TOWARD A BREATHABLE FABRIC FOR PROTECTION AGAINST AIRBORNE TOXIC CHEMICALS, AND AN OLEFIN-FORMING CASCADE REACTION EN ROUTE TO 2,2'-BI(GLYCEROL)

Except where reference is made to the work of others, the work described in this dissertation is my own or was done in collaboration with my advisory committee. This dissertation does notinclude proprietary or classified information.

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Xiaoxun Li

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TOWARD A BREATHABLE FABRIC FOR PROTECTION AGAINST AIRBORNE TOXIC CHEMICALS, AND AN OLEFIN-FORMING CASCADE REACTION EN ROUTE TO 2,2'-BI(GLYCEROL)

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VITA

Xiaoxun Li, son of Yunfeng Li and Shuqing Zhao, was born February 24, 1978, in Xi'an, Shaanxi, the People's Republic of China. He graduated with a Bachelor of Science degree in Chemistry in 2001 from Hunan University. In the fall of 2003, he entered the Graduate School in the Department of Chemistry and Biochemistry where he joined the laboratory of Peter Livant and is currently pursuing a Ph.D. degree. In 2007, he married Xiaoyan Ma, daughter of Baosheng Ma and Xiang Li.

DISSERTATION ABSTRACT

TOWARD A BREATHABLE FABRIC FOR PROTECTION AGAINST AIRBORNE TOXIC CHEMICALS AND AN OLEFIN-FORMING CASCADE REACTION EN ROUTE TO 2,2'-BI(GLYCEROL)

Xiaoxun Li

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Part I. Several compounds that were envisioned to interact strongly with airborne chemical warfare agents, principally organophosphorus nerve agents, were synthesized. This was part of a multi-site, multi-investigator effort to make a breathable fabric that offered protection against airborne toxins. The compounds consisted of an "active protection element" and a linker moiety for attaching to the surface of the fabric. In our work, the active protection element was an aromatic carboxylic acid flanked by poly(ethylene glycol) sidechains. As the focus of the project shifted from nerve gases to toxic industrial chemicals, our strategy for countering the toxins shifted. We designed a multi-layer fabric with each porous layer surface-modified with a different reactive

element. We found that attachment of compounds to the surface was highly satisfactory using the azide + alkyne click reaction. We prepared compounds to be used for creating an acidic porous layer, a basic porous layer, and an oxidative porous layer.

Part II. 2,2’-bi(glycerol) or 2,3-bis(hydroxymethyl)-1,2,3,4-butanetetraol **73** is a new six-hydroxyl compound that is a potential precursor to novel dendrimers, unnatural lipids, and open framework coordination polymers. A synthesis of **73** in five steps and 18.9% overall yield was achieved. Starting from commercially available nitromethane, our synthesis makes **73** available in multigram quantities. A new olefin-forming cascade reaction for a nitrobromo compound was discovered. Treatment of 5-bromo-5-nitro-2,2-dimethyl-1,3-dioxane with NaH in various solvents leads in one step to 2,2,2',2'-tetramethyl[5,5']bi[1,3]dioxanylidene. The cascade reaction subsumes three separate steps, and gives a higher yield than the overall yield of the three steps separately.The X-ray crystal structure of **73** is reported.

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LIST OF ABBREVIATIONS

bp	boiling point
br	broad
°C	degree Celsius
^{13}C NMR	carbon nuclear magnetic resonance
$CDCl_{13}$	deuterated chloroform
d	doublet
dd	doublet of doubles
DEPT	distortionless enhancement by polarization transfer
DMSO-d_6	deuterated dimethyl sulfoxide
D_2O	deuterium oxide
equiv	equivalent
Et_2O	diethyl ether
EtOAc	ethyl acetate
^{1}H NMR	proton nuclear magnetic resonance
h	hour

Hz	Hertz
J	coupling constant
LAH	lithium aluminum hydride
lit.	literature
m	multiplet
mL	milliliter
mmol	millimole
mp	melting point
ppm	parts per million
q	quartet
quat	quaternary
rt	room temperature
s	singlet
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane

1. I. TOWARD A BREATHABLE FABRIC FOR PROTECTION AGAINST AIRBORNE TOXIC CHEMICALS

Introduction

A remarkable increase in emphasis on protection of humans from chemical hazards was seen in the late twentieth century. Workers in certain jobs require protective garments. The threat of biological and terrorist attacks also makes protective garments important and valuable. The range of chemical hazards and the means of combating them continue to grow and become ever more complex. A consequence of this is the development and exploitation of new fabric and methods whose purpose is to provide im- proved protection.

The following work is part of a collaboration with Professor Yasser Gowayed, Professor Gisela Buschle-Diller, both of the Department of Polymer and Fiber Engineer at Auburn University, Professor Igor Luzinov of the School of Materials Science and Engineering at Clemson University, and Jason Michael Lyons of NovaComp, Inc., Philadelphia, Pennsylvania. The overall goal of the project was to invent a fabric and construct a garment from that fabric in order to offer to the wearer protection from harmful chemicals.

Performance of protective materials depends on the resistance of the materials to the permeation of harmful chemicals, *i.e.* so-called barrier properties. Unfortunately, protective clothing materials coated with carbon-loaded foam[1] and nonwoven layers[2] which have good barrier properties, are heavy and provide limited breathability, causing discomfort and heart stress. On the other hand, increased permeability results in reduced protection. A more efficient approach can be achieved by the use of selectively permeable materials that allow water vapor molecules to pass due to their relatively small size, while preventing some of the larger organic vapor molecules from permeating through the polymeric structure. [3] However, such passive selective diffusion barrier materials do not suffice for some of the toxins used as warfare agents.

In short, current state-of-the-art chemical protection materials are either completely impermeable with limited breathability, or selectively impermeable and breathable with limited efficiency for harmful chemicals.

A design philosophy based on active protection and selective permeation was adopted by our research team. During the course of the project, the type of toxic chemicals against which the fabric would protect changed, at the request of the funding agency, from chemical warfare agents, initially, to toxic industrial chemicals ("TICs") later.

1.1 Previous approaches to chemically protective garments.

Threat of biological and chemical terrorist attacks is currently a topical issue.

Common chemical toxins can be manufactured easily and inexpensively, and terrorist activities have increased drastically. Not only the military and emergency personnel face this kind of threat; the general public is not far away from the threat anymore.

Protection via activated carbon inclusion

In early approaches to protection from chemical and biological toxins, multi-layered textile structures were proposed and tested for their effectiveness. Probably the most studied materials for adsorption of harmful chemical vapors and other organic molecules are activated carbon fibers (ACF) and granular activated carbon (GAC). Aron[4] developed a sheath/core polypropylene fiber with carbon powder in the core. As an alternative it was suggested to laminate a layer of carbon fabric between two layers of polypropylene. Kirayoglu[5] recommended a fabric layer of activated charcoal cloth, while De Ruiter[6] proposed a layer containing granular activated carbon coated with a crosslinking agent or an additional light fabric. In order to reduce the absorption of water vapor on activated carbon, which caused a decrease in effectiveness, organosilicone thin films were deposited via plasma treatment on fabrics impregnated with active carbon.[7]

Activated carbon, although capable of adsorbing hazardous chemical compounds and preventing them from getting to the skin, cannot destroy or react with these agents, thus cannot be termed “active” protection materials. This limits the time of protection and raises disposal problems. Further, protective fabrics that contain activated carbon as an adsorbent layer have higher weight and do not allow moisture vapor transport from the

body. Both factors combined to cause heat stress and low performance.

Adsorption of gases on inorganic metal oxides

Besides activated carbon, other adsorbents are considered effective. These include inorganic metal oxides, such as magnesium or calcium oxide, incorporated in the form of nanoparticles or microencapsulated, or aluminum silicate and aluminum oxide applied to textile materials as thin films by chemical vapor deposition.[8] Upon contact with certain nerve gases (e.g., VX) hydrolysis reactions to nontoxic compounds occur, or complexation takes place. It could be demonstrated that the reactive nanoparticles or thin films were attached to textiles without lowering their ability to detoxify chemical agents. Initial tests with sulfur mustard and soman showed that both agents can be decomposed with a variable degree of success,[9] however undesired adsorption reactions of benign substances might occur. It has also been claimed that they are able to react with biological agents such as viruses or bacterial spores and thus might still be a better choice than activated carbon for chemical/biological protection with greater efficiency and safety.

Deactivation of chemical warfare agents by enzymatic means

This approach has gained the increasing interest of the research community. For example, organophosphate-based pesticides similar to soman can be degraded by organophosphate hydrolase[10] which can be obtained in sufficient amounts from *Escherichia coli*. Immobilized organophosphorus hydrolase in the form of a

nanocomposite polymer-silicone has also been investigated and claimed as an effective and stable protection agent.[11]

1.2 Active protection against nerve gases (Project 1).

Initially, this project focused on organophosphorus nerve gases, which comprise an important category of chemical warfare agent. Sarin, soman, tabun, VX, and its structural isomer VR are examples of this type of nerve gas (Figure 1).

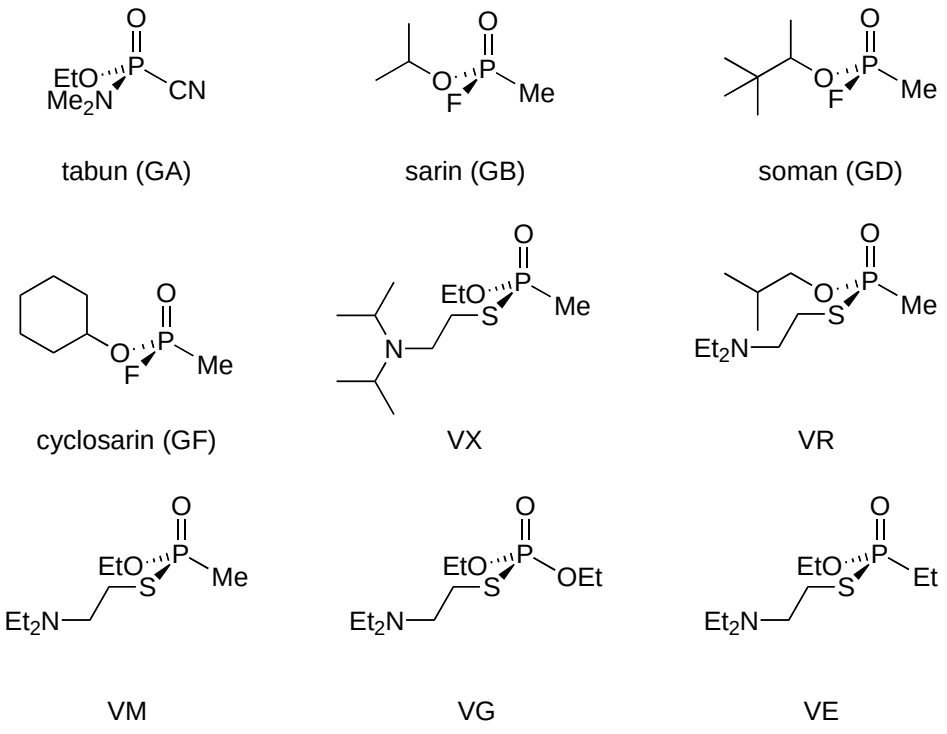


Figure 1. Organophosphorus-based nerve agents.

Effective decontamination for compounds such as sarin or VX via treatment with an

oil-in-water microemulsion of oxidizing agents has been claimed by Menger and Rourk.[12] The microemulsion was composed of glycol, water, surfactant and hydrogen peroxide, which replaced the formerly used hypochlorite. This formulation showed potential to be effective against mustard gas as well (see below). In a similar approach, Wagner and Yang[13] developed a broad-spectrum decontamination system based on activation of peroxide with molybdate and bicarbonate. Schroeder-Gibson *et al.*[14] used electrospinning of microfibers with cyclodextrin iodobenzoates enclosed for deactivation of soman.

Physical immobilization

Physical immobilization of chemical warfare agents is based on the concept of attaching to the fabric's surface molecules capable of forming complexes with the chemical warfare agents. Such complexes would rely on hydrogen-bond formation. For example, nerve agents, *e.g.* sarin, tabun, soman, *etc.*, have as a common element the phosphoryl linkage, P=O. Triphenylphosphine oxide, another P=O containing compound, is known to form strong hydrogen-bond complexes with a variety of functional groups.[15] It will be our approach to model and synthesize a "receptor" for phosphorus-based nerve agents using spatial placement of functional groups like carboxylic acids and phenols which bind the P=O group strongly. Some candidates for this approach are shown in Figure 2.

In general, a hydrogen-bond donor element ("D") and a one or more side chains ("S") capable of "solvating" or stabilizing the hydrogen-bonded complex are envisioned,

as shown in Figure 2. The assembly of donor group and sidechains will be referred to collectively as the active element. Possible "D" structures are: $-CO_2H$, $-SO_3H$, -OH (phenol), among others. Possible side chains ("S") might be oligo(ethylene glycol) units as shown in Figure 2 with various chain lengths, or short oligopeptide structures. A linker group is required to tether the active element to the polymer membrane.

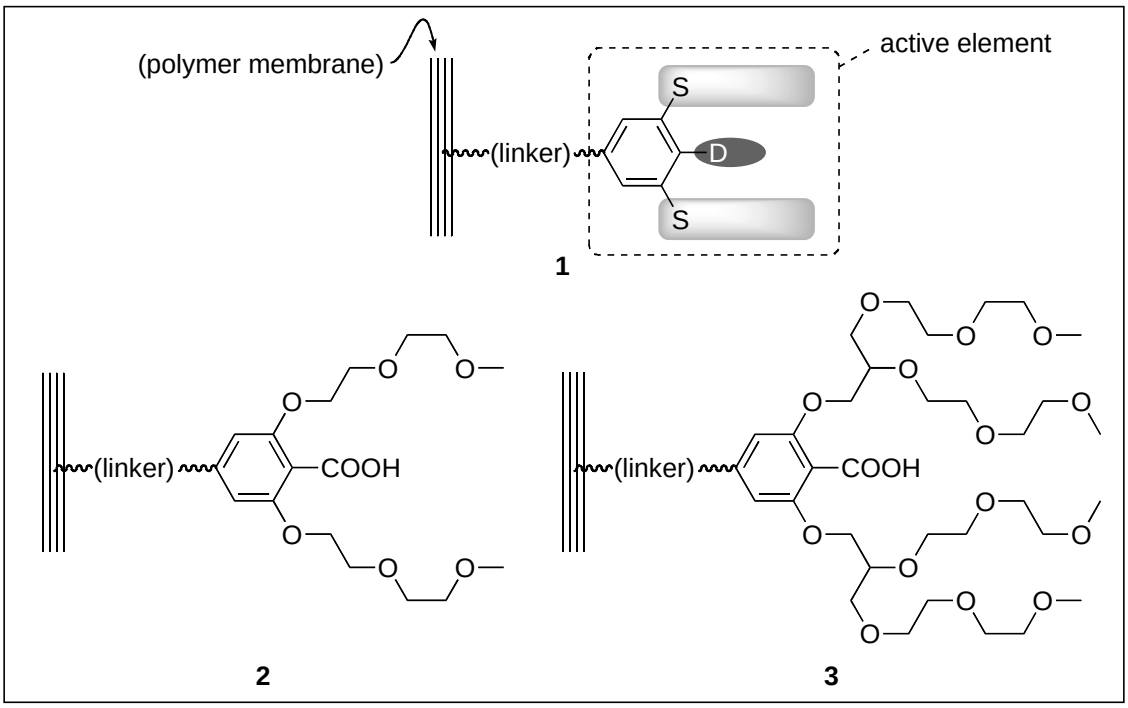


Figure 2. Potential receptors for phosphorus-based nerve gases. Vertical lines represent the surface of the fabric. **1** is a general design, and **2** and **3** are examples of **1**.

1.3 Active protection against toxic industrial chemicals ("TICs") (Project 2).

Later in our project, the funding agency requested that we shift our attention away

from nerve gases and focus instead on toxic industrial chemicals.

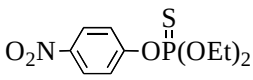
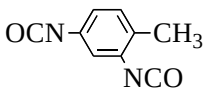
Table 1[16] presents the current high volume toxic industrial chemicals (top 27 TIC's) and their major properties. The list contains organic and inorganic chemicals in gaseous and liquid form. The chemicals are in alphabetical order. High volume chemical manufacturing sites in the U.S. could be the target of a terrorist attack or simply a site affected by a natural disaster such as an earthquake or a hurricane. Potentially catastrophic results could affect densely populated areas and especially emergency personnel. "Neutralization" of the toxicants to the extent that they are no longer harmful would be most desirable. Due to the varied nature of these agents this is a difficult task. The immediate goal is to organize TICs in groups that would allow us to suggest a common detoxification mechanism for each group.

Several possibilities to organize the compounds into broader categories include:

- ❖ Acidity/basicity
- ❖ Nucleophilicity
- ❖ Ability to polymerize easily
- ❖ Effectiveness as oxidizing or reducing agent
- ❖ Vapor pressure (high/low volatility)
- ❖ Capacity for H-bond formation

For example, all amines could be grouped and a common decontamination mechanism devised.

Table 1. Top 27 toxic industrial chemicals (TICs).[16]

Name	Formula	Toxicity threshold (ppm/h)	
		Impairment	Fatality
allyl alcohol	$H_2C=CHCH_2OH$	7.7	22
acrolein	$H_2C=CH-CHO$	0.1	1.4
acrylonitrile	$H_2C=CH-CN$	35	75
ammonia	NH_3	110	1100
arsine	AsH_3	0.2	0.5
chlorine	Cl_2	0.2	22
diborane	B_2H_6	>1	15
ethylene oxide		45	200
formaldehyde	$H_2C=O$	10	25
hydrogen bromide	HBr	3	30
hydrogen chloride	HCl	22	104
hydrogen cyanide	HCN	7.0	15-50
hydrogen fluoride	HF	24	44
hydrogen selenide	H_2Se	0.2	1.5+
hydrogen sulfide	H_2S	30	100
methyl isocyanate	$CH_3N=C=O$	0.5	5
methyl mercaptan	CH_3SH	5.0	23
nitrogen dioxide	NO_2	12	20
nitric acid	HNO_3	4.0	22+
parathion		0.2	0.8
phosgene	$Cl_2C=O$	0.3	0.8-5
phosphine	PH_3	0.3	11-30
sulfuric acid	H_2SO_4	2.5	7.5
sulfur dioxide; sulfur trioxide	SO_2, SO_3	>3	15-100
toluene-2,4-diisocyanate		0.08	0.51

1.3.1 Possible protection scheme against a diverse collection of toxic compounds.

The compounds comprising Table 1 bear little resemblance to each other and to chemical warfare agents that were the focus of our efforts initially. How can a fabric be designed to protect the wearer from such a varied mixture of hamful compounds?

Our approach is to construct a fabric having multiple porous layers. Each layer would be surface-modified with a reactive compound. The nature of the underlying porous material will be discussed in the next section. With reference to the broad categories listed above, we propose to equip layers with independent specific functionalities that could address separate aspects, such as acidity/basicity or nucleophilicity/electrophilicity characteristics. Other combination of layers addressing different parameters can be also envisioned. We view this as a flexible, yet comprehensive approach to a complex and multifaceted problem. A schematic of our proposed solution, a layered protective material composed of a number of porous polymer membrane layers, is presented in Figure 3.

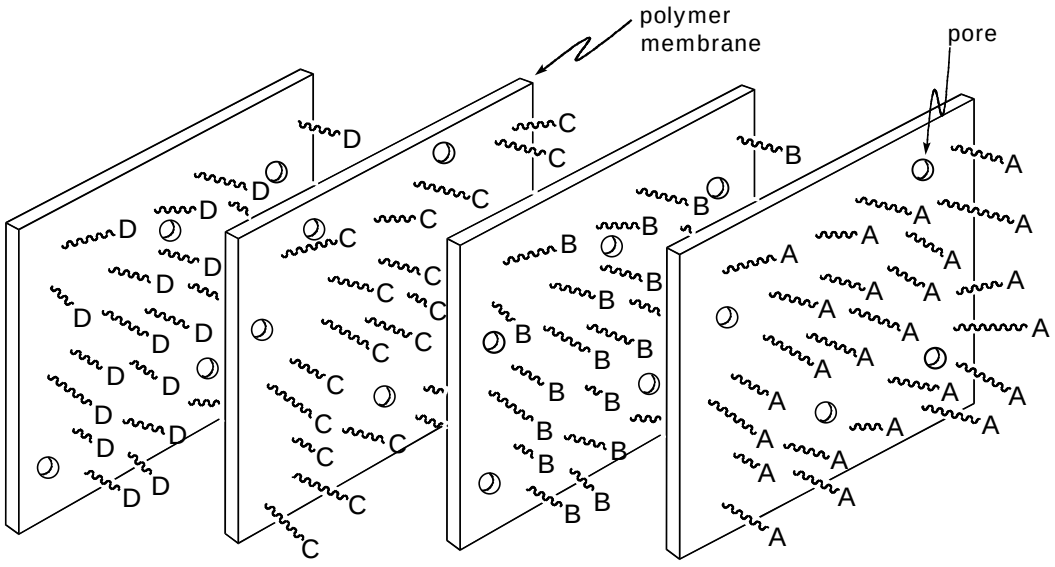


Figure 3. Proposal for a fabric of multiple reactive layers.

In Figure 3, A, B, C, and D represent different reactive functionalities. For example, A might be a strongly acidic site. B might be a strongly basic site. C might be a Lewis acidic site, and so forth. These are bound to successive layers of polymer membranes. Although the Figure shows groups A, B, *etc*. attached to one face of the membrane, in fact the entire membrane would be functionalized. To prevent mutually incompatible layers from coming in contact, a spacer between layers would be required. This is discussed in Section 1.4.

Figure 4 gives an example of how this multiple layer idea might work, by focusing on one membrane layer in the stack.

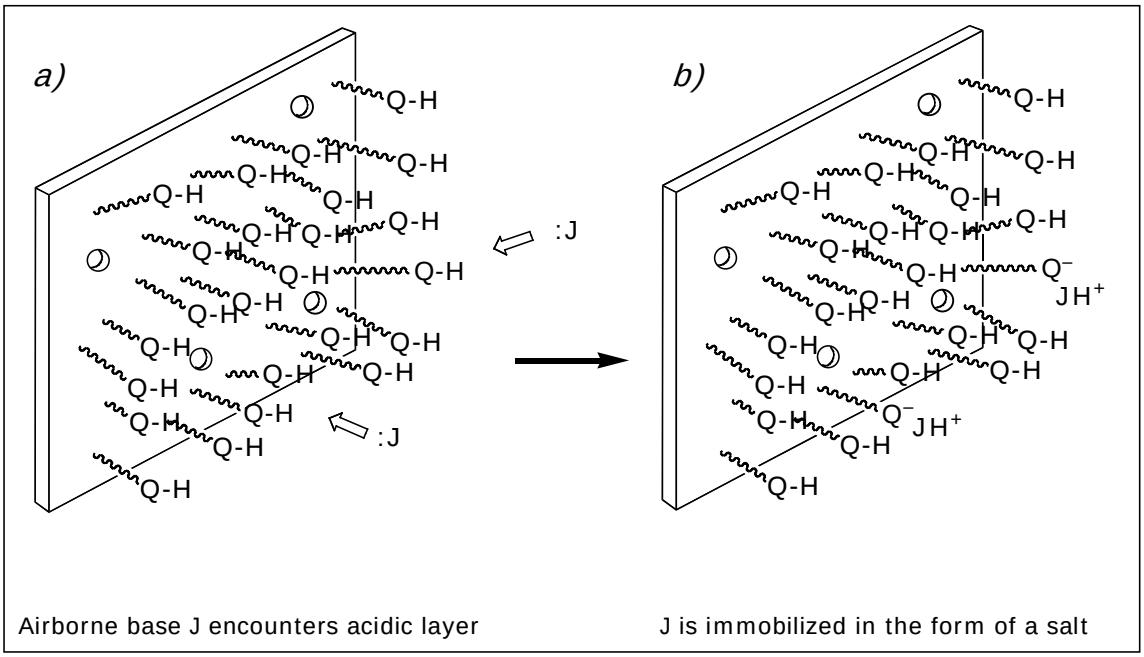


Figure 4. An acidic layer encounters a basic TIC. Here QH represents a Bronsted acid, and J a gas-phase Bronsted base.

If a basic toxic industrial chemical (TIC) like ammonia or hydrazine were present in an industrial chemical emergency, it would be present in the gas phase and would be mobile by virtue of gaseous diffusion as well as air currents. However, upon reaction with an uncharged acid layer, an uncharged basic TIC would produce an ion pair - that is, a salt - with virtually no vapor pressure, and hence virtually no mobility through the membrane layers. The idea would be extended to a variety of layers, each with either general (e.g. acidic or basic) or specific (e.g. a receptor designed to bind one particular TIC) chemical properties, sufficient to protect against most of TICs on the list.

1.4 Design and manufacture of microporous membranes

In the both projects, a reactive membrane will be produced employing microporous polymeric films, and using grafting techniques developed by Professor Luzinov's group at Clemson University[17] to modify their surface and interior. Microporous poly(ethylene terephthalate) ("PET") membranes are commercially available. Figure 5 shows an AFM image of the surface morphology of such a membrane. Measurements in Professor Luzinov's laboratories showed an average pore diameter of 215 nm. Figure 7 shows a cross-section, obtained by scanning electron microscopy. (Images are courtesy of Professor Luzinov).

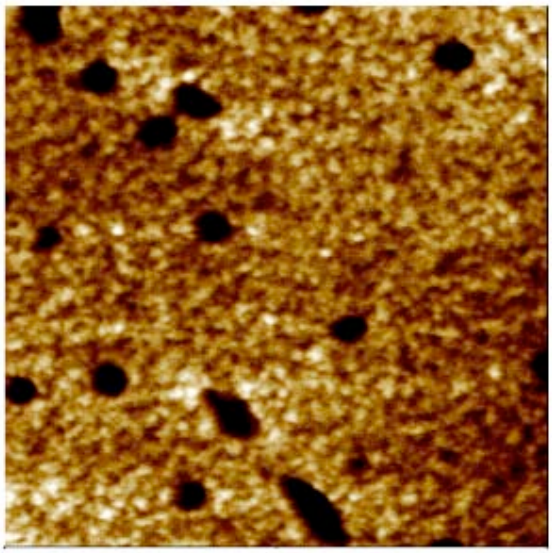


Figure 5. AFM image of surface morphology of microporous PET membrane. (2 μm x 2 μm)

Microporous films were initially treated with air corona or low intensity plasma to produce functional groups on the surface and inside the pores of the membrane. After

washing with ethanol and water, the membrane was dipped in a 5% (w/v) solution of poly(glycidyl methacrylate) ("PGMA") in MEK. (The structure of glycidyl methacrylate is shown in Figure 6a.) The membrane was withdrawn at constant speed using a dip-coater, annealed at 120 °C for 2 h, and washed with MEK. Surface coverage is complete when 5% PGMA solution is used. Therefore, the membrane presents to the surroundings essentially a thin layer of epoxide groups. These epoxide groups will be used to attach the active element to the membrane by reaction with an appropriate functional group on the linker portion (Figure 6b).

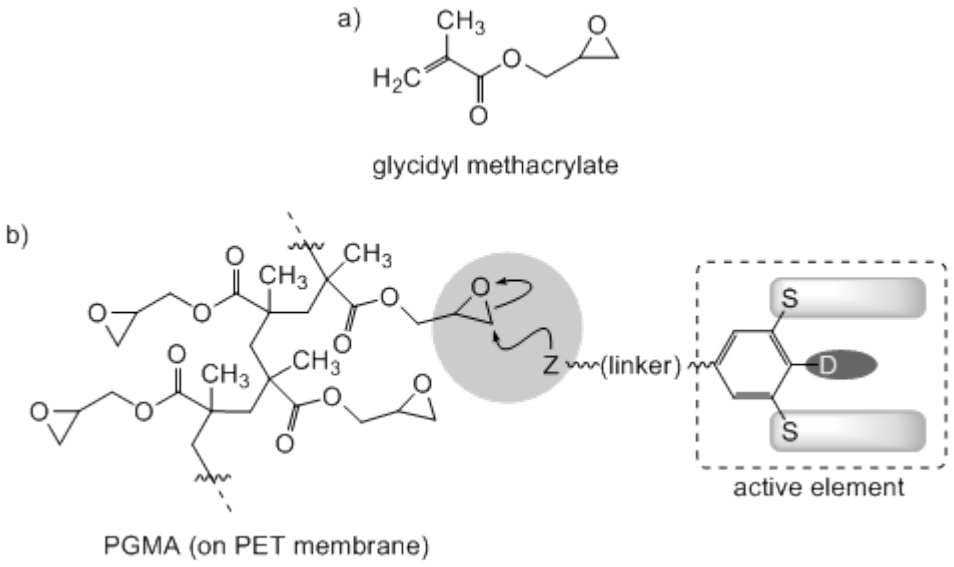


Figure 6. (a) Structure of glycidyl methacrylate (b) Attachment of active element to PGMA via epoxide ring-opening.

In Project 2, we propose the use of multiple layers. As mentioned before, mutually incompatible layers must not be allowed to come in contact with each other. Professor

Luzinov addressed this problem by inserting inert spacer particles between the membrane layers. He has found that silica microparticles (average diameter ~1 μm) placed between membrane layers and fixed in place by application of heat and pressure function well as a spacer system. Figure 7 shows SEM micrographs of a two-membrane stack. The particles appear not to be pressed into the membranes, and there is a clear gap between layers.

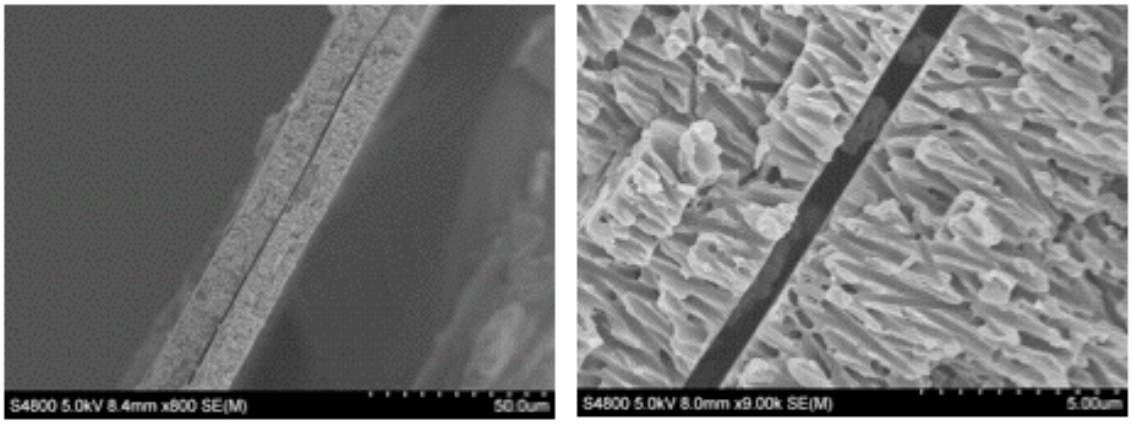


Figure 7. SEM micrographs of a two-membrane stack

2. Part I. TOWARD A BREATHABLE FABRIC FOR PROTECTION AGAINST AIRBORNE TOXIC CHEMICALS

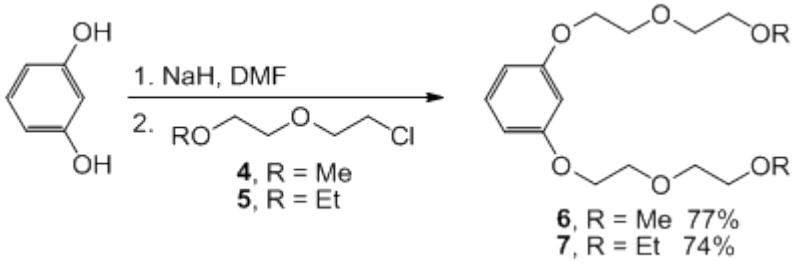
Results and Discussion

2.1 Protection against chemical warfare agents

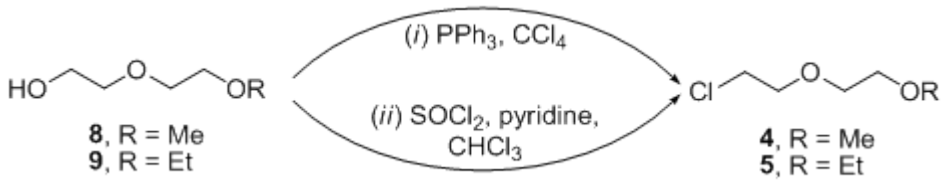
*Donor moieties 2,6-bis(2-(2-methoxyethoxy)ethoxy)benzoic acid (**6**) and 2,6-bis(2-(2-ethoxyethoxy)ethoxy)benzoic acid (**7**)*

Resorcinol (1,3-dihydroxybenzene) was deprotonated by NaH in DMF at 0 °C, and reacted with 1-chloro-2-(2-methoxyethoxy)ethane **4** or 1-chloro-2-(2-ethoxyethoxy)-ethane **5** to give 1,3-bis(2-(2-methoxyethoxy)ethoxy)benzene **6** or 1,3-bis(2-(2-ethoxyethoxy)ethoxy)benzene **7** (eq [1]).[18]

[1]



There are two ways to produce 1-chloro-2-(2-methoxyethoxy)ethane **4** and 1-chloro-2-(2-ethoxyethoxy)ethane **5**, as shown in Scheme 1.

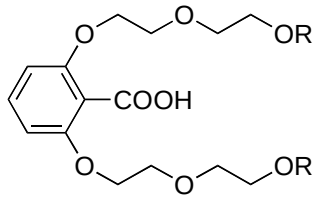


Scheme 1. Two ways to synthesize compounds **4** and **5**.

Method (*i*).[18] A mixture of 2-(2-ethoxyethoxy)ethanol **9**, triphenylphosphine, carbon tetrachloride and acetonitrile was refluxed. After removal of triphenylphosphine oxide, the crude product was distilled under vacuum to give a 73.4 % yield of 1-chloro-2-(2-ethoxyethoxy)ethane **5**. Method (*ii*).[19] A solution of thionyl chloride was added slowly over 15 min to a stirred solution of alcohol **8 or 9**, pyridine, and $CHCl_3$ under nitrogen. The mixture was refluxed overnight. The workup consisted of washing with water, drying over Na_2SO_4, filtering, and evaporating under vacuum. Method (*i*) employed the highly toxic carbon tetrachloride as reagent and co-solvent and required distillation under high vacuum (0.35 mm Hg) to give a lower yield (73.4 % for **9**) than that obtained in method (*ii*) (91.3 % for **9** and 91.5% for **8**). Method (*ii*) used less toxic compounds, and involved easy workup. The desired material was obtained in high yield and required no further purification. Method (*ii*) was the better choice to be applied in this kind of reaction.

The conversion of 1,3-bis(2-(2-ethoxyethoxy)ethoxy)benzene **7** to 2,6-bis(2-(2-ethoxyethoxy)ethoxy)benzoic acid **11** (eq [2]) was carried out by lithiation,

and treatment of the aryllithium with dry ice (solid CO_2).

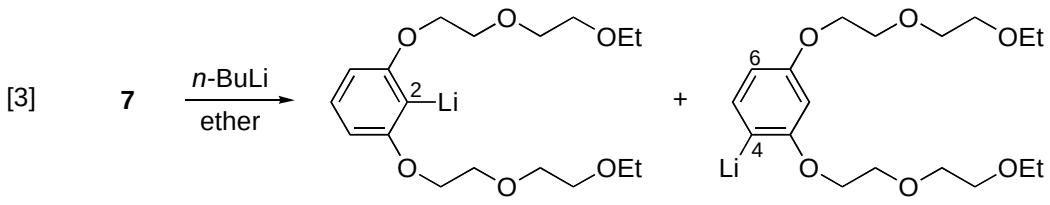
[2] **6** or **7** —(1. *n*-BuLi, ether; 2. $CO_{2(s)}$)→ 

10, R = Me 0%
11, R = Et 47%

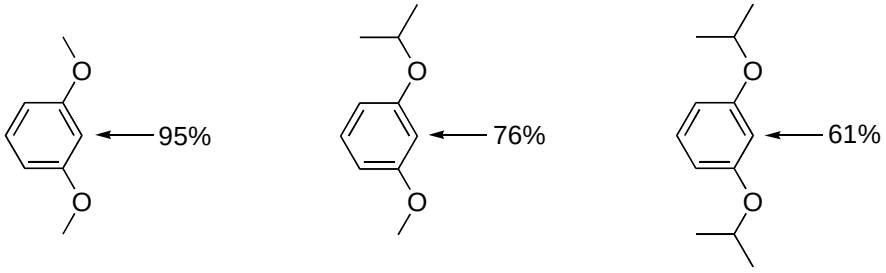
The yield on this step was only fair: 47.2%. When the same reaction conditions were applied to 1,3-bis(2-(2-methoxyethoxy)ethoxy)benzene **6,** no desired compound 2,6-bis(2-(2-methoxyethoxy)ethoxy)benzoic acid **10** was isolated.

It is well-known that certain substituents containing heteroatoms are able to promote the lithiation of an aromatic ring at the ortho position ("ortho-lithiation") by proton-metal exchange with an alkyl lithium reagent.[20] Because of its high degree of regioselectivity, ortho-lithiation has become an important tool in the synthesis of substituted benzenes.[21]

However, in our case, because there are two ortho directing heteroatoms on the ring, there are three possible lithiation sites. Lithiation at position 2 would lead to one product, and lithiation at either position 4 or position 6 would lead to another product (eq [3]). Only lithiation at position 2 would lead to the desired product. This may have accounted for the low yield of 2,6-bis(2-(2-ethoxyethoxy)ethoxy)benzoic acid **11**.



Plumitallo and his coworkers studied the steric effects in the metalation of 1,3-dialkoxy benzenes with n-butyl lithium.[21, 22] The results indicated that the yields of the metalation in the position ortho to both the substituents decreased as the size of the alkyl substituents was increased (Scheme 2). When both of the alkoxy groups were methoxy, the yield of lithiation at position 2 was 95%. When one of the alkoxy groups was changed into isopropoxy, the yield dropped to 71%. When both alkoxy groups were isopropoxy, the yield was reduced further to 61%.

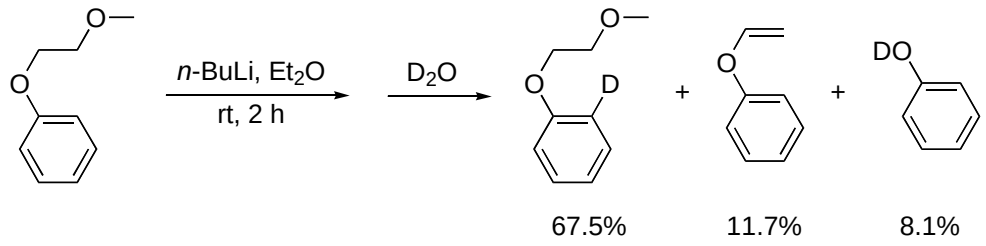


Scheme 2. Metallation of 1,3-dialkoxy substituted benzenes.

The group in compound **7** should have a smaller size than the isopropyl group. Thus based on Plumitallo's results, a much higher lithiation yield (on position 2) for compound **7** than 76% would be expected.

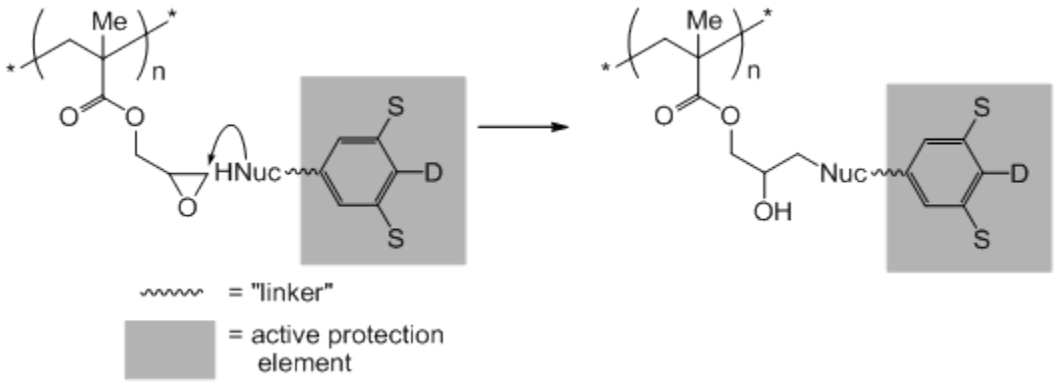
Another possible side reaction which might occur in the lithiation step is elimination of the alkoxyl groups (eq [4]), as reported by R. Ellison.[23] This however does not explain why **7** (OEt chain terminus) gives a fair yield of lithiation product while **6** (OMe chain terminus) gives no product of lithiation at all.

[4]



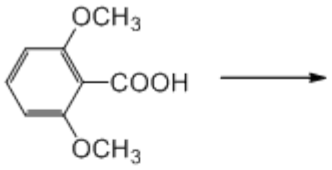
Linker moieties

At this stage of our project, the reactive functionality on the polymer membrane was the epoxide moiety of PGMA. Therefore, to attach the active protection element to the polymer membrane, the active protection element must contain a nucleophilic site with the capability to open the epoxide ring (eq [5]).

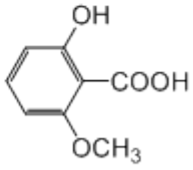


There are two common methods to introduce a sidechain to an aromatic ring. One is Friedel-Crafts alkylation or acylation, and the other is carbon-carbon coupling reactions such as Heck, Stille, and Suzuki reactions. The carbon-carbon coupling reactions need a halogen on the aromatic ring. Since the aromatic ring of **11** is activated toward electrophilic aromatic substitution, we chose the Friedel-Crafts acylation as our first attempt to attach a linker sidechain. We used commercially available 2,6-dimethoxybenzoic acid, **12**, to model **11** during preliminary studies (Table 2.)

Table 2. Acylation of **12**.

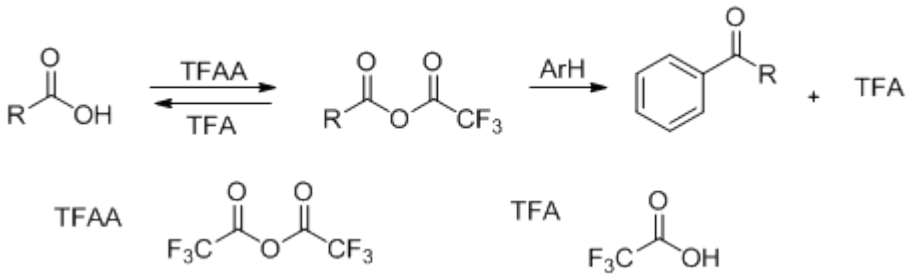


12

Entry	Reaction conditions	Product
1	$AlCl_3$, CH_3COCl, CH_2Cl_2 0 °C, 5 h	Starting material
2	$AlCl_3$, CH_3COCl (excess), 0 °C, 4 h	Starting material
3	$AlCl_3$, CH_3COCl, CH_3NO_2 60 °C, 3 h	 **13**, 65%

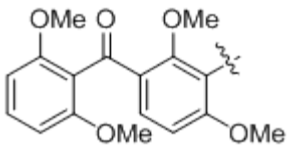
The negative results of Table 2 caused us to turn to mixed anhydrides of trifluoroacetic acid. These are particularly reactive acylating agents.[24] The mixed

anhydride is produced *in situ* when 5 equiv of a carboxylic acid are mixed with stoichiometric trifluoroacetic anhydride (TFAA),[25] as shown in Scheme 3.



Scheme 3. Course of benzene ring acylation by mixed anhydride method.

The reaction of **12** with trifluoroacetic anhydride and acetic acid apparently occurred, because the solution became dark red. After work up, the product exhibited many spots on silica gel TLC. From examination of NMR spectra of the crude product, it appeared that a **14**-like compound was formed. This indicated that the aromatic acid **12** was competing with acetic acid for TFAA.

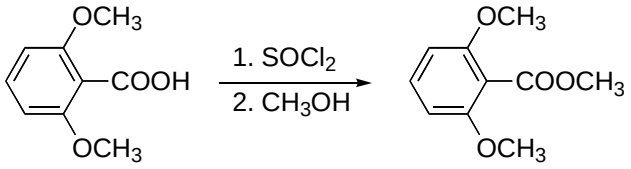


14

Protection of the carboxylic acid group of **12** as the methyl ester, followed by acetylation using the mixed anhydride method gave methyl 3-acetyl-2,6-dimethoxy-

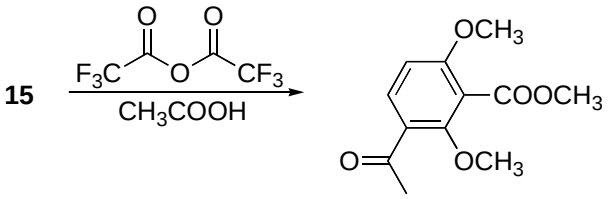
benzoate **16** in 87% yield (eqs [6] and [7]).

[6]



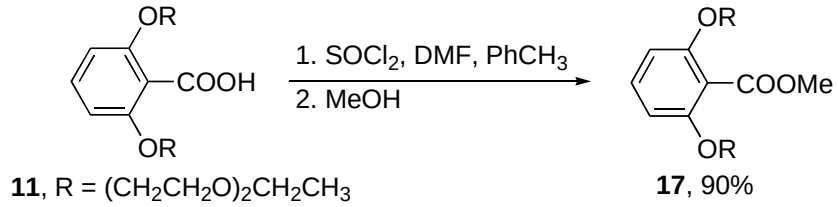
12 **15**, 91.3%

[7]

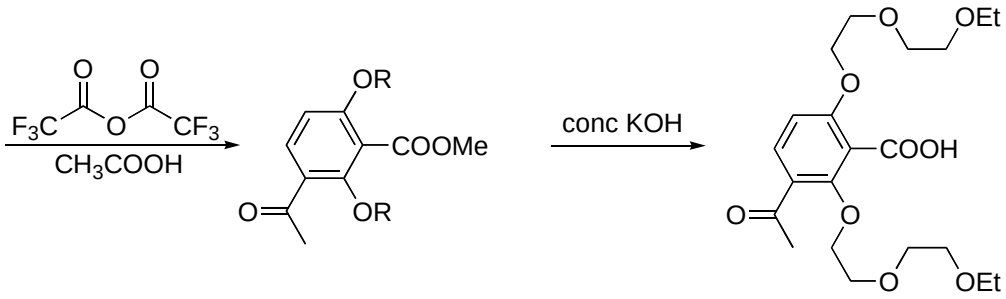


16, 86.5%

When the conditions of eq [7] were applied to **17** (Scheme 4), the yield was considerably lower: 42%. This may have been due to the increase in steric bulk of the polyether sidechains compared to the methoxy groups of **15**.



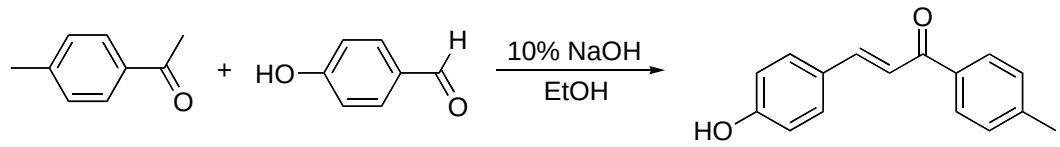
11, R = $(CH_2CH_2O)_2CH_2CH_3$ **17**, 90%



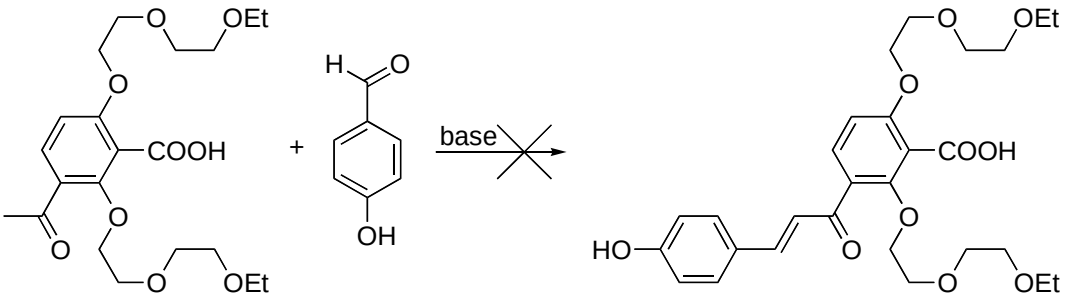
18, 42% **19**, 72%

Scheme 4. Planned synthesis of **19**

We planned to extend the acetyl sidechain by doing an aldol condensation with a substituted benzaldehyde. A model reaction, eq [8] afforded aldol product **22** in 44% yield. However, the analogous reaction using **19** gave no product **20** with NaOH, NaH, or NaOMe as base (eq [9]).

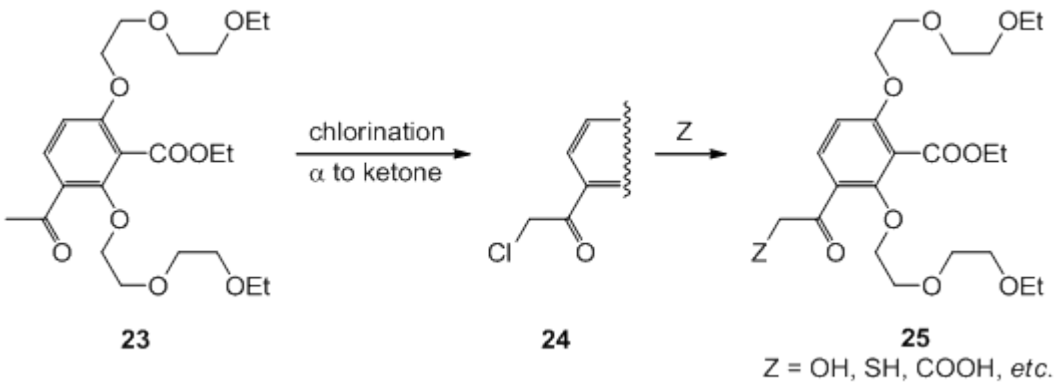
[8] 

21 **22**, 44%

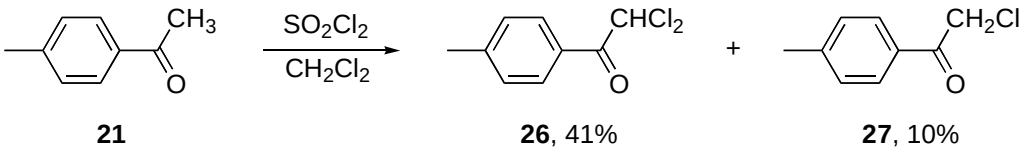
[9] 

19 **20**

Another route we began to pursue was to monochlorinate the acetyl substituent, and then replace the chlorine with a nucleophilic atom or group that could react with the epoxide on the membrane surface. This is shown in eq [10] for ester **23**, prepared by treating **19** with thionyl chloride, then ethanol, yield 86.7%.

[10] 

Wayman and Kaufman used sulfuryl chloride as a chlorinating reagent for the chlorination of ketones and aldehydes, as well as of several other substrates containing other functional groups.[26] Unfortunately, when this method was applied to the model compound **21**, the dichloride compound was obtained in 41.0% yield, and the desired monochloride compound **27** in only 10.4% yield (eq [11]).

[11] 

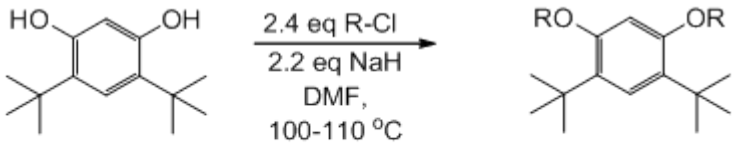
Masilamani and Rogic proposed that selective monochlorination would occur if the solution contained a slight excess of methanol.[27] Using the conditions suggested by those workers, the monchlorination of **23** gave 41.2% yield of ethyl 3-(2-chloroacetyl)-2,6-bis-(2-(2-ethoxyethoxy)ethoxy)benzoate, **24**.

Work on the conversion of **24** to examples of **25** was not pursued, due to other

developments in the overall project.

The use of a transition metal catalyzed carbon-carbon coupling reaction was investigated. As shown in eqs [12], the polyether sidechains could be installed on resorcinol derivative **28**. Bromo de-*tert*-butylation at low temperature was achieved in excellent yield, affording aryl bromide **30** (eq [13]). Finally, Heck reaction of **31** with 5-hexenyl acetate produced a mixture of inseparable isomers **32a** and **32b** in total 52.6% yield. Compound **32** was prepared to gauge how useful the Heck reaction would be for attaching linker elements to the aryl ring. Clearly, it lacks the carboxylic acid functionality, so could not be considered an active protection element. It would, however, serve as a useful control compound.

[12]

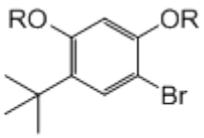


1.0 eq
28

R = $(CH_2CH_2O)_2CH_3$

29, 76.1 %

[13]



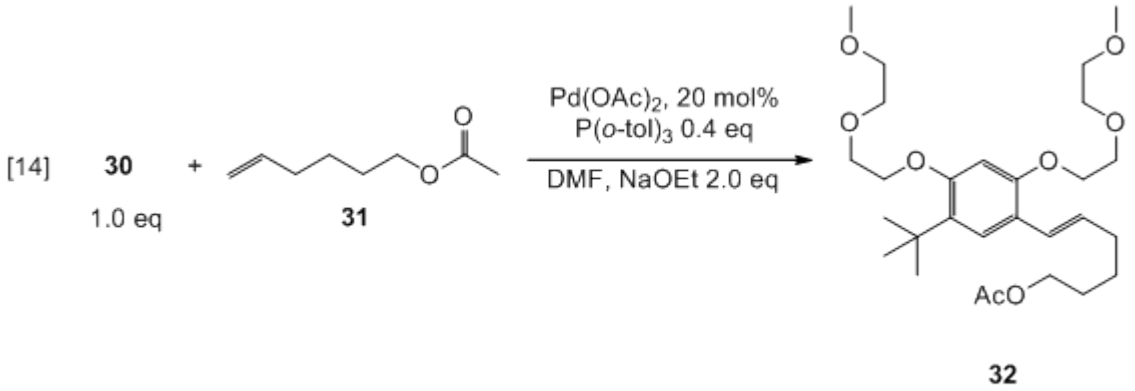
29

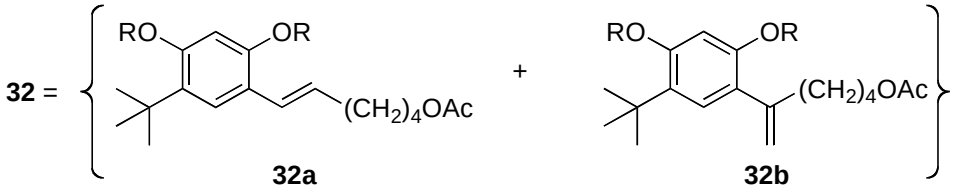
Br_2 1.1 eq
$CHCl_3$, -30 °C

1.0 eq

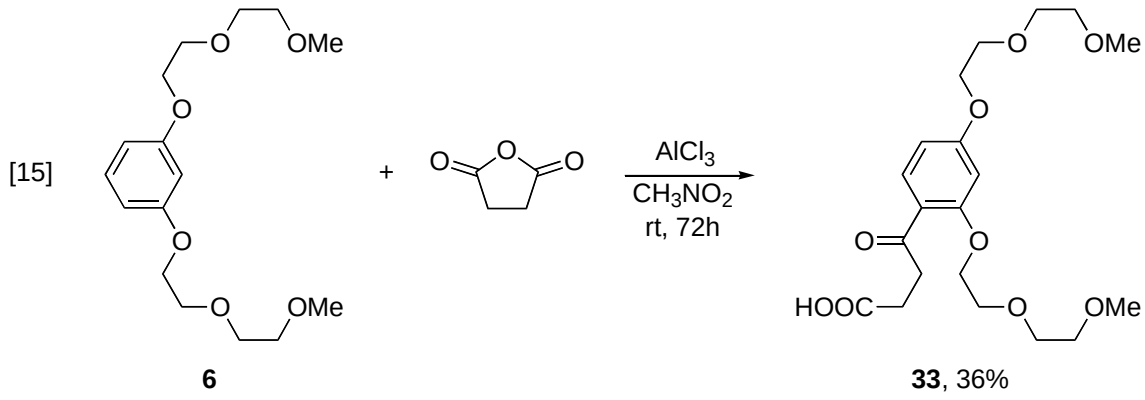
R = $(CH_2CH_2O)_2CH_3$

30, 90.8%





Another control compound was synthesized according to eq [15].



2.2 Change in attachment methodology.

Compound **33** utilizes a carboxylic acid to open the surface epoxide ring and thereby

attach the aryl bis(triether) to the polymer membrane. In fact, **33** was successfully bound to the membrane this way in the laboratory of Professor Luzinov. This points up a problem with many of the target compounds discussed so far: they contain a carboxylic acid group as part of the active protection element. That carboxylic acid group could compete with the linker group for the surface epoxide (Figure 8).

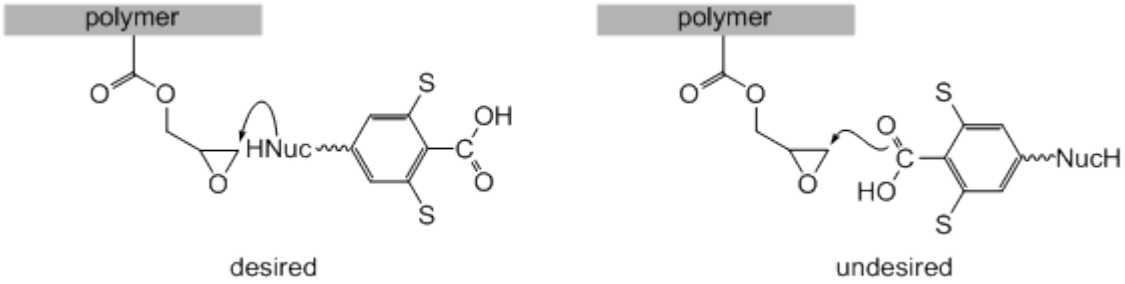


Figure 8. Two modes of attack on the polymer-bound epoxide.

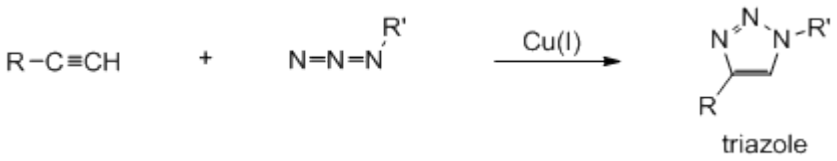
Additionally, installation of both the carboxylic acid group on the benzene ring and the nucleophilic atom or group on the linker sidechain requires some protection/deprotection steps.

In view of these two factors, we decided to explore whether so-called “click chemistry” would be helpful as an attachment methodology.

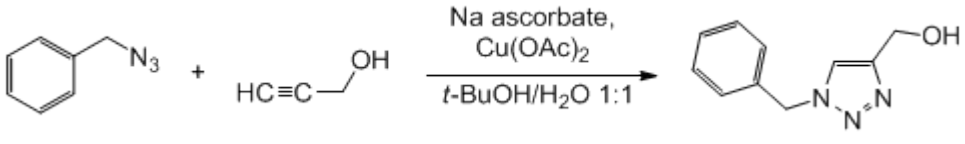
2.3 Click reaction.

The click reaction is a 1,3-dipolar cycloaddition between an azide and a terminal or

internal alkyne to give a 1,2,3-triazole. Rolf Huisgen was the first to understand the scope of this organic reaction, so this reaction was also called Huisgen Cycloaddition. K. Barry Sharpless has referred to this cycloaddition as "the cream of the crop" of click chemistry. The click reaction (eq [16]) has gained considerable attention in recent years due to the introduction in 2001 of Cu(I) catalysis by Tornøe and Meldal,[28] leading to a major improvement in both rate and regioselectivity of the reaction, as realized independently by the Meldal and the Sharpless laboratories.[29, 30]

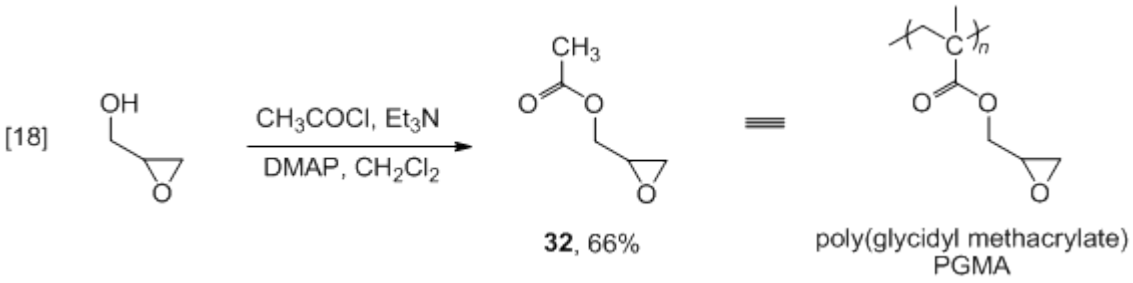
[16] 

The click reaction draws our attention for high functional group tolerance, solvent insensitivity (the reaction is also highly active in water), and simple reaction conditions. To gain experience with the click reaction, the following reaction was performed in our lab (eq [17), giving the triazole in 80.4 % yield.

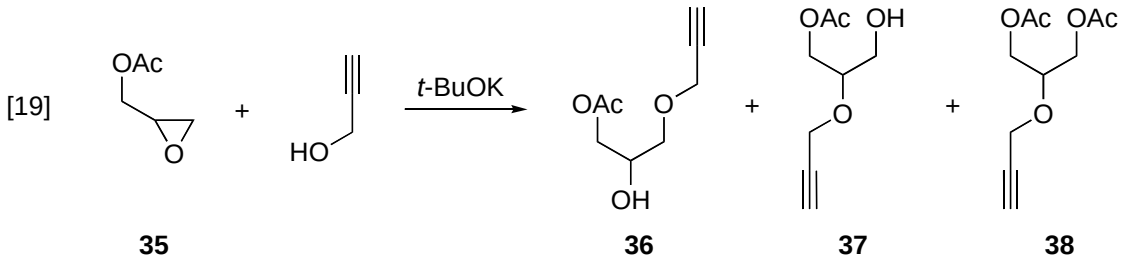
[17] 

To gain experience with attachment protocols, **32** was prepared as a model for the

membrane polymer, poly(glycidyl methacrylate), PGMA (eq [18]).

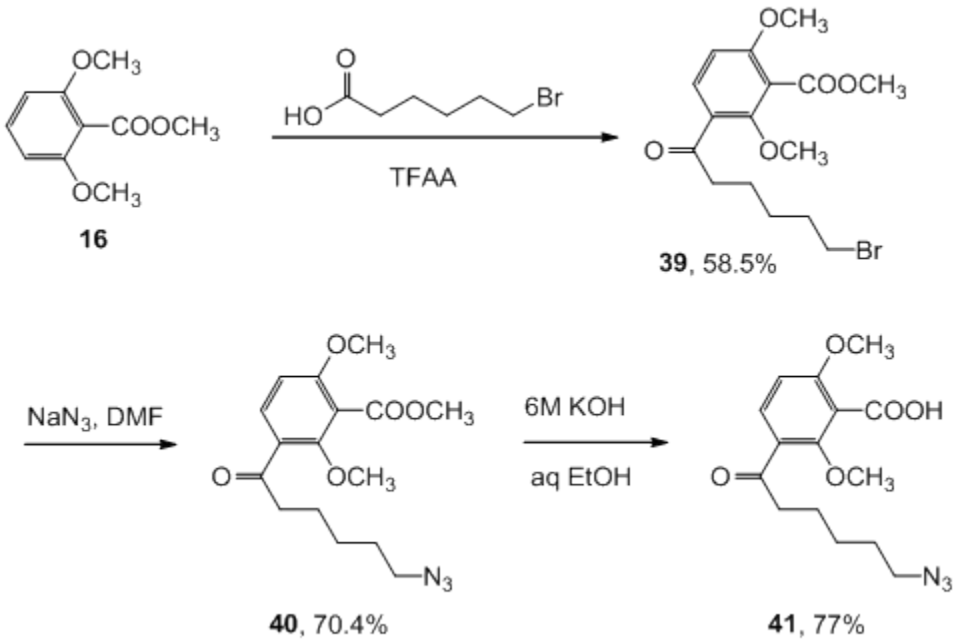


Epoxide opening using propargyl alcohol was carried out, leading to a mixture of three products, as shown in eq [19]. Fortunately, the product need not be a single pure compound. The important feature is simply that the alkyne functionality be attached to the polymer.



2.4 Project 1 azide compounds.

The target compound **41** (Scheme 5) was similar to compound **19**. We had hoped to cleave the methoxy groups of **40** or **41**, and install polyether chains of various lengths. Due to time constraints, only **41** was synthesized.



Scheme 5. Synthesis of **41**.

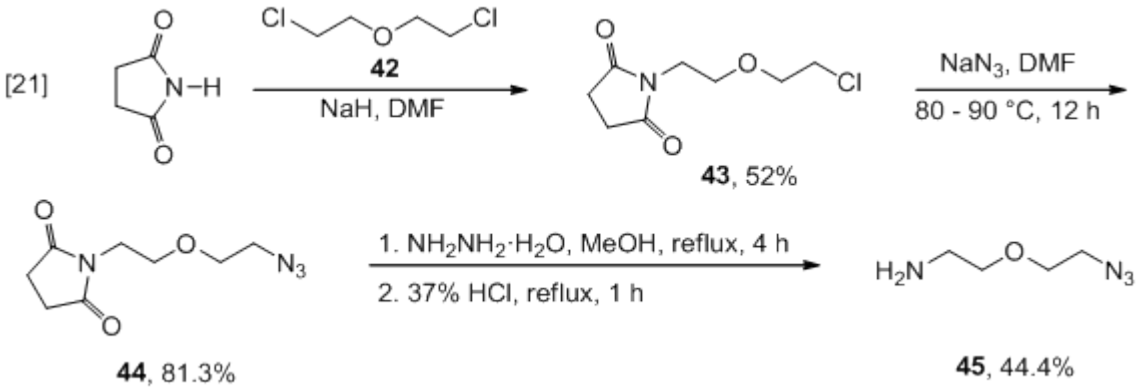
Methyl 2,6-dimethoxybenzoate **16** reacted with the mixed anhydride of 6-bromohexanoic acid and TFAA to introduce the side chain, giving methyl 3-(6-bromohexanoyl)-2,6-dimethoxybenzoate**, 39**, in 58.5%. yield. Compound **39** was converted to compound **40** using 3 eq NaN_3 in DMF at 80 - 90 °C for 12 h. Finally, hydrolysis of methyl ester **40** gave our desired benzoic acid **41**.

2.5 Project 2 azide compounds.

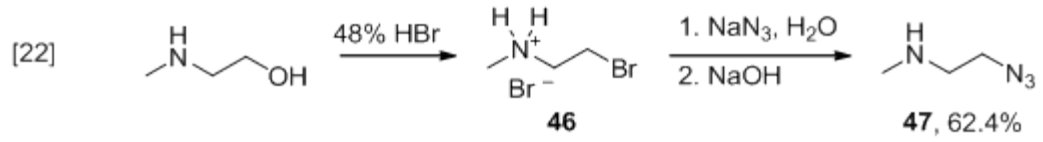
Compounds for a basic membrane

The first compound for a basic membrane ws a primary amine. The synthesis of the primary amine **45** having an azide group iss shown in eq [21]. Pyrrolidine-2,5-dione **43**

was chosen because its N atom will not compete with azide anion in the conversion of **43** to **44**. This reaction successfully provided azide **44** in 81% yield. Hydrazinolysis of the succinimide released the primary amine-azide **45**.



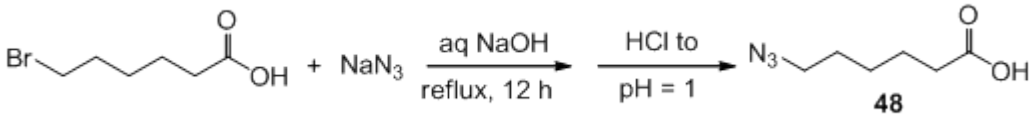
The secondary amine **47** was another compound for the basic membrane. In the synthesis route (eq [22]), 2-(methylamino)ethanol reacted with 48% HBr solution at reflux to give salt **46** whose amine group was protected by the proton instead of the amide in eq [21]. Compound **46** was treated with 3 eq NaN_3 in water, followed by NaOH pellets to give compound **47.**

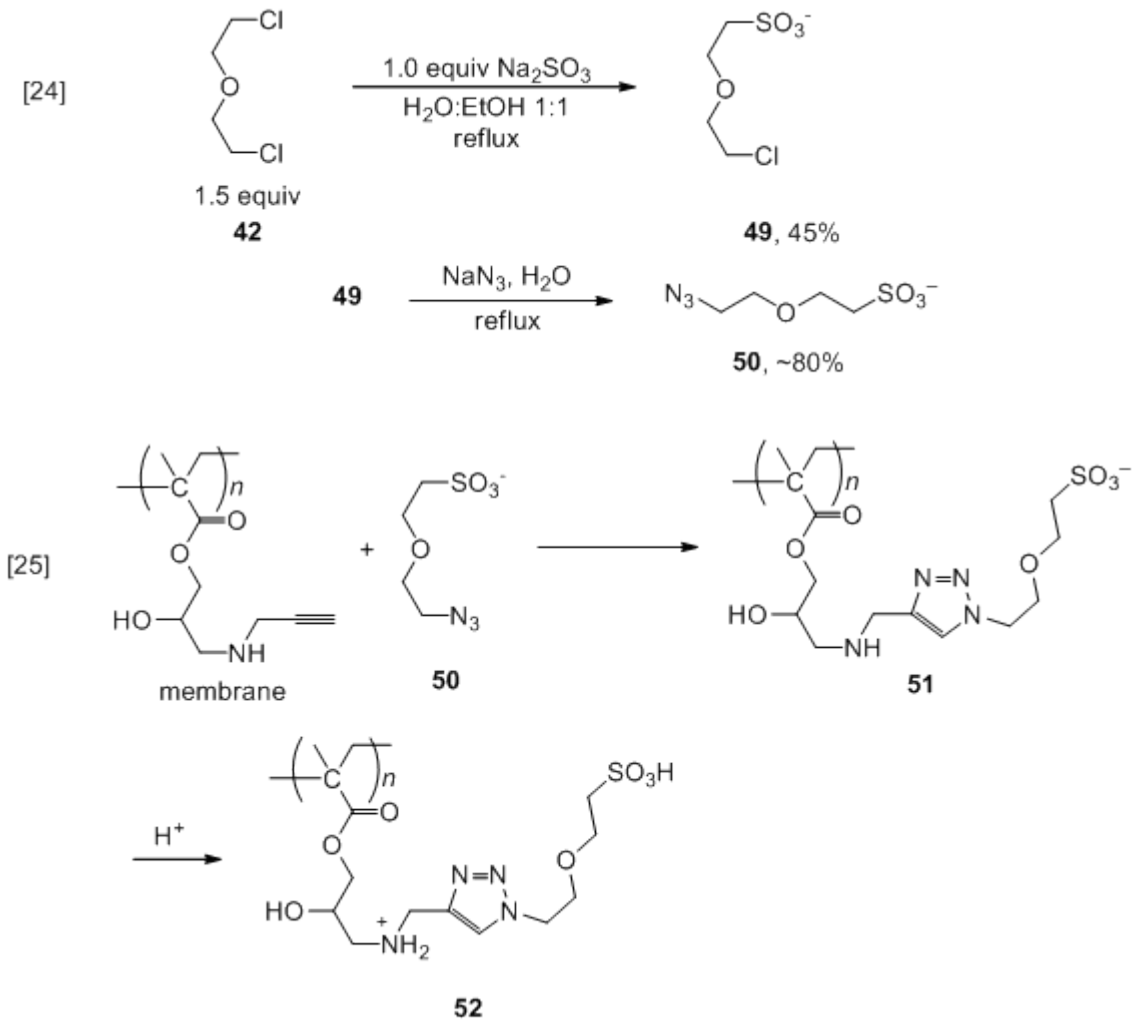


Compounds for an acidic membrane

The compounds for an acidic membrane were synthesized from commercially available chemicals. 6-Bromohexanoic acid (eq [23]) was treated with base to make it water soluble, was reacted with NaN_3, and finally was acidified to give compound **48** (eq [23]. Another acid **50** was prepared from 2,2’’-dichlorodiethyl ether, **42**. One of the two chlorides was substituted by SO_3^- to give compound **49**. Then **49** was converted to **50** by treating **49** with NaN_3 in water. We envisioned attaching sulfonate **50** to the modified membrane by click chemistry, and converting the membrane bound sulfonate to the sulfonic acid by treatment with strong acid, as outlined in eq [25].

It should be noted that despite our preliminary experiments using propargyl alcohol to open the PGMA membrane epoxides (eq [19]), Professor Luzinov’s group found that epoxide opening using propargylamine was more satisfactory. The structure of the membrane drawn in eq [25] represents our best guess at the regiochemistry of the ring opening.

[23] 

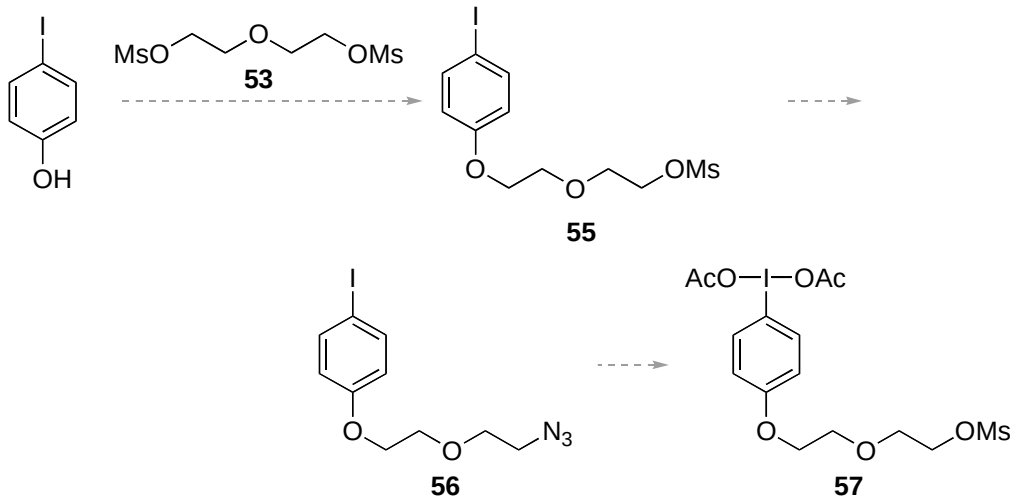


Compounds for an oxidizing membrane

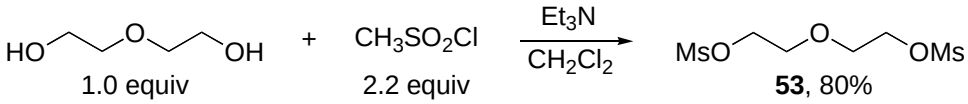
Since so-called hypervalent iodine compounds are common oxidative reagents in modern organic chemistry, we chose this class of compounds to use to create a membrane surface with oxidative properties.

Our plan was to substitute one mesylate of dimethanesulfonate **53** with azide and the other with an iodoaromatic group (Scheme 6). Dimesylate **53** was prepared in 80.2%

yield as shown in eq [26].

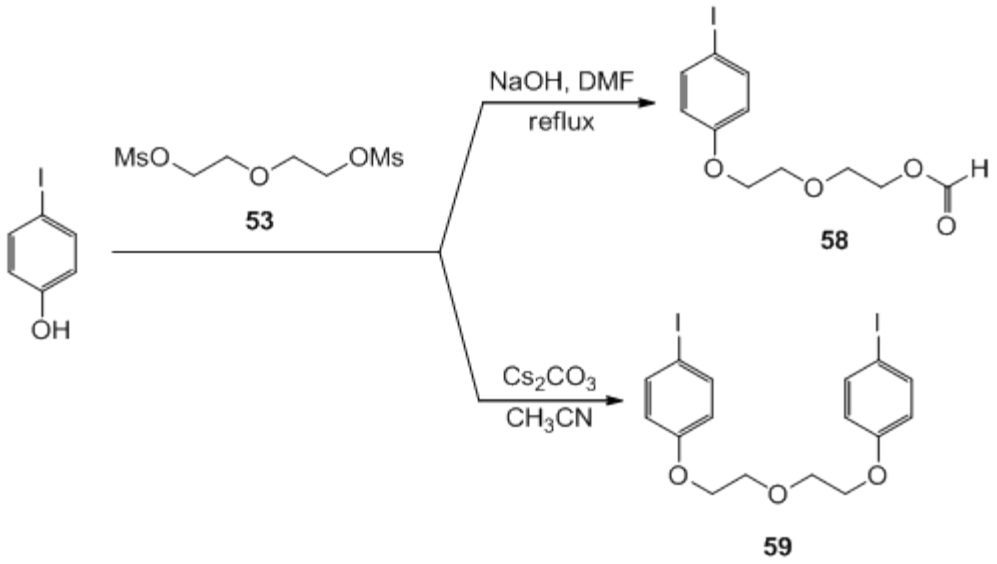


Scheme 6. Plan for a membrane-ready hypervalent iodine reagent.

[26] 

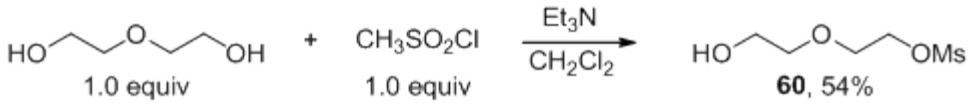
We encountered undesired side products when 4-iodophenol reacted with **53** in DMF or acetonitrile solution in the first step (eq [27]). The reason is the methanesulfonate was so active toward nucleophilic attack.

[27]

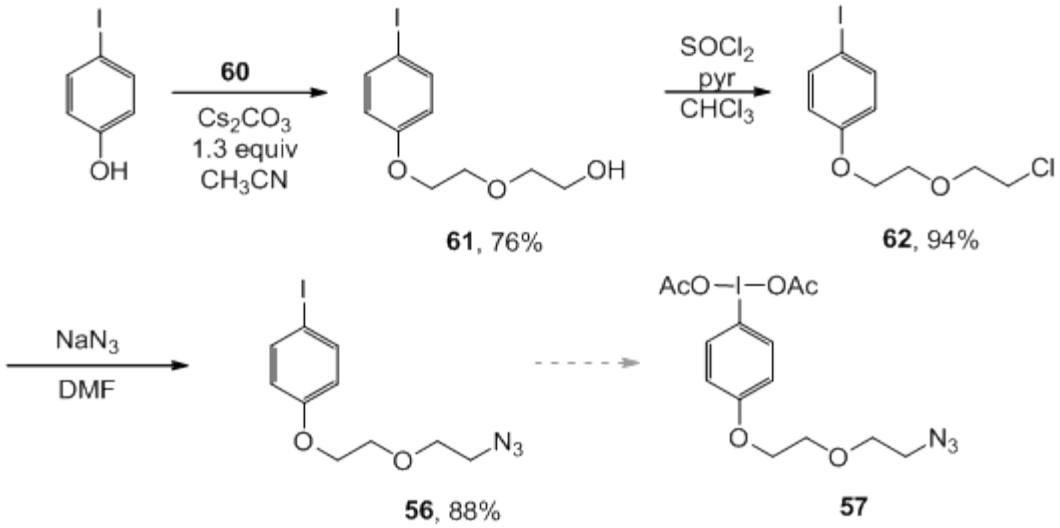


We modified the synthesis of **57** by starting with the monomesylate **60**, rather than dimesylate **53**, eq [28]. Subsequent steps are shown in eq [29]. Transformation of alcohol **61** to chloride **62** and then to azide **56** was uneventful. However, oxidation of compound **56** failed to give compound **57** using various oxidative reagents, such as sodium perborate with acetic acid, peracetic acid, and sodium periodate with acetic anhydride.

[28]

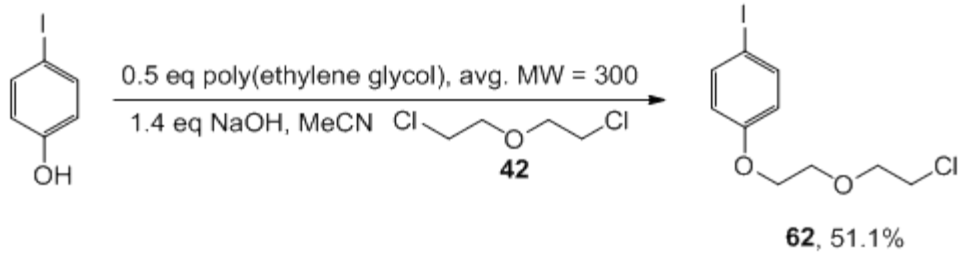


[29]



We found that we could prepare **62** in one step as shown in eq [30]. When 0.5 equiv poly(ethylene glycol) average M.W 300 was added to the reaction between 4-iodophenol and **42**, we obtained compound **62**, in 51.1 % yield.

[30]



2.6. Conclusions.

The funding for this research lasted roughly two years. During that time, the funding agency changed the group of target toxic compounds from chemical warfare agents, principally nerve gases, to toxic industrial chemicals (TICs), a widely diverse collection of compounds. This was a major change, and we coped as best we could.

Our initial work with “active protection elements” like compound **11**, for example, bore limited fruit. Compound **33** was attached to the PGMA membrane *via* epoxide opening.

Later work directed toward a multi-layer fabric was significant. Such a multi-layer approach, proposed in our laboratory, is unprecedented, and holds promise as a way to offer protection against more than just one toxic compound or one class of toxic compounds. The switch from epoxide ring opening to click chemistry for the linking methodology has broadened the scope of functional groups able to be present in the molecule to be attached.

Our laboratory was one of four sites engaged in the funded project. Our compounds have been passed on to other team members for attachment to the membrane and subsequent testing. We await those results.

3. II. AN OLEFIN-FORMING CASCADE REACTION EN ROUTE TO 2,2'-BI(GLYCEROL)

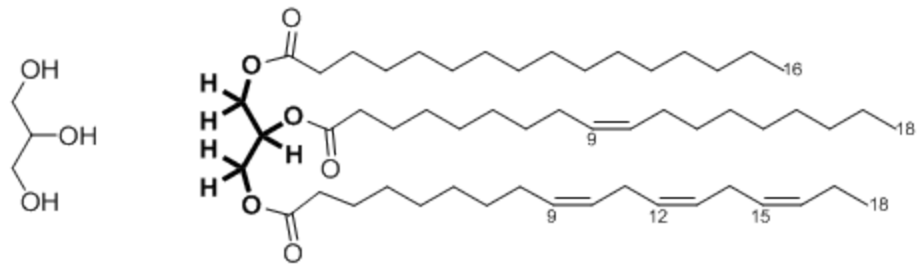
Introduction

Polyols

The name polyols, or polyalcohols, refers to organic compounds containing multiple hydroxyl groups, which are generally considered as analogues of sugars. Polyols are important structural components of antibiotic macrolides,[31] building blocks of polymers[32] and dendrimers,[33] and they have the ability to interact with certain cations to form polyol-metal complexes.[34] They have attracted the attention of biologists, chemists, and pharmaceutical scientists for a long time.

1.1 Glycerol

The most valuable polyol, 1,2,3-propanetriol, or glycerol (sometimes called glycerin), **1**, was first isolated in 1779 by the Swedish scientist Carl Scheel while making lead plaster soap from olive oil and lead oxide. Scheel eventually realized that glycerin was common ingredient in fats and oils. An example of a fat or oil is **64**, (glycerol portion highlighted). Scheel referred to glycerol, **63**, as "sweet principal of fat."[3]



63 **64**

In 1811, the French chemist Michel Eugène Chevreul, who was a pioneer in the study of oils and fats, proposed the name glycerin after the Greek word *glycos* which means sweet. Chevreul decomposed soap, isolating various acids such as stearic acid and butyric acid. He discovered that glycerol was liberated when oils and fats were boiled in a basic mixture. Jules Pelouze established glycerol's empirical formula in 1836. In 1883, Berthelot published the structural formula **63**.[36] Glycerin sometimes occurs in uncombined form, notably as a constituent of palm oil, and is also a product of fermentation; but it is obtained on the large scale only by the decomposition of fats.

Glycerin found its way into many vital industrial applications after 1867, when Alfred Nobel reported transforming trinitroglycerol into the safely transportable explosive called "dynamite" [37] Apart from use in explosives, one of the earlier large single uses of glycerol was in "alkyd resins." Although a modern type alkyd resin was produced as far back as in 1901, the full commercial potential was not realized until 1927, when Kienel of General Electric Company registered his first patent covering modification of the basic resin.

In addition to being the backbone of the triglycerides (oils and fats) discovered by Chevreul, glycerol was also shown to be the backbone structure of phospholipids. The structures of some important phospholipids are shown in Figure 9.

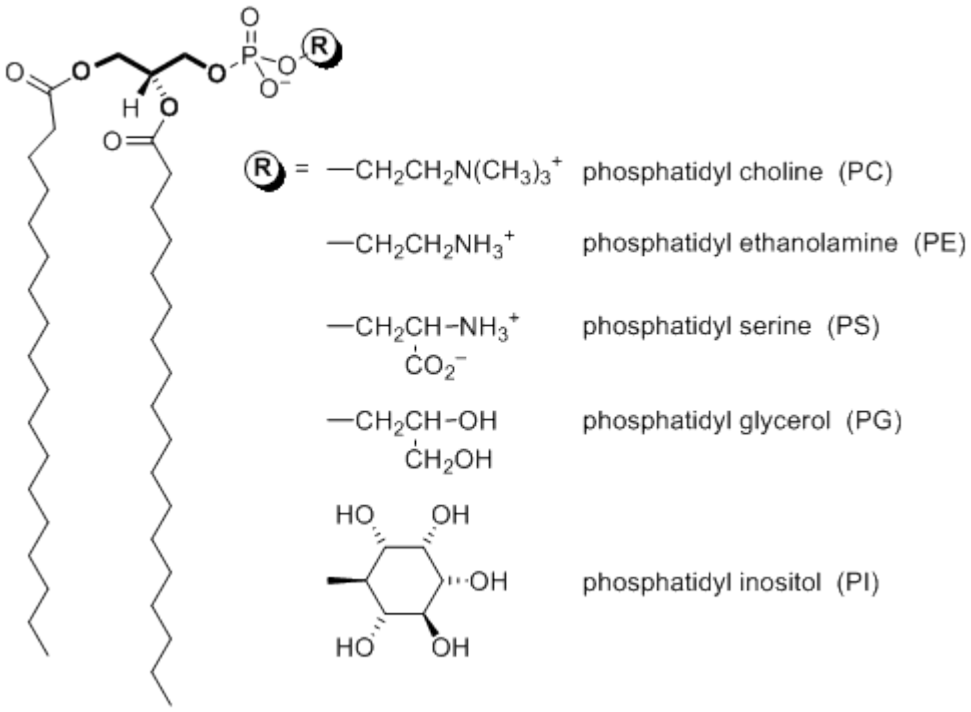


Figure 9. Important phospholipids classified by head-group. (Acyl groups are shown as stearate arbitrarily). The glycerol backbone is highlighted.

In 1925, two Dutch physicians, E. Gorter and F. Grendel found that phospholipids were building blocks of biological membranes.[38] Triglycerides ("triacylglycerols") and phospholipids play important roles in living creatures. Thus, much research on glycerol has been carried out by biologists and biochemists. Recent studies show that glycerol is a precursor for synthesis of triacylglycerols and of phospholipids in the liver and adipose

tissue. When the body uses stored fat as a source of energy, glycerol and fatty acids are released into the bloodstream.[39] The glycerol component can be converted to glucose by the liver and provides energy for cellular metabolism. Glycerol also plays a considerable physiological role in animals. For instance, acting as a converter of toxic substance, generated metabolically, in bears during hibernation.[40] Other animals can survive arctic cold is related to the presence of glycerol in the bloodstream.

During the 20th century, chemists started to find new applications of glycerol, especially in the pharmaceutical and cosmetic industries, where it was used for its skin-softening ("emollient"), soothing film-forming ("demulcent"), and hygroscopic ("humectant") properties. Later, glycerol was also used as a plasticizer in the polymer industry and as a moistening agent or solvent in the food industry.

In recent years, attention has been focused on the selective use of glycerol as a safe organic building block for organic chemistry. Many reviews[41] have focused on its transformation in single-component reactions, such as reduction, oxidation, hydrogenolysis, oligomerization, and gasification as shown in Figure 10.

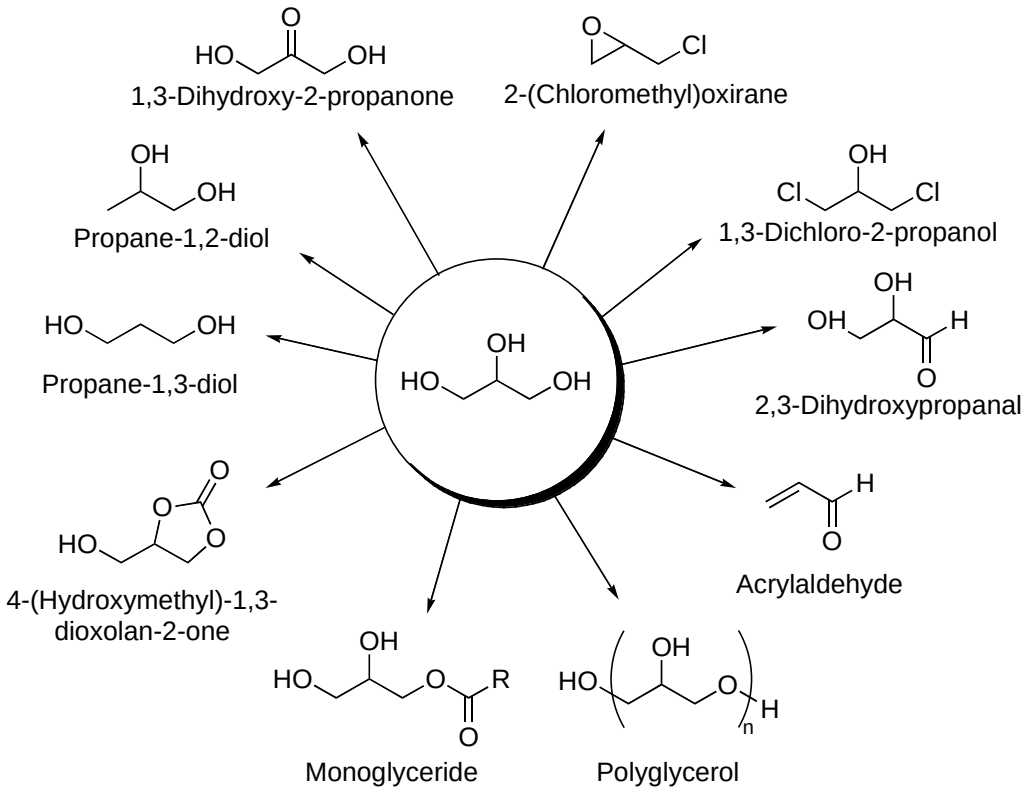


Figure 10. Some reactions of glycerol.

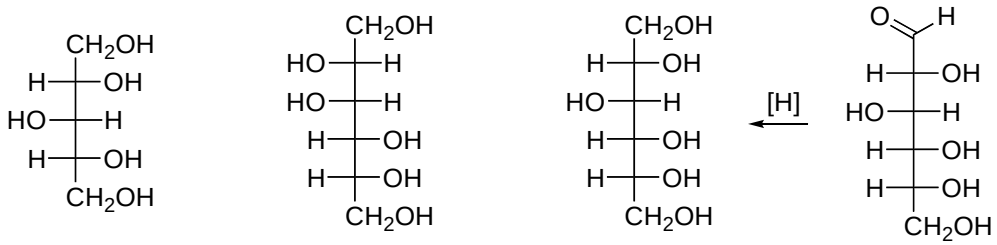
1.2 Sugar alcohols

Some consider glycerol a sugar alcohol, but others don't. Sugar alcohols are related to aldoses and ketoses, *i.e.* sugars, by formal reduction of the sugar carbonyl groups to alcohol groups, and are also called alditols. Sugar alcohols make up a large group of polyols, commonly added to foods because of their lower caloric content than sugars (Table 3).

Table 3. Sugar alcohols used as sweeteners

Name	Sweetness	Caloric content (kcal/g)	Sweetness per caloric content
Arabitol	0.7	0.2	3.5
Erythritol	0.812	0.213	3.5
Isomalt	0.5	2.0	0.25
Lactitol	0.4	2.0	0.2
Maltitol	0.9	2.1	0.43
Mannitol	0.5	1.6	0.31
Sorbitol	0.6	2.6	0.23
Xylitol	1.0	2.4	0.42
Sucrose	**1.0**	**4.0**	**0.25**

Xylitol, the "super-star" of the sugar alcohol group, was first derived from birch trees in Finland in the 20th century and was first popularized in Europe as a safe sweetener for people with diabetes that would not impact insulin levels. Then, a xylitol-based breath mint, *Smint*, made by a Dutch-Italian company, and *Extra* xylitol chewing gum were marketed worldwide and made this sugar alcohol part of everyday living.



In addition to dietary use worldwide, xylitol has many medical applications. Tooth-friendly xylitol is not only safe for pregnant and nursing women, but studies show that regular use significantly reduces the probability of transmitting the *Streptococcus mutans* bacteria, which is responsible for tooth decay, from mother to child during the first two years of life by as much as 80%.[42] Recently researchers have shown that xylitol chewing gum can help prevent ear infections[43] (acute *otitis media*). Xylitol also appears to have potential as a treatment for osteoporosis. A group of Finnish researchers has found that dietary xylitol prevents weakening of bones in laboratory rats, and actually improves bone density.[44]

Mannitol and sorbitol are two other important sugar alcohols which are acyclic six carbon molecules. Mannitol was originally isolated from the secretions of the flowering ash, but sorbitol is obtained by reduction of glucose, changing the aldehyde group to a hydroxyl group. Mannitol is able to deliver various drugs directly to the brain, because it can open the blood–brain barrier (BBB) by producing osmotic shrinking of the endothelial cells that form the BBB.[45] Mannitol may be administered in cases of severe

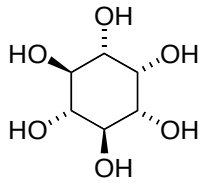
ciguatoxin poisoning which can produce stroke-like symptoms. Sorbitol is often used in modern cosmetics as a humectant (hygroscopic substance) and thickener. Some transparent gels can only be made with sorbitol as it has a refractive index sufficiently high for transparent formulations. It is also used as a humectant in some cigarettes.

1.3 Citiols

Citiol are hydroxylated cycloalkanes containing at least three hydroxyl groups, each attached to a different ring carbon atom. The important compounds of this group are inositol and carbasugars.

1.3.1 Inositol

Inositol, (of which the most prominent naturally occurring form is *myo*-inositol, *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexaol), is a cyclo-hexaol that plays an important role as the structural basis for a number of secondary messengers such as inositol phosphates, phosphatidylinositol (PI) and phosphatidylinositol phosphate (PIP) lipids in eukaryotic cells. Inositol is found in many foods, in particular, in cereals with high bran content, nuts, beans, and fruit, especially cantaloupe melons and oranges. Other naturally occurring isomers (though in minimal quantities) are *scyllo*-, *chiro*-, *muco*-, and *neo*-inositol.



myo-inositol

As the basis for a number of signaling and secondary messenger molecules, inositol is involved in a number of biological processes, including: insulin signal transduction,[46] cytoskeleton assembly, nerve guidance, and gene expression.[47] Thus, the synthesis of the different inositols was hot field in the chemistry.

1.3.2 Carba-sugar

Carba-sugar,[48] previously known as pseudo-sugar, is a family of sugar mimics currently attracting great interest among chemists and biochemists in various fields. Almost thirty years ago, McCasland et al.,[49] synthesized the first example, 5a-carba-oc-DL-talopyranose **65**, followed by two new isomeric compounds, and called them "pseudo-sugars". Carba-sugars are (hydroxymethyl)-branched-chain cyclitols. They are similar topologically to normal sugars particularly in the arrangement of the hydroxyl and hydroxymethyl groups, but have the oxygen atom of the pyranose ring replaced by a methylene. Their biological features are well exemplified by the fact that humans cannot differentiate carba- from true-glucoses by their taste. Furthermore free carbasugars exist in structurally stable six-member ring forms, and chemical modification at anomeric positions may therefore be possible, thus providing biologically interesting derivatives

analogous to C-glycosides.

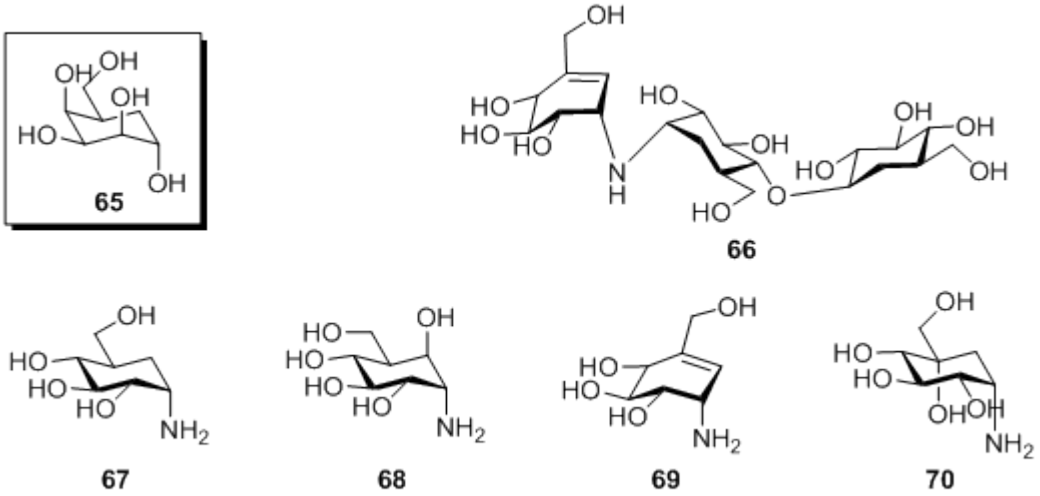


Figure 11. Carbasugar samples

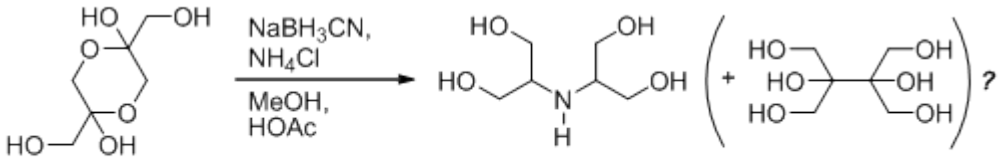
The agricultural antibiotic validamycin A **66**, a naturally occurring biologically active compound composed of carba-sugars, was discovered[50] in 1970 and was shown to possess a unique pseudo-trisaccharide structure. Extensive studies on isolation of minor components of the fermentation broth have led to the discovery[51] of seven homologous antibiotics (validamycins B-H) and four examples of new carba-amino sugar classes of compounds: validamine (**67**), hydroxy validamine (**68**), valienamine (**69**), and valiolamine **(70**).

1.4 Objective of present research

Members of the Livant research group have focused on the synthesis of various

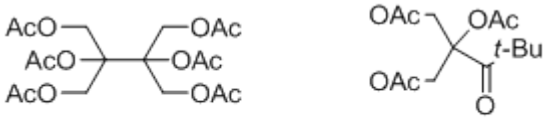
hypervalent compounds. When group member Yuanping Jie performed the reaction shown in equation [31], she obtained a minor byproduct that she tentatively identified as hexa-alcohol **73**.

[31]



71 **72** **73**

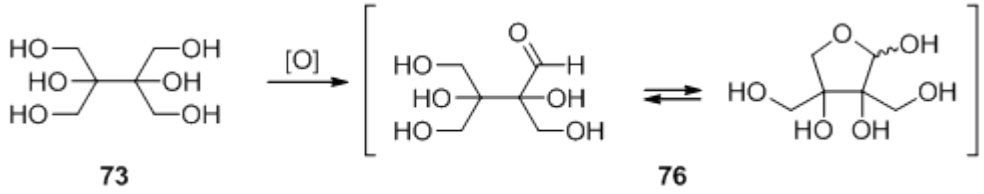
To confirm the identity of the byproduct, she turned to the chemical literature for NMR chemical shift information on **73**. However, she found that **73** had never before been synthesized. The literature search revealed that (*i*) FAB ionization of glycerol produced mass spectral peaks attributable to **73** and isomers thereof,[52] and (*ii*) **74** seems to have formed in unreported amount *via* photolysis of **75** in an ESR cavity.[53] Subsequent work showed that the byproduct was not **73**, but rather glycerol. However our interest in **73** had been piqued.



74 **75**

As starting material for synthesis of new sugar, the idea is that one of six –OH groups

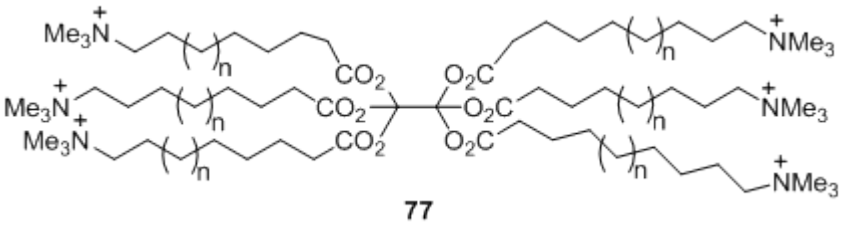
of alcohol **73** could be oxidized to an aldehyde (eq [32]).

[32] 

73 **76**

*Ester and phosphate derivatives of glycerol-like hexaol **73***

It is well-known that lots of ester and phosphate derivatives of polyols especially the glycerols (glyceride,[54] glycerophospholipids[55]) and inositols (inositol esters,[56] phosphoinositide[57]) were made. There is potential to make interesting ester and phosphate derivatives from the glycerol-like hexaol **73**. One example of these derivatives is hexaester, a kind of biopolymer mimic. The interesting of these compound **77** maybe form phospholipid bilayer mimic.



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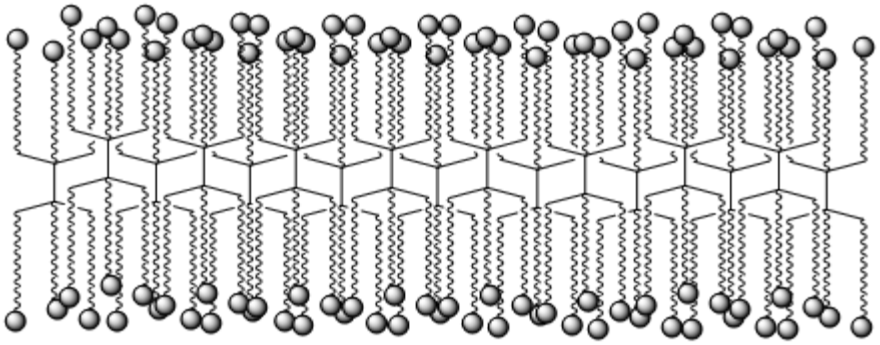
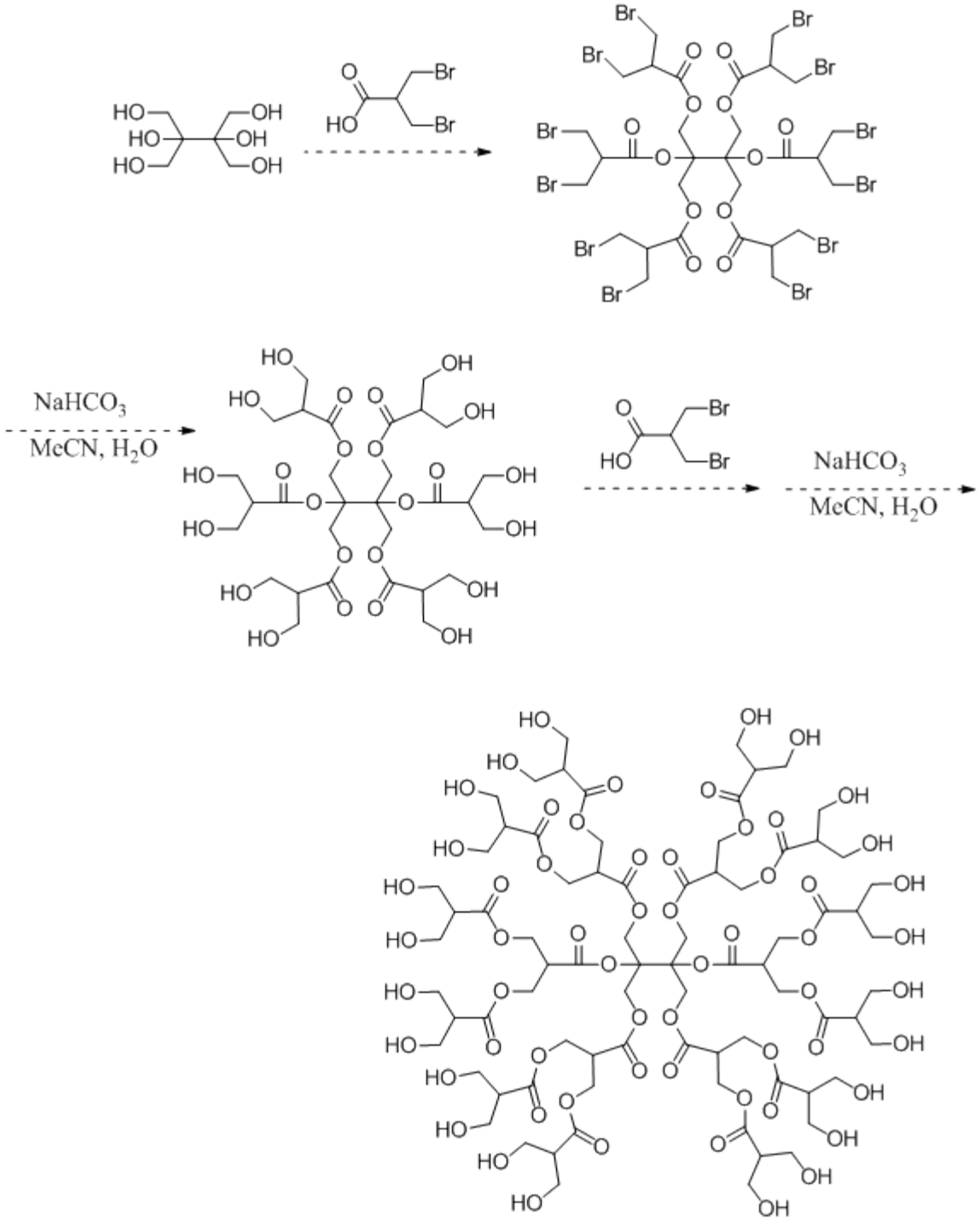


Figure 12. Phospholipid bilayer mimic

Building block for AB_6 type dendrimer which is repeatedly branched molecule



Scheme 7. Proposed synthesis of AB_6 type dendrimer from **73**

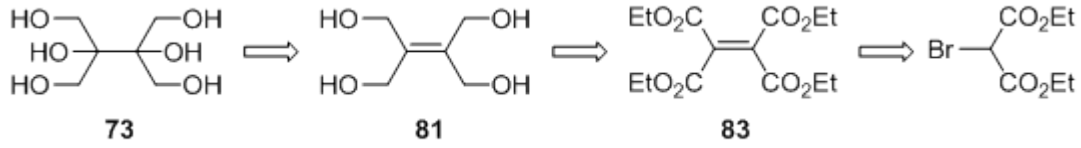
4. II. AN OLEFIN-FORMING CASCADE REACTION EN ROUTE TO 2,2'-BI(GLYCEROL)

Results and Discussion

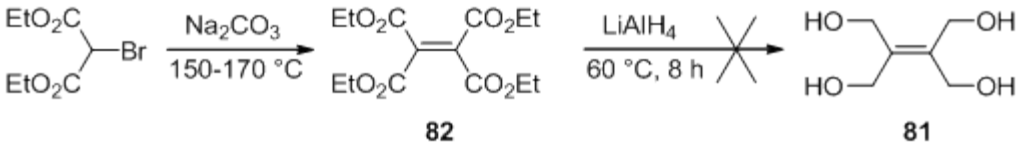
2.1 Synthesis of 2,3-bis(hydroxymethyl)butane-1,2,3,4-tetraol, 73

2.1.1 Synthesis of hexaol 73. First route.

A retrosynthetic analysis for **73** is shown in eq [33].

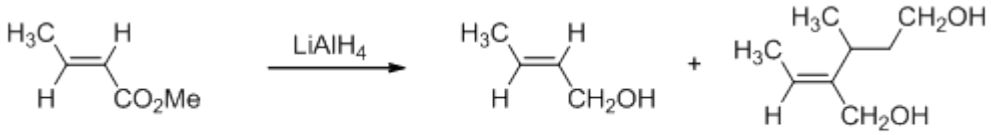
[33] 

We reasoned that the hydroxymethyl groups of **73** could be derived from the reduction of ester groups, namely **82** $\rightarrow$ **81**. Diethyl 2-bromomalonate was dimerized in 42% yield to give olefin **82** under basic conditions at 150 °C (eq [34]).[58] When **82** was reduced by $LiAlH_4$ at 60 °C for 8 hour, many products were detected by TLC. After workup, the NMR spectrum didn't show any desired product **81**.

[34] 

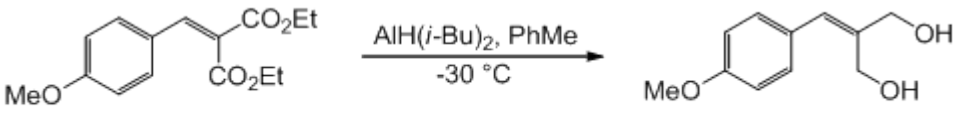
82 81

Reduction of α,β-unsaturated esters with $LiAlH_4$ has been well-studied. Reduction of the carbon-carbon double bond may accompany ester reduction, or, more prevalently, occur instead of ester reduction.[59] Bohlmann and coworkers [60] detected dimer formation in their study of the reduction of acrylate ester derivatives (eq [35]).

[35] 

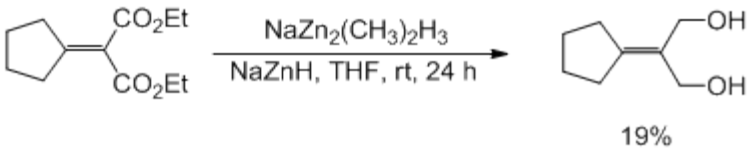
84 85 86

There are some reported routes (eq [36][61], [37] [62], [38] [63]) for reduction of α,β-unsaturated diesters. The methodologies for the reduction have several drawbacks such as low temperature and low yields.

[36][61] 

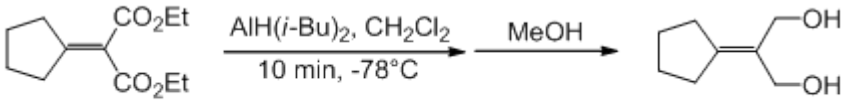
48%

[37][62]



19%

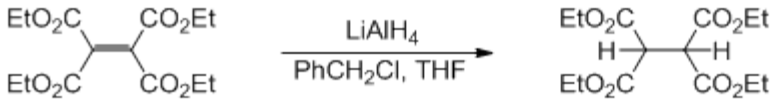
[38][63]



35%

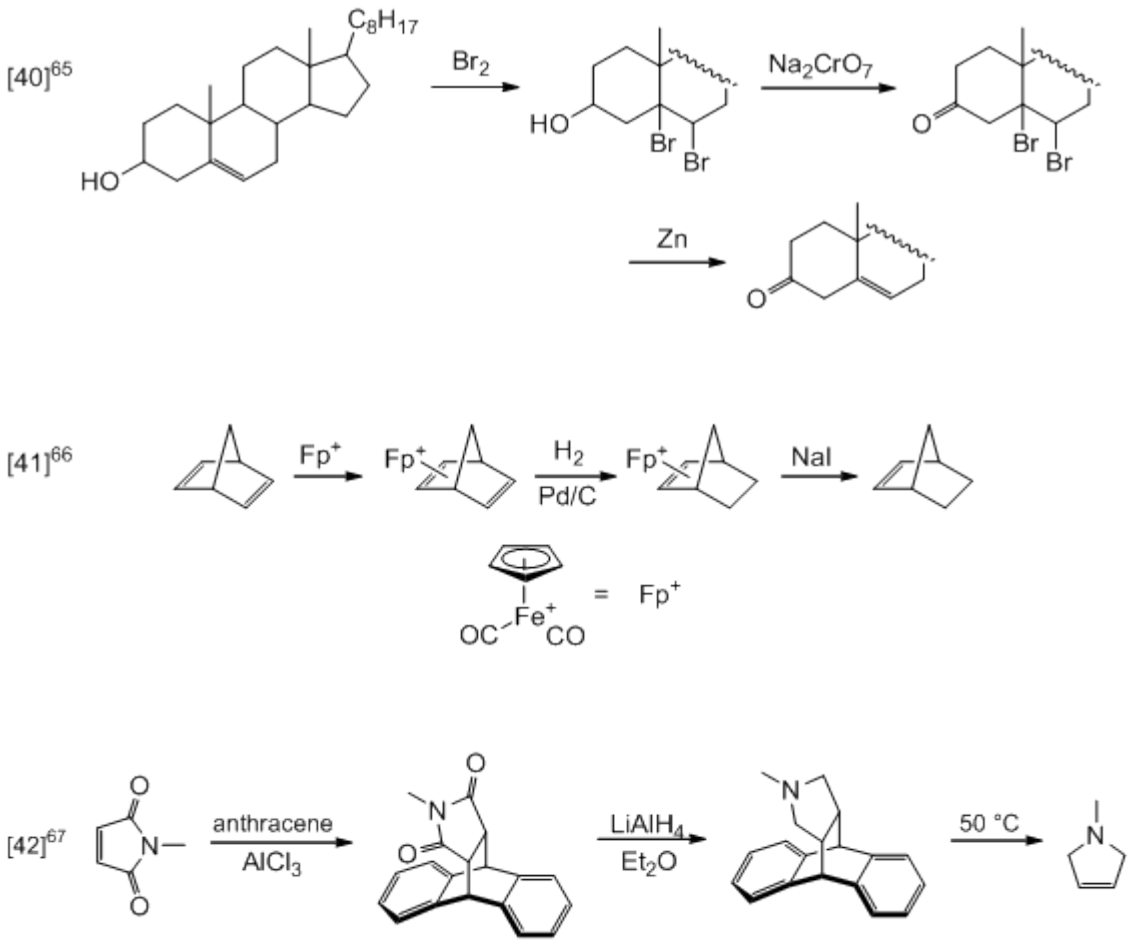
There have been no reductions of α,β-unsaturated triesters reported to the best of our knowledge. We decided to attempt the selective reduction of the ester groups of **82** using a recently-reported method[64] employing $LiAlH_4$ and benzyl chloride. This method was claimed to lead to selective ester reduction of α,β-unsaturated esters. However, in our hands, reduction of **82** gave exclusively alkene reduction and no ester reduction (eq [38]).

[39][64]



82 **87** (**81** not formed)

To circumvent this problem, it is important to find a way to protect the double bond before the reduction of esters of **82**. Standard carbon-carbon double bond protection/deprotection schemes are halogenation-dehalogenation,[65] addition/elimination of organometallic complex,[66] and Diels-Alder/retro-Diels-Alder methods (eqs [40] - [42]).[67]



The first method was unsuitable because the hydride in the $LiAlH_4$ can replace the halogen. There are no particular metal complexes in hand for the second method. It was then decided to use anthracene as a diene in the last method because anthracene is available in our lab, and there were ample literature precedents.[67,68] The modified route is shown in Figure 13.[68]

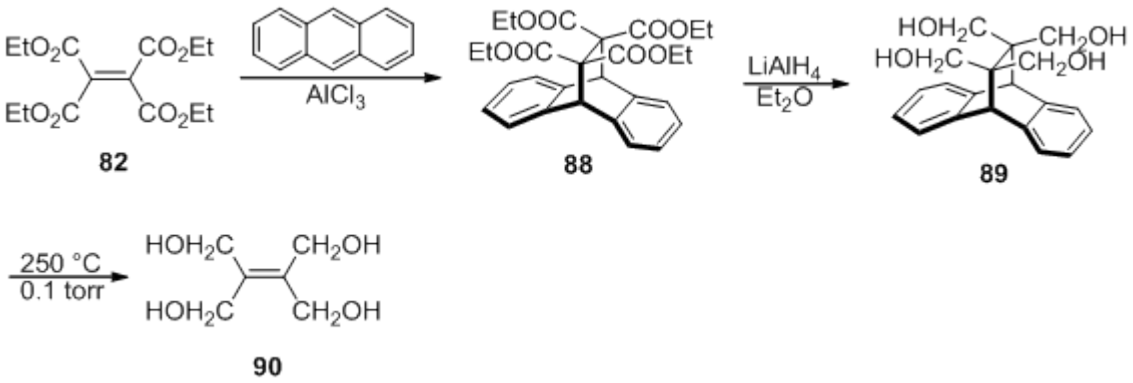
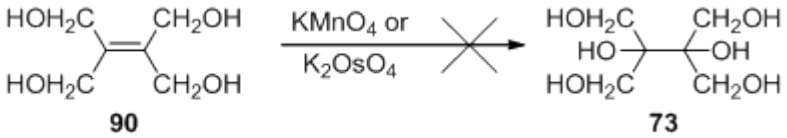


Figure 13. Route to **90**

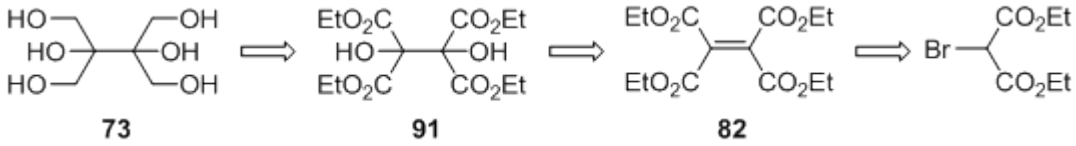
The tetracarboxylated olefin was protected by anthracene using $AlCl_3$ as Lewis acid catalyst to give tetraethyl 9,10-dihydro-9,10-ethanoanthracene-11,11,12,12-tetra-carboxylate, **88**, (yield: 70.1%) which was reduced by $LiAlH_4$ in ethyl ether to 9,10-ethano-9,10-dihydroanthracene-11,11,12,12 tetramethanol, **89** (yield: 51.3%). The workup procedure of this reduction called for sequential addition of ethyl acetate and water. Then, 6 N HCl solution was added to adjust the pH to 1. This step is somewhat dangerous and easy to catch fire; addition of HCl must be done slowly, carefully, and at low temperature.

When tetramethanol **89** was heated at 250 °C in a sand bath under 0.1 torr for 2 h, the retro-Diels-Alder reaction happened, forming 2,3-bis(hydroxymethyl) but-2-ene-1,4-diol which was water soluble. Unfortunately, the last step, dihydroxylation of **90** to **73**, was unsuccessful using $KMnO_4$ or K_2OsO_4 (eq [43]).

[43] 

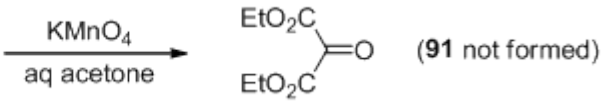
2.1.2 Synthesis of hexaol 73. Second route.

The retrosynthetic analysis is shown in Equation [44].

[44] 

Here, we again start with tetraester **82**. This time, we planned to first dihydroxylate **82** instead of reducing of it. Then tetraethyl 1,2-dihydroxyethane-1,1,2,2-tetracarboxylate **91** was to be reduced to target compound **73** in the final step.

The first conditions that we tried for dihydroxylation of **82** to **91** were $KMnO_4$ as reagent, and aqueous acetone as co-solvent. After $KMnO_4$ in aqueous acetone was added to the solution of tetracarboxylate **82** in the same solvent at 5 °C, the color changed from purple to dark very quickly. The isolated compound however was diethyl 2-oxomalonate (eq [45]).

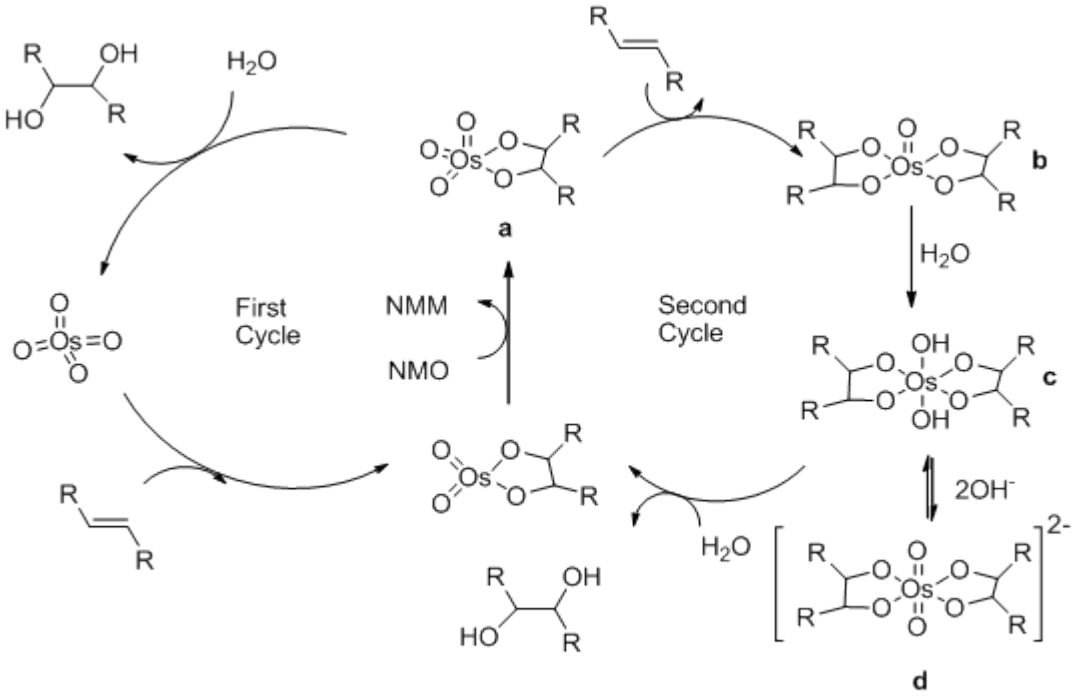
[45] 

Many references[69] show that the yields are low and the ketone is produced when $KMnO_4$ is used in the dihydroxylation reaction, because most functional groups are not stable in the presence of highly oxidative $KMnO_4$. The $KMnO_4$ as dihydroxlation reagent was therefore discarded.

Osmium-based oxidants appeared to be the best choice because they react with virtually all olefins but slowly, if at all, with other common organic functional groups. In many cases, we used potassium osmate dihydrate as catalyst instead of osmium tetroxide which is more volatile. Disappointingly, we found the 5 mol% potassium osmate(VI) dihydrate and 1.1 equiv 4-methylmorpholine N-oxide (NMO) failed to dihydroxylate **73,** even after stirring for one week.

Since OsO_4 is an electrophilic reagent, the rate of osmylation of electron-deficient olefins, such as α, β-unsaturated carbonyl compounds can be very low. In a recent reexamination of the Os-catalyzed dihydroxylation reaction, Sharpless and co-workers reported that citric acid, when added to the reaction mixture, greatly improved rates and yields of diol from these normally recalcitrant compounds.[70] The authors attribute this effect to low pH blocking the major OsO_4 decomposition pathway. Under conditions where reoxidant has access to all the catalytic intermediates, turnover is achieved only through the second cycle (Scheme 8). Sharpless proposed that a major loss of catalytic osmium is through the deprotonation of bis-glycolate intermediate **c**, found in the second cycle, which results in the formation of the inert osmium dianion **d**. This therefore

explains the poor reactivity of electron-deficient olefins, for example, as intermediate c would be easier to deprotonate than usual, even in the presence of a relative weak base, like 4-methylmorpholine. Studies in Sharpless group showed that addition of citric acid in this kind of reaction better than acetic, malic, tartaric, phosphoric, sulfuric and citric acids provided consistently high yields of outstandingly pure diol from all olefins.



Scheme 8. Proposed mechanism of osmium-catalyzed dihydroxylation[70]

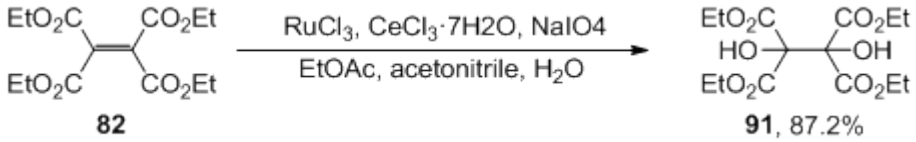
Diethyl maleate was used by us as a substrate to test the reaction conditions reported by Sharpless' group: 0.75 equiv. citric acid and 0.63 mol% potassium osmate dihydrate in 1:1 *t*-butyl alcohol and water at room temperature. After a half hour, the mixture's green

color disappeared, and after an additional two and a half hours, the mixture was close to colorless. Very pure product was obtained after easy workup, in a yield of 46.7%. (literature yield 90%).[70] Unfortunately, the same conditions didn't work for tetraester **82**. The reason is that hydrolysis of osmate esters derived from tetrasubstituted olefins is very slow, resulting in serious turnover problems according to the review article.[71] To improve the yield in our case, we modified the reaction conditions as follows: the reaction temperature was raised to reflux temperature, and potassium osmate loading was increased to 2.45% from 0.63%. After the mixture was stirred overnight under these conditions, the desired product diol **91** yield was about 20% judging from the NMR spectrum, which also showed 70% starting tetraester **82** remaining.

Although the osmium-catalyzed dihydroxylation of C=C double bonds is one of the most successful catalytic transformations, it also uses reagents that are very expensive, volatile, and toxic. Hence, the search for a less expensive and toxic albeit comparably selective oxidation catalyst is still of current interest.[72] In 1994, Shing reported the dihydroxylation using catalytic amounts of RuO_4.[73] This kind of reaction is in general very fast (Shing coined the term "flash dihydroxylation"). However, high catalyst loading and undesired side reactions (scission reactions) were severe drawbacks in RuO_4-catalyzed oxidations. Bernd Plietker and Meike Niggemann found that addition of Brønsted acid improved RuO_4-catalyzed dihydroxylation; the catalyst concentration could be decreased to 0.25 mol%, and the scope of the reaction was broadened.[71]

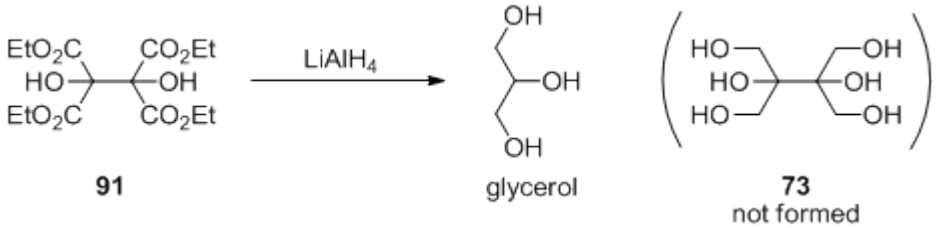
Futhermore competing scission reactions were suppressed and oxidation of electron-deficient tetrasubstituted double bonds that could not be oxidized using previous dihydroxylation protocols could be achieved with the Ru catalyst systems.

The conditions reported[72] in their paper proved to be excellent for the tetraester **82** eq [46]): 2 mmol scale olefin, using 5 mol% of $RuCl_3$ (instead of 0.25 mol% in the paper), 10 mol % $CeCl_3{\cdot}7H_2O$, and 1.5 equiv of $NaIO_4$ at 0 °C in a solvent mixture of ethyl acetate, acetonitrile, and water (3 mL/3 mL/1 mL). Use of this protocol on **82** gave diol **91** in 87.2% yield.

[46] 

82 **91**, 87.2%

With the dihydroxyl-tetraester **91** in hand, the direct reduction of it by $LiAlH_4$ was carried out in hopes of producing **73** (eq [47]).

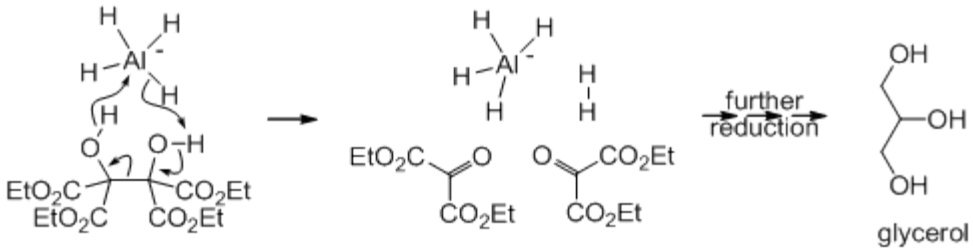
[47] 

91 glycerol **73** not formed

In this case, it was very hard to separate the organic product from the metal salts. After

acid work up, the only product isolated was glycerol. NMR spectra of the crude reaction mixture indicated that glycerol was the sole organic product. A rationalization of this unexpected result is given in eq [48].

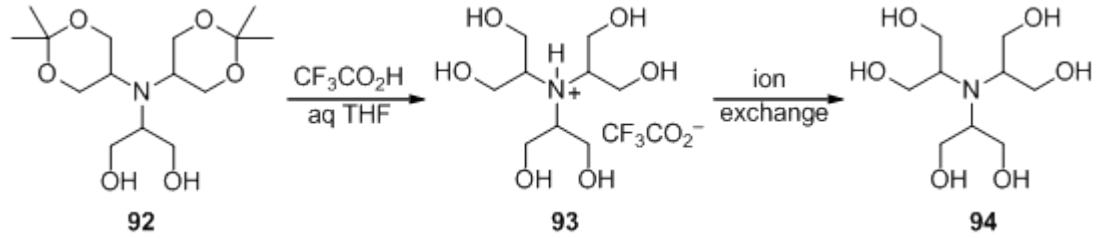
[48]



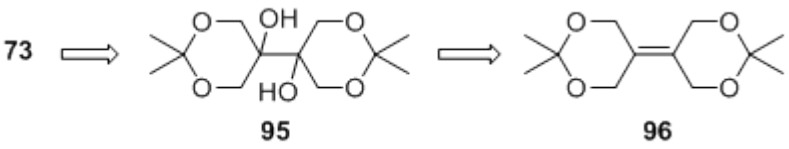
2.1.3 **Synthesis of hexaol 73. Third route.**

The difficulty in workup of the reaction shown in eq [47] pointed out the difficulty which would be faced isolating water-soluble **73** from any reaction mixture containing inorganic salts. Even if $LiAlH_4$ reduction of **91** had produced **73**, the likelihood of a difficult workup made this route less attractive.

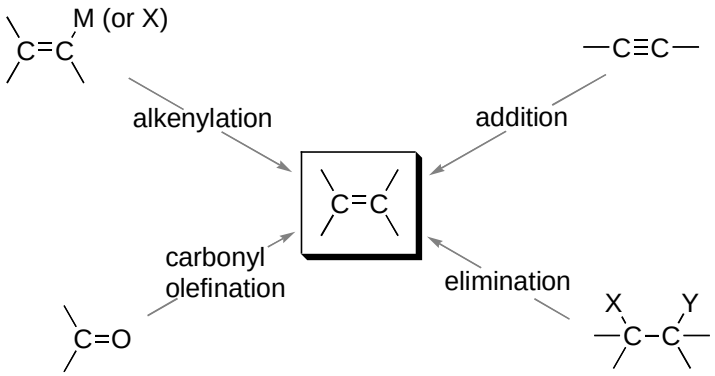
In our research group, former members had also encountered the problem of synthesizing a water-soluble target compound, namely **94** (eq [49]). The deprotection of an acetal worked well in the final stages of the synthesis of **94**. We thought that we could adapt this strategy to our synthesis of **73**.

[49] 

A partial retrosynthesis is shown in eq [50]. The final step is the deprotection of bis(acetonide) **95**. Aside from **73**, the product mixture from this deprotection step would contain acetone, water, trifluoroacetic acid, and THF; all of these could be removed under vacuum, leaving only **73**, we hoped.

[50] 

We turned our attention to olefin **96**. Broadly speaking, there are four routes to alkenes (Scheme 9).

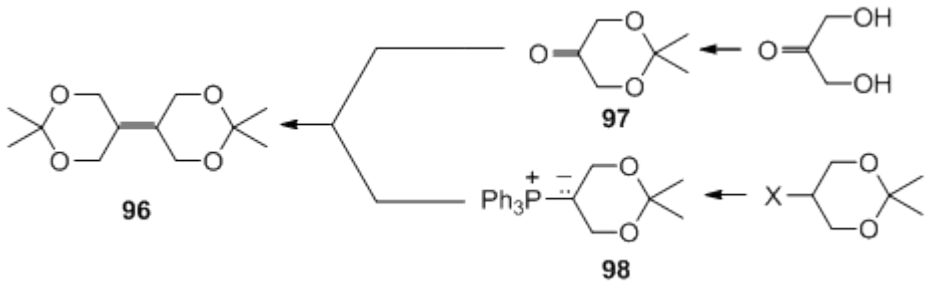


Scheme 9[74]**.** General routes to alkenes

The most popular carbonyl olefination method is the Wittig reaction, which in our

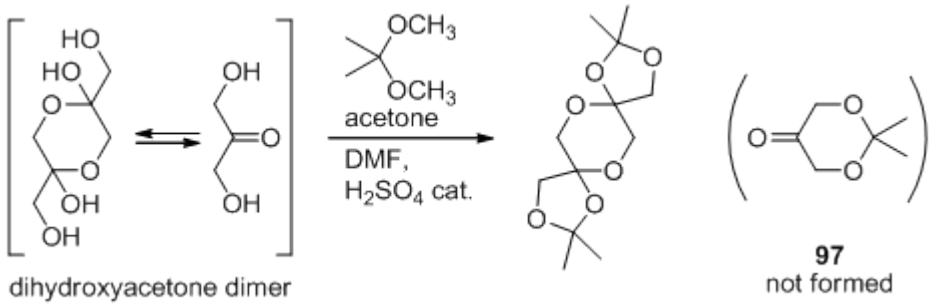
case would require ketone **97**, derived from dihydroxyacetone, and phosphorus ylide **98** (eq [51]).

[51]



The seemingly simple protection of dihydroxyacetone is complicated by the monomer-dimer equilibrium that dihydroxyacetone is known to undergo (eq [52]).[75] It was found in our laboratory previously that the attempted synthesis of 2,2-dimethyl-1,3-dioxan-5-one **97** starting from dihydroxacetone dimer did not give the desired product.[76]

[52]

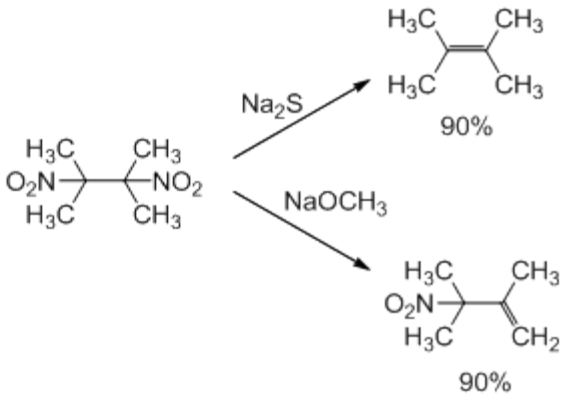


We decided to instead explore elimination methods of alkene synthesis. The radical elimination of nitrogen dioxide to form olefins was first reported by Kornblum et al.[77]

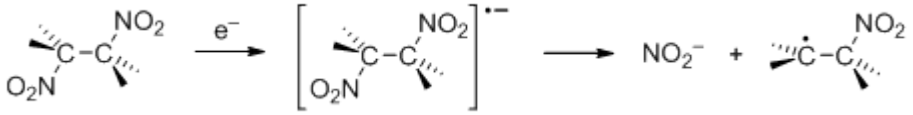
[53] 

[54] 

Kornblum proposed that the elimination of two nitro groups from a vicinal dinitro compound by the agency of sodium sulfide or sodium thiophenoxide is not a simple ionic process for these reactions are unambiguously accelerated by the light of an ordinary 20-W fluorescent lamp. Also, when a strong base such as sodium methoxide is employed an alternative type of elimination reaction occurs (eq [55]).

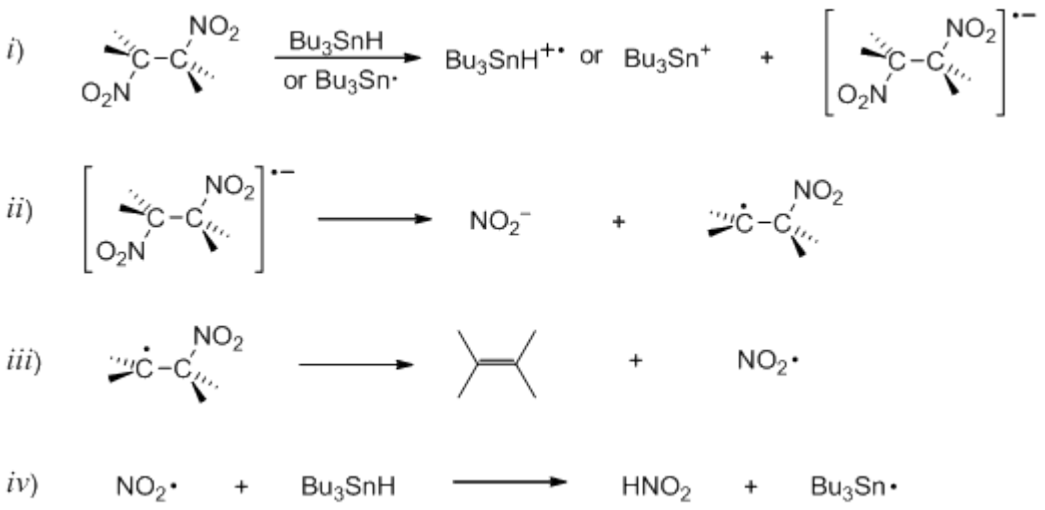
[55] 

These facts, and observations with other aliphatic nitro systems,[78] suggest that elimination of two nitro groups from vicinal dinitro compounds involves radical anions.



Kornblum just said that various pathways are readily envisioned for the loss of the second nitro group; but didn't give the any pathway in his paper.

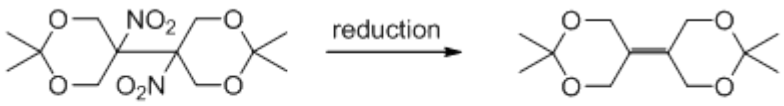
Ono and coworkers discovered that elimination of vicinal dinitro compounds proceeds by way of an electron transfer chain mechanism. In this kind of process, tributyltin hydride is evidently more effective than other reagents in converting vicinal dinitro compounds to olefins due to its good electron donor properties.[79] The mechanism of this elimination appears to be $E_{RC}1$ which is named for a radical anion-radical chain elimination process (Scheme 10).[80] The fact that the elimination is greatly retarded in the presence of a small amount of *m*-dinitrobenzene provides support for the proposed electron-transfer chain mechanism.



Scheme 10.[81] Proposed mechanism of tri-*n*-butyltin hydride reduction of *vic*-dinitro compounds.

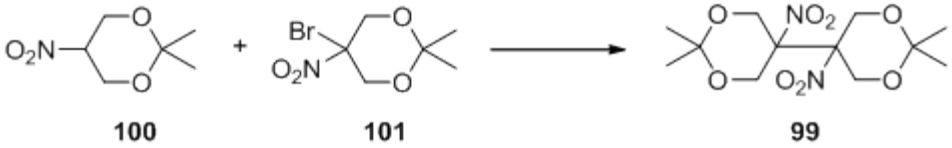
Since there are many procedures reported,[82,83,84] in addition to those of Kornblum and Ono just discussed, for the synthesis of tetrasubstituted olefins *via* the reductive elimination of nitro groups from *vic*-dinitro compounds, the transformation of dinitro compound **99** to alkene **96** seemed quite feasible (eq [56]).

[56]



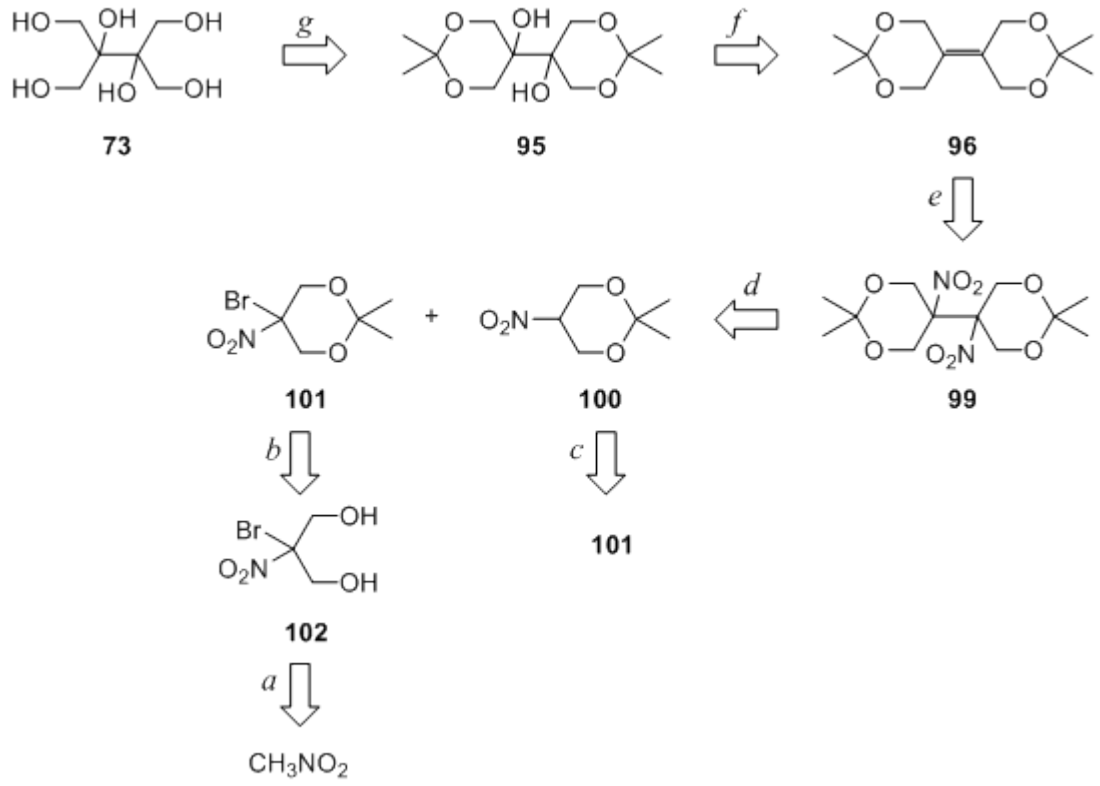
99 **96**

Synthesis of dinitro compound **99** by the method shown in eq [57] requires **100** and **101**.

[57] 

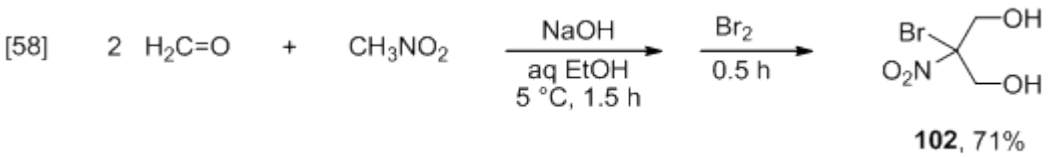
100 **101** **99**

At this stage, there are two choices: (*i*) synthesis of 2,2-dimethyl-5-nitro-1,3-dioxane **99** which may then be brominated to give 5-bromo-2,2-dimethyl-5-nitro-1,3-dioxane **101**; or (*ii*) synthesis of **101** which may then be reduced to **100**. In our hands, the synthesis of 2-nitro-1,3-propanediol, a precursor of **100**, produced mixtures, and the conversion of 2-nitro-1,3-propanediol to **100** was unsatisfactory. Therefore we turned to choice (*ii*). The overall plan of the third route to **73** is shown in Scheme 11. Our discussion will follow the letters assigned to the steps in Scheme 11.



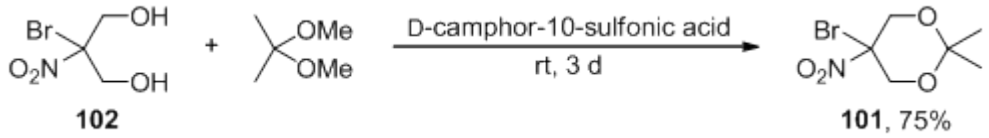
Scheme 11. Retrosynthetic plan for third route to **73.**

(*a*) Synthesis of 2-bromo-2-nitro-1,3-propanediol **102**. Unlike the synthesis of 2-nitro-1,3-propanediol, a precursor of **100,** the synthesis of 2-bromo-2-nitropropane-1,3-diol **102** (eq [58]) went more smoothly.[85] The crude product was recrystallized from water and ethanol to give a 70.6% yield of **102**. Later we discovered that **102**, trivial name bronopol, is commercially available.



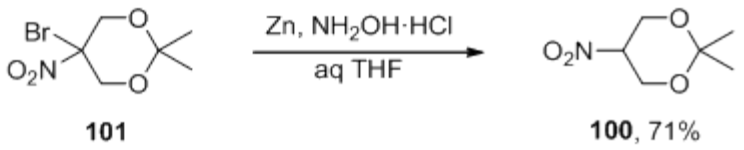
(*b*) Synthesis of acetonide **101**. Protection of diol **102** by stirring it in acetone in the presence of a catalytic amount of sulfuric acid at room temperature failed. A literature procedure for the synthesis of **101**,[86] using a Soxhlet extractor filled with dry 4Å molecular sieves, and catalytic *p*-toluenesulfonic acid in a mixture of diol **102**, acetone, and toluene gave only traces of the desired acetonide.

Another literature method,[87] using 2,2-dimethoxypropane as the solvent and the more soluble D-camphor-10-sulfonic acid as the catalyst, and stirring at room temperature for three days gave **101** in good yield. (75%)

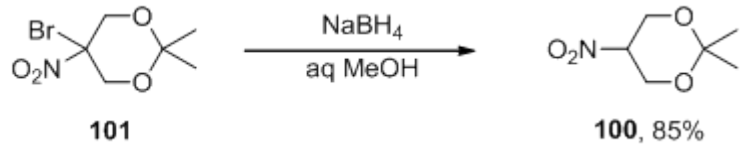
[59] 

102 **101**, 75%

(*c*) Synthesis of 2,2-dimethyl-5-nitro-1,3-dioxane, **100**. Bromo nitro compound **101** was reduced to nitro compound **100** two ways. Zinc in the presence of hydroxylamine hydrochloride[86] gave **100** in 71% yield (eq [60a]). Alternatively, treatment of **101** with $NaBH_4$ afforded **100** in 85.1% yield (eq [60b]).[87] The borohydride reduction was the preferred method: the reaction was easier to control, the yield was higher, and the product was pure enough to be used directly in the next step.

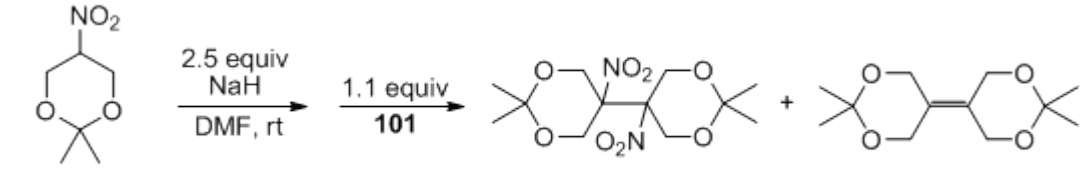
[60a] 

101 **100**, 71%

[60b] 

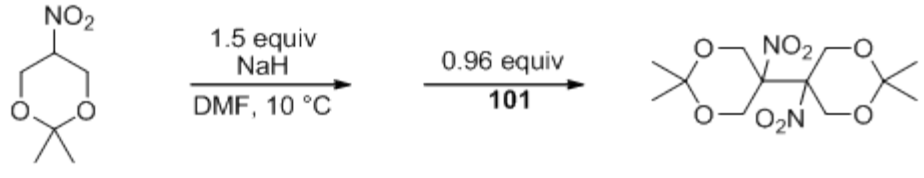
101 **100**, 85%

d) Synthesis of 2,2,2',2'-tetramethyl-5,5'-dinitro-5,5'-bi(1,3-dioxane), **99.** Treating **100** with sodium hydride, and reacting the resulting nitronate anion with bromo nitro compound **101** gave a modest yield of **99** (eq [61]). NMR spectra indicated that about 10% of **96** was also formed. We found that we could suppress the formation of **96** by

[61] 

1.0 equiv **100** **99**, 38% **96**, ~10%

using a smaller excess of sodium hydride, and by generating the nitronate at a slightly lower temperature (eq [62]).

[62] 

1.0 equiv **100** **99**, 51%

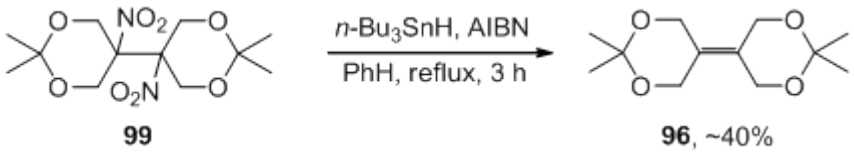
(*e*) Synthesis of 2,2,2',2'-tetramethyl-[5,5']bi[1,3]dioxanylidene **96**.

Initial attempts. The preparation of olefin **96** in 40% yield, using the sodium sulfide procedure of Kornblum,[77] has been reported in the literature.[82] However, when we treated **99** with 2.5 equivalents of $Na_2S{\cdot}9H_2O$ in DMF and irradiated the mixture with two 20 W fluorescent lights for 12 h, no reaction occurred. The reason why the sodium sulfide method didn't work for compound **99** was explained by N. Kornblum and L. Cheng who stated that sodium sulfide couldn't be used for the synthesis of highly functionalized olefins owing to its strong nucleophiliticity.[83] Calcium amalgam has been suggested as an alternative to sodium sulfide in this reaction,[83] however, the toxicity of this reagent caused us to try other alternatives. Nickel boride with ultrasound irradiation is reported to reduce compound **99** to alkenes **96**,[84] but the Kaszynski group[88] reduced the similar 5,5'-dinitro-5,5'-bi(1,3-dioxane) under these conditions to give only 20% 1,3-Dioxane, 5-(1,3-dioxan-5-ylidene) compared to 95% yield[84] reported for **96**. Since our laboratory lacked the necessary ultrasound equipment, we could not try this method. Similarly, electrochemical reduction of 2,3-dinitro-2,3-dimethylbutane was reported to afford an 80% yield of tetramethylethylene (and two equivalents of nitrite anion),[89] but our laboratory was not equipped to carry out preparative scale electrolysis. Photolysis of 9,9'-dinitro-9,9'-bifluorenyl was reported to give 9,9'-bifluorenylidene[90] but we speculated that an aromatic system UV chromophore was an essential part of the success

of this photolysis. Since **99** lacked this feature, we did not pursue this method.

Tri-*n*-butyltin hydride has also been used to effect the reductive elimination.[81] In our hands, treatment of **99** with tri-*n*-butyltin hydride and AIBN in refluxing benzene for 3 h afforded **96** in 40% yield, as estimated from NMR spectra (eq [63]).

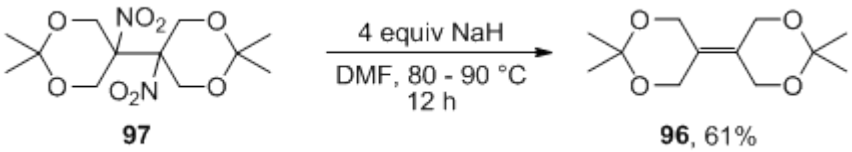
[63]



99 **96**, ~40%

Development of a new method. The results summarized in equations [61] and [62] appeared to suggest that compound **96** could arise from **99** *by the action of NaH*. Since **96** is a desired synthetic intermediate, we investigated the possibility of transforming **99** to **96** employing NaH as the reducing agent. Sodium hydride has been used as a reducing agent in a variety of reactions, such as the transformation of $LaNi(III)O_3$ to $LaNi(I)O_2$,[91] conversion of ketones to alcohols,[92] and reduction of azides to amines.[93]

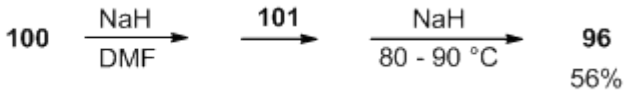
As a control experiment, **99** was treated with 4 equivalents of NaH in DMF at room temperature. No **96** was detected after 12 hours. Also as a control, **99** was heated in the absence of NaH at 80 - 90 °C in DMF for 12 h. No **96** was detected. When **99** was heated at 80 - 90 °C for 12 h in the presence of 4 equivalents of NaH, a 61% yield of **96** was obtained (eq [64]).

[64] 

97 **96**, 61%

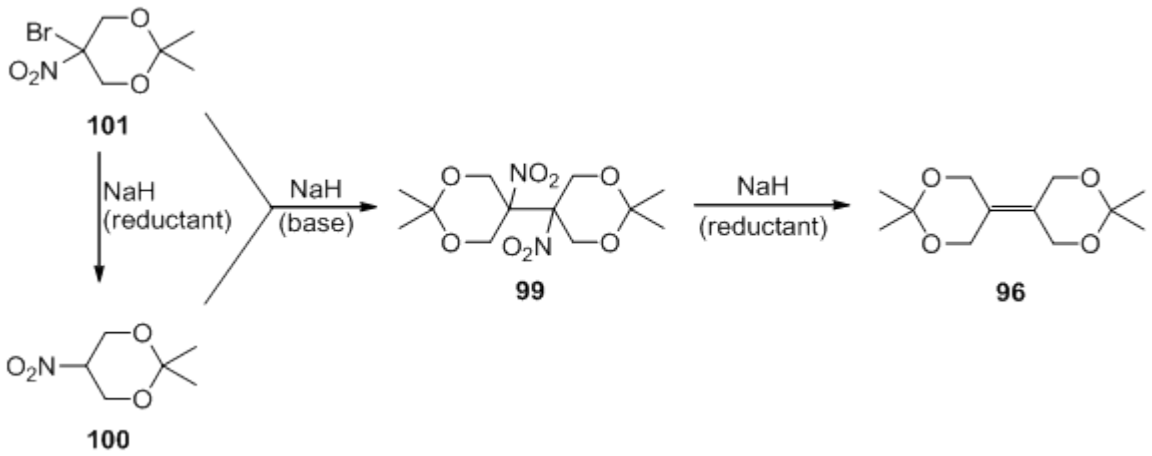
The previous step - the reaction of deprotonated **100** with **101** to form **99** (eq [62]) - used NaH as a base. The step under consideration now (eq [64]) also used NaH, but as a reductant. We thought it would be reasonable to attempt to combine these two steps in a one-pot process to transform a mixture of **100** and **101** to **96** without isolating **99.**

Sodium hydride was added portionwise to a solution of **100** in anhydrous DMF at 10 °C over 15 minutes. After addition, the mixture was stirred for 2 h at 10 °C. Compound **101** was added in one portion. The mixture was stirred overnight under an atmosphere of N_2 at room temperature. The starting material was undetectable by silica gel TLC (hexane/EtOAc 4:1), and dinitro compound **99** was detected. Another portion of NaH was added and the temperature was raised to 80 - 90 °C, to give product **96** in 56% yield, eq [65]. This should be compared to the overall yield of eq [62] and eq [64], 31%.

[65] 

The reduction of **101** to **100** was accomplished using either of the reducing agents shown in eq [60a] or [60b]. Based on the apparent ability of NaH to function as a reducing agent for nitro compounds, to wit eq [64], we speculated that the reduction of

101 to **100** might alternatively be accomplished using NaH, which would open up the possibility that treatment of **101** with NaH could lead in a three-reaction cascade to **96** in a one-pot process without the isolation of any intermediates. The idea is shown in Scheme 12.



Scheme 12. Proposal for a cascade reaction leading from **101** to **96**.

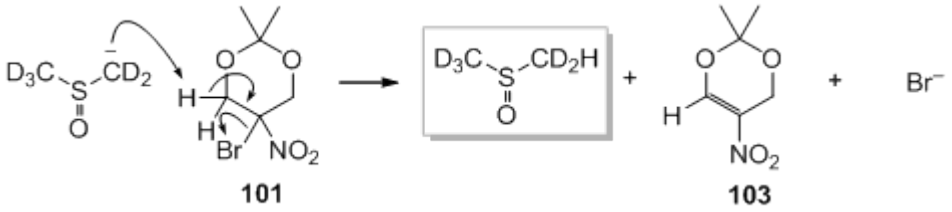
In our first attempt, **101** was added to 1.0 equivalent of NaH in DMF and stirred 14 h at 10 °C. TLC showed that very little reaction had occurred. In all our subsequent work with this reaction, we found that heating was essential, as was the use of large excesses of NaH. We now describe in detail our investigations of this cascade reaction.

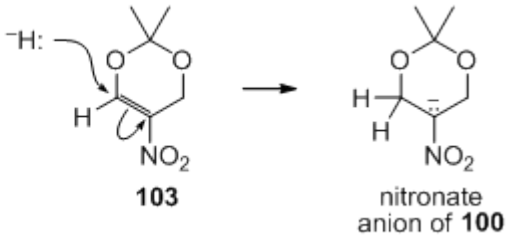
A solution of **101** in DMF was added dropwise with stirring to a suspension of 5.1 equivalents of NaH in DMF at 10 °C over the course of 10 minutes. The mixture was stirred and placed in a pre-heated oil bath and brought to 80-90 °C. During 3 h at this

temperature, the reaction mixture became progressively more yellowish. Then, all at once, the mixture turned black and copious gas evolution took place over about 20 seconds. The volume of bubbles produced caused very rapid foaming, and nearly resulted in the foam escaping the reaction vessel. After this 20 second episode of violent gas evolution, the reaction became calm. After stirring for one more hour, the mixture was quenched with water. After workup, dioxanylidene **96** was obtained in 39% yield.

We modified this procedure as follows. The NaH dispersion in mineral oil was rinsed repeatedly with hexanes to remove the oil. The NaH was added in one portion to a stirred solution of **101** in DMF. After heating to 80 - 90 °C, the course of the reaction was as before. The workup was altered: rather than purify **96** chromatographically, the crude product was recrystallized from hexanes. The yield was 67%.

We desired to follow the progress of the reaction by ^{1}H-NMR, to detect intermediates if possible. The solvent was changed to DMSO-d_6. Five equivalents of NaH were added to **101** in DMSO-d_6 and heated to 80 - 90 °C. In this case, the reaction was very violent, bordering on an explosion. After 10 minutes, the ^{1}H-NMR spectrum revealed that **96** was essentially the only product in the reaction mixture. After 40 minutes, the reaction was complete, and ^{1}H-NMR showed only **96** was present. On this basis, we estimate the yield of **96** as above 95%. In another NMR scale experiment, it was observed that the DMSO ^{1}H signal grew after the reaction began. A reasonable explanation is shown in equations [66] and [67].

[66] 

[67] 

Although we had proved that the cascade reaction could deliver **96** from **101** in "one step," the extremely vigorous gas evolution was undesirable, to say the least. We tried THF as the solvent next. In this case, after 24 h at reflux, the reaction mixture was a 1:1 mixture of **99** and **96**, as shown by ^{1}H-NMR. Significantly, no **100** was noted.

We next tried a mixed solvent of toluene and DMSO. We used about 4 drops of DMSO per mL of toluene. There was no "explosion" of bubbles in this reaction. TLC indicated that the reaction was complete after 4 hours at 80 – 90 °C, showing only the spot corresponding to product **96**. Despite the indication by TLC of a very high yield, after workup the isolated yield was 50.2%. We are not sure where the loss of product is occurring during the workup. Work is continuing to try to improve the yield of the cascade process. Even so, a yield of 50.2% in one step is much better than the overall

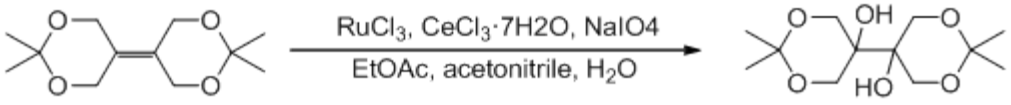
yield of the single reactions the cascade replaces, namely the reactions of eq [60b], eq [62], and eq [64], which was 26%.

(f) Synthesis of diacetonide diol **95**.

Now that we had **96** in hand, all that remained to do to produce the target hexaol **73** was to dihydroxylate, and then deprotect.

We used the same procedure for dihydroxylation of dioxanylidene **96** as was used for dihydroxylation of the tetraester **82**, eq [68]. The tetraester case gave a higher yield (87%) than the bis-acetonide (67%). We suggest that the Lewis acids present in this reaction may have catalyzed partial hydrolysis of the acetonide protecting group(s). Hydrolysis of one acetonide group would lead to a tetraalcohol, and hydrolysis of both would lead to **73**; both of these would be water soluble and would be lost in aqueous washes.

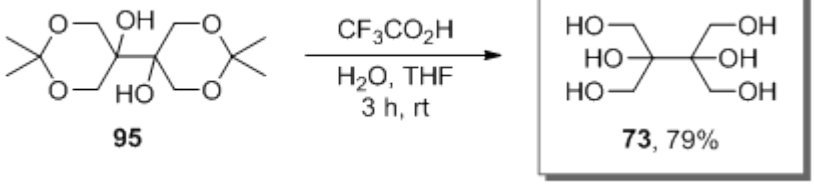
[68]



96 **95**, 67%

(f) Synthesis of hexaol **73**.

The last step was deprotection by trifluoroacetic acid in aqueous THF. The mixture was evaporated under vacuum to give colorless solid hexaol **73**.

[69] 

In the course of our investigations, we obtained crystals of **95** and **73** suitable for X-ray crystallography. Ms Yaqin Yu, a member of the research group of Professor Thomas Albrecht-Schmitt, performed the crystallographic data collection, solution, and refinement of the structures of **95** and **73**.

The X-ray crystal structure of **95** is shown in Figure 14. The crystal was triclinic, $P\ \bar{1}$, Z = 2, *a* = 5.4479(8) Å, *b* = 10.4700(14) Å, *c* = 12.5954(17) Å, α = 114.420(2)°, β = 93.277(2)°, γ = 91.346(2)°. A total of 6284 reflections to a maximum 2θ of 56.72° were collected at 193 K, of which 3126 were unique (R_{int} = 0.0381), data-to-parameter ratio = 19.7. Full matrix least-squares refinement on F^2 gave final R indices of R1 = 0.0635, wR2 = 0.1686 ($I > 2\sigma(I)$); R1 = 0.1036, wR2 = 0.2091 (all data); goodness of fit = 1.064. There are two independent molecules in the asymmetric unit. The C(10)-C(10) bond length is 1.546(4) Å in one and the corresponding distance in the other, C(11)-C(11) is 1.537(5) Å.

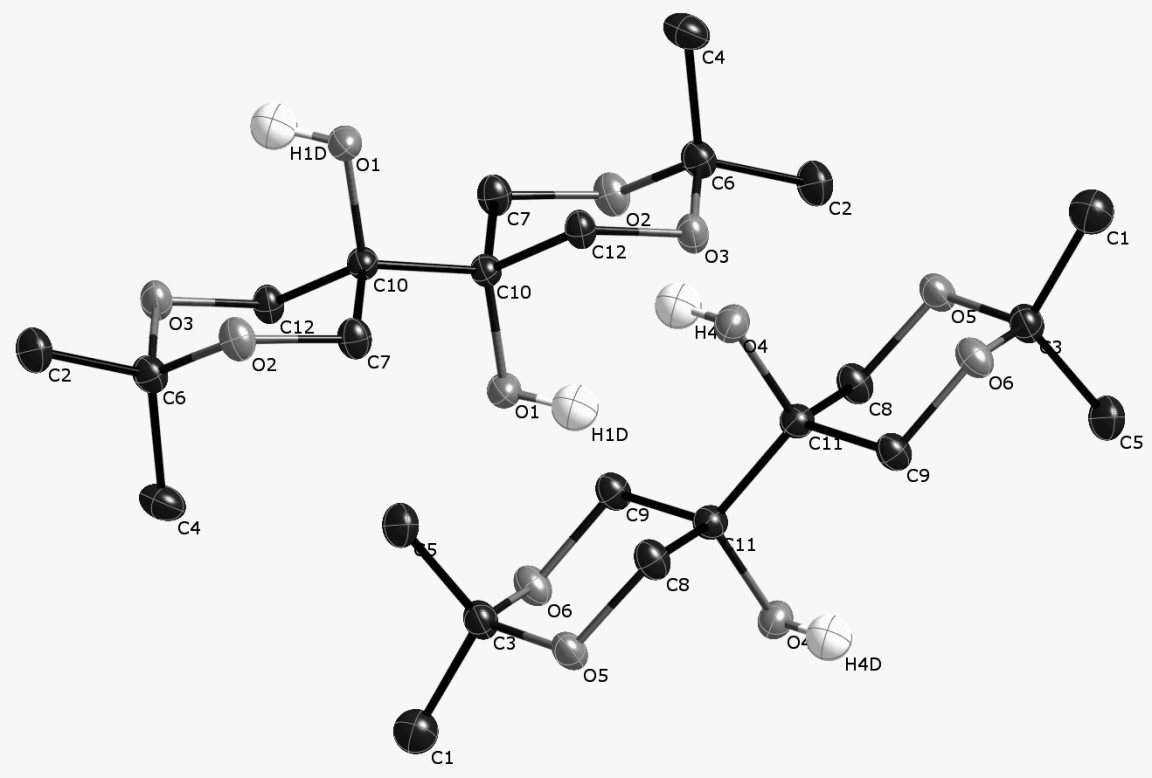


Figure 14. The crystal structure of **95**. Atoms are represented by thermal ellipsoids at the 50% probability level. Hydrogens bonded to carbon are omitted.

The X-ray crystal structure of **73** is shown in Figure 15.

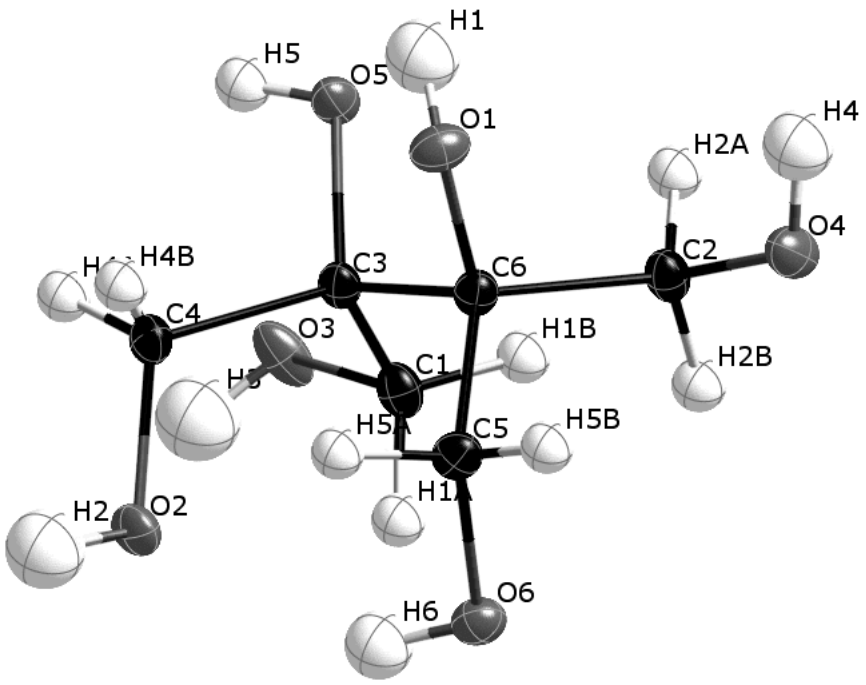


Figure 15. The X-ray crystal structure of hexaol **73**. Atoms are represented by thermal ellipsoids at the 50% probability level.

Hexaalcohol **73** is extensively hydrogen-bonded. Figure 16 shows both internal and external hydrogen bonds. Geometrical parameters of these hydrogen-bonds are listed in Table 4.

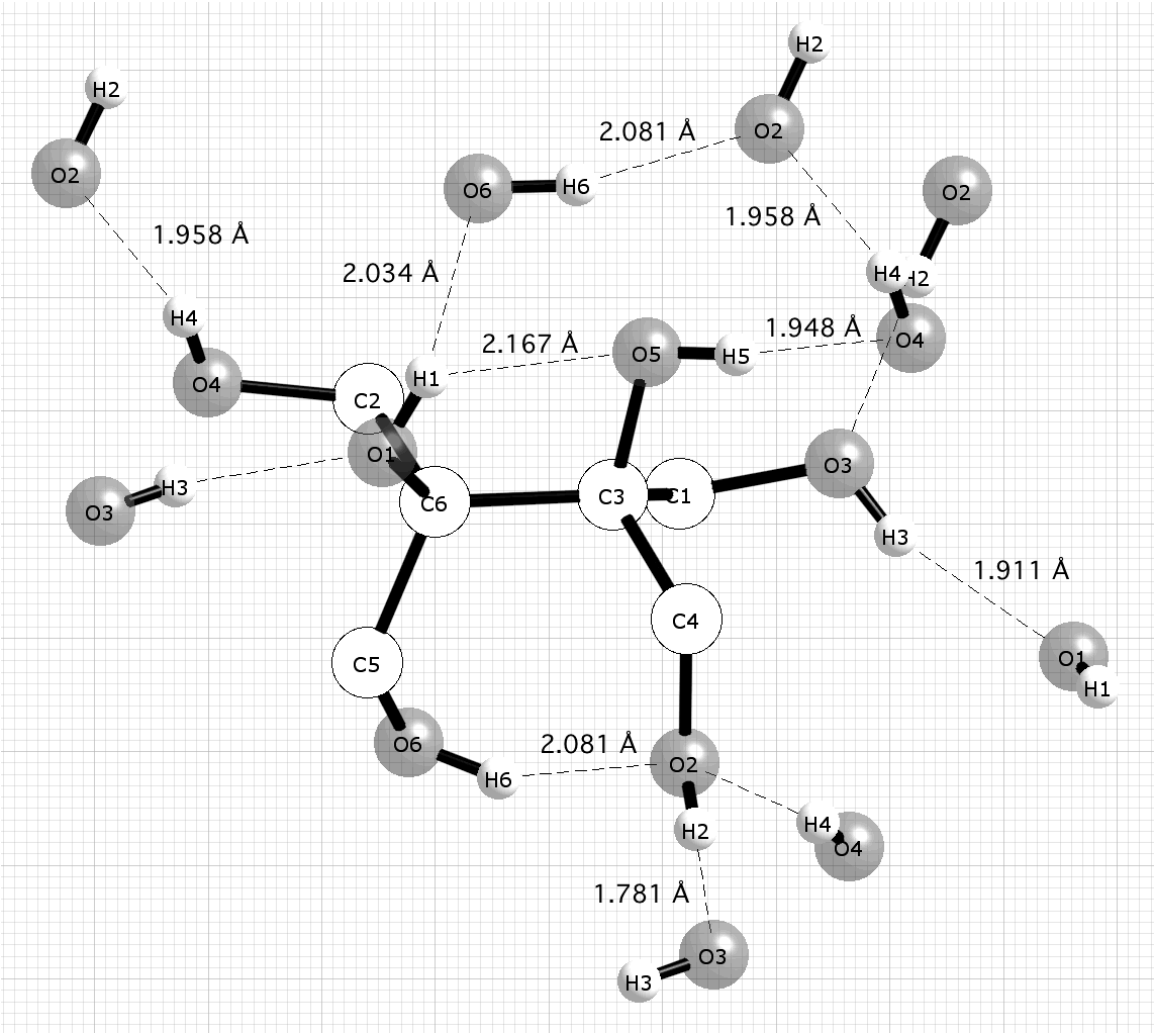


Figure 16. Hydrogen bonding network of **73**.

The carbon-carbon bond length between the two central carbons, C(3) and C(6), is fairly long, namely 1.5675(15) Å. By comparison, the average bond length for all the other C-C bonds in this molecule is 1.5334(15) Å.

Table 4. Hydrogen bonds of hexaalcohol **73**.

	O···O distance (Å)	OH···O distance (Å)	θ(°)[a]

O1 - O3[b]	2.690	1.911	12.576
O1 - O5[c]	2.590	2.167	50.610
O1 - O6[b]	2.808	2.034	14.740
O2 - O3[b]	2.627	1.781	4.152
O2 - O4[b]	2.767	1.958	12.953
O2 - O6[c]	2.812	2.081	27.155
O4 - O5[b]	2.727	1.948	14.927

[a] angle between O-H bond direction and O···O direction. [b] intermolecular H-bond

[c] intramolecular H-bond.

5. EXPERIMENTAL

General: Toluene, THF and ethyl ether were distilled over sodium benzophenone ketyl, and methylene chloride, carbon tetrachloride and acetonitrile were distilled over calcium hydride all under a nitrogen atmosphere. Other reagents used in the synthesis were purchased from the Aldrich Chemical Company and were used without further treatment.

Melting points were recorded on capilliary melting point apparatus and uncorrected. NMR spectra were obtained at room temperature from either a Bruker Avance-250 spectrometer operating at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C or a Bruker Avance-400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. TMS was used as internal standard. The results are presented as parts per million (ppm or δ) and coupling constants are reported in Hz. DEPT experiments were conducted at $\theta=135°$, which corresponded to a pulse width of 21.4 μsec.

X-ray crystallography was performed on either a Siemens R3m/v single crystal X-ray diffractometer with a CCD detector by Dr. Yaqin Yu.

TLC was performed on Sorbent Technologies precoated silica gel glass plate. Preparative column chromatography employed Scientific Adsorbents Incorporated (SAI) silica gel (60 Å 70-230 mesh or 60 Å, 200-425 mesh).

1-Chloro-2-(2-ethoxyethoxy)ethane, 5.[18] Method A. 2-(2-Ethoxyethoxy)ethanol (33.8 g, 0.252 mol), triphenylphosphine (73.0 g, 0.279 mol), 125 mL carbon tetrachloride, and 50 mL acetonitrile were placed in a 500 mL three necked round bottom flask which was equipped with a magnetic stirrer and condenser. The reaction solution was heated gently, and allowed to reflux for three hours. After the reaction, the mixture was cooled in ice water. The white solid triphenylphosphine oxide was removed by filtration, and the solid was rinsed with cold hexane. The filtrate was combined, and the solvent was removed on the rotary evaporator. The resulting liquid and white solid was distilled under reduced pressure to give colorless liquid 21.6 g, yield 56.3% ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, t, *J* = 7.1 Hz), 3.54 (2H, q, *J* = 7.1 Hz), 3.64 (6H, m), 3.77 (2H, t, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 42.8, 66.9, 69.9, 70.9, 71.5.

Method B.[19] A solution of thionyl chloride (14.4 mL, 0.203 mol) in 30 mL $CHCl_3$ was added slowly over 15 min to a stirred solution of 2-(2-ethoxyethoxy)ethanol (19.3 g, 0.144 mol) and pyridine (11.6 mL, 0.144 mol) in 120 mL $CHCl_3$ under N_2, followed by refluxing the reaction mixture for 3 h. The mixture was washed with 2 x 300 mL of water, dried over $MgSO_4$, and concentrated under reduced pressure. The yellow crude product (20.1 g, yield 91.5%) was spectroscopically pure and was used in the next step without

further purification.

1-Chloro-2-(2-methoxyethoxy)ethane, 4.[19] A solution of thionyl chloride (43.8 g, 0.368 mol) in 60 mL $CHCl_3$ was added slowly over 15 min to a stirred solution of 2-(2-methoxyethoxy)ethanol (34.6 g, 288 mmol) and pyridine (23.0 mL, 286 mmol) in $CHCl_3$ (240 mL) under nitrogen, followed by refluxing the reaction mixture for 3 h. The mixture was washed with 1200 mL of water, dried over $MgSO_4$, and concentrated under reduced pressure to give a light yellow oil, 36.4 g, 91.3% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 (3H, s), 3.46 (2H, m), 3.56 (4H, m), 3.66 (2H, t, *J* = 6.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.6, 58.9, 70.4, 71.3, 71.8.

1,3-Bis(2-(2-methoxyethoxy)ethoxy)benzene, 6.[18] Sodium hydride 60% w/w dispersion in mineral oil (1.10 g, 27.6 mmol) and 12 mL dry DMF were placed in a 50 mL three necked round bottom flask which was equipped with a thermometer, a condenser, an addition funnel and magnetic stirrer. A solution of resorcinol (1.34 g, 12.0 mmol) in 10 mL DMF was added to the flask through the addition funnel at 0 °C under N_2 atmosphere. The solution was stirred for 2 h at rt. 2-Chloroethyl 2-methoxyethyl ether (4.18 g, 27.4 mmol) was added all at once to the solution at rt. The temperature was raised to 100-110 °C and allowed to react under N_2 atmosphere overnight. The cooled reaction solution was quenched with 10 mL water, and extracted with 3 x 10 mL CH_2Cl_2. The organic extracts were combined, washed with 10 mL 5% NaOH, 10 mL water, and dried over anhyd $MgSO_4$. After filtration, the crude product was purified by silica gel

column chromatography (hexane/ EtOAc 2:1 (v/v)) to give a colorless liquid, 2.91 g, 77.0% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (6H, s), 3.58 (4H, m), 3.72 (4H, m), 3.85 (4H, t, *J* = 5.0 Hz), 4.11 (4H, t, *J* = 5.0 Hz), 6.51 (3H, m), 7.15 (1H, t, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.1, 67.4, 69.8, 70.7, 72.0, 101.8, 107.1, 129.8.

1,3-Bis(2-(2-ethoxyethoxy)ethoxy)benzene, 7.[18] Sodium hydride 60% w/w dispersion in mineral oil (14.0 g, 0.350 mol) and 120 mL dry DMF were placed in a 500 mL three necked round bottom flask which was equipped with a thermometer, a condenser, an addition funnel and magnetic stirrer. A solution of resorcinol (13.4 g, 0.120 mol) in 100 mL DMF was added dropwise to the flask through the addition funnel at 0 °C under N_2 atmosphere. The solution was stirred for 2 h at rt. 2-Chlorethyl 2-ethoxyethyl ether (43.2 g, 0.284 mmol) was added all at once to the solution at rt. The temperature was raised to 100-110 °C and allowed to react under N_2 atmosphere at this temperature overnight. The cooled reaction solution was quenched with 10 mL water, and extracted with 3 x 10 mL CH_2Cl_2. The organic extracts were combined, washed with 10 mL 5% NaOH, 10 mL water, and dried over anhyd $MgSO_4$. After filtration, the solvent was removed by on the rotary evaporator. The resulting liquid was distilled under vacuum to give colorless liquid 30.4 g, yield 74.1%, b.p. 198/0.8 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (6H, t, *J* = 7.1 Hz), 3.55 (4H, q, *J* = 7.1 Hz), 3.61 (4H, m), 3.71 (4H, m), 3.84 (4H, t, *J* = 4.9 Hz), 4.10 (4H, t, *J* = 4.9 Hz), 6.51 (3H, m), 7.14 (1H, t, *J* = 8.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 66.7, 67.4, 69.7, 69.9, 70.9, 101.8, 107.1, 129.8, 160.0.

2,6-Bis(2-(2-ethoxyethoxy)ethoxy)benzoic acid, 11.

1,3-Bis-(2-(2-ethoxyethoxy)-ethoxy)benzene **7** (21.2 g, 6.54 mmol) and 150 mL dry ethyl ether were placed in a 500 mL three necked round bottom flask which was equipped with an addition funnel and a magnetic stirrer. *n*-BuLi/hexane solution (30 mL, 2.5 M, 75 mmol) was slowly added to the flask through the addition funnel at 0 °C under N_2 atmosphere. After the addition, the solution was stirred at 0 °C for 2 h. The mixture was poured onto an excess of freshly crushed dry ice. When the temperature of the mixture had risen to 25 °C, 150 mL of a 1.0 M aqueous solution of sodium hydroxide was added. The organic layer was decanted. The aqueous phase was washed with 50 mL diethyl ethyl before being acidified to pH 1 and extracted with 3 x 100 mL diethyl ether. The combined organic solution was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by silica gel column chromatography (hexane: EtOAc, 2:1 (v/v)) to give a yellow oil, 11.3 g, 47.3% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (6H, t, *J* = 7.0 Hz), 3.40 (4H, q, *J* = 7.0 Hz), 3.46 (4H, m), 3.59 (4H, m), 3.71 (4H, t, *J* = 5.0 Hz), 4.06 (4H, t, *J* = 5.0 Hz), 6.47 (2H, d, *J* = 8.4 Hz), 7.13 (1H, t, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 66.8, 69.3, 69.4, 70.0, 71.0, 106.6, 114.2, 131.7, 157.2, 166.7.

2-Hydroxy-6-methoxybenzoic acid, 13. A 50 mL three-necked flask was fitted with a dropping funnel, a stirrer and condenser under N_2. 2,6 Dimethoxybenzoic acid (0.237 g, 1.30 mmol) was added into 10 mL nitromethane followed by anhydrous $AlCl_3$ (0.72 g, 5.4 mmol). Acetyl chloride was added through the dropping funnel to the suspension. The

temperature of the mixture was raised to 60 °C and maintained at this temperature for 3 h. The cooled solution was poured upon an ice-hydrochloric acid mixture and extracted with ethyl ether. The organic layer was washed with brine and water. The ether layer was dried over $MgSO_4$, and concentrated to solid. From crude NMR spectrum, there are starting material 30% left, and 65% compound **13**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (3H, s), 6.50 (1H, d, *J* = 8.4 Hz), 6.73 (1H, d, *J* = 8.4 Hz), 7.42 (1H, t, *J* = 8.4 Hz), 12.18 (1H, s).

Methyl 2,6-dimethoxybenzoate, 15.[25] 2,6-Dimethoxybenzoic acid (10.2 g, 56.0 mmol) dissolved in 50 mL toluene was treated with an excess of thionyl chloride and a few drops of DMF until the solid was totally dissolved. The solvent and excess of thionyl chloride were evaporated. The residue was dissolved in 100 mL methanol. The mixture was stirred at rt 2 h. The solvent was evaporated under vacuum. The crude product was dissolved in 100 mL CH_2Cl_2. The organic solution was washed with 2 x 50 mL satd Na_2CO_3 solution, water, and dried over Na_2SO_4 to give white product l0.1 g, 91.3 % yield, mp 87-89 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.85 (6H, s), 3.94 (3H, s), 6.59 (2H, d, *J* = 8.5 Hz), 7.32 (1H, t, *J* = 8.5 Hz).

Methyl 3-acetyl-2,6-dimethoxybenzoate, 16.[25] (1.97 g, 1.01 mmol) was heated with trifluoroacetic anhydride (7.0 mL, 5.0 mmol) and acetic acid (3.1 mL, 5.4 mmol) at 40 °C for 8 h followed by 16 h at rt. Chloroform, 20 mL, was added, and the mixture was washed with 3 x 5 mL water, and 4 mL 2 N NaOH. The organic solvent was separated,

dried over Na_2SO_4, filtered, and evaporated under vacuum to give a dark yellow solid. The crude product was purified by a short silica gel column (hexanes/EtOAc, 4:1 (v/v)) to give a yellow solid, 2.08 g, 86.5% yield. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.62 (3H, s), 3.85 (3H, s), 3.89 (3H, s), 3.96 (3H, s), 6.76 (1H, d, *J* = 9.0 Hz), 7.82 (1H, d, *J* = 9.0 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3, 52.9, 56.5, 63.7, 106.9, 118.6, 125.5, 133.6, 158.6, 160.7, 166.4, 198.1.

Methyl 2,6-bis(2-(2-ethoxyethoxy)ethoxy)benzoate, 17.[25]

2,6-Bis(2-(2-ethoxyethoxy)ethoxy)benzoic acid **11** (9.65 g, 25.0 mmol) dissolved in 50 mL toluene was treated with an excess of thionyl chloride and a few drops of DMF. The solvent and excess thionyl chloride were evaporated for 2h. The residue was dissolved in 100 mL methanol. The mixture was stirred at rt overnight. The solvent was evaporated under vacuum. The crude product was purified by the silica gel column chromatography (hexanes/EtOAc, 2:1 (v/v)) to give 9.01 g of a yellow oil, 90.1% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (6H, t, *J* = 5.0 Hz), 3.52 (4H, t, *J* = 5.0 Hz), 3.58 (4H, m), 3.69 (4H, m), 3.82 (4H, t, *J* = 5.2 Hz), 3.86 (3H, s), 4.15 (4H, t, *J* = 5.2 Hz), 6.56 (2H, d, *J* = 8.4 Hz), 7.24 (1H, t, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 52.1, 66.6, 68.8, 69.4, 69.9, 71.0, 105.5, 114.0, 131.0, 156.5, 166.7.

Methyl 3-acetyl-2,6-bis(2-(2-ethoxyethoxy)ethoxy)benzoate, 18. Methyl 2,6-bis(2-(2-ethoxyethoxy)ethoxy)benzoate **17** (7.24 g, 18.1 mmol) was heated with trifluoroacetic anhydride (30.0 mL, 220 mmol) and acetic acid (11.4 mL, 193 mmol) at

40 °C for 8 h followed by 16 h at rt. Chloroform, 100 mL, was added, and the mixture was washed with 3 x 20 mL water, and 20 mL 2 N NaOH. The organic solvent was separated, dried over Na_2SO_4, filtered, and evaporated under vacuum to give a black oil. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 2:1 (v/v)) to give a yellow oil, 3.36 g, 41.8% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.190 (3H, t, *J* = 7.0 Hz), 1.195 (3H, t, *J* = 7.0 Hz), 3.506 (2H, q, *J* = 7.0 Hz), 3.510 (2H, q, *J* = 7.0 Hz), 3.57 (4H, m), 3.63 (2H, m), 3.67 (2H, m), 3.83 (2H, m), 4.20 (2H, t, *J* = 4.8 Hz), 6.75 (1H, d, *J* = 8.8 Hz), 7.73 (1H, d, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 30.5, 52.5, 66.6, 68.9, 69.2, 69.8, 69.9, 70.7, 71.0, 75.5, 107.8, 119.0, 126.3, 133.0, 156.8, 160.0, 166.1, 198.3.

3-Acetyl-2,6-bis(2-(2-ethoxyethoxy)ethoxy)benzoic acid, 19. Methyl 3-acetyl-2,6-bis(2-(2-ethoxyethoxy)ethoxy)benzoate **18** (6.6 g, 15.0 mmol) was dissolved in 30 mL 6 M aq KOH solution. The mixture was refluxed overnight. Sufficient 6 M HCl was added to adjust the solution to pH = 1. The mixture was extracted with 3 x 50 mL EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated under vacuum to give a dark yellow oil, 4.6 g, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, t, *J* = 7.0 Hz), 1.23 (3H, t, *J* = 7.0 Hz), 2.60 (3H, m), 3.50 (2H, q, *J* = 7.0 Hz), 3.57 (4H, m), 3.63 (4H, m), 3.69 (2H, m), 3.73 (2H, m), 3.84 (2H, t, *J* = 4.8 Hz), 4.16 (2H, m), 4.22 (2H, t, *J* = 4.8 Hz), 6.75 (1H, d, *J* = 8.8 Hz), 7.70 (1H, d, *J* = 8.8 Hz) 7.95 (1H, m broad). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 15.0, 30.3, 66.7, 66.9,

69.0, 69.2, 69.7, 69.8, 70.0, 70.9, 75.4, 76.6, 108.2, 120.0, 126.2, 132.8, 156.9, 159.5, 166.5, 198.5.

1-(4-Methylphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one, 22. 4-Hydroxy-benzaldehyde (0.52 g, 4.3 mmol) and 4-methylacetophenone (0.46 g, 3.4 mmol) were dissolved in 10 mL 10% (w/v) NaOH in ethanol at room temperature. After stirring for 10 h at rt, a light yellow material precipitated. The reaction mixture was acidified with 10% HCl and was extracted with 3 x 10 mL EtOAc. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a yellow solid. The crude product was purified by silica gel column chromatography with hexanes/EtOAc 3:1 (v/v) to give a light yellow solid, 0.36 g, 44% yield, mp 158-161 °C. (lit mp 160 °C)[94] ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.43 (3H, s), 6.93 (2H, d, *J* = 8.5 Hz), 7.27 (2H, d, *J* = 8.0 Hz), 7.41 (1H, d, *J* = 16.0 Hz), 7.54 (2H, d, *J* = 8.5 Hz), 7.79 (1H, d, *J* = 16.0 Hz), 7.93 (2H, d, *J* = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.9, 116.3, 119.6, 127.5, 128.9, 129.6, 130.8, 135.9, 144.0, 145.5, 159.0, 191.3.

Ethyl 3-acetyl-2,6-bis(2-(2-ethoxyethoxy)ethoxy)benzoate, 23.[25]

2,6-Bis(2-(2-ethoxyethoxy)ethoxy)benzoic acid **19** (4.30 g, 1.00 mmol) dissolved in 50 mL toluene was treated with an excess of thionyl chloride and a few drops of DMF. The solvent and excess of thionyl chloride were evaporated for 2 h.The residue was dissolved in 30 mL absolute ethanol. The mixture was stirred at rt for 3 h. The solvent was evaporated under vacuum. The crude product was purified by silica gel column

chromatography (hexanes/EtOAc, 2:1 (v/v)) to give a yellow oil, 3.95 g, 86.7 % yield. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23 (3H, t, *J* = 7.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz), 1.41 (3H, t, *J* = 7.1 Hz), 2.67 (3H, s), 3.55 (4H, q, *J* = 7.0 Hz), 3.61 (4H, m), 3.69 (4H, m), 3.78 (2H, t, *J* = 4.8 Hz), 3.87 (2H, t, *J* = 4.8 Hz), 4.14 (2H, t, *J* = 4.8 Hz), 4.23 (2H, t, *J* = 4.8 Hz), 4.42 (2H, t, *J* = 7.0 Hz), 6.77 (1H, d, *J* = 9.0 Hz), 7.76 (1H, d, *J* = 9.0 Hz).

Ethyl 3-(2-chloroacetyl)-2,6-bis(2-(2-ethoxyethoxy)ethoxy)benzoate, 24.[25] To a solution of ethyl 3-acetyl-2,6-bis(2-(2-ethoxyethoxy)ethoxy)benzoate **23** (2.35 g, 50.1 mmol) in 50 mL CH_2Cl_2 at 25 °C was added sulfuryl chloride (1.3 g, 96 mmol), followed by dropwise addition of methanol (0.48 g, 0.15 mol). The solution was stirred at rt for 3 d and concentrated. The crude residue was purified by silica gel column chromatography with hexanes/EtOAc 2:1 (v/v) to give a colorless oil 1.01 g, 41.2% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (6H, t, *J* = 7.0 Hz), 1.31 (3H, t, *J* = 7.2 Hz), 3.44 (4H, q, *J* = 7.0 Hz), 3.47 (4H, m), 3.64 (4H, m), 3.77 (2H, t, *J* = 4.8 Hz), 4.12 (4H, m), 4.32 (2H, q, *J* = 7.2 Hz), 4.90 (2H, s), 6.72 (1H, d, *J* = 8.8 Hz), 7.76 (1H, d, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 15.3, 50.7, 61.9, 66.80, 66.83, 69.0, 69.4, 69.6, 69.9, 70.0, 70.9, 71.2, 75.4, 108.2, 118.5, 123.6, 133.7, 156.6, 160.7, 165.7, 191.8.

2,2-Dichloro-1-*p*-tolylethanone, 26 and 2-chloro-1-*p*-tolylethanone, 27.[26] To a solution of 4'-methylacetophenone **21** (1.34 g, 10.0 mmol) in 10 mL CH_2Cl_2 added dropwise a solution of sulfuryl chloride (1.6 g, 12 mmol) in 5 mL CH_2Cl_2. The mixture was stirred for one day and evaporated under reduced pressure. The residue was purified

by silica gel column chromatography (hexanes/EtOAc 4:1 (v/v)) to give dichloride **26**, 828 mg, 41.0 % yield, and monochloride **27**, 175 mg, 10.4 % yield. Compound **26**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.23 (3H, s), 6.63 (1H, s), 7.11 (2H, d, *J* = 8.3 Hz), 7.78 (2H, d, *J* = 8.3 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.7, 67.8, 128.6, 129.6, 145.8, 185.4. Compound **27**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.42 (3H, s), 4.69 (2H, s), 7.28 (2H, d, *J* = 8.1 Hz), 7.85 (2H, d, *J* = 8.1 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.7, 46.0, 128.6, 129.6, 131.8 (C), 145.0, 190.7.

1,5-Di-*tert*-butyl-2,4-bis(2-(2-methoxyethoxy)ethoxy)benzene, 29.[18] Sodium hydride 60% w/w in mineral oil (6.03 g, 151 mmol) and 40 mL dry DMF were placed in a 250 mL three necked round bottom flask which was equipped with a thermometer, a condenser, an addition funnel and magnetic stirrer. A solution of 4,6-di-*tert*-butylresorcinol (11.1 g, 50.0 mmol) in 80 mL DMF was added to the flask through the addition funnel at 0 °C under N_2 atmosphere. The solution was stirred for two hours at rt. 2-Chloromethyl 2-ethoxylethyl ether (27.2 g, 197 mmol) was added all at once to the solution at rt. The temperature was raised to 100-110 °C and allowed to reaction under N_2 atmosphere overnight. The cooled reaction solution was quenched with 50 mL water, and extracted with 3 x 60 mL CH_2Cl_2. The organic extracts were combined, washed with 5% NaOH (40 mL) and water (50 mL) and dried over anhydrous $MgSO_4$. After filtration, the crude product was purified by silica gel column chromatography (hexanes/EtOAc 2:1 (v/v)) to give a colorless oil 16.2 g, 76.1 % yield. ^{1}H NMR (400

MHz, $CDCl_3$) δ 1.37 (18H, s), 3.34 (6H, s), 3.53 (4H, t, *J* = 4.8 Hz), 3.67 (4H, t, *J* = 4.8 Hz), 3.86 (4H, t, *J* = 5.0 Hz), 4.12 (4H, t, *J* = 5.0 Hz), 6.50 (1H, s), 7.17 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2, 34.5, 59.0, 67.4, 70.0, 70.6, 72.0, 98.7, 124.7, 129.0, 156.1.

1-Bromo-5-*tert*-butyl-2,4-bis(2-(2-methoxyethoxy)ethoxy)benzene, 30.[18] 1,5-di-*tert*-butyl-2,4-bis(2-(2-methoxyethoxy)ethoxy)benzene (11.4 g, 26.7 mmol) was dissolved in 27 mL $CHCl_3$, then and mixture was cooled to -30 °C, (1.51 mL, 29.3 mmol). Br_2 (1.51 mL, 29.3 mmol) was added dropwise into the stirred mixture. The reaction was kept at -30 °C for 3 h. The mixture was evaporated under vacuum. The crude product was purified by silica gel column chromatography (hexanes/EtOAc 4:1 (v/v)) to give a colorless oil. 10.91 g, 90.8% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (9H, s), 3.39 (6H, s), 3.57 (4H, m), 3.70 (2H, m), 3.78 (2H, m), 3.89 (4H, m), 4.13 (2H, m), 4.16 (2H, m), 6.55 (1H, s), 7.35 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 34.5, 59.10, 59.12, 67.6, 69.6, 69.7, 69.8, 70.7, 71.1, 72.04, 72.07, 100.3, 102.3, 130.7, 132.9, 154.0, 157.7

4-(2,4-Bis(2-(2-methoxyethoxy)ethoxy)phenyl)-4-oxobutanoic acid, 33. A mixture of 1,3-bis(2-(2-methoxyethoxy)ethoxy) benzene **6** (628 mg, 2.00 mmol), succinic anhydride (237 mg, 2.35 mmol), and $AlCl_3$ (540 mg, 4.05 mmol) in 10 mL nitromethane was stirred at rt for 3 d. The reaction was quenched with 10% HCl solution. The mixture was extracted by 3 x 10 mL EtOAc. The organic solvent was combined and was

evaporated under the vacuum. The crude product was purified by the silica gel column chromatography (EtOAc eluent) to give a white solid, 229 mg, 36.2% yield, mp 60-64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (2H, t, *J* = 6.6 Hz), 3.35 (2H, t, *J* = 6.6 Hz), 3.38 (3H, s), 3.40 (3H, s), 3.58 (4H, m), 3.70 (4H, m), 3.88 (4H, m), 4.19 (4H, m), 6.47 (1H, d, *J* = 2.4 Hz), 6.53 (2H, dd, *J* = 8.8, 2.4 Hz), 7.84 (1H, d, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.3, 38.9, 59.07,59.14,69.7, 67.8, 69.5, 69.6, 70.6, 70.8, 71.94,71.96, 99.8, 106.2, 120.5, 132.8, 160.4, 163.8, 178.5, 198.3.

(1-Benzyl-1H-1,2,3-triazol-4-yl)methanol, 34. Benzyl azide (1.06 g, 8.01 mmol) and propargyl alcohol (0.45 g, 8.0 mmol) were dissolved in a 1:1 mixture of water and t-butyl alcohol (36 mL). Sodium ascorbate (0.16 g, 0.81 mmol) was added, followed by copper (II) sulfate pentahydrate (20 mg, 0.082 mmol). The mixture was stirred for 16 h, and *t*-butyl alcohol was evaporated under vacuum. The aqueous solution was extracted with 2 x 20 mL EtOAc. The combined organic solvent was dried over Na_2SO_4, filtered and evaporated under vacuum to give dark yellow oil. The oil was put into the ether and solidified to dark yellow solid 1.20 g, 80.4% yield, mp mp 76-78 °C (lit mp 76-78 °C,[95] 73-75 °C [96]).^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (1H, b), 4.68 (2H, s), 5.43 (2H, s), 7.22 (2H, m), 7.31 (3H, m), 7.47 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.1, 56.0, 122.1, 128.1, 128.7, 129.1, 134.7, 148.4.

Oxiran-2-ylmethyl acetate, **35.** A solution of glycidol (3.70 g, 50.0 mmol), Et_3N (10.4 mL, 75.2 mmol), and DMAP (0.61 g, 0.51 mmol) in dry 50 mL CH_2Cl_2 was stirred

at rt for 12 h. The 30 mL water was added to the mixture. The layers were separated and aqueous solution was extracted with ethyl ether. The combined organic solvent was dried over Na_2SO_4, filtered, and evaporated under vacuum to give a yellow oil. The residue was purified with silica gel (hexanes/EtOAc 2:1 (v/v)) to give colorless oil 3.82 g, 65.9% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (3H, s), 2.65 (1H, dd, *J* = 4.8, 2.8 Hz), 2.85 (1H, t, *J* = 4.8 Hz), 3.22 (1H, m), 3.90 (1H, dd, *J* = 12.0, 6.4 Hz), 4,41 (1H, dd, *J* = 12.0, 2.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 44.5, 49.2, 64.9, 170.6.

2-Hydroxy-3-(prop-2-ynyloxy)propyl acetate, 36, 3-hydroxy-2-(prop-2-ynyloxy)-propyl acetate, 37, and 2-(prop-2-ynyloxy)propane-1,3-diyl diacetate, 38. Oxiran-2-ylmethyl acetate **35** (1.16 g, 10.0 mmol), prop-2-yn-1-ol (0.67 g, 12 mmol) and potassium *tert*-butoxide (0.08 g, 4% of total weight) were put into flask. The mixture was heated to 80 °C and stirred overnight. The residue was purified by silica gel column chromatography (hexanes/EtOAc 1:1 (v/v) to give colorless oil mixture of **36** and **37** (5:1) 897 mg, yield: 52.2%, and **38** 276 mg, yield 12.9%. Compound **36** and **37**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (3H, s), 2.61 (1H, s), 3.61 (2H, m), 3.72 (1H, m), 4.02 (1H, broad, s), 4.16 (2H, m), 4.21 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (20.8), 58.2 (58.1), 65.3 (60.9), 68.0 (67.9), 70.5 (72.9), 75.00 (75.04), 79.13 (79.05), 171.0 (170.8); compound **38** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (3H, s), 2.10 (3H, s), 2.49 (1H, t, *J* = 2.4 Hz), 3.69 (2H, d, *J* = 5.0 Hz), 4.17 (1H, dd, *J* = 12.0, 6.2 Hz), 4.19 (2H, s), 4.33 (1H, *J* =12.0, 4.0 Hz), 5.21 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 21.0, 58.6, 62.8, 67.9, 70.1, 75.2,

79.1, 170.4, 170.7.

Methyl 3-(6-bromohexanoyl)-2,6-dimethoxybenzoate, 39. To a mixture of **16** (1.01 g, 5.15 mmol) and 6-bromohexanoic acid (1.47 g, 7.58 mmol) was added trifluoroacetic anhydride (3.16 g, 15.0 mmol). The solution was stirred at 40 °C for 2 d. The solution was put into ice water, and was extracted with 3 x 20 mL EtOAc. The combined organic solution was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/EtOAc 3:1 (v/v)) to give 1.12 g of a yellow oil, 58.5 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (2H, m), 1.71 (2H, m), 1.89 (2H, m), 2.97 (2H, t, *J* = 7.4 Hz), 3.41 (2H, t, *J* = 6.8 Hz), 3.83 (3H, s), 3.88 (3H, s), 3.95 (3H, s), 6.75 (2H, d, *J* = 8.8 Hz), 7.72 (2H, d, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 27.9, 32.7, 33.8, 42.1, 52.8, 56.4, 63.7, 106.9, 118.5, 125.6, 133.1, 157.9, 160.2, 163.8, 200.7.

Methyl 3-(6-azidohexanoyl)-2,6-dimethoxybenzoate, 40. The mixture of **39** (744 mg, 2.00 mmol) and sodium azide (405 mg, 6.23 mmol) in 10 mL anhydrous DMF was stirred at 80 °C overnight. The mixture was evaporated under vacuum. The residue was dissolved in 20 mL EtOAc. The organic solution was washed with 3 x 20 mL water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (hexanes/EtOAc 3:1 (v/v)) to 226 mg of a yellow oil, 70.4%. yield. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.45 (2H, m), 1.69 (4H, m), 2.97 (2H, t, *J* = 7.3 Hz), 3.41 (2H, t, *J* = 6.8 Hz), 3.83 (3H, s), 3.88 (3H, s), 3.95 (3H, s), 6.75 (2H, d, *J* = 8.8 Hz),

7.73 (2H, d, J = 8.8 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 23.9, 26.4, 28.7, 42.2, 51.2, 52.7, 56.3, 63.6, 106.8, 118.5, 125.6, 133.0, 157.9, 160.1, 163.7, 200.1.

3-(6-Azidohexanoyl)-2,6-dimethoxybenzoic acid, 41. The solution of **40** (20 mg, 0.060 mmol) in 1 mL (H_2O/EtOH 1:1) 6 M KOH was stirred at rt for 4 h. The ethanol was evaporated, and the solution was adjusted to pH 1 with 10% HCl solution. The solution was extracted with 3 x 5 mL EtOAc. The combined organic solution was washed with 5 mL water, dried over Na_2SO_4, filtered and evaporated to give white solid, 15 mg, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (2H, m), 1.68 (4H, m), 3.00 (2H, t, J = 7.4 Hz), 3.29 (2H, t, J = 6.8 Hz), 3.90 (3H, s), 3.93 (3H, s), 6.79 (2H, d, J = 8.8 Hz), 7.76 (2H, d, J = 8.8 Hz), 10.18 (1H, s, b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 26.5, 28.9, 42.2, 51.4, 56.6, 64.2, 107.1, 117.9, 125.9, 133.6, 158.2, 160.4, 170.7, 201.1.

1-Chloro-2-(2-chloroethoxy)ethane, 42. A solution of thionyl chloride (18.7 mL, 256 mmol) in 42 mL $CHCl_3$ was added slowly over 15 min to a stirred solution of 2,2'-oxydiethanol (10.7 g 101 mmol) pyridine (16.3 mL, 200 mmol) in 85 mL $CHCl_3$ under nitrogen. The mixture was refluxed overnight. The cooled mixture was washed with 2 x 150 mL water, dried over Na_2SO_4, filtered, and evaporated under vacuum to give yellow oil 13.0 g, 93.8% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (4H, t, J = 5.8 Hz), 3.78 (4H, t, J = 5.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.8, 71.3.

1-(2-(2-Chloroethoxy)ethyl)pyrrolidine-2,5-dione, 43. To a suspension of 60% w/w NaH in mineral oil (3.32 g, 33.0 mol%) in 70 mL of dry DMF was added dropwise a

solution of succinimide (3.01 g, 30.0 mmol) in 10 mL dry DMF at 0 °C. After addition was complete, the resulting suspension was stirred at 0 °C for an additional 40 minutes, before treating with a solution of 1-chloro-2-(2-chloroethoxy)ethane (10.4 g, 72.8 mmol). The reaction was heated to 65 °C and maintained at this temperature for 22 h. The solution was concentrated under vacuum and residue was dissolved in H_2O. The aqueous solution was extracted by 2 x 100 mL CH_2Cl_2. The combined organic solution was washed with satd brine, water, dried over anhydrous $MgSO_4$, filtered, concentrated under vacuum to give solid, 32.0 g, 52.0% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (4H, s), 3.59 (2H, t, *J* = 5.6 Hz), 3.71 (6H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.9, 37.5, 42.8, 66.6, 70.1, 177.0.

1-(2-(2-Azidoethoxy)ethyl)pyrrolidine-2,5-dione, 44. A solution of 1-(2-(2-chloroethoxy)ethyl)pyrrolidine-2,5-dione **43** (2.89 g, 14.1 mmol) and sodium azide (2.7 g, 42 mmol) in 20 mL DMF was stirred at 80 - 90 °C for 12 h and concentrated under vacuum. The residue was dissolved in 20 mL water and aqueous solution was extracted with 2 x 20 mL EtOAc. The combined organic solution was washed with water three times, dried over $MgSO_4$, and evaporated under vacuum to give solid 2.43 g, 81.3% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (4H, m), 3.33 (2H, m), 3.70 (6H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.9, 37.7, 50.3, 66.8, 69.5, 177.2.

2-(2-Azidoethoxy)ethanamine, 45. The solution of 1-(2-(2-azidoethoxy)ethyl) pyrrolidine-2,5-dione **44 (**626 mg, 3.00 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.5 mL, 13 mmol) in

10 mL MeOH was refluxed 4 h. When the solution was cooled to rt, it was acidified with 37% HCl. The mixture was refluxed for additional 1 h. The solution was basified by 4 N NaOH and was extracted by 3 x 20 mL EtOAc. The combined organic solution was washed with water, dried with $MgSO_4$, and concentrated under vacuum to give an oil, 173 mg, 44.4% yield. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.41 (3H, t, *J* = 4.8 Hz), 3.51 (2H, t, *J* = 5.1 Hz), 3.60 (2H, t, *J* = 5.0 Hz), 3.71 (2H, t, *J* = 4.8 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 39.4, 50.8, 70.1, 70.4.

1-Bromo-2-(N-methylamino)ethane hydrobromide, 46. To a solution of 50 mL (0.442 mol) of HBr (48% w/w) at 4 °C in a ice bath, ice cold 2-(methylamino)ethanol (17.5 mL, 0.219 mol) was added dropwise with stirring. The temperature of the mixture was raised to distill the H_2O. The distillation was allowed to continue slowly (9 - 11 h) until 30 mL of distillate was collected. After distillation of H_2O ceased, distillation of crude HBr began when the mixture temperature was raised. The HBr distillation was continued for approximately 2 h, after which time the solution was allowed to cool. After the solution had cooled to 60 °C, it was slowly poured with stirring into a 250 mL beaker containing 150 mL of ice cold acetone, whereupon the desired white product precipitated from solution. This heterogeneous solution was capped and placed in the freezer overnight. The white precipitate was then vacuum filtered, washed with 3 x 50 mL ice cold acetone, and dried in the funnel, yielding 75.2 g (78%) of crude product. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.75 (3H, s), 3.44 (2H, b), 3.81 (2H, t, *J* = 6.8 Hz). ^{13}C NMR (63

MHz, $CDCl_3$) δ 24.7, 32.9, 49.8.

2-Azido-N-methylethanamine, 47. A solution of 1-bromo-2-(N-methylamino) ethane hydrobromide **46** (4.38 g, 20.2 mmol) and sodium azide (3.95 g, 60.7 mmol) in 20 mL water was stirred at rt for 12 h. After removing most of the water by distillation under vacuum, the reaction mixture was cooled in an ice bath. Diethyl ether (20 mL) was added followed by NaOH pellets which adjusted the mixture to pH 14 keeping the temperature below 10 °C. After separation of the organic phase, the aqueous layer was further extracted with 2 x 10 mL diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated to give an oil, 1.26 g, 62.4% yield. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (1H, s, br), 2.46 (3H, s), 2.77 (2H, t, *J* = 5.7 Hz), 3.44 (2H, t, *J* = 5.7 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 36.1, 50.5, 51.2.

6-Azidohexanoic acid, 48. 6-Bromohexanoic acid (1.95 g, 10.0 mmol), NaOH (0.40 g, 10 mmol) and NaN_3 (1.97 g, 30.3 mmol) were dissolved in water. The mixture was refluxed overnight, and the pH was adjusted to 1. The aqueous solution was extracted with EtOAc. The organic solution was evaporated under vacuum to give an oil. The residue was purified with silica gel column chromatography (hexanes/EtOAc 1:1 (v/v)) to give a colorless oil, 1.08 g, 66.3% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (2H, m), 1.64 (4H, m), 2.38 (2H, t, *J* = 7.2 Hz), 3.28 (2H, t, *J* = 7.2 Hz), 11.5 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 26.2, 28.6, 34.0, 51.3, 180.2.

2-(2-Chloroethoxy)ethanesulfonate, 49. A solution of bis(2-chloroethyl) ether (1.47 g, 10.3 mmol) in 10 mL 95% ethanol was added to a solution of Na_2SO_3 (1.29 g, 10.2 mmol) in 10 mL water and the mixture was refluxed 1 d. The solution was evaporated to give a yellow oil and a solid. The mixture was dissolved in 10 mL water, and the aqueous solution was washed with 2 x 5 mL CH_2Cl_2, and evaporated to give a yellow solid. The solid was recrystallized from 95% ethanol to give 0.85 g **49**, yield 45%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (2H, t, *J* = 6.8 Hz), 4.08 (2H, t, *J* = 5.0 Hz), 4.15 (2H, t, *J* = 5.0 Hz), 4.22 (2H, t, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 50.7, 66.1, 71.0.

2-(2-Azidoethoxy)ethanesulfonate, **50**. Compound **49** (2.38 g, 12.7 mmol) and NaN_3 (1.97 g, 30.3 mmol) were dissolved in 50 mL water. The mixture was refluxed 24 h and evaporated under vacuum. The residue was recrystallized from 95 % ethanol to give light 1.97 g yellow solid, yield 80.0%. ^{1}H NMR (400 MHz, D_2O) δ 3.17 (2H, t, *J* = 6.5 Hz), 3.46 (2H, t, *J* = 4.8 Hz) , 3.68 (2H, t, *J* = 4.8 Hz), 3.87 (2H, t, *J* = 6.5 Hz). ^{13}C NMR (100 MHz, D_2O) δ 50.2, 50.5, 65.7, 69.1.

2,2'-Oxybis(ethane-2,1-diyl) dimethanesulfonate, 53. Diethylene glycol (1.06 g, 10.0 mmol), Et_3N (4.3 mL, 31 mmol), and methanesulfonyl chloride (2.52 g, 22.0 mmol) were added to 100 mL of dry CH_2Cl_2 and stirred in an ice-acetone cold bath (-10 °C) until the starting material disappeared as determined by TLC. The reaction mixture was diluted with CH_2Cl_2 and washed with 0.12 N HCl, saturated $NaHCO_3$, and H_2O. The solution was dried over $MgSO_4$, filtered, and evaporated under vacuum to give 2.10 g

pale yellow solid, 80.2% yield, mp 53-56 °C. The crude product didn't need to be further purified. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.07 (6H, s), 3.80 (4H, t, *J* = 7.0 Hz), 4.38 (4H, t, *J* = 7.0 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 37.6, 68.97, 69.0.

2-(2-(4-Iodophenoxy)ethoxy)ethyl formate, 54. 2,2'-Oxybis(ethane-2,1-diyl) dimethanesulfonate (0.314 g, 1.20 mmol), 4-iodophenol (0.221 g, 1.00 mmol) and NaOH (0.040 g, 1.0 mmol) were dissolved in 5 mL dry DMF. The mixture was refluxed overnight. The solution was evaporated under vacuum. The residue was purified with silica gel column chromatography (hexanes/EtOAc v/v (4:1)) to give white solid 135 mg, 40.2% yield, mp 66-68 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.79 (2H, t, *J* = 4.8 Hz), 3.85 (2H, t, *J* = 4.8 Hz), 4.90 (3H, t, *J* = 4.8 Hz), 4.34 (3H, t, *J* = 4.8 Hz), 6.69 (2H, d, *J* = 9.0 Hz), 7.55 (2H, d, *J* = 9.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 63.1, 67.7, 69.3, 69.8, 83.3, 117.2, 138.4, 158.7, 161.1.

4,4'-(2,2'-Oxybis(ethane-2,1-diyl)bis(oxy))bis(iodobenzene), 55. To a solution of 2,2'-oxybis(ethane-2,1-diyl) dimethanesulfonate (0.315 g, 1.20 mmol) and 4-iodophenol (0.221g, 1.00 mol) in 15 mL acetonitrile, Cs_2CO_3 (0.272 g, 0.834 mmol) was added in portions. The mixture was refluxed overnight. The solution was evaporated under vacuum. The residue was purified with silica gel column chromatography (hexanes/EtOAc 4:1 (v/v)) to give white solid, 90 mg, 35% yield, mp 103-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (4H, m), 3.65 (4H, m), 6.46 (4H, d, *J* = 9.0 Hz), 7.46 (4H, d, *J* = 9.0 Hz).

2-(2-Hydroxyethoxy)ethyl methanesulfonate, 56. Methanesulfonyl chloride (7.13 mL, 94.3 mmol) was added dropwise to a solution of diethylene glycol (10.0 g, 98.0 mmol) and Et_3N (13.2 mL, 94.9 mmol) in 150 mL dry THF. The mixture was stirred at rt overnight. The solvent was evaporated under vacuum. The residue was purified with silica gel column chromatography (hexanes/EtOAc 4:1 (v/v)) to give colorless solid 6.72 g, 54.1% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ3.09 (3H, s), 3.62 (2H, m), 3.74 (2H, m), 3.78 (2H, m), 4.39 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.6, 61.5, 68.8, 69.3, 72.6.

2-(2-(4-Iodophenoxy)ethoxy)ethanol, 57. To a solution of 2-(2-hydroxy–ethoxy)ethyl methanesulfonate (0.202 g, 1.10 mmol), and 4-iodophenol (0.220 g, 1.00 mmol) in 15 mL MeCN was added Cs_2CO_3 (5.22 g, 1.60 mmol) portionwise. The mixture was refluxed overnight and evaporated under vacuum. The residue was purified with silica gel column chromatography (hexanes/EtOAc 4:1 (v/v)) to give white solid 240 mg, 76.2% yield, mp 75-77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 (1H, t, *J* = 5.8 Hz), 3.63 (2H, t, *J* = 4.6 Hz), 3.73 (2H, m), 3.81 (2H, t, *J* = 4.6 Hz), 4.06 (2H, t, *J* = 4.6 Hz), 6.68 (2H, d, *J* = 8.8 Hz), 7.53 (2H, d, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.6, 67.5, 69.5, 72.8, 83.2, 117.1, 138.3, 158.5.

1-(2-(2-Chloroethoxy)ethoxy)-4-iodobenzene, 58. Method A. To a solution of pyridine (61 mg, 0.77 mmol) and 2-(2-(4-iodophenoxy)ethoxy)ethanol (220 mg, 0.690 mmol) in 10 mL chloroform, thionyl chloride (108 mg, 0.908 mmol) in 3 mL chloroform was added dropwise at rt. The mixture was refluxed overnight. The cooled solution was

washed with 3 x 5 mL water. The organic solution was dried over Na_2SO_4, filtered and evaporated under vacuum to give yellow solid, 0.218 g, 93.7% yield, mp 48-49 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (2H, t, *J* = 6.0 Hz), 3.77 (2H, t, *J* = 6.0 Hz), 3.81 (2H, t, *J* = 4.8 Hz), 4.04 (2H, t, *J* = 4.8 Hz), 6.67 (2H, d, *J* = 8.8 Hz), 7.51 (2H, d, *J* = 8.8 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.9, 67.6, 69.6, 71.6, 83.2, 117.1, 138.3, 158.6.

Method B. A solution of poly(ethylene glycol) average M.W 300 (0.75 g, 2.5 mmol) and 4-iodophenol (1.10 g, 5.00 mmol) in 5 mL MeCN was added dropwise to a solution of NaOH (0.28 g, 7.0 mmol) in 20 mL MeCN. The solution was stirred at rt for 0.5 h, and 1-chloro-2-(2-chloroethoxy)ethane (1.07 g, 7.48 mmol) was added. The mixture was refluxed for 2 days. Water was added to the cooled solution until the precipitate disappeared. The solution was extracted with 3 x 10 mL chloroform. The combined organic solution was washed with 10 mL water, dried (Na_2SO_4), filtered, and evaporated under vacuum to give white solid 855 mg, 51.1% yield, mp 48-49 °C.

1-(2-(2-Azidoethoxy)ethoxy)-4-iodobenzene, 59. The mixture of 1-(2-(2-chloroethoxy)ethoxy)-4-iodobenzene (0.851 g, 2.50 mmol), NaN_3 (0.496 g, 7.63 mmol) in 30 mL DMF was stirred at 100 °C overnight. Following removal of solvent, the residue was purified by silica gel column chromatography (hexanes/EtOAc 4:1 v/v) to give white solid, 0.754 g, 87.8% yield, mp 48-49 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.33 (2H, t, *J* = 5.0 Hz), 3.65 (2H, t, *J* = 5.0 Hz), 3.77 (2H, t, *J* = 4.8 Hz), 4.01 (2H, t, *J* = 4.8 Hz), 6.62 (2H, d, *J* = 8.8 Hz), 7.46 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ

50.7, 67.5, 69.6, 70.3, 83.1, 117.1, 138.2, 158.6.

Tetraethyl ethene-1,1,2,2-tetracarboxylate, 82.[58] A mixture of anhyd Na_2CO_3 (6.01 g, 5.70 mmol) and ethyl bromomalonate (9.03 g, 0.375 mol) was heated for 3 h at 150-170 °C. After the heating period, 9 mL of toluene was added while the mixture was still hot. After cooling, the reaction mixture was dissolved in water and extracted with EtOAc (3 x 10 mL). Combined organic layer was washed with brine and dried over anhyd Na_2SO_4. After filtration, the solvent was distilled under reduced pressure. The forerun up to 170 °C/15 mm Hg was discarded. The product was collected at 170-230 °C/15mm Hg. The crude product was recrystallized from 95% ethanol to give a colorless product, 2.43 g, 40.4% yield, mp 53.5-56 °C. (lit mp 56 °C,[97] 56-57 °C[98]) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (12H, t, *J* = 7.0 Hz) 4.32 (8H, q, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 62.6, 135.4, 162.4.

Tetraethyl ethane-1,1,2,2-tetracarboxylate, 87. [64] To a stirred suspension of $LiAlH_4$ (1.09 g, 28.7 mmol) in 60 mL dry THF, a solution of benzyl chloride (3.65 g, 28.8 mol) in dry THF (10 mL) was added dropwise through a dropping funnel at rt. After the suspension was stirred for 15 min, a solution of α,β-unsaturated ester **82** (960 mg, 3.02 mol) in dry THF was added dropwise. The reaction mixture was stirred at rt for 2.5 d. The reaction was quenched with water, filtered, and the filtrate dried over Na_2SO_4. After filtration, the solvent was evaporated under vacuum and the crude product was purified by column chromatography on silica gel with hexane/EtOAc 3:1 (v/v) to give a white

solid, 502 mg, 52.2% yield, mp 72-73 °C. (lit mp 76 °C,[99] 71-74 °C[100]) ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28 (12H, t, *J* = 7.0 Hz), 4.13 (2H, s), 4.24 (8H, qd, *J* = 7.0, 2.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.9, 51.4, 62.1, 167.1.

Tetraethyl 9,10-dihydro-9,10-ethanoanthracene-11,11,12,12-tetracarboxylate, 88. [68] Aluminum chloride (1.61 g, 12.1 mmol), 0.7 mL absolute ethanol, anthracene (1.07 g, 6.01 mmol) and tetraester **82** (1.81 g, 5.73 mmol) were added to 10 mL CH_2Cl_2. The mixture was stirred for 72 h at rt. The reaction was quenched with 10 mL of 2 N HCl. The aqueous solution was extracted with 2 x 10 mL CH_2Cl_2. The combined organic solution was washed with aq $NaHCO_3$ solution, water, and dried over anhyd Na_2SO_4. The solvent was filtered and evaporated under vacuum to give a yellow solid. The crude product was recrystallized from 95% ethanol to give a colorless solid, 1.98 g, 70.1% yield, mp 132-134 °C. (lit mp 135 °C[68]) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (12H, t, *J* = 7.20 Hz), 4.03 (8H, q, *J* = 7.20 Hz), 5.03 (2H, s), 7.12 (4H, m), 7.36 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 51.8, 66.0, 125.4, 126.7, 140.3, 168.3.

9,10-Ethanoanthracene-11,11,12,12-tetramethanol, 89. [68] Tetraethyl ester **88** (1.76 g, 3.56 mmol) and $LiAlH_4$ (1.61 g, 42.4 mmol) were added to 20 mL dry ethyl ether under N_2. The mixture was stirred for 4 d at rt. After the stirring, 17 mL EtOAc was added slowly and cautiously followed by 9 mL water. Finally, 6 N HCl solution was added to the mixture in an ice bath to adjust pH to 1. A precipitate formed and was filtered and washed with 1 M HCl solution, water, and ether to give 3.34 g of a yellow

solid, 51.3% yield, mp 256-259 °C. (lit mp 264 °C)[68] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (8H, AB quartet, *J* = 11.2 Hz), 4.33 (2H, s), 7.12 (4H, dd, *J* = 5.4, 3.4 Hz), 7.32 (4H, dd, *J* = 5.4, 3.4 Hz).

2,3-Bis(hydroxymethyl)but-2-ene-1,4-diol, 90.[68] Tetramethanol **89** (3.11 g, 9.60 mmol) was heated at 250 °C in a sand bath at 0.1 torr for 2 h. After cooling, 10 mL water was added to the residue. The mixture was refluxed for 3 h and the precipitate was filtered. The filtrate was evaporated under vacuum to give a colorless solid, which was recrystallized from ethanol-ether to give 0.67 g of a colorless solid, 47% yield, mp 97-99 °C. (lit mp 102 °C) [68] ^{1}H NMR (400 MHz, D_2O) δ 4.21 (s, 8H). ^{13}C NMR (100 MHz, D_2O) δ 138.6, 58.3.

Tetraethyl 1,2-dihydroxyethane-1,1,2,2-tetracarboxylate, 91. Method A.[71] In a 200 mL round-bottomed flask equipped with magnetic stirring bar were stirred $NaIO_4$ (1.60 g, 7.48 mmol), and $CeCl_3 \cdot 7H_2O$ (190 mg, 0.501 mmol, 10 mol%) in 2.5 mL H_2O and gently heated until a bright yellow suspension was formed. After cooling to 0 °C, 6.25 mL ethyl acetate and 7.5 mL acetonitrile were added, and the suspension was stirred for 2 min. After the addition of $RuCl_3 \cdot 3H_2O$ (63 mg, 0.25 mmol, 5 mol%), the mixture was stirred for 2 min. A solution of olefin **80** (1.59 g, 5.03 mol) in 1.25 mL ethyl acetate was added in one portion. The mixture was stirred until all starting material was consumed (2 h). Solid Na_2SO_4, 2.5 g, was added followed by 15 mL ethyl acetate. The solid was filtered off. The filtrate was washed with 13 mL satd aq Na_2SO_3 solution. The

organic layer was dried over Na_2SO_4, filtered, and concentrated in a vacuum. The crude product was purified by silica gel column chromatography (hexane/EtOAc 1:1 (v/v)) to give a colorless oil, 249 mg, 70.3% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (12H, t, *J* = 7.2 Hz), 4.32 (8H, q, *J* = 7.2 Hz), 4.87 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 80.7, 63.1, 13.8.

Method B. [69] The olefin (0.632 g, 1.98 mmol) and citric acid (0.288 g, 1.50 mmol) were dissolved in 12 mL of a 1:1 mixture of *t*-butyl alcohol and water in a 50 mL flask. Potassium osmate (0.018 g, 0.056 mmol, 2.45 mol%) was added followed by 4-methylmorpholine N-oxide (0.258 g, 2.20 mmol). The reaction mixture turned green and the temperature was raised to reflux. Several minutes later, the green color disappeared. The reaction was allowed to run overnight at reflux. The volume of solvent was reduced to half on a rotary evaporator. The residue was acidified with 2.4 mL of 1M HCl and extracted with 2 x 8 mL EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated on a rotary evaporator to give a white solid with oil. From the NMR spectra, there appeared to be around 20% product, and 70% starting material.

Reduction of 91 with LAH. Compound **91** (350 mg, 1.00 mmol) and $LiAlH_4$ (1.0 g, 26 mmol) was added into 5.0 mL dry diethyl ether. The mixture was stirred at rt 12 h under N_2. Then, the 5 mL H_2O, followed by the 6M HCl to adjust the mixture to PH 1. The total stuff was evaporated under vacuum to give light yellow solid. The solid was

extracted with 3 x 20 mL mixture of EtOAc/MeOH (1:1). The combined solvent was evaporated to give light yellow solid 283 mg. ^{1}H NMR (250 MHz, D_2O) δ 3.81 (dd, 2H, *J* = 11.8, 6.5 Hz), 3.92 (dd, 2H, *J* = 11.8, 4.0 Hz), 4.08 (m, 1H). ^{13}C NMR (63 MHz, D_2O) δ 62.4, 71.9.

2-Bromo-2-nitropropane-1,3-diol, 102. To a stirred mixture of 68 mL H_2O, 164 mL 95% ethanol, 50.0 mL 37% formaldehyde solution (0.61 mol) and 16.3 mL CH_3NO_2 (0.304 mol) in a 500 mL three-necked flask at 20 °C was added 24 mL 40% NaOH (0.34 mol) dropwise. After addition, the solution was cooled to 5 °C, and was stirred for an additional 1.5 h at this temperature. Bromine (17.6 mL, 0.342 mol) was added dropwise and the mixture was stirred for 0.5 hour. The solution was concentrated to one third volume on the rotary evaporator and the precipitate was collected to give colorless product, 50.9 g, 70.6% yield, mp 128-130 °C. (lit. mp 129.7-130.0 °C,[101] 128-129 °C[102]). ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.05 (d of AB quartets, 4H, *J* = 12.3, 6.0 Hz, Δν = 19.1 Hz), 5.98 (t, 2H, *J* = 6.0 Hz). ^{13}C NMR (63 MHz, DMSO-d_6), 100.8, 64.1.

2,2-Dimethyl-5-bromo-5-nitro-1,3-dioxane, 101. To a solution of diol **103** (20.0 g, 0.101 mol) in 2,2-dimethoxypropane (80 mL) was added D-camphor-10-sulfonic acid (1.62 g, 8.09 mmol). The mixture was stirred 3 d at rt under nitrogen. The solvent was evaporated on the rotary evaporator and residual solid was purified by chromatography on silica gel (hexane/EtOAc 4:1 (v/v)) to give 17.5 g of a colorless solid, yield 75.3%, mp: 79 - 81 °C (lit mp 76-77 °C,[86] 81-83 °C[103]) ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.78 (d, 2H, *J* =

13.5 Hz), 4.27 (d, 2H, *J* = 13.5 Hz) 1.54 (s, 3H) 1.37 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 99.6, 66.3, 28.1, 18.6.

2,2-Dimethyl-5-nitro-1,3-dioxane, 100.

Method A.[86] To a solution of **101** (15.0 g, 62.8 mmol) in 230 mL THF was added hydroxylamine hydrochloride (5.2 g, 75 mmol) in 38 mL water. The resulting solution was cooled to 0 °C and zinc (7.6 g, 0.12 mol) was added in portions over 20 min. After 2.5 h, the reaction mixture was concentrated to 60 mL. Satd aq $NaHCO_3$, 30 mL, was added and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated. The crude solid was purified by chromatography on silica gel (hexane/EtOAc 6:1 (v/v)) to give a white solid, 7.1 g, 71% yield, mp 65 - 66.5 °C. (lit mp 68 °C).[86] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (dd, 2H, *J* = 13.0, 4.0 Hz) 4.35 (quintet, 1H, *J* = 4.0 Hz), 4.25 (dd, 2H, *J* = 13.0, 4.0 Hz), 1.46 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.3, 77.4, 60.0, 25.8, 21.3.

Method B. To a solution of dioxane **101** (8.57 g, 36.0 mmol) in 100 mL 75% aq MeOH was added $NaBH_4$ (4.80 g, 144 mmol) slowly at 0 °C. The mixture was stirred at rt for 3 h and acidified with 5% HCl solution. The solution was extracted with 3 x 80 mL CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, evaporated under vacuum, and recrystallized from hexane to give a white solid, 4.93 g, 85.1% yield, mp 65 - 67 °C.

2,2,2',2'-Tetramethyl-5,5'-dinitro-5,5'-bi(1,3-dioxane), 99. To a solution of **100**

(161 mg, 1.00 mol) in 3.6 mL DMF was added in one portion 2.5 equiv NaH 60% w/w in mineral oil (101 mg, 2.52 mol). The mixture was stirred at rt for 2 h, then **101** (263 mg, 1.10 mol) was added under N_2. The mixture was stirred overnight and concentrated. The crude product was purified by chromatography on silica gel (hexane/EtOAc 4:1 v/v) to give a white solid 120 mg, 37.7% yield, mp 129-131°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.42 (3H, s), 4.39 (4H, AB quartets, J = 13.4 Hz, Δν = 44.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 24.1, 60.5, 90.2, 100.8. A small amount of 2,2,2',2'-tetramethyl[5,5']bi[1,3]dioxanylidene, **96**, estimated at roughly 10% yield, was isolated also. For **96**, mp 133.5-135 °C. ^{1}H NMR (400 MHz, CD_3COCD_3**)** δ 4.22 (s, 4H), 1.31 (s, 6H); ^{13}C NMR (100 MHz, CD_3COCD_3**)** δ 125.7, 99.0, 58.2, 22.3.

It was found that the minor product **96** could be suppressed and the yield of **99** increased by using 1.5 instead of 2.5 equivalents of NaH and performing the NaH addition at 10 °C instead of rt, as follows. To a solution of **100** (4.3 g, 0.027 mol) in 70 mL DMF 1.5 equiv NaH (60% in mineral oil) was added at 10 °C during 20 min. The mixture was stirred at 10 °C for 2 h and **101** (6.3 g, 0.026 mol) was added in one portion. The mixture was stirred overnight at rt, and concentrated. The crude product was purified by chromatography on silica gel (hexane/EtOAc 4:1 (v/v)) to give a white solid 4.2 g, 51% yield, mp: 129-131 °C. No **96** was obtained.

Reactions of 2,2,2',2'-tetramethyl-5,5'-dinitro-5,5'-bi(1,3-dioxane) 99.

(a) Reaction with NaH. To a solution of **99** (108 mg, 0.338 mmol) in 1.2 mL DMF, 2.5 equiv NaH was added at rt. The mixture was stirred at rt overnight. Silica gel TLC (hexanes/EtOAc 4:1 (v/v)) indicated that the starting material had not reacted.

(b) Thermal stability. A solution of **99** (2.0 g, 5.5 mmol) in 20 mL DMF was stirred at 80-90 °C overnight under N_2. Silica gel TLC (hexanes/EtOAc 4:1 (v/v)) indicated that the starting material had not reacted.

2,2,2',2'-Tetramethyl-[5,5']bi[[1,3]dioxanylidene, 96. Compound **96** was synthesized several ways, described below, with varying results.

(a) A quantity of NaH 60% (w/w) dispersion in mineral oil (3.0 g, 75 mmol) was added to a solution of **100** (8.05 g, 50.0 mmol) in 160 mL anhydrous DMF at 10 °C over 15 minutes. After addition, the mixture was stirred for another 2 h at the same temperature. Compound **101** (12 g, 50 mmol) was added in one portion. Stirring was continued overnight. The starting material was undetectable by silica gel TLC (hexane/EtOAc 4:1 v/v). Another portion of NaH (3.0 g, 60% dispersion in mineral oil, 75 mmol) was added and the temperature was raised to 80 - 90 °C under N_2. At this temperature, the mixture was stirred for an additional 12 h. The solution was concentrated to 30 mL on the vacuum line. Water (30 mL) was added to the mixture. The solution was extracted with 3 x 80 mL ethyl acetate. The organic extracts were combined, and washed with 30 mL water, and 30 mL satd aq NaCl. The organic phase was

concentrated on the rotary evaporator. The solid thus obtained was purified by chromatography on silica gel (hexane/EtOAc 4:1 (v/v)) to give **96** as a white solid 6.38 g, 56% yield, mp 133.5-135 °C. ^{1}H NMR (400 MHz, CD_3COCD_3**)** δ 4.22 (s, 4H) 1.31 (s, 6H). ^{13}C NMR (100 MHz, CD_3COCD_3**)** δ 125.7, 99.0, 58.2, 22.3.

(b) A solution of **101** (1.22 g, 5.08 mmol) in 5 mL DMF was added dropwise to a solution of 1.05 g NaH (60% dispersion in mineral oil, 26 mmol) in 10 mL DMF at 10 °C during 10 min. The temperature of the mixture was raised quickly to 80-90 °C by placing it in a pre-heated oil bath. Over 3 h, the reaction mixture took on a yellow color. Suddenly the color became black and very rapid gas evolution occurred. The foam created by the bubbles nearly climbed out of the flask. The bubbling subsided after about 20 seconds. The reaction was stirred for 1 h more, and quenched by pouring onto 30 mL ice-water. The solution was extracted with 3 x 50 mL ethyl ether. The organic extracts were combined and washed with 30 mL brine, 2 x 30 mL water, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 4:1 (v/v)) to give white solid 227 mg, 39.2% yield.

(c) A solution of **101** (1.22 g, 5.08 mmol) in 5 mL DMF was added dropwise to a solution of 0.212 g NaH (60% dispersion in mineral oil, 5.30 mmol) in 10 mL DMF at 10 °C during 10 min. The mixture was stirred at 10 °C for 14 h. From TLC, the desired dinitro compound **99** was absent. After another 0.805 g NaH (60% dispersion in mineral oil, 20.1 mmol) was added in one portion, the temperature of the mixture was raised

quickly to 80 - 90 °C by placing it in a pre-heated oil bath. Over 3 h, the reaction progressed as described in paragraph (b), and workup was the same as described in paragraph (b). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 4:1 (v/v)) to give white solid 167 mg, 28.8% yield.

(d) NaH (205 mg, 60% dispersion in mineral oil, 5.1 mmol) was rinsed repeatedly with hexane to remove mineral oil. This was added in one portion to a stirred solution of **101** (240 mg, 1.00 mmol) in 2 mL DMF. The temperature of the mixture was raised quickly to 80 - 90 °C by placing it in a pre-heated oil bath. Copious gas evolution, as before, was observed. The reaction was quenched by pouring onto 4 mL ice-water. The solution was extracted with 3 x 10 mL ethyl ether. The ether extracts were combined and washed with 10 mL brine, 2 x 10 mL water, dried over $MgSO_4$, filtered, and concentrated. The crude product was recrystallized from hexane to give 76 mg, 67% yield.

(e) To a stirred solution of **101** (240 mg, 1.00 mmol) in 2 mL DMF was added 205 mg NaH (60% dispersion in mineral oil, 5.1 mmol) over 10 min at 10 °C. The mixture was stirred 24 h at 10 °C. Silica gel TLC revealed the presence of mainly the starting material, and the absence of olefin **96**.

(f) To a solution of 48 mg **101** (0.20 mmol) in 1.2 mL DMSO-d_6 was added NaH 60% (w/w) dispersion in mineral oil (40 mg, 1.0 mmol). The temperature of the mixture was raised quickly to 80 - 90 °C in an oil bath. During the heating, the mixture nearly exploded. After 10 min, a ^{1}H NMR spectrum showed that the reaction had almost

finished. After 40 min, another ^{1}H NMR spectrum showed that the reaction was complete and **96** was the only product in evidence. On this basis, the yield may be estimated to be above 95%.

(g) NaH (1.05 g, 60% (w/w) dispersion in mineral oil, 26 mmol) was rinsed repeatedly with hexane to remove mineral oil. This was added in one portion to a stirred solution of **101** (1.20 g, 5.00 mmol) in 10 mL toluene. To this 0.5 mL DMSO was added. The temperature of the reaction mixture was raised quickly to 80 - 90 °C in a pre-heated oil bath and stirred at this temperature for 7 - 8 h. The mixture was quenched by pouring onto 5 g ice-water. The mixture was extracted with 10 mL ethyl ether. The organic layer was separated and washed with 5 mL brine, 5 mL water, dried over Na_2SO_4, filtered and concentrated. The crude product was recrystallized from hexane to give 287 mg **96**, 50% yield.

(h) To a solution of **101** (239 mg, 0.996 mmol) in 2 mL toluene was added NaH (202 mg, 60% (w/w) dispersion in mineral oil, 5.1 mmol), and four drops DMSO. The temperature of the mixture was raised quickly to 80 - 90 °C and stirred overnight at that temperature. The mixture was quenched by pouring onto 2 g ice-water. The mixture was extracted with 2 mL ethyl ether. The organic layer was separated and washed with 1 mL brine, 1 mL water, dried over Na_2SO_4, filtered, and concentrated. The crude product was subjected to silica gel chromatography on a short column (hexane:EtOAc 6:1 v/v) to give 52 mg **96**, 46% yield.

2,2,2',2'-Tetramethyl-[5,5']bi[[1,3]dioxanyl]-5,5'-diol, 95. In a 50 mL round-bottomed flask equipped with magnetic stirring bar were stirred $NaIO_4$ (160 mg, 0.75 mmol) and $CeCl_3 \cdot 7H_2O$ (19 mg, 0.051 mmol) in 0.25 mL water and gently heated until a bright yellow suspension was formed. After cooling to 0 °C, ethyl acetate 0.63 mL and acetonitrile 0.75 mL were added, and the suspension was stirred for 2 min. $RuCl_3$ (2.1 mg, 0.010 mmol) was added and the mixture was stirred for 2 min. A solution of 114 mg olefin **96** (0.499 mmol) in ethyl acetate 0.25 mL was added in one portion. The mixture was stirred until the starting material disappeared, monitored by TLC (hexanes/EtOAc 4:1 (v/v)) every half hour. Na_2SO_4 (250 mg) was added followed by 3 mL EtOAc. The solid was filtered off. The filtrate was washed with 1.2 mL satd Na_2SO_3 solution. The organic layer was dried over Na_2SO_4 and concentrated on the rotary evaporator. The crude product was purified by chromatography on silica gel (hexanes/EtOAc 2:1 (v/v)) to give 83 mg of a white solid, 63% yield, mp 187 - 190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (d, 4H, J = 12.0 Hz), 3.57 (d, 4H, J = 12.0 Hz), 3.31 (s, 2H), 1.46 (s, 6H), 1.43 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.7, 69.3, 64.5, 27.3, 20.0. A crystal (0.15 x 0.07 x 0.04 mm) was chosen for X-ray diffractometry at 193(2) K; triclinic, $P\ \bar{1}$, Z = 2, a = 5.4479(8) Å, b = 10.4700(14) Å, c = 12.5954(17) Å, α = 114.420(2)°, β = 103.7000(10)°, γ = 91.346(2)°. 6284 reflections (3126 unique, R_{int} = 0.0381) were collected to a maximum 2θ of 56.72°. Data-to-parameter ratio 19.8. Structure solution and refinement on F^2 resulted in final R indices of R1 = 0.0637, wR2 = 0.1688 (I >

$2\sigma(I)$), R1 = 0.1031, wR2 = 0.2085 (all data) and a goodness of fit on F^2 of 1.061.

2,3-Bis(hydroxymethyl)butane-1,2,3,4-tetraol, 73. At 0 °C, 0.10 mL trifluoroacetic acid (1 mmol) was added to a solution of **95** (71 mg, 0.27 mmol) in 2.5 mL aqueous THF (THF/H_2O 4:1 v/v). The mixture was stirred at rt for 3 h. The solution was evaporated on the rotary evaporator affording a colorless oil. After standing in the hood several days, the colorless oil solidified, giving 39 mg **73**, 79% yield. ^{1}H NMR (400 MHz, D_2O) δ 3.69 (s). ^{13}C NMR (100 MHz, D_2O) δ 76.9, 61.8. A crystal (0.34 x 0.21 x 0.18 mm) was selected for X-ray diffractometry at 193(2) K; monoclinic $P2_1/n$, Z = 4, a = 6.8670(5) Å, b = 11.1428(7) Å, c = 10.4647(7) Å, β = 100.2210(10)°, Z = 8. 4917 reflections (1796 independent) were collected to a maximum 2θ of 56.62°. Data-to-parameter ratio 16.3. Structure solution and refinement on F^2 resulted in final R indices of R1 = 0.0429, wR2 = 0.1240 ($I > 2\sigma(I)$), R1 = 0.0442 wR2 = 0.1269 (all data) and a goodness of fit on F^2 of 1.077.

BIBLIOGRAPHY

1. Rivin, D.; Kendrick, C. E. *Carbon* **1997**, 35.

2. Oakland, B. G.; Dodd, R. B.; Schabacker, D. J.; Clegg, L. X. *Bull Environ. Contam. Toxicol.* **1992**, 51-57.

3. Hexels, G. Protective clothing against chemical and biological substances that are detrimental to health, Eur. Pat. Appl., 1308186, 2003.

4. Aron, G. N. *Text. Chem. Color.* **1979**, *11*, 24-27.

5. Kirayoglu, B. Laminated fabric for protective clothing. U. S. Patent 4869947, Sept. 26, 1989.

6. DeRuiter, E. Schutzmaterial gegen chemische Gifte und Verfahren zu seiner Herstellung DE 19829975, May 1st, 2000.

7. Wertheimer, M.R.; Klemberg-Sapieha, J.E. *Cerny, J., Liang, S.* **1998**, 151-163

8. Richards, V.; Fahlman, B. D.; Abstracts of papers, 227th ACS National Meeting, Anaheim, CA, March 28-April, 2004.

9. Hartley, S. M.; Axtell, H.; Koper, O. B., Klabunde, K. J. *Nanoscale Materials, 23rd Army Science Conference Proceedings, LP-06, 2004.*

10. Yang, F.; Wild, J. R.; Russel, A. *J. Biotechnol. Prog*. **1995**, 471-474.

11. Gill, I.; Ballesteros, A. *Biotechnol. Bioeng.* **2000**, 400-410.

12. Menger, F. M.; Rourk, M. J. *Langmuir* **1999**, *15*, 309-313.

13. Wagner, G.W.; Yang, Y. C. *Ind. Eng. Chem. Res.* **2002**, *41*, 1925-1928.

14. Schroeder-Gibson, H. L.; Walker, J.; Yeomans, W.; Ball, D. *Polymer Preprints* **2004**, *45*, 546.

15. Etter, M. C.; Baures, P. W. *J. Am. Chem. Soc.* **1988**, *110*, 639-640.

16. Small, L. *Toxic Industrial Chemical: A m Weapons of Mass Destruction Threat.* U.S. Army Command and General Staff College, **2002**.

17. a) Zdyrko, B.; Varshney, S. K.; Luzinov, I. *Langmuir* **2004**, *20*, 6727. b) Liu, Y.; Klep, V.; Zdyrko, B.; Luzinov, I. *Langmuir* **2004**, *20*, 6710.

18. Mao, Jianhua "*synthesis and chemistry of novel ionophoric organic phosphines*" Ph.D Dissertation, Auburn University, December, 1991.

19. Gudipati V.; Curran, D. P.; Wilcox, C. S. *J. Org. Chem.* **2006**, *71*, 3599–3607.

20. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part B: Reaction and Synthesis*, 5th ed.; Springer; 2007; Chapter 7.

21. Napolitano, E.; Giannone, E.; Fiaschi, R.; Marsili, A. *J. Org. Chem.* **1983**, *48*, 3653-3657.

22. a) Cabiddus, S.; Maccioni, A; Plumitallo, A. *Gazz. Chim. Ital.* **1981**, *111*, 123-127. b) Bernard, A. M.; Piras, P. P.; Plumitallo, A. *Gazz. Chim. Ital.* **1982**, *112*, 443-446.

23. Ellison, R. A.; Kotsonis, F. N. *J. Org. Chem*. **1973**, *38*, 4194-4196.

24. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part B: Reaction and Synthesis*, 5th ed.; Springer; 2007; Chapter 11.

25. Bengtsson, S.; Hoegberg, T. *J. Org. Chem.* **1993**, *53*, 3538-3542.

26. Wayman, D. P.; Kaufman, P. R. *J. Org. Chem.* **1964,** *29*, 1956.

27. Masilamani, D.; Rogic, M. M. *J. Org. Chem.* **1981**, *46*, 4486-4489

28. Tornøe, C.W.; Meldal, M. *Peptidotriazoles: Copper(I)-catalyzed 1,3- dipolar cycloadditions on solid-phase, Peptides 2001, Proc. Am. Pept. Symp.*; American Peptide Society and Kluwer Academic Publishers:San Diego, 2001, 263-264.

29. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

30. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, B. K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

31. a) McGarvey, G. J.; Mathys, J. A.; Wilson K. J. *J. Org. Chem.* **1996**, *61*, 5704-5705. b) Zacuto, M. J.; Leighton, J. L. *Org. Lett.* **2005**, *7*, 5525-5527. c) Burova, S. A.. McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495-2500. d) Rychnovsky S. D.; Khire U. R.; Yang, G. *J. Am. Chem. Soc.* **1997**, *119*, 2058-2059. d) Smith, A. B.; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001-2004.

32. Sanda, F.; Sanada, H.; Shibasaki, Y.; Endo, T. *Macromolecules* **2002**, *35*, 680-683.

33. Halabi, A.; Strumia, M. C. *J. Org. Chem.* **2000**, *65*, 9210-9213.

34. (a) Richens, D. T.; Smith C. G.; Sawyer, D. T. *Inorg. Chem.* **1979**, *18*, 706-712. (b)

Oertel, R. P. *Inorg. Chem.* **1972**, *11*, 544-549**.** (c) Klaassen, M.; Khfers, P. *Z. Anorg. Allg. Chem.* **1993**, *61*, 661-668.

35. Jungermann, E.; Sonntag, N. O.V. *Glycerin: A key Cosmetic Ingredient,* Marcel Dekker, 1991, chapter 2.

36. Newman, A. A. *Glycerol*; C.R.C. Press, 1968, Chapter 1.

37. Leffingwell, G.; Lesser, M. A.; Bennett, H. Glycerin, Its Industrial and Commercial Application, Chemical Publishing Co., 1945, Chapter 1.

38. Gorter, E.; Grendel, F. *J. Exp. Med.* **1925**, *41*, 439-443.

39. Cori, C. F.; Shine, W. M. *Science* **1935**, *82,* 134–135.

40. Ahlquist, D. A.; Nelson, R. A.; Steiger, D. L.; Jones, J. D.; Ellefson, R. D. *J. Compar. Physiol., B. Biochem. Systematic Environ. Physiol.* **1984**, *155*, 75-79.

41. (a)Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411-2502. (b) Kamm, B. *Angew. Chem.* **2007**, *119*, 5146; *Angew. Chem. Int. Ed.* **2007**, *46*, 5056-5058. (c) Pagliaro, M.; Ciriminna, R.; Kimura, H.; Rossi, M.; Della Pina, C. *Angew. Chem.* **2007**, *119*, 4516; *Angew. Chem. Int. Ed.* **2007**, *46*, 4434; (d) Zhou, C.-H.; J. N. Beltrami, J. N.; Fan, Y.-X.; Lu, G. Q. *Chem. Soc. Rev*. **2008**, *37*, 527.

42. Yukie, N.; Chikako, I. S.; Mari, I. K.; Kyoko, M.; Mihoe, Y. T.; Kaori, Y.; Yukako, M. Ying, J.; Tsutomu, S.: 84th General Session & Exhibition of the IADR (June 28-July 1, 2006, Brisbane, Australia.

43. Uhari, M.; Kontiokari, T.; Niemela, M. *Pediatrics* **1998**, 879-884.

44. Mattila, P. T.; Svanberg, M. J.; Jämsä, T.; Knuuttila, M. L. *Metabolism* **2002**, *51*, 92-96.

45. a) Neuwelt, E. A.; Specht, H. D.; Howieson, J.; Haines, J. E.; Bennett, M. J.; Hill, S. A. *Am. J. Roentgenol.* **1983**, *141*, 829–35. b) Neuwelt, E. A.; Howieson, J.; Frenkel, E. P., Specht, H. D.; Weigel, R.; Buchan, C. G. *Neurosurgery* **1986**, *19*, 573–82.

46. Larner, J. *Int. J. Exp. Diabetes Res.* **2002**, *3*, 47–60.

47. Shen, X.; Xiao, H.; Ranallo, R.; Wu, W.-H.; Wu, C. *Science* **2003**, *299*, 112–4.

48. Suami, T.; Ogawa, S. *Advan. Carbohydr. Chem.* **1990**, *48*, 21.

49. a) McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1966**, *31*, 1516-1521. b) McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1968**, *33*, 2835-2841. c) McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1968**, *33*, 2841-2844.

50. Iwasa, T.; Yamamoto, H.; Shibata, M. *J. Antibiot.* **1970**, *23*, 595-602.

51. Horii, S.; Iwasa, T.; Mizuta, E.; Kameda, Y. *J. Antibiot.* **1971**, *24*, 59-63; Kameda, Y.; Asano, N.; Yoshikawa, M.; Takeuchi, M.; Yamaguchi, T.; Matsui, K.; Horii, S.; Fukase, H. *J. Antibiot.* **1984**, *37*, 1301-1307.

52. Keough, T.; Ezra, F. S.; Russell, A. F.; Pryne, J. D. *Org. Mass Spectrom.* **1987**, *22*, 241-247.

53. Müller, S. N.; Batra, R.; Senn, M.; Giese, B.; Kisel, M.; Shadyro, O. *J. Am. Chem. Soc.* **1997**, *119*, 2795-2803.

54. a) Hartman, L. *Chem. Rev.* **1958**, *58*, 845–867. b) Srisiri, W.; Lamparski, H. G.;

O'Brien, D. F. *J. Org. Chem.* **1996**, *61*, 5911–5915.

55. a) Bruzik, K. S.; Salamonczyk, G.; Stec, W. J. *J. Org. Chem.* **1986**, *51*, 2368–2370. b) Quesada, E.; Delgado, J.; Gajate, C.; Mollinedo, F.; Ulises-Acuña, A.; Amat-Guerri, F. *J. Med. Chem.* **2004**, *47*, 5333–5335.

56. May, E. L. *J. Org. Chem.* **1952**, *17*, 286–289.

57. (a) Chen, J.; Prestwich, G. D. *J. Org. Chem.* **1998**, *63*, 430–431; (b) Kubiak, R. J.; Bruzik, K. S. *J. Org. Chem.* **2003**, *68*, 960–968.

58. Corson, B. B.; Benson, W. L. *Org. Synth. Coll. Vol. 2* **1943**, 273-275.

59. Luche, J. L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

60. Bohlmann, F.; Ahrens, H. L.; Kritzler, H. *Abhandl. braunschweig. wiss. Ges.* **1957**, *9*, 173-176. (*Chem. Abstr.* 52:60857).

61. Miura, T.; Kawashima, Y.; Takahashi, M.; Murakami, Y.; Imai, N. *Synth. Commun* **2007**, *37*, 3105-3109.

62. Shriver, D. F.; Kubas, G. J.; Marshall, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 5076-5079.

63. Kuo, G. H.; Zhang, R.; Wang, A.; Deangelis, A. R. (Jan). ssen Pharmaceutica, N.V., Belg. PCT Int. Appl. 2005030694, Apr. 07, 2005

64. Wang, X. L.; Li, X. D.; Xue, J. J.; Zhao, Y. L.; Zhang, Y. M. *Tetrahedron Lett.* **2009**, 413-415.

65. Smith, C. W.; Norton, D. G. *Org. Synth. Coll. Vol. 4* **1963**, 348.

66. Nicholas, K. M. *J. Am. Chem. Soc.* **1975**, *97*, 3254-3255.

67. Anderson, W. K.; Milowsky, A. S. *J. Org. Chem.* **1985**, *50*, 5423-5424.

68. Ripoll, J. L. *Bull. Soc. Chim. France* **1974**, 2567–2571.

69. (a) Lyle, R. E.; Fielding, H. L.; Cauquil, G.; Rouzaud, J. *J. Org. Chem.* **1955**, 20, 623-6; (b) Nichols, J.; Schipper, E. *J. Am. Chem. Soc.* **1958**, 80, 5711-13; (c) Marsaioli, A. J.; Nurnberg, V.; Sarragiotto, M. H.; Castellano, E. E. *J. Org. Chem.* **1989**, 54, 5838-9.

70. Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421-433.

71. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.

72. Plietker, B.; Niggemann, M. *J. Org. Chem.* **2005**, *70*, 2402-2405.

73. Shing, T. K. M.; Tai, V. W.-F.; Tam, E. K. W. *Angew. Chem.* **1994**, *106*, 2408; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2312.

74. Negishi, E.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474-1485.

75. Bell, R. P.; Baughan, E. C. *J. Chem. Soc.* **1937**, 1947-53.

76. Jie, Yuanping. "*Tris(1,3-dihydroxy-2-propyl)amine, a planar trialkylamine: Synthesis, structure, and properties. A potential precursor to hypervalent nitrogen***"** Ph.D Dissertation, Auburn University, April, 2006.

77. Kornblum, N.; Boyd, S. D.; Pinnick, H. W.; Smith, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 4316-4318.

78. Kornblum, N.; Boyd, S. D. *J. Am. Chem. Soc.* **1970**, *92*, 5784.

79. (a) Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, 1705. (b) Tanner, D. D.; Blackburn, E. V.; Diaz, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 1557.

80. Girdler, D. J.; Norris, R. K. *Tetrahedron Lett.* **1975**, 2375.

81. Ono, N.; Miyake, H.; Tamura, R.; Hamamoto, I.; Kaji, A. *Chem. Lett.* **1981**, 1139-1142.

82. Crozet, M. P.; Archaimbault, G.; Vanelle, P.; Nouguier, R. *Tetrahedron Lett.* **1985**, 26, 5133-5134.

83. Kornblum, N.; Cheng, L. *J. Org. Chem.*, **1977**, 42, 2944-2945.

84. Madjdabadi, A. A.; Beugelmans, R.; Lechevallier, A. *Synth. Commun.* **1989**, *19*, 1631-1640.

85. Zhang, W. G. *Baoji Wenli Xueyuan Xuebao, Ziran Kexueban* **2002**, *22*, 51-52.

86. Calvet, G.; Guillot, R.; Blanchard, N.; Kouklovsky, C. *Org. Biomol. Chem.* **2005**, *3*, 4395-4401.

87. Hirayama, T.; Taki, M.; Nakamura, M.; Arata, T.; Yamamoto, Y. *Chem. Lett.* **2006**, 834-835.

88. Eccles, W.; Jasinski, M.; Kaszynski, P.; Zienkiewicz, K.; Stulgies, B.; Jankowiak, A. *J. Org. Chem.* **2008**, 73, 5732-5744.

89. Boyer, W. J.; Evans, D. H. *J. Org. Chem.* **1988**, *53*, 5234 - 5239.

90. Fukunaga, K.; Kimura, M. *Nippon Kagaku Kaishi* **1984**, 145-151.

91. Hayward, M. A.; Green, M. A.; Rosseinsky, M. J.; Sloan, J. *J. Am. Chem. Soc.* **1999**, *121*, 8843-8854.

92. Swamer, F. W.; Hauser, C. R. *J. Am. Chem. Soc.* **1946**, *68*, 2647-9.

93. Lee, Y. J.; Closson, W. D. *Tetrahedron Lett.* **1974**, 381-384.

94. Rajendra, P. Y. *Int. J. Chem. Sci.* **2005**, 685-689.

95. Girard, C. *Org. Lett.* **2006**, 8, 1689-1692.

96. Wang, Z. X. *J. Heterocycl. Chem.* **2007**, 44, 89-92.

97. Saalfrank, R. W. *Angewandte Chemie* **1985**, 97, 870-1

98. Oka, K. *Tetrahedron Lett.* **1980**, 21, 3579-82.

99. Jones, W. O. *J. Chem. Soc.* **1954** 3490-2.

100. Bates, R. B. *J. Am. Chem. Soc.* **1958**, 80, 3413-20.

101. Challis, B. C.; Yousaf, T. I.; J. Chem. Soc., Perkin Trans. 2: 1991; 283 - 286;

102. Chem.Abstr. **1957**, 51, 14717.

103. Chem.Abstr. **1957**, 51, 8754.

APPENDIX 1

CRYSTAL STRUCTURE DATA FOR COMPOUND 73

```
data_li85new

_audit_creation_method          SHELXL-97
_chemical_name_systematic
;
 ?
;
_chemical_name_common           ?
_chemical_melting_point         ?
_chemical_formula_moiety        ?
_chemical_formula_sum
 'C3 H7 O3'
_chemical_formula_weight        91.09

loop_
 _atom_type_symbol
 _atom_type_description
 _atom_type_scat_dispersion_real
 _atom_type_scat_dispersion_imag
 _atom_type_scat_source
 'C'  'C'   0.0033   0.0016
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'H'  'H'   0.0000   0.0000
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'O'  'O'   0.0106   0.0060
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_symmetry_cell_setting          'Monoclinic'
_symmetry_space_group_name_H-M   'P2(1)/n'

loop_
 _symmetry_equiv_pos_as_xyz
 'x, y, z'
 '-x+1/2, y+1/2, -z+1/2'
 '-x, -y, -z'
 'x-1/2, -y-1/2, z-1/2'

_cell_length_a                6.8670(5)
_cell_length_b                11.1428(7)
```

```
_cell_length_c                 10.4647(7)
_cell_angle_alpha               90.00
_cell_angle_beta                100.2210(10)
_cell_angle_gamma               90.00
_cell_volume                   788.03(9)
_cell_formula_units_Z           8
_cell_measurement_temperature    193(2)
_cell_measurement_reflns_used    'all'
_cell_measurement_theta_min      2.69
_cell_measurement_theta_max      28.31

_exptl_crystal_description       'Block'
_exptl_crystal_colour           'Colorless'
_exptl_crystal_size_max          0.34
_exptl_crystal_size_mid          0.21
_exptl_crystal_size_min          0.18
_exptl_crystal_density_meas      'Not measured'
_exptl_crystal_density_diffrn    1.536
_exptl_crystal_density_method    'not measured'
_exptl_crystal_F_000            392
_exptl_absorpt_coefficient_mu    0.138
_exptl_absorpt_correction_type   'Multi-scans'
_exptl_absorpt_correction_T_min  0.9541
_exptl_absorpt_correction_T_max  0.9759
_exptl_absorpt_process_details   'SHELXPREP'

_exptl_special_details
;
 ?
;

_diffrn_ambient_temperature      193(2)
_diffrn_radiation_wavelength     0.71073
_diffrn_radiation_type          MoK\a
_diffrn_radiation_source        'fine-focus sealed tube'
_diffrn_radiation_monochromator  graphite
_diffrn_measurement_device_type  'Bruker APEX'
_diffrn_measurement_method       '0.3 wide w/exposures'
_diffrn_detector_area_resol_mean  0
_diffrn_standards_number        'na'
```

```
_diffrn_standards_interval_count  'na'
_diffrn_standards_interval_time   'na'
_diffrn_standards_decay_%        0
_diffrn_reflns_number           4917
_diffrn_reflns_av_R_equivalents   0.0259
_diffrn_reflns_av_sigmaI/netI     0.0271
_diffrn_reflns_limit_h_min       -9
_diffrn_reflns_limit_h_max       8
_diffrn_reflns_limit_k_min       -14
_diffrn_reflns_limit_k_max       14
_diffrn_reflns_limit_l_min       -11
_diffrn_reflns_limit_l_max       13
_diffrn_reflns_theta_min         2.69
_diffrn_reflns_theta_max         28.31
_reflns_number_total            1796
_reflns_number_gt               1704
_reflns_threshold_expression     >2sigma(I)

_computing_data_collection       'SMART'
_computing_cell_refinement       'SMART,SAINT'
_computing_data_reduction        'SAINT'
_computing_structure_solution    'SHELXS-97 (Sheldrick, 1990)'
_computing_structure_refinement  'SHELXL-97 (Sheldrick, 1997)'
_computing_molecular_graphics    'SHELXP-97 (Sheldrick, 1997)'
_computing_publication_material  'SHELXCIF-97 (Sheldrick, 2000)'

_refine_special_details
;
 Refinement of F^2^ against ALL reflections.  The weighted R-factor wR and
 goodness of fit S are based on F^2^, conventional R-factors R are based
 on F, with F set to zero for negative F^2^. The threshold expression of
 F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is
 not relevant to the choice of reflections for refinement.  R-factors based
 on F^2^ are statistically about twice as large as those based on F, and R-
 factors based on ALL data will be even larger.
;

_refine_ls_structure_factor_coef  Fsqd
_refine_ls_matrix_type           full
```

```
_refine_ls_weighting_scheme      calc
_refine_ls_weighting_details
 'calc w=1/[\s^2^(Fo^2^)+(0.0793P)^2^+0.2341P] where P=(Fo^2^+2Fc^2^)/3'
_atom_sites_solution_primary     direct
_atom_sites_solution_secondary   difmap
_atom_sites_solution_hydrogens   geom
_refine_ls_hydrogen_treatment    mixed
_refine_ls_extinction_method     SHELXL
_refine_ls_extinction_coef       0.35(2)
_refine_ls_extinction_expression
 'Fc^*^=kFc[1+0.001xFc^2^\l^3^/sin(2\q)]^-1/4^'
_refine_ls_number_reflns         1796
_refine_ls_number_parameters     134

_refine_ls_number_restraints     0
_refine_ls_R_factor_all          0.0442
_refine_ls_R_factor_gt           0.0429
_refine_ls_wR_factor_ref         0.1269
_refine_ls_wR_factor_gt          0.1240
_refine_ls_goodness_of_fit_ref   1.077
_refine_ls_restrained_S_all      1.077
_refine_ls_shift/su_max          0.009
_refine_ls_shift/su_mean         0.001

loop_
 _atom_site_label
 _atom_site_type_symbol
 _atom_site_fract_x
 _atom_site_fract_y
 _atom_site_fract_z
 _atom_site_U_iso_or_equiv
 _atom_site_adp_type
 _atom_site_occupancy
 _atom_site_symmetry_multiplicity
 _atom_site_calc_flag
 _atom_site_refinement_flags
 _atom_site_disorder_assembly
 _atom_site_disorder_group
O1 O 0.45440(13) 0.72605(8) 0.56037(9) 0.0240(3) Uani 1 1 d . . .
C1 C 0.53701(18) 0.84934(10) 0.23608(12) 0.0208(3) Uani 1 1 d . . .
```

```
H1A H 0.4642 0.7964 0.1679 0.025 Uiso 1 1 calc R . .
H1B H 0.4524 0.9196 0.2454 0.025 Uiso 1 1 calc R . .
O2 O 0.62239(13) 0.59968(7) 0.24157(9) 0.0228(3) Uani 1 1 d . . .
C2 C 0.25302(17) 0.85965(10) 0.40954(12) 0.0215(3) Uani 1 1 d . . .
H2A H 0.3280 0.9332 0.4398 0.026 Uiso 1 1 calc R . .
H2B H 0.1957 0.8703 0.3165 0.026 Uiso 1 1 calc R . .
O3 O 0.71679(15) 0.88847(8) 0.19909(10) 0.0292(3) Uani 1 1 d . . .
C3 C 0.58253(16) 0.78100(9) 0.36511(11) 0.0177(3) Uani 1 1 d . . .
O4 O 0.09716(13) 0.84361(9) 0.48174(10) 0.0281(3) Uani 1 1 d . . .
C4 C 0.70845(17) 0.66970(10) 0.35205(12) 0.0210(3) Uani 1 1 d . . .
H4A H 0.8435 0.6948 0.3427 0.025 Uiso 1 1 calc R . .
H4B H 0.7190 0.6203 0.4316 0.025 Uiso 1 1 calc R . .
O5 O 0.69614(13) 0.85883(8) 0.45858(9) 0.0227(3) Uani 1 1 d . . .
C5 C 0.28496(17) 0.63653(10) 0.37442(12) 0.0199(3) Uani 1 1 d . . .
H5A H 0.3750 0.5674 0.3973 0.024 Uiso 1 1 calc R . .
H5B H 0.1705 0.6255 0.4190 0.024 Uiso 1 1 calc R . .
O6 O 0.21627(14) 0.63590(8) 0.23851(9) 0.0236(3) Uani 1 1 d . . .
C6 C 0.39429(16) 0.75193(9) 0.42504(11) 0.0175(3) Uani 1 1 d . . .
H2 H 0.672(3) 0.530(2) 0.255(2) 0.056(6) Uiso 1 1 d . . .
H1 H 0.536(3) 0.774(2) 0.595(2) 0.049(6) Uiso 1 1 d . . .
H5 H 0.810(3) 0.8584(15) 0.4454(18) 0.028(4) Uiso 1 1 d . . .
H6 H 0.316(3) 0.6182(17) 0.202(2) 0.041(5) Uiso 1 1 d . . .
H4 H 0.132(3) 0.8630(19) 0.560(2) 0.044(5) Uiso 1 1 d . . .
H3 H 0.768(4) 0.844(2) 0.154(3) 0.065(7) Uiso 1 1 d . . .

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 _atom_site_aniso_U_33
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C1 0.0231(6) 0.0134(5) 0.0274(6) 0.0013(4) 0.0089(4) -0.0002(4)
O2 0.0276(5) 0.0135(4) 0.0270(5) -0.0021(3) 0.0037(3) 0.0043(3)
C2 0.0185(6) 0.0169(5) 0.0302(7) -0.0034(4) 0.0071(4) 0.0002(4)

O3 0.0378(6) 0.0152(4) 0.0407(6) -0.0053(4) 0.0240(4) -0.0069(4)
C3 0.0163(5) 0.0120(5) 0.0248(6) -0.0025(4) 0.0040(4) -0.0009(3)
```

```
O4 0.0182(5) 0.0351(5) 0.0323(6) -0.0105(4) 0.0085(4) -0.0024(3)
C4 0.0203(6) 0.0164(5) 0.0256(6) -0.0018(4) 0.0022(4) 0.0035(4)
O5 0.0176(5) 0.0217(5) 0.0293(5) -0.0082(3) 0.0057(3) -0.0049(3)
C5 0.0208(6) 0.0144(5) 0.0240(6) 0.0005(4) 0.0023(4) -0.0030(4)
O6 0.0247(5) 0.0208(4) 0.0240(5) -0.0026(3) 0.0007(3) -0.0019(3)
C6 0.0161(5) 0.0149(5) 0.0214(6) -0.0002(4) 0.0029(4) -0.0013(4)

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;
 All esds (except the esd in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix.  The cell esds are taken
 into account individually in the estimation of esds in distances, angles
 and torsion angles; correlations between esds in cell parameters are only
 used when they are defined by crystal symmetry.  An approximate (isotropic)
 treatment of cell esds is used for estimating esds involving l.s. planes.
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O1 C6 1.4323(13) . ?
C1 O3 1.4260(14) . ?
C1 C3 1.5333(16) . ?
O2 C4 1.4326(14) . ?
C2 O4 1.4266(15) . ?
C2 C6 1.5337(15) . ?
C3 O5 1.4306(13) . ?
C3 C4 1.5317(15) . ?
C3 C6 1.5675(15) . ?
C5 O6 1.4168(14) . ?
C5 C6 1.5351(15) . ?

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 _geom_angle_publ_flag
O3 C1 C3 109.87(10) . . ?
O4 C2 C6 111.46(10) . . ?
O5 C3 C4 107.69(9) . . ?
O5 C3 C1 107.59(9) . . ?
C4 C3 C1 110.71(9) . . ?
O5 C3 C6 103.89(9) . . ?
C4 C3 C6 112.77(9) . . ?
C1 C3 C6 113.66(9) . . ?
O2 C4 C3 110.76(9) . . ?
O6 C5 C6 113.95(9) . . ?
O1 C6 C2 109.15(9) . . ?
O1 C6 C5 102.13(9) . . ?
C2 C6 C5 110.95(9) . . ?
O1 C6 C3 108.89(8) . . ?
C2 C6 C3 110.30(9) . . ?
C5 C6 C3 115.00(9) . . ?

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_diffrn_measured_fraction_theta_full   0.918
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_refine_diff_density_rms    0.083
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APPENDIX 2

CRYSTAL STRUCTURE DATA FOR COMPOUND 101

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;
 ?
;
_chemical_name_common           ?
_chemical_melting_point         ?
_chemical_formula_moiety        ?
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 'C12 H22 O6'
_chemical_formula_weight        262.30

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 _atom_type_scat_dispersion_imag
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 'C'  'C'   0.0033   0.0016
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'H'  'H'   0.0000   0.0000
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'O'  'O'   0.0106   0.0060
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_symmetry_cell_setting          'Triclinic'
_symmetry_space_group_name_H-M   'P-1'

loop_
 _symmetry_equiv_pos_as_xyz
 'x, y, z'
 '-x, -y, -z'

_cell_length_a                 5.4479(8)
_cell_length_b                 10.4700(14)
_cell_length_c                 12.5954(17)
_cell_angle_alpha              114.420(2)
```

```
_cell_angle_beta               93.277(2)
_cell_angle_gamma              91.346(2)
_cell_volume                   652.22(16)
_cell_formula_units_Z          2
_cell_measurement_temperature    193(2)
_cell_measurement_reflns_used    'all'
_cell_measurement_theta_min      1.78
_cell_measurement_theta_max      28.36

_exptl_crystal_description       'colorless'
_exptl_crystal_colour           'Plate'
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_exptl_crystal_size_mid          0.07
_exptl_crystal_size_min          0.04
_exptl_crystal_density_meas      'not measured'
_exptl_crystal_density_diffrn    1.336
_exptl_crystal_density_method    'not measured'
_exptl_crystal_F_000            284
_exptl_absorpt_coefficient_mu    0.106
_exptl_absorpt_correction_type   'Multi-scans'
_exptl_absorpt_correction_T_min  0.9840
_exptl_absorpt_correction_T_max  0.9958
_exptl_absorpt_process_details   'SHELXPREP'

_exptl_special_details
;
 ?
;

_diffrn_ambient_temperature      193(2)
_diffrn_radiation_wavelength     0.71073
_diffrn_radiation_type          MoK\a
_diffrn_radiation_source        'fine-focus sealed tube'
_diffrn_radiation_monochromator  graphite
_diffrn_measurement_device_type  'Bruker APEX'
_diffrn_measurement_method       '0.3 wide w/exposures'
_diffrn_detector_area_resol_mean  0
_diffrn_standards_number        'na'
_diffrn_standards_interval_count  'na'
_diffrn_standards_interval_time  'na'
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_diffrn_reflns_av_sigmaI/netI    0.0738
_diffrn_reflns_limit_h_min       -7
_diffrn_reflns_limit_h_max       7
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_diffrn_reflns_limit_l_min       -16
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_diffrn_reflns_theta_min         1.78
_diffrn_reflns_theta_max         28.36
_reflns_number_total            3126
_reflns_number_gt               1857
_reflns_threshold_expression     >2sigma(I)

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_computing_cell_refinement       'SMART,SAINT'
_computing_data_reduction        'SAINT'
_computing_structure_solution    'SHELXS-97 (Sheldrick, 1990)'
_computing_structure_refinement  'SHELXL-97 (Sheldrick, 1997)'
_computing_molecular_graphics    'SHELXP-97 (Sheldrick, 1997)'
_computing_publication_material  'SHELXCIF-97 (Sheldrick, 2000)'

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 Refinement of F^2^ against ALL reflections.  The weighted R-factor wR and
 goodness of fit S are based on F^2^, conventional R-factors R are based
 on F, with F set to zero for negative F^2^. The threshold expression of
 F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is
 not relevant to the choice of reflections for refinement.  R-factors based
 on F^2^ are statistically about twice as large as those based on F, and R-
 factors based on ALL data will be even larger.
;

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_refine_ls_weighting_details
 'calc w=1/[\s^2^(Fo^2^)+(0.1084P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3'
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_atom_sites_solution_secondary   difmap
_atom_sites_solution_hydrogens   geom
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_refine_ls_number_reflns         3126
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 _atom_site_occupancy
 _atom_site_symmetry_multiplicity
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O1 O 0.7112(3) 0.12723(17) 0.48627(15) 0.0301(4) Uani 1 1 d . . .
H1D H 0.7165 0.2152 0.5216 0.045 Uiso 1 1 calc R . .
O2 O 0.8415(3) 0.15898(17) 0.72514(15) 0.0301(4) Uani 1 1 d . . .
O3 O 0.5172(3) 0.29203(17) 0.70788(14) 0.0287(4) Uani 1 1 d . . .
O4 O 0.2117(3) 0.57101(17) 0.42876(15) 0.0292(4) Uani 1 1 d . . .
H4D H 0.1390 0.6453 0.4417 0.044 Uiso 1 1 calc R . .
O5 O -0.0737(3) 0.36943(17) 0.22989(14) 0.0303(4) Uani 1 1 d . . .
O6 O 0.2515(3) 0.27570(17) 0.29692(14) 0.0290(4) Uani 1 1 d . . .
```

```
C1 C 0.1704(6) 0.2086(3) 0.0964(2) 0.0409(7) Uiso 1 1 d . . .
H1A H 0.2803 0.2873 0.1029 0.061 Uiso 1 1 calc R . .
H1B H 0.0424 0.1898 0.0332 0.061 Uiso 1 1 calc R . .
H1C H 0.2653 0.1249 0.0794 0.061 Uiso 1 1 calc R . .
C2 C 0.8144(6) 0.3892(3) 0.8666(2) 0.0392(7) Uani 1 1 d . . .
H2A H 0.9121 0.4225 0.8193 0.059 Uiso 1 1 calc R . .
H2B H 0.9245 0.3697 0.9218 0.059 Uiso 1 1 calc R . .
H2C H 0.7024 0.4614 0.9100 0.059 Uiso 1 1 calc R . .
C3 C 0.0520(5) 0.2452(3) 0.2101(2) 0.0294(6) Uani 1 1 d . . .
C4 C 0.5117(5) 0.2012(3) 0.8576(2) 0.0385(7) Uani 1 1 d . . .
H4A H 0.4177 0.1156 0.8039 0.058 Uiso 1 1 calc R . .
H4B H 0.3978 0.2722 0.9010 0.058 Uiso 1 1 calc R . .
H4C H 0.6191 0.1798 0.9126 0.058 Uiso 1 1 calc R . .
C5 C -0.1219(5) 0.1267(3) 0.2060(2) 0.0363(7) Uani 1 1 d . . .
H5A H -0.1936 0.1546 0.2814 0.054 Uiso 1 1 calc R . .
H5B H -0.0302 0.0420 0.1895 0.054 Uiso 1 1 calc R . .
H5C H -0.2536 0.1075 0.1442 0.054 Uiso 1 1 calc R . .
C6 C 0.6675(5) 0.2572(3) 0.7881(2) 0.0284(6) Uani 1 1 d . . .
C7 C 0.7353(5) 0.0329(3) 0.6322(2) 0.0276(6) Uani 1 1 d . . .
H7A H 0.6398 -0.0217 0.6654 0.033 Uiso 1 1 calc R . .
H7B H 0.8681 -0.0255 0.5895 0.033 Uiso 1 1 calc R . .
C8 C -0.1677(4) 0.4330(3) 0.3430(2) 0.0277(6) Uani 1 1 d . . .
H8A H -0.2912 0.3678 0.3518 0.033 Uiso 1 1 calc R . .
H8B H -0.2494 0.5198 0.3516 0.033 Uiso 1 1 calc R . .
C9 C 0.1793(4) 0.3342(2) 0.4138(2) 0.0256(5) Uani 1 1 d . . .
H9A H 0.3268 0.3557 0.4692 0.031 Uiso 1 1 calc R . .
H9B H 0.0705 0.2651 0.4260 0.031 Uiso 1 1 calc R . .
C10 C 0.5663(4) 0.0672(2) 0.5473(2) 0.0225(5) Uani 1 1 d . . .
C11 C 0.0438(4) 0.4682(2) 0.4378(2) 0.0235(5) Uani 1 1 d . . .
C12 C 0.3848(4) 0.1718(2) 0.6186(2) 0.0257(5) Uani 1 1 d . . .
H12A H 0.2809 0.2017 0.5667 0.031 Uiso 1 1 calc R . .
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O3 0.0349(10) 0.0234(9) 0.0234(9) 0.0053(7) 0.0012(7) 0.0040(7)
O4 0.0295(9) 0.0237(9) 0.0335(10) 0.0105(8) 0.0055(8) 0.0003(7)
O5 0.0378(10) 0.0303(10) 0.0211(9) 0.0085(8) 0.0038(7) 0.0068(8)
O6 0.0267(9) 0.0316(10) 0.0230(9) 0.0051(8) 0.0040(7) 0.0054(7)
C2 0.0472(17) 0.0328(15) 0.0289(15) 0.0051(12) -0.0020(12) -0.0054(13)
C3 0.0324(14) 0.0284(13) 0.0243(13) 0.0074(11) 0.0038(10) 0.0042(11)
C4 0.0424(16) 0.0475(17) 0.0278(15) 0.0171(13) 0.0077(12) 0.0006(13)
C5 0.0400(15) 0.0306(14) 0.0314(15) 0.0068(12) -0.0020(12) -0.0045(12)
C6 0.0304(13) 0.0296(13) 0.0222(13) 0.0081(11) 0.0002(10) 0.0004(11)
C7 0.0278(13) 0.0247(12) 0.0258(13) 0.0063(11) -0.0010(10) 0.0036(10)
C8 0.0257(13) 0.0292(13) 0.0252(13) 0.0081(11) 0.0021(10) 0.0079(10)
C9 0.0249(12) 0.0273(13) 0.0233(13) 0.0088(10) 0.0025(10) 0.0067(10)
C10 0.0233(12) 0.0209(11) 0.0212(12) 0.0064(10) 0.0040(9) -0.0003(10)
C11 0.0211(12) 0.0242(12) 0.0257(13) 0.0106(10) 0.0036(9) 0.0022(10)
C12 0.0269(12) 0.0237(12) 0.0223(12) 0.0052(10) 0.0007(10) 0.0039(10)

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 All esds (except the esd in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix.  The cell esds are taken
 into account individually in the estimation of esds in distances, angles
 and torsion angles; correlations between esds in cell parameters are only
 used when they are defined by crystal symmetry.  An approximate (isotropic)
 treatment of cell esds is used for estimating esds involving l.s. planes.
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O2 C6 1.429(3) . ?
O2 C7 1.434(3) . ?
O3 C6 1.431(3) . ?
O3 C12 1.437(3) . ?
```

```
O4 C11 1.440(3) . ?
O5 C3 1.419(3) . ?
O5 C8 1.432(3) . ?
O6 C9 1.425(3) . ?
O6 C3 1.428(3) . ?
C1 C3 1.509(4) . ?
C2 C6 1.502(3) . ?
C3 C5 1.524(4) . ?
C4 C6 1.521(4) . ?
C7 C10 1.530(3) . ?
C8 C11 1.532(3) . ?
C9 C11 1.526(3) . ?
C10 C12 1.524(3) . ?
C10 C10 1.546(4) 2_656 ?
C11 C11 1.537(5) 2_566 ?

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C6 O2 C7 114.80(18) . . ?
C6 O3 C12 112.90(18) . . ?
C3 O5 C8 113.96(18) . . ?
C9 O6 C3 113.98(17) . . ?
O5 C3 O6 109.6(2) . . ?
O5 C3 C1 105.7(2) . . ?
O6 C3 C1 105.4(2) . . ?
O5 C3 C5 111.7(2) . . ?
O6 C3 C5 112.0(2) . . ?
C1 C3 C5 112.2(2) . . ?
O2 C6 O3 109.09(19) . . ?
O2 C6 C2 106.3(2) . . ?
O3 C6 C2 106.5(2) . . ?
O2 C6 C4 111.9(2) . . ?
O3 C6 C4 111.3(2) . . ?
C2 C6 C4 111.5(2) . . ?
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O2 C7 C10 110.83(19) . . ?
O5 C8 C11 109.66(19) . . ?
O6 C9 C11 110.33(19) . . ?
O1 C10 C12 110.27(19) . . ?
O1 C10 C7 109.38(18) . . ?
C12 C10 C7 107.82(19) . . ?
O1 C10 C10 106.2(2) . 2_656 ?
C12 C10 C10 111.9(2) . 2_656 ?
C7 C10 C10 111.3(2) . 2_656 ?
O4 C11 C9 108.60(18) . . ?
O4 C11 C8 108.72(18) . . ?
C9 C11 C8 107.7(2) . . ?
O4 C11 C11 107.1(2) . 2_566 ?
C9 C11 C11 111.7(2) . 2_566 ?
C8 C11 C11 112.8(2) . 2_566 ?
O3 C12 C10 109.62(19) . . ?

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_refine_diff_density_rms    0.078
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