October, 1985] © *1985 The Chemical Society of Japan* NOTES *Bull. Chem. Soc. Jpn., 58, 3057—3058 (1985)* 3057

# Synthesis of Chiral 18-Crown-6 Derivatives and Dibenzocrown Ethers Incorporating *trans*-Tetrahydrofuran-2,5-diylbis(methylene) Units of Known Absolute Configuration

Koichiro Naemura,* Iwao Ebashi, and Atsushi Matsuda
*Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560*

(Received May 22, 1985)

**Synopsis.** By using (−)-*trans*-2,5-bis(hydroxymethyl)-tetrahydrofuran (**1**) of known absolute configuration as a chiral diethylene glycol unit, 18-crown-6 derivatives **8**, **9**, **12**, and dibenzocrown ethers **14**, **15** containing *trans*-tetrahydrofuran-2,5-diylbis(methylene) unit were prepared in enantiomerically pure forms. Their abilities to extract alkali metal picrates were investigated.

A variety of crown ethers incorporating 2,5-disubstituted tetrahydrofuranocycle have been prepared. Most of them, however, were composed of achiral *cis*-tetrahydrofuran-2,5-diylbis(methylene) unit. Stoddart[1] prepared chiral 18-crown-6 derivative possessing *trans*-tetrahydrofuran-2,5-diylbis(methylene) unit by using 2,5-anhydro-D-mannitol. In our preceding paper,[2] we reported the synthesis of some dibenzo-18-crown-6 derivatives **16**, **17**, and **18** containing two *trans*-tetrahydrofuran-2,5-diylbis(methylene) units as a chiral diethylene glycol fragment. Here we describe the preparation of chiral 18-crown-6 derivatives **8**, **9**, and **12** containing one, two, and three *trans*-tetrahydrofuran-2,5-diylbis(methylene) units and chiral dibenzocrown ethers **14** and **15** incorporating the same unit, and the solvent extraction of alkali metal picrates with these crown ethers. Stereoisomers of **8** and **12** containing *cis*-tetrahydrofuran-2,5-diylbis(methylene) units have been prepared by Cram.[3]

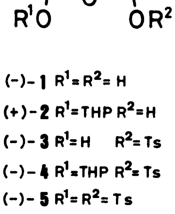
Condensation of (−)-**5**, obtained from (−)-(2*R*,5*R*)-2,5-bis(hydroxymethyl)tetrahydrofuran (**1**),[2] with tetraethylene glycol in THF and NaH provided a 42% yield of (−)-*trans*-tetrahydrofurano-18-crown-6 (**8**). Crown ether **9** composed of two tetrahydrofuranocycles was synthesized stepwise. Treatment of (−)-**5** with ethylene glycol mono(tetrahydropyranyl) ether in THF and NaH followed by acid hydrolysis gave (−)-**7** in 48% overall yield. The glycol **7** was condensed with (−)-**5** to provide a 12% yield of (−)-**9**. Crown ether **12** incorporating three tetrahydrofuranocycles was also prepared stepwise *via* the glycol **11**. Treatment of (−)-**1** with 1 equiv of 3,4-dihydro-2*H*-pyran gave (+)-**2**. Tosylation of (−)-**1** with 1 equiv of tosyl chloride gave the monotosylate **3** together with the ditosylate (−)-**5**, and tetrahydropyranylation of **3** provided (−)-**4**. Treatment of (+)-**2** with (−)-**4** and NaH gave (+)-**10**, hydrolysis of which afforded (−)-**11**. Condensation of (−)-**11** with (−)-**5** in DMSO–diethylene glycol dimethyl ether (diglyme) and NaH gave a 17% yield of (+)-**12**. Dibenzo-15-crown-5 derivative **14** and dibenzo-18-crown-6 derivative **15** were prepared *via* the common intermediate (+)-**13** which was obtained by condensation of (−)-**5** with pyrochatechol mono(tetrahydropyranyl) ether followed by acid hydrolysis. Treatment of (+)-**13** with ethylene glycol ditosylate in THF and KOBu$^t$ provided a 30% yield of (−)-**14**, and (+)-**15** was prepared in 60% yield by condensation of (+)-**13** with diethylene glycol ditosylate. The cation-binding ability of crown ethers was assessed by solvent extraction of aqueous solution of alkali metal picrate with chloroform solution containing crown ether. The results are summerized in Table 1.

Table 1. Extraction of alkali metal picrates[a)]

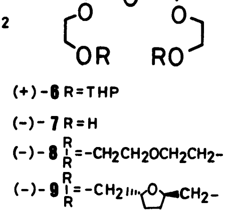
| Host | Extractability/% | | | |
|---|---|---|---|---|
| | Li$^+$ | Na$^+$ | K$^+$ | Cs$^+$ |
| **8** | 3 | 5 | 54 | 24 |
| **9** | 2 | 4 | 53 | 22 |
| **12** | 2 | 3 | 48 | 19 |
| 18-crown-6 | 3 | 6 | 66 | 33 |
| **14** | 1 | 10 | 16 | 3 |
| **15** | 0 | 16 | 42 | 7 |
| **16** | 0 | 15 | 38 | 10 |
| **17** | 0 | 20 | 46 | 7 |
| **18** | 0 | 23 | 36 | 8 |
| dibenzo-18-crown-6 | 0 | 3 | 35 | 7 |

a) The solvent extraction was carried out according to the procedure reported in our preceding paper.[4]

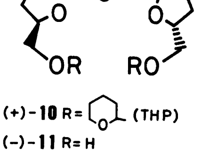
18-Crown-6 derivatives **8**,**9**, and **12** possess low extractabilities for alkali metal ions as compared with the parent 18-crown-6. The origin of the decrease in



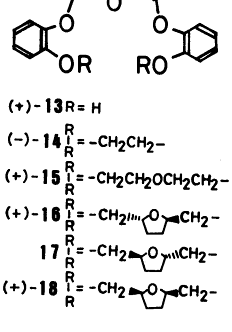
(−)-**1** R$^1$=R$^2$=H
(+)-**2** R$^1$=THP R$^2$=H
(−)-**3** R$^1$=H R$^2$=Ts
(−)-**4** R$^1$=THP R$^2$=Ts
(−)-**5** R$^1$=R$^2$=Ts



(+)-**6** R=THP
(−)-**7** R=H
(−)-**8** R–R=-CH$_2$CH$_2$OCH$_2$CH$_2$-
(−)-**9** R–R=



(+)-**10** R= (THP)
(−)-**11** R=H
(+)-**12** R–R=



(+)-**13** R=H
(−)-**14** R–R=-CH$_2$CH$_2$-
(+)-**15** R–R=-CH$_2$CH$_2$OCH$_2$CH$_2$-
(+)-**16** R–R=
**17** R–R=
(+)-**18** R–R=

extractabilities may be attributed to the restricted conformation of crown ether ring, resulting from incorporation of the constrained *trans*-2,5-disubstituted tetrahydrofuran moiety into the 18-crown-6 constitution. On the other hand, rather high extractabilities of dibenzo-18-crown-6 derivatives **15**—**18** are probably ascribed to the increased basicity of tetrahydrofuran oxygen atoms over ordinary crown ether oxygen atoms.

## Experimental

*(+)-(2R,5R)-2-Hydroxymethyl-5-(2-tetrahydropyranyloxymethyl)tetrahydrofuran (**2**).* Tetrahydrophyranylation of (−)-**1**[2] (4.50 g, 34.0 mmol) was carried out according to Parham's procedure[5] to give **2** (3.35 g, 46% yield), bp 120—125 °C (air-bath temp) (1 mmHg); $[\alpha]^{22}_{405}$+3.8° (*c* 0.798, EtOH). Found: C, 59.90; H, 9.28%. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32%.

*(−)-(2R,5R)-2-(2-Tetrahydropyranyloxymethyl)-5-(tosylmethyl)tetrahydrofuran (**4**).* Tosylation[2] of (−)-**1** (2.68 g, 20.3 mmol) with tosyl chloride (3.86 g, 20.3 mmol) in pyridine followed by chromatography on alumina gave (−)-**5** (2.05 g), $[\alpha]^{22}_{D}$ −10.8°[2] and **3** (1.31 g). Tetrahydropylanylation[4] of **3** (1.31 g) followed by chromatography (benzene eluent) provided **4** (1.33 g, 18% overall yield) as a liquid, $[\alpha]^{25}_{405}$ −4.2° (*c* 0.811, EtOH); MS *m/z* 370 ($M^+$).

*(−)-(5R,8R)-5,8-Epoxy-3,10-dioxadodecane-1,12-diol (**7**).* A mixture of ethylene glycol mono(tetrahydropyranyl) ether (2.32 g, 15.9 mmol) and NaH (760 mg, 31.8 mmol) in 50 mL of DMSO–diglyme (1/3 volume ratio) was stirred at 30—35 °C for 2.5 h under $N_2$ and then to the mixture was added a solution of (−)-**5** (3.50 g, 7.94 mmol), $[\alpha]^{22}_{D}$ −10.8°, in 25 mL of the same solvent. The mixture was stirred at 50—55 °C for further 24 h under $N_2$. After a usual workup, chromatography on alumina (benzene) gave (+)-**6** (1.69 g), $[\alpha]^{23}_{405}$ +4.6° (*c* 0.917, EtOH), acid hydrolysis of which in MeOH and *p*-toluenesulfonic acid[2] provided (−)-**7** (830 mg, 48% overall yield) as a liquid, $[\alpha]^{24}_{D}$ −18.8° (*c* 0.894, $CHCl_3$); MS *m/z* 220 ($M^+$).

*(−)-(15R,18R)-15,18-Epoxy-1,4,7,10,13-pentaoxacyclononadecane (**8**).* To a boiling suspension of NaH (720 mg, 30.0 mmol) in dry THF (180 mL) was added a solution of (−)-**5** (4.00 g, 9.08 mmol) and tetraethylene glycol (1.76 g, 9.08 mmol) in dry THF (270 mL) over a 22 h period under $N_2$. The mixture was refluxed for further 48 h. After a usual workup, alumina chromatography ($CHCl_3$) provided (−)-**8** (1.11 g, 42% yield) as a liquid, $[\alpha]^{22}_{D}$ −8.7° (*c* 0.963, $CHCl_3$); MS *m/z* 290 ($M^+$); $^1$H NMR ($CDCl_3$) $\delta$=1.45—2.05 (4H, m), 3.40—3.55 (4H, m), 3.69 (16H, t), 4.10—4.35 (2H, m). Found: C, 57.65; H, 9.01%. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03%.

*(−)-(6R,9R,16R,19R)-6,9:16,19-Diepoxy-1,4,11,14-tetraoxacycloeicosane (**9**).* Condensation of (−)-**7** (830 mg, 3.77 mmol) with (−)-**5** (1.66 g, 3.77 mmol) in DMSO–diglyme and NaH followed by alumina chromatography ($CHCl_3$) gave (−)-**9** (159 mg, 12% yield) as a viscous liquid, $[\alpha]^{25}_{D}$ −16.4° (*c* 0.825, $CHCl_3$); MS *m/z* 316 ($M^+$). Found: C, 60.65; H, 8.89%. Calcd for $C_{16}H_{28}O_6$: C, 60.74; H, 8.92%.

*(−)-(2R,5R,9R,12R)-2,5:9,12-Diepoxy-7-oxatridecane-1,13-diol (**11**).* Condensation of (+)-**2** (730 mg, 3.38 mmol) with (−)-**4** (1.25 g, 3.38 mmol) in DMSO–diglyme and NaH gave **10** (1.04 g), $[\alpha]^{24}_{405}$ +2.4° (*c* 0.639, EtOH). Hydrolysis of **10** (1.04 g) in MeOH and *p*-toluenesulfonic acid followed by chromatography (ether–MeOH 9:1) provided **11** (520 mg, 62% overall yield) as a liquid, $[\alpha]^{20}_{D}$ −3.7°(*c* 0.369, EtOH); MS *m/z* 246 ($M^+$). Found: C, 58.30; H, 8.91%. Calcd for $C_{12}H_{22}O_5$: C, 58.51; H, 9.00%.

*(+)-(3R,6R,10R,13R,17R,20R)-3,6:10,13:17,20-Triepoxy-1,8,15-trioxacyclohenicosane (**12**).* Condensation of (−)-**11** (457 mg, 1.85 mmol) with (−)-**5** (817 mg, 1.85 mmol) in DMSO–diglyme and NaH followed by alumina chromatography ($CHCl_3$) gave (+)-**12** (108 mg, 17% yield) as a viscous liquid, $[\alpha]^{22}_{405}$ −9.9° (*c* 0.527, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$=1.5—2.1 (12H, m), 3.45 (12H, d, *J*=5 Hz), 4.0—4.4 (6H, m); MS *m/z* 342 ($M^+$). Found: C, 62.95; H, 8.84%. Calcd for $C_{18}H_{30}O_6$: C, 63.13; H, 8.83%.

*(−)-(6R,9R)-2,3:12,13-Dibenzo-6,9-epoxy-1,4,11,14-tetraoxacyclohexadeca-2,12-diene (**14**).* Condensation of (+)-**13**[2] (1.00 g, 3.16 mmol), $[\alpha]^{22}_{D}$ +17.0°, with ethylene glycol ditosylate (980 mg, 6.32 mmol) in dry THF and KOBu$^t$ was carried out according to the procedure as described for **16**.[2] Chromatography on alumina (benzene) followed by recrystallization (hexane) provided (−)-**14** (322 mg, 30% yield), mp 107—108 °C; $[\alpha]^{20}_{D}$ −23.1° (*c* 0.755, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$=1.6—2.2 (4H, m), 4.0—4.2 (4H, m), 4.32 (4H, s), 4.60 (2H, br s), 6.90 (8H, s); MS *m/z* 342 ($M^+$). Found: C, 69.91; H, 6.49%. Calcd for $C_{20}H_{22}O_5$: C, 70.15; H, 6.48%.

*(+)-(6R,9R)-2,3:12,13-Dibenzo-6,9-epoxy-1,4,11,14-pentaoxacyclononadeca-2,12-diene (**15**).* A procedure similar to that for **16**[2] using (+)-**13** (1.50 g, 4.74 mmol) and diethylene glycol ditosylate (1.64 g, 3.95 mmol) gave (+)-**15** (1.11 g, 60% yield), mp 172—174 °C (hexane–benzene); $[\alpha]^{22}_{D}$ +7.0° (*c* 0.840, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$=1.75—2.40 (4H, m), 4.0—4.2 (12H, m), 4.60 (2H, br s), 6.82 (8H, s); MS *m/z* 386 ($M^+$). Found: C, 68.29; H, 6.64%. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78%.

## References

1) J. A. Haslegrave, J. F. Stoddart, and D. J. Thompson, *Tetrahedron Lett.*, **1979**, 2279.

2) M. Nakazaki, K. Naemura, M. Makimura, A. Matsuda, T. Kawano, and Y. Ohta, *J. Org. Chem.*, **47**, 2429 (1982).

3) J. M. Timko, S. S. Moore, D. M. Walba, P. C. Hiberty, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 4207 (1977).

4) K. Naemura, I. Ebashi, and M. Nakazaki, *Bull. Chem. Soc. Jpn.*, **58**, 767 (1985).

5) W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.*, **70**, 4187 (1948).