Synthesis of Novel Bis-Crown and Double-Armed Crown Ethers Having the 18-Crown-6 Residue

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(Received May 8, 1987)

Synopsis. The 18-crown-6 derivative possessing two hydroxyl groups was prepared from the Diels–Alder adduct of 1,7-(1,2-ethanediylidene)-18-crown-6 with dimethyl 2-butynedioate. By using the crown ether as the key intermediate, novel bis-crown and double-armed crown ethers having the 18-crown-6 residue were synthesized, and their abilities to extract metal picrates were investigated.

Since Smid and co-workers first prepared the bis-crown ether,[1] a variety of bis-crown ethers have been synthesized and their complexing properties have been investigated, because of interests in their unique binding properties. Here we report the syntheses of novel bis-crown and double-armed crown ethers having the 18-crown-6 residue and the solvent extraction of metal picrates with these crown ethers. Bis-crown ethers are divided into several groups according to a variation of the linkage holding two macrorings[2] together and bis-crown ethers described in this paper may be classified into a group which is referred to as a "hinged" bis-crown ether.[2,3]

We chose the crown ether **8** possessing two hydroxyl groups as well as the 18-crown-6 residue as the key intermediate for the preparation of bis-crown and double-armed crown ethers having the 18-crown-6 residue. Treatment of **1**[4] with dimethyl 2-butynedioate in refluxing toluene gave the adduct **4** in 71% yield. Catalytic hydrogenation of **4** over 10% Pd/C in methanol afforded the diester **7** in 79% yield. The diester **9** containing the 15-crown-5 residue was obtained from **2**[5] in 52% overall yield via the adduct **5**.

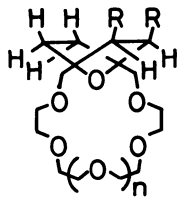
Assignment of the configuration of **7** and **9** was based on their ^{1}H NMR spectra with those of **11** and **12** with known configurations.[6] Chemical shifts on endo- and exo-protons on the ethano bridge in **7**, **9**, **11**, and **12** are summarized in Table 1. The endo-protons in **11** are shifted considerably downfield due to a deshieding effect of the endo-carbonyl groups on C2 and C3, and the endo-protons in **7** and **9** are also shifted to downfield. From the data described above, we assigned the endo-configuration to **7** and **9** as shown in their structural formulas.

Table 1. Chemical Shifts of Endo- and Exo-Protons on the Ethano Bridge

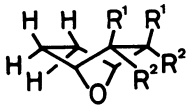
	endo-proton	exo-proton
7	1.9—2.2	1.4—1.7
9	1.9—2.2	1.4—1.7
11	1.9—2.1	1.6—1.8
12	1.4—1.6	1.7—1.9

Reduction of **7** and **9** with $LiAlH_4$ in tetrahydrofuran (THF) gave **8** (81%) and **10** (78%), respectively. High dilution condensation of **8** with triethylene glycol, tetraethylene glycol, and pentaethylene glycol ditosylate in dimethyl sulfoxide (DMSO)–1,2-dimethoxyethane (DME) in the presence of NaH gave **15** (22%), **16** (26%), and **17** (45%), respectively. Treatment of **10** with pentaethylene glycol ditosylate in high dilution conditions afforded **18** in 42% yield. The structures of these crown ethers were confirmed on the basis of their ^{1}H NMR and mass spectra as well as elemental analyses.

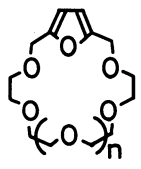
Double-armed crown ethers **19** and **20** containing the 18-crown-6 residue were also prepared from **8**. Treatment of **8** with 3,6-dioxaheptyl and 3,6,9-trioxadecyl *p*-toluenesulfonate in *N*,*N*-dimethylformamide (DMF) in the presence of NaH provided **19** (68%) and **20** (20%), respectively. Our attempts to prepare directly **19** from **1** by the Diels–Alder reaction of **1** with 2,5,8,13,16,19-hexaoxa-10-icosyne, prepared by condensation of 2-butyne-1,4-diol with 3,6-dioxaheptyl *p*-toluenesulfonate and KOBu^t in THF,



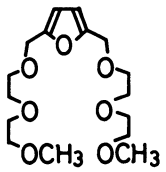
7 n=1 R=CO_2CH_3
8 n=1 R=CH_2OH
9 n=0 R=CO_2CH_3
10 n=0 R=CH_2OH



11 R^1=CO_2CH_3 R^2=H
12 R^1=H R^2=CO_2CH_3



1 n=1
2 n=0



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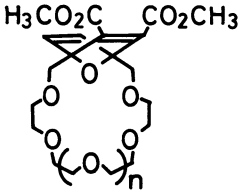
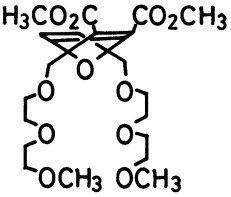


4 n=1
5 n=0



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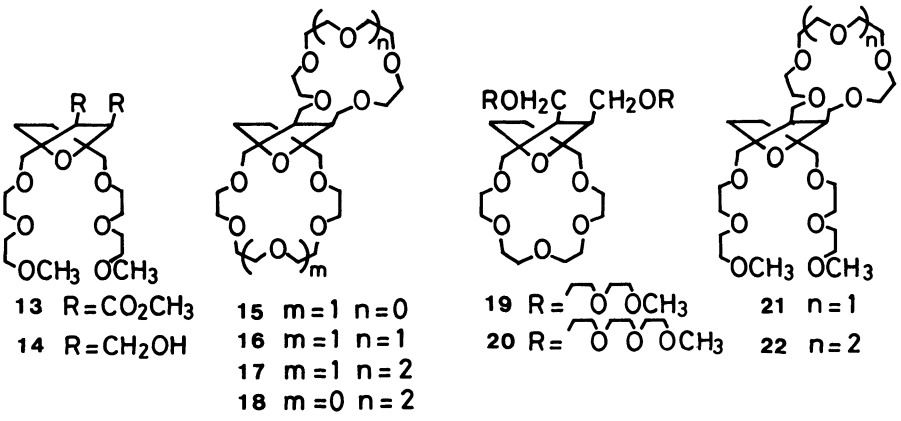

were unsuccessful, because the reaction did not give any Diels-Alder adduct.

We next turned our attention to the preparation of the other type of polyether that is O_7-monopodand[7] bound to a crown ether framework by two single bonds. A similar set of reactions described for **8** transformed the monopodand **3** into the key intermediate **14** (25% overall yield) via **6** and **13**. The structure of **13** was confirmed by its ^{1}H NMR spectrum exhibiting signals of the endo-protons at C5 and C6 at δ 2.0—2.2 and the exo-protons at δ 1.5—1.7. High dilution condensation of **14** with tetraethylene glycol and pentaethylene glycol ditosylate gave **21** (47%) and **22** (37%), respectively.

The cation-binding ability of these crown ethers was estimated by solvent extraction of aqueous solution of metal picrate with a chloroform solution containing crown ether, and the results are given in Table 2.

Among crown ethers described here, the bis-crown ether **16** containing the 18-crown-6 and the 17-crown-5 residue possesses the highest extractability towards all cations examined in this study, and both double-armed crown ethers **19** and **20** also exhibit higher extractabilities towards all cations than the parent 18-crown-6. However, in the case of the bis-crown ethers **15** and **17**, both of which contain also the 18-crown-6 residue, the additional crown ether framework contributes hardly to raise the extractability of the bis-crown ether.

Table 2. Extraction of Metal Picrates[a]

Host	Extractability/%					
	Li^+	Na^+	K^+	Rb^+	Cs^+	Ag^+
15	3.0	9.5	66.5	56.0	34.8	43.0
16	4.3	21.2	76.5	68.3	41.4	56.6
17	1.2	13.3	66.3	57.8	35.0	44.0
18	1.0	5.3	9.2	9.1	8.3	28.9
19	3.0	16.2	77.1	68.3	40.5	51.4
20	5.8	14.0	71.0	57.2	37.8	50.5
21	2.2	1.1	1.5	0	0	7.0
22	0	3.0	3.8	7.3	1.5	3.2
18-Crown-6	3.1	6.0	66.3	55.2	34.7	29.2

a) The solvent extraction was carried out according to the procedure reported in our preceding paper.[8]

Experimental

2,5-Bis(2,5,8-trioxanonyl)furan (3). To a suspension of potassium *t*-butoxide (11.2 g, 0.100 mol) in dry THF (300 mL) was added 2,5-bis(hydroxymethyl)furan[4] (3.84 g, 0.0300 mol) and then a solution of 3,6-dioxaheptyl *p*-toluenesulfonate (27.4 g, 0.100 mol) in dry THF (100 mL) was added to the reaction mixture. After the mixture was refluxed for 12 h, a solid was filtered off and the filtrate was condensed in vacuo. The residue was chromatographed on alumina (benzene eluent) to give **3** (4.06 g, 41% yield): bp 160—162 °C (0.02 mmHg (1 mmHg=133.322 Pa)). Found: C, 57.50; H, 8.41%. Calcd for $C_{16}H_{28}O_7$: C, 57.81; H, 8.49%.

18,19-Bis(methoxycarbonyl)-3,6,9,12,15,22-hexaoxatricyclo-[15.2.2.1^{1,17}]docosa-18,20-diene (4). A solution of **1**[4] (1.00 g, 3.50 mmol) and dimethyl 2-butynedioate (5.82 g, 41.0 mmol) in toluene (20 mL) was refluxed for 15 h. After evaporation of volatile materials, the residue was chromatographed on alumina ($CHCl_3$) to give **4** (1.06 g, 71%): mp 84—86 °C (lit,[4] mp 55—60 °C); ^{1}H NMR ($CDCl_3$) δ=3.5—3.9 (16H, m), 3.75 (6H, s), 4.15 (2H, d J=12 Hz), 4.31 (2H, d J=12 Hz), 6.99 (2H, s). Found: C, 55.88; H, 6.50%. Calcd for $C_{20}H_{28}O_{10}$: C, 56.07; H, 6.59%.

15,16-Bis(methoxycarbonyl)-3,6,9,12,19-pentaoxatricyclo-[12.2.2.1^{1,14}]nonadeca-15,17-diene (5). The diester **5** (1.31 g, 69%) was prepared from **2**[5] (1.20 g, 4.95 mmol) and dimethyl 2-butynedioate (7.10 g, 50.0 mmol) as an oil: ^{1}H NMR ($CDCl_3$) δ=3.5—3.9 (12H, m), 3.82 (6H, s), 4.08 (2H, d J=12 Hz), 4.42 (2H, d J=12 Hz), 7.03 (2H, s). Found: C, 55.92; H, 5.97%. Calcd for $C_{18}H_{24}O_9$: C, 56.24; H, 6.29%.

2,3-Bis(methoxycarbonyl)-1,4-bis(2,5,8-trioxanonyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene (6). The diester **6** (1.68 g, 41%) was prepared from **3** (2.86 g, 8.61 mmol) and dimethyl 2-butynedioate (12.2 g, 86.1 mmol) as an oil: ^{1}H NMR ($CDCl_3$) δ=3.35 (6H, s), 3.5—3.7 (16H, m), 3.75 (6H, s), 4.20 (4H, s), 7.03 (2H, s). Found: C, 55.05; H, 7.30%. Calcd for $C_{22}H_{34}O_{11}$: C, 55.68; H, 7.22%.

***cis*-18,19-Bis(methoxycarbonyl)-3,6,9,12,15,22-hexaoxatricyclo[15.2.2.1^{1,17}]docosane (7).** A mixture of **4** (2.85 g, 6.65 mmol) and methanol (70 mL) was shaken at room temperature with 10% Pd/C (390 mg) at 1 atm of hydrogen. After a usual workup, chromatography (Al_2O_3, benzene-$CHCl_3$ 1:1) gave **7** (2.27 g, 79%): mp 62—63 °C (hexane-benzene) ^{1}H NMR ($CDCl_3$) δ=1.4—1.7 (2H, m), 1.9—2.2 (2H, m), 3.5—3.7 (22H, m), 3.62 (6H, s). Found: C, 55.08; H, 7.44%. Calcd for $C_{20}H_{32}O_{10}$: C, 55.54; H, 7.46%.

***cis*-15,16-Bis(methoxycarbonyl)-3,6,9,12,19-pentaoxatricyclo[12.2.2.1^{1,14}]nonadecane (9).** The diester **9** (992 mg, 75%) was obtained from **5** (1.31 g, 3.41 mmol): mp 58—60 °C (hexane-benzene); ^{1}H NMR ($CDCl_3$) δ=1.4—1.7 (2H, m), 1.9—2.2 (2H, m), 3.66 (6H, s), 3.6—3.9 (18H, m). Found: C,

55.42; H, 7.24%; Calcd for $C_{18}H_{28}O_9$: C, 55.66; H, 7.27%.

***cis*-2,3-Bis(methoxycarbonyl)-1,4-bis(2,5,8-trioxanonyl)-7-oxabicyclo[2.2.1]heptane (13).** The diester **13** (1.20 g, 71%) was obtained from **6** (1.68 g, 3.54 mmol) as an oil after chromatography (Al_2O_3, benzene): ^1H NMR ($CDCl_3$) δ= 1.5—1.7 (2H, m), 2.0—2.2 (2H, m), 3.36 (6H, s), 3.37 (2H, s), 3.64 (6H, s), 3.5—3.8 (20H, m). Found: C, 55.03; H, 7.94%; Calcd for $C_{22}H_{38}O_{11}$: C, 55.24; H, 8.01%.

***cis*-18,19-Bis(hydroxymethyl)-3,6,9,12,15,22-hexaoxatricyclo[15.2.2.1^{1,17}]docosane (8).** A solution of **7** (800 mg, 1.85 mmol) in dry THF (40 mL) was added to a suspension of $LiAlH_4$ (220 mg, 5.80 mmol) in dry THF (40 mL) and the mixture was refluxed for 12 h. After a usual workup, chromatography on alumina ($CHCl_3$–methanol 20:1) gave **8** (563 mg, 81%) as a hygroscopic oil: ^1H NMR ($CDCl_3$) δ=1.54 (4H, s), 2.60 (2H, br s), 3.67 (2H, s), 3.5—3.9 (24H, m); MS *m/z* 376 (M^+).

***cis*-15,16-Bis(hydroxymethyl)-3,6,9,12,19-pentaoxatricyclo-[12.2.2.1^{1,14}]nonadecane (10).** The diol **10** (300 mg, 78%) was obtained from **9** (450 mg, 1.16 mmol) as a hygroscopic oil after chromatography on alumina ($CHCl_3$–methanol 100:1): ^1H NMR ($CDCl_3$) δ=1.51 (4H, s), 2.64 (2H, br s), 3.5—3.9 (20H, m), 3.88 (2H, s); MS *m/z* 332 (M^+).

***cis*-2,3-Bis(hydroxymethyl)-1,4-bis(2,5,8-trioxanonyl)-7-oxabicyclo[2.2.1]heptane (14).** The diol **14** (585 mg, 60%) was obtained from **13** (1.10 g, 2.30 mmol) as an oil after chromatography (Al_2O_3, $CHCl_3$): ^1H NMR ($CDCl_3$) δ=1.6—1.8 (4H, m), 2.58 (2H, br s), 3.37 (6H, s), 3.49 (2H, s), 3.5—3.8 (24H, m). Found: C, 56.38; H, 9.30%. Calcd for $C_{20}H_{38}O_9$: C, 56.85; H, 9.07%.

2,5,8,11,14,19,22,25,28,33-Decaoxatetracyclo[15.14.2.1^{1,16}.0^{17,30}]-tritriacontane (15). To a suspension of NaH (96 mg, 4.0 mmol) in 30 mL of DMSO–DME (1:3) was added **8** (486 mg, 1.30 mmol) and then the mixture was heated at 50 °C for 1 h. A solution of triethylene glycol ditosylate (595 mg, 1.30 mmol) in 60 mL of DMSO–DME (1:3) was added to the mixture at 50±5 °C over a 10 h period and the reaction mixture was heated at this temperature for an additional 30 h. After a small amount of water was added to the chilled reaction mixture, the solvent was evaporated in vacuo. The residue was extracted with $CHCl_3$. After a usual workup, chromatography on alumina ($CHCl_3$) gave **15** (140 mg, 22%) as an oil: ^1H NMR ($CDCl_3$) δ=1.68 (4H, br s), 2.50 (2H, br s), 3.4—3.8 (36H, m); MS *m/z* 490 (M^+). Found: C, 58.25; H, 8.49%. Calcd for $C_{24}H_{42}O_{10}$: C, 58.75; H, 8.63%.

4,7,10,13,16,21,24,27,30,33,37-Undecaoxatetracyclo-[17.15.2.1^{1,19}.0^{2,18}]heptatriacontane (16). Compound **16** (144 mg, 26%) was prepared from **8** (400 mg, 1.06 mmol) and tetraethylene glycol ditosylate (530 mg, 1.06 mmol) as an oil after chromatography (Al_2O_3, $CHCl_3$–methanol 50:1): ^1H NMR ($CDCl_3$) δ=1.73 (4H, br s), 2.23 (2H, br s), 3.3—3.9 (40H, m); MS *m/z* 534 (M^+). Found: C, 58.02; H, 8.60%. Calcd for $C_{26}H_{46}O_{11}$: C, 58.41; H, 8.67%.

4,7,10,13,16,19,24,27,30,33,36,40-Dodecaoxatetracyclo[20.15.2.1^{1,22}.0^{2,21}]tetracontane (17). Compound **17** (230 mg, 45%) was obtained from **8** (330 mg, 0.877 mmol) and pentaethylene glycol ditosylate (480 mg, 0.877 mmol) as an oil: ^1H NMR ($CDCl_3$) δ=1.67 (4H, br s), 2.44 (2H, br s), 3.3—3.9 (44H, m); MS *m/z* 578 (M^+). Found: C, 57.58; H, 8.65%. Calcd for $C_{28}H_{50}O_{12}$: C, 58.11; H, 8.71%.

4,7,10,13,16,19,24,27,30,33,37-Undecaoxatetracyclo[20.12.2.1^{1,22}.0^{2,21}]heptatriacontane (18). Compound **18** (204 mg, 42%) was obtained from **10** (300 mg, 0.903 mmol) and pentaethylene glycol ditosylate (500 mg, 0.914 mmol) as an oil: ^1H NMR ($CDCl_3$) δ 1.72 (4H, br s), 2.50 (2H, br s), 3.4—3.8 (40H, m); MS *m/z* 534 (M^+). Found: C, 57.72; H, 8.79%. Calcd for $C_{26}H_{46}O_{11}$: C, 58.41; H, 8.67%.

18,19-Bis(2,5,8-trioxanonyl)-3,6,9,12,15,22-hexaoxatricyclo[15.2.2.1^{1,17}]docosane (19). To a suspension of NaH (40 mg, 1.7 mmol) in dry DMF (10 mL) was added a solution of **8** (200 mg, 0.532 mmol) in dry DMF (10 mL). After the mixture was heated at 50±5 °C for 1 h, a solution of 3,6-dioxaheptyl *p*-toluenesulfonate (320 mg, 1.17 mmol) in DMF (10 mL) was added to the mixture and then it was heated at 50±5 °C for an additional 30 h. After a similar workup described for the preparation of **15**, chromatography (Al_2O_3, benzene–$CHCl_3$) provided **19** (210 mg, 68%) as an oil: ^1H NMR ($CDCl_3$) δ=1.70 (4H, br s), 2.48 (2H, br s), 3.36 (6H, s), 3.4-3.8 (40H, m); MS *m/z* 580 (M^+). Found: C, 57.47; H, 9.09%. Calcd for $C_{28}H_{52}O_{12}$: C, 57.91 H, 9.03%.

18,19-Bis(2,5,8,11-tetraoxadodecyl)-3,6,9,12,15,22-hexaoxatricyclo[15.2.2.1^{1,17}]docosane (20). Compound **20** (135 mg, 20%) was obtained from **8** (376 mg, 1.00 mmol) and 3,6,9-trioxadecyl *p*-toluenesulfonate (795 mg, 2.50 mmol) as an oil: ^1H NMR ($CDCl_3$) δ=1.68 (4H, br s), 2.45 (2H, br s), 3.32 (6H, s), 3.4—3.8 (48H, m); MS *m/z* 668 (M^+). Found: C, 56.72; H, 9.08%. Calcd for $C_{32}H_{60}O_{14}$: C, 57.46; H, 9.04%.

1,19-Bis(2,5,8-trioxanonyl)-4,7,10,13,16,22-hexaoxatricyclo-[17.2.1.0^{2,18}]docosane (21). Compound **21** (160 mg, 47%) was prepared from **14** (250 mg, 0.592 mmol) and tetraethylene glycol ditosylate (300 mg, 0.597 mmol) as an oil: ^1H NMR ($CDCl_3$) δ=1.70 (4H, br s), 2.50 (2H, br s), 3.38 (6H, s), 3.5—3.9 (40H, m); MS *m/z* 580 (M^+). Found: C, 57.06; H, 9.10%. Calcd for $C_{28}H_{52}O_{12}$: C, 57.91; H, 9.03%.

1,22-Bis(2,5,8-trioxanonyl)-4,7,10,13,16,19,25-heptaoxatricyclo[20.2.1.0^{2,22}]pentacosane (22). Compound **22** (164 mg, 37%) was obtained from **14** (300 mg, 0.710 mmol) and pentaethylene glycol ditosylate (390 mg, 0.710 mmol) as an oil: ^1H NMR ($CDCl_3$) δ=1.69 (4H, br s), 2.50 (2H, br s), 3.37 (6H, s), 3.5—3.9 (44H, m); MS *m/z* 624 (M^+). Found: C, 57.08; H, 8.97%. Calcd for $C_{30}H_{56}O_{13}$: C, 57.67; H, 9.04%.

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