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SYNTHESIS OF NOVEL CROWNOPHANES CONTAINING TWO PHENOLIC MOIETIES *VIA* A TANDEM CLAISEN REARRANGEMENT

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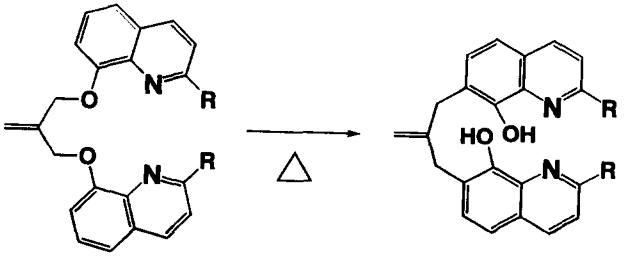
Abstract: A series of crownophanes containing two phenolic moieties within a macrocyclic ring have been successfully synthesized by a one-step thermal reaction from the corresponding macrocyclic polyethers by using a "Tandem Claisen Rearrangement". © 1997 Elsevier Science Ltd.

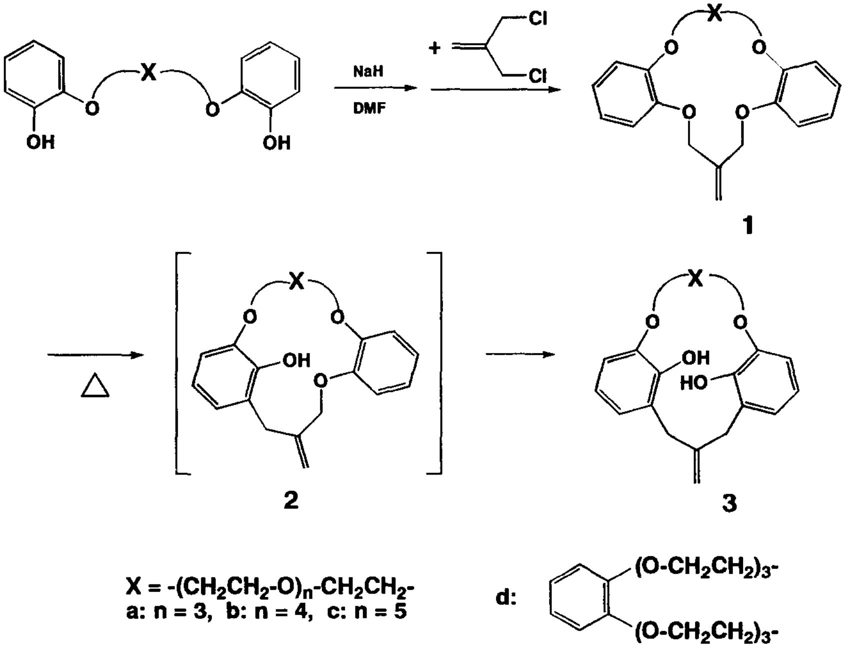
Macrocycles, which have rigid aromatic moieties and flexible oligoethylene glycol moieties within the macrocyclic rings, are called "crownophanes".(1) These structurally-hybridized macrocycles are expected to exhibit special functions or properties, which are different from those of basic macrocyles such as crownethers,(2) cyclophanes,(3) calixarenes,(4) and spherands.(5) So far, several interesting properties have been reported on crownophanes having one or more phenolic moieties.(6-8) It was recently reported that calixcrowns, one of which exhibits excellent selectivity toward the sodium ion as a metal ionophore, may also be a remarkable example of this type of compounds.(9) However, although these compounds show potential high performance, their synthesis entails laborious work. Hence, new strategies for the synthesis of structurally-hybridized macrocycles such as crownophanes have been sought.

Recently, we have found that 1,1-bis(aryloxymethyl)ethylene derivatives can be converted thermally to bis(hydroxyaryl) derivatives in high yield by using a Claisen rearrangement, which we call a "Tandem(or Double) Claisen Rearrangement".(10) This reaction is quite effective to generate plural phenolic moieties in a molecule simultaneously and could be applicable to the synthesis of a number of not only acyclic but also macrocyclic compounds. In this paper we present a novel method for the one-step synthesis of crownophanes having two phenolic moieties from the corresponding macrocyclic polyethers *via* a Claisen rearrangement.



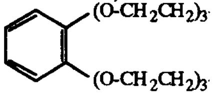
Macrocyclic polyethers **1**(11) were obtained by the reaction of oligoethylene glycol derivatives having bis(*o*-hydroxyphenyl)oxy groups(12) with 3-chloro-2-chloromethyl-1-propene under the presence of a base such as sodium hydride as shown in Scheme 1. General procedure: to a solution of α,ω–bis(*o*-hydroxyphenyloxy)-oligoethylene glycol(10 mmol) in dimethylformamide(100 ml) was added sodium hydride(21 mmol) at 60 °C. Then, 3-chloro-2-chloromethyl-1-propene(10 mmol) was added to it and the solution was stirred at 60 °C for 12 h. After removal of the solvent under vacuum, the residue was extracted with chloroform and the chloroform solution was washed with water and dried over anhydrous sodium sulfate. After evaporation of chloroform, the residue was subjected to column chromatography on silica gel with chloroform as eluent. The yields of **1** are shown in Table 1. Products **1** were confirmed by high resolution mass, ^{1}H NMR, and IR spectra and elemental analysis. In this reaction, the high-dilution method was not used. The shorter the chain length between two *o*-hydroxyphenyl groups, the higher the yields of **1**.

Thermal reaction of these macrocyclic polyethers **1**(2 mmol) proceeded without a solvent for 6 h around at 195 °C under nitrogen atmosphere. The reaction products were subjected to column chromatography on silica gel with chloroform and then chloroform/ethyl acetate as eluent to give crownophanes **3** rearranged twice. Table 1 summarizes the yields of each product. Apparently, the ring size of **1** affects the yields of rearranged products **3**. As expected, reactants **1** which have rather large macrocycles with more than a 22-membered ring gave only the corresponding products **3** *via* the tandem Claisen rearrangement, while **2** rearranged once could not be detected under these conditions,13) and the larger macrocycles of **1**, the better the yields of **3**(**3a** < **3b** < **3c** < **3d**). Products **3** were confirmed by high resolution mass, ^{1}H NMR, and IR spectra and elemental analysis.14) Table 2 summarizes the physical and spectroscopic data.



Scheme 1. Synthetic route of novel crownophanes *via* a "Tandem Claisen Rearrangement"

Table 1. Yields of the macrocycles **1** and **3**[a]

X	**1**, %[b]	**3**, %
a. $-(CH_2CH_2{-}O)_3{-}CH_2CH_2-$	52	59
b. $-(CH_2CH_2{-}O)_4{-}CH_2CH_2-$	44	69
c. $-(CH_2CH_2{-}O)_5{-}CH_2CH_2-$	35	78
d. 	29	83
	29	83

a) Reaction conditions: see the text.

b) Yields are not optimized.

Table 2. Physical and spectroscopic data of compounds **3**.

Product	Mp °C	Precise Mass M^+	300 MHz ^1H NMR ($CDCl_3$) δ, ppm
$\mathbf{3_a}$	141-143	Found 430.1838 Calcd 430.1990 ($C_{24}H_{30}O_7$)	3.25(Ar-CH_2-C, 4H, s), 3.68(OCH_2, 4H, m), 3.73(OCH_2, 4H, m) 3.84(OCH_2, 4H, m), 4.13(OCH_2, 4H, m), 4.92($C{=}CH_2$, 2H, s) 6.70(Ar-H, 2H, dd(2, 8)), 6.74(Ar-H, 2H, dd(8, 8)) 6.84(Ar-H, 2H, dd(2, 8)), 7.42(OH, 2H, s)
$\mathbf{3_b}$	96 - 98	Found 474.2085 Calcd 474.2252 ($C_{26}H_{34}O_8$)	3.40(Ar-CH_2-C, 4H, s), 3.70(OCH_2, 12H, m), 3.76(OCH_2, 4H, m) 4.14(OCH_2, 4H, m), 4.69($C{=}CH_2$, 2H, s), 6.7 - 6.9(Ar-H, 6H, m) 7.30(OH, 2H, s)
$\mathbf{3_c}$	liquid	Found 518.2528 Calcd 518.2514 ($C_{28}H_{38}O_9$)	3.42(Ar-CH_2-C, 4H, s), 3.60-3.74(OCH_2, 16H, m), 3.75 - 3.78(OCH_2, 4H, m), 4.13 - 4.16(OCH_2, 4H, m), 4.63($C{=}CH_2$, 2H, s), 6.70 - 6.91 (Ar-H, 6H, m), 7.43(OH, 2H, s)
$\mathbf{3_d}$	77 - 78	Found 610.2847 Calcd 610.2775 ($C_{34}H_{42}O_{10}$)	3.38(Ar-CH_2-C, 4H, s), 3.6-3.8(OCH_2, 12H, m), 3.88-3.91(OCH_2, 4H, m), 4.13-4.22(OCH_2, 8H, m), 4.61($C{=}CH_2$, 2H, m), 6.68-6.93 (Ar-H, 10H, m), 7.53(OH, 2H, s)

Thus, one-step conversion of macrocyclic polyethers to novel crownophanes having two phenolic moieties has been achieved by using a "Tandem Claisen Rearrangement". These crownophanes have unique structures, which could not be found in any crownophane so far reported[1] and will become attractive candidates to create a novel type of host compounds. For example, complexation with divalent metal ions could be expected by releasing two acidic protons of the phenolic hydroxyl groups. In addition, these compounds show possibilities for further modification because they have some reactive sites such as C-C double bonds and phenolic rings. Further investigations on modifications of the structure and evaluation as host molecules are now in progress in our laboratory.

References and Notes

1) Inokuma, S.; Sakai, S.; Nishimura, J. *Top. Curr. Chem.*, **1994**, *172*, 87 and references cited therein.

2) (a) Izatt, R.M.; Pawlak, K.; Bradshaw, J.S. *Chem. Rev.*, **1991**, *92*, 1721. (b) Izatt, R.M.; Bradshaw, J.S.; Pawlak, K.; Bruening, R.L.; Tarbet, B.J. *Chem. Rev.*, **1992**, *92*, 1261.

3) Diederich, F. "Cyclophanes", ed. by Stoddart, J.F. *Monograghs in Supramolecular Chemistry,* **1991**, The Royal Society of Chemistry, Cambridge.

4) (a) Gutsche, C.D. "Calixarenes", ed. by Stoddart, J.F. *Monograghs in Supramolecular Chemistry,* **1989**, The Royal Society of Chemistry, Cambridge. (b) "Calixarenes: A Versatile Class of Macrocyclic Compounds", ed. by Vincens, J.; Bömer, V. *Topics in Inclusion Science*, ed. by Davies, J.E.D. **1990**, Kluwer Academic Publishers, Dordrecht.

5) Cram, D.J. *Angew. Chem. Int. Ed. Engl.,* **1986**, *25,* 1039.

6) (a)Kaneda, T.; Umeda, S.; Ishizaki, Y.; Kuo, H.S.; Misumi, S.; Kai, Y.; Kanehisa, N.; Kasai, N. *J. Am. Chem.Soc.,* **1989**, *111*, 1881. (b)Kaneda, T.; Hirose, K.; Misumi, S. *ibid.*, **1989**, *111*, 742.

7) (a)Koenig, K.; Lein, G.M.; Stuckler, P.; Kaneda, T.; Cram, D.J. *J. Am. Chem. Soc.,* **1979**,*101,* 3553. (b) Helgeson, R.C.; Tarnowski, T.L.; Dram, D.J. *J. Org.Chem.* **1979**,*44* , 2538. (c) Lein, G.M.; Cram, D.J. *J. Am. Chem. Soc.,* **1985**, *107,* 448.

8) (a)Sun, Y.; Martell, A.E.; Motekaitis, R.J. *Inorg. Chem.*, **1986**, *25*, 4780. (b) van Doorn, A.R.; Bos, M.; Harkema, S.; van Eerden, J.; Verbom, W.; Reinhoudt, D.N. *J. Org. Chem.*, **1991**, *56*, 2371. (c) van Doorn, A.R.; Schaafstra, R.; Bos, M.; Harkema, S.; van Eerden, J.; Verbom, W.; Reinhoudt, D.N. *ibid.,* **1991**, *56*, 6083.

9) Yamamoto, H.; Sasaki, T.; Shinkai, S. *Chem. Lett.*, **1994**, 469; Yamamoto, H.; Shinkai, S. *ibid.* **1994**, 1115

10) Hiratani,K.; Takahashi, T.; Kasuga, K.; Sugihara, H.; Fujiwara, K.; Ohashi, K. *Tetrahedron Lett.*, **1995**, *36*, 5567. Although we used "Double" in this reference, we would like to use "Tandem" instead of that word from now on.

11) Tomoi, M.; Abe, O.; Ikeda, M.; Kihara, K.; Kakiuchi, H. *Tetrahedron Lett.,* **1978**, *33*, 3031.

12) Kyba, E.P.; Helgeson, R.C.; Madan, K.; Gokel, G.W.; Tarnowski, T.L.; Moore, S.S.; Cram, D.J. *J. Am. Chem. Soc.*, **1977**, *99*, 2564.

13) When the smaller macrocyclic polyethers **1** were used in this thermal reaction, intermediates **2** were obtained together with other products in the case of **1**(R = -$CH_2CH_2OCH_2CH_2OCH_2CH_2$-). Otherwise, only **2** was obtained with the reactants in the case of **1**(R = -$CH_2CH_2OCH_2CH_2$-). Unpublished results.

14) All the new products gave satisfactory spectral and analytical data. The details of these products will be published elsewhere.

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