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Selective Selenoxide Elimination on the Secondary Face of beta-Cyclodextrin

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SELECTIVE SELENOXIDE ELIMINATION ON THE SECONDARY FACE OF β-CYCLODEXTRIN

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Master of Arts

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by

Ahmed M. Hafez

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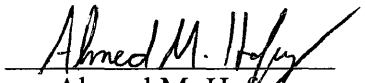

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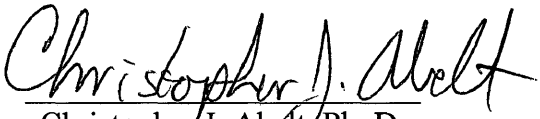
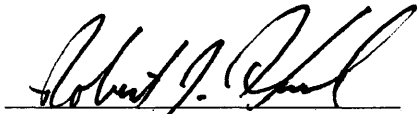


Christopher J. Abelt, Ph. D.



Robert J. Hinkle, Ph. D.

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TABLE OF CONTENTS

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LIST OF FIGURES

Figure:

Abstract

The selective oxidation of β-cyclodextrin at the C-2 position was attempted in order to prepare a precursor to a photochemically active enzyme model. A ketone derived from β-cyclodextrin was prepared via intermediates. Reaction of β-cyclodextrin with nitrophenyltosylate and sodium bicarbonate in DMF gave 2-*O*-(*p*-Toluenesulfonyl)-β-cyclodextrin (**1**). Compound **1** was converted to 2^A,3^A-anyhdro-β-cyclodextrin *manno* epoxide (**2**), in which one glucose subunit has been converted to a *manno*-epoxide. The reaction of **2** with diphenyl diselenide and sodium borohydride in ethanol gave 3^A-deoxy-3^A-phenylseleno-β-cyclodextrin (**3**). Compound **3** was oxidized with hydrogen peroxide to give 3^A-deoxy-3^A-phenylselenoxy-β-cyclodextrin (**4**). Subsequent elimination and keto-enol tautomerization converted **4** to 3^A-deoxy-β-cyclodextrin-2^A-ulose (**5**). The reaction of **5** with (9,10-dicyanoanthracenyl-2-methyl)triphenylphosphonium bromide gave the olefin tethered 2-deoxy-2-(9,10-dicyanoanthracenyl-2-methylene)-β-cyclodextrin (**6**).

An improved route for the selective oxidation of β-cyclodextrin on the secondary face was attempted. A ketone derived from heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin was prepared via intermediates. The reaction of β-cyclodextrin with tert-butyldimethylsilyl chloride in pyridine gave heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**7**). Treatment of **7** with benzyl-trimethylammonium methoxide in bezene gave mono(2-*O*-tosyl)-heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**8**). Compound **8** was converted to mono(2^A,3^A-anhydro)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**9**), in which one glucoside has been converted to the *manno*-epoxide, by treatment with pinacol in refluxing ethanol. The reaction of **9** with dinaphthyl diselenide and sodium borohydride in ethanol gave 3^A-deoxy-3^A-naphthylseleno heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**10**). Compound **10** was oxidized with hydrogen peroxide to give 3^A-deoxy-3^A-naphthylselenoxy heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**11**). The oxidation was followed by elimination and keto-enol tautomerization to convert **11** to 3^A-deoxy heptakis(6-*O*-*tert*-buyldimethylsilyl)-β-cyclodextrin-2^A-ulose (**12**). Subsequent removal of the silyl groups affords the attachment of a photochemically active molecule at the C-2 position.

SELECTIVE SELENOXIDE ELIMINATION ON THE SECONDARY FACE OF β-CYCLODEXTRIN

Introduction

Enzymes are essentially biological proteins which can catalyze reactions. They are able to bind to substrates to facilitate this catalysis. Synthesizing enzyme mimics in an effort to harness the catalytic power of enzymes has been well documented in recent years.[1,2,3,4]

Cyclodextrins can function as enzyme mimics. Because of their three-dimensional shape, they can form strong inclusion complexes with a substrate. They can catalyze in a covalent manner with their many hydroxyl groups acting as nucleophiles, or derivatives of the hydroxyl groups can act as nucleophiles as well (Figure 1). Not all catalysis need be covalent. Non-covalent catalysis in which the interior cavity of cyclodextrins acts as a medium is also known.

The cyclodextrin cavity can be functionalized to synthesize custom catalysts. The attached functional groups serve two purposes: molecular recognition and multifunctional catalysis. One can functionalize cyclodextrins that will bind to specific substrates thus producing a highly selective enzyme mimic. A specific catalytic switch may also be attached to cyclodextrins to create a controllable enzyme mimic.

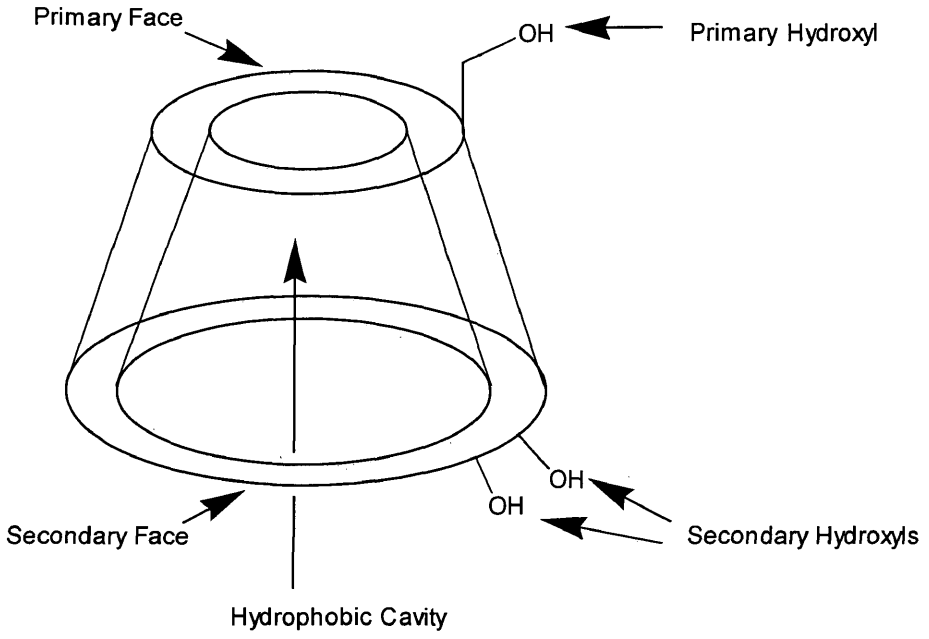


Figure 1: General functionalities of cyclodextrins

One such controllable derivatization involves the attachment of a photochemically active molecule to cyclodextrins. With this modification, the photochemically active cyclodextrin may be used to control the activity of a catalytic reaction. The size of this functionality as well as the manner in which it is attached to cyclodextrin contributes to its catalytic activity. A weak and labile linkage may cause the functionality to rearrange or even include in or obstruct the cyclodextrin cavity. The proximity of the functionality to the guest substrate is also an important variable. The catalytic activity of the cyclodextrin complex increases as the proximity of the photochemical functionality increases.

An ideal method in functionalizing cyclodextrin would be to attach the photochemical functionality on the side of the molecule in which the substrate will include and attach it in a relatively rigid manner. A carbon-carbon double

bond would allow for such a rigid connection (Figure 2). The Wittig reaction is a well documented reaction which can form these double bonds. Since the guest substrate will likely enter through the larger opening, linking the photochemical functionality to the rim of that face would allow for greater catalytic activity. In order to derivatize cyclodextrin at this opening via the Wittig reaction the secondary face must be selectively oxidized.

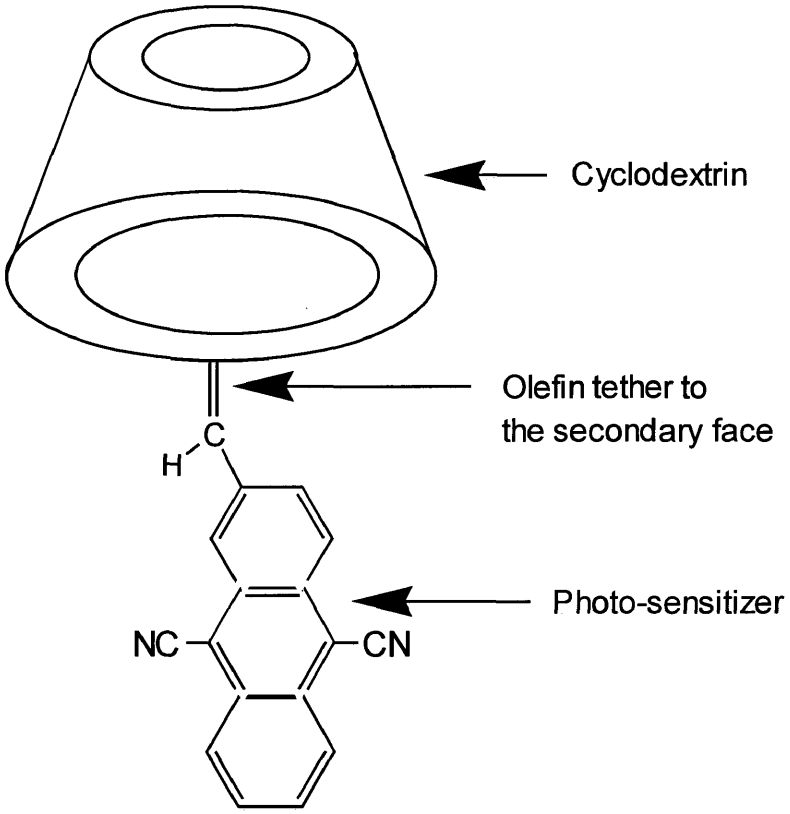


Figure 2: Photochemically functionalized cyclodextrin

Background

Cyclodextrins

Cyclodextrins are chiral, toirodal shaped oligosacharrides of 6, 7, and 8 D(+)-glucopyranose units connected by α-(1,4)-linkages. Greek letters are used to denote the number of units in the oligosacharide (α-6, β-7, γ-8). While cyclodextrins are doughnut shaped, all glucose units are in undistorted C_1 (D) (chair) conformations.[5]

Hydroxyl groups line both openings of cyclodextrins. On the smaller opening are primary hydroxyl groups which are connected to the C-6 carbon of each glucoside. By convention, this side of a cyclodextrin is termed the primary face for these primary hydroxyl groups. The larger opening, or secondary face, contains two secondary hydroxyl groups, one at the C-2 and C-3 positions, for each glucose unit. The primary hydroxyls are free to rotate which allows them to obstruct the opening of the primary face. The secondary hydroxyls are restricted in their movement. Additionally, these secondary hydroxyl groups are hydrogen bonded with secondary hydroxyl groups of contiguous glucose units (Figure 3).[5]

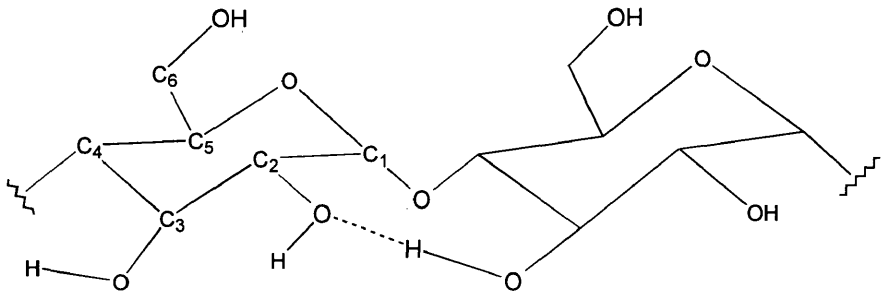


Figure 3: Hydrogen bonding between C-3 and C-2 hydroxyls

Cyclodextrins have cavities which contain C-H groups and glucosidic oxygens which make the interior apolar. Cyclodextrins' hydrophobic cavity affords the ability to bind small organic molecules and thus provide excellent binding sites to which catalytic functional groups can be added to form enzyme mimics. The 'V' shaped cavity affords a larger opening at the secondary face than at the primary face.

While the primary face of cyclodextrins has been extensively studied, the secondary face has just recently piqued interest in its properties. The environment at the primary side differs from the secondary side, which leads to enzyme mimics with different selectivities.[6] Having a larger opening, the secondary face would be a preferential site for binding larger molecules and allowing molecules to include more easily. It is also the site where cyclodextrin's chirality is more apparent.[1]

The hydroxyl groups at the 6-position are the most reactive towards electrophilic reagents because they are primary hydroxyls and their pKa are similar to that of other primary hydroxyl groups (pKa 15-16).[6] Conventional methods of tosylation using tosyl chloride in pyridine yields predominance of 6-tosyl derivatives.[6] Of the three types of cyclodextrin hydroxyl groups, those at the 3-position are the least reactive and resist functionalization. The hydroxyl groups at the 2-position are the most acidic of the three hydroxyl groups with a pKa of 12.1.[6] This can be attributed to the hydrogen bond between the hydroxyl groups at the 2 and 3-positions which can stabilize the alkoxide.

Selective functionalization of cyclodextrin's secondary face is complicated by statistical and steric problems.[6] Fourteen hydroxyl groups with relatively limited mobility on the secondary face of β-cyclodextrin can cause crowding during its functionalization. The conventional method of functionalization involves tosylation by group transfer at either the C-2 or C-3 positions (Figure 4).

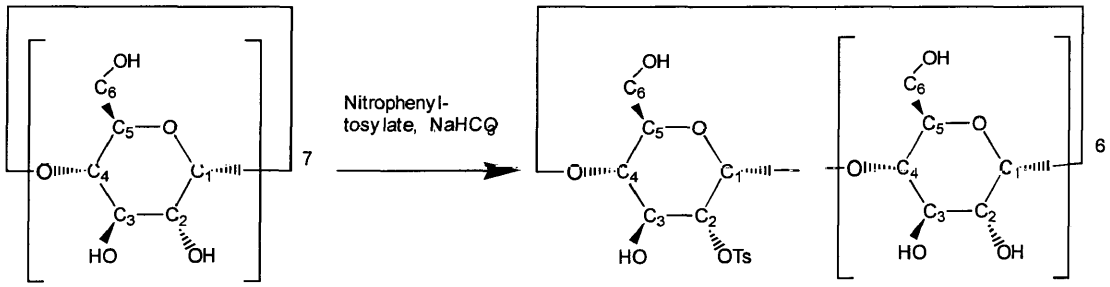


Figure 4: Tosylation scheme on a single glucoside[6]

Tosylation can be followed by an intramolecular nucleophilic substitution by the adjacent non-tosylated oxygen to give an epoxide. If the tosylation occurs at the C-2 position, the mono 2-tosylated cyclodextrin affords the mono *manno*-epoxide while the 3-sulfonated cyclodextrin produces the mono *allo*-epoxide (Figure 5).[7]

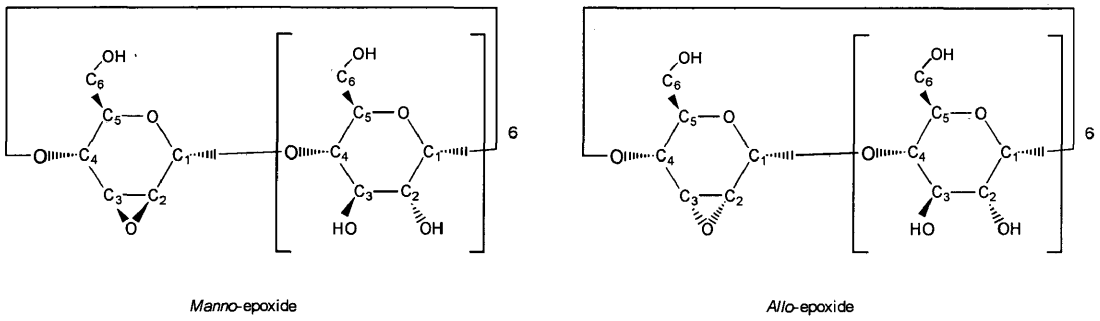


Figure 5: *Manno-* and *allo*-epoxide

Epoxidation of cyclodextrin affords intermediates in the synthesis of custom designed cyclodextrins because the epoxide can be opened by a nucleophilic attack. β-Cyclodextrin *manno*-epoxide reacts with a nucleophile to produce a 3-substituted derivative in which the conformation of the corresponding pyranose unit is inverted from $^4C_1$ to $^1C_4$ while the ring opening of the mono *allo*-epoxide does not undergo this inversion.[7]

Moderate yields predominate when functionalizing the secondary side of β-cyclodextrins. Reverse-phase chromatography, which is scale-limited, is used to purify synthesized cyclodextrin intermediates. Synthesis of cyclodextrin based enzyme models may be improved to allow for easier purification of intermediates, and thus for synthesis of a larger scale, if a partially silylated cyclodextrin is used

as the framework for derivatization.[8] The resulting silylated cyclodextrin will be much less polar than the unprotected cyclodextrin, making it soluble in organic solvents and also allowing for purification by normal-phase silica gel chromatography. The silyl groups are stable under ordinary conditions, but are easily removed as well. By making these derivatized cyclodextrins more easily purified, silylation affords preparatory methods on a large scale.

Oxidation of the hydroxyl groups of both the primary and secondary face has been attempted. The C-6 hydroxyl has been oxidized to form an aldehyde by oxidizing the 6-O-tosylate in DMSO/collidene.[9] Another method for oxidizing the C-6 hydroxyl was reported by Gibson, Melton, and Slessor where the hydroxyl was substituted with an amino group and then oxidized with ninhydrin to give the aldehyde.[10] The introduction of carbonyl groups on the secondary side of cyclodextrins has been limited. An opening of the pyranoside ring at C-2 and C-3 with sodium metaperiodate has formed a dual aldehyde.[11] The goal of this project, the selective oxidation of a single secondary hydroxyl to a ketone, has not yet been reported (Figure 6).

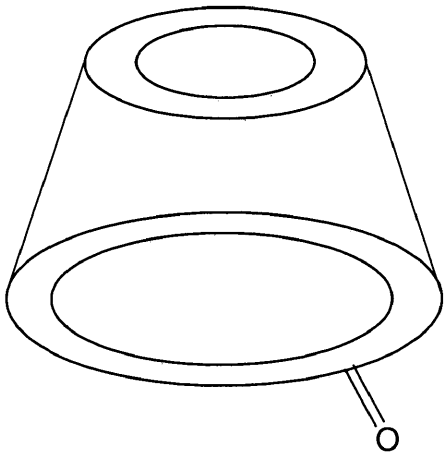


Figure 6: Selectively oxidized β-cyclodextrin on the secondary face

β-cyclodextrin in photocatalysis

The use of β-cyclodextrins as enzyme mimics has garnered much attention. There are examples where β-cyclodextrins have catalyzed reactions without any modification or functionalization of their structure.[5] Either a change in the conditions or a change in conformation due to binding to a substrate was sufficient to accelerate or control the specificity of the reaction. By attaching a chemically active molecule to β-cyclodextrin one could increase binding and reaction specificity by making a much more specific enzyme mimic.

A molecule linked to β-cyclodextrin at one point is termed a tether. If the molecule is linked to β-cyclodextrin at two points it is termed a cap. Tethers or caps can react chemically with the guest as well as increase binding capabilities by enlarging the hydrophobic surface area of the cavity. By attaching catalytic groups to cyclodextrins, several enzyme mimics have been synthesized. Breslow

has tethered a pyridoxamine to the 3-position of β-cyclodextrin mimicking a transaminase enzyme.[1] β-Cyclodextrin's secondary side has also been derivatized with hydroxylamine to synthesize a model to study the transacylation of *p*-nitrophenyl acetate.[12]

A few photochemically active cyclodextrins have been reported. Some of the photoreactive groups attached to cyclodextrins are benzophenone, rose bengal,[13] flavin, and porphyrin moieties. Photoreduction of benzoquinone has been demonstrated with a porphyrin-β-cyclodextrin system.[14,15] A flavin-β-cyclodextrin has provided for photo-oxidation of bound benzyl alcohols.[16] Benzophenone capped β-cyclodextrins have catalyzed the triplet-triplet energy transfer of bound naphthalene derivatives.[17] One problem with this capped compound is that it undergoes intramolecular hydrogen abstraction from β-cyclodextrin under irradiation.[18] Intramolecular hydrogen abstraction is also the fate of anthraquinone capped β-cyclodextrin.[19] The binding of a substrate to these quinone-capped β-cyclodextrins is insufficient to prevent hydrogen abstraction.

Dicyanoanthracene (DCA) has been used as a photo-oxidant with the hopes that it will not abstract hydrogens because it has a singlet excited state Figure 7). Several DCA derivatized β-cyclodextrins are known. A DCA-disulfonyl capped β-cyclodextrin has been reported, but that suffered from hydrolytically labile sulfonate ester bonds.[20] A DCA-ether tethered β-cyclodextrin possessed a stronger binding to β-cyclodextrin than the disulfonyl capped β-cyclodextrin. The DCA was tethered to the 2-position, but due to

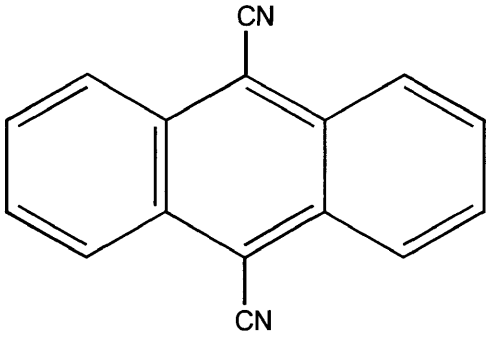


Figure 7: Dicyanoanthracene

rearrangements a 6-*O* tether was also produced. The 6-*O* derivative demonstrated better binding than non-derivatized β-cyclodextrin, while the 2-*O* tethered β-cyclodextrin showed slightly better binding than β-cyclodextrin.[20] The DCA may be including into the cavity for the 2-*O* tethered β-cyclodextrin because of the flexibility of the ether linkage.

A stronger bond is needed in order to attach DCA to β-cyclodextrin in order to prevent these inopportune rearrangements and orientations. A carbon-carbon double bond is expected to solve these problems. The Wittig reaction has been used to tether DCA to the 6-position on the primary face of β-cyclodextrin.[21] No photochemical studies have yet been performed to determine the photocatalytic abilities of this tethered complex. It is also of interest to tether DCA to β-cyclodextrin's secondary side with this method because of the differences in specificities secondary face functionalized β-cyclodextrins have shown.

Epoxides

Epoxides are compounds in which an ether oxygen is part of a three-membered ring. Epoxidation of cyclodextrin's secondary side affords an intermediate which can provide a variety of derivatizations by a nucleophilic ring opening. The desired functional group can be attached easily to either secondary carbon (C-2 or C-3), depending on the epoxide's conformation (*manno* or *allo*), by employing it as the nucleophile in which to open the ring.

Once tosylation of the C-2 hydroxyl is complete, thus derivatizing the 2-position with a good leaving group, further reaction with the addition of base can produce the epoxide. The base in the reaction mixture deprotonates the hydroxyl group at the 3-position forming the C-3 alkoxide, which then displaces the tosyl group at the 2-position from the backside to form the epoxide.

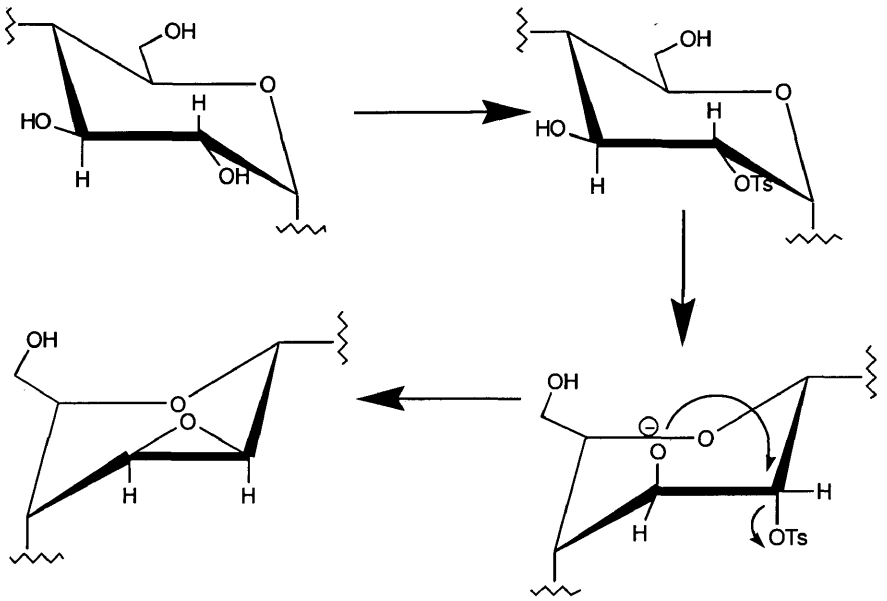


Figure 8: Epoxidation scheme on a single glucoside

The epoxide ring opening of carbohydrates is regiospecific. Reaction of these epoxides with nucleophiles favors the formation of products with the antiperiplanar arrangement of the 2- and 3-substituents (Figure 9). In the case of 2,3 *manno* epoxide of cyclodextrin, the approaching nucleophile would be oriented parallel to the glycosidic oxygen on the anomeric carbon.[22]

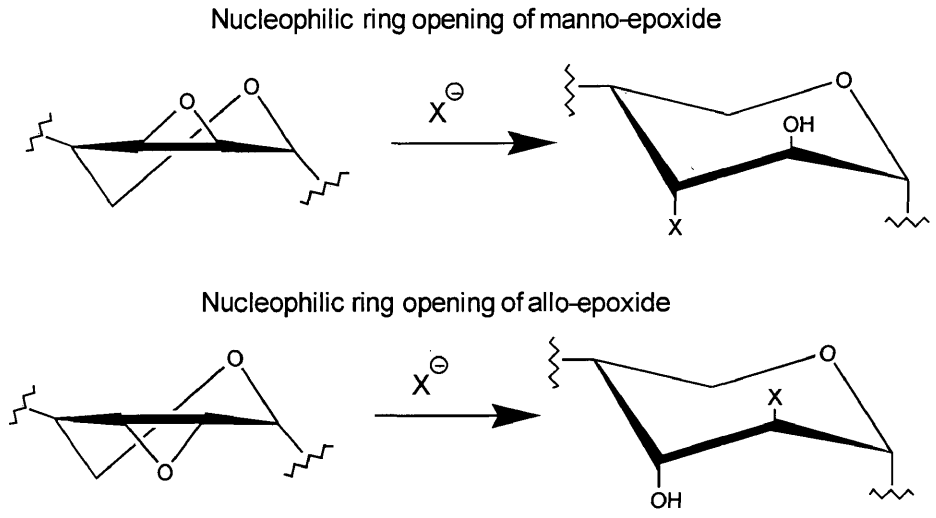
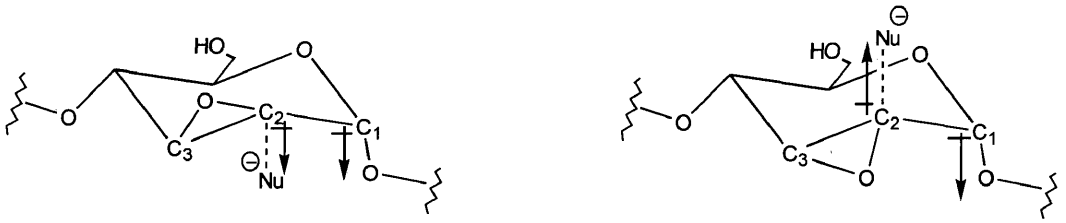


Figure 9: Antiperiplanar arrangement of 2- and 3- substituents after ring opening [22]

This approach would be unfavorable due to the dipole-dipole interaction at the 2 carbon.



Unfavorable interaction
For *manno* epoxides
C-3 is prefered

Favorable interaction
For *allo* epoxides
C-2 is prefered

Figure 10: Dipole-dipole interactions for nucleophilic attack on epoxides

Thus, the 2,3 *manno* epoxide is exclusively attacked at the 3-position (Figure 10). Conversely, the 2,3 *allo* epoxide is exclusively attacked at the 2-position because of the favorable dipole-dipole interaction at the 2-position by the nucleophile (Figure 11).

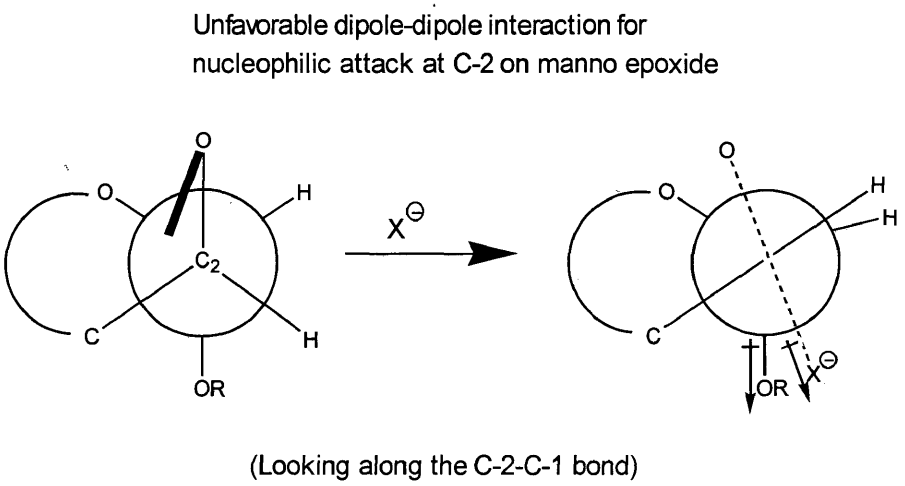


Figure 11: Newman projection of unfavorable dipole-dipole interaction

Aromatic Selenides

Organoselenium anions (specifically aromatic) are potent nucleophiles that exhibit strong preference for reactions with soft Lewis acids.[23] With a large, diffuse electron cloud coupled with its adjacent pi electrons from the aromatic group, phenyl and naphthyl selenides are easily polarizable making them excellent nucleophiles. According to the hard-soft acid-base theory, selenium anions are quite soft.[23] They posses low ionization potentials and their highest occupied molecular orbitals are very polarizable.[23] Once incorporated onto a substrate, a number of options become available for manipulating subsequent functional groups. Since an arylseleno moiety is a poor leaving group, a number

of synthetic transformations at remote sites may be manipulated without disturbing the selenium.[23]

The generation of the arylselenide can be conveniently accomplished by the reduction of diaryl diselenide with sodium borohydride.[24] The arylselenide anion generated from this reaction with sodium borohydride actually exists as a borane complex.[25] The nucleophilicity of this reagent can be prolonged by varying the concentration and/or degree of solvation of the anion.[23] Improved yields have been reported for aryl alkyl selenoxides bearing electron-withdrawing substitutents on the aromatic ring.[26]

Sharpless was the first to demonstrate some of the unique properties of nucleophilic selenium by using selenide anions in general epoxide/allylic alcohol interconversion.[27] First, the selenide anion was used to perform a ring opening on an epoxide. Then, regiospecific oxidative elimination of the phenyl seleno group was carried out to produce an allylic alcohol. Most Se(II) species are stable toward β-elimination, but their corresponding selenoxides undergo syn-elimination which is facile, carried out at or below room temperature.[28] In fact β-elimination of selenoxide represents one of the mildest, general olefin-forming reactions known.[28]

It has been reported that an allylic alcohol should be produced preferentially in the case of a hydroxyl or an alkyl ether at the β-position.[29] A vinylic cyanide is produced when CN is at the β-position. This selectivity has been attributed to the electron-withdrawing characteristic of the groups at the β-position. It has not been previously noted whether or not the fission of the Se-C_α

bond and that of the C_β-H bond take place in a concerted manner. Fujimoto, et al. may have answered that question in their study of the regioselectivity of selenoxide elimination.[29] They concluded that the elimination occurs via a transition state with a five membered ring structure, and the breaking of the C_β-H bond takes place earlier than that of the Se-C_α bond (Figure 12).

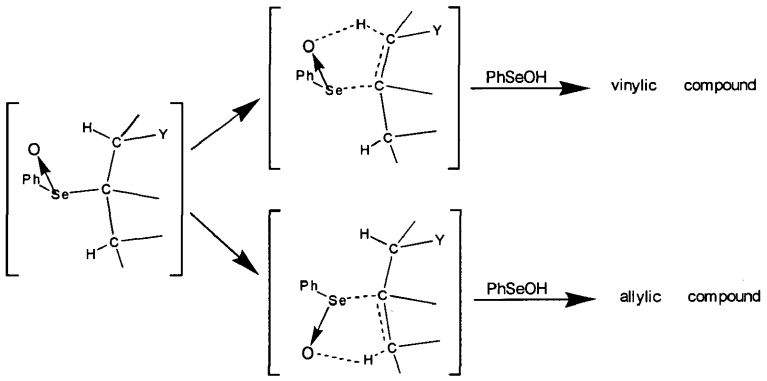


Figure 12: Transition state of a selenoxide elimination[29]

There are a few trouble spots when performing an elimination using selenoxides. Some kind of selenium species which is probably selenic acid or some derivative ("PhSeOH") reacts with the olefins to give β-hydroxy selenides at a rate comparable to the elimination rates.[26] Low and erratic yields have been reported as a result of these reactions. To alleviate this problem, high yields can be attained by thermolysis of the selenoxide in the presence of an amine.[26] These competing reactions are prevented by the presence of an unhindered secondary amine which converts the PhSeOH to $PhSeNR_2$.

In sterically unhindered acyclic systems it might be expected that the rate of elimination would be similar for each chiral selenide. Likewise, the rate for each selenoxide elimination would also be similar. In highly sterically hindered systems, the extreme situation could theoretically arise, namely that one of the pathways for the decomposition of a chiral selenoxide may be sterically inhibited leading to decomposition totally by the other available pathway.[30]

In a recent study of benzylidene methyl glucoside, it was reported that the use of a phenyl selenide ring opening of the manno-epoxide of a protected glucopyranose and subsequent oxidative elimination to form the 2-ulose derivative.[31] It was felt that the β-hydroxy selenides should react to form enols under appropriate conditions, such as when enol formation is the only option with no other β-hydrogens available.[31] In similar reactions involving sulfoxides, the enol has formed, but this is the first report of enol formation with selenoxides.

Wittig reaction

The Wittig reaction is a useful synthetic tool which involves the reaction a phosphorus ylide with an aldehyde or ketone to introduce a carbon-carbon double bond. Phosphorus ylides are usually stable, but reactive, compounds which can be represented by two resonance structures. Phosphorus ylides are usually prepared by the deprotonation of a phosphonium salt, most often alkyltriphenyl-phosphonium halides.

The originally proposed mechanism of the Wittig reaction the nucleophilic ylide carbon attack the carbonyl carbon to form an intermediate betaine.[32] The negatively charged oxygen then attacks the positively charged phosphorus to form an oxaphosphatan before dissociating into an alkene and phosphine oxide (Figure 13). An alternate mechanism has been put forth involving direct formation of an oxaphosphatan.

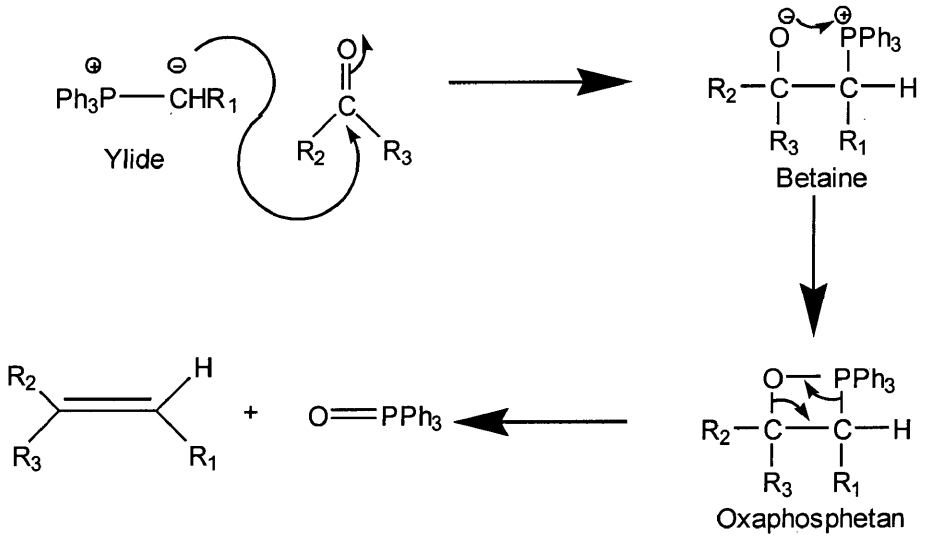


Figure 13: Originally proposed mechanism for the Wittig reaction[32]

The Wittig reaction is highly stereoselective due to the steric effects of the large phenyl substituents on the phosphorus. The *Z*-alkene predominates with the reaction of an unstabilized phosphorane. Conversely, stabilized phosphoranes produce the *E*-alkene.

The Wittig reaction has rarely been used on carbohydrates. Because the unstabalized ylide is so reactive, it will react with a number of oxygen containing

compounds, including hydroxyl groups. The hydroxyl groups must be protected before the desired reaction may be carried out. In order to get the Wittig reaction to work without protecting the hydroxyl groups first the ylide must be forced to act as a nucleophile on the carbonyl carbon and not as a base on the hydroxyl group.[21] The use of a polar, aprotic medium such as DMSO effectively weakens the basicity of the ylide relative to that of the alkoxide.

A DCA-stabilized ylide has been reacted with β-CD-6-aldehyde to give the tethered 6-deoxy-6-(9,10-dicyanoanthracenyl-2-methylene)-β-cyclodextrin.[21] With the synthesis of the β-CD-2-ulose, the Wittig reaction could be used in a similar manner to tether a DCA with β-cyclodextrin onto the secondary face (Figure 14).

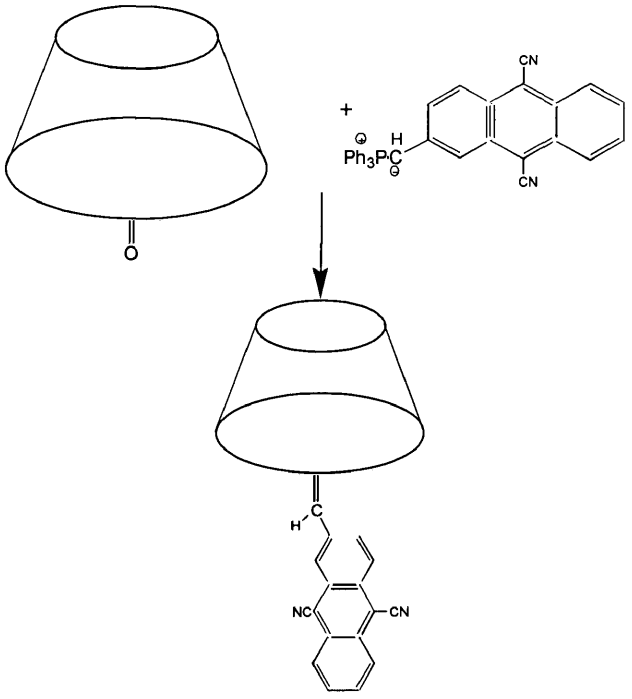


Figure 14: DCA tethered β-cyclodextrin via the Wittig reaction

Experimental

Thin-layer chromatography was performed on Analtech silica gel HLF plates (250 microns, organic binder, UV 254) with a solvent system of 5:4:3 n-butanol:ethanol:water by volume for nonsilylated cyclodextrin compounds, and 12:2:1: ethyl acetate:ethanol:water by volume for *per*-silylated cyclodextrin compounds. Spots were visualized by UV lamp and with vanillin stain and heat. Reverse-phase liquid chromatography was performed with RP-18 reverse phase silica gel (Whatman, LRP-2, 37-53 mm) in flash columns with a gradient elution of 13 fractions (100mL each) with compositions of 0%, 1%, 2%, 3%, 4%, 6%, 8%, 10%, 15%, 20%, 30%, 40%, 50%, and 80% acetonitrile in water. Normal-phase liquid chromatography was performed with normal phase silica gel (200-400 mesh, 60 A) in flash columns with a gradient elution of 14 fractions (100mL each) with compositions of 0%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, and 13% ethanol in water. Preparative high performance liquid chromatography was performed on a Waters 244 system equipped with a UV absorption detector 254nm, using a Whatman Magnum 20 ODS column for nonsilylated cyclodextrin compounds, and on a Waters 600E system equipped with a UV absorption detector (320nm), using a Alltech Econosil 10 micron column for *per*-silylated cyclodextrins. ^{1}H NMR spectra were obtained using a GE QE-300 spectrometer.

3-Nitrophenyltosylate

3-Nitrophenol (5.70 g, 40.9 mmol) was added to DMF (25 mL) and stirred. NaH (1.48 g, 62.7 mmol) was added in portions to the mixture followed by toluenesulfonyl chloride (3.97 g, 20.8 mmol) in portions, and the solution was allowed to stir for one hour. The solution was precipitated into to 500 mL of ice water, and the solid was filtered by suction yielding the nitrophenyltosylate. TLC R_f=0.64 in n-butanol:ethanol:water (5:4:3).

2-*O*-(*p*-Toluenesulfonyl)-β-cyclodextrin (1)[33]

β-cyclodextrin (12.0 g, 10.57 mmol) was dissolved in DMF (120 mL, reagent grade) with stirring and was warmed in an oil bath (60°C). 3-Nitrophenyltosylate (3.10 g, 10.57 mmol) was added to the solution, followed by a carbonate buffer (72 mL H_2O, 1.12 g Na_2CO_3, 0.32 g $NaHCO_3$). The solution was stirred for one hour at 60°C. The mixture was neutralized with cation exchange beads (20 mL in H_2O). The beads were filtered off. The mixture was added dropwise into acetone (1 L), and the precipitated solid was removed by suction filtration. The filtrate was concentrated to dryness, collected with acetone and removed by suction filtration. The solid was purified by reverse-phase chromatography, yielding **1** (0.58 g, 0.450 mmol, 4%). ^{1}H NMR spectrum found in Figure 19. TLC R_f=0.58.

$2^A,3^A$-Anhydro-β-cyclodextrin *manno* epoxide (2)[1]

2-*O*-(*p*-Toluenesulfonyl)-β-cyclodextrin (**1**) (1.00 g, 0.77 mmol) was added to an aqueous solution of ammonium bicarbonate (1.94 g in 40 mL H_2O) with stirring. The solution was heated in an oil bath (60°C) to reflux and monitored by TLC. After 6 hours the reaction was determined to be complete by TLC. The solution was treated with four portions of cation exchange beads (10 mL each) and two portions of bicarbonate anion exchange beads (10 mL each). The solution was filtered by gravity and concentrated to dryness. The solid was collected with acetone and filtered by suction yielding **2** (0.65 g, 0.58 mmol, 76%). TLC R_f=0.40.

3^A-Deoxy-3^A-phenylseleno-β-cyclodextrin (3)

2,3-Anhydro-β-cyclodextrin-*manno* epoxide (**2**) (0.65 g, 0.58 mmol) was added to water (10 mL). Diphenyl diselenide (0.136 g, 0.44 mmol) was dissolved in ethanol (20 mL). Sodium borohydride (0.022 g, 0.58 mmol) was added to the diphenyl diselenide solution in small amounts until the solution became colorless. The epoxide solution was added to the phenyl selenide solution. The mixture was heated to reflux in an oil bath and allowed to reflux overnight under nitrogen gas. After cooling, the solvents were removed *in vacuo*. The solid was collected with acetone and filtered by suction giving 0.74 g of material. Separation by reverse-phase high performance liquid chromatography (ret. time=19 min) yielded 0.17 g of **3**. ^{1}H NMR spectrum found in Figure 20. TLC R_f=0.53.

3^A-Deoxy-3^A-phenylselenoxy-β-cyclodextrin (4)

3^A-Deoxy-3^A-phenylseleno-β-cyclodextrin (**3**) (0.76 g, 0.590 mmol) was dissolved in water (10 mL) in an ice water bath. Hydrogen peroxide (30%, 2 mL, 660 mg, 19.41 mmol) was added portion by portion via a syringe. The reaction was allowed to gradually come to room temperature and stir overnight. TLC indicated that the reaction was complete. TLC R_f=0.58.

3^{A}-Deoxy-β-cyclodextrin-2^{A}-ulose (5)

Ethanol (15 mL) was added to the solution of 3^{A}-deoxy-3^{A}-phenylselenoxy-β-cyclodextrin (**4**) was made in order to dilute the mixture to a volume of 25 mL. The mixture was heated in an oil bath and allowed to reflux for 3 hours. The ethanol was removed *in vacuo*. The remaining solution was precipitated into 500 mL of acetone. The solid was collected by suction filtration yielding 0.52 g of material. No purification was performed.

(9,10-Dicyanoanthracenyl-2-methyl)triphenylphosphonium Bromide[21]

2-Bromomethyl-9,10-dicyanoanthracene (1.0 g, 3.12 mmol) and triphenylphosphine (0.82 g, 3.12 mmol) were dissolved in benzene (150 mL), and the reaction was heated at reflux overnight. The reaction was allowed to cool and the benzene was removed in vacuo. The solid was collected with acetone and filtered by suction yielding the phosphonium salt (3.86 g, 6.61 mmol). ^{1}H NMR spectrum found in Figure 21.

2-Deoxy-2-(9,10-dicyanoanthracenyl-2-methylene)-β-cyclodextrin (6)[21]

3^A-Deoxy-β-cyclodextrin-2^A-ulose (5) (0.52 g, 0.459 mmol) was dissolved in DMSO (50 mL) and benzene (50 mL) under nitrogen. The reaction was heated to reflux overnight, and water was collected in a Dean-Stark trap. The Wittig reagent was prepared by adding KO-t-Bu (5.0 mg, 0.459 mmol) to a solution of (9,10-dicyanoanthracenyl-2-methyl)triphenylphosphonium bromide (0.289 g, 0.459 mmol) in DMSO (20 mL) under nitrogen. The reaction was stirred for 30 min, then the mixture was added via syringe in one portion to the cooled β-cyclodextrin-2-ulose solution. The reaction was heated to reflux for 5 h under nitrogen. The benzene was removed *in vacuo*, and the DMSO was removed by vacuum distillation (0.1 Torr). The residue was collected with acetone and filtered with suction. The solid was ground with mortar and pestle in acetone to remove any unreacted dicyanoanthracene. The solid was purified by reverse-phase liquid chromatography and high performance reverse-phase liquid chromatography (ret. time=22min) yielding the dicyanoanthracene tethered β-cyclodextrin (0.04g, 0.03mmol, 6%). TLC showed one spot which fluoresced under UV and stained with vanillin. TLC R_f=0.54.

Dinaphthyl diselenide[34]

The Grignard reagent was prepared by adding 1-bromonaphthylene (10.4 g, 0.050 mol) and magnesium turnings (1.22 g, 0.050 mol) in ether (50 mL) under nitrogen with stirring. After the initiation of the Grignard reaction, selenium powder (3.95 g, 0.050 mol) was added to the solution which was heated to reflux under nitrogen overnight. After cooling, the solution was diluted with 200 mL of water and treated with dilute HCl (5 mL). The aqueous layer was extracted with ether (3x100 mL portions). The organic layer was removed from the solution and air was bubbled directly through the solution with stirring overnight. The solid formed in the oxidation was filtered with suction yielding the dinaphthyl diselenide (9.96 g, 24.18 mmol, 97%). ^{1}H NMR spectrum found in Figure 23.

Heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (7)[8]

Dried β-cyclodextrin (12.54 g 11.0 mmol) was dissolved in pyridine (122.5 mL). Tert-butyldimethylsilyl chloride (12.73g, 0.08 mol) was added to the solution. The reaction mixture was stirred overnight under nitrogen. The mixture was poured over ice-cold water and stirred vigorously for 10 min. The resulting precipitate was filtered off, washed with ice-cold water, and dissolved in ethyl acetate (245 mL). The solution was washed with 5% aqueous HCl solution (3 x 175 mL), saturated aqueous $NaHCO_3$ solution (1 x 175 mL), and 10% aqueous NaCl solution (1 x 175 mL). The solution was dried by stirring with anhydrous Na_2SO_4, filtered, concentrated, and dried under vacuum. The crude product was purified by normal-phase flash chromatography yielding **7** (6.63 g, 3.43 mmol, 31%). TLC R_f=0.62.

Mono(2-*O*-tosyl) heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (8)[8]

Heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**7**) (4.04 g, 2.08 mmol) was added to benzene (200 mL). Benzyltrimethylammonium methoxide (3.3 mL, 40% by wt., 7.28 mmol) was added to the solution. In order to remove any methanol which may have formed, a small volume (50 mL) was distilled off by heating the mixture in an oil bath (50°C) under aspirator (30 torr). After cooling, tosyl chloride (0.44 g, 2.28 mmol) was added to the mixture with stirring and left overnight. The solid was collected with water and filtered with suction. The solid was purified by normal-phase liquid chromatography yielding **8** (1.02 g, 0.52 mmol, 25%). TLC R_f=0.41.

Mono(2^A,3^A-anhydro)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (9)[8]

Mono(2-*O*-tosyl) heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**8**) (10.8g, 5.14 mmol) was added to ethanol (50 mL) and brought to reflux in an oil bath (110°C). Pinacol (1.34 g, 5.66 mmol) and potassium tert-butoxide (1.15 g, 5.14 mmol) were added to ethanol with stirring and added dropwise to the β-cyclodextrin mixture. The mixture was heated to reflux for an additional 30 min and allowed to cool. The cooled mixture was precipitated into water (600 mL). The solid was filtered with suction. ^{1}H NMR spectrum found in Figure 22. TLC R_f=0.47.

3^A-Deoxy-3^A-naphthylseleno heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (10)

Dinaphthal diselenide was added to ethanol (120 mL) with stirring under nitrogen. Sodium borohydride (0.068 g, 1.81 mmol) was added to the mixture. Mono(2^A,3^A-anhydro)heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**9**) (3.49 g, 1.81 mmol) was added to the mixture, and the mixture was heated to reflux in an oil bath (110°C) overnight under nitrogen. The ethanol was removed *in vacuo*. The solid was collected with water and filtered with suction. The solid was purified by normal-phase liquid chromatography yielding **10**. (0.26 g. 0.12 mmol, 7%). TLC R_f=0.57.

3^A-Deoxy-3^A-naphthylselenoxy heptakis(6-*O*-*tert*-butlydimethylsilyl)-β-cyclodextrin (11)

3^A-Deoxy-3^A-naphthylseleno heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**10**) (0.25 g, 0.117mmol) was added to ethanol (8 mL) with stirring in an ice water bath. H_2O_2 (30 %, 2 mL, 660 mg, 19.41 mmol) was added portion by portion via a syringe. The reaction was allowed to gradually come to room temperature and stir overnight.

3^A-Deoxy heptakis(6-*O*-*tert*-butlydimethylsilyl)-β-cyclodextrin-2^A-ulose (12)

Diisopropylamine (1 mL, 0.74 mmol) was added to the 3^A-deoxy-3^A-naphthalselenoxy heptakis(6-*O*-*tert*-butlydimethylsilyl)-β-cyclodextrin (**11**) reaction mixture. The mixture was heated to reflux and allowed to stir overnight. After cooling, the mixture was precipitated into water (300 mL) The ethanol was removed *in vacuo* and the solid was filtered with suction. The solid was purified by normal-phase liquid chromatography yielding **12** (0.02 g, 0.01 mmol, 9%).

Results

β-Cyclodextrin was tosylated with 3-nitrophenyl tosylate according to the procedure of Breslow.[33] TLC was used to determine the extent of the reaction by comparing unreacted β-cyclodextrin with tosylated β-cyclodextrin. Compound **1**'s R_f value was comparably higher. After purification by reverse-phase chromatography the ^{1}H NMR spectrum indicated the presence of a tosylate group in the aromatic region. The yields for the tosylation were quite low (2-4%), and the literature value (10%) was never achieved.

The epoxidation of the isolated tosylated β-cyclodextrin went in much better yield. TLC was used to monitor the progress of the reaction. The one new spot on TLC suggested the reaction had gone to completion. There was no further purification of **2**.

The phenyl selenide anion was generated according to the procedure of Sharpless and Lauer.[27] This proved to be an effective method of opening the ring of **2**. TLC was used to monitor the reaction. A faster moving spot than the epoxide appeared and was also active under UV. This was taken as an indication that the phenyl selenide derivative **3** had been formed. The product was purified using reverse-phase high performance liquid chromatography. The ^{1}H NMR spectrum indicated aromatic protons from the aryl selenide (Figure 20).

The oxidation and elimination of the phenyl selenide derivative was performed without purification of the product **5**. A ^{1}H NMR spectrum was taken of the product showed no phenyl selenide.

The Wittig reagent was prepared by adding potassium *tert*-butoxide to the DCA-derived phosphonium salt. This reagent was added to the dried β-cyclodextrin ketone in solution. The crude product was purified first by reverse-phase flash column chromatography, and then by reverse-phase high performance liquid chromatography. A ^{1}H NMR of the DCA tethered β-cyclodextrin was inconclusive.

In an attempt to make the compounds more easily purifiable and thus work on a larger scale, β-cyclodextrin was per-silylated making it soluble in organic solvents and more easily purified by silica gel chromatography. There was a marked increase in yield for the tosylation using tosyl chloride instead of nitrophenyl tosylate. Benzyltrimethylammonium methoxide was used as the base in place of carbonate. TLC indicated the tosylation had been achieved. After purification by normal-phase liquid chromatography, the ^{1}H NMR spectrum confirmed the tosylation had worked. The epoxidation reaction was performed with pinacol as the base. The reaction was monitored by TLC. The crude product was not purified.

In order to detect the aryl selenide better, naphthyl selenide was as the nucleophile to open the ring. Since dinaphthyl diselenide is not commercially available it had to be synthesized. A simple Grignard reaction followed by direct

oxidation with air produced the dinaphthyl diselenide in good yield (97%). A ^{1}H NMR spectrum was taken which agreed with the literature (Figure 23).

The naphthyl selenide anion for the ring opening was formed in the same fashion as the phenyl selenide anion. TLC was used to monitor the reaction. A faster moving spot than the epoxide appeared and was UV active indicating the naphthyl selenide derivative had been formed. After purification with normal-phase liquid chromatography, two separate routes were followed to determine the best path. In one path the naphthyl selenide β-cyclodextrin was desilylated with tetrabutyl ammonium fluoride (TBAF) and then purified by reverse-phase high performance liquid chromatography. In the other route, the naphthyl selenide β-cyclodextrin was purified by normal-phase high performance liquid chromatography. A ^{1}H NMR spectrum was used to analyze the latter, while the former has yet to be studied (Figure 24).

The oxidation and elimination of the selenide was done using a similar procedure as with the unprotected β-cyclodextrin. The crude product was purified by normal-phase liquid chromatography. A ^{1}H NMR spectrum has yet to be taken of this suspected β-cyclodextrin-2-ulose.

Discussion

The pathway from β-cyclodextrin and per-silylated β-cyclodextrin are similar and contain many previously known mechanisms. β-Cyclodextrin was per-silylated in an attempt to improve the yield of reaction affording the opportunity to work on larger scales.

The tosylation of β-cyclodextrin proceeds in an S_N2 fashion (Figure 15). For the unprotected β-cyclodextrin, the carbonate ion abstracts the most acidic proton, which is the hydrogen of the C-2 hydroxyl group, forming the C-2 alkoxide. The C-2 alkoxide attacks the nitrophenyl tosylate from the backside, displacing the chloride ion, and thus forming **1**. The tosylation went in extremely poor yield due to steric interferences caused by the size of β-cyclodextrin and because the stabilization of the C-2 alkoxide by the C-3 hydroxyl of the adjacent glucose unit. For the per-silylated β-cyclodextrin, the tosylation also follows and S_N2 mechanism, the only difference being that tosyl chloride was employed and not the nitrophenyl tosylate. The reaction was performed with an incredible increase in yield from the former procedure to give **8**. By not using an aqueous medium, hydrolysis of the nitrophenyl tosylate and possibly the C-2 tosylated β-cyclodextrin is prevented. Also, a better separation can be attained using silica gel instead of reverse-phase silica yielding more C-2 tosylate.

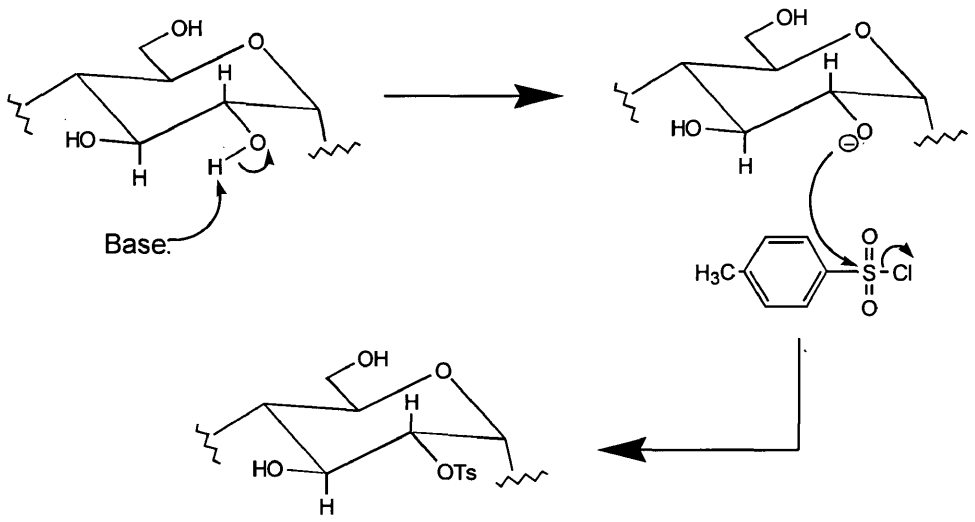


Figure 15: Mechanism for the synthesis of C-2 tosylated β-cyclodextrin

The epoxidation of β-cyclodextrin is also an S_N2 reaction. This time, however, the attack takes place intramolecularly. The ammonium bicarbonate deprotonates the C-3 hydroxyl to form the C-3 alkoxide. The alkoxide attacks the backside of the C-2 carbon displacing the tosyl group to form the **2**. The C-3 hydroxyl and C-2 tosylate must adopt a trans-diaxial orientation through a ring flip in order for the reaction to proceed. For the per-silylated β-cyclodextrin a softer approach was taken (Figure 16). Potassium *tert*-butoxide, a strong base, was used to deprotonate pinacol. The pinacol was slowly added to the per-silylated β-cyclodextrin to allow the pinacol to deprotonate the C-3 hydroxyl. With its steric baggage, pinacol would be a milder base for this reaction. Without pinacol there is a high concentration of strong base. This may lead to a cleavage

reaction with the 2-tosylated β-cyclodextrin. Similarly, the alkoxide attacks the C-2 carbon and forms **9** with the ring flip.

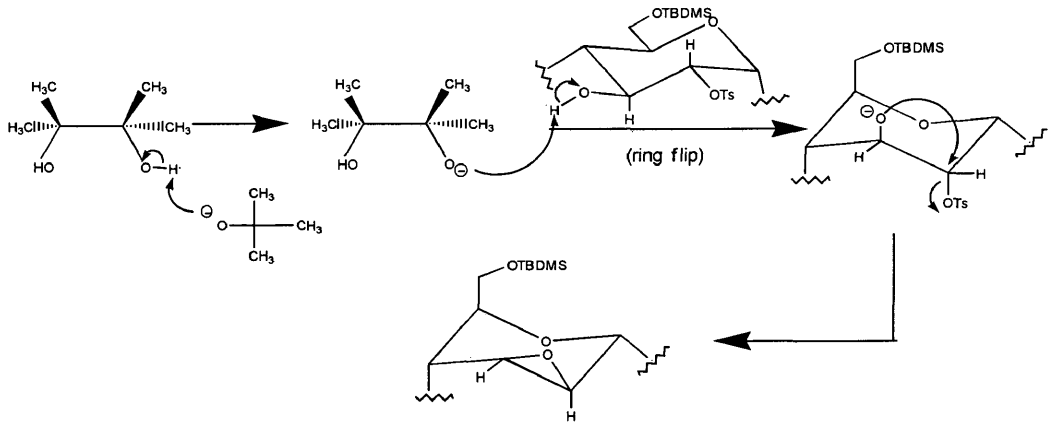


Figure 16: Mechanism for the epoxidation of *per*-silylated β-cyclodextrin

For the ring opening of the epoxide of the unprotected β-cyclodextrin, the phenyl selenide anion attacks at the C-3 position because of the unfavorable dipole interactions at the C-2 position. The epoxide opens with a ring inversion. The C-2 alkoxide is then protonated by the solvent to form an alcohol. The phenyl selenide anion is actually a phenyl seleno (triethoxy) borane complex. The naphthyl selenide anion is also assumed to be a borane complex. The naphthyl selenide anion works in a similar fashion on **9** (Figure 17). Naphthyl selenide was employed in order to achieve better purification because of its greater UV activity.

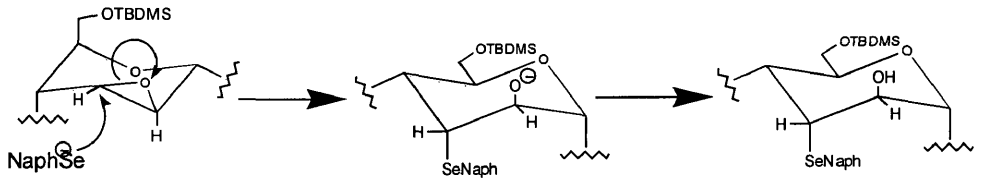


Figure 17: Mechanism for ring-opening of *per*-silylated β-cyclodextrin manno-epoxide

Both selenides were oxidized to the selenoxides by using hydrogen peroxide. The selenoxide was heated to reflux to induce elimination (Figure 18). Diisopropylamine was added to suppress any side reactions which may occur after the formation of the selenic acid.

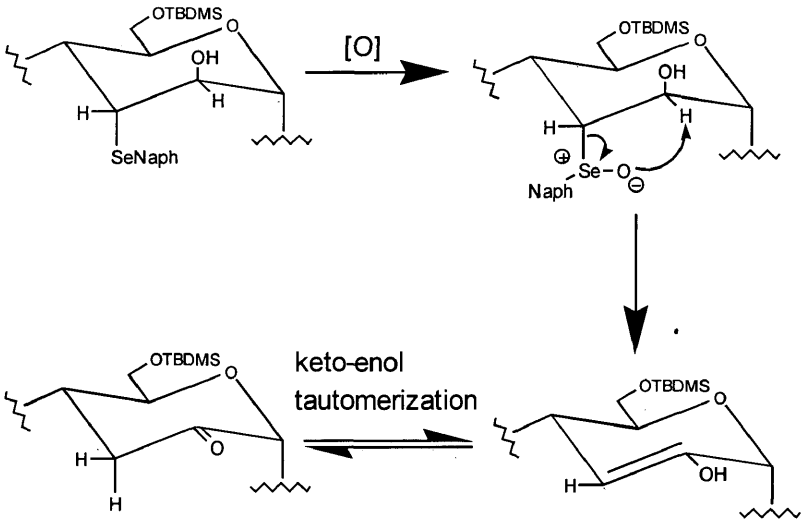


Figure 18: Mechanism of the selenoxide elimination to form the β-cyclodextrin-2-ulose

The Wittig reaction has only been performed on the unprotected β-cyclodextrin pathway. A triphenylphosphine derived DCA was used as the Wittig reagent. The ^{1}H NMR spectrum did show both β-cyclodextrin proton's and

DCA's protons, but whether the two were linked was unable to be determined.

TLC analysis did show a spot which fluoresced and stained.

Conclusion

Preliminary indications show that the pathway involving the epoxidation of the secondary face of β-cyclodextrin, ring-opening with an aryl selenide, and selenoxide elimination to form the β-cyclodextrin-ulose proceeds as intended. Left with no other alternative, selenoxide elimination can be forced to yield the vinylic compound. The Wittig reaction can be used to tether functionalities to the secondary face of β-cyclodextrin. The used of per-silylated β-cyclodextrin improves yields of certain reactions, especially tosylation, and improves separation. Further examination must be done to determine the presence of the ketone functionality. A scale-up of this pathway is needed in order to examine its viability.

APPENDIX OF SPECTRA

Figure 19: ^{1}H NMR of 2-*O*-(*p*-Toluenesulfonyl)-β-cyclodextrin (**1**) in DMSO

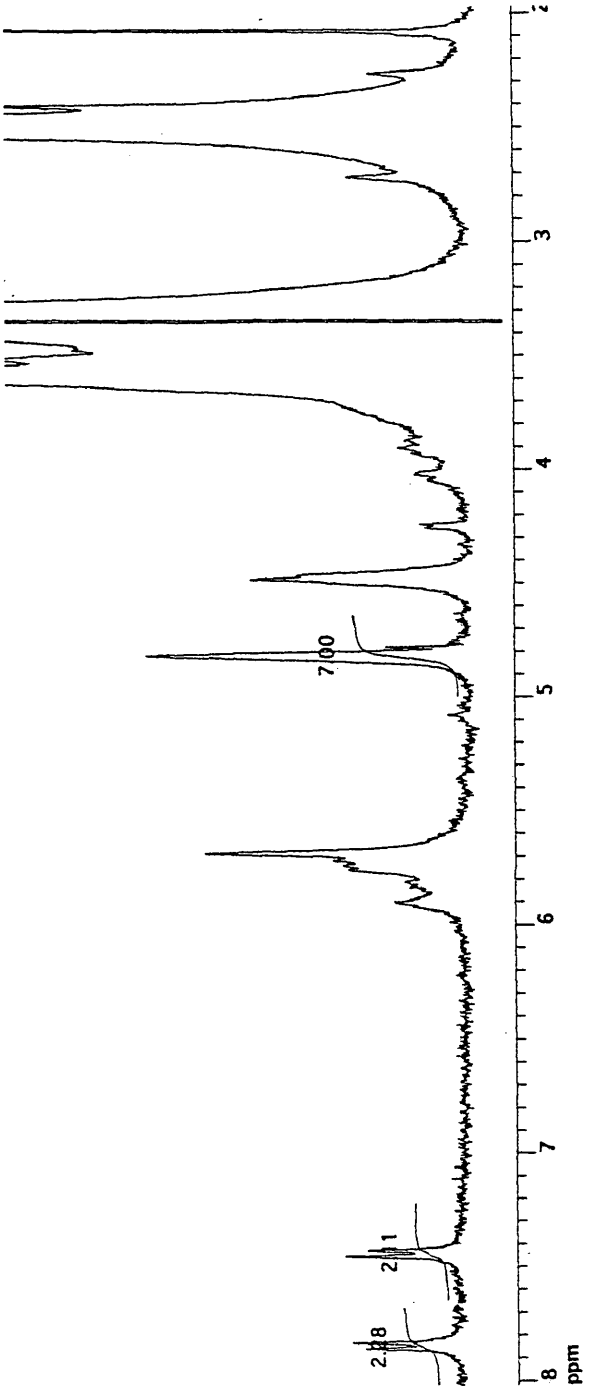


Figure 20: ^{1}H NMR of 3^{A}-Deoxy-3^{A}-phenylseleno-β-cyclodextrin (**3**) in D_2O

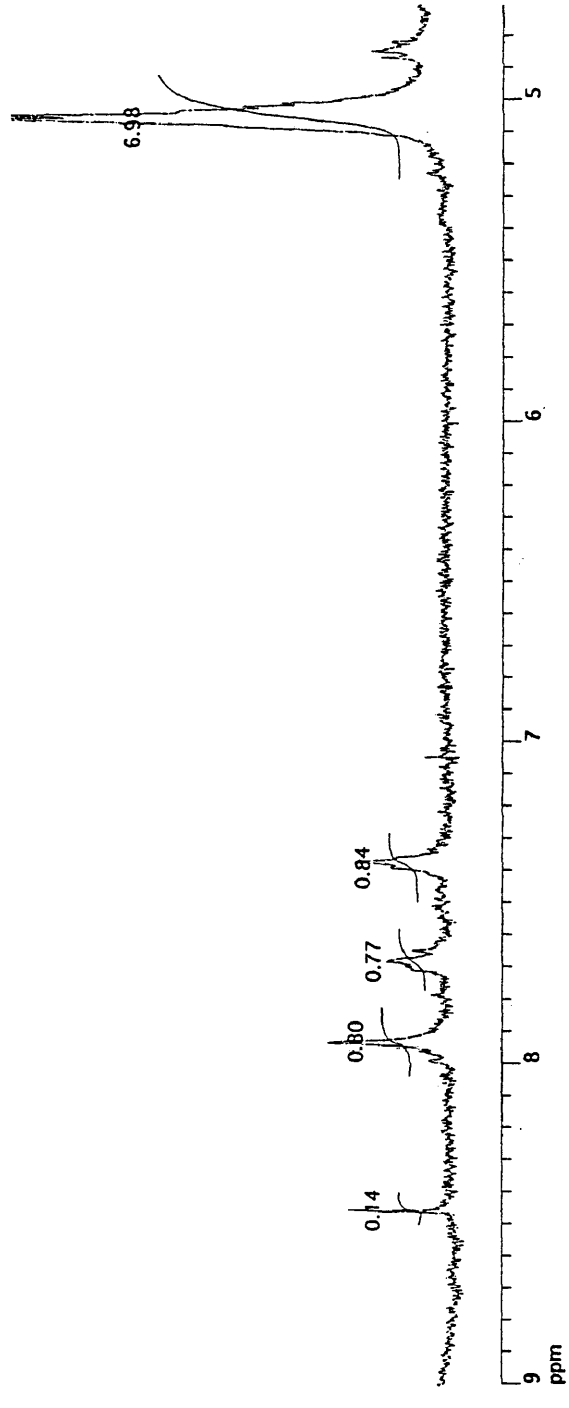


Figure 21: ^{1}H NMR of (9,10-Dicyanoanthracenyl-2-methyl)triphenyl-phosphonium Bromide in $CDCl_3$

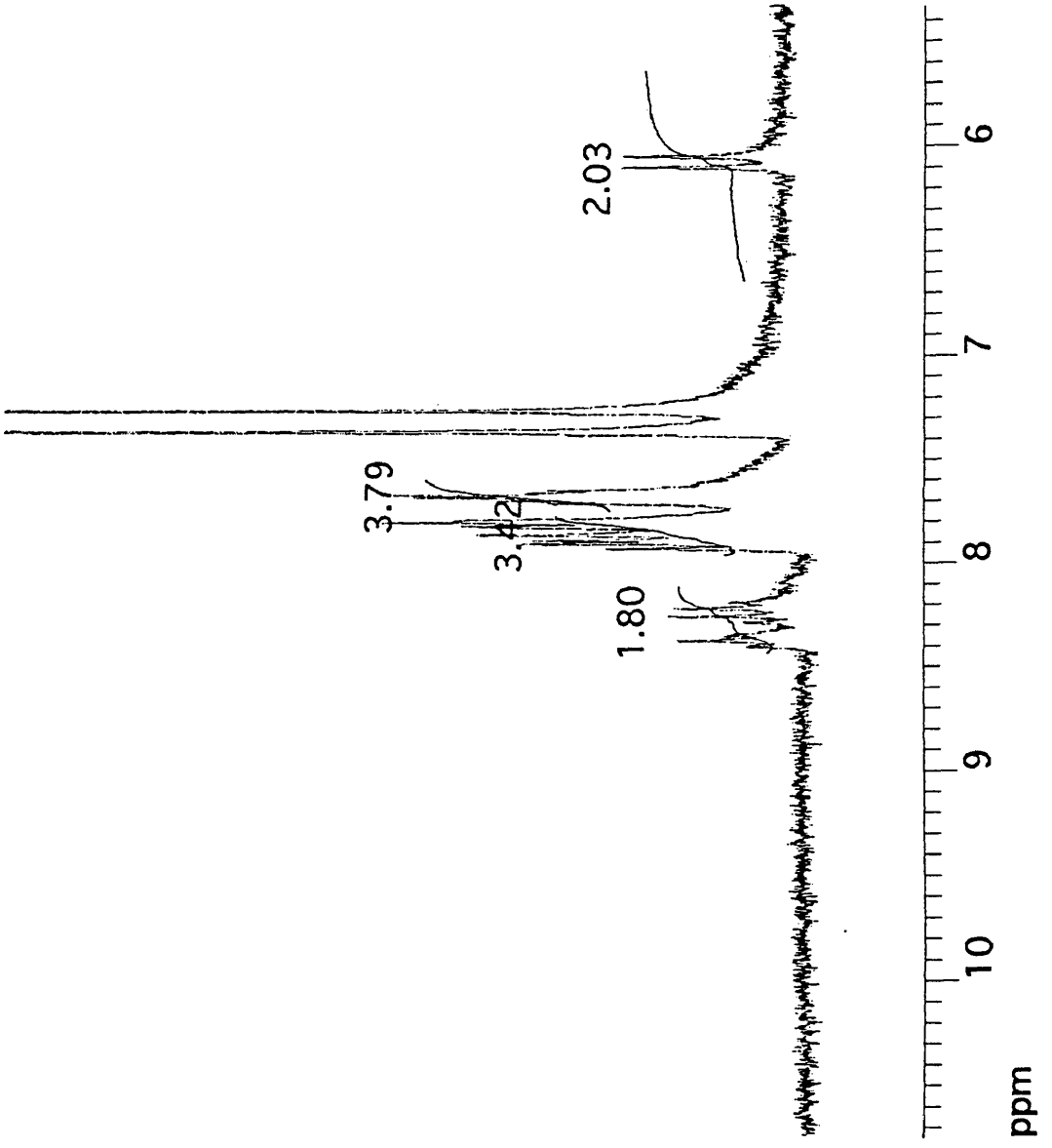


Figure 22: ^{1}H NMR of Mono(2^{A},3^{A}-anhydro)heptakis(6-*O*-*tert*-butyldimethyl-silyl)-βcyclodextrin (**9**) in $CDCl_3$

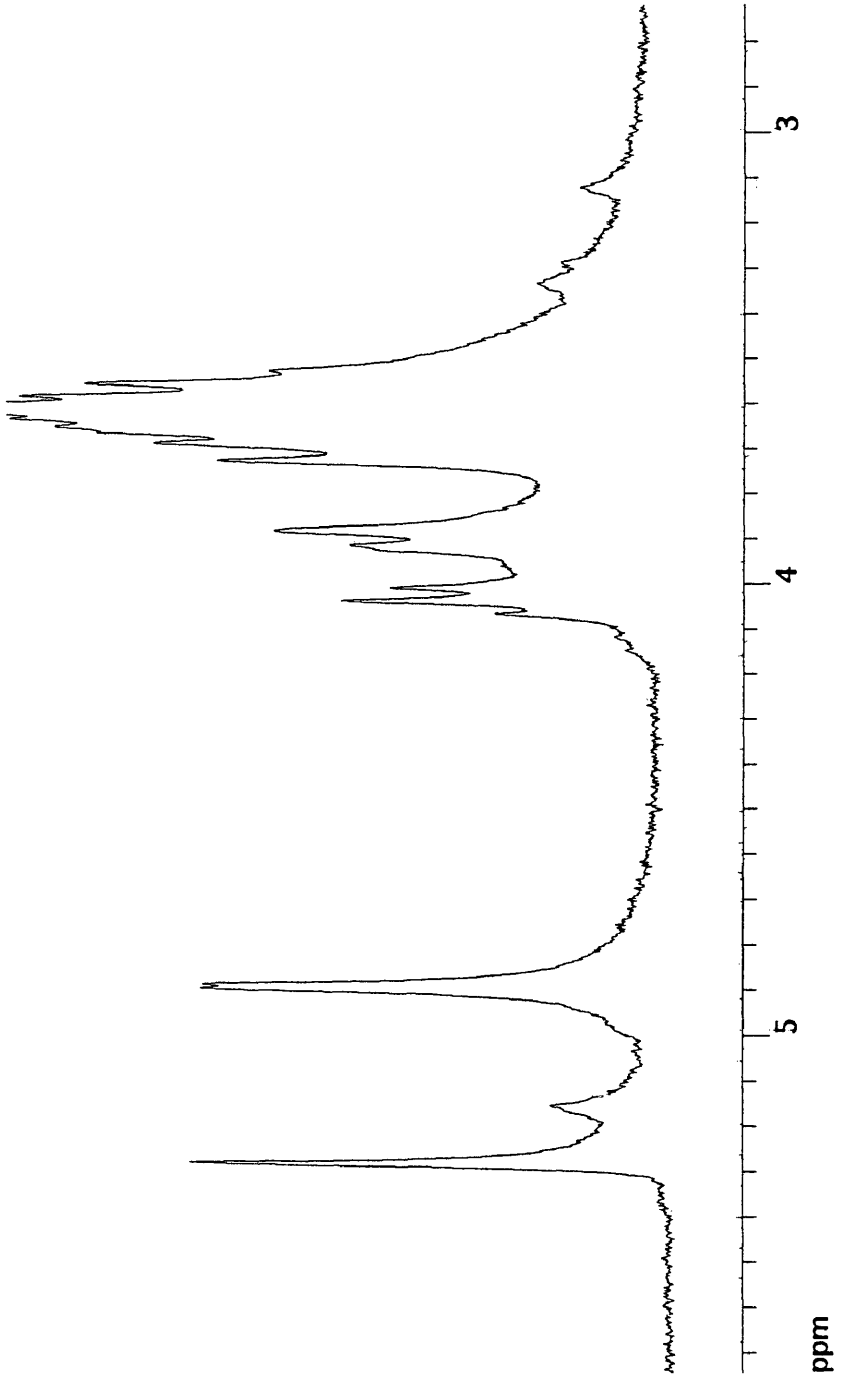


Figure 23: ^{1}H NMR of Dinaphthyl diselenide in $CDCl_3$

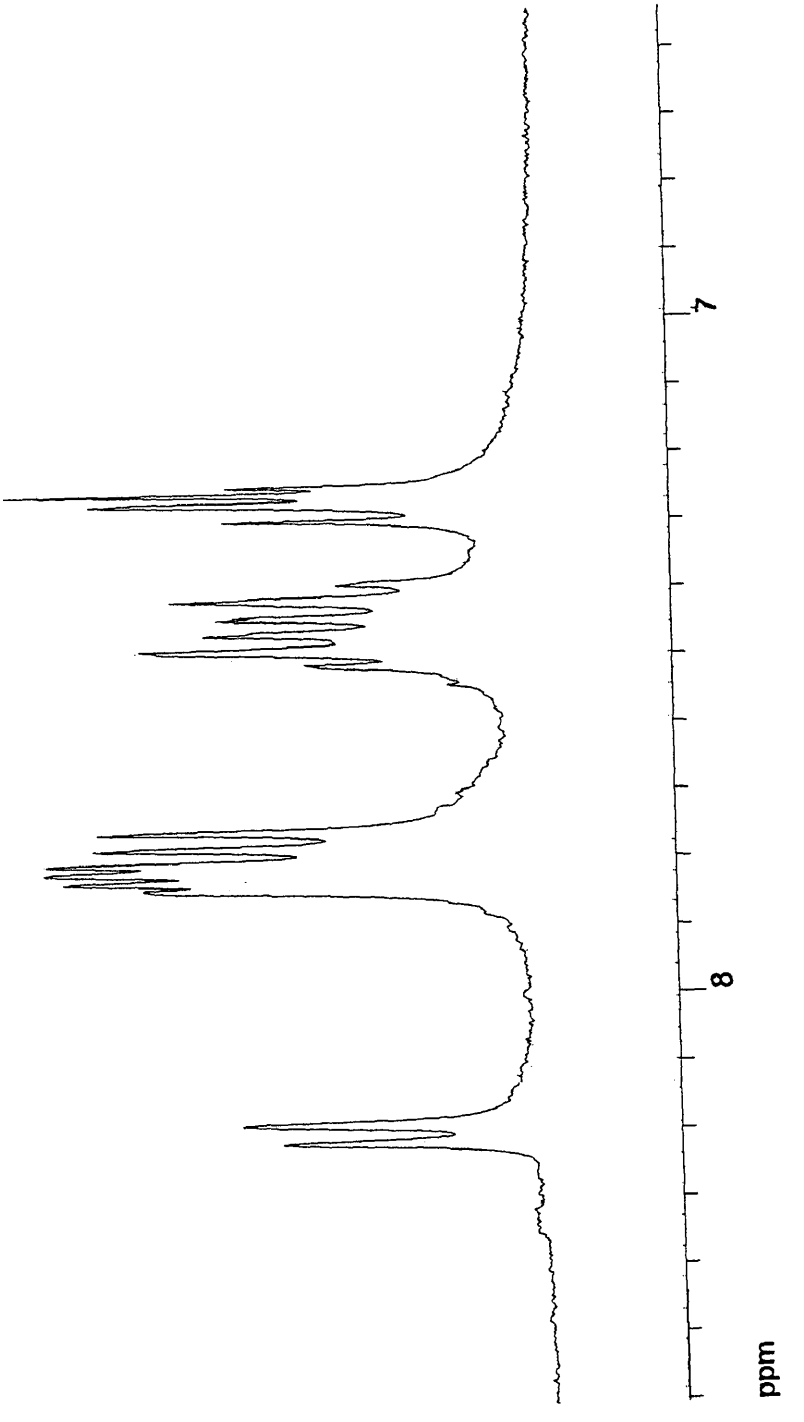


Figure 24: ^{1}H NMR of 3^{A}-Deoxy-3^{A}-naphthylseleno heptakis(6-*O-tert*-butyldimethyl- silyl)-β-cyclodextrin **(10)** in $CDCl_3$

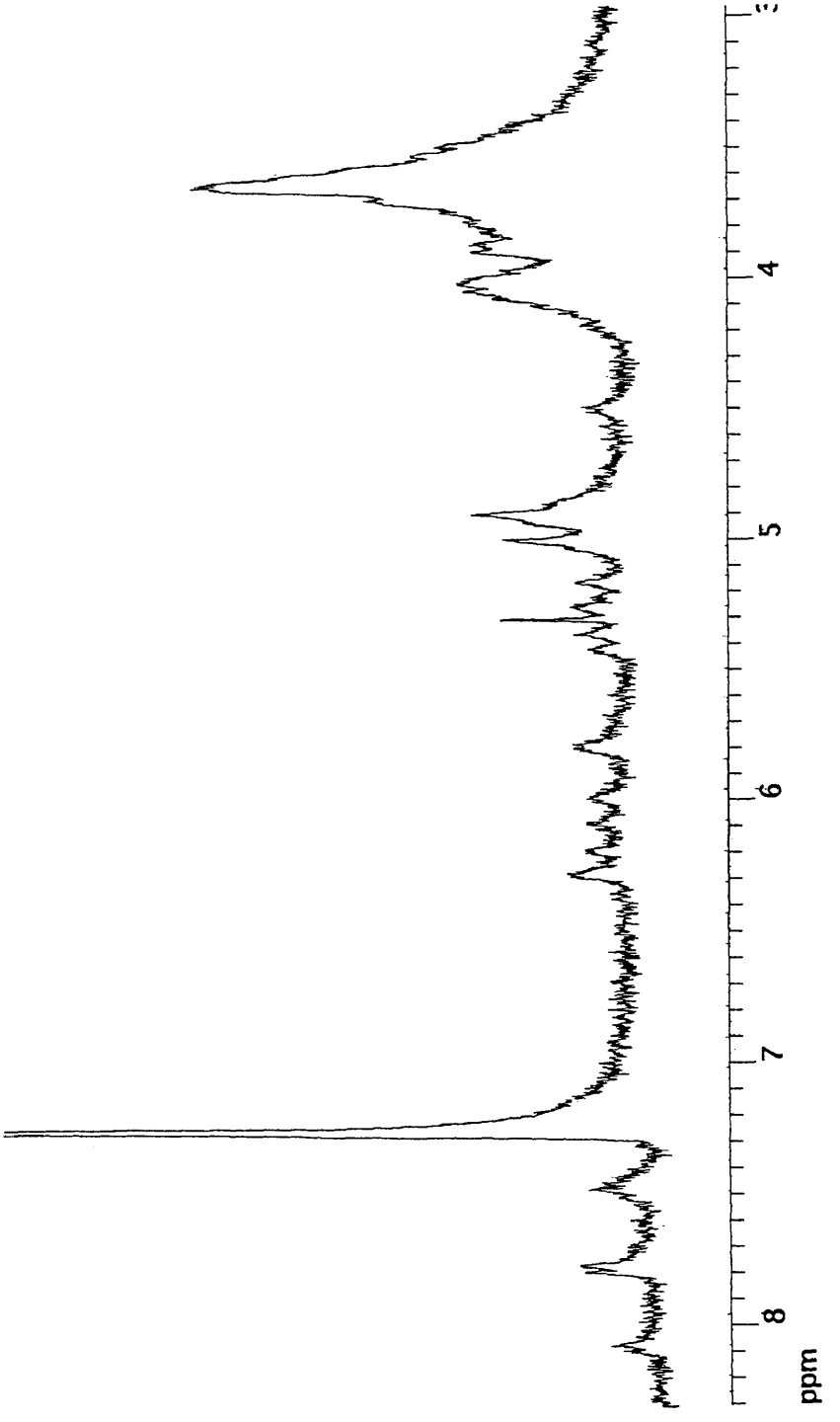
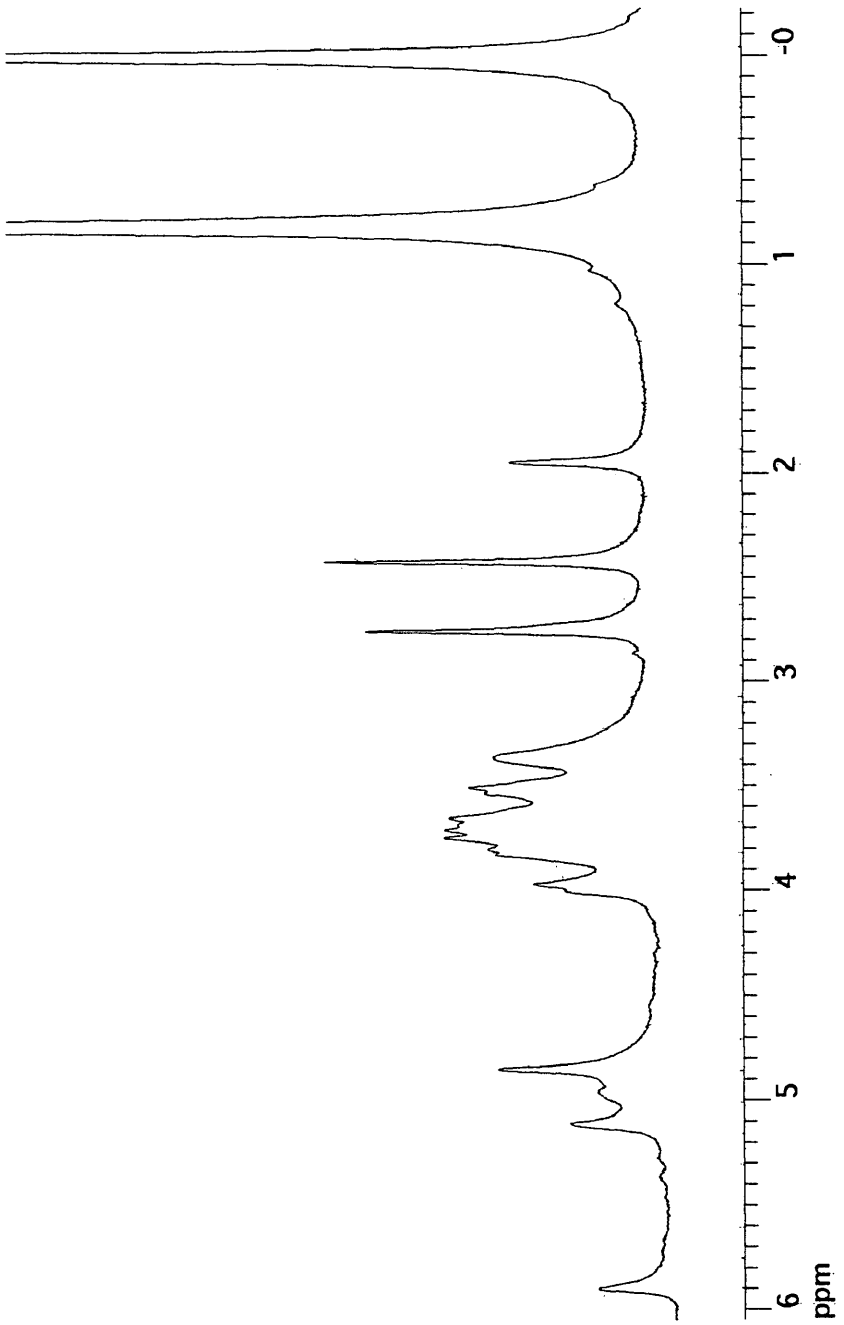


Figure 25: ^{1}H NMR of 3^{A}-Deoxy heptakis(6-*O*-*tert*-buyldimethylsilyl)-β-cyclodextrin-2^{A}-ulose (**12**) in acetone



References

[1] Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390-1391.
[2] Breslow, R.; Czarnik, A. W.; Lauer, M.; Leppkes, J.; Winkler, J.; Zimmerman, S. *J. Am. Chem. Soc.* **1986**, *108*, 1969-1979.
[3] Fujita, K.; Tahara, T.; Nagamura, S.; Imoto, T.; Koga, T. *J. Org. Chem.* **1987**, *52*, 636-640.
[4] Martin, K. A.; Mortellaro, M. A.; Swenger, R. W.; Fikes, L. E.; Winn, D. T.; Clary, S.; Johnson, M. P.; Czarnik, A.W. *J. Am. Chem. Soc.* **1995**, *117*, 10443-10448.
[5] Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978.
[6] Rong, D.; D'Souza, V. T. *Tetrahedron Lett.* **1990**, *31*, 4275-4278.
[7] Khan, A. R.; Barton, L.; D'Souza, V. T. *J. Org. Chem.* **1996**, *61*, 8301-8303.
[8] Pregel, M. J.; Buncel, E. *Can. J. Chem.* **1991**, *69*, 130-137.
[9] Yoon, J.; Hong, S.; Martin K.A.; Czarnik, A. W. *J Org. Chem.* **1995**, *60*, 2792-2795.
[10] Gibson, A.R.; Melton, L. D.; Slessor, K. N. *Can. J. Chem.* **1974**, *52*, 3905-3912.
[11] Kobayashi, M.; Urayama, T.; Suzawa, I.; Takagi, S.; Matsude, K.; Ichishima, E. *Agric. Biol. Chem.* **1988**, *52*, 2695-2702.
[12] Martin, K. A.; Mortellaro, M. A.; Swenger, R. W.; Fikes, L. E.; Winn, D. T.; Clary, S.; Johnson, M. P.; Czarnik, A.W. *J. Am. Chem. Soc.* **1995**, *117*, 10443-10448.
[13] Neckers, D. C.; Paczkowski, J. J. Am. Chem. Soc. 1986, 108, 291; Neckers, D. C.; Paczkowski, J. *Tetrahedron* **1986**, *42*, 4671.
[14] Gonzalez, M.C.; McIntosh, A. R.; Bolton, J. R.; Weedon, A. C. *J. Chem. Soc., Chem. Commun.* **1984**,1138-1140.
[15] Kuroda, Y.; Ito, M.; Sera, T.; Ogoshi, H. *J. Am. Chem. Soc.* **1993**, *115*, 7003-7004.
[16] Ye, H.; Tong, W.; D'Souza, V. T. *J. Am. Chem. Soc.* **1992**, *114*, 5470.
[17] Tabushi, I.; Fujita, K.; Yuan, L. C.; *Tetrahedron Lett.* **1977**, *18*, 2503.
[18] Berger, K. L.; Nemecek, A. L.; Abelt, C. J. *J. Org. Chem.* **1991**, *56*, 3514-3520.
[19] Aquino, A. M.; Abelt, C. J.; Berger, K. L.; Daragh, C. L.; Kelley, S. E.; Cossette, M. V. *J. Am. Chem. Soc.* **1990**, *112*, 5817.
[20] Acquavella, M. F.; Evans, M. E.; Farraher, S. W.; Novoret, C. J.; Abelt, C. J. *J. Chem. Soc. Perkin Trans. 2* **1995**, 385-388.
[21] Ivy, R. L.; Hafez, A. M.; Abelt, C. J. *J. Org. Chem.* 1997, 62, 6415-6416.
[22] Richardson, A. C. *Carbohydrate Res.* **1969**, *10*, 395.
[23] Liotta, D. *Acc. Chem. Res.* **1984**, *17*, 28-34.

[24] Liotta, D.; Markiewicz, W.; Santiesteban, W. *Tetrahedron Lett.* **1977**, *18*, 4365-4368.
[25] Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron Lett.* **1988**, *29*, 347-350.
[26] Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697-1705.
[27] Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.
[28] Martin, O. R.; Rafka, R. F.; Szarek, W. A. *Carbohydrate Res.* **1989**, *185*, 77-89.
[29] Kondo, N.; Fueno, H.; Fujimoto, H.; Makino, M.; Nakaoka, H.; Aoki, I.; Uemura, S. *J. Org. Chem.* **1994**, *59*, 5254-5263.
[30] Salmond, W. G.; Barta, M. A.; Cain, A. M.; Sobala, M. C. *Tetrahedron Lett.* **1977**, 1683-1686.
[31] Heath, C. E.; Gillam, M. C.; Callis, C. S.; Patto, R. R.; Abelt, C. J. *Carbohydrate Res.* **1998**, *307*, 371-373.
[32] Carey, F. A.; Sundberg, R. J. "Reactions of Carbon Nucleophiles with Carbonyl Groups" in *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, Plenum Press: New York, 1990.
[33] Ueno, A.; Breslow, R. *Tetrahedron Lett.* **1982**, *23*, 3451.
[34] Jen, K.; Cava, M. P. *J. Org. Chem.* **1983**, *48*, 1449-1451.

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