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Synthesis and Conformational Property of Tannin-like *p-tert*-Butylcalix[4]arene 1,3-Diesters Stabilized by Intramolecular Hydrogen Bonds

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Tannin-like *p-tert*-butylcalix[4]arene 1,3-digallate was synthesized, and its conformational property was investigated by dynamic ^{1}H NMR and X-ray crystallography. It was found that the 3-OH (or 5-OH) group of the galloyl group in *p-tert*-butylcalix[4]arene 1,3-digallate is placed at the position where an unusual nonbonded close contact is observed between the OH group and the aromatic ring of the galloyl group facing each other. The calixarene 1,3-diesters of various hydroxybenzoic acids were also prepared, and the conformational properties of those calixarenes were compared with that of *p-tert*-butylcalix[4]arene 1,3-digallate. A significant contribution of the 3- and 5-OH groups in pendant groups toward the close contact was found. It was suggested that the conformation of *p-tert*-butylcalix[4]arene 1,3-digallate was stabilized by intramolecular hydrogen bonds including OH···O and OH−π interactions.

Introduction

Considerable attention has been paid to the synthesis and properties of functionalized calixarenes because of their potential utility as molecular receptors and ionophores.[1] The design of calixarenes having desired properties requires the control of their conformation, which possibly is achieved by the use of intramolecular hydrogen bonding interaction between substituents on the calixarene skeleton.[2]

Gallic acid is a component of plant tannin and fundamental structures of hydrolyzable tannins are condensed compounds of gallic acids with core compounds such as glucose, quinic acid, and so on.[3] These tannins exhibit a variety of chemical and biological properties that include pharmacological activity[4] and also binding abilities to proteins[5] and metal ions.[6] Three hydroxyl groups of gallic acid play an important role in these propaties.[4,5] In a preliminary report, *p-tert*-butylcalix[4]arene 1,3-digallate **3a** as a synthetic tannin was synthesized and a selective binding property of this compound toward Ag$^+$ ion was studied.[7] One of the OH groups in the galloyl group was placed at the position where significant nonbonded contact is observed between the OH group and the aromatic ring of the galloyl group facing each other. This nonbonded contact makes it possible to exert an OH−π interaction.[8] The selective binding property of **3a** was explained by this specific geometry of **3a**. These observations prompted us to undertake a systematic study on the fundamental significance of the galloyl group in the calixarene to provide valuable information regarding the functional group in tannin.

In this paper, we report a high-yield synthesis of the calixarene 1,3-diesters having various hydroxybenzoyl groups and the conformational properties of these molecules by means of dynamic ^{1}H NMR and X-ray crystallography. The contribution of the hydroxyl groups in the pendant groups to conformational stability of the calixarenes was examined in solution and solid state.

Results and Discussion

Synthesis of the Calixarenes 3a−e. The selective 1,3-esterification of *p-tert*-butylcalix[4]arene **1** was established,[9] and the synthetic route was outlined in Scheme 1. The calixarene 1,3-diesters **2a−e** were prepared by the reaction of **1** with *O*-acetylbenzoyl chlorides in CH_2Cl_2 in the presence of base in high yields. For **2a**, **2c**, and **2e**, deacetylation was performed by using hydrazine monohydrate at room temperature to give **3a**, **3c**, and **3e** in high yields. The removal of acetyl groups

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[1] (a) Gutsche, C. D. *Calixarenes, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1989. (b) Gutsche, C. D. *Calixarenes Revisited, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998. (c) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Böhmer, V., Ed.; Kluwer Academic Pub: Dordrecht, 1991.

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[3] *Plant Polyphenols*; Hemingway, R. W., Laks, P. E., Eds.; Plenum Press: New York, 1992.

[4] *Economic and Medicinal Plant Research*; Wagnner, H., Farnsworth, N. R., Eds.; Academic Press: New York, 1991; Vol. 5.

[5] Okuda, T. Mori, K.; Hatano, T. *Chem. Pharm. Bull.* **1985**, *33*, 1424.

[6] Okuda, T.; Mori, K.; Shiota, M.; Ida, K. *Yakugaku Zasshi* **1982**, *102*, 735.

[7] Nomura, E.; Hosoda, A.; Taniguchi H. *Org. Lett.* **2000**, *2*, 779.

[8] For OH−π interaction between H_2O and aromatic π electrons, see: Atwood, J. L.; Hamada, F.; Robinson, K. D.; Orr, G. W.; Vincent, R. L. *Nature* **1991**, *349*, 683.

[9] See, K. A.; Fronczek, F. R.; Watson, W. H.; Kashyap, R. P.; Gutsche, C. D. *J. Org. Chem.*, **1991**, *56*, 7256.

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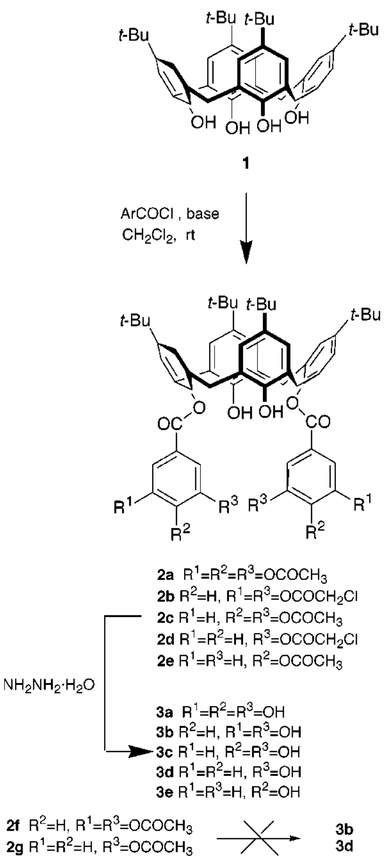
Scheme 1



for **2f** and **2g** was not achieved under the same conditions. Hydrolytic cleavage for the benzoate esters was preferred to that for the acetyl esters under any basic conditions. Therefore, chloroacetyl ester as a protective group, which is hydrolyzed much faster than the acetyl group,[10] was introduced to hydroxybenzoic acids instead of the acetyl group. The calixarene 1,3-diesters **2b** and **2d** were prepared under the same conditions described above in high yields. Chloroacetyl groups in **2b** and **2d** were removed by using hydrazine monohydrate at room temperature to give products **3b** and **3d** in high yields.

^{1}H NMR Studies. The ^{1}H NMR spectra of **3a**−**e** in THF-d_8 at 20 °C were obtained as simple patterns. A pair of singlet signals arising from the *tert*-butyl protons and a pair of doublet signals from the $ArCH_2Ar$ methylene protons strongly suggest that these compounds have a C_2 symmetry and a cone conformation.[11]

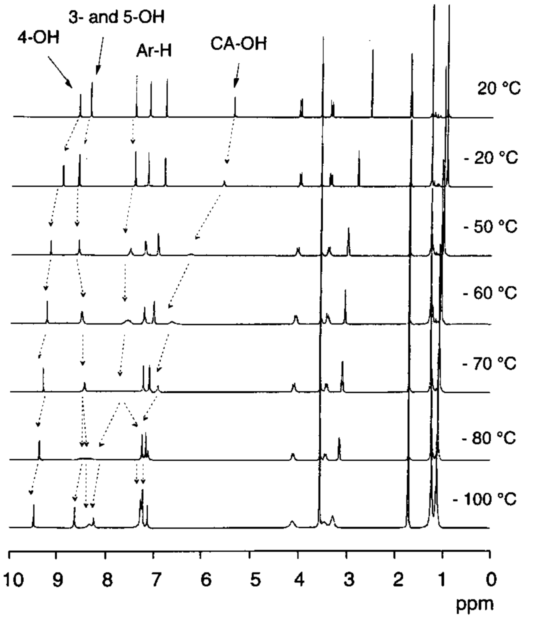


Figure 1. Temperature-dependent ^{1}H NMR spectra of **3a** (400 MHz, THF-d_8).

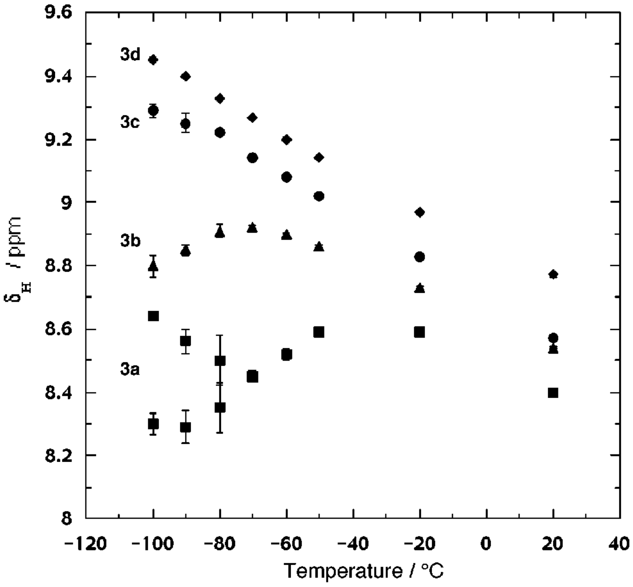


Figure 2. Temperature dependence of chemical shifts for the OH protons at the 3- and 5-positions of the benzoyl groups of **3a**−**d** (400 MHz, THF-d_8). Error bars represent signal widths at half-maxima.

The 3-OH and 5-OH proton signals of the galloyl groups in **3a** gave the same resonance at 8.36 ppm. This indicates that the galloyl groups in **3a** undergoes rapid rotation on a NMR time scale at 20 °C. The chemical shifts of the OH proton signals of the galloyl groups and the calixarene skeleton varied with loss of temperature (Figure 1). The signal arising from the 3-OH and 5-OH protons at 8.36 ppm at 20 °C shifted downfield upon cooling to −40 °C and then upfield until reaching to −70 °C. This signal separated into two signals that appeared at 8.64 and 8.32 ppm at −100 °C. The separated upfield signal of the OH proton at 8.32 ppm suggests that the OH group is situated at the position where it is affected by a ring current effect associated with the facing galloyl group. The aromatic proton signals of the galloyl groups were also observed as two separated signals at 8.24 and 7.13 ppm at −100 °C. The temperature dependence of the 3-OH and 5-OH proton signals for the benzoyl groups in **3a**−**d** was summarized in Figure 2. The signal arising from the 3-OH and 5-OH protons of the benzoyl groups of **3b** appeared at 8.54 ppm at 20 °C and shifted downfield upon cooling to −70 °C and then upfield without separating such as **3a**. The 3-OH proton signals for **3c** and **3d** shifted downfield continually until reaching to −100 °C. These results show that the OH groups at the 3- and 5-positions of the benzoyl groups suppress the rotation of the pendant groups on a NMR time scale and

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(10) Reese, C. B.; Stewart, C. M.; van Boom, J. H.; de Leeuw, H. P. M.; Nagel, J.; de Rooy, J. F. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 934.

(11) Mogck, O.; Böhmer, V.; Furguson, G.; Vogt, W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1711.

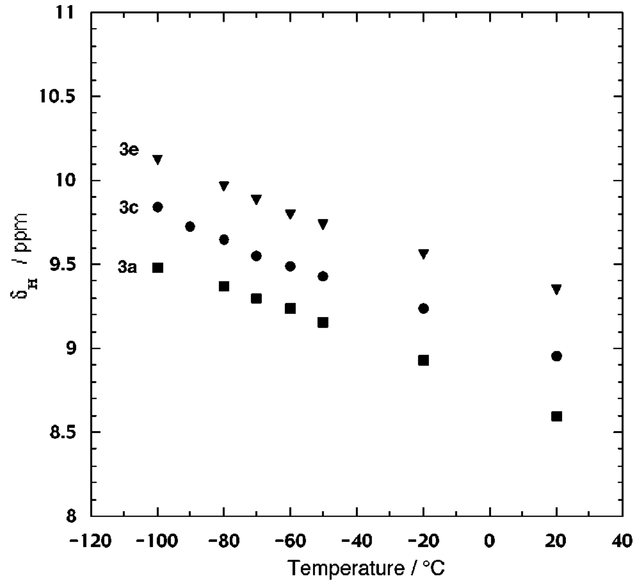

Figure 3. Temperature dependence of chemical shifts for the OH protons at the 4-position of the benzoyl groups of **3a**,**c**,**e** (400 MHz, THF-d_8).

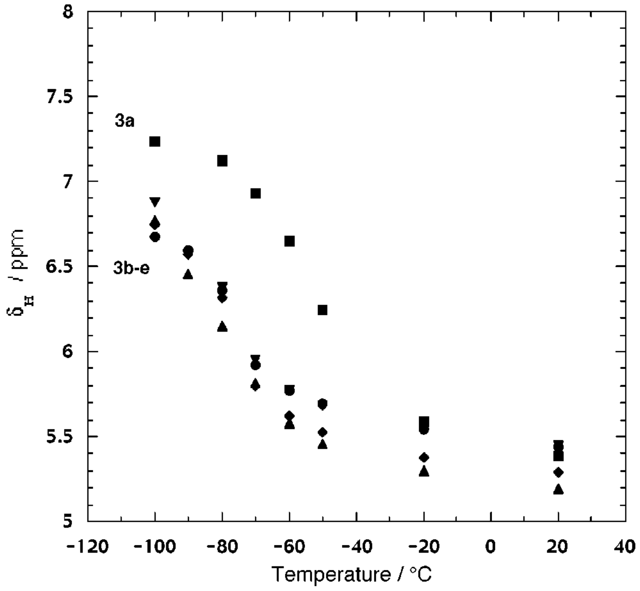

Figure 4. Temperature dependence of chemical shifts for the OH protons at the calixarene skeleton of **3a**−**e** (400 MHz, THF-d_8).

that the existence of the OH group at the 4-position enhances the effect. The chemical shifts for the 4-OH proton of **3a**, **3c**, and **3e** at variable temperatures are shown in Figure 3. The signals arising from the 4-OH protons at 8.60, 8.96, and 9.35 ppm at 20 °C for **3a**, **3c**, and **3e** shifted downfield in parallel upon cooling to −100 °C. The 3-OH or 5-OH proton signals for **3a**−**d**, also appeared at downfield in the same order. It seems likely to reflect the magnitude of a ring current effect of the facing pendant group.

The chemical shifts for the OH proton signals in calixarene skeleton of **3a**−**e** also varied with loss of temperature as shown in Figure 4. The OH proton signals for **3a**−**e** shifted downfield upon cooling from 20 to −100 °C. In particular, the signals for **3a** shifted drastically downfield under −40 °C. This suggests that the OH groups form strong hydrogen bonds with the neighboring ether oxygen atoms[11] because the facing galloyl groups must be situated in positions that permit close contact. From these observations based on the temperature-dependent ^{1}H NMR, the galloyl group seems to play an important role to stabilize the conformation of **3a**.

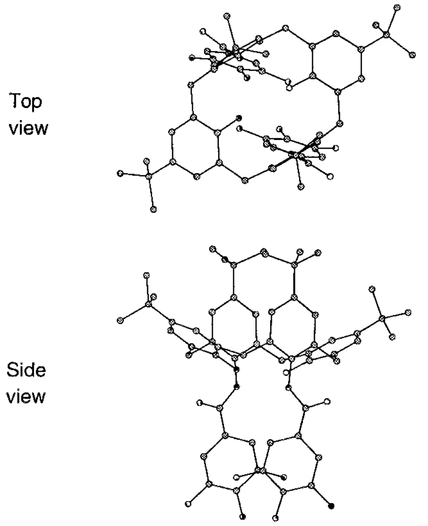

Figure 5. MM2-optimized geometry of **3a** in the cone conformation.

To substantiate the low-temperature conformer of **3a** in solution, theoretical calculations were performed using the MM2 force field.[12] There are three types of possible conformers of **3a** because conformational inversion through the annulus for the galloyl group larger than ethyl are prohibited,[13] i.e., cone, 1,3-alternate (two *tert*-butylphenol units are a reverse direction), and partial cone (one *tert*-butylphenol unit is a reverse direction). The starting geometry of **3a** for the calculations was taken from the optimized cone conformation of *p*-*tert*-butylcalix[4]arene. It is the structure that allows the formation of hydrogen bonds between phenolic hydroxyl groups and proximal ether oxygen atoms in the cone conformation, in accordance with the ^{1}H NMR data of **3a**. The result shows that the two galloyl groups of **3a** are more or less parallel and the 3-OH group is above the other side of the aryl ring (Figure 5). In this connection, it is particularly noteworthy that the cone conformation of **3a** is the lowest energy conformer in the calculations.[14]

Single-Crystal X-ray Diffraction. When compounds **3a** and **3b** were recrystallized from acetone, prism crystals that include acetone molecules inside the crystals were obtained, and on standing the crystals changed gradually from clear to opaque crystals with a loss of acetone molecules. The crystal structures of **3a** and **3b** were determined by single-crystal X-ray analysis (Figure 6). The calixarenes **3a** and **3b** were found to have a similar cone conformation with a C_2 symmetry and to form a 1:5 clathrate with acetone molecules. Four acetone molecules are captured in the channel of the crystal lattice, and one acetone molecule is held inside the molecular cavity of both **3a** and **3b** with the CH_3 group

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[12] Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

[13] Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955.

[14] Relative potential energies (kcal/mol) for three conformers: cone, 0; 1,3-alternate, +7.0; partial cone, +3.56.

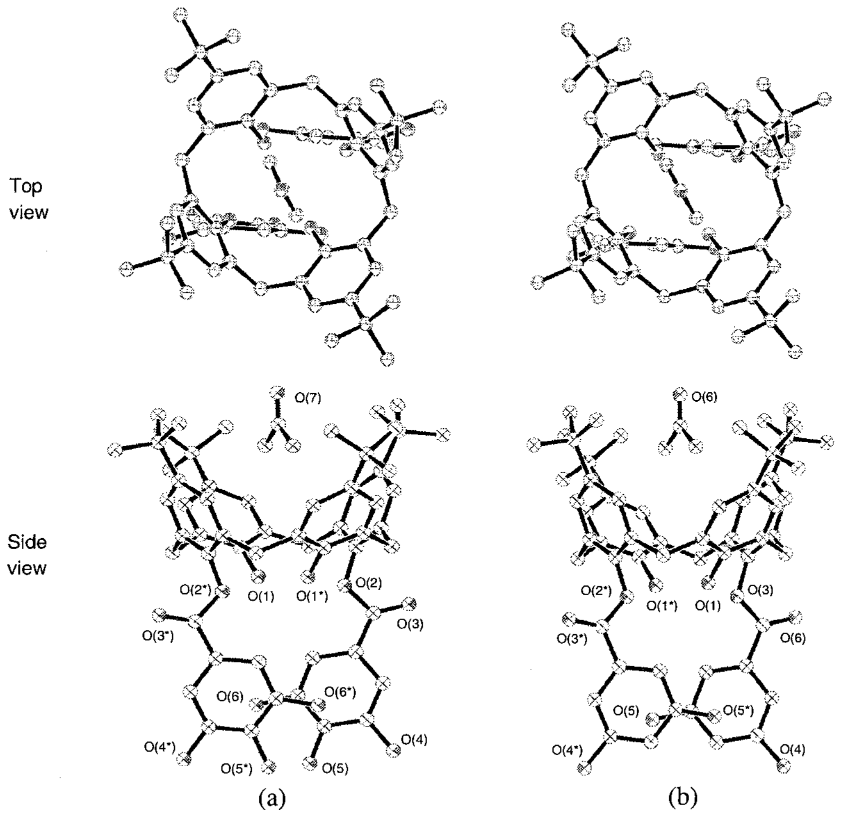

Figure 6. X-ray crystallographic structure of **3a** (a) and **3b** (b). Hydrogen atoms have been omitted for clarity. Two acetone molecules in the channel of the crystal lattice for **3a** and **3b** have been omitted for clarity.

pointing into the cavity.[15] The acetone molecules within the cavities exist at the position where a $CH_3-\pi$ interaction is possible to operate between one of the CH_3 groups of acetone and the aromatic ring of the calixarenes.[16] In fact, the CH_3 carbon of acetone is situated at distances of 3.54(4) and 3.55(3) Å above the center of the phenyl ring of **3a** and **3b**, respectively. There are two intramolecular OH···O hydrogen bonds between the phenolic hydroxyl groups of the calixarene ring in **3a** and the proximal ether O atoms in which the distances of O(1)···O(2) and O(1*)···O(2) are the same length of 2.871(5) Å. On the other hand, for **3b**, the distances of O(1)···O(2) and O(1*)···O(2) are 2.803 and 2.887 Å, respectively. These hydrogen bonds were found in common for calix[4]arenes.[17] There is possible weak hydrogen bonding between the OH groups at the 4-position of facing galloyl groups in **3a** and the distance of O(5)···O(5*) is 3.224(8) Å. Furthermore, the OH group at the 3- or 5-position of the galloyl group in **3a** is placed at the position where significant nonbonded contact is observed between the OH group and the aromatic ring of the galloyl groups facing each other, which is consistent with the model predicted from the ^{1}H NMR spectral data and the MM2 calculation. The hydroxyl oxygen O(6) is situated at the position, which is 3.247(7) Å above the least-squares plane of the facing phenyl ring of the galloyl group. This close contact makes it possible to exert an $OH-\pi$ interaction.[8] For **3b** in which there is no contribution to the hydrogen bonding between the 4-OH groups of facing pendant groups, the OH group at the 3- (or 5-) position is also placed at the position where the nonbonded contact are observed. The hydroxyl oxygen O(5) is situated at 3.412(7) Å above the least-squares plane of the facing phenyl ring. It suggests that the OH-π interaction may still exert on keeping the close contact in **3b**. Additionally, the intermolecular hydrogen bonds between hydroxyl groups of the pendant groups and acetone molecules exist for **3a** and **3b**, and the distances are as follows: O(6)···O(8) = 2.760(7) Å, O(4)···O(9) = 2.74(1) Å for **3a**; O(4)···O(8) = 2.732(8) Å, O(5)···O(7) = 2.859(6) Å for **3b**.

The molecular structure of **3c** was not obtained by a single-crystal X-ray analysis because the crystals were extremely small and fragile. The crystals of **3d** and **3e** were obtained as colorless prisms from methanol/water and chloroform (ethanol free), respectively. Fortunately, further observation for **3d** and **3e** came from the X-ray spectroscopy.

There are two independent molecules of **3d** in the asymmetric unit, and these molecules are in the same cone conformation with a slight difference between the two molecules (Figure 7).[18] Obviously, there is no close contact between pendant groups and these groups are on the approximately same plane. This conformation is

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(15) For calixarene−acetone clathrates, see: Ungaro, R.; Pochini, A.; Andreetti, G. D.; Sangermano, V. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1979.

(16) For $CH_3-\pi$ interactions between the methyl groups of the host and the aromatic moiety of pyridine, see: Andreetti, D.; Ori, O.; Ugozzoli, F.; Alfieri, C.; Pochini, A.; Ungaro, R. *J. Inclusion Phenom.* **1988**, *6*, 523.

(17) (a) Böhmer, V.; Ferguson, G.; Gallagher, J. F.; Lough, A. J.; Mckervey, M. A.; Madigan, E.; Moran, M. B.; Fhillips, J.; Williams, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1521. (b) Collins, E. M.; Mckervey, M. A.; Madigan, E.; Moran, M. B.; Owens, M.; Ferguson, G.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3137.

(18) Groenen, L. C.; van Loon, J.-D.; Verboom, W.; Harkema, S.; Casnati, A.; Ungaro, R.; Pochini, A.; Ugozzoli, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 2385.

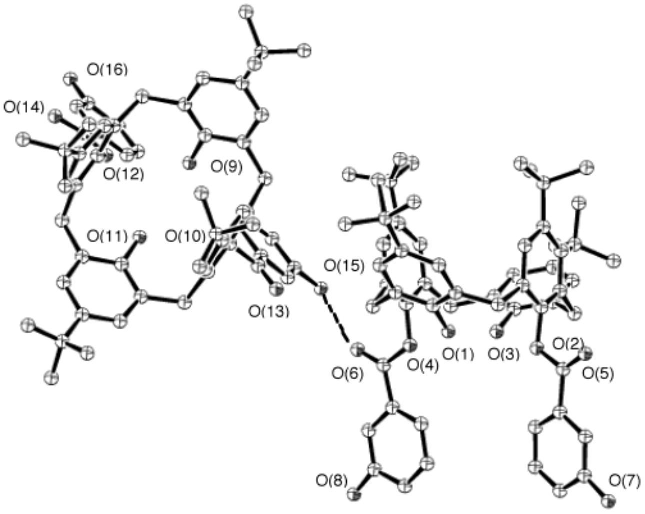

Figure 7. X-ray crystallographic structure of **3d**. There are two independent molecules in a unit cell. Hydrogen atoms and water molecules outside the cavities have been omitted for clarity. Intermolecular hydrogen bonds (Å): O(7)···O(14), 2.75(1); O(6)···O(15), 2.74(1) Å.

found in common for 1,3-substituted calix[4]arenes.[10] No molecule is included inside the calixarene cavity of **3d**. The *tert*-butylphenol units in **3d** are more flattened than those in **3a** and **3b**, and the two ester unit are more parallel to each other. The distances of possible intramolecular OH···O hydrogen bonds between the phenolic hydroxyl group of the calixarene ring and the proximal ether O atoms are follows: O(1)···O(2) = 3.11(1) Å, O(2)···O(3) = 3.082(9) Å, O(3)···O(4) = 3.01(1) Å, O(4)···O(1) = 3.068(9) Å. The possible hydrogen bond is also observed between the facing phenolic hydroxyl groups of the calixarene ring and the distance is O(1)···O(3) = 3.056(9) Å. In addition, the OH group of pendant group of **3d** forms an intermolecular hydrogen bond with the C=O groups of the neighboring molecules and the distance of O(7)···O(14) is 2.75(1) Å. The C=O group of **3d** also forms an intermolecular hydrogen bond with the OH groups of the neighboring molecules and the distance of O(6)···O(15) is 2.74(1) Å.

Furthermore, the molecular structure of **3e** no longer has a cone but a partial-cone conformation as shown in Figure 8. The crystal **3e** captures two chloroform and two water molecules in the crystal lattice, and some of these molecules were highly disordered. One water molecule was bound between the hydroxyl groups at the *p*-position of the benzoyl groups and the distances of O(7)···O(9) and O(8)···O(9) are 2.75(1) and 2.94(1) Å. This water molecule also forms an intermolecular hydrogen bond with the OH group of the neighboring molecules of **3e** and the distance of O(9)···O(3) is 2.878(8) Å. In addition, one of the OH groups of the benzoyl group in **3e** forms an intermolecular hydrogen bond with the C=O group of the neighboring calixarene and the distance of O(8)···O(6) is 2.785(5) Å. There are possible intramolecular OH···O hydrogen bonds between the hydroxyl group of the *tert*-butylphenol unit and the proximal ether O atoms in which the distances of O(1)···O(2) and O(1)···O(4) are 3.01(1) and 2.90(1) Å, respectively.

These crystallographic structures of **3a**,**b**,**d**,**e** demonstrated that the calixarenes **3a** and **3b** are specific for intramolecular hydrogen bonding, rather than intermolecular hydrogen bonding. There is no intermolecular hydrogen bond between the calixarene molecules. The crystal structures of **3d** and **3e**, however, show that intermolecular hydrogen bonds are preferentially formed between the pendant groups of adjacent calixarenes.

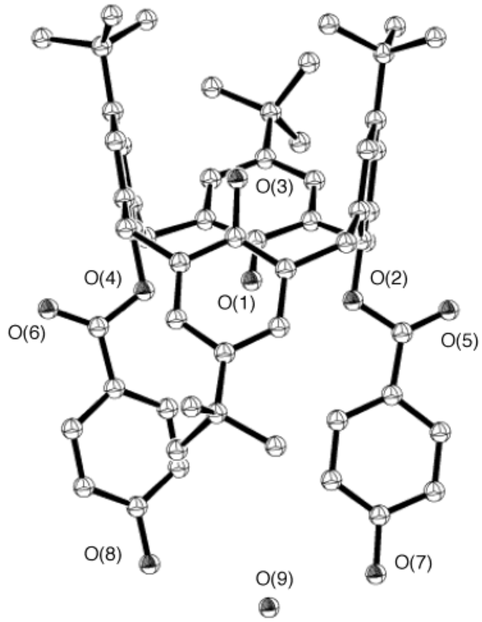

Figure 8. X-ray crystallographic structure of **3e**. Hydrogen atoms have been omitted for clarity. Two chloroform and one water molecule outside the cavities have been omitted for clarity.

Conclusion

Tannin-like *p*-*tert*-butylcalix[4]arene 1,3-diesters **3a**−**e** have been synthesized. The galloyl groups in **3a** are placed near each other at a position where an unusual nonbonded close contact is observed by means of dynamic ^{1}H NMR and X-ray crystallography. This contact makes it possible to exert an OH−π interaction between the OH group and the aromatic ring of the galloyl group facing each other. This close contact was also observed in **3b**. The 3-OH and 5-OH groups of the pendant groups in the calixarene show a significant contribution to the close contact. We believe that the function of galloyl group in the calixarene must provide significant information regarding functional groups in plant tannin. It is expected that the availability of the tannin-like calixarenes will allow further exploitation of their biological activities. Studies in this direction are in progress.

Experimental Section

General Methods. Melting points were uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer using residual solvent as an internal standard. Mass spectra were recorded using ESI-TOF apparatus. Calculations were performed with MM2 force field in the program CAChe WorkSystem released 3.8.[19]

Acetylation for hydroxyl groups of benzoic acids was performed by using acetic anhydride in aqueous NaOH. Chloroacetylation[20] for 3,5-dihydroxybenzoic acid and 3-hydroxybenzoic acid was carried out by the reaction with chloroacetyl chloride in anhydrous THF in the presence of pyridine.

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(19) CAChe WorkSystem release 3.8 1995, CAChe Scientific, Inc.

(20) Naruto, M.; Ohno, K.; Naruse, N.; Takeuchi, H. *Tetrahedron Lett.* **1979**, 251.

O-Acylbenzoic acids were converted to acid chlorides by using thionyl chloride in the presence of pyridine and a small amount of DMF.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-[(3,4,5-triacetoxybenzoyl)oxy]calix[4]arene (2a). To a solution of 1 g (1.54 mmol) of *p-tert*-butylcalix[4]arene and 1.25 g (12.4 mmol) of triethylamine in anhydrous CH_2Cl_2 (30 mL) was added 3.9 g (12.4 mmol) of 3,4,5-triacetoxybenzoyl chloride. The mixture was stirred for 5 h at room temperature under nitrogen. The reaction mixture was washed with water and dried over $MgSO_4$. After removal of the solvent, the product was purified through a SiO_2 column ($CHCl_3$/hexane = 10/2) to afford 1.68 g (87%) of product that was recrystallized from $CHCl_3$/hexane and dried under reduced pressure to give 1.2 g of crystals: mp = 299−306 °C; IR (KBr) ν 3562, 1782 cm^{-1}; ^1H NMR ($CDCl_3$, 20 °C) δ 0.87 (s, 18H), 1.30 (s, 18H), 2.05 (s, 12H), 2.30 (s, 6H), 3.39 (d, 4H), 3.95 (d, 4H), 5.38 (s, 2H), 6.75 (s, 4H), 7.11 (s, 4H), 8.29 (s, 4H); ^{13}C NMR ($CDCl_3$ 20 °C) δ 20.2, 30.8, 31.6, 31.8, 34.0, 122.8, 125.4, 125.7, 127.0, 128.4, 131.3, 139.6, 142.2, 143.1, 144.2, 148.9, 149.9, 163.4, 166.4, 167.6; MS (ESI-TOF) calcd for $C_{70}H_{77}O_{18}$ 1205.51, found 1205.58 $[M + H]^+$. Anal. Calcd for $C_{70}H_{76}O_{18}$: C, 69.75; H, 6.36. Found: C, 69.43, H, 6.33.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-[(3,4,5-trihydroxybenzoyl)oxy]calix[4]arene (3a). To a solution of 1 g (0.8 mmol) of **2a** in CH_3CN (60 mL) was added 0.24 g (4.8 mmol) of hydrazine monohydrate. The mixture was stirred for 30 min at room temperature. Acetic acid (0.27 mL) and water (20 mL) were added. The organic potion was extracted with ethyl acetate (50 mL × 2), washed with water (30 mL × 2) and saturated aqueous NaCl, and dried over $MgSO_4$. The organic solvent was evaporated, and acetone was added to produce precipitates. The precipitates were filtrated and washed with acetone to afford 0.58 g (76%) of white solid that was recrystallized and dried under reduced pressure to give prisms: mp = 225−229 °C; IR (KBr) ν 3535, 3300, 3700−3740 cm^{-1}; ^1H NMR (THF-d_8, 20 °C) δ 0.96 (s, 18H), 1.28 (s, 18H), 3.38 (d, 4H), 4.01 (d, 4H), 5.34 (s, 2H), 6.80 (s, 4H), 7.13 (s, 4H), 7.43 (s, 4H), 8.36 (s, 4H), 8.60 (s, 2H); ^{13}C NMR (THF-d_8, 20 °C) δ 31.4, 31.9, 32.8, 34.4, 34.5, 111.0, 120.1, 125.9, 126.2, 129.3, 132.9, 140.5, 142.9, 144.4, 146.1, 148.3, 151.3, 165.4; MS (ESI-TOF) calcd for $C_{58}H_{65}O_{12}$ 953.45, found 953.47 $[M + H]^+$. Anal. Calcd for $C_{58}H_{64}O_{12}\cdot 2H_2O$: C, 70.43; H, 6.93. Found: C, 70.23, H, 6.90.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-[(3,5-dichloroacetoxybenzoyl)oxy]calix[4]arene (2b). To a solution of 1.2 g (1.8 mmol) of *p-tert*-butylcalix[4]arene and 1.17 g (15 mmol) of pyridine in 20 mL of anhydrous CH_2Cl_2 was added 2.34 g (12.3 mmol) of 3,5-dichloroacetyloxybenzoyl chloride. The mixture was stirred for 4 h at room temperature under nitrogen. The reaction mixture was washed with water (30 mL × 3) and dried over $MgSO_4$. The solvent was evaporated, and methanol was added to produce the precipitate of the product (1.71 g, 79%), which was recrystallzed from $CHCl_3$/MeOH to give crystals: mp = 223−226 °C; IR (KBr) ν 3566, 1775, 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 20 °C) δ 0.88 (s, 18H), 1.29 (s, 18H), 3.40 (d, 4H), 3.95 (d, 4H), 4.05 (s, 8H), 5.32 (s, 2H), 6.75 (s, 4H), 7.11 (d, 4H), 7.36 (t, 2H), 8.22 (d, 4H); ^{13}C NMR ($CDCl_3$, 20 °C) δ 30.8, 31.6, 31.9, 34.0, 40.5, 120.2, 121.1, 125.5, 125.8, 128.3, 131.2, 132.1, 142.3, 143.2, 149.1, 149.9, 150.8, 163.4, 165.3; MS (ESI-TOF) calcd for $C_{66}H_{69}O_{14}Cl_4$ 1225.34, found 1225.48 $[M + H]^+$. Anal. Calcd for $C_{66}H_{68}O_{14}Cl_4$: C, 64.60; H, 5.59. Found: C, 64.59, H, 5.51.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-[(3,5-dihydroxybenzoyl)oxy]calix[4]arene (3b). To a solution of 0.5 g (0.43 mmol) of **2b** in 20 mL of CH_2Cl_2 was added 0.086 g (1.7 mmol) of hydrazine monohydrate. The mixture was stirred for 5 min at room temperature. HCl (1 M) and ethyl acetate (50 mL) were added. The organic potion was washed with water (30 mL × 2) and saturated aqueous NaCl (20 mL) and dried over $MgSO_4$. The solvent was evaporated and chloroform (ethanol free) was added to produce 0.33 g of crystals (75%) that were recrystallized from MeOH/H_2O to give fine needles: mp = 303−305 °C; IR (KBr) ν 3572, 3563, 3344, 1736, 1723 cm^{-1}; ^1H NMR (THF-d_8, 20 °C) δ 0.98 (s, 18H), 1.26 (s, 18H), 3.40 (d, 4H), 3.99 (d, 4H), 5.19 (s, 2H), 6.54 (t, 2H), 6.84 (s, 4H), 7.12 (s, 4H), 7.28 (d, 4H), 8.54 (s, 4H); ^{13}C NMR (THF-d_8, 20 °C) δ 31.4, 31.9, 33.0, 34.4, 34.6, 108.9, 109.4, 126.1, 126.3, 129.3, 131.9, 132.8, 143.0, 144.5, 148.5, 151.3, 159.7, 165.4; MS (ESI-TOF) calcd for $C_{58}H_{65}O_{10}$ 921.46, found 921.54 $[M + H]^+$. Anal. Calcd for $C_{58}H_{64}O_{10}\cdot 2H_2O$: C, 72.78; H, 7.16. Found: C, 72.39, H, 7.09.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-[(3,4-diacetoxybenzoyl)oxy]calix[4]arene (2c). To a solution of 2 g (3.08 mmol) of *p-tert*-butylcalix[4]arene and 2.49 g (24.7 mmol) of triethylamine in 30 mL of anhydrous CH_2Cl_2 was added 3.16 g (12.3 mmol) of 3,4-diacetylbenzoyl chloride. The mixture was stirred for 3 h at room temperature under nitrogen. The reaction mixture was washed with water and dried over $MgSO_4$. The solvent was evaporated, and methanol was added to produce of precipitates of the product (2.52 g, 75%). Recrystallzed from $CHCl_3$/MeOH gave crystals: mp = 309−313 °C; IR (KBr) ν 3566, 3526, 1778, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 20 °C) δ 0.95 (s, 18H), 1.20 (s, 18H), 2.26 (s, 6H), 2.33 (s, 6H), 3.45 (d, 4H), 3.92 (d, 4H), 5.09 (s, 2H), 6.85 (s, 4H), 7.03 (d, 4H), 7.36 (d, 2H), 8.14 (d, 2H), 8.26 (dd, 2H); ^{13}C NMR ($CDCl_3$, 20 °C) δ 20.5, 20.8, 31.0, 31.5, 32.9, 33.9, 34.0, 124.6, 125.5, 126.1, 127.7, 127,8, 128.4, 131.7, 142.6, 142.8, 146.8, 149.0, 150.1, 163.5, 167.5, 168.0; MS (ESI-TOF) calcd for $C_{66}H_{73}O_{14}$ 1089.50, found 1089.57 $[M + H]^+$. Anal. Calcd for $C_{66}H_{72}O_{14}$: C, 72.77; H, 6.66. Found: C, 72.69, H, 6.68.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-[(3,4-dihydroxybenzoyl)oxy]calix[4]arene (3c). To a solution of 0.5 g (0.46 mmol) of **2c** in 20 mL of CH_2Cl_2 was added 0.09 g (1.8 mmol) of hydrazine monohydrate. The mixture was stirred for 10 min at room temperature.Two milliliters of 1 M HCl was added. The organic potion was washed with water (30 mL × 2) and dried over $MgSO_4$. After removal of the solvent, the product was purified through a SiO_2 column ($CHCl_3$/MeOH = 40/1) to afford 0.26 g of product (61%) that was recrystallized from MeOH/H_2O to give plates: mp = 222−230 °C; IR (KBr) ν 3570, 3280, 1740, 1700 cm^{-1}; ^1H NMR (THF-d_8, 20 °C) δ 0.99 (s, 18H), 1.25 (s, 18H), 3.40 (d, 4H), 3.98 (d, 4H), 5.44 (s, 2H), 6.86 (s, 4H), 6.97 (d, 2H), 7.11 (s, 4H), 7.69 (d, 2H), 7.90 (dd, 2H), 8.66 (s, 2H), 8.96 (s, 2H); ^{13}C NMR (THF-d_8, 20 °C) δ 31.4, 31.9, 33.1, 34.4, 34.6, 116.2, 117.9, 121.4, 124.2, 126.1, 129.0, 133.0, 142.7, 144.4, 146.2, 148.4, 151.4, 152.1, 165.0; MS (ESI-TOF) calcd for $C_{58}H_{65}O_{10}$ 921.46, found 921.49 $[M + H]^+$. Anal. Calcd for $C_{58}H_{64}O_{10}\cdot 2H_2O$: C, 72.78; H, 7.16. Found: C, 72.43, H, 7.04.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-[(3-chloroacetoxybenzoyl)oxy]calix[4]arene (2d). To a solution of 2 g (3.08 mmol) of *p-tert*-butylcalix[4]arene and 1.95 g (25 mmol) of pyridine in 30 mL of anhydrous CH_2Cl_2 was added 2.89 g (12.4 mmol) of 3-chloroacetyloxybenzoyl chloride. The mixture was stirred for 2 h at room temperature under nitrogen. HCl (1 M) was added to the mixture. The reaction mixture was washed with water and dried over $MgSO_4$. The solvent was evaporated, and methanol was added to produce a precipitate of the product (2.3 g, 70%) that was recrystallized from $CHCl_3$/MeOH to give crystals: mp = 273−279 °C; IR (KBr) ν 3568, 1784, 1742 cm^{-1}; ^1H NMR ($CDCl_3$, 20 °C) δ 0.96 (s, 18H), 1.19 (s, 18H), 3.46 (d, 4H), 3.94 (d, 4H), 4.21 (s, 4H), 5.09 (s, 2H), 6.86 (s, 4H), 7.03 (d, 4H), 7.49 (d, 4H), 8.10 (s, 2H), 8.25 (t, 2H); ^{13}C NMR ($CDCl_3$, 20 °C) δ 31.0, 31.5, 33.0, 33.9, 34.0, 40.7, 123.3, 125.6, 126.1, 126.7, 127.8, 128.0, 130.2, 131,2, 131.6, 142.8, 142.9, 149.0, 150.2, 150.6, 163.9, 165.6; MS (ESI-TOF) calcd for $C_{62}H_{67}O_{10}Cl_2$ 1041.41, found 1041.49 $[M + H]^+$. Anal. Calcd for $C_{62}H_{66}O_{10}Cl_2\cdot H_2O$: C, 70.17; H, 6.16. Found: C, 70.24, H, 6.47.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-[(3-hydroxybenzoyl)oxy]calix[4]arene (3d). To a solution of 0.5 g (0.48 mmol) of **2d** in 20 mL CH_2Cl_2 was added 0.048 g (0.96 mmol) of hydrazine monohydrate. The mixture was stirred for 20 min at room temperature. 1 M HCl and ethyl acetate (50 mL) was added. The organic potion was washed with water (30 mL X 2) and saturated aqueous NaCl (20 mL), and dried over $MgSO_4$. The solvent was evaporated, and methanol was added to produce a precipitate of the product

(0.395 g, 93%) that was recrystallized from MeOH/H_2O to give needles: mp > 260 °C dec; IR (KBr) ν 3566, 1740 cm^{-1}; ^1H NMR (THF-d_8, 20 °C) δ 1.01 (s, 18H), 1.21 (s, 18H), 3.45 (d, 4H), 3.96 (d, 4H), 5.29 (s, 2H), 6.92 (s, 4H), 7.11 (s and d, 6H), 7.44 (t, 2H), 7.69 (s, 2H), 7.89 (d, 2H), 8.77 (s, 2H); ^{13}C NMR (THF-d_8, 20 °C) δ 31.4, 31.8, 33.4, 34.4, 34.6, 117.5, 121.5, 122.0, 126.2, 126.4, 128.9, 131.0, 131.6, 132.9, 142.9, 144.4, 148.7, 151.4, 158.9, 165.1; MS (ESI-TOF) calcd for $C_{58}H_{65}O_8$ 889.47, found 889.55 $[M + H]^+$. Anal. Calcd for $C_{58}H_{64}O_8 \cdot H_2O$: C, 76.79; H, 7.33. Found: C, 76.83, H, 7.13.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-[(4-acetoxybenzoyl)oxy]calix[4]arene (2e). To a solution of 2 g (3.1 mmol) of *p-tert*-butylcalix[4]arene and 2.49 g (24.7 mmol) of triethylamine in 30 mL of anhydrous CH_2Cl_2 was added 2.46 g (12.4 mmol) of 4-acetylbenzoyl chloride. The mixture was stirred for 2 h at room temperature under nitrogen. The reaction mixture was washed with water (30 mL × 3) and dried over $MgSO_4$. The solvent was evaporated, and the product was purified through SiO_2 column (CH_2Cl_2) to afford 2.52 g of product (84%). Recrystallzed from $CHCl_3$/MeOH gave crystals: mp = 318−323 °C; IR (KBr) ν 3557, 1767, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 20 °C) δ 0.97 (s, 18H), 1.17 (s, 18H), 2.37 (s, 6H), 3.46 (d, 4H), 3.92 (d, 4H), 5.13 (s, 2H), 6.87 (s, 4H), 7.01 (d, 4H), 7.25 (d, 4H), 8.35 (d, 4H); ^{13}C NMR ($CDCl_3$, 20 °C) δ 21.2, 31.0, 31.5, 33.2, 33.8, 34.0, 122.4, 125.5, 126.0, 126.7, 127.7, 131.8, 132.0, 142.7, 143.0, 148.9, 150.2, 155.0, 164.2, 168.6. Anal. Calcd for $C_{62}H_{68}O_{10} \cdot H_2O$: C, 75.13; H, 7.12. Found: C, 74.85, H, 6.79.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-[(4-hydroxybenzoyl)oxy]calix[4]arene (3e). To a solution of 0.5 g (0.48 mmol) of **2e** in 5 mL of CH_2Cl_2 and 20 mL of CH_3CN was added 0.05 g (1.0 mmol) of hydrazine monohydrate. The mixture was stirred for 30 min at room temperature. The solvent was evaporated, and methanol was added to produce a precipitate of the product (0.29 g, 63%) that was recrystallized from $CHCl_3$ (ethanol free) to give needles: mp > 250 °C dec; IR (KBr) ν 3565, 3310, 1700−1740 cm^{-1}; ^1H NMR (THF-d_8, 20 °C) δ 1.00 (s, 18H), 1.24 (s, 18H), 3.42 (d, 4H), 3.97 (d, 4H), 5.45 (s, 2H), 6.90 (s, 4H), 6.94 (d, 4H), 7.11 (s, 4H), 8.26 (d, 4H), 9.35 (s, 2H); ^{13}C NMR (THF-d_8, 20 °C) δ 31.4, 31.9, 33.2, 34.4, 34.6, 116.4, 121.3, 126.1, 126.3, 128.9, 133.1, 133.4, 142.8, 144.3, 148.6, 151.4, 163.6, 164.7; MS (ESI-TOF) calcd for $C_{58}H_{65}O_8$ 889.47, found 889.55 $[M + H]^+$. Anal. Calcd for $C_{58}H_{64}O_8 \cdot H_2O$: C, 76.79; H, 7.33. Found: C, 76.69, H, 7.25.

Single-Crystal X-ray Diffraction. All the crystals were mounted on glass fibers and were coated with nail polish to keep solvents included. The single-crystal X-ray data was collected on a Rigaku R-AXIS RAPID Imaging plate diffractometer. All calculations were performed with the crystallographic software package teXsan (Molecular Structure Corporation, 1985&1999). The structure was solved by direct method (SHELXS-97)[21] and expanded using Fourier techniques (DIRDIF94).[22] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms except OH groups were included at calculated positions.

Crystal data for $C_{58}H_{64}O_{12} \cdot 5(C_3H_6O)$ (3a):[7] $M = 1243.54$, tetragonal, $a = b = 13.9382(3)$ Å, $c = 35.3234(8)$ Å, $V = 6862.4(3)$ Å^3, $T = -100$ °C, space group $P4_12_12$ (no. 92), $Z = 4$, μ (Cu Kα) = 6.89 cm^{-1}, $D_c = 1.204$ g cm^{-3}, 69 324 reflections measured, 1216 unique ($R_{int} = 0.039$). Full-matrix least-squares refinement was based on 2652 observed reflections ($I > 2.00\sigma(I)$) and 408 variable parameters. $R = 0.069$, Rw = 0.109, GOF = 1.18.

Crystal data for $C_{58}H_{64}O_{10} \cdot 5(C_3H_6O)$ (3b): $M = 1211.54$, tetragonal, $a = b = 13.8980(4)$ Å, $c = 35.933(1)$ Å, $V = 6940.7(3)$ Å^3, $T = -40$ °C, space group $P4_12_12$ (no. 92), $Z = 4$, μ(Cu Kα) = 6.46 cm^{-1}, $D_c = 1.159$ g cm^{-3}, 38 480 reflections measured, 3703 unique ($R_{int} = 0.011$). Full-matrix least-squares refinement was based on all observed reflections ($I > 0.00\sigma(I)$) and 399 variable parameters. $R = 0.101$, Rw = 0.075, GOF = 0.70.

Crystal data for $C_{58}H_{64}O_8 \cdot 2(H_2O)$ (3d): $M = 925.17$, monoclinic, $a = 31.883(2)$ Å, $b = 43.077(2)$ Å, $c = 22.629(2)$ Å, $\beta = 134.279(2)$°, $V = 22251(2)$ Å^3, $T = -20$ °C, space group $C2/c$ (no.15), Z = 16, μ(Cu Kα) = 5.98 cm^{-1}, $D_c = 1.105$ g cm^{-3}, 62 616 reflections measured, 20 034 unique ($R_{int} = 0.034$). Full-matrix least-squares refinement was based on 8445 observed reflections ($I > 1.00\sigma(I)$) and 1208 variable parameters. $R = 0.134$, Rw = 0.184, GOF = 1.16.

Crystal data for $C_{58}H_{64}O_8 \cdot 2H_2O \cdot 2(CHCl_3)$ (3e): $M = 1163.92$, monoclinic, $a = 41.675(1)$ Å, $b = 12.9899(3)$ Å, $c = 26.7527(6)$ Å, $\beta = 119.4351(8)$°, $V = 12613.2(5)$ Å^3, $T = -80$ °C, space group $C2$/c (no. 15), $Z = 8$, μ(Cu Kα) = 29.14 cm^{-1}, $D_c = 1.226$ g cm^{-3}, 66 675 reflections measured, 11 247 unique ($R_{int} = 0.049$). Full-matrix least-squares refinement was based on 6938 observed reflections ($I > 2.00\sigma(I)$) and 704 variable parameters. $R = 0.126$, Rw = 0.186, GOF = 1.59.

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Supporting Information Available: Crystallographic data and structure refinement details for **3b**,**d**,**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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