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Stepwise synthesis of crownophanes having either one or two hydroxy groups via Claisen rearrangement

Yoshinobu Nagawa,[a] Naoki Fukazawa,[b] Jun-ichi Suga,[b] Michael Horn,[a] Hideo Tokuhisa,[a] Kazuhisa Hiratani[a,*] and Kunihiro Watanabe[b]

[a]*National Institute for Advanced Interdisciplinary Research, 1-1-4, Higashi, Tsukuba, Ibaraki 305-8562, Japan*
[b]*Tokyo University of Science, Faculty of Science and Technology, 2641, Yamazaki, Noda, Chiba 278-8510, Japan*

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Abstract

Bis(naphthyl)crownophanes having an isobutenyl group and different ring size were synthesized. By control of the reaction temperature and time, both the first-step product having one hydroxyl group and the second-step product having two hydroxy groups can be isolated in high yields. © 2000 Elsevier Science Ltd. All rights reserved.

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Much attention has recently been paid to crownophanes[1] and cryptophanes[2], the macrocycles of which are composed from hybridization of both the aromatic moieties and a flexible polyether chain, because they exhibit some excellent functions such as high ion selectivity, [3] high uptake property for guest molecules,[4] etc. That is, hybridization of both the rigid and flexible parts in a molecule could result in the development of excellent molecular recognition. Crownophanes and their analogues having aromatic hydroxy groups would also be attractive for designing and constructing precise molecular recognition. Aromatic hydroxyl groups could be changed to various kinds of functional groups by their nucleophilic substitution reaction. Therefore, it could be meaningful to control the number of aromatic hydroxy groups in a macrocycle.

We have reported the synthesis and the properties of crownophanes having two phenolic hydroxy groups from the corresponding macrocyclic polyethers in one step via tandem Claisen rearrangement.[5,6] However, in the case of Ref. 5, it was very difficult to control the reaction for the synthesis of the once-rearranged product, because the rearrangement needs a high temperature over 180–190°C and a long time. In the case of Ref. 6, on the contrary, the thermal rearrangement occurs very smoothly at lower temperature, probably because of the release of the strain energy due to binaphthyl moiety. This could be the reason why the once-rearranged product was not detected after 120°C, 15 h in two compounds having different chain lengths.

* Corresponding author. Fax: +81 298 61 3029; e-mail: hiratani@nair.go.jp

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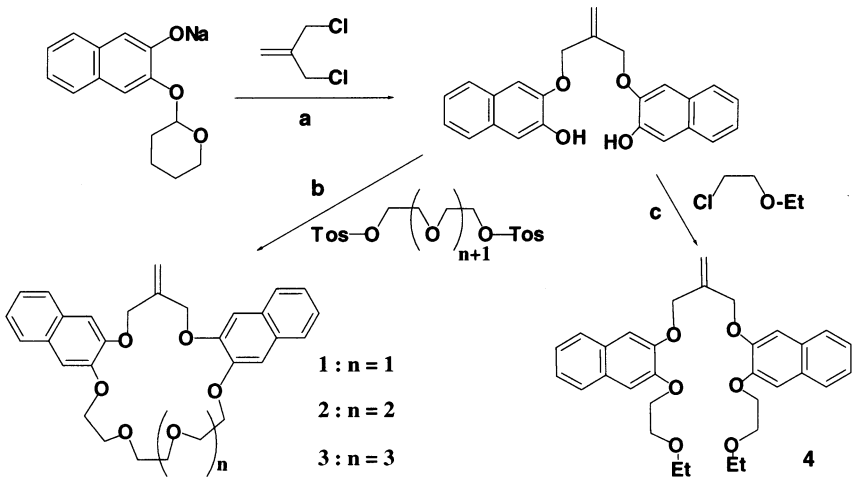
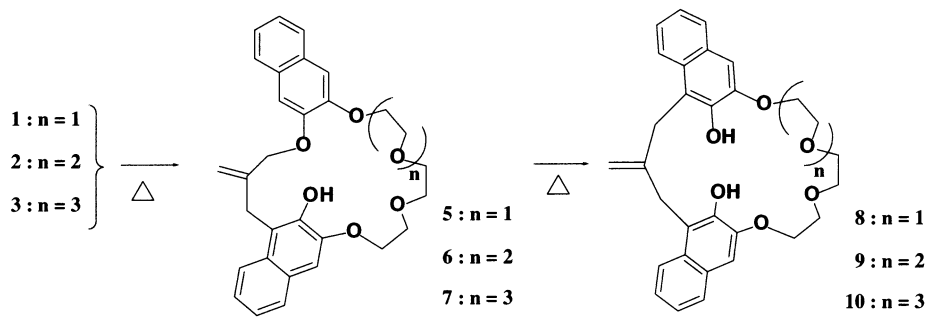
In this paper, we report the successful control of the reaction to get either a once- or twice-rearranged product. We used here 2,3-naphthalenediol instead of catechol as the starting material and tried to control the thermal reaction step and to isolate the products at each step. Such a stepwise reaction in this study could be of important significance because each compound is expected to exhibit the drastic change of selectivity towards guest species; that is, the selectivity could be largely affected both by the ring-size and the number of the proton-ionizable moiety.[7] Macrocyclic polyethers having naphthalene moieties were synthesized by the reaction of 2-[2-(3-hydroxynaphthyl-2-oxy)methyl]allyloxy-3-naphthol with oligo-ethylene glycol ditosylate in the presence of a base in DMF as shown in Scheme 1. These compounds (**1**, **2** and **3**) were identified by NMR, IR, and precise mass spectroscopies.[8] For comparison, acyclic polyether (**4**) was also prepared.[9] According to the procedure reported in Ref. 5, the polyethers were obtained in moderate yields.



Scheme 1. Synthetic route of polyethers (**1**–**4**) having an isobutenyl group: (a) DMF, 50°C, overnight, then aq. HCl in EtOH, 67%; (b) NaH, DMF, 70°C, overnight; (c) NaH, DMF, 70°C, overnight

The thermal rearrangement was tried in the range of 130–180°C, changing the reaction time either under vacuum without a solvent for a small scale (5–10 mg), such as in an NMR tube, or under a nitrogen gas atmosphere in decalin for a relatively large scale (more than 0.1 g). All reactants changed to once- and/or twice-rearranged products according to the Claisen rearrange-



Scheme 2. Tandem Claisen rearrangement of macrocyclic polyethers having an isobutenyl group

ment without formation of any by-product in the ^{1}H NMR spectra. As shown in Scheme 2, the rearrangement occurred step-by-step. Typical reaction yields of once- and twice-rearranged compounds with the times are plotted in Fig. 1.

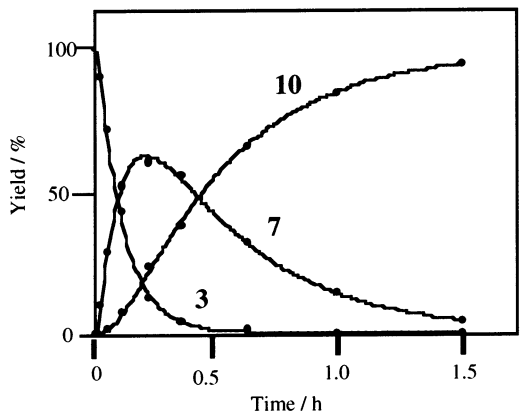


Figure 1. Time course of the tandem Claisent rearrangement of **3** at 160°C[13]

Fig. 1 shows the time dependence of the yields by the thermal reaction at 160°C in the case of **3**. Each yield was determined by the relative change of the proton signals in the ^{1}H NMR spectrum. After 15 min at 160°C, the once-rearranged product could be predominantly obtained at maximum 61%, and could be separated from a relatively small amount of the twice-rearranged product. After 1.5 h at 160°C the twice-rearranged product could be produced quantitatively. In other cases, the reaction occurred at lower temperature, compared with the case of phenyl derivatives[5] and almost similar curves were obtained with the reaction time. Therefore, either the once- or twice-rearranged product could be obtained predominantly by controlling the temperature and time. In Table 1 the representative results of each macrocycle are summarized. In the case of the acyclic one (**4**), the rearrangement occurred at the lowest temperature and even at 150°C, 1.5 h, the twice-rearranged product (**11**) was obtained almost quantitatively.[10] The

Table 1
Yields of crownophanes having one or two hydroxyl groups via tandem Claisen rearrangement

Run	Polyether	Reaction conditions[a]		Polyether unreacted (%)	Yield (%)[a]	
		Temperature (°C)	Time (min)		CP–OH[b]	CP–2OH[c]
1	**1**	160	80	10	67	23
2	**1**	180	90	1	6	93
3	**2**	150	80	28	63	9
4	**2**	170	60	1	4	95
5	**3**	140	45	17	61	22
6	**3**	160	90	0	3	97

[a] The reaction was carried out in an NMR tube under vacuum (each polyether: 5 mg) without a solvent. The yields were determined by the direct comparison of the integral magnitude among the three components in the NMR spectrum.[13]

[b] CP–OH: crownophanes (**5**–**7**) having one hydroxy group.

[c] CP–2OH: crownophanes (**8**–**10**) having two hydroxy groups.

larger the macrocyclic polyethers become, the more appropriate the lower temperature or the shorter time for rearrangement becomes. Furthermore, the conditions at lower temperature and shorter time give once-rearranged crownophanes (**5**–**7**)[11] as the major products, while the higher temperature and longer time give twice-rearranged crownophanes (**8**–**10**)[12] as the major products, respectively. The products were isolated by column chromatography on silica gel with chloroform as eluent.

In summary, both once- and twice-rearranged products having naphthyl moieties can successfully be obtained in high yields by controlling the reaction temperature and time. We were able to design high-performance crownophanes based on thermally once- or twice-rearranged macrocycles. Furthermore, we are now applying this methodology to the synthesis of macrocycles having plural isobutenyl groups.

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7. For example, as a preliminary result, compound **5** exhibits the selectively fluorescent increase at 421 nm toward sodium ion in acetonitrile among alkali and alkaline earth metal ions, when exposed to UV light of 280 nm.
8. Synthesis: typical procedure: to 200 ml of DMF with suspended NaH (0.24 g, 10 mmol), which was maintained at 70°C under stirring, was added 50 ml of DMF solution containing 2-[2-(3-hydroxynaphthyl-2-oxy)methyl]allyloxy-3-naphthol (1.5 g, 4 mmol) and triethylene glycol di-*p*-tosylate (1.85 g, 4 mmol) dropwise over a period of 12 h at 70°C. The dark solution was heated at 70°C overnight and then treated carefully with some drops of water to hydrolyze the excess of NaH. After the solvent was evaporated under reduced pressure, the residue was extracted with dichloromethane and the extractant was washed with water. After drying over sodium sulfate, the solvent was removed. The crude product was purified by column chromatography on silica gel with chloroform as eluent and then recrystallized from toluene to give 1.3 g of compound **1**: colorless crystal; yield 52%; mp 138–139°C; ^{1}H NMR (500 MHz, in $CD_2Cl_2/CDCl_3$ 9:1, δ (ppm)) 3.76 (s, 4H), 3.90 (m, 4H), 4.23 (m, 4H), 4.84 (s, 4H), 5.57 (s, 2H), 7.13 (s, 2H), 7.26 (s, 2H), 7.31 (m, 4H), 7.62 (dd, $J=7$, 2 Hz, 2H), 7.66 (dd, $J=7$, 2 Hz, 2H); IR (KBr, cm^{-1}) 3055, 2929, 1627, 1600, 1507, 1257, 1165, 1116; Precise mass, calcd for $C_{30}H_{30}O_6$ 486.204, found 486.201. Compound **2**: colorless crystal; yield 64%; mp 164–165°C; ^{1}H NMR (500 MHz, in $CD_2Cl_2/CDCl_3$ 9:1, δ (ppm) 3.61 (m, 4H), 3.71 (m, 4H), 3.87 (m, 4H), 4.23 (m, 4H), 4.86 (s, 4H), 5.47 (s, 2H), 7.15 (s, 2H), 7.20 (s, 2H), 7.32 (m, 4H), 7.63 (dd, $J=7$, 3 Hz, 2H), 7.67 (dd, $J=6$, 3 Hz, 2H); IR (KBr, cm^{-1}) 3050, 2902, 2864, 1626, 1600, 1508, 1485, 1260, 1174, 1118; precise mass, calcd for $C_{32}H_{34}O_7$ 530.230, found 530.230. Compound **3**: colorless crystal; mp 108–109°C; yield 48%; ^{1}H NMR (500 MHz, in $CD_2Cl_2/CDCl_3$ 9:1, δ (ppm)) 3.54 (s, 4H), 3.56 (m, 4H), 3.67 (m, 4H), 3.88 (m, 4H), 4.23 (m, 4H), 4.86 (s, 4H), 5.50 (s, 2H), 7.15 (s, 2H), 7.20 (s, 2H), 7.32 (m, 4H), 7.62 (d, $J=7$, 2 Hz, 2H), 7.67 (d, $J=7$, 2 Hz, 2H); IR (KBr, cm^{-1}) 3052, 2909, 2864, 1626, 1600, 1509, 1487, 1261, 1172, 1114; precise mass, calcd for $C_{34}H_{38}O_8$ 574.256, found 574.249.
9. Compound **4**: colorless oil; yield 65%; ^{1}H NMR (500 MHz, CD_2Cl_2, δ (ppm)) 1.17 (t, $J=7.0$ Hz, 6H), 3.56 (q, $J=7.0$ Hz, 4H), 3.81 (m, 4H), 4.21 (m, 4H), 4.87 (s, 4H), 5.51 (s, 2H), 7.16 (s, 2H), 7.21 (s, 2H), 7.31 (m, 4H), 7.60 (dd, $J=7$, 2 Hz, 2H), 7.67 (dd, $J=7$, 2 Hz, 2H); IR (KBr, cm^{-1}) 3056, 2974, 2927, 2869, 1663, 1627, 1600, 1583, 1508, 1486, 1257, 1173, 1117; precise mass, calcd for $C_{32}H_{36}O_6$ 516.251, found 516.246.
10. Compound **11**: colorless crystal; isolated yield 80% (150°C, 90 min); mp 73–75°C; ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm)) 1.26 (t, $J=7$ Hz, 6H), 3.62 (q, $J=7$ Hz, 4H), 3.84 (t, $J=5$ Hz, 4H), 3.95 (s, 4H), 4.31 (t, $J=4$ Hz, 4H), 4.49 (s, 2H), 6.54 (s, 2H), 7.12 (s, 2H), 7.25 (m, 4H), 7.64 (d, $J=8$ Hz, 2H), 7.69 (d, $J=8$ Hz, 2H); IR (KBr, cm^{-1}) 3420, 3066, 2976, 2927, 2871, 1627, 1604, 1510, 1475, 1448, 1282, 1185, 1110; precise mass, calcd for $C_{32}H_{36}O_6$ 516.251, found 516.244.

11. Compound **5**: to 20 ml of decalin was added 0.40 g of polyether **1** and the mixture was stirred at 160°C, 80 min under N_2 atmosphere. Then, decalin was removed at 100°C under vacuum and the residue was subjected to column chromatography on silica gel with chloroform as eluent to give 0.195 g of **5** as a main product (colorless crystal recrystallized from acetonitrile; isolated yield 49%); mp 131–132°C; ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm)) 3.83 (m, 6H), 4.09 (s, 2H), 4.10 (t, $J=5$ Hz, 2H), 4.21 (m, 2H), 4.37 (t, $J=5$ Hz, 2H), 4.57 (s, 2H), 5.09 (s, 1H), 5.31 (s, 1H), 7.14 (s, 1H), 7.17 (s, 1H), 7.22 (s, 1H), 7.30 (m, 3H), 7.37 (dd, $J=7$, 7 Hz, 1H), 7.64 (m, 4H), 7.92 (d, $J=9$ Hz, 1H); IR (KBr, cm^{-1}) 3435, 3057, 2922, 2871, 1627, 1601, 1508, 1483, 1259, 1173, 1118; precise mass, calcd for $C_{30}H_{30}O_6$ 486.204, found 486.209. Compound **6:** colorless crystal; isolated yield 52% (150°C, 80 min); mp 78–83°C; ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm)) 3.76 (s, 4H), 3.90 (m, 4H), 4.23 (m, 4H), 4.84 (s, 4H), 5.57 (s, 2H), 7.13 (s, 2H), 7.26 (s, 2H), 7.31 (m, 4H), 7.62 (dd, $J=7$, 2 Hz, 2H), 7.66 (dd, $J=7$, 2 Hz, 2H); IR (KBr, cm^{-1}) 3435, 3058, 2924, 2871, 1627, 1601, 1508, 1260, 1175, 1116; precise mass, calcd for $C_{32}H_{34}O_7$ 530.230, found 530.229. Compound **7**: colorless crystal; isolated yield 45% (140°C, 45 min); mp 75–78°C; ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm)) 3.62 (s, 4H), 3.66 (m, 4H), 3.73 (s, 2H), 3.95 (m, 4H), 4.08 (m, 4H), 4.31 (m, 4H), 4.61 (s, 1H), 4.75 (s, 2H), 5.15 (s, 1H), 7.06 (s, 1H), 7.18 (m, 2H), 7.31 (m, 4H), 7.66 (m, 3H), 7.73 (d, $J=8$ Hz, 1H), 8.48 (s, 1H); IR (KBr, cm^{-1}) 3490, 3064, 2923, 2867, 1627, 1601, 1508, 1477, 1260, 1176, 1115; precise mass, calcd for $C_{34}H_{38}O_8$ 574.256, found 574.260.
12. Compound **8**: colorless crystal; isolated yield 77% (180°C, 90 min); mp 140–144°C; ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm)) 3.74 (s, 4H), 3.75 (s, 4H), 3.88 (m, 4H), 4.28 (m, 4H), 5.20 (s, 2H), 6.6 (broad, 2H), 7.33 (dd, $J=7$, 7 Hz, 2H), 7.63 (d, $J=8$ Hz, 2H), 8.12 (d, $J=9$ Hz, 2H); IR (KBr, cm^{-1}) 3448, 3066, 2922, 2871, 1627, 1601, 1509, 1475, 1283, 1184, 1120; precise mass, calcd for $C_{30}H_{30}O_6$ 486.204, found 486.196. Compound **9**: colorless crystal; isolated yield 81% (170°C, 60 min); mp 165–170°C; ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm)) 3.61 (m, 4H), 3.71 (m, 4H), 3.87 (m, 4H), 4.23 (m, 4H), 4.86 (s, 4H), 5.47 (s, 2H), 7.15 (s, 2H), 7.20 (s, 2H), 7.32 (m, 4H), 7.63 (dd, $J=7$, 3 Hz, 2H), 7.67 (dd, $J=7$, 3 Hz, 2H); IR (KBr, cm^{-1}) 3393, 3064, 2914, 2876, 1626, 1602, 1511, 1473, 1262, 1187, 1118; precise mass, calcd for $C_{32}H_{34}O_7$ 530.230, found 530.222. Compound **10**: colorless crystal; isolated yield 75% (160°C, 90 min); mp 165–167°C; ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm)) 3.56 (m, 12H), 3.87 (m, 4H), 3.93 (s, 4H), 4.29 (m, 4H), 4.49 (s, 2H), 4.86 (s, 4H), 7.22 (s, 2H), 7.26–7.34 (m, 4H), 7.65 (d, $J=7$ Hz, 2H), 7.78 (d, $J=7$ Hz, 2H); IR (KBr, cm^{-1}) 3359, 3069, 2903, 2874, 1628, 1604, 1509, 1477, 1288, 1192, 1119; precise mass, calcd for $C_{34}H_{38}O_8$ 574.256, found 574.249.
13. In NMR spectra, any other species was never observed except the three components, and all of the sample solutions in $CDCl_3$ are clear without any precipitate.