general synthesis of substituted benzocyclobutenediones in a simple, straightforward fashion. Our interest in the organic and organometallic chemistry of cyclobutenediones and benzocyclobutenediones[2h-n,v,w,4] mandated that we find a practical method for the construction of these strained-ring compounds. We recently disclosed, in detail, our procedures used for the synthesis of substituted cyclobutenediones,[5] and we now describe a simple preparation of substituted benzocyclobutenediones.



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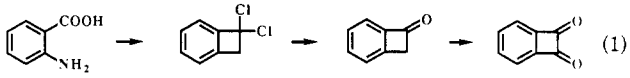
Results and Discussion

We have previously described a very practical route to the parent benzocyclobutenedione **1**, R^1–R^4 = H, that proceeded by the double benzylic bromination of benzocyclobutenone with *N*-bromosuccinimide (NBS) followed by acid-catalyzed hydrolysis of the geminal dibromo group.[3j,m] Benzocyclobutenone (**2**) was readily available from anthranilic acid by routine conversion to benzyne and trapping with vinylidene chloride followed by hydrolysis of the geminal dichloride (eq 1).[6] Utilization of this



(1)

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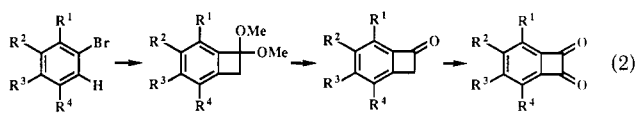
synthetic sequence for the preparation of substituted benzocyclobutenediones was not considered practical because it required the synthesis of substituted anthranilic acids, a task that would diminish the convenience of the chemistry.[7] However, Stevens and Bisacchi had shown that 1,1-dimethoxyethylene participated in a [2 + 2] reaction with benzynes generated by the $NaNH_2$-induced dehydrobromination of bromobenzenes **3**, and after hydrolysis of the intermediate benzocyclobutenone ketals **4**, moderate to very good yields of substituted benzocyclobutenones **5** were obtained.[8] We simply repeated and extended the Stevens and Bisacchi chemistry and then introduced the α-diketone moiety of the benzocyclobutenone through the NBS route mentioned above. This chemistry provided a simple and straightforward method for the synthesis of substituted benzocyclobutenediones **1** (eq 2).



(2)

3 **4** **5** **1**

During the 1,1-dimethoxyethylene trapping of benzyne generated by dehydrohalogenation of bromobenzenes with $NaNH_2$, Stevens and Bisacchi observed an unexplained induction period to the reaction that could vary from 0.5 to several hours, even within multiple runs of the same system. In our early attempts to repeat some of the results of Stevens and Bisacchi, we noticed a similar variability in the benzyne reaction. After some study, we were able to correlate the occurrence of the induction period with the purity of the $NaNH_2$. A freshly opened jar of commercially available $NaNH_2$ always reacted without an in-

(1) Camille and Henry Dreyus Foundation Teacher-Scholar, 1986–1991.

(2) (a) Jung, M. E.; Lowe, J. A. *J. Org. Chem.* **1977**, *42*, 2371. (b) Spangler, L. A.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1986**, 828. (c) Spangler, L. A.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 1800. (d) Anderson, D. K.; Coburn, C. E.; Haag, A. P.; Swenton, J. S. *Tetrahedron* **1984**, *40*, 4633. (e) Anderson, D. K.; Coburn, C. E.; Haag, A. P.; Swenton, J. S. *Tetrahedron Lett.* **1983**, *24*, 1329. (f) Anderson, D. K.; Jackson, D. K.; Narasimhan, L.; Swenton, J. S. *J. Org. Chem.* **1981**, *46*, 4825. (g) Jackson, D. K.; Narasimhan, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3898. (h) Liebeskind, L. S.; Baysdon, S. L.; South, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 7397. (i) Baysdon, S. L.; Liebeskind, L. S. *Organometallics* **1982**, *1*, 771. (j) South, M. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 4181. (k) Liebeskind, L. S.; Jewell, C. F., Jr. *J. Organomet. Chem.* **1985**, *285*, 305. (l) Liebeskind, L. S.; Baysdon, S. L.; South, M. S.; Iyer, S.; Leeds, J. P. *Tetrahedron Symposium in Print* **1985**, *41*, 5839. (m) Liebeskind, L. S.; Baysdon, S. L.; Chidambaram, R.; Goedken, V. *Organometallics* **1986**, *5*, 1086. (n) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065. (o) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067–3068. (p) Moore, H. W.; Reed, M. W. *J. Org. Chem.* **1987**, *52*, 3491–3492. (q) Perri, S. T.; Moore, H. W. *Tetrahedron Lett.* **1987**, *28*, 4507–4510. (r) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996–1003. (s) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392. (t) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067. (u) Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 1174. (v) Liebeskind, L. S.; Mitchell, D. M.; Foster, B. S. *J. Am. Chem. Soc.* **1987**, *109*, 7908. (w) Liebeskind, L. S.; Chidambaram, R.; Mitchell, D. M.; Foster, B. S. *Pure Appl. Chem.* **1988**, *60*, 2734.

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(5) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482. A similar synthetic approach to substituted cyclobutenediones was simultaneously disclosed by Moore and co-workers: Ree, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477–2482.

(6) Dürr, H.; Nickels, H.; Pacala, L. A.; Jones, M., Jr. *J. Org. Chem.* **1980**, *45*, 973.

(7) 3,6-Dimethoxybenzocyclobutenedione has been prepared by this method (ref 3h).

(8) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2393–2396.

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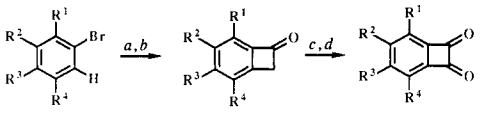
Table I. Synthesis of Substituted Benzocyclobutenediones



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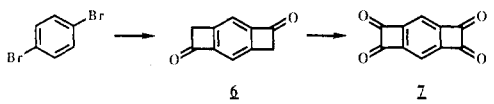
entry	bromoarene	benzocyclobutenone	yield, %	benzocyclobutenedione	yield, %
1	R^1 = OMe; $R^{\neq 1}$ = H	**5a**: R^1 = OMe; $R^{\neq 1}$ = H	44	**1a**: R^1 = OMe; $R^{\neq 1}$ = H	55
2	R^3 = OMe; $R^{\neq 3}$ = H	**5b**: R^2 = OMe; $R^{\neq 2}$ = H **5b′**: R^3 = OMe; $R^{\neq 3}$ = H	33	**1b**: R^2 = OMe; $R^{\neq 2}$ = H	50
3	$R^{2,3}$ = OMe; $R^{1,4}$ = H	**5c**: $R^{1,2}$ = OMe; $R^{3,4}$ = H	51	**1c**: $R^{1,2}$ = OMe; $R^{3,4}$ = H	60
4	$R^{2,4}$ = OMe; $R^{1,3}$ = H	**5d**: $R^{1,3}$ = OMe; $R^{2,4}$ = H	46	**1d**: $R^{1,3}$ = OMe; $R^{2,4}$ = H	88
5	$R^{1,4}$ = OMe; $R^{2,3}$ = H	**5e**: $R^{1,4}$ = OMe; $R^{2,3}$ = H	40	**1e**: $R^{1,4}$ = OMe; $R^{2,3}$ = H	66
6	$R^{2,3}$ = OCH_2O; $R^{1,4}$ = H	**5f**: $R^{1,2}$ = OCH_2O; $R^{3,4}$ = H	70	**1f**: $R^{1,2}$ = OCH_2O; $R^{3,4}$ = H	53
7	R^1 = F; $R^{\neq 1}$ = H	**5g**: R^1 = F; $R^{\neq 1}$ = H	32	**1g** R^1 = F; $R^{\neq 1}$ = H	66

[a] $NaNH_2/(MeO)_2C{=}CH_2$. [b] H_3O^+. [c] 2NBS, CCl_4, Δ. [d] H_3O^+.

duction period. However, if special precautions (beyond the standard procedure of resealing the jar under an inert atmosphere) were not taken to protect the $NaNH_2$ after the jar was opened, subsequent reactions using the old jar of $NaNH_2$ led to highly variable reaction times. As a precaution, all manipulations of $NaNH_2$ were performed in a glovebag with the utilization of a nitrogen atmosphere. Under these conditions, the benzyne generation and 1,1-dimethoxyethylene [2 + 2] reactions proceeded smoothly.

The benzocyclobutenones and benzocyclobutenediones prepared by the route shown in eq 2 are listed in Table I. All reactions were performed on a multigram scale. As originally described by Stevens and Bisacchi, the benzyne reaction proceeded with remarkable regioselectivity, producing in most cases only one regioisomer. We attempted a few benzyne reactions using 1,1-di-*n*-butoxyethylene in place of the less accessible 1,1-dimethoxyethylene, but found the reaction sequences to be more tractable with the lower molecular weight ketene acetal.

We attempted to prepare a "bis" benzocyclobutenedione **7** by the sequence shown in eq 3. Subjection of 1,4-dibromobenzene to the benzyne generation with $NaNH_2$ in the presence of 1,1-dimethoxyethylene produced the novel "bis" benzocyclobutenone **6** in 20% yield after acid-catalyzed hydrolysis. Initial attempts to convert **6** into **7** were not successful, and this reaction was not explored further; however, we withhold judgement on the feasibility of the transformation **6** to **7** until more detailed studies can be performed.



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Conclusions

Substituted benzocyclobutenediones are easily prepared on a multigram scale via benzocyclobutenones. The requisite benzocyclobutenones are available from hydrolysis of benzocyclobutenone ketals, which are generated from substituted bromoarenes and $NaNH_2$ reacted in the presence of 1,1-dimethoxyethylene. The benzocyclobutenones undergo double benzylic bromination with 2 equiv of *N*-bromosuccinimide, and hydrolysis then provides the substituted benzocyclobutenediones. This procedure provides the most direct and practical method for the synthesis of large quantities of substituted benzocyclobutenediones.

Experimental Section

General Considerations. Microanalyses were carried out by Atlantic Microlabs, Atlanta, GA. Infrared spectra were recorded on a Perkin-Elmer 1420 ratio recording infrared spectrophotometer. Proton and carbon nuclear magnetic resonance spectra were obtained on a GE QE-300 instrument operating at 300.151410 and 75.480824 Hz, respectively. All NMR absorptions are expressed in parts per million (δ) relative to the solvent used, 7.26 and 77 ppm for $CDCl_3$ and 2.04 and 206 ppm for acetone-d_6. Melting points were obtained on a Hoover-Thomas melting point apparatus and are uncorrected. Mass spectral data were obtained by low-resolution electron impact on a VG 70 S high-resolution mass spectrometer. Column chromatography was effected by using a 60-270 mesh silica gel purchased from Fisher Scientific. Thin-layer chromatography was performed with EM Scientific 60 F_{254} 0.25 mm plates purchased from American Scientific Products. Visualization of TLC plates was achieved with UV light, phosphomolybdic acid, or "halo stain", which refers to a stain made from 0.5 g of zinc chloride and 0.5 g of diphenylamine in 100 mL of acetone.[9]

Starting Materials. For the ketene acetal preparations, A.C.S. bromine was purchased from Fisher and was used as received. Certified A.C.S. methanol was obtained from Fisher and dried over 4-Å molecular sieves. Vinyl acetate was purchased from Aldrich and distilled to remove water and inhibitor. Potassium was purchased from Aldrich, as was 95% α-terpineol, which was distilled from calcium hydride to dry and purify. **Bromoacetaldehyde dimethyl acetal** was prepared via a modification of an *Organic Syntheses* procedure.[10] Vinyl acetate was distilled at atmospheric pressure, the first cloudy portion of the distillate being discarded. Methanol (500 mL) and 155 mL (1.67 mol) of vinyl acetate were placed in a 1-L three-necked flask equipped with an addition funnel and a drying tube. The flask was placed in an ice–salt bath maintained at −10 °C. Bromine (85 mL, 1.67 mol) was added through the addition funnel over 5 h. The reaction was then allowed to warm to room temperature and was stirred for 48 h. The mixture was poured onto 600 g of crushed ice and swirled vigorously. When the ice had melted, the two phases were separated. The denser organic layer was washed twice with 100-mL of cold water followed by two 100-mL portions of 10% sodium carbonate solution. The resulting product was dried over two 10-g portions of crushed calcium chloride for 30 min each. This was distilled at aspirator pressure (~30 mm). The product boiled at 60 °C at this pressure providing 155 g (55%) of product. **Ketene dimethyl acetal** was made from bromoacetaldehyde dimethyl acetal by the method of Corey,[11] a modified version of an earlier procedure.[12]

Ketene di-*n*-butyl acetal was prepared by modifying the *Organic Syntheses* preparations of bromoacetaldehyde diethyl acetal[10] and ketene diethyl acetal[12] accordingly: bp 81 °C at 1 mm; IR (CH_2Cl_2) 2950, 2920, 2860, 1638, 1460, 1375, 1278, 1060,

(9) Hamilton, R.; Hamilton, S. *Thin Layer Chromatography*; John Wiley and Sons: New York, 1987; p 65.
(10) *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 123.
(11) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.
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1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.74 (t, J = 6.6 Hz, 4 H), 3.07 (s, 2 H), 1.67 (m, 4 H), 1.42 (m, 4 H), 0.921 (t, J = 7.5 Hz, 6 H).

For the benzyne cycloadditions, sodium amide was purchased from Aldrich in 50-g jars; it was stored in a dessicator and handled under an inert atmosphere. THF was freshly distilled from sodium and benzophenone. Bromoarenes were purchased from Aldrich and were used as received. *N*-Bromosuccinimide (NBS) was obtained from Aldrich and was recrystallized from water and then dried on a vacuum pump for at least 12 h, the flask being held at 100 °C throughout. The dried product was stored in a flask wrapped in aluminum foil to protect it from light. Carbon tetrachloride was obtained from Fisher as HPLC grade and, apart from deoxygenation by sparging with N_2, was used as received.

General Procedures. Benzocyclobutenones were prepared by a slightly modified version of the Stevens and Bissachi synthesis.[8] Inside a glovebag filled with dry N_2, 2 equiv of sodium amide was placed into a flamed and vacuum-dried airless-ware flask equipped with a magnetic stirring bar. Under a nitrogen atmosphere with syringe/septum techniques, 20 mL of dry THF, 10 g of bromoarene, and 2 equiv of ketene acetal were added to the flask. The reaction was heated at reflux for 2–24 h, during which time TLC and ^{1}H NMR were used to monitor the reaction for disappearance of starting material. TLC was not effective in all cases, but by watching the changes in the aromatic region of the NMR spectrum all systems were easily monitored. The reaction was quenched in a hood by carefully pouring the cooled solution into a 500-mL separatory funnel containing a large excess of ice. After addition of 200 mL of water, the reaction mixture was extracted with four 100-mL portions of methylene chloride. Occasionally a thick black solid formed that would not go into solution, and filtration through a Celite pad with methylene chloride removed the insolubles. The organic layers were combined and washed with two 100-mL portions of saturated sodium chloride solution. Solvent was removed on a rotary evaporator to give the crude ketal, which was directly hydrolyzed to the ketone in 100 mL of water, 20 mL of THF, and 1 mL of 12 N HCl. The hydrolysis reaction was monitored over a 24-h period. If the hydrolysis reaction did not occur, an additional 3 mL of 12 N HCl was added, and stirring was continued at room temperature until reaction was complete. The reaction mixture was extracted with methylene chloride, and the organic layers were combined, dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator. The resulting product was purified by column chromatography or by sublimation.

2,2-Dibromobenzocyclobutenones were prepared by adding the benzocyclobutenone into a round-bottomed flask containing 50 mL of deoxygenated CCl_4 per 1 g of ketone. To this was added 2.1 equiv of freshly recrystallized *N*-bromosuccinimide and 1 mol % of benzoyl peroxide. A reflux condensor equipped with a drying tube was attached to the flask, and the mixture was refluxed vigorously for 24 h. When analysis by TLC showed no starting material remaining, the reaction was allowed to cool to ambient temperature. Petroleum ether (50 mL) was added to precipitate the succinimide. The solid was filtered off on a Büchner funnel and washed with petroleum ether. The filtrate was concentrated and filtered through a short silica column, eluting with methylene chloride to provide relatively pure product. These compounds were not purified but were directly hydrolyzed to the benzocyclobutenediones.

Benzocyclobutenediones were prepared by adding 1 g of the dibromo compound per 25 mL of the acid solution indicated below to a round-bottomed flask. The mixture was stirred at reflux until analysis by TLC showed no starting material remaining. The solution was cooled to room temperature, poured over 100 g of ice, and extracted with methylene chloride until the organic layer was colorless. The solvent was removed, and the residue was chromatographed on a 100 × 2.5 cm SiO_2 gravity column with use of the eluents indicated below. The solvent was removed on a rotary evaporator to give the benzocyclobutenedione.

Physical Data. 6-Methoxybenzocyclobutenone (5a).[8] *o*-Bromoanisole (10 g, 0.0535 mol), 18.4 g (0.170 mol) of ketene di-*n*-butyl acetal, and 4.06 g (0.107 mol) of sodium amide were refluxed for 4 h in 20 mL of THF. The reaction was monitored by ^{1}H NMR. The crude ketal was hydrolyzed by adding 10% HCl until the solution was acidic to pH paper, and then the reaction was stirred at room temperature for 16 h. The crude material was purified on a 200 × 10 cm silica gel column with 15% ethyl acetate/hexane as the eluent. The product was allowed to solidify in the refrigerator and then was recrystallized from a minimum amount of cold hexanes to give 3.5 g (44%) of pale pink crystals. Mp: 38–39 °C (hexanes) (lit.[13] mp 32–34 °C). IR (CH_2Cl_2): 1770, 1610, 1580, 1489 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 7.46 (dd, J_1 = 8.44 Hz, J_2 = 7.07 Hz, 1 H), 7.05 (d, J = 6.90 Hz, 1 H), 6.79 (d, J = 8.43 Hz, 1 H), 4.02 (s, 3 H), 3.85 (s, 2 H). ^{13}C NMR (acetone-d_6): δ 185, 154, 152, 138, 133, 116, 115, 60, 52.

3-Methoxybenzocyclobutenedione (1a).[2a] 6-Methoxybenzocyclobutenone (2.00 g, 0.0135 mol), 4.97 g (0.0284 mol) of NBS, and 16 mg of benzoyl peroxide were refluxed in 50 mL of carbon tetrachloride for 24 h. Monitoring was accomplished by TLC (10% ethyl acetate in hexanes) with UV light visualization. The dibromo compound was hydrolyzed in 50 mL of 2.5 N HCl at reflux for 24 h. Extraction with methylene chloride, drying, and evaporation gave crude product, which was purified by recrystallization from water to give 1.2 g (55%) of pure product. Mp: 116–118 °C (water) (lit.[2a] mp 112.5–113.5 °C). IR (CH_2Cl_2): 1788, 1770, 1608, 1490 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 7.87 (dd, J_1 = 7.96 Hz, J_2 = 7.34 Hz, 1 H), 7.66 (dd, J_1 = 7.35 Hz, J_2 = 0.41 Hz, 1 H), 7.27 (dd, J_1 = 7.95 Hz, J_2 = 0.39 Hz, 1 H), 4.21 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 194, 189, 171, 158, 155, 138, 121, 113, 60.

Mixture of 5-Methoxybenzocyclobutenone (5b) and 4-Methoxybenzocyclobutenone (5b').[8] *p*-Bromoanisole (10.0 g, 0.0538 mol), 14.2 g (0.0824 mol) of ketene di-*n*-butyl acetal, $NaNH_2$ (4.9 g, 0.125 mol), and 20 mL of THF were refluxed under a nitrogen atmosphere for 24 h. The crude ketal was hydrolyzed by heating to 100 °C in 100 mL of 2 N HCl and then allowing the reaction to stir unheated for 3 h. After extraction with diethyl ether, the combined organic layers were dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude product was distilled at aspirator pressure to remove 1-butanol, and the crude benzocyclobutenone came over at 97 °C, solidifying to a white solid after distillation. The white solid was placed under vacuum overnight at 1 mmHg to remove any residual 1-butanol, leaving 2.61 g (33%) of product *as a mixture of isomers*. The crude product was taken on directly in the next step.

4-Methoxybenzocyclobutenedione (1b).[3h] The mixture prepared above (2.61 g, 0.0176 mol), 15.1 g (0.0659 mol) of NBS, and 42.6 mg of benzoyl peroxide were refluxed for 24 h. After the reaction mixture was passed through a short silica scrub column with methylene chloride, the dibromo compound was refluxed for 3 h in 75 mL of 50% sulfuric acid. Chromatography on SiO_2 with CH_2Cl_2 yielded 1.5 g (50%) of product. Mp: 98–101 °C (water) (lit.[3h] mp 101–103 °C). IR (CH_2Cl_2): 1803, 1782, 1662, 1608, 1587, 1559, 1499 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 8.05 (d, J = 8.01 Hz, 1 H), 7.60 (d, J = 1.50 Hz, 1 H), 7.47 (dd, J = 8.40 Hz, J = 2.10 Hz, 1 H), 4.07 (s, 3 H). ^{13}C NMR (acetone-d_6): δ 195, 192, 177, 168, 167, 127, 124, 103, 57.

5,6-Dimethoxybenzocyclobutenone (5c).[8] 4-Bromoveratrol (5.97 g, 0.028 mol), 4.86 g (0.055 mol) of ketene dimethyl acetal, and 2.1 g (0.055 mol) of sodium amide were reflux for 9.5 h in 20 mL of THF with monitoring by ^{1}H NMR spectroscopy. The crude ketal was hydrolyzed in 100 mL of 5% HCl by stirring at room temperature for 24 h. Purification on 200 g of silica gel with 30% ethyl acetate in hexanes gave 2.55 g (51%) of product. Mp: 84–86 °C (water) (lit.[8] mp 86–87 °C). IR (CH_2Cl_2): 3040, 2965, 2920, 2860, 2806, 1760, 1725, 1600, 1592, 1490, 1450, 1433, 1409, 1380, 1348 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.04 (d, J = 7.61 Hz, 1 H), 6.94 (d, J = 7.56 Hz, 1 H), 4.21 (s, 3 H), 3.87 (s, 5 H). ^{13}C NMR (acetone-d_6): δ 184, 149, 144, 142, 133, 121, 115, 60, 57, 50.

3,4-Dimethoxybenzocyclobutenedione (1c). The dibromobenzocyclobutenone was made by refluxing 1.7 g (0.0096 mol) of 5,6-dimethoxybenzocyclobutenone with 4.72 g (0.0201 mol) of NBS and 23.2 mg of benzoyl peroxide for 24 h in CCl_4. Monitoring was accomplished by TLC (50:50 hexanes–ether) with halo stain visualization. The crude product was refluxed with 75 mL of 10% HCl for 3 h and then stirred three additional hours while being cooled to room temperature. Chromatography on a 60 × 2 cm silica gel column, eluting with methylene chloride gave 1.1 g (60%) of product. Mp: 146 °C (water). IR (CH_2Cl_2): 1780,

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1592, 1550, 1497, 1453, 1433, 1360, 1260, 1200, 1185, 1122, 1030 cm^{-1}. ^1H NMR (acetone-d_6): δ 7.67 (d, J = 8.04 Hz, 1 H), 7.60 (d, J = 8.04 Hz, 1 H), 4.23 (s, 3 H), 4.03 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 191, 190, 162, 157, 153, 144, 120, 115, 61, 57. MS: (M^+) 192. Anal. Calcd for $C_{10}H_8O_4$: C, 62.5; H, 4.17. Found: C, 62.3; H, 4.10.

4,6-Dimethoxybenzocyclobutenone (5d). 1-Bromo-2,4-dimethoxybenzene (10 g, 0.046 mol), 9.89 g (0.112 mol) of ketene dimethyl acetal, and 4.27 g (0.112 mol) of sodium amide were refluxed in 20 mL of THF and monitored by TLC (10% EtOAc/hexanes) visualized with halo stain and phosphomolybdic acid. After completion of the reaction, hydrolysis of the crude ketal at room temperature in 100 mL of 5% HCl for 20 h followed by chromatography on SiO_2 (10% EtOAc/hexanes) gave 3.7 g (46%) of product. Mp: 51–52 °C (water). IR (CH_2Cl_2): 1760, 1607, 1570, 1478, 1430, 1368, 1210, 1170, 1150, 1140 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.51 (s, 1 H), 6.22 (s, 1 H), 4.02 (s, 3 H), 3.77 (s, 3 H), 3.72 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ 182, 168, 155, 152, 125, 102, 60, 56, 50. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.4; H, 5.62. Found: C, 67.5; H, 5.72.

3,5-Dimethoxybenzocyclobutenedione (1d). 4,6-Dimethoxybenzocyclobutenone (3.0 g, 0.0169 mol), 6.3 g (0.0354 mol) of NBS, and 20 mg (0.845 mmol) of benzoyl peroxide were combined and refluxed in CCl_4 for 18 h as in the general procedure. The reaction was monitored by TLC and visualized with halo stain. The crude dibromo compound was hydrolyzed in 100 mL of 1.2 N HCl for 3 h. Chromatography on a 150 × 10 cm silica gel column, eluting with methylene chloride, gave 2.85 g (88%) of product. Mp: 147–148 °C (hexanes). IR (CH_2Cl_2): 1790, 1769, 1605, 1583, 1308, 1209, 1153 cm^{-1}. ^1H NMR (acetone-d_6): δ 7.18 (d, J = 1.61 Hz, 1 H), 6.75 (d, J = 1.62 Hz, 1 H), 4.15 (s, 3 H), 4.02 (s, 3 H). ^{13}C NMR (acetone-d_6): δ 195, 188, 174, 170, 157, 155, 109, 98, 60. Anal. Calcd for $C_{10}H_8O_4$: C, 62.5; H, 4.17. Found: C, 62.7; H, 4.23.

3,6-Dimethoxybenzocyclobutenone (5e).[3h,14] 1-Bromo-2,5-dimethoxybenzene (10 g, 0.046 mol), 8.1 g (0.092 mol) of ketene dimethyl acetal, and 3.6 g (0.092 mol) of sodium amide were refluxed in 20 mL of THF for 21 h. The crude ketal was isolated and hydrolyzed for 6 days at room temperature in 100 mL of 10% HCl with 20 mL of THF cosolvent. Chromatography on a 100 × 5 cm silica gel column with 25% ethyl acetate in hexanes and then recrystallization from hexanes gave 3.3 g (40%) of yellow product. Mp: 104 °C (hexanes) (lit.[3h] mp 107–108 °C). IR (CH_2Cl_2): 1768, 1580, 1500, 1435, 1252, 1149, 1052, 1000, 835 cm^{-1}. ^1H NMR (acetone-d_6): δ 7.00 (d, J = 9.00 Hz, 1 H), 6.77 (d, J = 9.00 Hz, 1 H), 4.05 (s, 2 H), 3.99 (s, 3 H), 3.87 (s, 1 H). ^{13}C NMR (acetone-d_6): δ 185, 149, 148, 134, 133, 125, 118, 60, 57, 51. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.4; H, 5.62. Found: C, 67.4; H, 5.70.

3,6-Dimethoxybenzocyclobutenedione (1e).[3h] The dibromobenzocyclobutenone was made by refluxing 2.0 g (0.0112 mol) of 3,6-dimethoxybenzocyclobutenone with 4.2 g (0.0235 mol) of NBS and 27.1 mg of benzoyl peroxide for 22 h in CCl_4. Monitoring was accomplished by TLC (methylene chloride) visualized with halo stain. The crude dibromo compound was refluxed in 1.2 N HCl for 5 h. The reaction mixture was extracted with methylene chloride until the organic layer was clear. The solvent was removed on a rotary evaporator to give the crude product, which was purified by recrystallization from water providing 1.4 g (66%) of deep yellow needles. Mp: 188–189 °C dec (H_2O) (lit.[3h] mp 190–192 °C). IR (CH_2Cl_2): 1800, 1772, 1499, 1430, 1270, 1038 cm^{-1}. ^1H NMR (acetone-d_6): δ 7.24 (s, 2 H), 4.14 (s, 6 H). ^{13}C NMR (acetone-d_6): δ 190, 155, 149, 126, 60.

5,6-(Methylenedioxy)benzocyclobutenone (5f). 3,4-(Methylenedioxy)bromobenzene (10 g, 0.050 mol), 8.8 g (0.010 mol) of ketene dimethyl acetal, and 3.8 g (0.010 mol) of sodium amide were refluxed for 4.5 h in 20 mL of THF. The crude ketal was hydrolyzed in 3% HCl with 30% THF/H_2O for 25 h. The ketone was purified on a short silica column with 10% ethyl acetate and then recrystallized from water to obtain fine white needles, 5.7 g (70%). Mp: 88 °C (H_2O). IR (CH_2Cl_2): 3060, 3010, 2970, 2900, 1785, 1765, 1628, 1611, 1500, 1467, 1411, 1245, 1208, 1160, 1143, 1109, 1048, 1021, 919 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.97 (d, J = 7.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 184, 149, 141, 138, 128, 116, 115, 102, 52. MS: (M^+) 162. Anal. Calcd for $C_9H_6O_3$: C, 66.7; H, 3.70. Found: C, 66.8; H, 3.78.

3,4-(Methylenedioxy)benzocyclobutenedione (1f). The dibromo compound was made with 2.63 g (0.0162 mol) of 5,6-(methylenedioxy)benzocyclobuten-1-one, 6.07 g (0.0341 mol) of NBS, and 39.2 mg of benzoyl peroxide by refluxing in CCl_4 for 21.5 h (monitored by TLC eluted with 10% ethyl acetate in hexanes and visualized with halo stain). The crude dibromo compound was hydrolyzed in 75 mL of 10% HCl at reflux for 5 h. Chromatography on a 125 × 5 cm silica column with methylene chloride followed by recrystallization from hot 50/50 acetone/water gave 1.1 g (53%) of product. Mp: 164–166 °C. IR (CH_2Cl_2): 2925, 2855, 1783, 1502, 1473, 1118 cm^{-1}. ^1H NMR (acetone-d_6): δ 7.72 (d, J = 7.96 Hz, 1 H), 7.47 (d, J = 7.96 Hz, 1 H), 6.45 (s, 2 H). ^{13}C NMR (acetone-d_6): δ 192, 190, 164, 154, 151, 140, 118, 117, 105. Anal. Calcd for $C_9H_4O_4$: C, 61.4; H, 2.27. Found: C, 61.3; H, 2.51.

6-Fluorobenzocyclobutenone (5g). 2-Fluorochlorobenzene (10 g, 0.057 mol), 19.6 g (0.11 mol) of ketene di-*n*-butyl acetal, and 4.33 g (0.11 mol) of sodium amide were refluxed for 22 h in 20 mL of THF. The crude ketal was hydrolyzed at room temperature in 100 mL of 10% HCl with 50 mL of THF as cosolvent for 6 days. Sublimation at water aspirator pressure with a hot water bath gave 2.5 g (32%) of pure product. Mp: 39–42 °C (sublimed). IR (CH_2Cl_2): 2930, 1882, 1770, 1600, 1472, 1405, 1339, 1245, 1220, 1130, 1027, 943, 785, 695 cm^{-1}. ^1H NMR (acetone-d_6): δ 7.71 (m, 1 H), 7.48 (dd, J = 7.22 Hz, J = 2.02 Hz, 1 H), 7.16, (t, J = 8.67 Hz, 1 H), 4.03 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ 183, 152 (d, J = 4.5 Hz), 151 (d, J = 267 Hz), 138 (d, J = 6.8 Hz), 134 (d, J = 17 Hz), 120 (d, J = 3.8 Hz), 115 (d, J = 20 Hz), 53. Anal. Calcd for C_8H_5FO: C, 70.6; H, 3.70. Found: C, 70.8; H, 3.85.

3-Fluorobenzocyclobutenedione (1g). 6-Fluorobenzocyclobutenone (1.9 g, 0.014 mol), 6.95 g (0.031 mol) of NBS, and 33.9 mg of benzoyl peroxide were refluxed 24 h in CCl_4 to produce the dibromo compound, which was hydrolyzed for 6 h at reflux in 50% sulfuric acid followed by stirring an additional 6 h at room temperature. Purification was accomplished on a 40 × 3 cm SiO_2 column, eluting with methylene chloride followed by recrystallization from hexanes to provide 1.4 g (66%) of product. Mp: 95 °C (hexanes). IR (CH_2Cl_2): 1840, 1792, 1766, 1600, 1479, 1210, 1125, 995, 790 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.84 (m, 2 H), 7.41 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 193, 188, 172, 159 (d, J = 23.2 Hz), 153 (d, J = 269 Hz), 139 (d, J = 6.80 Hz), 122 (d, J = 19.6 Hz), 118 (d, J = 3.77 Hz). Anal. Calcd for $C_8H_3FO_2$: C, 64.0; H, 2.00. Found: C, 63.7; H, 2.00.

Tricyclo[6.2.0.0^{3,6}]deca-1,3,7-triene-4,9-dione (6). Sodium amide (4.64 g, 0.122 mol) was added to a dried flask equipped with a stirring bar. To this was added via syringe 5.00 g (0.0212 mol) of *p*-dibromobenzene dissolved in 20 mL of dry THF and 11 mL (0.0848 mol, 4 equiv) of ketene dimethyl acetal, and the solution was stirred and refluxed for 3.5 h. TLC analysis (10% ethyl acetate in hexanes) showed no starting material remained. Extraction of the reaction with CH_2Cl_2 and condensation of the combined organic layers left a brown liquid. Chromatography on a 35 × 5 cm silica gel column, eluting with 30% ethyl acetate in hexanes, gave crude product that was hydrolyzed at room temperature in 10 mL of 1.2 N HCl containing 3 mL of THF. After the mixture was stirred for 5.25 h, the THF was removed on a rotary evaporator, and the water layer was extracted with methylene chloride. The combined organic layers were dried and concentrated, and the crude residue was recrystallized from cyclohexane. The product was then dissolved in boiling 25% ethanol/H_2O and filtered hot. The pure product slowly crystallized from the hot filtrate; 0.192 g (20%). Mp: 180–183 °C dec (H_2O/EtOH). IR (CH_2Cl_2): 1772, 1699, 1605, 1573, 1408, 1242, 1161, 1130, 1012 cm^{-1}. ^1H NMR (acetone-d_6): δ 7.86 (s, 1 H), 4.05 (s, 4 H). ^{13}C NMR (acetone-d_6): δ 185, 154, 141, 130, 53. Anal. Calcd for $C_{10}H_6O_2$: C, 76.0; H, 3.80. Found: C, 75.7; H, 3.89.

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Registry No. **1a**, 62416-22-2; **1b**, 41634-29-1; **1c**, 118112-21-3; **1d**, 118112-22-4; **1e**, 75833-47-5; **1f**, 118112-23-5; **1g**, 118112-24-6; **3** (R^1 = OMe, $R^{\neq 1}$ = H), 578-57-4; **3** (R^3 = OMe, $R^{\neq 3}$ = H),

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104-92-7; **3** ($R^{2,3}$ = OMe, $R^{1,4}$ = H), 2859-78-1; **3** ($R^{2,4}$ = OMe, $R^{1,3}$ = H), 17715-69-4; **3** ($R^{1,4}$ = OMe, $R^{2,3}$ = H), 25245-34-5; **3** ($R^{2,3}$ = OCH_2O, $R^{1,4}$ = H), 2635-13-4; **3** (R^1 = F, $R^{\neq 1}$ = H), 1072-85-1; **5a**, 66947-60-2; **5b**, 55171-77-2; **5b'**, 22246-27-1; **5c**, 81447-58-7; **5d**, 118112-18-8; **5e**, 75833-45-3; **5f**, 118112-19-9; **5g**, 118112-20-2; **6**, 118112-25-7; *p*-dibromobenzene, 106-37-6.

Syntheses of Symmetric α,α,α-Tris(imidazolylmethyl)acetonitriles: A New Class of Tripod M^{2+}-Chelating Ligands

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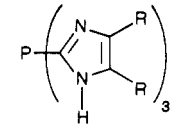
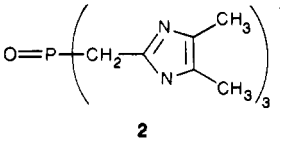
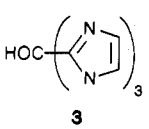
We have been interested in investigating the properties of tris(imidazolyl)·M^{2+} complexes (**1**, **2**) as potential models for the active site of carbonic anhydrase (CA).[1] Of these, **1c,d**·Zn^{2+} show good activity in facilitating attainment of the $HCO_3^- \rightleftarrows CO_2$ equilibrium in alcohol/H_2O media[1c,e] and **2**·Co^{2+} is a good spectroscopic model for Co^{2+}·CA.[1d]

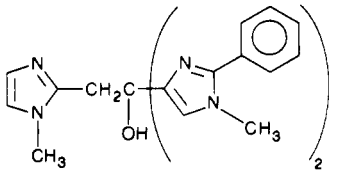






1a: R = H
b: R = CH_3
c: R = $CH(CH_3)_2$
d: R = $CH_2CH_2CH_3$

2 **3**



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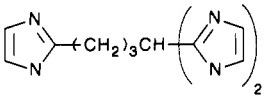

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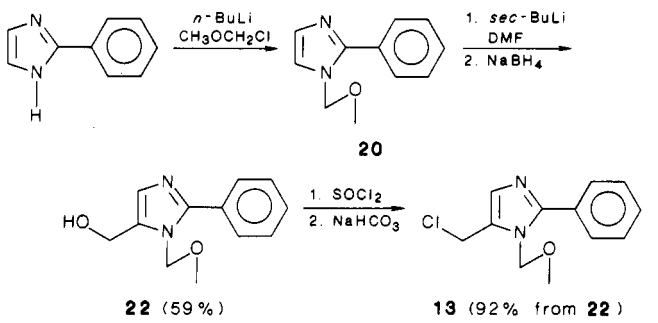
Synthetic studies have been reported by Breslow's group on related ligands including **3**–**5**,[2] but the metal complexes of these are deficient as active CA models. In the case of **3** and related tris(imidazolyl) carbinols[1a,2] the ligands are too small to encapsulate the metal in a four coordinate geometry since (2L·M^{2+}) octahedral coordination is observed. Attempts to suppress the 2:1 complexation by inserting sterically demanding groups distal to the imidazole C_2 or C_4 point of attachment to the carbinol lead to dehydration and the production of highly colored quinoid-type species.[1a,2b] Both the binding and dehydration problem were circumvented by replacing the HOC anchor with a phosphorus as in **1** or **2**. However, these compounds too were deficient since they exhibited a limited solubility in H_2O and required EtOH/H_2O solvent systems for physical study. Even so, they were unstable as their Zn^{2+} complexes for prolonged periods in these media and suffered P–C cleavage to produce bis(imidazolyl)phosphinic acid·Zn^{2+} products.[3]

Scheme I



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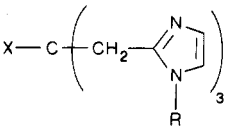
22 (59%) **13** (92% from **22**)

In order to address the above problems, we initiated a synthetic project to create symmetric ligands with a CH_2 unit inserted between the imidazole unit and a central carbon atom as in **6** or **7**. Despite the obvious interest in



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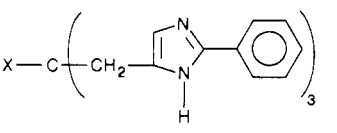

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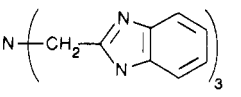

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so-called "tripod" ligands as models for metallo enzymes,[4] we are unaware of general approaches to carbon-based examples of this class[5] although the synthesis of the tetracoordinating **8**[6] and related tris(pyrazolylmethyl)amines[7] has been reported. In this paper we describe the general method for the syntheses of **6** and **7** (X = CN): We will describe elsewhere the properties of the M^{2+} complexes.

Results and Discussion

Several initial attempts at simple nucleophilic approaches to a tris(imidazolylmethyl) ligand were unsuccessful. For example, attempted 3-fold displacement of I^- from tris(iodomethyl)methane[8] with 3 equiv of the lithio anions **9**, **10**, or **11** in THF (–60 °C → room temperature) afforded only the starting materials, presumably from elimination of HI. The same occurred when the coupling reactions were conducted with the cuprates prepared[9] from **9** or **10**. Although the reaction of 3 equiv of **12** with diethyl carbonate is unlikely to produce a trisalkylated product due to proton abstraction from an intermediate imidazole acetic ester,[2a] we tried the reactions with the Ce(III) anions since these are reported to be useful in nucleophilic additions to easily enolized C=O units.[9] This too was unsuccessful.

Since the nucleophilic routes were unsuccessful, sequential halide displacement from three chloromethyl im-

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