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SYNTHESIS OF NOVEL CROWN ETHERS BEARING THE *exo-cis*-2,3-NORBORNYL GROUP AS POTENTIAL Na^+ AND K^+ EXTRACTANTS

Rachel M. Robeson and Peter Bonnesen

ABSTRACT

The synthesis of a series of novel dinorbornyl-16-crown-5 and dinorbornyl-18-crown-6 ethers that incorporate the *exo-cis*-2,3-norbornyl moiety within the macrocycle framework is described. The key starting material for the crown ethers, *exo-cis*-2,3-norbornanediol, was successfully prepared on a large (>30g) scale in 88% yield from norbornylene by osmium tetroxide-catalyzed hydroxylation. The *syn* and *anti* isomers of the dinorbornyl-16-crown-5 ether family were prepared using diethylene glycol with ring closure achieved using a methallyl linkage. The isomers *cis-syn-cis* and *cis-anti-cis* di-norbornano-15-methyleno-16-crown-5 (**6A** and **6B**) could be separated using column chromatography, and a single crystal of the *syn* isomer **6A** suitable for X-ray crystal structure analysis was obtained, thereby confirming the *syn* orientation. The *syn* and *anti* isomers of the dinorbornyl-18-crown-6 ether family were successfully prepared employing a different synthetic strategy, involving the potassium–templated cyclization of two *bis*-hydroxyethoxy-substituted *exo-cis*-2,3-norbornyl groups under high dilution conditions. Attempts to fully separate *cis-syn-cis* di-norbornano-18-crown-6 (**10A**) and *cis-anti-cis* di-norbornano-18-crown-6 (**10B**) from one another using column chromatography were unsuccessful. All intermediates and products were checked for purity using either thin layer chromatography or gas chromatography, and characterized by proton and carbon NMR. Crown ethers **6AB** and **10AB** are to our knowledge the first crown ethers to incorporate the *exo-cis*-2,3-norbornyl moiety into the crown ring to be successfully synthesized and characterized.

INTRODUCTION

The ability to coordinate and mobilize sodium (Na^+) and potassium (K^+) ions is of great interest and importance in areas as diverse as medical applications, industrial processes, and even nuclear waste remediation. Ever since the discovery by Charles Pedersen in 1967 [1] that cyclic polyethers or "crown ethers" have the ability to effectively complex metal cations (see Figure 1 for examples) there have been tremendous research efforts aimed at understanding and controlling the factors that influence both the metal-ion binding strength and the selectivity. Among these factors are the basicity of the ether oxygens, the size and shape of the crown cavity, and the degree of "preorganization" of the cavity. As observed by Cram [2], preorganization can reduce conformational changes that occur during metal ion complexation, thereby increasing metal ion binding strength.

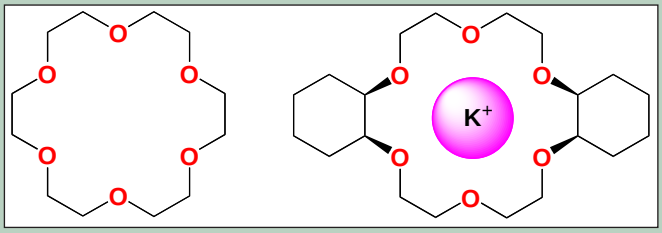
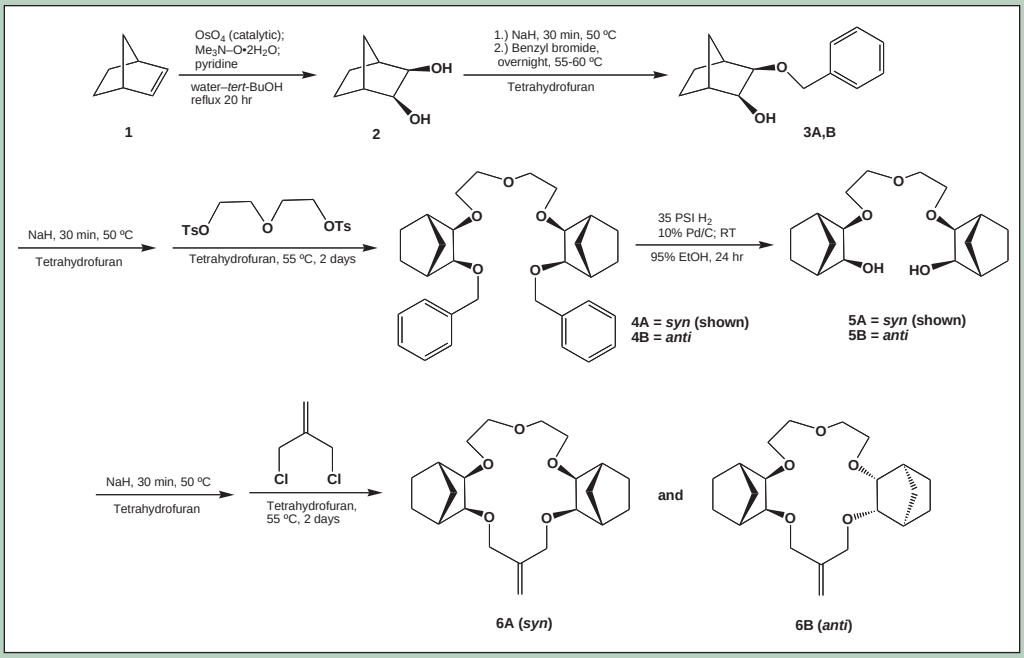


Figure 1. Two examples of crown ethers: on the left 18-crown-6, on the right, a representation of potassium complexed by *cis-syn-cis*-diclohexano-18-crown-6.



Scheme 1. Synthetic route to *cis-syn-cis*- and *cis-anti-cis*-di-norbornano-15-methyleno-16-crown-5.

At ORNL there is interest in developing a novel class of crown ethers with enhanced binding strength for Na^+ (and to a lesser extent for K^+), for use in nuclear waste remediation applications, though it is anticipated such crown ethers would find many other important uses. In the nuclear waste application, the objective was to develop lipophilic crown ethers that could be used in solvent extraction processes for the removal of sodium and potassium hydroxide and nitrate, which could then be potentially recycled for use in other processes. Previous research demonstrated that the crown ether *cis-syn-cis*-dicyclohexano-18-crown-6 (DCH18C6), in combination with lipophilic phenols or fluorinated alcohols, could be used to enhance extraction of sodium hydroxide [3]. However, crown ethers that are more preorganized for sodium would be expected to possess higher binding strength for sodium, and accordingly could be far more effective than DCH18C6. One way preorganization might be enhanced is by rigidifying the ether oxygens, and molecular modeling has suggested that use of *exo-cis*-norbornanediol, in which both oxygens are exo to the bridgehead and are more rigidly directed toward the center of a binding cavity with a radius specific to that of the Na^+ ion, may confer higher binding strength than the more flexible *cis*-1,2-cyclohexanediol moiety that is present in DCH18C6. Accordingly, for the first time, a series of 16-crown-5 and 18-crown-6 ethers incorporating the *exo-cis*-norbornanediol moiety have been synthesized, and their preparation is described.

MATERIALS AND METHODS

General

All solvents and chemical reagents were used as received without further purification, with the exception of *p*-tosyl chloride, which was purified as described by Peletier [4]. Sodium hydride was used as a 57% dispersion in mineral oil. Diethyleneglycol ditosylate was previously prepared following the procedure described by Ouchi et al [5]. Ozonolysis was performed using an OZONOLOGY Ozone Generator. A Hewlett Packard 6850 gas chromatograph was used for all GC analyses. Proton and carbon (proton decoupled) NMR spectra were obtained in $CDCl_3$, unless otherwise noted (acetone-d6), on a Bruker Avance DRX 400MHz spectrometer. Proton chemical shifts (See Table 1) were referenced to internal tetramethylsilane, and carbon chemical shifts to the solvent peaks (77.0ppm for $CDCl_3$, or 29.8ppm for acetone-d6).

Synthesis of cis-syn-cis and cis-anti-cis di-norbornano-15-methyleno-16-crown-5 (6AB)

The synthesis was performed as outlined in Scheme 1 and as described below.

Exo-cis-2,3-norbornanediol (2)

Norbornylene (28.26g, 0.300mol), trimethylamine N-oxide dihydrate (45.01g, 0.405mol), pyridine (25.4g), *tert*-butanol (300mL), and water (200mL) were added to a 3-neck 1-L round bottom flask equipped with an addition funnel containing a solution of OsO_4 (0.23g, 0.90mmol) in *tert*-butanol [6]. The OsO_4 solution was slowly added to the reaction mixture at room temperature with constant stirring. The reaction mixture was then refluxed for ~19 hours at 100°C. The reaction was allowed to cool to room temperature whereupon 20% aqueous sodium bisulfite (160mL) solution was added with stirring followed by *in vacuo* removal of *tert*-butanol. A solution of saturated sodium chloride (200mL) was added to the reaction mixture, which was then extracted with diethyl ether (3 x 300mL). The combined ether extracts were dried over anhydrous Na_2SO_4 and the solution concentrated and placed in the refrigerator overnight, affording a first crop of **2** (15.5g) as highly pure white crystalline flakes (≥99% by GC) suitable for subsequent reaction. MP 139–140°C (lit [6] 139.5–140.5°C). An additional 18.4g of material of ~98% purity by GC with slightly lower melting point can be obtained from the filtrate, affording a combined yield of 33.9g (88%).

Bicyclo[2.2.1]-3-benzyloxy-2-heptanol (3AB)

Exo-cis-2,3-norbornanediol (10.0g, 78.0mmol) was dissolved in 200mL dry THF in a 1-L 3-neck round bottom flask under argon. Sodium hydride (3.61g, 85.8mmol) was added to the stirred contents using a Merlic-type solid addition funnel, and the solution warmed to 50°C and stirred for 30 minutes. A solution of benzylbromide (12.0g, 70.2mmol) in dry THF (200mL) was then added dropwise to the stirred contents under argon at 50°C. The progress of the reaction was followed by TLC using a mixture of ethyl acetate and hexanes (1:9) and GC. After 16 hours at 50°C the reaction was judged complete. After cooling, excess sodium hydride was hydrolyzed by slow addition of methanol. The solvents were then removed *in vacuo*, and the crude product oil purified by silica gel (70/230 mesh) chromatography to afford racemic **3** as a pale yellow oil (6.3g, 45%). ^{1}H NMR: δ 0.89–1.07 (m, 3H), 1.40–1.42 (m, 2H), 1.77 (d, 1H, *J*= 10 Hz), 2.14 (s, 1H), 2.24 (s, 1H), 3.38–3.41 (m, 2H), 3.67 (s, 1H), 4.51–4.60 (m, 2H), 7.26–7.30 (m, 5H). ^{13}C NMR: δ 23.88, 24.40, 31.76, 39.32, 42.86, 72.19, 74.64, 81.79, 127.26, 127.43, 128.10, 137.59.

Di(ethylene glycol) di(exo-3-benzyloxy-exo-2-bicyclo [2.2.1] heptyl) ether (4AB)

To a solution of **3AB** (5.70g, 26.1mmol) in dry THF (50mL) was added sodium hydride (1.265g, 30.0mmol) under argon, and the reaction warmed to 50°C with stirring for 30 minutes. A solution of diethyleneglycol ditosylate (4.99g, 12.0mmol) in dry THF (50mL) was added dropwise under argon over 10 minutes to the stirred reaction mixture at 55–60°C, and heating continued at 55–60°C for two days, during which the reaction's progress was monitored by TLC using ethylacetate and hexanes (1:3). After 2 days the reaction was judged complete, and after cooling, the reaction mixture was treated with a few mL of 95% ethanol. Solvents were evaporated *in vacuo*, and the residue was extracted into 100mL of dichloromethane, washed with 0.1M HCl (50mL) and brine (50mL), and dried over anhydrous Na_2SO_4. The solvents were then removed *in vacuo*, and the crude product oil purified by silica gel (70/230 mesh) chromatography to afford **4AB** as a clear oil (3.594g, 59%). ^{1}H NMR: δ 0.94–1.06 (m, 6H), 1.40–1.44 (m, 4H), 1.89–1.92 (m, 2H), 2.25 (s, 4H), 3.36-3.43 (m, 4H), 3.59-3.65 (m, 8H), 4.51–4.63 (m, 4H), 7.23–7.37 (m, 10H). ^{13}C NMR: δ 24.68, 24.80, 32.97, 40.26, 40.45, 69.89, 70.68, 72.13, 83.00, 84.66, 127.58, 17.92, 128.39, 139.10.

Diethylene glycol di(exo-3-hydroxy-exo-2-bicyclo [2.2.1] heptyl) ether (5AB)

To a solution of **4AB** (3.594g, 7.09mmol) in 95% ethanol (35mL) in an Ace-threaded hydrogenation vessel, 10% Pd/C catalyst (700mg) was added. The solution was placed on a Parr shaker and was hydrogenated under 35 PSI hydrogen for 6 hours, after which additional catalyst (110mg) was added before continuing with the hydrogenation for another 19 hours. The catalyst was removed by filtration through Celite, and the filtrate was diluted with dichloromethane (75mL), and washed with 0.1M HCl (75mL), water (50mL), and dried over anhydrous Na_2SO_4. Removal of the solvents afforded 1.87g (81%) of **5AB** that was sufficiently pure as judged by NMR to use without further purification. ^{1}H NMR: δ 0.99–1.07 (m, 6H), 1.42-1.45 (m, 4H), 1.76-1.78 (m, 2H), 2.14–2.21 (m, 4H), 3.33–3.35 (m, 2H), 3.60–3.85 (m, 12H). ^{13}C NMR: δ 24.00, 24.75, 31.98, 40.00, 40.14, 42.95, 42.97, 69.95, 70.03, 70.26, 70.29, 74.96, 75.02, 83.30, 83.39.

Cis-syn-cis- and cis-anti-cis-di-norbornano-15-methyleno-16-crown-5 (6AB)

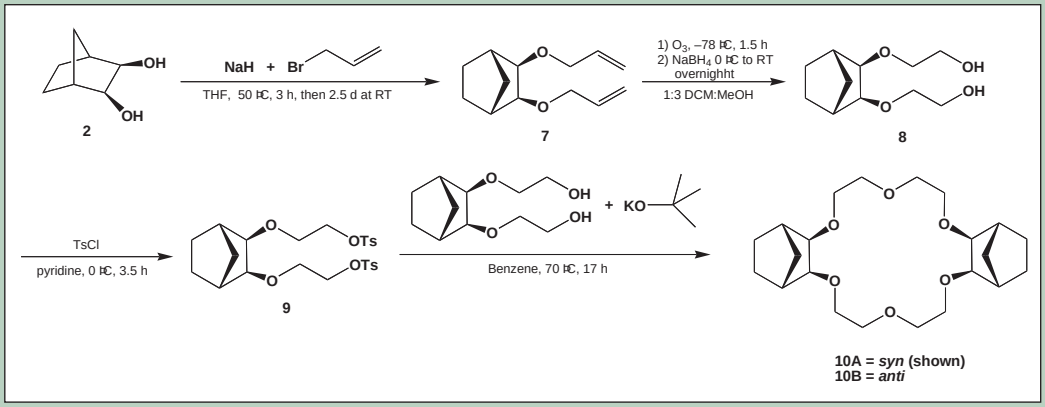
To a solution of **5AB** (1.87g, 5.7mmol) in dry THF (200mL) sodium hydride (0.607g, 14.3mmol) was added under argon at room temperature. The reaction mixture was warmed to ~50° C and stirred for 30 minutes, after which a solution of methallyl dichloride (0.82g, 6.6mmol) in dry THF (100mL) was slowly added dropwise over the course of an hour. The reaction mixture was heated at 55–60°C for two days, during which the reaction's progress was monitored by TLC using ethylacetate and hexanes (1:3), and GC. After 2 days the reaction was judged complete, and after cooling and treatment with a few mL of 95% ethanol, the mixture was diluted with dichloromethane (200mL), washed with 0.1M HCl (200mL), and water (200mL), and dried (anhydrous Na_2SO_4). Removal of the solvents *in vacuo* afforded the crude product mixture (2.171g). Chromatography on 40–micron silica gel with ethyl acetate and hexanes (1:2) allowed partial separation of the *cis-anti-cis* isomer (**6B**) as an oil, and the *cis-syn-cis* isomer (**6A**) as a low melting solid. The combined yield on **6AB** was 1.27g (59%). Slow evaporation of a 1:2 ethyl acetate/hexane solution of **6A** afforded a single crystal suitable for X-ray crystallographic analysis revealing **6A** to be the *cis-syn-cis* isomer. **6A** ^{1}H NMR: δ 0.96–1.06 (m, 6H), 1.42–1.45 (m, 4H), 1.84–1.87 (m, 2H), 2.23 (s, 4H), 3.40 (s, 4H), 3.51-3.76 (m, 8H), 4.07 (d, 2H, *J*=12 Hz), 4.20 (d, 2H, *J*=12 Hz), 5.12 (s, 2H). ^{13}C NMR: δ 24.66, 24.92, 32.89, 39.45, 40.88, 69.73, 70.88, 71.58, 82.49, 84.74, 111.15, 144.19. **6B** ^{1}H NMR: δ 0.93-1.06 (m, 6H), 1.43-1.48 (m, 4H), 1.87-1.89 (m, 2H), 2.21–2.26 (m, 4H), 3.37 (d, 2H, *J*=8 Hz), 3.42 (d, 2H, *J*=4 Hz), 3.52–3.64 (m, 6H), 3.73–3.76 (m, 2H), 4.01 (d, 2H, *J*=13 Hz), 4.29 (d, 2H, *J*=13 Hz) 5.12 (s, 2H). ^{13}C NMR: δ 24.55, 25.01, 33.00, 39.18, 41.27, 69.44, 70.17, 72.45, 83.44, 84.89, 110.22, 144.87.

Synthesis of cis-syn-cis and cis-anti-cis di-norbornano-18-crown-6 (10AB)

The synthesis was performed as outlined in Scheme 2 and as described below.

Exo-cis-2,3-bis allyloxy-bicyclo [2.2.1] heptane (7)

Allybromide (18.9g, 156mmol) and **2** (6.43g, 50.0mmol) were dissolved in dry THF (100mL) under argon. Sodium hydride (6.30g, 150mmol) was slowly added, and the reaction mixture was allowed to stir for 1 hour at room temperature before being heated to 50°C for ~60 hours, with the progress of the reaction followed by GC. After cooling to room temperature, methanol (~2mL) was added, and the solvents evaporated *in vacuo*. The residue was



Scheme 2. Synthetic route to *cis-syn-cis-* and *cis-anti-cis*-di-norbornano-18-crown-6.

extracted with dichloromethane (2 x 75mL), washed with water (75mL) and brine (75mL), dried over Na_2SO_4, and evaporated solvents to obtain 10.44g of crude 7. Chromatography on silica gel (70/230 mesh) using ethyl acetate/hexanes (1:9) as an eluent gave purified 7 (5.236g, 50%). ^{1}H NMR: δ 0.96–1.01 (m, 2H), 1.05-1.08 (m, 1H), 1.42-1.48 (m, 2H), 1.87-1.90 (m, 1H), 2.25 (m, 2H), 3.40 (d, 2H, *J*=1.5 Hz), 4.05 (d, 4H, *J*=5.6 Hz), 5.14 (dd, 1H, J_1= 1.2 Hz, J_2= 10.4 Hz), 5.27 (dd, 1H, J_1= 1.2 Hz, J_2= 17.2 Hz), 5.89-5.99 (m, 1H). ^{13}C NMR: δ 24.75, 32.92, 40.29, 71.45, 83.22, 116.34, 135.38.

Exo-cis-2,3-bis (2'-hydroxyethoxy)-bicyclo [2.2.1] heptane (8)

A solution of 7 (5.00g, 24.0mmol) in dichloromethane and methanol (1:3) was placed under argon in a 3-neck round bottom flask (300mL) equipped with a dry ice cold finger condenser with a $CaCl_2$ drying tube. An argon/ozone bubbler inlet was attached to one of the side arms of the flask. The reaction mixture was cooled to –78°C under argon with stirring; the argon inlet was replaced with an inlet from the ozone generator, and ozone (~5% O_3 in O_2) was bubbled through the solution, with stirring, until a blue color (signifying the presence of excess ozone) persisted for 15 minutes. The ozone inlet was then replaced with an argon inlet; argon was bubbled through the solution for 10 minutes during which the solution became clear. The –78°C bath was replaced with an ice water bath and $NaBH_4$ (5.02g, 133mmol) was slowly added to the reaction using a Merlic-type solid addition funnel. Once the $NaBH_4$ was added, the ice water bath was removed, and the reaction allowed to stir at room temperature for ~20 hours. The solvents were removed *in vacuo*, and the residue dissolved in dichloromethane (150mL) and water (75mL), with 1 M HCl (25mL) added. The layers were separated and the organic layer was washed with brine (100mL). The aqueous layer was back-extracted with dichloromethane (100mL), and the combined dichloromethane layers were dried over anhydrous Na_2SO_4. The solvent was evaporated to afford **8** (4.19g, 81%) of sufficient purity to use in the subsequent reaction without further purification. ^{1}H NMR: δ 1.0-1.02 (m, 2H), 1.09 (d, 1H, *J*=10 Hz), 1.47–1.49 (m, 2H), 1.84 (d, 1H, *J*=10 Hz), 2.25 (s, 2H), 3.44 (s, 2H), 3.49–3.76 (m, 8H), 3.99 (s, 2H). ^{13}C NMR: δ 24.58, 32.81, 40.21, 61.71, 71.93, 83.85.

Exo-cis-2, 3-bis (2'-hydroxyethoxy)-bicyclo [2.2.1] heptane di-p-toluene sulfonate (9)

A solution of recrystallized tosyl chloride (4.7g, 25.0mmol) in pyridine (5mL) was cooled under argon to 0°C in an ice bath. A solution of **8** (2.17g, 10.0mmol) in pyridine (mL) was added dropwise to the reaction mixture, and stirring was continued for 3 hours at 0°C. Water (5mL) was added to stop the reaction, and the mixture was stirred for 15 minutes, and then transferred to a 1-L separatory funnel. Refrigerated water (100mL) and diethyl ether (100mL) were added to the funnel; the organic phase was separated and washed with cold 4M HCl (75mL) and water (50mL), and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the product oil dried under high vacuum for ~1 hour to obtain **9** (3.8g, 92%) of sufficient purity for direct use in the subsequent reaction. ^{1}H NMR: δ 0.92-94 (m, 2H), 0.99 (d, 1H, *J*=9.9 Hz), 1.40-1.42 (m, 2H), 1.67 (d, 1H, *J*=9.9 Hz), 2.11 (s, 2H), 2.44 (s, 6H), 3.31 (s, 2H), 3.47-3.67 (m, 4H), 4.08-4.12 (m, 4H), 7.33 (d, 4H, *J*= 8.2 Hz), 7.78 (d, 4H, *J*= 8.2 Hz). ^{13}C NMR: δ 21.62, 24.55, 32.72, 40.29, 67.96, 69.60, 84.54, 127.91, 129.82, 133.03, 144.74.

Cis-syn-cis- and cis-anti-cis-di-norbornano-18-crown-6 (10AB)

A solution of **8** (1.54g, 7.12mmol) and **9** (3.75g, 7.15mmol) dissolved in dry benzene (230mL) were combined in a 3-neck round bottom flask under argon. Potassium *tert*-butoxide (2.72g, 24.2mmol) contained in a Merlic-type solid addition funnel was slowly added under argon to the solution at room temperature with stirring. The solution was then heated to 60°-65°C under argon for ~17 hours and monitored for completion by TLC. Upon cooling, a precipitate formed and was removed by filtration. The filtrate was washed with water (2 x 150mL). The aqueous layers were back extracted with benzene (50mL); the benzene layers were then combined and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*; the residue was further dried by oil pump vacuum to obtain crude **10AB** (3.30g). Chromatography on silica gel (40 micron) using 95% ethanol as eluent gave **10AB** as mixed isomers as a solid (0.786g, 28%). Earlier fractions were enriched in one isomer, and latter fractions enriched in the other, but separation was not achieved using these chromatographic conditions. ^{1}H NMR (acetone-d6): δ 0.98-1.02 (m, 6H), 1.41-1.43 (m, 4H), 1.78–1.82 (m, 2H), 2.14 (s, 4H), 3.33-3.38 (m, 4H), 3.55–3.67 (m, 16H). ^{13}C NMR (acetone-d6): δ 25.22, 25.27, 33.35, 33.45, 41.05, 41.20, 70.67, 70.70, 70.93, 71.10, 84.94, 84.99.

RESULTS AND DISCUSSION

Synthesis of di-norbornano-15-methyleno-16-crown-5 (6AB)

The synthesis of *exo-cis* diol **2** has been obtained in high yield (88%) and high purity (≥98% by GC) through the use of catalytic OsO_4 [6,8]. The course of this reaction is *syn* hydroxylation resulting in the expected *exo-cis* stereochemistry. The OsO_4–catalyzed procedure affords diol **2** in a significantly higher yield compared to previous reactions employing stoichiometric $KMnO_4$ [7,9] (40–52%). The crown ethers **6AB** were prepared from **2**, as shown in Scheme 1, using diethylene glycol and methallyl linkages. Monobenzyl protection of **2** afforded enantiomeric pair **3AB**, which was separated from unreacted **2** and dibenzylated **2** by silica-gel column chromatography. Reaction of **3AB** with diethylene glycol ditosylate produced **4AB** in reasonable yield (59%) as an equimolar mixture of the *syn* and *anti* isomers revealed by carbon-13 NMR. Removal of the benzyl groups proceeded well using standard Pd/C hydrogenation conditions [10] to give diol **5AB**. The cyclization of **5AB** was initially attempted using 1,3-propanediol ditosylate, but was unsuccessful due to elimination. Methallyl dichloride, which does not possess any beta-hydrogens for elimination, was employed to successfully complete the cyclization; thereby, forming **6AB** in a combined 59% isolated yield. The *syn* and *anti* isomers were distinguishable by GC with some separation possible by column chromatography (40 micron silica gel) with ethylacetate/hexanes (1:3), affording a product distribution of ca. 35% pure **6A** as a solid, ca. 20% mixed **6A** and **6B** fractions, and ca. 45% pure **6B** as an oil. It was not possible to unambiguously determine which isomer was *syn* and *anti* by NMR; however, X-ray crystallography on a single crystal of **6A** revealed **6A** to be the *syn* isomer (Figure 2), indicating **6B** as the *anti* isomer.

Synthesis of cis-syn-cis and cis-anti-cis dinorbornano-18-crown-6 (10AB)

The synthesis of **10AB** from **2** was accomplished employing a technique similar to that reported by Whitman et al [11] for the synthesis of *trans-syn-trans*-dicyclohexyl-18-crown-6 from *trans*-cyclohexane-1,2-diol. Allylation of **2**, obtaining bis-allyl **7**, proceeded well, but the final yield of pure product was reduced a bit (to 50%) during isolation by column chromatography. Ozonolysis of **7**, followed by reduction of the ozonide using $NaBH_4$ to afford diol **8**, proceeded in good yield (81%). A portion of **8** was converted to ditosylate **9** in high yield (92%), and equimolar amounts of **8** and **9** were reacted together under high dilution conditions in benzene using potassium *tert*-butoxide to afford **10AB** in 28% isolated yield following chromatography as an isomeric mixture.

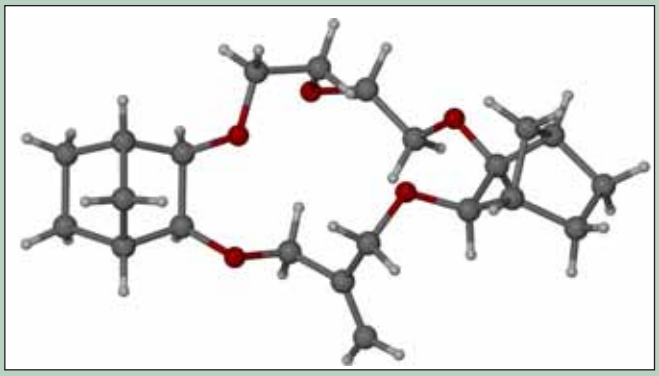


Figure 2. Crystal structure of **6A**.

CONCLUSION

Crown ethers **6AB** and **10AB**, which to our knowledge are the first crown ethers to incorporate the *exo-cis*-2,3-norbornyl moiety into the crown ring, have been successfully synthesized. Purification and separation of **6AB** isomers was achieved; however, separation of **10A** from **10B** requires further investigation. Column chromatography provided purified mixed-isomer material, but yielded no distinct separation of the **10AB** isomers. Future work toward separating **10A** from **10B** may include separation methods utilizing differences in solubility properties between each isomer either as the free crown or as a complex with an ion pair. Future research will evaluate the sodium and potassium binding properties of **6A**, **6B**, and **10AB** and compare to the binding properties of crown ethers such as DCH18C6 and octamethyl-16-crown-5.

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