Proton-Ionizable Crown Compounds. 19. The Synthesis of Chiral Dialkyl-Substituted Triazolo-18-Crown-6 Macrocycles

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Four new chiral macrocyclic polyether ligands containing the proton-ionizable triazole subcyclic unit have been prepared. The triazolo-crowns contain two isopropyl, two isobutyl, two (*S*)-*sec*-butyl or two benzyl substituents on chiral macro ring carbon atoms. A racemic triazolo-18-crown-6 containing two (1-naphthoxy)methyl substituents was also prepared.

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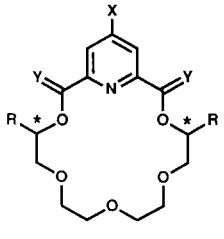
Introduction.

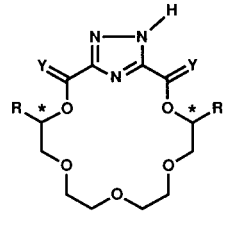
Proton-ionizable crown ethers have been the subject of many studies [1]. The crown ethers containing proton-ionizable groups are of interest because in the anion form they can neutralize positive cationic charge in metal complexation reactions. Often, cation-crown complex stability is increased when the crown is ionized [2]. Transport of cations through liquid membrane systems by proton-ionizable ligands is *p*H dependent so that transport can be turned on and off by adjusting the *p*H [3-5]. Other uses for the proton-ionizable crowns are given in a recent review [1].

We have been interested in the enantiomeric recognition of organic amines and ammonium salts by chiral macrocyclic ligands [6-10]. Non-proton-ionizable chiral pyridino-crowns **1-3** (see Figure 1) with methyl and phenyl substituents exhibited recognition for the enantiomers of α-(1-naphthyl)ethylammonium perchlorate and the methyl ester of phenylalaninium perchlorate as measured by a temperature dependent ^{1}H nmr technique and by titration calorimetry in methanol [6,7]. An X-ray crystallographic study of the complex of **1** with both enantiomers of α-(1-naphthyl)ethylammonium perchlorate showed that the methyl groups on the chiral macroring carbon atoms of (*S,S*)-**1** interacted sterically with one of the naphthalene hydrogen atoms in the (*S,S*)-**1**-salt complex [6,11]. In a more recent study, the chiral recognition of chiral crowns **1-3** and **6** for the enantiomers of α-(1-naphthyl)ethylammonium perchlorate were found to correlate well with energy differences calculated from empirical energy functions [10].

Figure 1. Macrocyclic Compounds



1, X = H; Y = O; R = CH_3 (S,S)
2, X = H; Y = H_2; R = CH_3 (S,S)
3, X = H; Y = O; R = C_6H_5 (R,R)
4, X = H; Y = H_2; R = $CH(CH_3)_2$ (R,R)
5, X = H; Y = H_2; R = $CH_2CH(CH_3)_2$ (R,R)
6, X = H; Y = H_2; R = $CH(CH_3)C_2H_5$ (R,R)
7, X = H; Y = H_2; R = $CH_2C_6H_5$ (R,R)
8, X = OH; Y = O; R = CH_3 (S,S)
9, X = OH; Y = O; R = C_6H_5 (R,R)



10, Y = O; R = CH_3 (S,S)
11, Y = H_2; R = CH_3 (S,S)
12, Y = H_2; R = $CH(CH_3)_2$ (R,R)
13, Y = H_2; R = $CH_2CH(CH_3)_2$ (R,R)
14, Y = H_2; R = $CH(CH_3)C_2H_5$ (R,R)
15, Y = H_2; R = $CH_2C_6H_5$ (R,R)
16, Y = H_2; R = CH_2O-1-Nap

Chiral proton-ionizable 4-hydroxypyridino-crowns **8** and **9** also exhibited chiral recognition for the enantiomers of various organic ammonium salts [9]. It is interesting to note that the 4-hydroxypyridine unit of **8** and **9** is acidic enough to allow these crowns to form complexes with amines wherein the amine becomes an ammonium cation and a negative charge resides in the oxypyridine moiety. Thus, chiral ligands **8** and **9** exhibited chiral recognition for the enantiomers of α-(1-naphthyl)ethylamine. Proton-ionizable **10** with an acidic triazole group likewise exhibited chiral recognition for the enantiomers of α-(1-naphthyl)ethylamine [8].

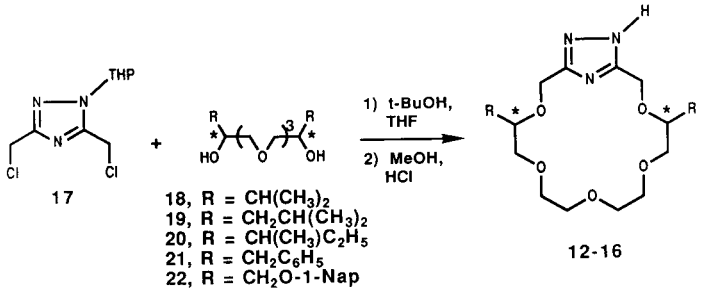
This paper describes the synthesis of triazolo-crowns **12-16**. Chiral recognition of the enantiomers of organic amine salts by **12-15** is currently under investigation.

Results and Discussion.

Chiral crowns **12-15** and *bis*-1-naphthoxymethyl-substituted crown **16** were prepared by the reaction of dichloride **17** [12] and the appropriate chiral dialkyltetraethylene glycol, **18-22** (see Scheme I). These macrocycles were difficult to purify. The crude maroon-colored reaction mixture was extracted with *n*-heptane by a continuous extraction for 36 hours except for crown **15**. The dark oil that was left when the solvent was removed was passed through a thick pad of basic alumina to give the THP-blocked cyclic product. After the resulting oil was deprotected in methanol and hydrochloric acid, the product was

chromatographed using preparative hplc on a C_{18}-reverse phase column using 15% water in methanol as the solvent except for crown **15** which was carefully purified on neutral alumina. The most difficult to remove impurity was the 2:2 cycloaddition product. These latter by-products were not isolated. The structures proposed for the new macrocycles are consistent with data obtained from their ir and ^{1}H nmr spectra and combustion analyses.

Scheme I. Preparation of Chiral Triazolo-18-Crowns

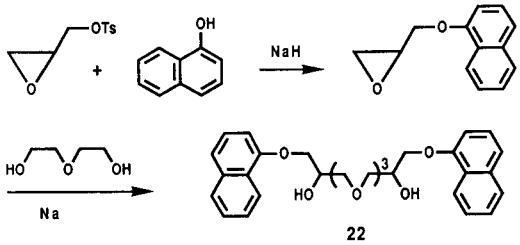


18, R = $CH(CH_3)_2$
19, R = $CH_2CH(CH_3)_2$
20, R = $CH(CH_3)C_2H_5$
21, R = $CH_2C_6H_5$
22, R = CH_2O-1-Nap

The starting chiral tetraethylene glycols containing two isopropyl, **18**, two isobutyl, **19**, two (*S*)-*sec*-butyl, **20**, or two benzyl, **21** groups (see Scheme I) were prepared as reported [10] from the reaction of the appropriate chiral alkyl-substituted ethylene oxide [13,14] and diethylene glycol containing a catalytic amount of sodium. The *bis*-1-naphthoxymethyl-substituted tetraethylene glycol **22** was prepared as shown in Scheme II. The 1-naphthyl glycidyl ether was prepared in optically active form by Sharpless and his coworkers [15].

Enantiomeric recognition for the organic ammonium salts by these new chiral triazolo ligands has not been studied. Results of this work will be reported when finished.

Scheme II. Preparation of Bis-1-naphthoxymethyl Tetraethylene Glycol (22)



EXPERIMENTAL

Infrared (ir) spectra were obtained on Matson Sirius or Perkin Elmer 1600 FTIR Spectrometers. The proton magnetic resonance (^{1}H nmr) spectra were obtained on a Varian Gemini 200 spectrometer using deuteriochloroform as the solvent. Molecular weights were determined by the electron impact method on a Finnegan 8430 High Resolution Mass Spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Optical rotations were obtained on a Perkin Elmer 241 polarimeter. Starting chiral glycols **18-21** were prepared as reported [10].

Preparation of 1,13-*Bis*(1-naphthoxy)-4,7,10-trioxatetradecane-2,12 diol (**22**) (Scheme II).

Glycidyl tosylate was first prepared from glycidol and tosyl chloride as reported [15]. Optically active glycidyl tosylate can be purchased from Aldrich. 1-Naphthol (9.96 g, 0.07 mole) in 100 ml of anhydrous DMF was slowly added to a mixture of 3.2 g (0.08 mole) of hexane washed sodium hydride (60% dispersion in oil) in 75 ml of anhydrous DMF in a 500 ml three-necked round bottom flask under a nitrogen atmosphere. This mixture was stirred at room temperature for 15-20 minutes and formed a green sludge. Glycidyl tosylate (15.0 g, 0.066 mole) was added to the sludge *via* a cannula and the mixture was stirred at room temperature for 20 hours. The brown reaction mixture was then poured onto 300 ml of crushed ice. This mixture was washed with three 250 ml portions of ether. The combined ether phases were washed with 200 ml of water then 200 ml of saturated brine solution. The ether phase was then dried over anhydrous magnesium sulfate, filtered and evaporated to leave a brown liquid. This liquid was evaporated under high vacuum to remove the remaining DMF. The resulting oil was purified using preparative hplc (ethyl acetate/hexane:1/9) to give 10.0 g of glycidyl 1-naphthyl ether as a yellow oil; ^{1}H nmr: δ 8.28 (m, 1H), 7.76 (m, 1H), 7.60-7.30 (m, 4H), 6.80 (dd, 1H), 4.48-4.04 (m, 2H), 3.50 (m, 1H), 2.90 (m, 2H); ir (neat): 3500, 3100, 1570, 1500, 1460, 1390, 1265, 1095, 850 cm^{-1}.

Diethylene glycol (2.13 g, 0.02 mole) and a catalytic amount of sodium metal were placed in an oven dried 250 ml three-necked round bottom flask equipped with a 125 ml addition funnel, nitrogen inlet, magnetic stirring bar, and a dry ice/isopropyl alcohol or acetone condenser. This mixture was heated to between 90° and 100° and the sodium was dissolved. Glycidyl 1-naphthyl ether (8.0 g, 0.04 mole) was added over a period of 1.5 hours. The reaction mixture was stirred for 22 hours at 100°, cooled to room temperature and sodium bicarbonate was added to neutralize the base. Ethyl ether (100 ml) was added to the cooled mixture and the solution was extracted with 150 ml of 10% brine solution. The brine solution was then washed with two 200 ml portions of ether. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and evaporated to leave a brown oil. This oil was chromatographed twice on silica gel using ethyl acetate/hexane:2/8 and ethanol/ethyl acetate/toluene:1/1/8 as eluants to give 6.2 g (61%) of **22** as a yellow oil; ^{1}H nmr: δ 8.2 (m, 2H), 7.74 (m, 2H), 7.41 (m, 8H), 6.77 (m, 2H), 4.19 (m, 8H), 3.71 (m, 2H); ms m/e 506. This material was used without further purification to prepare **16**.

General Procedure for the Preparation of the Triazolo-Crowns.

Dry tetrahydrofuran (THF) (300 ml) was placed in an oven dried three-necked round bottom flask equipped with a magnetic stirring bar, condenser, two addition funnels and a nitrogen gas inlet. In one addition funnel was placed the 2,5-*bis*-(chloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4-triazole (**17**) [12] in dry THF ($\leq$0.1 molar solution). In another addition funnel was placed 1 equivalent of the appropriate chiral oligoethylene glycol and 2.2 equivalents of fresh potassium *t*-butoxide in a like amount of dry THF. These two solutions were added simultaneously over a period of 2-4 hours to the refluxing THF in the flask. This mixture was refluxed for 24-48 hours under nitrogen gas. The reaction was checked by tlc for the disappearance of the starting glycol and dichloride. When the reaction was complete the mix-

ture was cooled to room temperature, filtered, and the solvent was evaporated leaving a maroon oil. The crude oil was extracted with heptane using a continuous liquid-liquid extraction apparatus for 24-36 hours. The resulting oil was run through a thick pad of basic alumina using an appropriate solvent system. The resulting clear to slightly yellow oil was deprotected using methanolic hydrogen chloride for about 1 hour at room temperature. After evaporation of the methanol, the solution was neutralized with aqueous sodium bicarbonate and the product was extracted into dichloromethane. The organic phase was dried over anhydrous magnesim sulfate, filtered, and the solvent evaporated to leave a yellow oil. The oil was chromatographed using preparative hplc on a C_{18}-reverse phase column with methanol:water as the eluent. Specific details are given for each macrocycle.

(4*R*,14*R*)-*Bis*(isopropyl)-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1(19),17-diene (**12**).

The general procedure to prepare triazole crowns was followed to make compound **12** using 7.03 g (0.025 mole) of **18**, 6.52 (0.058 mole) of potassium *t*-butoxide and 6.30 g (0.025 mole) of **17** to give an orange oil (2.23 g, 24%); ^{1}H nmr: δ 4.79 (m, 4H), 3.56 (bm, 14H), 1.88 (m, 2H), 0.94 (d, 6H), 0.90 (d, 6H); $[\alpha]_D^{20} = -51.63°$ (c = 0.1160, chloroform).

Anal. Calcd. for $C_{18}H_{33}N_3O_5$: C, 58.20; H, 8.95; M^+ 371.47. Found: C, 58.05; H, 8.91; M^+ 371.

(4*R*,14*R*)-*Bis*(isobutyl)-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1(19),17-diene (**13**).

Compound **13** was prepared as described above using 9.2 g (0.03 mole) of **19**, 8.55 g (0.076 mole) of potassium *t*-butoxide, and 7.50 g (0.03 mole) of **17** to give 2.5 g (21%) of **13**; ^{1}H nmr: δ 4.87 (bm, 2H), 4.72 (bm, 2H), 3.63 (bm, 12H), 3.44 (m, 2H), 1.72 (bm, 2H), 1.42 (sept, 2H), 1.23 (bm, 2H), 0.90 (d, 12H); $[\alpha]_D^{20} = -22.25°$ (c = 0.0519, chloroform).

Anal. Calcd. for $C_{20}H_{37}N_3O_5$: C, 60.13; H, 9.33; M^+ 399.52. Found: C, 59.95; H, 9.26; M^+ 399.

(4*R*,14*R*)-*Bis*[(2*S*)-*sec*-butyl]-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1(19),17-diene (**14**).

Crown **14** was prepared as described above using 9.22 g (0.03 mole) of **20**, 9.13 g (0.081 mole) of potassium *t*-butoxide, and 7.52 g (0.03 mole) of **17** to give 2.4 g (20%) of a yellow oil; ^{1}H nmr: δ 4.9 (m, 2H), 4.7 (m, 2H), 3.6 (m, 14H), 1.6 (b, 2H), 0.9 (m, 16H); $[\alpha]_D^{20} = -39.58°$ (c = 0.1031, chloroform).

Anal. Calcd. for $C_{20}H_{37}N_3O_5$: C, 60.13; H, 9.33; M^+ 399.53. Found: C, 59.89; H, 9.10; M^+ 399.5.

(4*R*,14*R*)-*Bis*(benzyl)-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo-[15.2.1]eicosa-1(19),17-diene (**15**).

Crown **15** was prepared as described above using 1.88 g (0.005 mole) of **21**, 1.25 g (0.005 mole) of **17** and 1.5 g (0.013 mole) of potassium *t*-butoxide. After the reaction mixture was evaporated, the residue was mixed with few grams of neutral alumina. This material was put on the top of a neutral alumina column and the material was eluted with toluene/ethanol:50/1 to give a yellow oil. The crown was deprotected as above and purified using neutral alumina (toluene/ethanol:25/1) to give 0.45 g (20%) of a yellow oil; ^{1}H nmr: δ 7.2 (m, 10H), 4.7 (m, 4H), 3.85 (m, 2H), 3.5 (m, 14H), 2.8 (m, 4H); $[\alpha]_D^{20} = -17.65°$ (c = 3.4, benzene).

Anal. Calcd. for $C_{26}H_{33}N_3O_5$: C, 66.76; H, 7.11; M^+ 467.745. Found: C, 66.81; H, 7.18; M^+ 467.

4,14-*Bis*(1-napthoxymethyl)-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1(19),17-diene (**16**).

Crown **16** was prepared as described above using 4.41 g (8.7 mmoles) of glycol **22**, 2.17 g (8.7 mmoles) of **17** and 2.18 g (19.4 mmoles) of potassium *t*-butoxide. The liquid-liquid extraction process was not used. The material was dissolved in a small amount of toluene and injected onto a preparative hplc using 20% water in methanol. The product was obtained as a white glass (0.5 g, 9.6%); ^{1}H nmr: δ 8.3 (m, 2H), 7.82 (m, 2H), 7.45 (m, 8H), 6.8 (m, 2H), 5.2 (m, 4H), 4.25 (m, 6H), 3.75 (m, 12H).

Anal. Calcd. for $C_{34}H_{37}N_3O_7$: C, 68.09; H, 6.22; M^+, 599.68. Found: C, 67.88; H, 6.46; M^+, 600; M + 1, 601.

Acknowledgement.

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REFERENCES AND NOTES

[1] For a review, see C. W. McDaniel, J. S. Bradshaw and R. M. Izatt, *Heterocycles*, **30**, 665 (1990).

[2] R. A. Bartsch, W. A. Charewicz, S. I. Kang and W. Walkowiak, *ACS Symp. Ser., 347 (Liq. Membr.)*, 86 (1987).

[3] C. A. Chang, J. Twu and R. A. Bartsch, *Inorg. Chem.*, **25**, 396 (1986).

[4] A. Hriciga and J.-M. Lehn, *Proc. Natl. Acad. Sci. USA*, **80**, 6426 (1983).

[5] R. M. Izatt, G. C. Lindh, G. A. Clark, Y. Nakatsuji, J. S. Bradshaw, J. D. Lamb and J. J. Christensen, *J. Membr. Sci.*, **31**, 1 (1987).

[6] R. B. Davidson, J. S. Bradshaw, B. A. Jones, N. K. Dalley, J. J. Christensen, R. M. Izatt, F. G. Morin and D. M. Grant, *J. Org. Chem.*, **49** 353 (1984).

[7] J. S. Bradshaw, P. K. Thompson, R. M. Izatt, F. G. Morin and D. M. Grant, *J. Heterocyclic Chem.*, **21**, 897 (1984).

[8] J. S. Bradshaw, D. A. Chamberlin, P. E. Harrison, B. E. Wilson, G. Arena, N. K. Dalley, J. D. Lamb, R. M. Izatt, F. G. Morin ad D. M. Grant, *J. Org. Chem.*, **50**, 3065 (1985).

[9] J. S. Bradshaw, M. L. Colter, Y. Nakatsuji, N. O. Spencer, M. F. Brown, R. M. Izatt, G. Arena, P.-K. Tse, B. E. Wilson, J. D. Lamb, N. K. Dalley, F. G. Morin and D. M. Grant, *J. Org. Chem.*, **50**, 4865 (1985).

[10] J. S. Bradshaw, P. Huszthy, C. W. McDaniel, C. Y. Zhu, N. K. Dalley, R. M. Izatt and S. Lifson, *J. Org. Chem.*, **55**, 3129 (1990).

[11] R. B. Davidson, N. K. Dalley, R. M. Izatt, J. S. Bradshaw and C. F. Campana, *Israel J. Chem.*, **25**, 33 (1985).

[12] J. S. Bradshaw, R. B. Nielsen, P.-K. Tse, G. Arena, B. E. Wilson, N. K. Dalley, J. D. Lamb, J. J. Christensen and R. M. Izatt, *J. Heterocyclic Chem.*, **23**, 361 (1986).

[13] B. Koppenhoefer and V. Schurig, *Org. Synth.*, **66**, 151 (1987).

[14] B. Koppenhoefer and V. Schurig, *Org. Synth.*, **66**, 160 (1987).

[15] J. M. Klunder, S. Y. Ko and K. B. Sharpless, *J. Org. Chem.*, **51**, 3710 (1986).