Tandem Claisen Rearrangement: A Novel, One-Step Synthesis of Calixarene Analogues from Macrocyclic Polyethers

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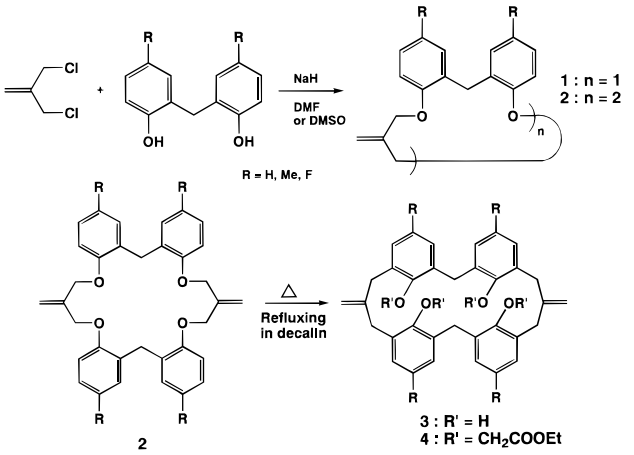
Calixarenes and their analogues have received much attention over the past 15 years from the viewpoint of host−guest chemistry.[1,2] Synthetic routes for various types of calixarenes have been established and their properties and functions investigated.[3] However, it is difficult to change their basic macrocyclic framework composed of *m*-phenylene-2-methylene units, by the processes reported so far, such as the one-pot condensation reaction of *p-tert*-butylphenol with formaldehyde,[3,4] or stepwise reaction of phenols with formaldehyde.[3,5] New synthetic routes for calixarenes and their analogues would expand the field of cyclophane chemistry.

The Claisen rearrangement of aromatic compounds containing allyloxy groups is a well-known versatile reaction for the formation of intramolecular C−C bonds.[6,7] In this paper, we report the first example of a new synthetic route for calixarene analogues with a different macrocyclic structure from that of the calixarene analogues reported so far. We used Claisen rearrangement successfully and obtained moderate yields of the new analogues.

We have recently found that 1,1-bis((aryloxy)methyl)ethylene derivatives, which can be obtained from the reaction of 2-(chloromethyl)-3-chloro-1-propene with various kinds of aromatic compounds that have a hydroxyl group, efficiently produce high yields of bis(hydroxyaryl) derivatives via tandem Claisen rearrangement.[8] On the basis of the mechanistic consideration of the reaction, we elaborated a new method for the preparation of calix[4]arene analogues with four phenolic hydroxyl groups from the corresponding macrocyclic polyether compounds containing aromatic rings.

The equimolar reaction of 2,2′-bis(1-hydroxyphenyl)methane derivatives[9] with 2-(chloromethyl)-3-chloro-1-propene in the presence of a base in dimethyl sulfoxide or *N*,*N*′-dimethylformamide gave a cyclic monomer (**1**), dimer (**2**), and higher oligomerized products as shown in Scheme 1. When the mixture of products was subjected to column chromatography on silica gel with chloroform as eluent, the first species was a 2:2 adduct (**2**), the second was a 1:1 adduct (**1**), and then a

Scheme 1. Synthetic Route of Calixarene Analogues



mixture of unidentified oligomers was obtained. After recrystallization from cyclohexane, pure **1** and **2** were isolated.

If the Claisen rearrangement of such cyclic compounds could be made to occur in the same way as with acyclic allyl ether compounds,[8] corresponding macrocyclic compounds having hydroxylphenyl groups would be produced. Note especially that compound **3** rearranged from **2** would be a calix[4]arene analogue with four phenolic hydroxyl groups and would be expected to exhibit the same functions as calixarenes.

Therefore, we tried Claisen rearrangement of the corresponding macrocyclic polyethers by heating them with or without solvent. The reaction of **1** and **2** without solvent at 180−200 °C for 2 h under N_2 atmosphere gave a dark brown solid, which was insoluble in any solvent. However, after compound **2** was

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(9) 2,2′-Bis(1-hydroxyphenyl)methane derivatives (R = H, Me, and F) were supplied from Honshu Kagaku Co., Ltd., in Japan. 2-(Chloromethyl)-3-chloro-1-propene is commercially available from Aldrich Chemical Co.

(10) A typical experimental procedure is exemplified by the preparation of **3** (R = Me). Preparation of **1** and **2** (for R = Me): To a solution of 2,2′-bis(*p*-methylphenol)methane (4.6 g, 20 mmol) in dry dimethylformamide(100 mL) was added sodium hydride(1.0 g, 41 mmol) at 60 °C. After 2 h of stirring at 60 °C, 2-(chloromethyl)-3-chloro-1-propene (2.5 g, 20 mmol) was poured into the solution. After 24 h at 60 °C, dimethylformamide was removed from the reaction mixture under reduced pressure. The residue was extracted with $CHCl_3$ (150 mL); the $CHCl_3$ solution was washed with water three times and dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the residue was subjected to column chromatography on silica gel (300 mesh) with $CHCl_3$ as eluent which gave **2** (1.6 g, 29%) as the first eluate, **1** (2.5 g, 45%) as the second eluate, and other unidentified eluates (0.9 g). For **1** (R = Me): colorless crystal, mp 122−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 2.26 (6H, s, CH_3), 3.93 (2H, s, Ar−CH_2−Ar), 4.72 (4H, s, CH_2O), 5.08 (2H, s, CH_2═C), 6.85 (2H, d, J = 8 Hz, Ar−H), 6.93 (2H, dd, J = 2, 8 Hz, Ar−H), 7.05 (2H, d, J = 2 Hz, Ar−H); ^{13}C NMR ($CDCl_3$, TMS) δ 20.75, 30.92, 76.05, 117.59, 118.89, 127.97, 131.11, 132.26, 133.37, 142.10, 155.27; IR (KBr) 3077, 3019, 1649, 1497 cm^{-1}; UV (λ_{max}, $CHCl_3$) 280 nm (ϵ = 3400); precise mass calcd for $C_{19}H_{20}O_2$ 280.1462, found 280.1436. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.35; H, 7.18. For **2** (R = Me): colorless crystal, mp 222−223 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 2.25 (12H, s, CH_3), 3.93 (4H, s, Ar−CH_2−Ar), 4.28 (8H, s, CH_2O), 5.27 (4H, s, CH_2═C), 6.54 (4H, d, J = 8 Hz, Ar−H), 6.87 (4H, d, J = 8 Hz, Ar−H), 6.91 (4H, dd, J = 2, 8 Hz, Ar−H); ^{13}C NMR ($CDCl_3$, TMS) δ 20.60, 68.47, 111.68, 114.32, 127.16, 129.46, 129.69, 130.96, 133.37, 133.89, 140.94, 153.83; IR (KBr) 3023, 1661, 1611, 1501 cm^{-1}; UV (λ_{max}, $CHCl_3$) 280 nm (ϵ = 9400); precise mass calcd for $C_{38}H_{40}O_4$ 560.2924, found 560.2913. Anal. Calcd for $C_{38}H_{40}O_4$: C, 81.40; H, 7.19. Found: C, 80.99; H, 7.31. Other derivatives of **1** and **2** (R = H and F) have been obtained in a manner similar to that described above. For **3** from **2** for R = Me): compound **2** (0.50 g, 0.89 mmol) was dissolved in decalin (20 mL). After the gas was removed from the solution, the solution was refluxed under nitrogen atmosphere for 8 h. After the solvent was removed under reduced pressure, the residue was subjected to column chromatography on silica gel (300 mesh) with $CHCl_3$ as eluent which gave **3** (0.21 g, 42%). For **3** (R = Me): colorless crystal, mp 263−264 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 2.25 (12H, s, CH_3), 3.29 (8H, s, C═C−CH_2−Ar), 3.86 (4H, s, Ar−CH_2−Ar), 4.73 (4H, s, CH_2═C), 6.81 (4H, d, J = 2 Hz, Ar−H), 7.03 (4H, d, J = 2 Hz, Ar−H), 7.85 (4H, s, OH); ^{13}C NMR ($CDCl_3$, TMS) δ 20.49, 31.31, 38.12, 112.38, 125.83, 127.47, 129.73, 130.26, 130.38, 146.51, 148.59; IR (KBr) 3424, 3374, 3011, 1644 cm^{-1}; UV (λ_{max}, $CHCl_3$) 287 nm (ϵ = 10 700); precise mass calcd for $C_{38}H_{40}O_4$ 560.2924, found 560.2907. Anal. Calcd for $C_{38}H_{40}O_4$: C, 81.40; H, 7.19. Found: C, 81.13; H, 7.08.

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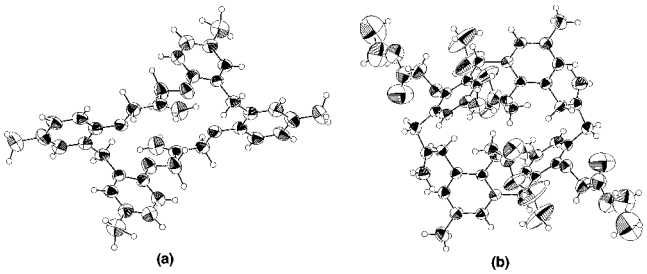

Figure 1. Molecular structures of macrocycles **2** (R = Me) (a) and **4** (R = Me, R′ = CH_2COOEt) (b). Thermal elipsoids are scaled to the 50% probability level.

refluxed for 8 h in decahydronaphthalene (decalin; trans and cis mixture, bp 189−191 °C) and the solvent was evaporated, the residue obtained was soluble in organic solvents such as chloroform and benzene. The residue was subjected to column chromatography on silica gel with chloroform as eluent, giving compound **3** as the main product. After recrystallization from cyclohexane, a moderate yield of the product was obtained.[10] Under these conditions, we failed to detect any intermediate products, as are obtained when Claisen rearrangement occurs step-by-step in a molecule.

Elemental analysis, precise mass spectroscopy, ^{1}H and ^{13}C NMR spectroscopies, UV, and IR confirmed the structure of **3**. In the proton NMR spectrum of **3** in deuterated chloroform, most of the signals showed singlet peaks, quite different from those of macrocyclic polyether **2**. Thus, whether there is a substituent at the *para*-position of the aromatic ring, this reaction can proceed smoothly to give *ortho*-rearranged compound as the main product.[11] Additionally, the reason the half-rearranged compounds are not observed might be due to the reaction conditions, above all enough time to complete the rearrangement. Thus, this reaction could be a candidate for the synthesis of calixarene analogues such as compound **3**.

Single crystals of both **2** (R = Me) and **4** (a derivative of **3** (R = Me, R′ = CH_2COOEt))[12] suitable for X-ray crystallographic analyses were obtained by layering each solution in cyclohexane. As shown in Figures 1a and b, single-crystal X-ray diffraction analysis indeed identified macrocyclic polyether **2**[13] and (ethoxycarbonyl)methyl ether **4**[14] derived from **3**, respectively. The chain structure of **3** seems flexible because the cavity is occupied by ethyl ester moieties. Additionally, the ^{1}H NMR spectrum of the ethyl ester of **3** (R = Me) gave sharp singlet signals except the signals of ethyl protons in deuterated chloroform at room temperature. However, compound **1** does not give the corresponding cyclic phenol derivative by pyrolytic reaction either with or without solvent.

In conclusion, we have developed a new method for the preparation of calixarene analogues via intramolecular successive C−C bond formation; we call this reaction a "tandem Claisen rearrangement".[15] This reaction is an entirely new route for the synthesis of new types of calixarene analogues. To our knowledge, this is the first example of calixarene analogues produced from macrocyclic polyether **2** in a one-step reaction. Also, compound **3** is expected to act as a host for some organic compounds.[16] Such unique calixarene analogues could expand the dimensions and potential of host−guest chemistry and supramolecular chemistry.

Supporting Information Available: Table of crystallographic data including final coordinates, bond lengths, bond angles, and anisotropic displacement parameters for **2** and **4** (25 pages). A crystallographic file, in CIF format, is available through the Internet only. See any current masthead page for ordering and Internet access instructions.

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(11) Two other derivatives of type **3** (R = H and F) have been obtained in a similar manner. For **3** (R = H): colorless crystal, yield 46%, mp 184−186 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 3.36 (8H, s, C═C−CH_2−Ar), 3.95 (4H, s, Ar−CH_2−Ar), 4.76 (4H, s, CH_2═C), 6.86 (4H, dd, J = 8, 8 Hz, Ar−H), 7.01 (4H, dd, J = 1.5, 8 Hz, Ar−H), 7.24 (4H, dd, J = 1.5, 8 Hz, Ar−H), 7.84 (4H, s, OH); IR (KBr) 3418, 3030, 1642, 1593, 1466, 752 cm^{-1}; precise mass calcd for $C_{34}H_{32}O_4$ 504.2299, found 504.2249. For **3** (R = F): colorless crystal, yield 22%, mp 208−209 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 3.32 (8H, s, C═C−CH_2−Ar), 3.88 (4H, s, Ar−CH_2−Ar), 4.78 (4H, s, CH_2═C), 6.76 (4H, dd, J = 3, 8 Hz, Ar−H), 6.92 (4H, dd, J = 3, 8 Hz, Ar−H), 7.58 (4H, s, OH); IR (KBr) 3472, 3391, 3011, 1606, 1478, 1454 cm^{-1}; precise mass calcd for $C_{34}H_{28}O_4F_4$ 576.1922, found 576.1922.

(12) A good yield of compound **4** (derivative of **3** (R = Me, R′ = CH_2-COOEt)) was obtained from the reaction of **2** with 4 equiv of bromoacetic acid ethyl ester in the presence of 4 equiv of NaH in DMF at 70 °C for 10 h.

(13) Crystal data for **2** (R = Me): $C_{38}H_{40}O_4$, M_w = 560.0, crystal size 0.9 × 0.8 × 0.2 mm^3, monoclinic, space group $P2_1/a$ (No. 14), a = 6.154-(1), b = 16.585(3), and c = 15.461(4) Å, β = 91.44(1)°, V = 1577.6(6) Å,^{3} Z = 2, D_{calcd} = 1.18 g/cm^3. The data were collected on an Enlaf-Nonius CAD4 diffractometer, λ(Cu Kα) = 1.5418 Å, ω-scan, μ = 5.6 cm^{-1}, 2671 measured and 2335 unique reflections ($0 \le h \le 6$, $0 \le k \le 18$, $-17 \le l \le 17$, $2\theta_{max}$ = 120°, R_{int} = 0.03). Absorption correction: empirical ψ-scan, (T_{min} = 0.85, T_{max} = 0.99). The structure was solved by direct methods (Multan 11/82 from MolEN, An Interactive Structure Solution Procedure, Enraf-Nonius, Delft, The Netherlands, 1990). F(000) = 600; 2129 observed reflections ($|F_o| \ge 3\sigma|F_o|$) used for the refinement. Refinement on F, number of parameters = 211. The positions of the hydrogen atoms were calculated in ideal positions and their positions were not refined. R = 0.066 (R_w = 0.080, $w = 1/\sigma^2(F_o)$). Extinction cocorrection applied; extinction coefficient 0.0000073; residual electron density: −0.41, +0.40 eÅ^{-3}. See also ref 14b.

(14) (a) Crystal data for **4** (ethyl ester derivative of **3** (R = Me, R′ = CH_2COOEt)): $C_{54}H_{64}O_{12}$, M_w = 904.0, crystal size 0.4 × 0.2 × 0.2 mm^3, triclinic, space group $P\bar{1}$ (No. 2), a = 11.018(2), b = 11.137(2), and c = 12.817(2) Å, α = 109.31(1)°, β = 96.70(1)°, γ = 116.34(1)°, V = 1264.0-(6) Å,^{3} Z = 1, D_{calcd} = 1.18 g/cm^3. The data were collected on a MacScience MXC18 diffractometer, λ(Mo $K\alpha$) = 0. 71073 Å, scan method $\omega - 2\theta$, 6187 measured and 5706 unique reflections ($-12 \le h \le 3$, $-13 \le k \le 0$, $-15 \le l \le 15$, $2\theta_{max}$ = 50°. The structure was solved by direct methods (SIR92, from Crystan-GM, version 6.2, MacScience, Japan, 1994). F(000) = 484; 2852 observed reflections ($|F_o| \ge 3\sigma|F_o|$) used for the refinement. Refinement on F, number of parameters = 387. The 19 hydrogen atoms were located by the difference Fourier method and isotropically refined. The remainder were located by calculation, and their positions were fixed. R = 0.061(R_w = 0.103, $w = 1/\sigma^2(F_o)$): residual electron density −0.35, +0.38 eÅ^{-3}. (b) Further details of the crystal structure, such as atomic coordinates, bond lengths and angles, may be obtained from the Director of the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, GB-Cambridge CB21EZ (U.K.) by quoting the full journal citation.

(15) "Tandem Claisen rearrangement" means that Claisen rearrangement reactions occur two times at the same group within a molecule successively. Although we used "double"in ref 8, we would prefer the use of "tandem". The term "tandem rearrangement" has been used in a recent review,[17] for example, of successive Claisen−Cope rearrangement to synthesize aliphatic compounds.

(16) As a preliminary result, in the liquid (**3** in $CHCl_3$)−solid (anilinium chloride) extraction, anilinium chloride can be solubilized into $CHCl_3$ in which anilinium chloride is hardly soluble, and it is also observed that the ^{1}H chemical shifts of **3** change from the original chemical shifts of free **3** at the NMR measurement. Additionally, host molecule **3** (R = Me) has been confirmed to form a 1:1 complex with anilinium chloride in $CHCl_3$/CH_3CN (2:1(v/v)) by the NMR titration method. The details will be described in a full paper.

(17) For a review, see: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.