Southern Adventist University
KnowledgeExchange@Southern

Senior Research Projects

Southern Scholars

2004

Synthesis of the Novel Crown Ether 1 ,9-Dioxa-4,6-Dithiacycloundecane

Cassie Booth

Follow this and additional works at: https://knowledge.e.southern.edu/senior_research

Part of the Biology Commons, and the Chemistry Commons

Recommended Citation

Booth, Cassie, "Synthesis of the Novel Crown Ether 1 ,9-Dioxa-4,6-Dithiacycloundecane" (2004). *Senior Research Projects*. 39.
https://knowledge.e.southern.edu/senior_research/39

This Article is brought to you for free and open access by the Southern Scholars at KnowledgeExchange@Southern. It has been accepted for inclusion in Senior Research Projects by an authorized administrator of KnowledgeExchange@Southern. For more information, please contact jspears@southern.edu.

Synthesis of the Novel Crown Ether 1,9-Dioxa-4,6-Dithiacycloundecane

Cassie L. Booth

Southern Scholars
Senior Project
Advisor: Dr. Loren A. Barnhurst

Key Words: crown ether / crown thioether / cyclization / novel crowns, synthesis of / selective ligation / thioacetal, functionalization of / thioacetal-oxygen crowns

TABLE OF CONTENTS

PAGE

ABSTRACT

Attempts to produce novel crowns, incorporating a thioacetal fragment, were made via two synthetic pathways. Despite the well-established reactions found in path A (see figure 3), this method failed to produce the desired crown. Path B, a one-pot reaction originally designed to close rings via the addition of a thioacetal fragment, yielded an oily product that was purified with a silica gel column (48.3% yield). Initial analysis by ^1H NMR showed a structure consistent with that of the desired crown (figure 2). Mass spectroscopy was used to verify product identity, confirming the creation of our target molecule 1,9-dioxa-4,6-dithiacycloundecane.

INTRODUCTION

Host-guest chemistry studies the interactions of small molecules bound within larger compounds. Among these large binding-compounds, cyclic polydentate ligands, such as crown ethers, form the most stable host-guest complexes. Crown ethers are macrocyclic compounds – closed chains of twelve or more carbon (C) atoms. Crowns vary from this general macrocyclic format in that they have noncarbon atoms (usually oxygen, O) separating repeating ethylene units.[1]

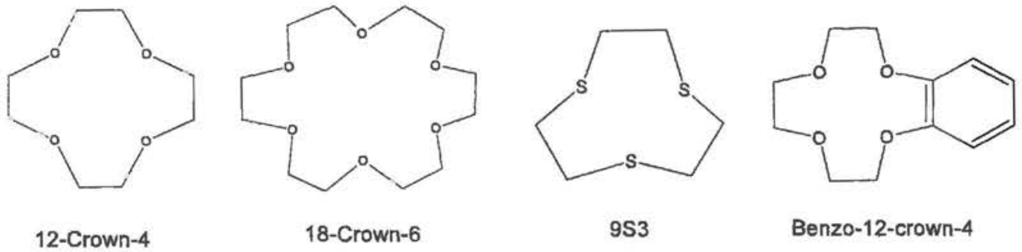
To bypass the unwieldy International Union of Pure and Applied Chemistry (IUPAC) names, Charles Pedersen, their discoverer, developed a unique crown ether nomenclature.[2] The ring size is given first, followed by a family name, and then the number of non-carbon molecules. Any functional groups are listed before the first number. For example, a crown of four ethylene units separated by oxygens would be 12-crown-4. If the oxygens were replaced

---

[1] Lagowski, J., Ed. *Macmillan Encyclopedia of Chemistry (Vol. II)*; Simon & Schuster Macmillan: New York, 1997.

[2] Gokel, G.W. *AccessScience*. **2002**, http://www.accessscience.com/server-java/Arknoid/science/AS/Encyclopedia/1/16/Est_169200_printable.html, (28 Sept. 2003).

with sulfur atoms, it would become 12S4, as S is the family symbol for thiacrowns while "crown" refers to oxacrowns. Figure 1 shows several examples of crown structures and their names.



12-Crown-4 18-Crown-6 9S3 Benzo-12-crown-4

Figure 1 – Structures and names of various crown ethers

Oxacrown Ethers

Pedersen first described crown ethers in the early 1960's when he produced an unwanted side-product during catechol reactions. Purification of this side-product produced minute yields of fibrous white crystals, which Pedersen studied. Analysis revealed an 18-membered ring with a center-oriented oxygen separating every two carbons. Upon the discovery that sodium and other alkali metal ions fit into this central cavity and were held in place by electrostatic attraction, Pedersen began an extensive program of syntheses. This was the first compound able to form stable complexes with sodium and potassium ions, and he was curious about the factors which induced this stability.[3]

Pedersen found that the relative size of the cavity to the cation and the number/arrangement of oxygen atoms were key factors in complex stability. His myriad experiments showed that the most effective compounds contain between 5 and 10 oxygen atoms each separated by 2 carbons.[3] These will bind a variety of ions and small molecules, but are most

---

[3] Pedersen, C.J. *Science.* **1988**, *241*, 536.

effective when the non-sterically hindered diameter of the cavity and complexed species are nearly identical.[4]

Besides their ability to complex Na^+ and K^+, crown ethers have other practical functions. First, they are among the best synthetic ionophores – carriers that move ions from hydrophilic into hydrophobic media. Second, they render inorganic salts soluble in nonpolar solvents, allowing reactions to be conducted in the absence of water. This increases the inorganic reagents reactivity. When unsolvated, the anion becomes a powerful nucleophile.[5]

Crown Thioethers

Although discovered nearly 30 years before oxacrowns, the ligating abilities of crown thioethers remained largely unexplored until 1969. One reason for this was the lack of a safe, high-yield path of synthesis. Today, this problem has been largely overcome, and crown thioethers are now well-studied molecules. While they are similar to oxacrowns in many ways, thioether crowns tend to stabilize the low oxidation states of 'soft' metals due to their lower electronegativity. They also have an interesting structural difference because sulfur is larger than oxygen and the C-S-C bond angle is smaller than the C-O-C bond angle[6] (~90° vs. ~110°).

The sulfur atoms of most macrocyclic thioethers are exodentate (Figure 2). This conformation results because the C-S linkage adopts a gauche conformation. Conversely, in oxacrowns the C-O bond is anti, and the heteroatoms are endodentate. This difference is attributed to the "1,4 interactions in gauche C-C-E-C and E-C-C-E units (E = S,O)."[7] Due to their free form exodentate structure, substantial rearrangements must occur for ligation, and

---

[4] Inoue, Y.; Hakushi, T.; Liu, Y.; Tong, L.H. *J. Org. Chem.* **1993**, *58*, 5411.

[5] Veale, C.A. *AccessScience*. **2002**, http://www.accessscience.com/server-java/Arknoid/science/AS/Encyclopedia/7/75/Est_757310_printable.html, (28 Sept. 2003).

[6] Pedersen, C.J. *J. Org. Chem.* **1971**, *36*, 255.

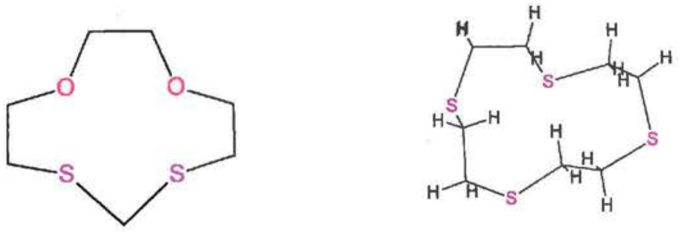
[7] Cooper, S.R. *Acc. Chem. Res.* **1988**, *21*, 141

sulfur crowns generally bridge, rather than chelate, metals. Two exceptions to this trend are the 9S3 and 18S6 crowns. Both are endodentate and suited to ligation, but the 9S3 in particular is not properly sized for many metal ions.

Bradshaw and Izatt[8] manipulated crown ethers in search of selective ion ligating agents. By replacing one or more of the oxygens with sulfur or nitrogen, they drastically changed the affinity of crowns for various metals, and yielded some selective ligators. With these, cations were separated in solution using both liquid membranes and solid-phases.

Purpose

While successful, Bradshaw and Izatt's experiments involved ethers with exodentate (Fig. 2) sulfur atoms.[8] If, however, novel crowns were produced which included a thioacetal fragment, with only one carbon separating the sulfurs, an endodentate conformation would theoretically be assumed.



Endodendate

Exodendate

Figure 2 – Comparison of endodendate and exodendate conformations of crown thioethers (experimental crown pictured on left).

This is expected because the greater steric interactions of the large sulfur atoms should force the lower energy anti conformation of the C-C-S-C fragment to be adopted, as in endodentate oxacrowns. With these inward pointing sulfur atoms, these crowns would be more

---

[8] Bradshaw, J.S.; Izatt, R.M. *Acc. Chem. Res.* **1997**, *30.8*, 338.

versatile complexing agents. They could attract metals that chelate in both oxygen and sulfur crowns. An additional benefit would be the ability to functionalize the crown with side groups through the reactive thioacetal fragment. The purpose of this experiment is to produce such hybrid crown thioethers.

EXPERIMENTAL

Computer modeling (CambridgeSoft Chem3D Pro) was used to perform a molecular mechanics energy minimization on the structure of the novel crown. From this, the approximate cavity diameter was obtained.

Two synthetic pathways were proposed for the synthesis of these novel crowns (Figure 3 A&B).

Path A

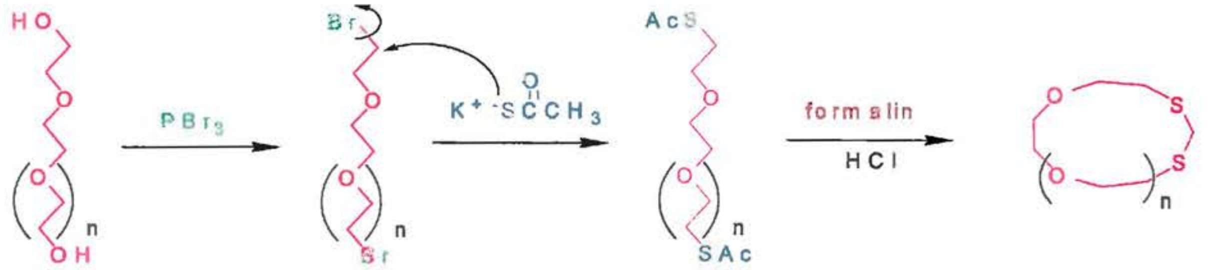


Figure 3A – Outline of the first proposed synthetic pathway

Path B

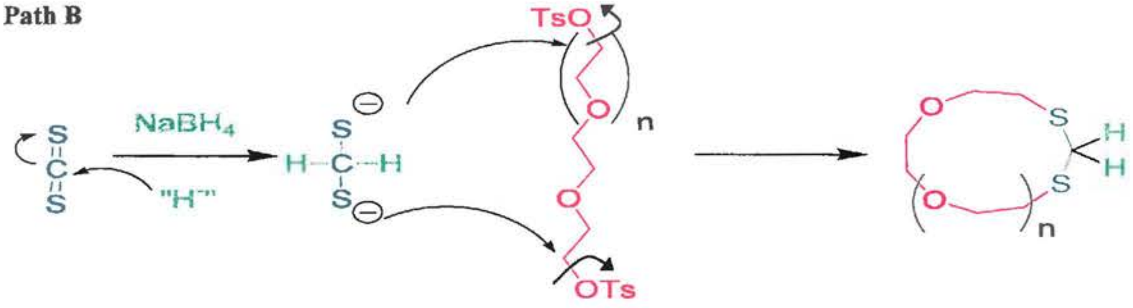


Figure 3B – Outline of the second proposed synthetic pathway

Path A

The bromination of triethylene glycol in path A followed Cason and Correia's[9] procedure on a microscale. 2.25 g (15 mmols) triethylene glycol (Aldrich) was dissolved in 20 ml dry ether. The solution was cooled to below 0°C and kept there while 5.8 g (21 mmols) of PBr_3 was added drop-wise with stirring; the amount of PBr_3 used was more than doubled from that in the published procedure because two –OH groups were being displaced . This mixture was stored for 48 hours at -4°C before extraction of the product was attempted. Neutralization with crushed ice, washing with 10% Na_2CO_3, and drying with K_2CO_3 were carried out according to the published protocol. Several solvent were tried in an attempt to extract the product: diethyl ether, methylene chloride, chloroform, and ethyl acetate. Infrared (IR, M series, Midac Corporation) analysis showed each extraction to be unsuccessful. A broad peak in the 3100 cm^{-1} range indicated an –OH group was still present, either because of an incomplete reaction or a mixed extraction. This first step of the reaction was abandoned in favor of starting with tri[ethylene glycol] di-*p*-tosylate (tosylate), which does not require bromination.

The second step of path A, replacing the tosylate groups with thioacetate was done according to Barnhurst's[10] protocol. 0.377 g (3.3 mmols) KSAc (Aldrich) was dissolved in 30 ml of acetonitrile. 0.507 g (1.1 mmols) tosylate (Aldrich) was added, and the system was refluxed for 48 hours – the solution became orangish-brown, and off-white crystals formed. Silica gel plate thin-layer chromatography (TLC, with 0.05% acetic acid in ethyl acetate solvent) of these crystals dissolved in acetone revealed the absence of both starting products, which were still present in the solution. The crystals were collected by vacuum filtration (63.2% yield). A melting point could not be determined, as the crystals burned up at 325°C.

---

[9] Cason, J.; Correia J. *J. Org. Chem.* **1961**, *26*, 3645.

[10] Barnhurst, L.A. *ET-Induced Cleavage in Novel Dithiane Systems*; Denver Bookbinding Company: Denver, 2002.

Finally, also according to Barnhurst's[10] protocol, formalin in acid was used to close the ring. 0.051 g (0.19 mmols) of crystals from step 2 were dissolved in 20 ml of 2 M HCl, then 0.00565 g (0.19 mmols) formalin (Aldrich) was added. The solution was refluxed for 48 hours, neutralized with Na_2CO_3 (monitored with pH paper), and extracted twice with methylene chloride. After drying over $MgSO_4$, the product was concentrated with a rotary evaporator (Brinkmann RE111). Only traces were obtained – a percent yield could not be calculated. ^1H NMR (Anasazi Instruments, Eft-60) analysis did not indicate that the desired crown had formed.

Path B

Path B involves a direct transformation of tri(ethylene glycol) di-*p*-tosylate (tosylate) to the thio-oxacrown following Wan et. al.'s[11] "one-pot" double reduction of CS_2 method. 1.013 g (2.2 mmols) tosylate (Aldrich) was dissolved in 20 ml triglyme, then cooled to -3°C. 0.257 g (6.8 mmols) $NaBH_4$ was added, immediately followed by 200 μl (3.3 mmols) of CS_2. Contents were stirred at room temperature for 48 hours. A powdery white precipitate formed, although most dissolved after dilution with 42 ml saturated NH_4Cl. After the addition of 50 ml ether, traces of precipitate were removed by vacuum filtration, then the ether layer was extracted. This organic layer was washed twice with 20-30 ml saturated NaCl, dried over Na_2SO_4, and concentrated via rotary evaporation.

0.429 g of oily crude product was collected, but silica gel TLC in 50:50% ethyl acetate-hexanes revealed the presence of two product spots (average Rf values = 0.57 and 0.75). Both spots appeared to contain product, but aromatic peaks in ^1H NMR of the 2nd spot indicated that it could also contain either unreacted starting materials or some side product involving the leaving

---

[11] Wan, Y.; Kurchan A.N.; Barnhurst, L.A.; Kutateladze, A.G. *Org. Lett.* **2000**, *2.8*, 1133.

tosylate groups. A silica gel column was used to purify and separate the constituents of both spots (0.222 g combined, 48.3% yield), which were analyzed with ^{1}H NMR and mass spectroscopy (ThermoFinnigan Trace GC 2000 interfaced with Polaris Q iontrap mass spec).

RESULTS AND DISCUSSION

The crude computer modeling of the proposed crown revealed a cavity diameter of approximately 4.52 Å. It is expected that with this diameter and the complexing properties of sulfur, either Hg^{2+} (radii = 0.83-1.28 Å) or Pb^{2+} (radii = 1.33-1.63 Å) will complex within the cavity.

While both proposed pathways to the desired crown (Fig. 3 A&B) were theoretically feasible, path A was preferable for preliminary attempts at synthesis (Fig. 3A). It called for less expensive starting materials, and the well-established chemistry of the individual steps seemed to assure success, even though the number of reactions involved would lower yields. However, Cason and Correia's[9] procedure for the replacement of –OH with –Br was unsuccessful with triethylene glycol. To compensate, the starting material was changed to tri[ethylene glycol] di-*p*-tosylate, which already has a good leaving group and thus does not require bromination. Despite this change, ^{1}H NMR revealed no products from path A consistent with the desired crown.

Once path A was exhausted, the odiferous path B (Fig. 3B) was attempted. Although this method[11] was designed with the exclusive purpose of forming thioacetal groups while closing alkyl chains into rings, the yield can vary from low to good. The first attempt of this reaction produced an oily product (48.3% yield after purification), and TLC revealed that both spots could contain the desired product. Aromatic peaks in ^{1}H NMR of the 2nd spot indicated that it could also contain either unreacted starting materials or some side product involving the leaving tosylate groups.

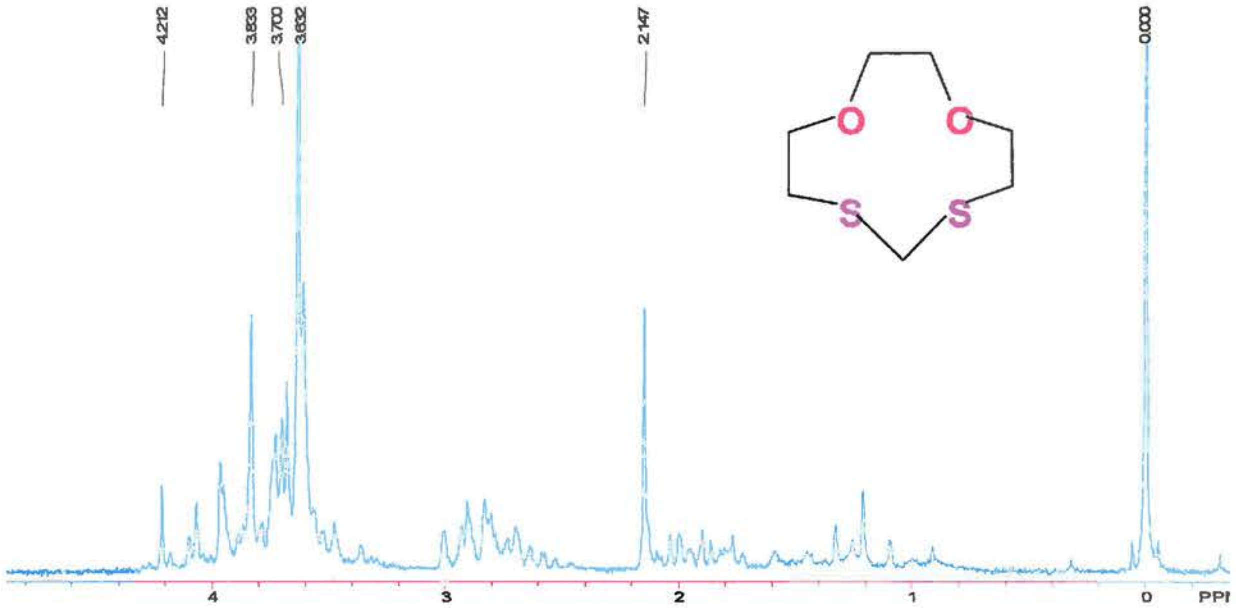


Figure 4 - ^{1}H NMR spectra of the product from path B

Mass spectroscopy confirmed the product's identity (Fig. 5 A-C). The product peak's mass was equivalent to that of the expected product (194 g/mol) and all major fragment peaks can be accounted for (Table 1).

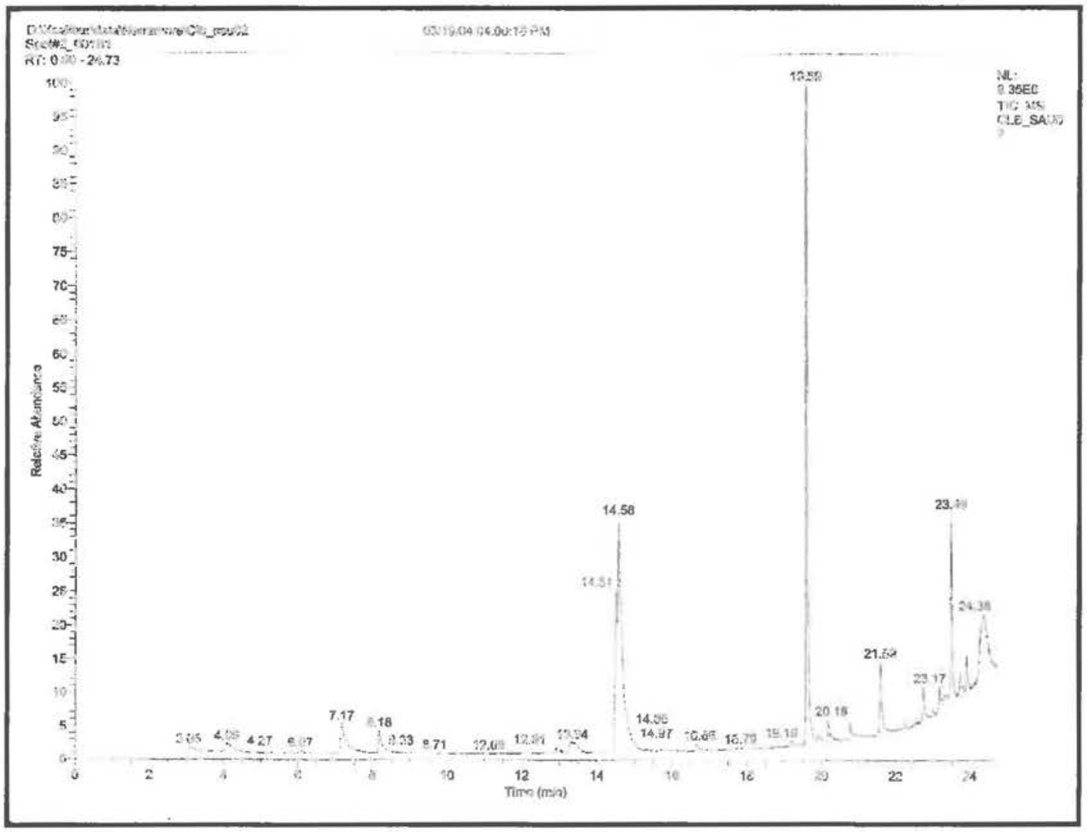


Figure 5A – Complete mass spec scan of the product from path B

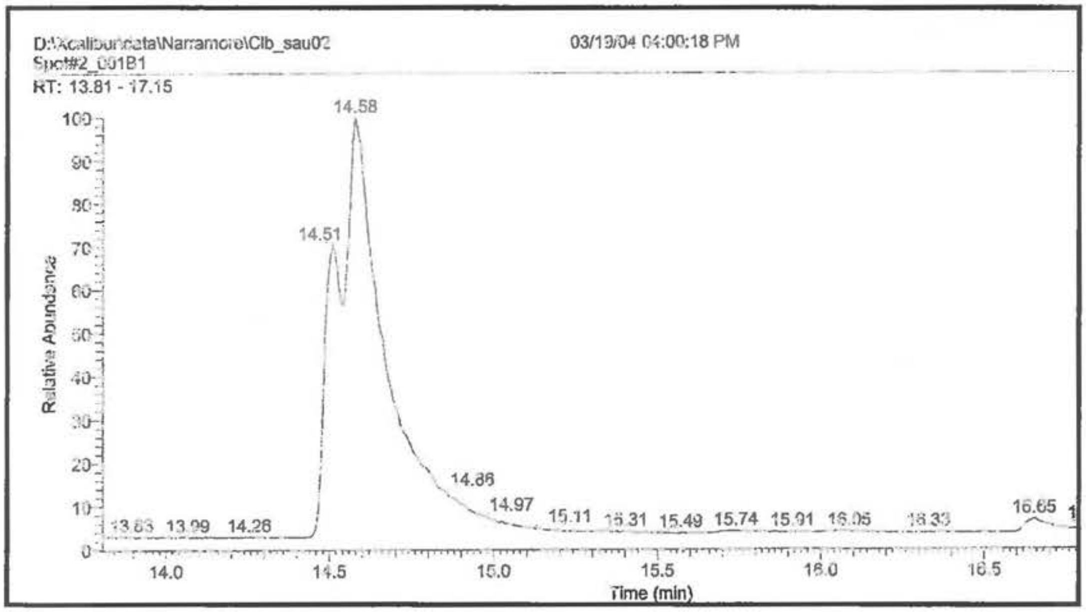


Figure 5B – Mass spec scan (zoomed in around product peak)

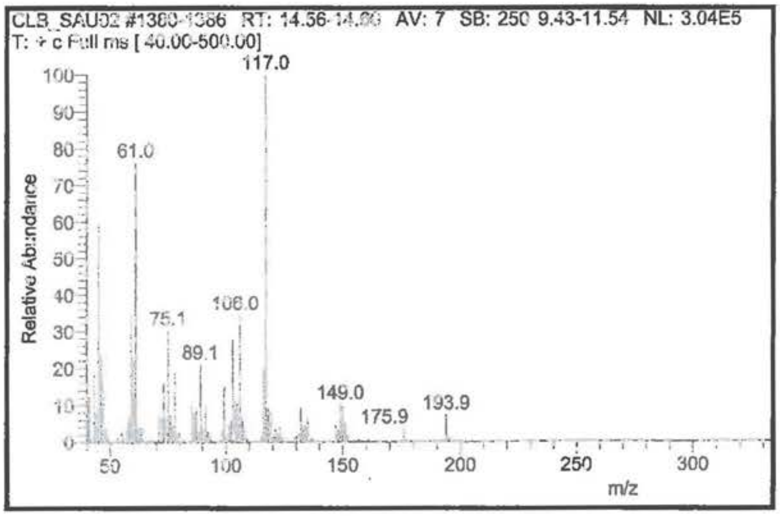
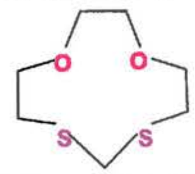
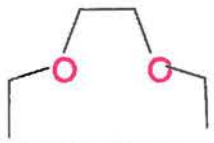
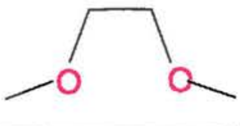
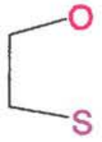
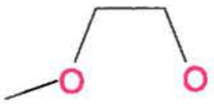


Figure 5C – Product and its constituent fragments

Table 1 – Explanation for major fragment peaks from mass spec scan.

Fragment Structure	Mass (g/mol)
	194
	117 +/- 1
	106 +/- 1
 or 	75 +/- 1
	61 +/- 1

Now that the crown has been synthesized, the procedure will require adjustment to improve product extraction and increase percent yield.

CONCLUSIONS

This research endeavor resulted in the first successful synthesis of the novel crown 1,9-dioxa-4,6-dithiacycloundecane. Two paths were compared for effectiveness, efficiency, and ease of production. Path A was eliminated as a possible synthetic route, and Wan, et. al.'s[11] "one-pot" reaction will require modification to produce a purer product and better yields before large scale synthesis occurs. However, once a suitable means of synthesis is in place, novel hybrid crowns can be produced in greater amounts for further experiments. It is proposed that these crowns will be especially good ligators of mercury and/or lead ions due to the size of the central cavity and properties of the sulfur atoms. A cation transport experiment to test this hypothesis is planned.

One application of such compounds is removal of heavy metal contaminants from water or reagents. Additionally, the thioacetal group lends itself to reversible functionalization.[11] With this capability, two or more crowns could be joined to form cryptands that ligate larger molecules. It could also be used to anchor the crowns to a solid support, such as a bead, for use in filters or chromatography columns. The successful production of the first of this novel class of hybrid crown thioethers will open the door to an extensive program of syntheses, leading to an unexplored branch of crown ether ligation chemistry.

WORKS CITED

1. Lagowski, J., Ed. *Macmillan Encyclopedia of Chemistry (Vol. II)*; Simon & Schuster Macmillan: New York, 1997.
2. Gokel, G.W. *AccessScience*. **2002**, http://www.accessscience.com/server-java/Arknoid/science/AS/Encyclopedia/1/16/Est_169200_printable.html, (28 Sept. 2003).
3. Pedersen, C.J. *Science*. **1988**, *241*, 536.
4. Inoue, Y.; Hakushi, T.; Liu, Y.; Tong, L.H. *J. Org. Chem*. **1993**, *58*, 5411.
5. Veale, C.A. *AccessScience*. **2002**, http://www.accessscience.com/server-java/Arknoid/science/AS/Encyclopedia/7/75/Est_757310_printable.html, (28 Sept. 2003).
6. Pedersen, C.J. *J. Org. Chem*. **1971**, *36*, 255.
7. Cooper, S.R. *Acc. Chem. Res*. **1988**, *21*, 141.
8. Bradshaw, J.S.; Izatt, R.M. *Acc. Chem. Res.* **1997**, *30.8*, 338.
9. Cason, J.; Correia J. *J. Org. Chem.* **1961**, *26*, 3645.
10. Barnhurst, L.A. *ET-Induced Cleavage in Novel Dithiane Systems*; Denver Bookbinding Company: Denver, 2002.
11. Wan, Y.; Kurchan A.N.; Barnhurst, L.A.; Kutateladze, A.G. *Org. Lett*. **2000**, *2.8*, 1133.

Southern Scholars Honors Program
Senior Project

SOUTHERN
ADVENTIST UNIVERSITY

Southern Scholars
southernscholars.southern.edu
wmclarty@southern.edu

Name Cassie Booth Date 4/16/04

Major Chemistry & Biology

A significant scholarly project, involving research, writing, or special performance, appropriate to the major in question, is ordinarily completed the senior year. The project is expected to be of sufficiently high quality to warrant a grade of A and to justify public presentation.

Under the guidance of a faculty advisor, the Senior Project should be an original work, should use primary sources when applicable, should have a table of contents and works cited page, should give convincing evidence to support a strong thesis, and should use the methods and writing style appropriate to the discipline.

<u>The completed project, to be turned in in duplicate, must be approved by the Honors Committee in consultation with the student's supervising professor three weeks prior to graduation.</u> Please include the advisor's name on the title page. The 23 hours of credit for this project is done as directed study or in a research class.

Keeping in mind the above Senior Project description, please describe in as much detail as you can the project you will undertake. You may attach a separate sheet if you wish:

See attached "project summary"

Signature of faculty advisor ______ Expected date of completion 4/16/04

This project has been completed as planned (date) 4/16/04

This is an "A" project ✓ This project is worth 2-3 hours of credit ✓

Advisor's Final Signature ______

Chair, Honors Committee ______ Date Approved ______

Dear Advisor, please write your final evaluation of the project on the reverse side of this page. Comment on the characteristics that make this A "quality work.

Project Summary

Attempts to produce novel crowns, incorporating a thioacetal fragment, were made via two synthetic pathways. Despite the well-established reactions found in path A (see figure 3), this method failed to produce the desired crown. Path B, a one-pot reaction originally designed to close rings via the addition of a thioacetal fragment, yielded an oily product that was purified with a silica gel column (48.3% yield). Initial analysis by 1H NMR showed a structure consistent with that of the desired crown (figure 2). Mass spectroscopy was used to verify product identity, confirming the creation of our target molecule 1,9-dioxa-4,6-dithiacycloundecane.

Dear Southern Scholars Committee,

Cassie's work on her research project was extraordinary. This project is 'A' quality work, and has built a foundation for my own professional development research at Southern.

Stemming from an undesired reaction which I encountered in my graduate studies, Cassie designed her project with the intent of synthesizing a new class of compounds that may prove to have interesting chemical properties, such as bindings metal cations. Considering the cumulative work of thousands of organic chemists over the past 150 years, finding a compound which has never been made (and reported in the literature) is a feat in and of itself. The success Cassie achieved in this project by synthesizing a 'new' hybrid crown ether is on the level of a first or even second year graduate student.

The independence Cassie showed throughout this project shows why she is a Southern Scholar. The initial part of the year was spent performing many reactions in the laboratory only to fail time and again. These failures are an inevitable part of becoming proficient in organic synthesis, not all reactions conceived theoretically will actually be able to be synthesized. This is why original research is so intriguing, you usually will fail, but every once in awhile you hit the jackpot. During Cassie's failures, she showed an inner strength and maintained a belief that she could overcome whatever chemical roadblocks were put in her way. She took the failures as a learning experience and chalked up the 'wasted' time as her introduction to learning new techniques and instruments.

After synthesizing a chemical, one must 'prove' that the oil or crystal is indeed what you say it is on paper. To this end, Cassie was the first student to learn how to use the nuclear magnetic resonance (NMR) spectrometer recently upgraded by our department. In addition, as a final confirmation of the product identity, a trip to the UTC Chemistry Department was required to use their GC-MS (an instrument used to measure molecular mass). During this afternoon spent at UTC, Cassie interacted in a very professional way with the UTC professor and showed her competence as a chemist, leading the professor to invite us back any time to use his instrument (for which I am very thankful).

Finally, Cassie's meticulous note-taking will allow future students to pick up where she left off, as opposed to spending 100+ hours to get to the point she has brought this project. Cassie has taken an idea and made it reality, for which she has my thanks and my highest recommendation for an 'A' in her project.

Sincerely,

Loren Barnhurst