3.3–4.2 (18 H, m), 4.47 (1 H, d, J 7 Hz, 1″-H), 6.04 (1 H, d, J 4.5 Hz, 6′-H); ^{13}C NMR (D_2O, 25.2 MHz) δ 31.8 (t), 54.5 (d), 56.4 (d), 63.2 (t), 64.3 (t), 67.1 (t), 72.1 (d), 72.5 (d), 72.9 (d), 74.3 (d), 75.4 (d), 75.8 (d), 76.2 (d), 78.5 (d), 78.7 (d), 79.0 (s), 86.0 (d), 105.8 (d), 125.0 (d), 142.0 (s); TLC R_f 0.18. Anal. Calcd for $C_{20}H_{35}NO_{14}\cdot H_2O$: C, 45.19; H, 7.01; N, 2.63. Found: C, 45.23; H, 7.22; N, 2.54.

Undeca-*O*-acetylvalidamycin G (6c). Acetylation of **6a** (25 mg, 0.047 mmol) with Ac_2O/pyridine (2:1, 15 mL) gave the undeca-*O*-acetate of validamycin G (**6c**, 20 mg, 54.5%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (1 H, dd, J 2.7, 15.3 Hz, 6-Hax), 1.90 (1 H, dd, J 3.1, 15.3 Hz, 6-Heq); 1.99, 2.00, 2.03, 2.04, 2.05, 2.06, 2.06, 2.07, 2.08, 2.10, and 2.14 (each 3 H, s, acetyl × 11); 3.43 (1 H, dt*, J 2.7, 3.1, 4.4 Hz, 1-H), 3.60 (1 H, m, 1′-H), 3.63 (1 H, ddd, J 2.3, 4.1, 9.1 Hz, 5″-H), 3.66 (1 H, d, J 9.9 Hz, 4-H), 3.92 and 4.13 (each 1 H, ABq, J 11.1 Hz, 7-H), 4.04 (1 H, dd, J 2.3, 12.5 Hz) and 4.40 (1 H, dd, J 4.1, 12.5 Hz) (6″-H), 4.37 and 4.60 (each 1 H, br ABq, J 13.3 Hz, 7′-H), 4.50 (1 H, d, J 9.1 Hz, 1″-H), 4.93 (1 H, dd, J 4.4, 9.9 Hz, 2-H), 4.97 (1 H, t, J 9.1 Hz, 2″-H), 4.99 (1 H, dd, J 5.1, 10.2 Hz, 2′-H), 5.09 (1 H, t, J 9.1 Hz, 4″-H), 5.16 (1 H, t, J 9.1 Hz, 3″-H), 5.38 (1 H, br d, J 6.6 Hz, 4′-H), 5.42 (1 H, dd, J 6.6, 10.2 Hz, 3′-H), 5.52 (1 H, t, J 9.9 Hz, 3-H), 5.97 (1 H, br d, J 5.1 Hz, 6′-H), 5.87 (1 H, br s, –NH–) (*apparent splitting pattern).

Acknowledgment. We are grateful to Toshihiko Matsuyama for assistance in synthetic work and Fumiko Kasahara for NMR measurements.

Registry No. **1a**, 83465-22-9; **1c**, 141042-85-5; **2a**, 83480-29-9; **2b**, 101540-73-2; **3**, 114250-39-4; **4a**, 38231-86-6; **4b**, 114779-32-7; **5a**, 106054-18-6; **5c**, 106357-01-1; **6a**, 106054-17-5; **6c**, 106357-02-2; **7**, 140926-93-8; **8**, 140926-94-9; *epi*-**8**, 141115-25-5; **9a**, 115250-39-0; **9b**, 140926-95-0; **10**, 13096-62-3; **11**, 140926-87-0; **12** (isomer 1), 115250-30-1; **12** (isomer 2), 115305-00-5; **13**, 115250-32-3; **14**, 110391-10-1; **15**, 99695-34-8; **16**, 140926-88-1; **17**, 83921-62-4; **18**, 88970-25-6; **19**, 140926-89-2; **20**, 140926-90-5; **20′**, 5328-46-1; **22**, 140926-91-6; **23**, 140926-92-7; 2-amino-1,3-propanediol, 534-03-2; dimethyl methanephosphonate, 756-79-6.

Supplementary Material Available: Complete ^{1}H NMR data of compounds **7**, **9a,b**, **11**, **12**, **14–16**, **18–20**, **22** and **23** (7 pages). Ordering information is given on any current masthead page.

Syntheses and NMR Behavior of Calix[4]quinone and Calix[4]hydroquinone

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Calix[4]quinone (7) and calix[4]hydroquinone (6) have been synthesized using three different synthetic pathways. The first pathway to 7 from calix[4]arene (1) consists of six steps: acetylation, Fries rearrangement, Baeyer–Villiger oxidation after acetylation, hydrolysis, and oxidation. The second pathway to 7 from 1 consists of four steps: acetylation, Fries rearrangement, reaction of the product obtained by Fries rearrangement with sodium azide, and oxidation. The third pathway to 7 from 1 is most convenient and consists of three steps: diazo coupling reaction, reduction, and oxidation. The NMR behavior of 6 and 7 is described.

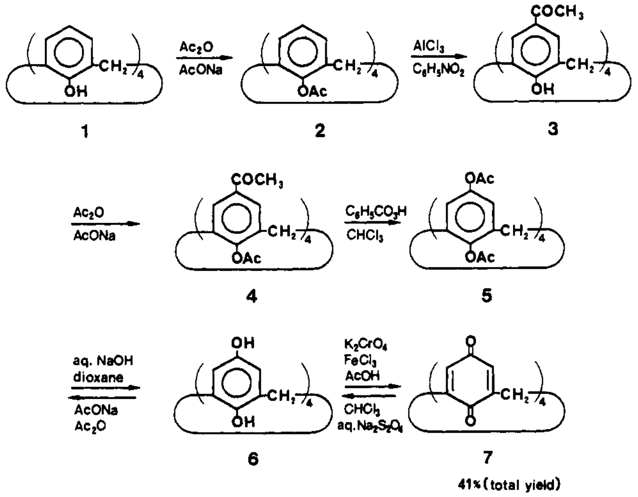
Calixarenes, which are accessible from base-catalyzed condensation of para-substituted phenols with formaldehyde, are now well-known compounds.[1] These compounds have lately attracted considerable attention because their potential as enzyme mimics has been suggested.[2]

Since the first paper of Gutsche on calixarenes[3] was issued, we have been studying the syntheses of various calixarenes and their characteristics.[4] On the other hand, we have been searching for a new redox system. If calix[4]hydroquinone (**6**) and calix[4]quinone (**7**), which are calixarene-type compounds comprised of cyclic arrays of *p*-hydroquinone residues and *p*-quinone residues attached by methylene groups, respectively, are synthesized from readily available *p-tert*-butylcalix[4]arene, they not only form new redox systems but also become new compounds which are able to form charge-transfer complexes.[5] Thus, we finally found a convenient synthesis of **6** and **7**. In this paper we report their synthetic methods using three different pathways and their NMR behavior.

Results and Discussion

Syntheses of 6 and 7. The synthesis of **7** has been attempted by Gutsche's group, that is, they have obtained a material which seems to have a calix[4]quinone structure, but attempts to purify it have not been successful.[6]

Scheme I



[†] Present address: Dainichiseika Color & Chemicals Mfg Co., Ltd, 7-6 Bakurocho 1-Chome, Nihonbashi, Chuo-Ku, Tokyo 103, Japan.

(1) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989.
(2) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161.
(3) Gutsche, C. D.; Muthukrishnan, R. *J. Org. Chem.* **1978**, *43*, 4905.

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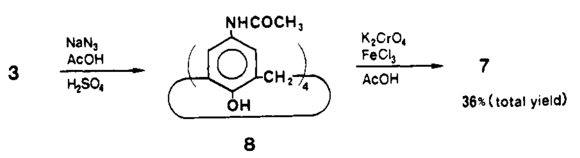
Scheme II



We planned out the stepwise synthesis of 7 from 25,26,27,28-tetrahydroxycalix[4]arene (1). Three possible pathways were taken into account.

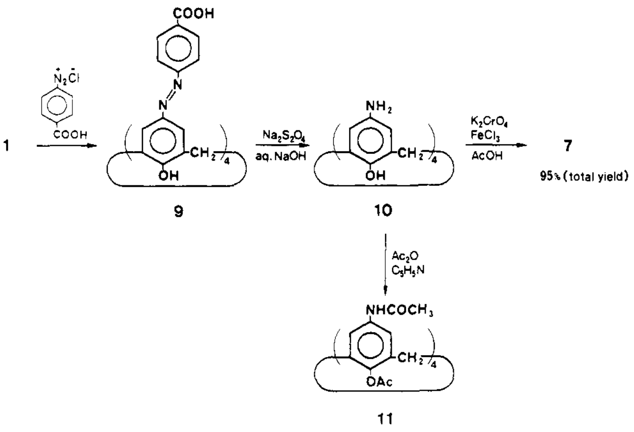
The first pathway is shown in Scheme I. Acetylation of 1 was carried out by using the method of Gutsche and Lin to afford 25,26,27,28-tetraacetoxycalix[4]arene (2) in an 84% yield.[7] The conversion of 2 to 5,11,17,23-tetraacetyl-25,26,27,28-tetrahydroxycalix[4]arene (3) was achieved successfully by the Fries rearrangement. In chlorobenzene the Fries rearrangement of 37,38,39,40,41,42-hexaacetoxycalix[6]arene has been reported not to take place.[8] However, we used nitrobenzene as a solvent for the rearrangement of 2 to 3. The calixarene 3 was allowed to react with acetic anhydride in the presence of sodium acetate to give 5,11,17,23-tetraacetyl-25,26,27,28-tetraacetoxycalix[4]arene (4) in 76% yield. The Baeyer–Villiger oxidation of 4 to 5,11,17,23,25,26,27,28-octaacetoxycalix[4]arene (5) using perbenzoic acid required prolonged times in the dark, with occasional shaking at room temperature for completion. The hydrolysis of 5 under basic conditions proceeded smoothly to produce 6 in a 95% yield. The recrystallization of 6 was carried out in methanol–water containing small amounts of hydrochloric acid and tin(II) chloride, because the product was liable to be oxidized by air. The hydroquinone 6 was oxidized readily with ferric chloride to yield the desired tetraquinone 7 in 89% yield. The total yield of 7 based on calixarene 1 was 41%.

The second pathway is shown in Scheme II. The acetylcalix[4]arene 3 was allowed to react with sodium azide in acetic acid in the presence of concentrated sulfuric acid to afford 5,11,17,23-tetraacetamido-25,26,27,28-tetrahydroxycalix[4]arene (8) in 75% yield. This compound was converted into 7 by ferric chloride in 57% yield. The total yield of 7 based on 1 was 36%. Although the total yield of 7 from the second pathway is lower than that from the first one, the second pathway is two steps shorter than the first one.

The third pathway is shown in Scheme III. This pathway is the most convenient method which gives the best yield of 7 among the three pathways.

We investigated the diazo coupling reactions of 1 with benzendiazonium chloride, 4-methylbenzendiazonium chloride, 4-methoxybenzenediazonium chloride, and 4-carboxybenzenediazonium chloride.[9] These reactions proceeded smoothly to produce the corresponding azo compounds in good yields. Above all, 4-carboxybenzendiazonium chloride reacted quantitatively with an equimolecular amount of 1. Besides, only the azo compound, 5,11,17,23-tetrakis[(*p*-carboxyphenyl)azo]-25,26,27,28-tetrahydroxycalix[4]arene (9), dissolved in an aqueous alkaline solution. This is very favorable for the subsequent reaction, because the reduction of 9 to 5,11,17,23-tetraamino-25,26,27,28-tetrahydroxycalix[4]arene (10) was carried out in an aqueous alkaline solution. The reduction proceeded quantitatively to produce 10 as scale-like white crystals, which were very unstable in air: In air the color of the crystals changed from white to black in several hours. Therefore, the confirmation of 10 was performed by the conversion of 10 to its acetyl derivatives (8 and 11). The calixarene 10 was easily oxidized to 7 in 95% yield by ferric chloride. The total yield of 7 based on 1 was 95%.

Scheme III



The quinone 7 was easily reduced by aqueous hydrosulfite solution to produce 6 in 93% yield.

NMR Behavior of 6. Temperature-dependent ^{1}H NMR (DNMR) spectra of 6 were measured in pyridine-d_5 and *N,N*-dimethylformamide-d_7 (DMF-d_7). Figure 1, parts a and b, show the results. The methylene resonances appear as a singlet at 3.99 ppm at 30 °C in pyridine-d_5 and at 3.76 ppm at 30 °C in DMF-d_7; however, they appear as a pair of doublets at 3.64 and 4.70 ppm at −35 °C in pyridine-d_5 and at 3.47 and 4.14 ppm at −30 °C in DMF-d_7 respectively. It is well-known that calix[4]arene molecules can have four kinds of conformations, refered to as cone, partial cone, 1,2-alternate, and 1,3-alternate, and that in a cone conformation their methylene protons appear as an AB quartet or doublet of doublets in the NMR measurement.[10] This fact shows that 6 has a cone conformation in pyridine or DMF and that the interconversion with mirror image cone conformation is slow on the NMR time scale at −35 or −30 °C. From this measurement, it can be derived that the coalescence temperatures for the methylene resonances are −2 °C in pyridine-d_5 and 0 °C in DMF-d_7, and $\Delta G^{\ddagger}$ values[11] for the ring inversion of 6 are 13.6 kcal/mol in pyridine-d_5 and 13.7 kcal/mol in DMF-d_7, respectively. Compound 6 has two kinds of hydroxy groups, i.e., the upper hydroxy groups which are located at meta positions toward methylene groups and the lower ones which are located at ortho positions. From the NMR measurements, it has been suggested that the lower hydroxy groups in 6 are more strongly intramolecularly hydrogen bonded than the upper ones, because the resonances of upper hydroxy groups appear as a singlet at 8.86 ppm and the lower ones appear at 9.67 ppm at 30 °C in DMF-d_7. Similar results were also obtained in acetone-d_6. When the NMR measurement was carried out at an or-

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(4) (a) Taniguchi, H.; Nomura, E. *Chem. Lett.* **1988**, 1773. (b) Nomura, E.; Taniguchi, H.; Tamura, S. *Chem. Lett.* **1989**, 1125. (c) Nomura, E.; Taniguchi, H.; Kawaguchi, K.; Otsuji, Y. *Chem. Lett.* **1991**, 2167.

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(6) Reference 1, p 146.

(7) (a) Gutsche, C. D.; Lin, L.-G. *Tetrahedron* **1986**, *42*, 1633. (b) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.

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(9) The diazonium chloride was prepared by the reported method with a slight modification: Schieman, G.; Winkelmuller, W. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 299.

(10) Reference 1, Chapter 4.

(11) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.

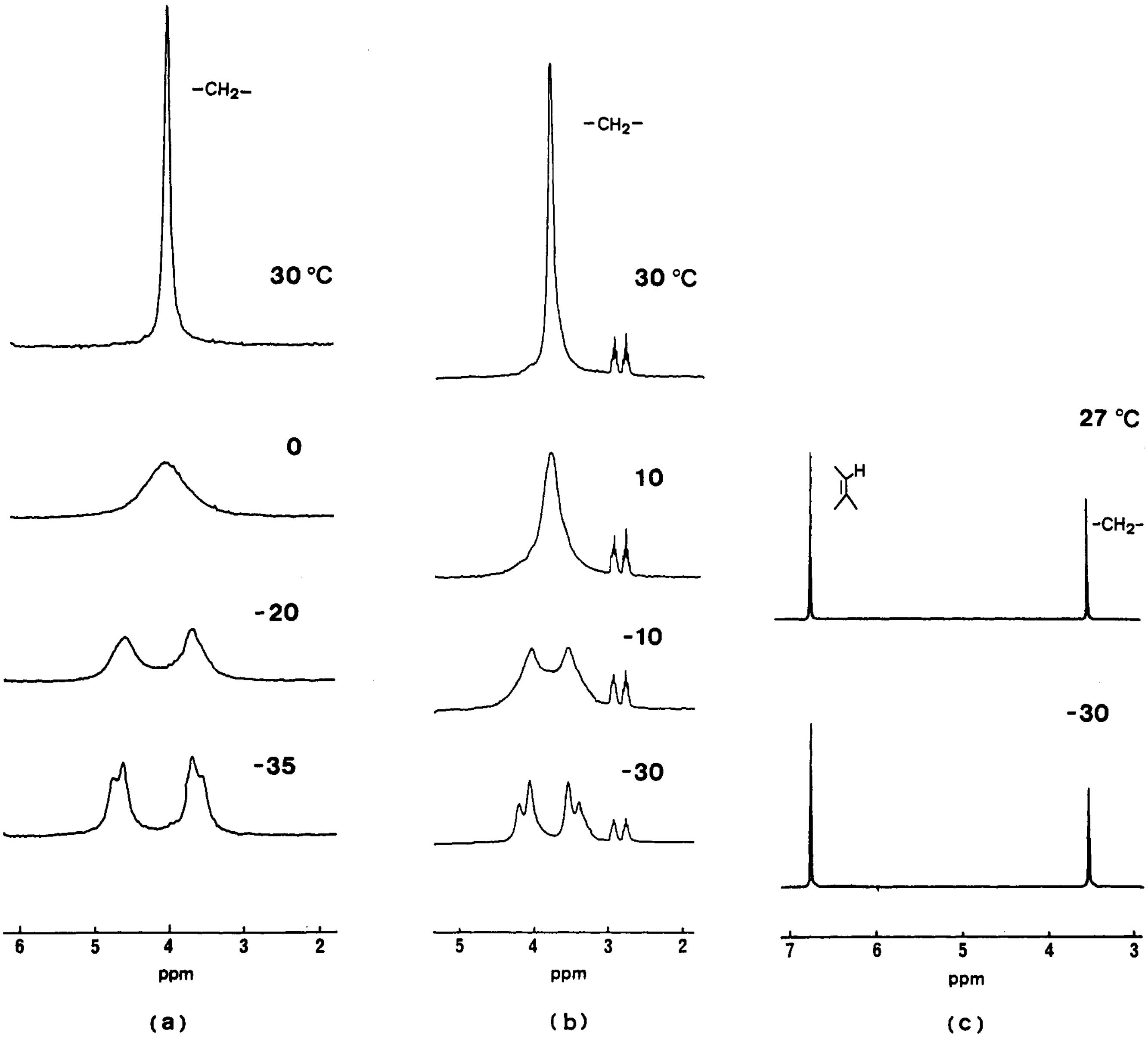

Figure 1. Temperature-dependent ^{1}H NMR spectra of **6** and **7** showing the CH$_2$ resonance: (a) **6** in pyridine-d_5 at 90 MHz, (b) **6** in DMF-d_7 at 90 MHz, (c) **7** in pyridine-d_5 at 400 MHz.

dinary temperature immediately after its NMR acetone-d_6 solution was prepared, the upper hydroxy protons appeared as a singlet at 7.82 ppm and the lower ones at 9.78 ppm. Only the signals of the upper hydroxy protons disappeared after 24 h. This is due to the deuteration of the upper hydroxy protons with the enol-type of acetone-d_6. This phenomenon implies that the intramolecular hydrogen-bonding among the lower hydroxy protons is very strong. In pyridine-d_5, however, the two kinds of hydroxy protons appeared at 9.17 ppm as a very broad singlet at 20 °C. This phenomenon may be attributable to an intermolecular hydrogen-bonding between the hydroxy groups and pyridine-d_5.

NMR Behavior of 7. We have reported in a previous communication that the molecular structure of **7** in the crystal state has a sort of partial cone conformation as shown in Figure 2.[12] However, **7** does not prefer the partial cone conformation in its organic solutions. The ^{1}H NMR pattern of **7** measured at −30 °C in pyridine-d_5 was very similar to that measured at 27 °C. The methylene resonances appeared at 3.56 ppm as a very sharp singlet and the olefin protons appeared at 6.77 ppm as a singlet as shown in Figure 1, part c. The methylene protons of *p*-*tert*-butylcalix[4]arene appear as one singlet when it has a 1,3-alternate conformation.[7b] Thus, this phenomenon suggests whether in its pyridine solution **7** has a 1,3-alternate conformation at −30 °C or the if ring inversion of **7** takes place at a rate that is fast on the NMR time scale even at −30 °C. The former appears to be more reasonable because of a Coulomb repulsion between the quinone ring and the neighboring quinone rings in **7**.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 90 or 400 MHz.

25,26,27,28-Tetrahydroxycalix[4]arene (**1**)[13] and 25,26,27,28-tetraacetoxycalix[4]arene (**2**)[7] were prepared by literature methods.

5,11,17,23-Tetraacetyl-25,26,27,28-tetrahydroxycalix[4]arene (3). A mixture of 5.0 g (8.45 mmol) of **2** and 6.77 g (51 mmol) of anhydrous AlCl$_3$ in 135 mL of nitrobenzene was stirred under

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[12] Morita, Y.; Agawa, T.; Kai, Y.; Kanehisa, N.; Kasai, N.; Nomura, E.; Taniguchi, H. *Chem. Lett.* **1989**, 1349.

[13] Gutsche, C. D.; Levine, J. A.; Sujeeth, P. K. *J. Org. Chem.* **1985**, *50*, 5802.

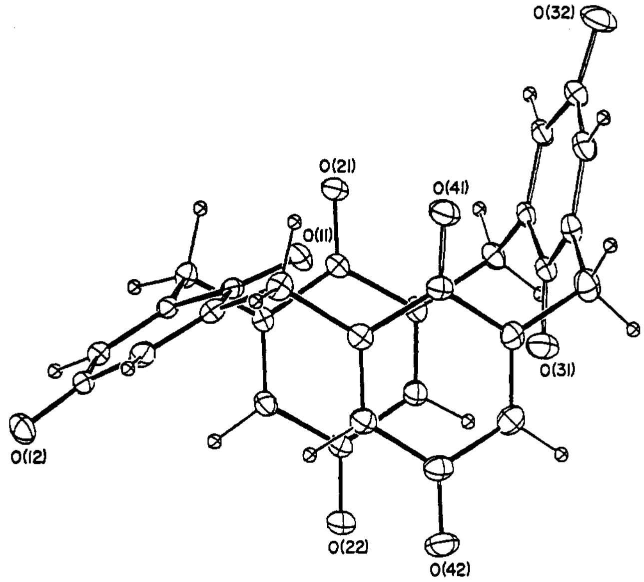

Figure 2. Molecular structure of 7.

N_2 for 2 h at rt. The mixture was stirred under N_2 for an additional 5 h at 60–70 °C. The reaction mixture was cooled with an ice bath, and then aqueous 10% HCl, which was cooled to 0 °C, was poured into the reaction mixture. The nitrobenzene layer was separated, washed with water, and dried over $MgSO_4$. Most of the nitrobenzene was removed under reduced pressure to give a residue, which was refluxed in 30 mL of acetone for 30 min and was allowed to come to rt to give 4.72 g (93%) of 3 as a white solid. Recrystallization from $CHCl_3$ gave 3.5 g (69%) of white needles: mp 365 °C; IR (KBr) 3170, 1680, 1670, 1290, 1190 cm^{-1}; ^1H NMR (DMSO-d_6) 2.48 (CH_3, s, 3 H), 3.98 (CH_2, s, 2 H), 6.76 (Ar, bs, 2 H), 7.76 (OH and $^1/_2$ H_2O, s, 2 H); ^{13}C NMR (DMSO-d_6) 26.4, 30.9, 129.3, 129.46, 129.49, 156.62, 195.96; MS m/e 593 (M + H). Anal. Calcd for $C_{36}H_{32}O_8{\cdot}{}^1/_2H_2O$: C, 71.86; H, 5.52. Found: C, 71.89; H, 5.48.

5,11,17,23-Tetraacetyl-25,26,27,28-tetraacetoxycalix[4]arene (4). A mixture of 3.0 g (5.1 mmol) of 3 and anhydrous sodium acetate in 100 mL of Ac_2O was refluxed for 2 h. After cooling, most of acetic anhydride was removed under reduced pressure to give a residue, which was washed with hot water. Recrystallization from $CHCl_3$ gave 2.93 g (76%) of 4 as a white solid: mp 338 °C; IR (KBr) 1768, 1689, 1295, 1176 cm^{-1}; ^1H NMR ($CDCl_3$) 1.68 (CH_3, s, 3 H), 2.23 (CH_3, s, 3 H), 3.68 (CH_2, bs, 2 H), 6.80 (Ar, s, 2 H); ^{13}C NMR ($CDCl_3$) 20.24, 20.82, 37.5, 121.7, 133.8, 147.8, 168.49, 169.01; MS m/e 761 (M + H). Anal. Calcd for $C_{44}H_{40}O_{12}$: C, 69.46; H, 5.30. Found: C, 69.55; H, 5.32.

5,11,17,23,25,26,27,28-Octaacetoxycalix[4]arene (5). A mixture of 1.9 g (2.5 mmol) of 4 and 2.76 g (20 mmol) of perbenzoic acid in 34 mL of $CHCl_3$ was allowed to stand for 25 d in the dark, with occasional shaking at rt. The amount of perbenzoic acid consumption was sometimes determined by a titration method. The reaction mixture was washed with 1 N Na_2CO_3, washed with water, and dried. The chloroform was evaporated under reduced pressure to give 1.8 g (81%) of 5. Recrystallization from acetone yielded a white powder: mp 271 °C; IR (KBr) 1760, 1598, 1465, 1218, 1179 cm^{-1}; ^1H NMR ($CDCl_3$) 1.68 (CH_3, s, 3 H), 2.23 (CH_3, s, 3 H), 3.68 (CH_2, bs, 2 H), 6.80 (Ar, bs, 2 H); ^{13}C NMR ($CDCl_3$) 20.27, 20.99, 37.53, 121.8, 133.7, 147.8, 168.6, 169.1. Anal. Calcd for $C_{44}H_{40}O_{16}{\cdot}C_3H_6O$: C, 63.94; H, 5.25. Found: C, 63.70; H, 5.18.

Hydrolysis of 5 to 6. A solution of 1.03 g (1.25 mmol) of 5 in 40 mL of dioxane–20 mL of aqueous (10%) NaOH was refluxed under N_2 for 2 h. After cooling, the solution was acidified with aqueous 1% HCl until the acidity of the solution reached pH 3. Most of the solvent was removed under reduced pressure to give an oily residue. To the residue was added 500 mL of water to yield a white precipitate. Recrystallization from MeOH–H_2O containing small amounts of HCl and $SnCl_2$ gave 0.58 g (95%) of 6 as white plates: mp 400 °C dec.

5,11,17,23-Tetraacetamido-25,26,27,28-tetrahydroxycalix[4]arene (8). A solution of 2.01 g (3.4 mmol) of 3 and 6 mL of concd H_2SO_4 was stirred under N_2. To this solution was added slowly 1.08 g (16.6 mmol) of NaN_3 over a period of 1 h at rt. The solution was then allowed to stir under N_2 for an additional 5 h at 60 °C. The reaction mixture was poured into 150 mL of ice–water and then was stirred for 30 min to give a precipitate. It was filtered and washed with water to yield 1.71 g (75%) of 8. Recrystallization from DMF gave white crystals: mp 421–423 °C; IR (KBr) 3500–3400, 3300, 1670, 1570 cm^{-1}; ^1H NMR (DMSO-d_6) 1.91 (CH_3, s, 3 H), 3.4 (bs, 1 H), 3.75 (CH_2, s, 2 H), 7.22 (Ar, s, 2 H), 9.59 (NH, s, 1 H); ^{13}C NMR (DMSO-d_6) 23.6, 31.3, 119.6, 127.8, 132.5, 144.9, 167.3. Anal. Calcd for $C_{36}H_{36}O_8N_4{\cdot}{}^3/_2H_2O$: C, 63.61; H, 5.78; N, 8.24. Found: C, 63.84; H, 5.59; N, 8.28.

5,11,17,23-Tetrakis[(*p*-carboxyphenyl)azo]-25,26,27,28-tetrahydroxycalix[4]arene (9). A solution of *p*-carboxybenzenediazonium chloride,[9] which was prepared from 1.37 g (10 mmol) of *p*-aminobenzoic acid, sodium nitrite, and concd HCl, in 25 mL of water, was added slowly into a cold (5 °C) solution of 1.0 g (2.36 mmol) of 1 and 4.08 g (30 mmol) of sodium acetate trihydrate in 26 mL of MeOH–DMF (5:8 v/v) to give a red suspension. After being allowed to stand for 2 h, the suspension was made acidic with 150 mL of aqueous (0.25%) HCl. The mixture was warmed at 60 °C for 30 min to produce 9 in a quantitative yield as a reddish solid, which was filtered and washed with water and MeOH. The analytical sample was obtained by the following method: 2 g of 9 was dissolved in 100 mL of a hot $NaHCO_3$ (4.2 g) solution. To the solution was added activated charcoal (1 g). After the charcoal was filtered out, the filtrate was cooled and acidified with 1 or 2 mL of concd HCl. The solution was heated again for 30 min and cooled. The obtained solid was filtered, washed with water, and dried: mp 290 °C dec; IR (KBr) 3400, 3170, 1710, 1695, 1600, 1520, 1260 cm^{-1}; ^1H NMR (pyridine-d_5) 4.0 and 4.9 (CH_2, AB q, 2 H), 7.9–8.5 (Ar, m, 6 H), 9.6 (OH and COOH, s, 2 H); ^{13}C NMR (pyridine-d_5) 33.5, 121.9, 125.0, 131.1, 131.8, 133.1, 146.0, 155.7, 161.2, 168.5. Anal. Calcd for $C_{56}H_{40}O_{12}N_8{\cdot}3H_2O$: C, 62.80; H, 4.32; N, 10.46. Found: C, 62,71; H, 4.05; N, 10.33.

5,11,17,23-Tetraamino-25,26,27,28-tetrahydroxycalix[4]arene (10). The resulting moist paste of the azo compound 9 described above was dissolved in 200 mL of an aqueous (1%) NaOH solution and reduced with 7.0 g (40 mmol) of sodium hydrosulfite for 1 h at 90 °C to give a white suspension. It was then cooled rapidly to 20 °C, filtered, and washed with water to give scale-like white crystals of 10, which were dried at rt under reduced pressure to yield 1.15 g (100%) of pale blue crystals. (The crystals were allowed to stand in air until they turned black.)

Confirmation of 10. A solution of 2.2 g (4.4 mmol) of the white crystals which were prepared by the method described above, 8.7 g (0.104 mol) of sodium acetate, and 2.3 g (0.0226 mol) of acetic anhydride in 80 mL of acetic acid was stirred for 1 h at rt and then refluxed for 2 h. After cooling, 800 mL of ice–water was added to the solution to yield a white precipitate, which was filtered and washed with hot water to give 2.65 g (90%) of a white solid. Recrystallization from DMF gave white crystals: mp 420 °C. IR and NMR spectra of this material were in accord with those of 8.

5,11,17,23-Tetraacetamido-25,26,27,28-tetraacetoxycalix[4]arene (11). A solution of 1.2 g (2.5 mmol) of 10 in 50 mL of pyridine was heated at 50 °C. To the warm solution was added 4.89 g of acetic anhydride. The solution was stirred for 30 min and then refluxed for 2 h. The pyridine was evaporated under reduced pressure to give a residue, which was washed with aqueous (1%) HCl and hot water. Recrystallization from MeOH gave 1.52 g (73%) of 11 as a white powder: mp 370–373 °C; IR (KBr) 3250, 1755, 1745, 1670, 1560, 1225, 1195 cm^{-1}; ^1H NMR (DMSO-d_6) 1.56 (CH_3, s, 3 H), 2.02 (CH_3, s, 3 H), 3.40 (bs, 2 H + 3 H), 7.28 (Ar, s, 2 H), 9.28 (s, 1 H); ^{13}C NMR (DMSO-d_6) 19.8, 23.8, 119.1, 132.3, 136.0, 143.0, 167.7, 168.1. Anal. Calcd for $C_{44}H_{44}O_{12}N_4{\cdot}{}^3/_2H_2O$: C, 62.38; H, 5.55; N, 6.62. Found: C, 62.35; H, 5.62; N, 6.42.

Calix[4]quinone (7). A solution of 1.15 g (2.36 mmol) of 10 in 50 mL of acetic acid was warmed to 50 °C. Into this solution was added slowly a solution of 4.9 g (30 mmol) of ferric chloride in 20 mL of aqueous (18%) HCl. The solution was stirred for 15 min to give a yellow suspension. It was poured into a solution of 2.94 g of potassium dichromate and 7.7 mL of concd H_2SO_4 in 130 mL of water and heated at 80–90 °C. After 15 min, the solution was cooled to 15 °C to precipitate 1.08 g (95%) of 7 as a yellow solid. Recrystallization from THF gave yellow needles: mp 250 °C dec; IR (KBr) 1660, 1615, 1296 cm^{-1}; ^{1}H NMR (DMSO-d_6) 3.47 (CH_2, s, 2 H), 6.70 (CH═C—, s, 2 H); ^{13}C NMR (DMSO-d_6) 28.9, 133.5, 146.06, 185.1, 186.8. Anal. Calcd for $C_{28}H_{16}O_8$: C, 70.00; H, 3.36. Found: C, 69.91; H, 3.49.

From 8. The calixarene 8 (1.0 g, 1.36 mmol) was oxidized by a similar method to that described above to yield 0.37 g (57%) of 7.

From 6. The calixarene 6 was oxidized by a similar method to that described above to give 7 in an 84% yield.

Calix[4]hydroquinone (6). 7 (0.6 g, 1.25 mmol) was dispersed in 250 mL of $CHCl_3$ at 65–70 °C. To the suspension was added a solution of 3.5 g of hydrosulfite in 30 mL of water. The mixture was refluxed vigorously for 2 h at 80–90 °C. After the reaction mixture had been cooled, it was allowed to stand overnight at rt to give a white crude solid. It was recrystallized from MeOH–H_2O, which contained a small amount of $SnCl_2$ and HCl, to yield 0.57 g (93%) of 6 as white plates: mp 400–450 °C dec; IR (KBr) 3200, 1620, 1470 cm^{-1}; ^{1}H NMR (acetone-d_6) 3.74 (CH_2, bs, 2 H), 6.60 (Ar, s, 2 H), 7.82 (OH, s, 1 H), 9.79 (OH, s, 1 H); ^{13}C NMR (acetone-d_6) 32.7, 116.7, 130.6, 143.2, 152.9; MS *m/e* 489 (M + H). Anal. Calcd for $C_{28}H_{24}O_8$: C, 68.85; H, 4.95. Found: C, 68.81; H, 4.94.

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Comparative Studies on the Reactivity of 4-Methylene-1-oxa-6,9-diazaspiro[4.5]decane-7,10-dione, 1-Acetyl-3-hydroxy-3-vinyl-2,5-piperazinedione, and Bicyclomycin. Examination of a Key Structural Element Necessary for Bicyclomycin-Mediated Transformations

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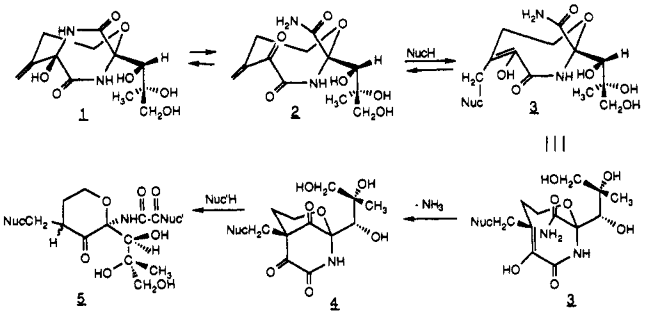
Two select mimics, 4-methylene-1-oxa-6,9-diazaspiro[4.5]decane-7,10-dione (8) and 1-acetyl-3-hydroxy-3-vinyl-2,5-piperazinedione (7) of the structurally novel antibiotic, bicyclomycin (1), have been prepared. Comparison of the chemical reactivity of 7 versus 1 both in the presence and absence of added nucleophiles at various "pH" values has provided important new information concerning the role of key structural elements present in bicyclomycin. The product profiles determined for 7 indicated that modification of the terminal double bond proceeded through an α,β-unsaturated ring imine intermediate (i.e., 43). Correspondingly, activation of the *exo*-methylene group in bicyclomycin is believed to occur through initial hemiaminal bond scission to give a ring-opened α,β-unsaturated carbonyl species (i.e., 2). Functionalization of the terminal double bond in 7 has been shown to proceed under milder conditions than that required for 1. These results demonstrated that incorporation of the *exo*-methylene group within the O(2)–C(3)–C(4)–C(5) bridge in 1 required that the terminal double bond activation pathway proceed by an alternative, energetically more-demanding pathway than that observed for 7. Ramifications of the decreased reactivity noted for 1 are to allow other functional groups (i.e., the C(1)-triol moiety) in the antibiotic to have important catalytic roles in the drug modification processes and to permit thiolate species (the proposed biological targets?) to effectively compete with other nucleophiles for 2.

Bicyclomycin (1) is a structurally unique antibiotic bearing no resemblance to any other known class of antibiotics.[1-3] The structure and relative configuration of 1 was determined by Tokuma and co-workers by single-crystal X-ray analysis.[4,5] Subsequently, Maag and his group established the absolute configuration through synthesis and X-ray analysis of a bicyclomycin acid-cata-

Scheme I. Proposed Pathway for the Mode of Action of Bicyclomycin (1)



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