

PART I: SYNTHESIS OF FUNCTIONALIZED BILE ACIDS TOWARDS THE  
CONSTRUCTION OF STEROIDAL MACROCYCLES.

PART II: EVALUATION AND EXPANSION OF A  
MODULAR CARD GAME FOR TEACHING  
ORGANIC CHEMISTRY

A DISSERTATION IN  
Chemistry  
and  
Pharmaceutical Sciences

Presented to the Faculty of the University of  
Missouri-Kansas City in partial fulfillment  
of the requirements for the degree

DOCTOR OF PHILOSOPHY

by

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2019

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University of Missouri-Kansas City, 2019

ABSTRACT

In Part I, the synthesis of chenodeoxychoic acid (CDCA) derivatives towards the construction of unique chemical architectures are reported. Building on previously described methods, CDCA based macrocycles with inner cavities have been synthesized and characterized. Attempts toward oxa-Michael coupling of CDCA monomers to form sulfonate ester linked dimers is described. CDCA was also functionalized with terminal alkynes (pentynyl, hexynyl, and heptynyl) and aryl iodide and cyclized to form the respective macrocycles. These have been coupled together via oxygen-free Sonogashira reaction conditions to form large barrel-like steroidal architectures. These structures were investigated by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR spectroscopy, and HR-MS, and MALDI-TOF spectroscopy. In part II a game to teach organic chemistry, ChemKarta was evaluated as a teaching tool. Analysis of an undergraduate class's impressions of the game showed that Chemkarta was an easy to learn and enjoyable game, but the amount of information in the game could be overwhelming for some students. Furthermore, the modular nature of the game was demonstrated by

developing new cards to fit into the examined card set, as well as additional card sets to teach different subjects using the same game rules.

The faculty listed below, appointed by the Dean of the School of Graduate Studies, have examined a dissertation titled “Synthesis of Functionalized Bile Acids towards the Construction of Steroidal Macrocycles and Evaluation and Expansion of a Modular Card Game for Teaching Organic Chemistry,” presented by Christopher A Knudtson, candidate for the Doctor of Philosophy degree, and certify that in their opinion it is worthy of acceptance.

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## ACKNOWLEDGEMENTS

I would first like to thank my research adviser Dr. Jerry R. Dias for his educational, financial, and technical support during my time at UMKC and wish him well in his retirement.

Secondly, I would like to express my gratitude to members of my committee Drs. Kathleen Kilway, David Van Horn, Thomas Johnston, and Bi Botti “Celestin” Youan for their valuable comment and advice on my dissertation, especially during my last year of research. I thank my committee chair Dr. Theodore White for his dedicated work in helping me complete my Ph.D. thesis, especially working from a distance. His guidance during the writing process has enabled me to complete this manuscript for presentation to my committee.

I also extend my thanks to my colleagues and technical staff at the Department of Chemistry at the University of Missouri-Kansas City and Kansas University for their help in administration, technical support, and chemical analysis.

I extend deep gratitude to current and former members of the School of Graduate Studies including Drs. Jennifer Friend, Denis Medeiros, Peggy Ward-Smith, and Joseph Parisi for meeting with me to review my progress through the graduate program and to help in seeking employment

I would like to thank my family and my fiancée, Mary Madden, for their help and support on my Ph.D. study during the past six years.

## DEDICATION

I wish to dedicate this work to memory of Arnold Knudtson, Bernard Anderson, and Anna Anderson.

PART I: SYNTHESIS OF FUNCTIONALIZED BILE ACIDS TOWARDS THE  
CONSTRUCTION OF STEROIDAL MACROCYCLES

CHAPTER 1

1. INTRODUCTION

1.1 Introduction

1.1.1 A Brief Review of Macrocyclic and Supramolecular Chemistry

Macrocycles are a class of large, cyclic molecules with greater than 12 atoms in their ring. They occur both in natural products and as synthetic compounds. These ring structures can be constructed from a variety of building blocks including carbohydrates, arenes, peptides, heterocycles, and bile acids, which give rise to a wide diversity of structures such as crown ethers, cyclopeptides, cyclodextrins, porphyrins, calixarenes, and cyclophanes. Macrocycles have a variety of applications including antibiotics, multidentate ligands, and commercial dyes (*see Figure 1.1*). Vancomycin and the more recently discovered Thermoactinoamide A are cyclic peptides that display antibacterial activity.<sup>1</sup> Calixarenes are chalice-like structures with multiple metal binding sites that have been used to design new metal catalysts.<sup>2</sup> Phthalo Blue (Phthalocyanine Blue BN) is widely used in printing ink and is the highest volume pigment produced in the world.<sup>3</sup> Of particular interest is the ability of macrocycles to participate in guest-host interactions. In nature, this can be observed in porphyrins, which bind metal cations and act as electron transfer agents (chlorophyll) and diatomic gas shuttles (heme).

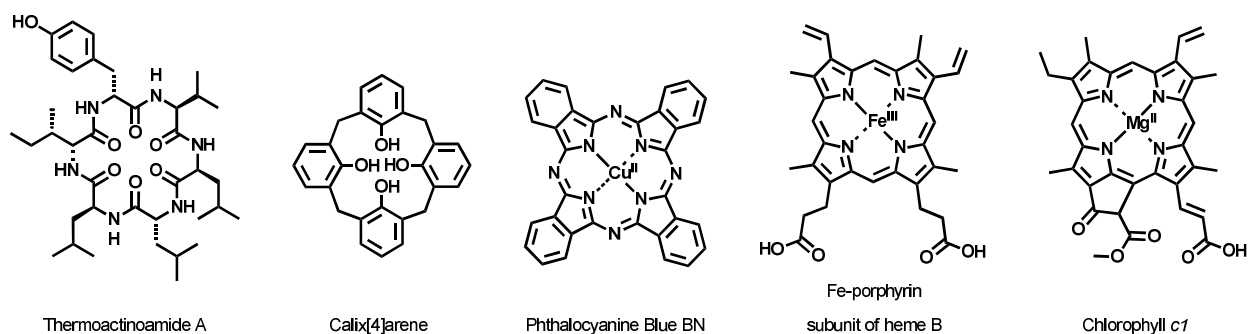


Figure 1.1 Artificial and Natural Macrocyces

The observation that crown ethers and cryptans demonstrated the ability to associate and solubilize charged cations in non-polar medium lead to the 1987 Nobel Prize for Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen and the founding of supramolecular chemistry.<sup>4</sup> Supramolecular chemistry focuses on the study of structured molecular frameworks and their ability to recognize and interact with smaller molecules. Through non-covalent interactions, these neutral macrocycles can capture other molecules to form complexes that are useful in solubilizing ions, chemical scavenging, molecular sensing, and drug delivery. During their initial discovery, crown ethers demonstrated affinity for metal ions with selectivity depending on the size of the macrocycle ring. For example, 18-crown-6 has high affinity for  $K^+$ , 15-crown-5 for  $Na^+$ , and 12-crown-4 for  $Li^+$ . These stable complexes solubilize otherwise insoluble salts in nonpolar mediums, which makes them useful phase transfer catalysts in organic synthesis. More recent work includes lariat structures, which incorporate additional stabilizing forces through cation- $\pi$  interactions (see *Figure 1.2*).<sup>5</sup>

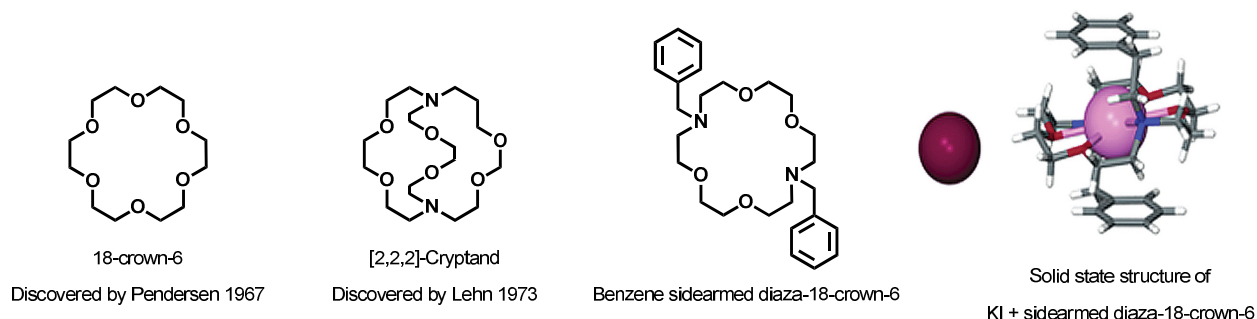


Figure 1.2 Crown Ethers, Cryptands, Lariat Structures, and Guest-Host Interactions.

Stoddart synthesized macrocyclic organic salts consisting of 1,4-phenylene-bridged bipyridinium units and scavenged a variety of polyaromatic hydrocarbons in both aqueous and organic solvents.<sup>6</sup> Cyclic  $\pi$ -conjugated paraphenylene rings called cycloparaphenylenes were synthesized by Yamago and demonstrated to encapsulate  $C_{60}$  fullerenes as “fullerene-peapods.”<sup>7</sup> Xia demonstrated the coupling of an anthracene dye to a dioxopolyamine receptor, which enabled the selective detection of  $Cu^{2+}$  through fluorescence suppression.<sup>8</sup>  $\beta$ -Cyclodextrin, a cylindrical oligosaccharide, has been complexed with the nonsteroidal anti-inflammatory drugs (NSAID) piroxicam to increase the solubility and absorption of the drug, resulting in more rapid onset of analgesia.<sup>9</sup>



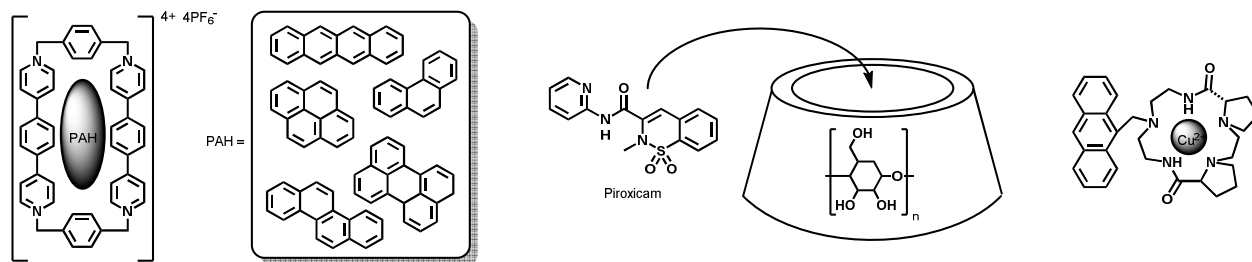


Figure 1.3 Macrocycles and Applications

There are a multitude of factors affecting the application of macrocycles in guest-host interactions including the rigidity of the macrocycle and the physical and electronic properties of the interior cavity and exterior shell. These molecular frameworks require rigid, predictable architectures to prevent warping into non-applicable shapes. Therefore, they are often constructed from rigid building blocks including benzene rings, aromatic heterocycles, alkyne units, and aliphatic six-membered rings<sup>10</sup> to reduce to lock the large structures into the desired conformations. Both physical and electronic interactions are of concern in the central cavity of a macrocycle as the nature of the guest molecule depends not only on the size of the macrocycle's cavity but also on the electronic environment. The exterior properties of the macrocycle are of consequence to their interactions with their environment including solubility and cell permeability.

### 1.1.2 Bile Acid Derivatives: Preparation, Structure and Applications

Bile acids (BA) are a type of steroid endogenous to a variety of animals, including humans, which are an increasing focus of study as architectural components in supramolecular

chemistry. These steroidal molecules are synthesized in the liver and act as surfactants to solubilize fats and vitamins for absorption in the colon (*see Figure 1.4*). This occurs through conjugation with amino acids like taurine or glycine to form water-soluble salts, followed by the formation of micelles around lipophilic molecules.<sup>11</sup> The primary BAs are cholic acid (CA) and chenodeoxycholic acid (CDCA), which are converted to BA-amino acid conjugates in the liver and further transformed by intestinal bacteria to secondary BAs deoxycholic acid (DCA) and lithocholic acid (LCA), respectively.

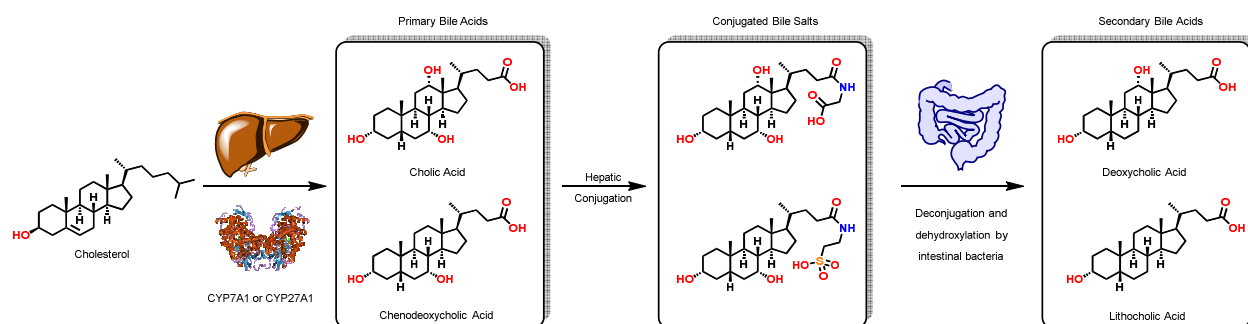


Figure 1.4 Bile Acids and Their Production

Like all steroids, BAs have large, rigid, polycyclic skeletons that result in highly stable curved structures that favor assembly of macrocycles with a cavity. They are facial amphiphiles, with defined hydrophilic concave (alpha,  $\alpha$ ) and hydrophobic convex (beta,  $\beta$ ) faces that promote self-assembly into micelles (*see Figure 1.5*).<sup>12</sup> They are biodegradable, membrane permeable, and decorated with hydroxy groups that serve as sites for functionalizing. The hydroxyl groups are chemically distinct and have increasing reactivity towards oxidation  $3\text{-OH} < 12\text{-OH} < 7\text{-OH}$

and decreasing reactivity to acylation, hydrolysis, and reduction 3-OH > 7-OH > 12-OH.<sup>13</sup> This variety of different diversification sites gives BAs structural diversity not seen in other steroids (*e.g.* cholesterol). Additionally, BAs are readily available and relatively cheap, making them an attractive target for research.

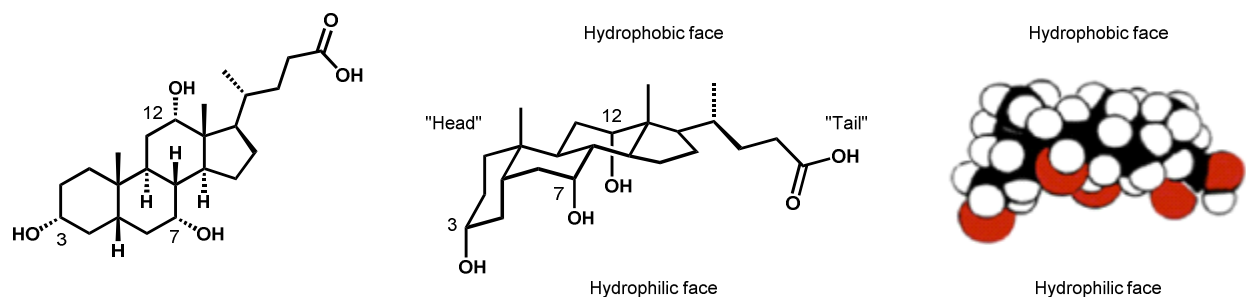


Figure 1.5 Flat, 3D, and Space Filling Drawings of Cholic Acid

BAs have been investigated as delivery systems for anticancer drugs, antimicrobial agents, and therapeutic peptides or proteins. These drug conjugates make use of BAs' tendency to encapsulate molecules in lipophilic shells to protect the drugs from degradation, reduce toxicity of drugs, target the liver as a site of delivery, or increase reabsorption via BA transport systems.<sup>14,15</sup> CDCA conjugates have been utilized to increase the oral bioavailability of peptide drugs and reduce their enzymatic hydrolysis in the GI tract.<sup>16</sup> Platinum-BA conjugates have been utilized as cisplatin analogues to specifically target liver tumors (*see Figure 1.6*).<sup>17</sup> Polymeric BA and insulin conjugates have also been developed as treatments for diabetes mellitus.<sup>18</sup> Polymeric BA gels have been investigated as biocompatible drug delivery systems, enabling controlled release of pharmacologically relevant molecules.<sup>19</sup>

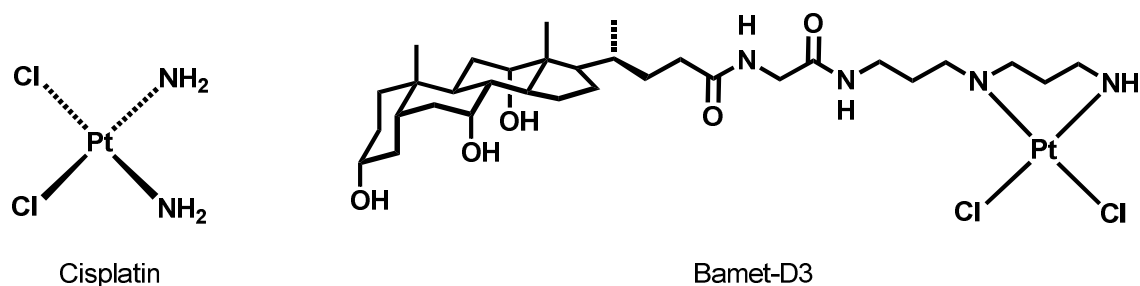


Figure 1.6 Platinum-Bile Acid Conjugate as a Cisplatin Analogue

Supramolecular research on BAs has used them as building blocks in a variety of structures to act as hosts for ions and small molecules, including acyclic functionalized scaffolds and polymeric macrocycles (*see Figure 1.7*). These structures have been constructed by a variety of methods including macrolactonization,<sup>20</sup> macrolactamization,<sup>21</sup> click chemistry,<sup>22</sup> and olefinic metathesis<sup>23</sup> reactions. Acyclic BAs include cholapods, functionalized acyclic scaffolds, and molecular umbrellas, steroids attached to central scaffold. Examples of cyclic polymers are cyclocholates, wherein 2-6 steroids are linked together head-to-tail, and cholaphanes, with 1-4 steroids joined via artificial spacers. Cyclocholates produce macrocycles with inward-facing hydroxyl groups for enclosing polar molecules and an external lipophilic shell. Cholaphanes, however, can incorporate a variety of functional groups in their spacers to tune properties such as cavity size and electronic environment.

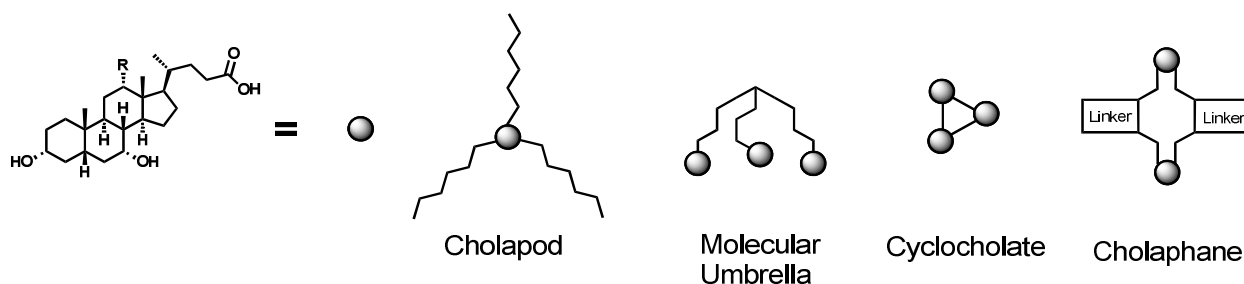


Figure 1.7 Basic Bile Acid Structures Used in Supramolecular Chemistry

Because of the rigid structure that BAs possess, simple functionalization of the hydroxyl groups produces pre-organized architectures capable of interacting with guest molecules (*see Figure 1.8*). These act like molecular tweezers, wrapping around and binding to a guest molecule. Kim<sup>24</sup> produced urea functionalized cholapods of different chain lengths which showed affinity for binding to fluoride anions as molecular tweezers. Davis<sup>25</sup> also introduced ureas for anion binding, although by transforming the hydroxyl groups instead of linking through ester bonds. These cholapods also acted as receptors for chloride and nitrate and demonstrated the capability to transport these anions through lipid membranes due to the lipophilicity of the steroid scaffold.

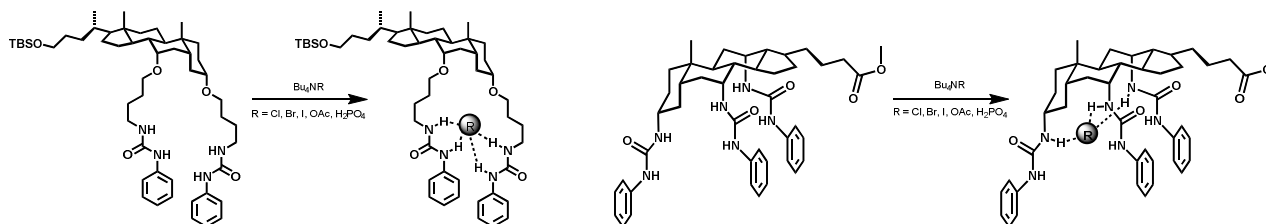


Figure 1.8 Acyclic Cholapods in Supramolecular Chemistry

Davis and co-workers have performed extensive work on the construction of bile acid-based supramolecular structures (see Figure 1.9). Cholaphanes were designed with rigid benzene spacers, producing cavities capable of binding carbohydrates in chloroform.<sup>26</sup> The secondary alcohols could H-bond to the host molecules but were prevented from forming intramolecular bonds due to the rigid spacers. Removal of the aromatic ring in the spacers increased the anion-binding properties of the macrocycles, however the synthesis was quite lengthy. Pandey and co-workers used “click” chemistry to overcome this problem, combining alkyne and triazide functionalities to form triazole linkers in good yields.<sup>27</sup> The macrocycle demonstrated a selective affinity toward chloride ions, with an association constant greater than six times the other halides.

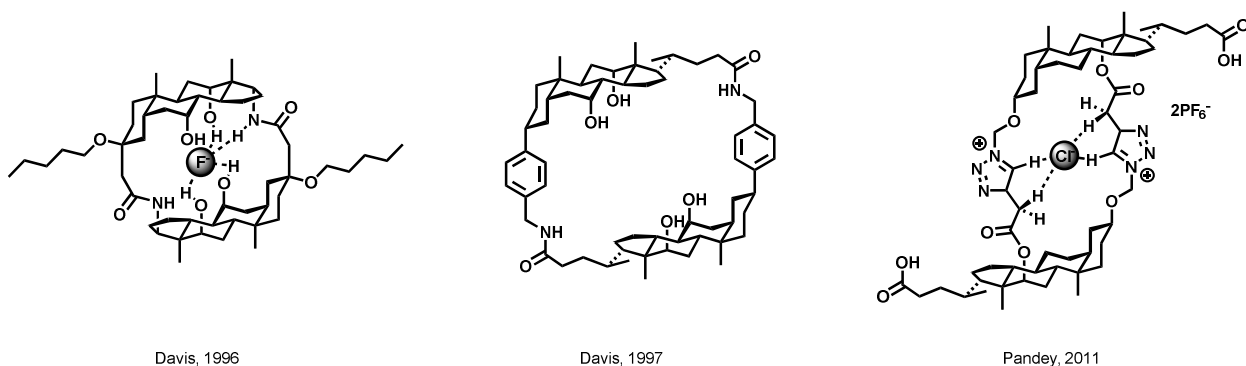


Figure 1.9 Cholaphanes in Supramolecular Chemistry

One of the challenges of macrocycle construction is the selection of appropriate methods for their synthesis, because they will affect the cavity size and properties. In addition, BAs have an additional challenge in functionalizing their multiple alcohols as the steric environment

around these groups affects their reactivity. Esterification is an obvious route, however this is often slow due to steric interference and hard to perform in sequence. The Yamaguchi esterification offers a mild method for coupling carboxylic acids and alcohols that has been successful in functionalizing even the least reactive alcohols on BAs.<sup>28,29</sup> This approach utilizes THF at room temperature and 2,6-dichlorobenzoyl chloride and DMAP as reagents. Reaction of the carboxylic acid and the acid chloride produces the corresponding anhydrides, which, after removal of solvent, are then added to the alcohol refluxing in toluene and DMAP (see Figure 1.10). This enables the addition of a variety of chemical moieties through functionalized carboxylic acids which can then serve as linkers for cyclization.

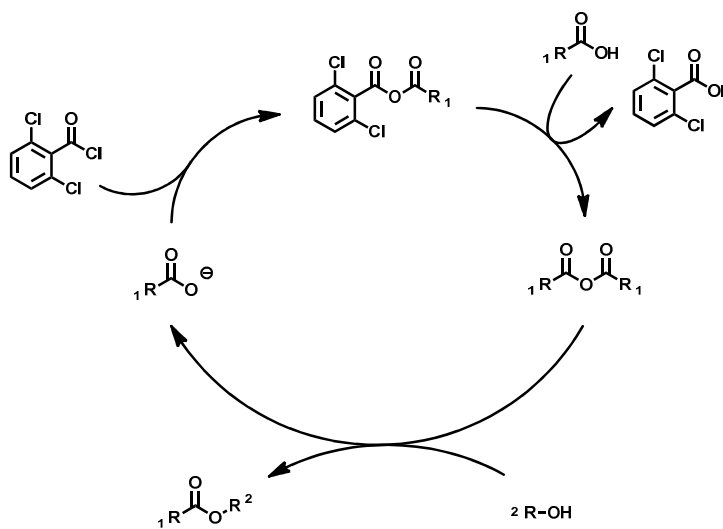


Figure 1.10 Yamaguchi Esterification Mechanism

As previously noted, alkynes and arenes are of particular interest as linkers due to their lack of flexibility. The synthesis of arylene-ethynylene macrocycles has been achieved through the use of the Sonogashira coupling to construct rigid, conjugated macrocycles through  $sp^2$ - $sp$  carbon-carbon bond formation.<sup>29</sup> This useful method for carbon-carbon bond formation can be carried out under mild conditions such as room temperature, aqueous media, and mild bases.<sup>30</sup> The mechanism of the Sonogashira coupling has two catalytic cycles, palladium and copper. In the copper cycles, the alkyne is deprotonated and coupled with the copper catalyst (*see Figure 1.11*). The activated palladium catalyst undergoes oxidative addition to the halide, followed by transmetalation to free the copper co-catalyst and coordinate the alkyne. Isomerization from *cis* to *trans* followed by reductive elimination forms the carbon-carbon bond and regenerates the palladium catalyst.<sup>31</sup> These methods have been utilized to link BAs via 1,4-diethynylbenzyl structures capable of acting as molecular rotors.<sup>32</sup>

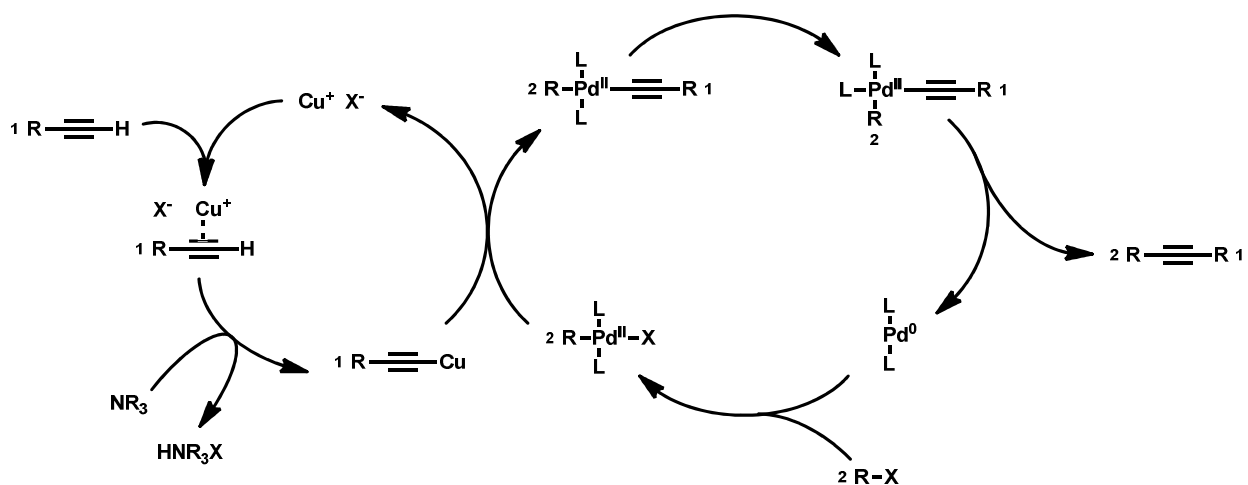


Figure 1.11 Sonogashira Coupling Mechanism



Work in the Dias lab has led to the synthesis of BA based di-, tri-, and tetramers via macrolactonization.<sup>33</sup> Gao synthesized cyclocholates by coupling BA monomers together via the Yamaguchi esterification in good yields. The C-17 side chain influenced the size of the macrocycles, with the 12-acetyl-deoxycholic and 1,12-diacetylcholic acid preferred the cyclotrimer, while 7,12-diacetyl-24-norcholeic acid primarily produced the cyclotetramer. Further work by Xinyan Bai produced 7 $\alpha$ -allyl functionalized CDCA, which was subjected to the Yamaguchi protocol produced cyclodimers, cyclotrimer, and cyclotetramers. These macrocycles demonstrated intramolecular reactivity via olefin metathesis with Grubb's catalyst.<sup>29</sup> The resulting bridged cyclodimers were isolated in a 3:1 *cis:trans* ratio determined by NMR spectroscopy (see Figure 1.12).

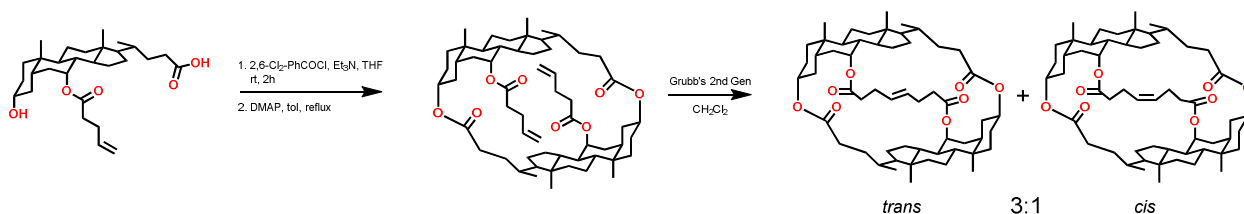


Figure 1.12 Intramolecular Olefin Metathesis of CDCA Dimers

A continuation of this work is focused on the synthesis of functionalized CDCA trimers and linking them via Sonogashira coupling to form new BA derived macrocycles. In addition, this coupling method will be applied to link functionalized steroids to halide-substituted aromatic rings. Finally, new methods will be explored for macrocycle formation including oxa-Michael addition and cyclotrimerization

## 1.2 Research Goals

### 1.2.1 Project Aims

This project was intended to develop new methods for constructing BA macrocycles and to investigate their structures and properties. CDCA and CA were chosen as building blocks for the construction of these macrocycles due to their rigid structures, biological properties, and availability. Functionalization of the BAs followed established routes toward steroidal modifications to install groups with reactive terminal moieties for cyclization. The chain lengths of the linkers were varied to create structures of different cavity sizes. In addition, cross-coupling of macrocycles was attempted to create new barrel-like bis-cyclocholates joined by rigid phenylene-ethynylene linkers. The synthesized macrocycles were analyzed by modern analytical techniques to determine structure their structures

The synthesized macrocycles are expected have a variety of properties making them subjects for supramolecular chemistry and drug delivery. This includes single, well-defined cavities with rigid linkers to reduce conformational freedom. The endogenous nature of the steroidal building block should make the macrocycles non-toxic to cells and capable of passing through lipid membranes due to their lipophilicity. Metabolism of the macrocycles by intestinal bacteria is expected to cleave them into unfunctionalized BAs, releasing any encapsulated guest molecules. The following section will briefly detail the synthetic routes toward the proposed BA macrocycles.

## 1.2.2 Proposed Methods

Selective silylation and sulfonylation of the  $3\alpha$  and  $7\alpha$  positions of CDCA respectively will yield the vinyl sulfonate functionalized monomer. Following desilylation with TBAF, the compound is expected to dimerize via an oxa-Michael reaction (see *Figure 1.13*).

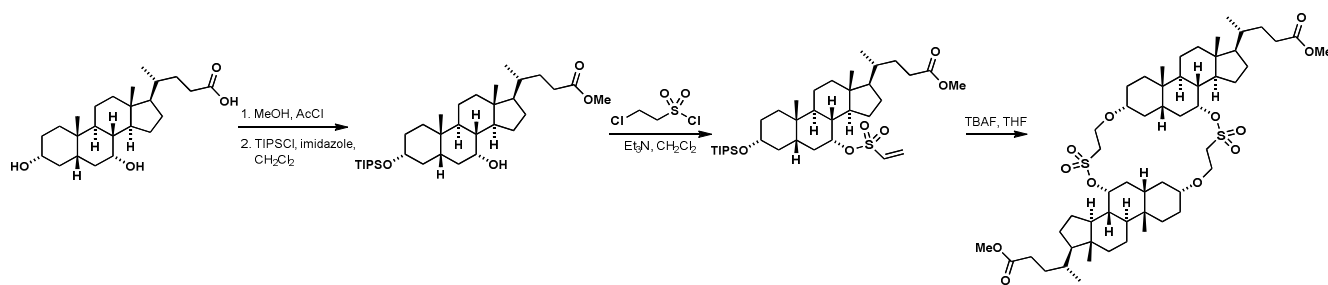


Figure 1.13 Oxa-Michael Route towards CDCA Dimers

Following previous methods, esterification of CDCA followed by selective de-esterification under mildly basic conditions would yield the  $7\alpha$ -monoester. Subjection of the  $7\alpha$ -monoester to Yamaguchi conditions is expected to yield the cyclic trimer (see *Figure 1.14*).

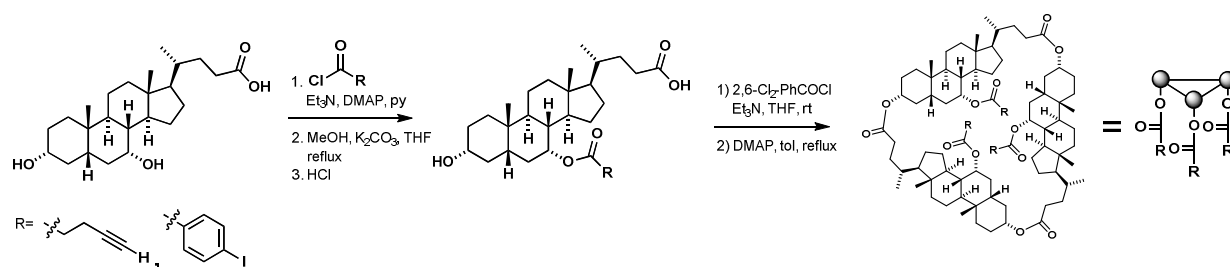


Figure 1.14 Synthesis of Functionalized CDCA Trimers

Coupling of the functionalized trimers would be accomplished via the Sonogashira coupling (*see Figure 1.15*). The resulting CDCA hexamer is expected to be isolated in good yield and, once constructed, will be investigated as a possible host macromolecule in guest-host interactions.

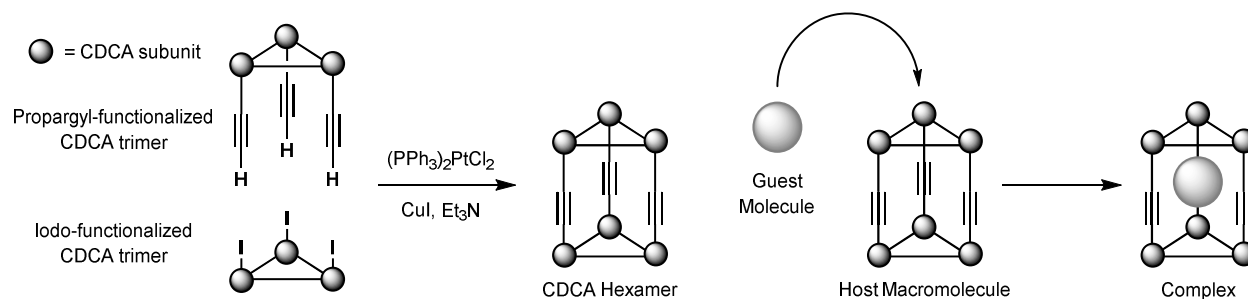


Figure 1.15 Sonogashira Coupling of CDCA Trimers and Guest-Host Interactions

Expansion of the scope of the alkyne-functionalized trimer would explore additional cage-forming reactions (*see Figure 1.16*). Through the Sonogashira reaction, there is the potential to couple the CDCA trimer to trihalobenzenes. In addition, palladium or ruthenium

catalyzed cyclotrimerization<sup>33-34</sup> would form an aromatic ring from the three alkynes. This approach would provide not only cage structures with a different cavity sizes, but also the potential for coordination to the outer face of the ring relative to the cavity.

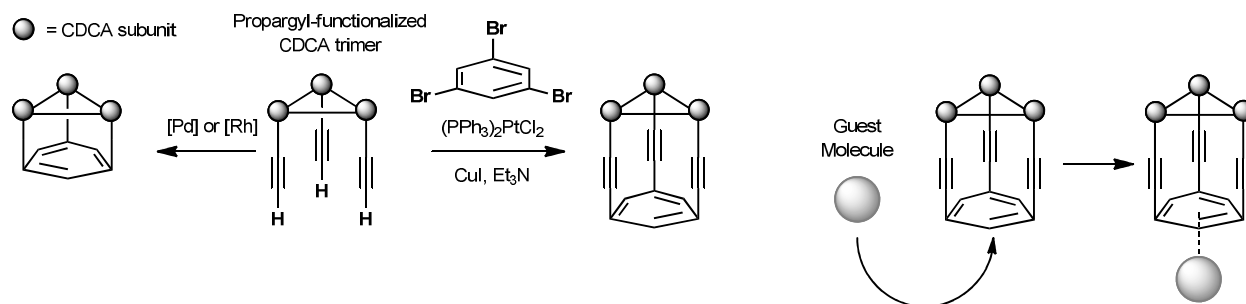


Figure 1.16 Benzene Functionalized Trimers

## CHAPTER 2

### 2. LITERATURE REVIEW

#### 2.1 Introduction

The tetracyclic steroid structure is one of the largest rigid, chiral, naturally occurring structures in nature and has a variety of derivatives including sterols, cholestenes, and cholanes or bile acids (BAs). Their large, curved structures are facial amphiphilic, with defined hydrophilic concave (alpha,  $\alpha$ ) and hydrophobic convex (beta,  $\beta$ ) faces (*see Figure 2.1*). This bifacial topography promotes self-assembly of BA molecules into micelles.<sup>12</sup> In addition to the structural rigidity of the steroid skeleton, BAs possess multiple points of diversification in the form of hydroxyl groups and a carboxylic tail. The carboxylic acid and hydroxyl groups of BAs have been transformed through a variety of reactions including esterification, etherification, amidation, oxidation, or reduction. The hydroxyl groups are chemically distinct. They have increasing reactivity towards oxidation  $3\text{-OH} < 12\text{-OH} < 7\text{-OH}$  and decreasing reactivity to acylation, hydrolysis, and reduction  $3\text{-OH} > 7\text{-OH} > 12\text{-OH}$ .<sup>13</sup> BAs are endogenous to many living organisms, biodegradable, membrane permeable, and they can selectively target specific organs due to naturally occurring transport systems. In addition, these compounds are affordable and readily available, which makes BAs and their derivatives desirable targets for research and other applications.

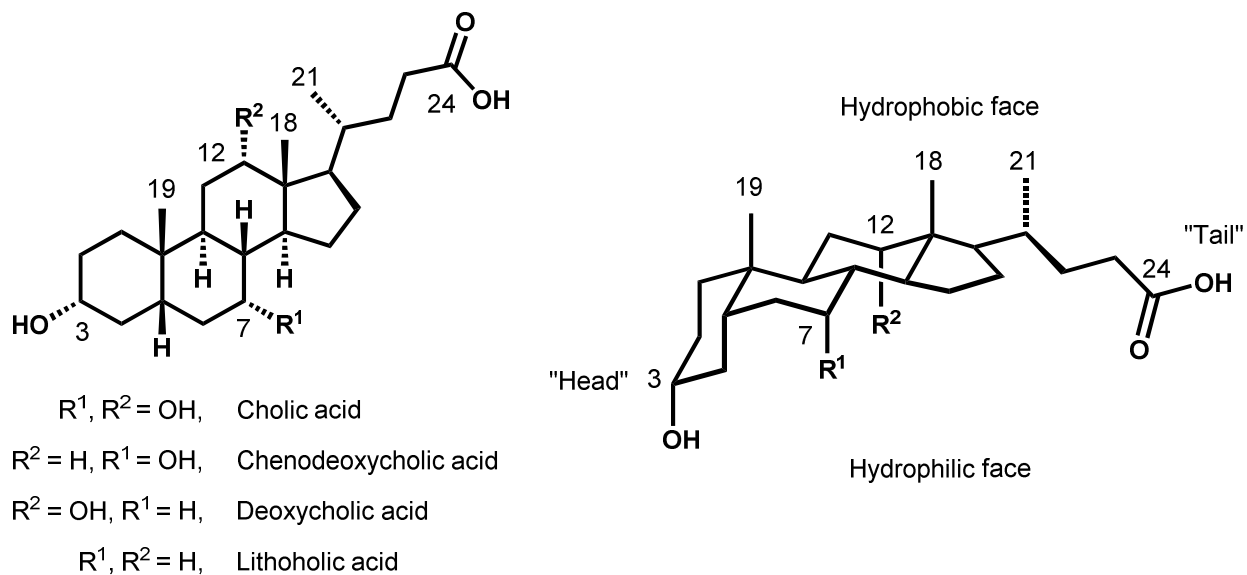


Figure 2.1 Bile Acid Structure, Names, and Numbering

These diversification methods have been used to construct numerous pharmacologically relevant structures, which act as chemical sensors, prodrugs, or molecular transport systems. BAs have been applied as molecular shuttles to carry drugs through cellular membranes via both active and passive transport processes. Drug-BA conjugates are the most common example of this, where the undesirable traits of the drug are masked by the BA's properties.<sup>15</sup> However, the versatility of BAs in research extends beyond single molecule conjugates to synthesizing novel complex structures including foldamers, dendrimers, oligomers, macrocycles, molecular baskets, and molecular tweezers. Continued research into new methods of functionalizing BAs and the construction of BA-based structures is of interest to access pharmacologically relevant structures or interesting molecular architectures.

## 2.2 The Physiological Functions of Bile Acids

Bile acids (BA) are a type of steroid endogenous to a variety of animals, including humans, which are an increasing focus of study as architectural components in supramolecular chemistry.<sup>34</sup> These steroidal molecules are synthesized in the liver and act as surfactants to solubilize fats and vitamins for absorption in the colon. The primary BAs are cholic acid (CA) and chenodeoxycholic acid (CDCA), which are converted to BA-amino acid conjugates in the liver and further transformed by intestinal bacteria to secondary BAs deoxycholic acid (DCA) and lithocolic acid (LCA), respectively.

In mammalian digestion, BAs act as surfactants to solubilize fats and vitamins for absorption in the colon. This process occurs through conjugation with amino acids like taurine or glycine to form water-soluble salts, followed by the formation of micelles around lipophilic molecules.<sup>35</sup> The micelles then deliver the encapsulated molecule to the epithelial cells lining the small intestine for absorption and processing (*see Figure 2.2*). Finally, BA micelles are deaminated and dehydroxylated by intestinal bacteria. They are transported through the luminal membrane via active transport systems (apical sodium-dependent BA transporters (ABST), ileal BA binding protein (I-BABP), organic solute transporter (Osta/b)) where they are eventually returned to the liver for digestion or re-excretion.<sup>11</sup> Around 2.5-5 g of BAs exist in the humans undergoing 6-15 cycles of hepatic circulation per day with less than 0.5 g lost via excretion, representing a very high capacity and efficient transport system.<sup>36</sup>



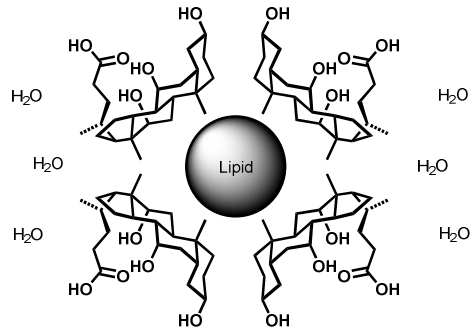


Figure 2.2 Bile Acid Micelle Formation

In addition, BAs act as hormone ligands for the Farnesoid X receptor (FXR) and G protein-coupled BA receptor 1 (GPBAR1).<sup>37</sup> FXR is expressed in the liver and small intestine and is involved with BA homeostasis. It suppresses the activity of CYP7A1, the enzyme responsible for the production of BAs, therefore acting as a negative feedback loop for BA synthesis. GPBAR1 play a variety of roles, both inter- and extra-cellular, including production of intracellular cAMP, suppression of macrophage functions, regulation of energy homeostasis by BAs, and activation enzymes which convert thyroxine ( $T_4$ ) to the active hormone triiodothyronine ( $T_3$ ). This last function affects almost every physiological process in the body, including growth and development, regulating metabolism, body temperature, and heart rate. It has been demonstrated artificial BA derivatives are recognized and transported by the same systems as the endogenous BAs. These conjugates often show increased bioavailability, decreased sensitivity to enzymatic degradation, and prolonged biological activity.

### 2.3 Methods for Diversification

### 2.3.1 Esterification

Nath sought to develop a fluorescent sensor using CDCA as a spacer for holding a receptor and fluorophore moiety in close proximity for photo-induced electron transfer.<sup>38</sup> To accomplish this, benzyl-protected CDCA was coupled to carboxylic acid functionalized pyrene via DCC coupling. Esterification with chloroacetyl chloride gave the chloroacetyl structure, which was then dimerized with 1,10-diaza-18-crown-6 to give a sensor with two fluorophores attached to a single sensor (see Figure 2.3).

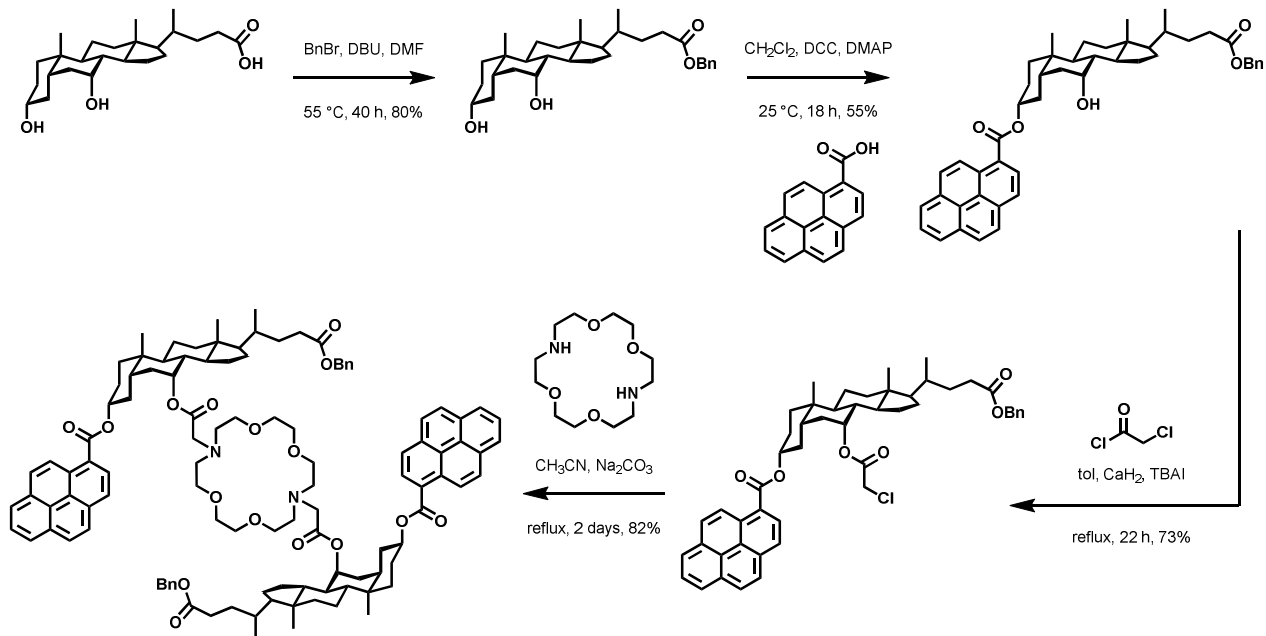


Figure 2.3 Dipyrene CDCA Dimer as a Fluorescent Sensor

Further investigation led to the development of tetrafluorophore dimers. Selective oxidation of the 7-OH followed by methylation of the acid allowed for the double esterification of remaining hydroxyl groups. Reduction, esterification, and then coupling to 1,10-diaza-18-crown-6 gave the tetrapyrene species (*see Figure 2.4*).

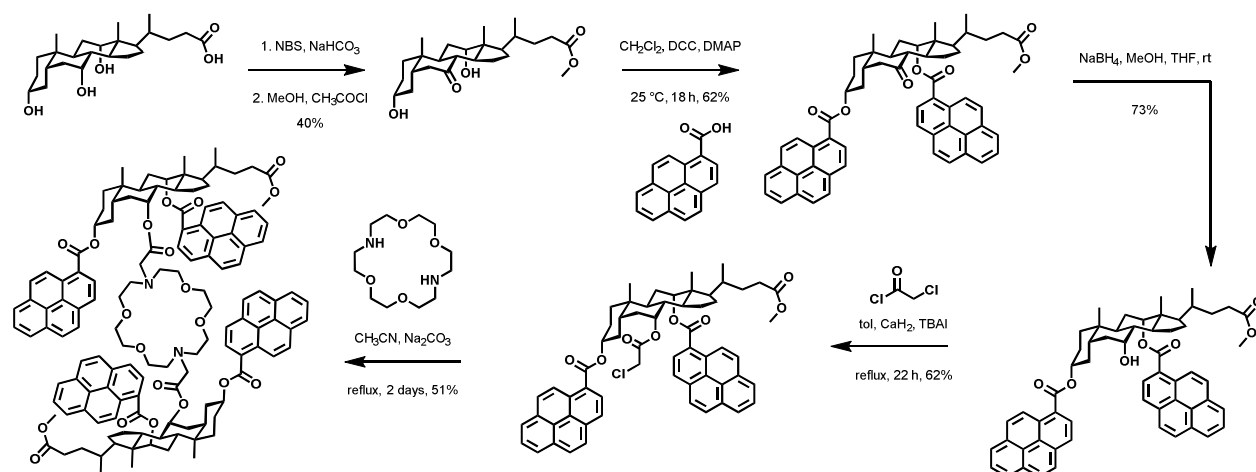


Figure 2.4 Tetrapyrene CDCA Dimer

Fluorescence titrations were carried out with in MeOH in the presence of  $\text{KClO}_4$ ,  $\text{NaClO}_4$ , and  $\text{Ba}(\text{ClO}_4)_2$ . The cation binding constants for the sensors were similar and followed the trend  $\text{Ba}^{2+} > \text{K}^+ > \text{Na}^+$ . Detection sensitivity varied as a function of the geometry of the molecule, with the dimeric sensors showing increased sensitivity for  $\text{Ba}^{2+}$ , while monomeric sensors favored  $\text{K}^+$ .

Lukashev proposed a bis-acylation of chenodeoxy, lithocholic, and cholic acids, exploiting the greater reactivity of the  $3\alpha$  position to acylation as a strategy for selectively

dimerizing the BAs with Linker A.<sup>39</sup> The resulting dimers were formed without significant side products even in the presence of the unprotected alcohols (*see Figure 2.5*). Cyclization was achieved by deprotecting under hydrogenation conditions, conversion to the pentafluorophenyl esters, and then amide formation with varying diamines in good yields compared to literature values (35%-50%). A second ester-bridged macrocycle was synthesized from the triflate-protected alcohol through similar procedures, although with noticeably lower cyclization yields (11%-19%).

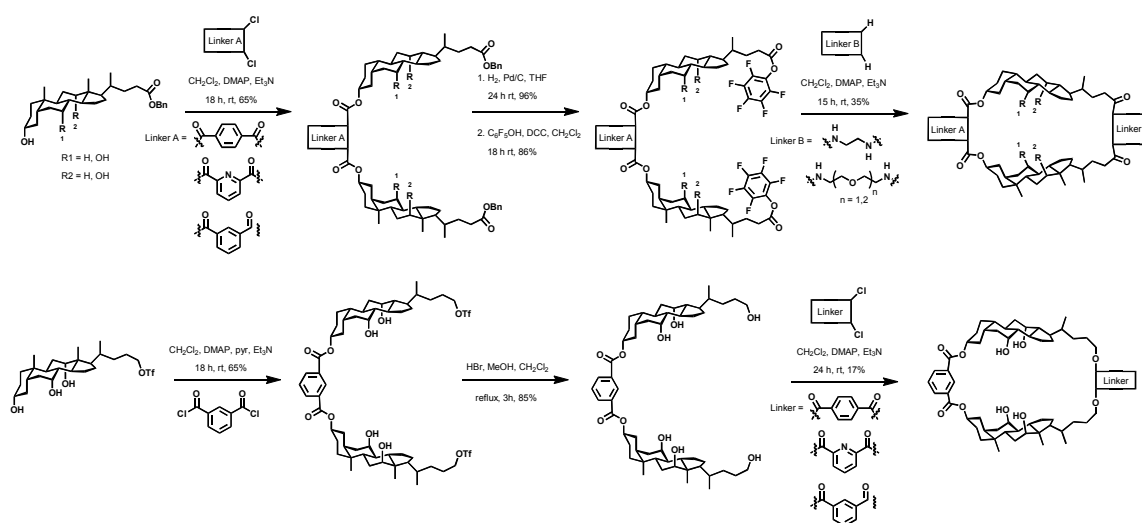


Figure 2.5 BA Macrocycles Joined by Linkers

Dias has demonstrated the Yamaguchi esterification as a good method for not only functionalizing the hydroxyl groups on BAs, but also for enabling cyclization into functionalized macrocycles.<sup>29</sup> Yamaguchi esterification of the protected CDCA followed by selective removal of the 3 $\alpha$ -ethoxycarbonyloxy and 24-ester methyl groups gave the 7 $\alpha$ -substituted monomer (*see*

Figure 2.6). Yamaguchi esterification conditions cyclized the monomer into functionalized dimers, which could then undergo intramolecular olefin cross coupling to give the *cis* and *trans* products in a 3:1 ratio.

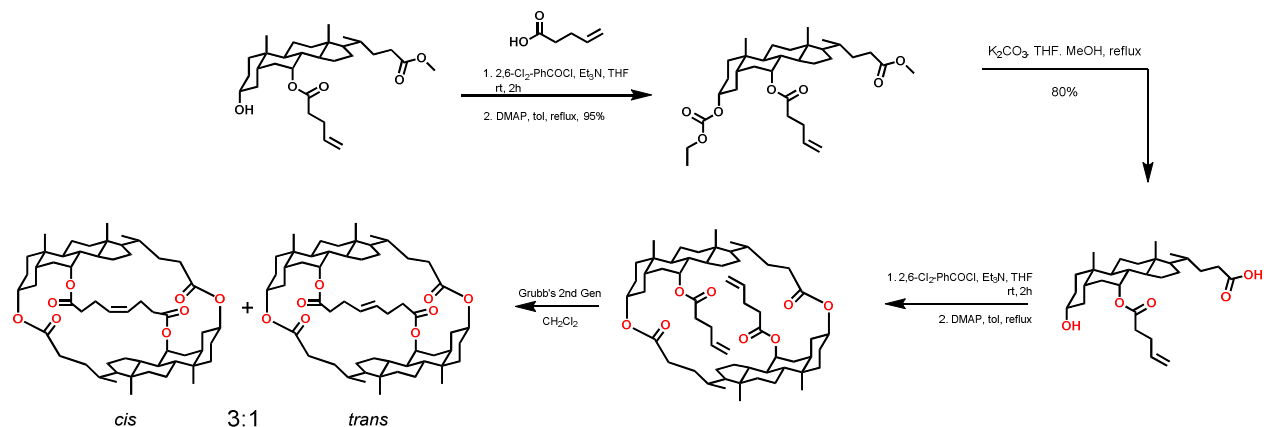


Figure 2.6 Yamaguchi Esterification and Intramolecular Cross Coupling

### 2.3.2 Amidation

Pandey and co-workers have demonstrated coordination of *N*(10)-hexylflavin derivatives to bile acids functionalized with diaminopyridine (DAP) receptors (see Figure 2.7).<sup>40</sup> These receptors have demonstrated previous flavin-coordinating behaviors in functionalized porphyrin systems through hydrogen bonding and  $\pi$ -stacking interactions. The bile acid-based receptors were synthesized by protection with formic acid followed by reaction with ethyl chloroformate and condensation of the resulting anhydride with 2,6-diaminopyridine. The functionalized bile acids were prepared by treatment with aromatic acid chlorides under basic conditions followed by basic hydrolysis to remove the protecting groups. Formation of one to one complexes of the

Flavin analogue to the functionalized bile acids was observed via NMR shift of the amidic protons. The highest binding constant of  $3500 \text{ M}^{-1}$  was observed in the benzyl substituted 2,6-diaminopyridine unit, while the anthracene derivative showed no complexation due to steric interactions with the larger substituent.

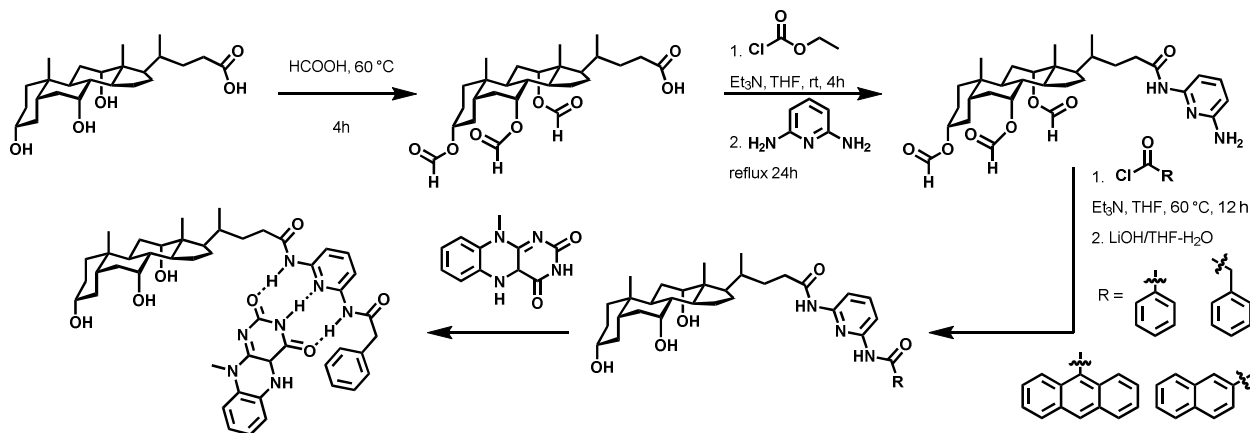


Figure 2.7 Flavin-Coordination of DAP functionalized BA

Zhu reported a cholic acid dimer linked via a secondary amine tether group produced hydrogels with selected carboxylic acids by the protonation and hydrogen bonding of its secondary amine and amide groups.<sup>41</sup> The dimer was produced by linking the acid sidechains of cholic acid with a triamine spacer, followed by addition of an organic acid (*see Figure 2.8*). The dimers self-assemble in aqueous solutions to form nanofibers at  $60 \mu\text{M}$ , which interact at concentrations greater than  $8 \text{ mM}$  to gelate the aqueous solution into a hydrogel. The randomly directed, fibrous network aligns upon stirring to form a liquid crystal-like arrangement, although with weaker mechanical strength, and therefore reduced elasticity, compared to the random network.<sup>42</sup>

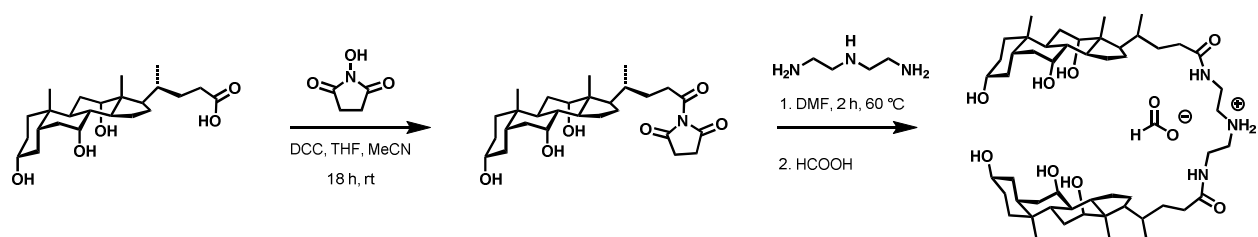


Figure 2.8 Amide Linked Dimers

Davis has reported the transformation of cholic acid into cyclocholamides with inward facing ammonium groups capable of transporting anions across lipid membranes.<sup>43</sup> Cholic acid was converted into the azide via previously reported methods.<sup>44</sup> It was predicted that bulky substituents could control the size of the resulting cavities, so selective N-protection was performed with bulky Cbz at positions 7 and 12 to prevent cyclodimerization, followed by Boc at position 3 (*see Figure 2.9*). The ester was then hydrolyzed, and coupled to pentafluorophenol using *N,N'*-diisopropylcarbodiimide to give the activated ester. Cyclization was achieved by first removing the Boc group with TFA, followed by the slow addition of DMAP in THF under high dilution conditions (0.8 mM). The resulting products were a mixture of cyclotrimer, cyclotetramer, and cyclopentamer in 34%, 16% and 2% yields respectively, which was separated by HPLC. The removal of the Cbz groups (HBr–AcOH) yielded the cyclocholamides with ammonium functionalities in quantitative yields. While the cyclotetramer would be much more flexible in structure, it was calculated that the cyclotrimer would have a rigid structure with inward facing ammonium groups. Self-assembly into distinct morphologies was seen in the different cyclocholamides, with the cyclotrimer forming cones and the cyclotetramer forming spheres in a MeOH–H<sub>2</sub>O (2:1) mixture. The cyclotrimer was shown to promote chloride transport

from egg yolk phosphatidylcholine (EYPC) micelles into external solution, as monitored by a chloride sensitive electrode.

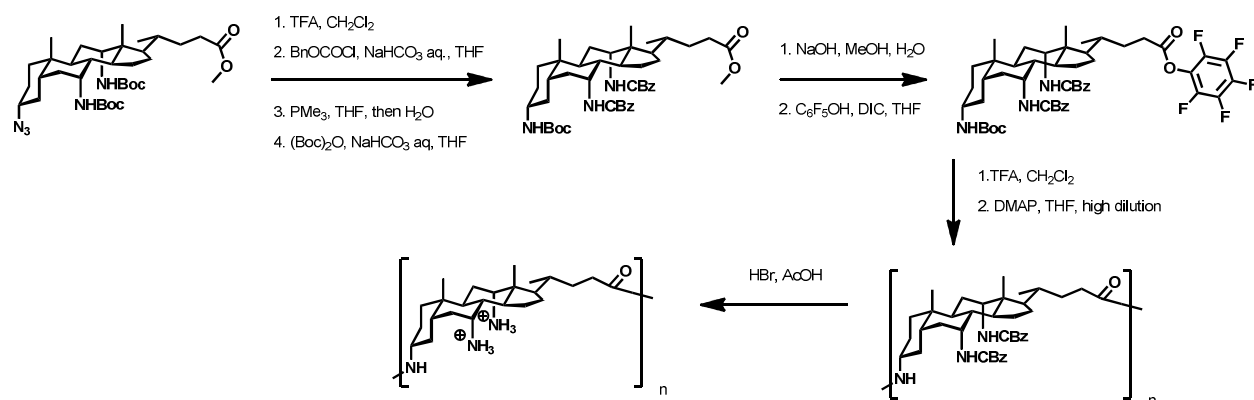


Figure 2.9 Ammonium Functionalized Cyclocholamides

Zhao had previously prepared tricholate macrocycles with inward facing hydroxy group capable of binding to carbohydrates.<sup>45</sup> The linear tricholate was hydrolyzed and coupled the propargyl-functionalized cysteine (*see Figure 2.10*). Macrolactonization under basic conditions afforded the cyclochololate, which was then coupled with terephthalic acid dimethyl ester through a click reaction. Hydrolysis with LiOH afforded the respective acid. The 1,4-substituted dicarboxylic acid functionalized macrocycles displayed significantly higher transport activity for glucose across POPC/POPG lipid membranes than the corresponding methyl ester, 1,3-substituted dicarboxylic acid, or linear tricholate. Based on the rate of glucose transport, it is believed that the macrocycles permeate the lipid bilayer by stacking into a nanopore assembly rather than acting as a simple molecular transport.



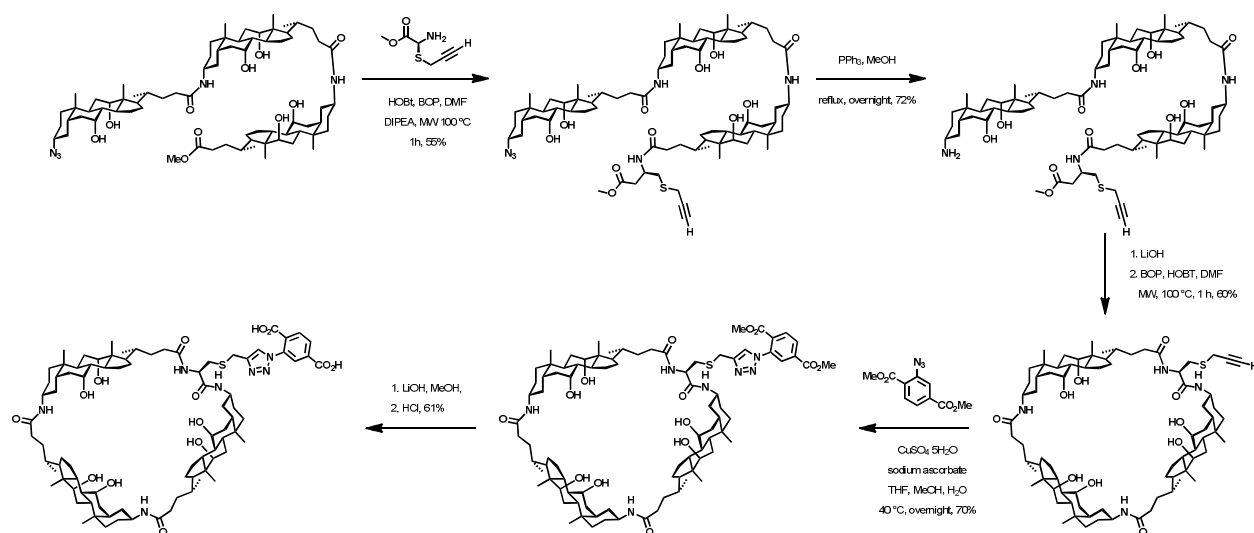


Figure 2.10 Glucose Sensing Tricyclocholates

Further work by Lukashov sought to develop pincer-like BA dimers with the 3 $\alpha$ -hydroxyl group intact.<sup>46</sup> For this purpose, the 3-oxo-lithocholic esters were converted to the 3-aminomethyl-3-trimethylsiloxy groups through the addition of trimethylsilyl cyanide and subsequent reduction of the cyano group (*see Figure 2.11*). The amines reacted with isophthaloyl chloride to form the dimeric pincher structures. Exposure of the dimers to silica in with a high concentration of

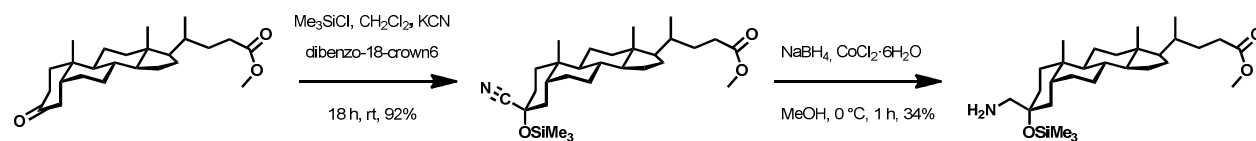


Figure 2.11 Silyoxylithocholate Ester

methanol deprotected the hydroxyl groups to yield the proposed 3 $\alpha$ -hydroxy dimer (see Figure 2.13).

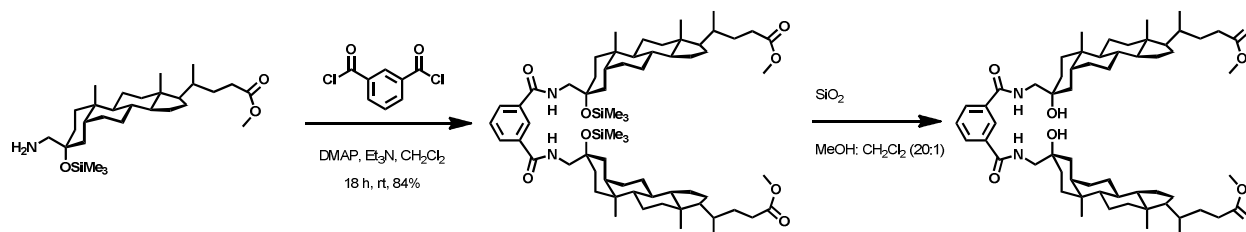


Figure 2.12 Pincher-Like BA Dimers

Li demonstrated the use of an azo bridged spacer to create BA dimers which exhibited conformational-based antibacterial activity.<sup>47</sup> Attempts at DCC coupling gave a mixture of products. Therefore, cholic acid was instead protected by formylation, converted to the acid chloride, coupled to the diazo spacer via amidation, and deprotected with LiOH to yield the dimer in 80% overall yield (see Figure 2.13). The azobenzene spacer was converted to the *cis* form via irradiation and could adopt one of two tweezer-like conformations with the hydroxyl groups facing either outwards or inwards. Antibacterial activity of the dimer against *E. coli* and *B. megaterium* increased upon conversion to the tweezer-like form, suggesting formation of hydrophilic channels, allowing for mass transport across the phospholipid membrane of the bacteria.

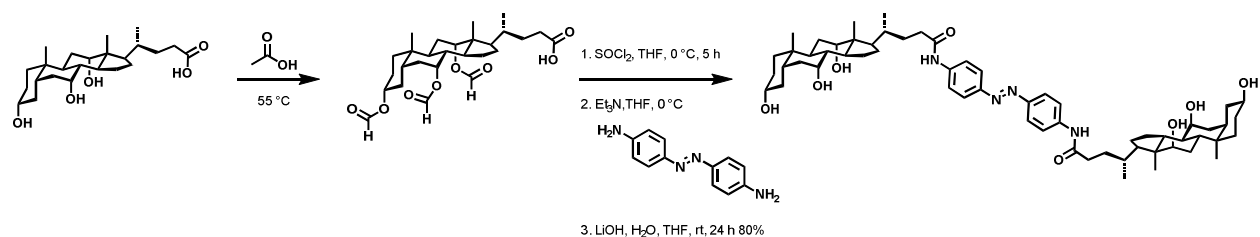


Figure 2.13 Cholate Dimers with Azobenzene Linkers

### 2.3.3 Carbonylation

Pospieszny investigated new methods for forming BA steroids. Chloroformates were known to react with a variety of nucleophiles, so attempts were made to convert the hydroxy groups of BA to a chloroformate with triphosgene in DCM with a catalytic amount of pyridine.<sup>48</sup> The resulting chloroformate reacted with a variety of dinucleophiles to give steroidal dimers with carbonate, nothiocarbonate, or urethane spacers (*see Figure 2.14*).

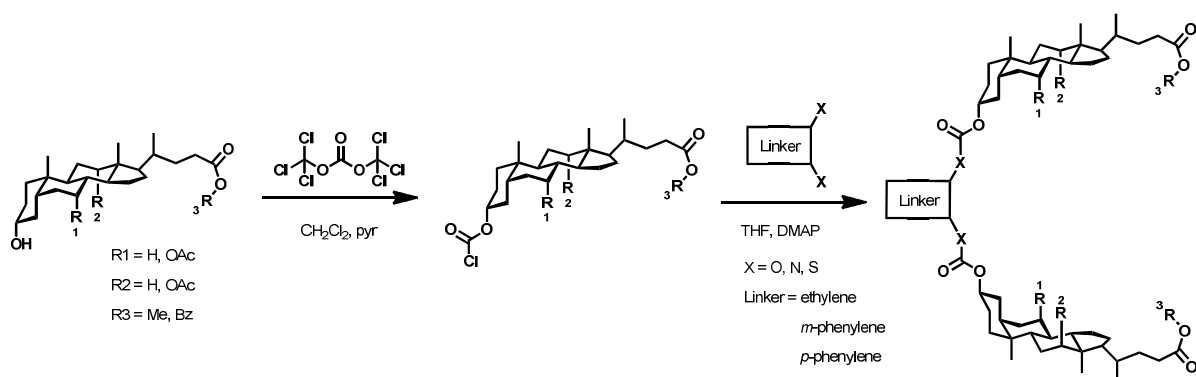


Figure 2.14 Cholate Dimers with Carbonyl Linkers

Semiempirical calculations (PM3, CAChe Fujitsu) on dimers showed a preference for the *syn* conformation with the benzyl ester having the highest preference, which was mostly attributed to  $\pi$ - $\pi$  stacking of the benzyl substituents. The dimers were investigated as components for constructing macrocycles by deprotection with KOH. They converted the free acid to anhydrides with ethyl chloroformate, and reacting with 1, 4-diaminobenzene to for the macrocyclic tetramer in a 19% yield (see Figure 2.15).

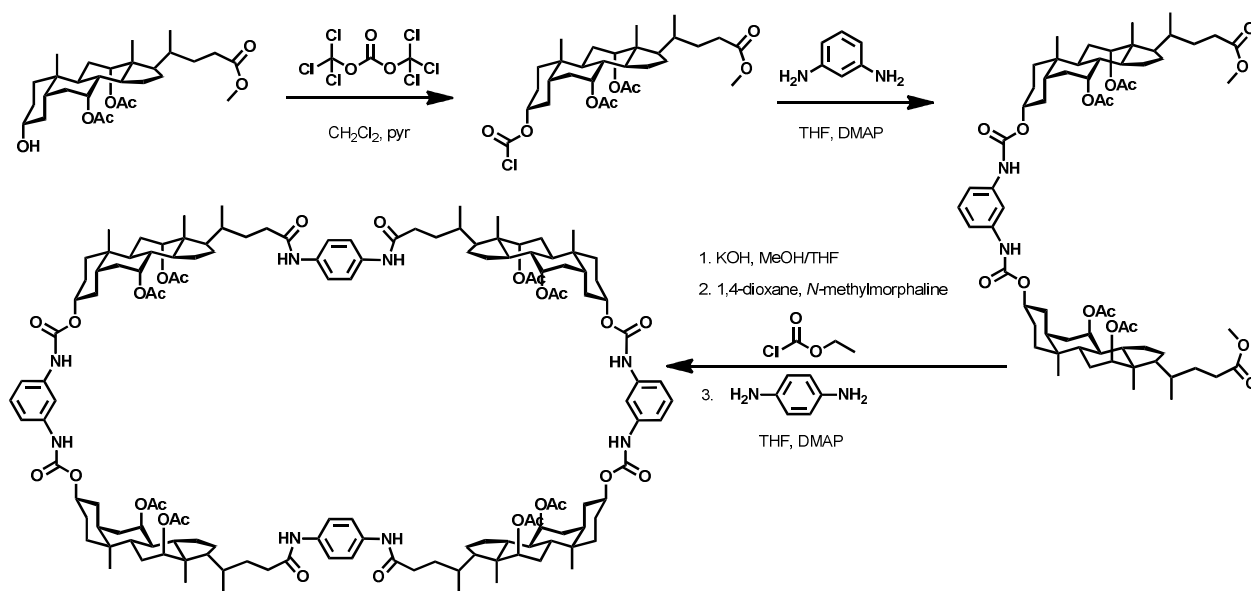


Figure 2.15 Urethane-linked Cyclotetramers

Wang sought to explore anion recognition with cholapods containing urea and hydrazine functionalities.<sup>49</sup> In order to increase reaction efficacy, microwave heating at 250 W was employed, which reduced reaction time by a factor of ten and a increase yield into the 90%

range. Reaction with triphosgene in DCM with pyridine produced the acid chloride in the 3 position, which was then coupled with 4-nitrobenzoylhydrazine (see Figure 2.16). Another triphosgene reaction, followed by coupling to a variety of amino alcohols produced the functionalized cholapods in good yields. Binding studies showed an affinity for acetate anions ( $K_a \approx 1.0 \times 10^4 \text{ M}^{-1}$ ) with a selectivity trend from  $\text{AcO}^- > \text{H}_2\text{PO}_4^- > \text{NO}_3^- > \text{I}^- > \text{Br}^- > \text{Cl}^-$ .

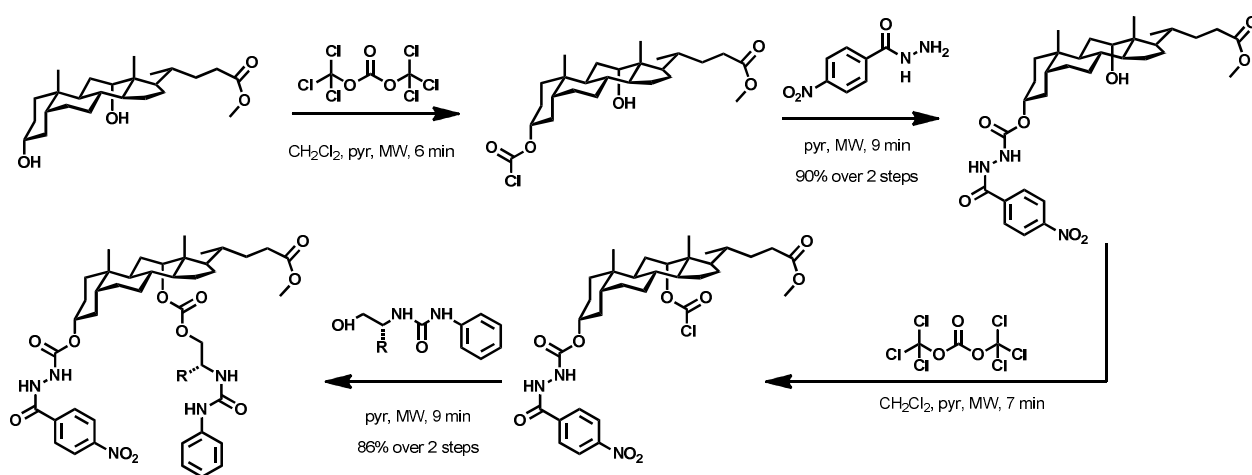


Figure 2.16 Anion-recognizing Cholapods

### 2.3.4 Etherification

Zhang described cage-like cholapods with tunable amphiphilicity.<sup>50</sup> The cage compounds are built by extending the three hydroxy groups underneath the steroid rings with ethyl bromide linkers, which were then capped with cyanuric acid in the presence of DBU and DBF (see Figure 2.17). The cage structures were highly rigid due to the short length of the linkers, as determined by X-ray crystallography.

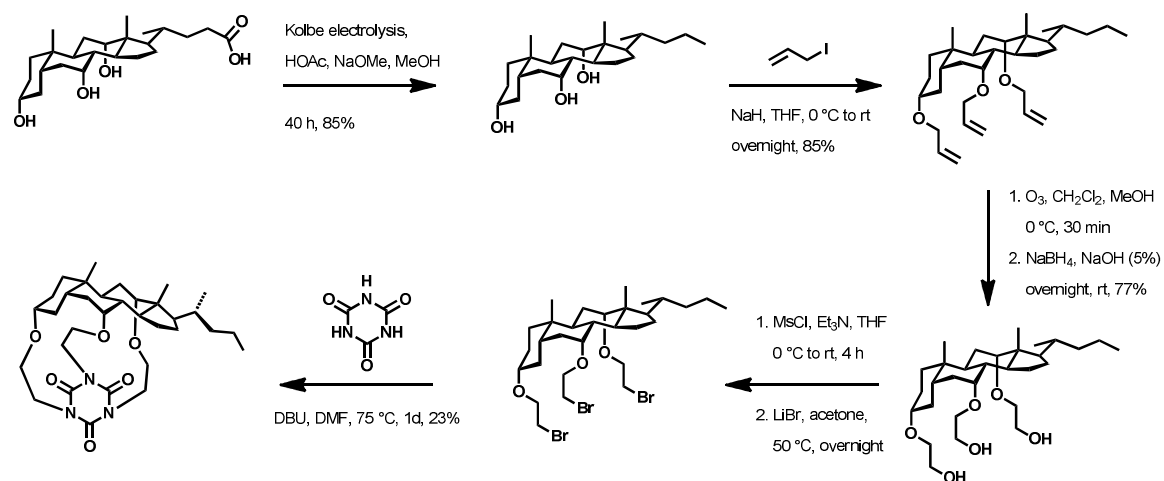


Figure 2.17 Cage-like Cholapods

The authors were interested in investigating the flexibility of the cage through further extension of the linkers.<sup>51</sup> Extension of the linkers was accomplished by treatment with tosyl chloride and coupling with oligo(ethylene glycol) chains (*see Figure 2.18*). Mesylation followed by reaction with LiBr yielded the analogous bromine-terminated chains which were then reacted with cyanuric acid under the previous conditions to give cages of varying size and flexibility. Anion recognition was accomplished through titration of  $KPF_6$  to a solution of the cage compounds in acetone- $d_6$ . Chemical shifts indicated binding into the  $n = 2$  and  $n = 3$  extended compounds, but not in the original rigid cage structure.

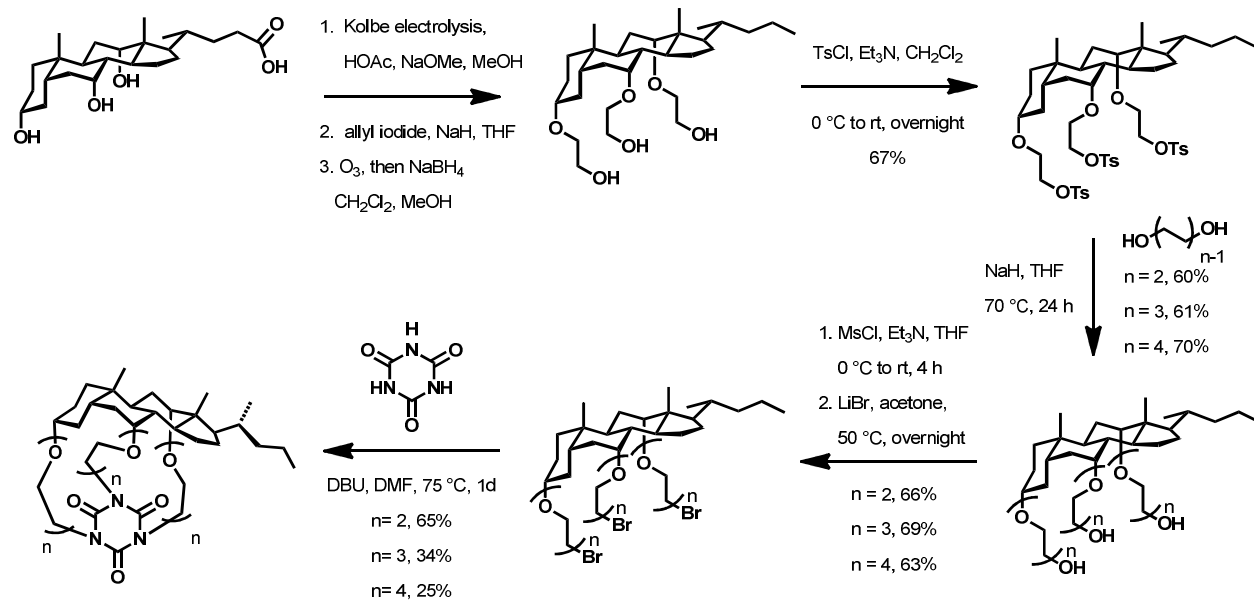


Figure 2.18 Increasing Chain Length

### 2.3.5 Click Reaction

Copper-catalyzed alkyne-azide 1, 3-dipolar cycloaddition (CuAAC), popularly known as the “click” reaction, is a facile, high-yielding reaction method for linking a terminal alkyne and an azide via the formation of a 1,4-disubstituted 1,2,3-triazole unit. Independently introduced by Sharpless and Meldal groups in 2002, the reaction has high chemoselectivity, is tolerant of a variety of reaction conditions, and is highly atom-economic with little or no byproducts.<sup>52-53</sup> It has seen application in coupling together building blocks to synthesize not only small molecules, but also complex molecular architectures such as clusters, dendrimers, polymers, peptides, and macrocycles.<sup>54</sup> The triazole ring is chemically inert and tolerant to a variety of chemical transformations including oxidation, reduction, and hydrolysis. It often also plays a key role in

the properties of these structures by locking parts of the molecule into position, affecting the polarity of the overall structure, or interacting with other smaller molecules.

Nejad-Ebrahimi used the click reaction to couple menthol to BAs in order to evaluate the antimicrobial effect of the BAs and triazole linkers on the parent molecule.<sup>55</sup> Mesylation of menthol followed by reaction with sodium azide in DMF afforded the azide in good yields (see Figure 2.19). The BA starting materials were esterified with propargyl bromide in the presence potassium carbonate. The click reaction proceeded in less than an hour under standard conditions, giving the menthol-tagged BA in excellent yields. An investigation of the *in vitro* antibacterial activity against *Enterococcus faecium* showed minimum inhibitory concentrations of the BA conjugates (< 10  $\mu\text{M}$ ) to be lower than menthol (410  $\mu\text{M}$ ), the unconjugated BAs (10, 20, 157, 410  $\mu\text{M}$ ), and the antibiotic cefixime (35, 410  $\mu\text{M}$ ). A comparison of these conjugates to Lipinski's rules suggests there should be no issues with oral bioavailability.

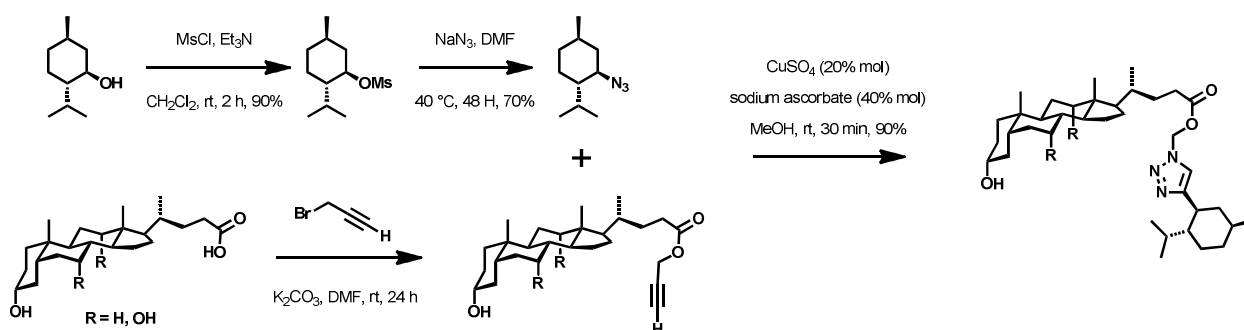


Figure 2.19 Functionalizing BA via Click Reaction



Protection of the hydroxyl groups with acyl chloride followed by reduction of the carboxylic acid led to the protected alcohol, which was then functionalized either by  $S_N2$  addition of the azide, or Mitsunobu conditions to install the propargyl ester (see Figure 2.20). Click reaction conditions afforded the dimer in good yields. Computational studies (PM3, CaChe Fujitsu) determined that the *syn* conformer with both steroid hydrophilic faces facing each other, was the most energetically stable orientation for the dimer.<sup>56</sup>

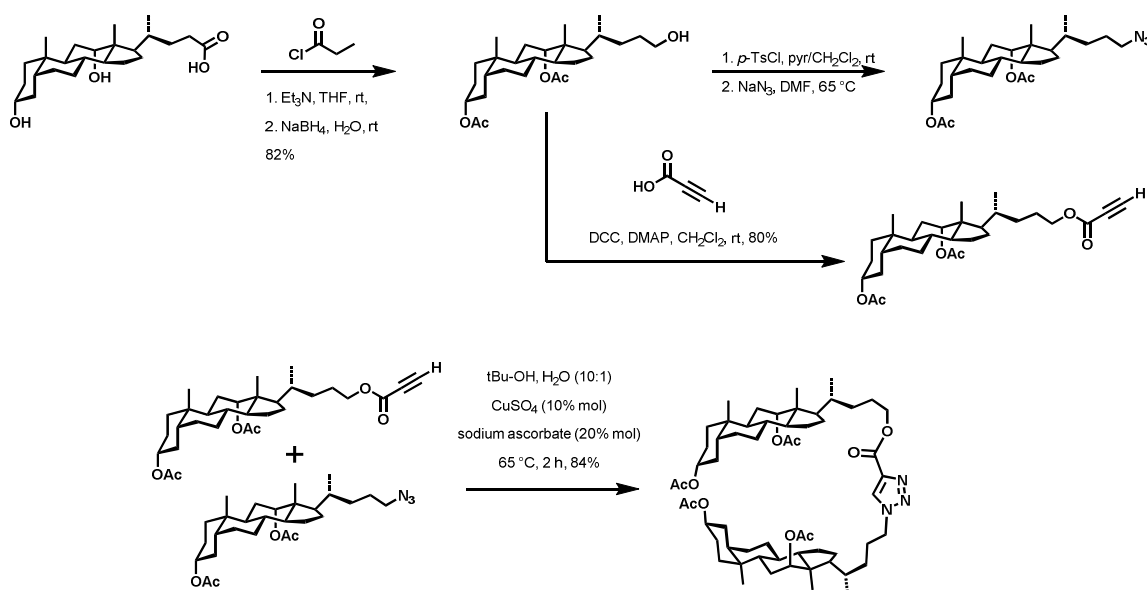


Figure 2.20 Dimerization via Click Reaction

Rajakumar made use of steroids as building blocks for construction of “molecular pocket” type dendrimers which showed anticancer activity.<sup>57</sup> Construction of the dendrimer core began with the reaction of 1,3,5-tris (azidomethyl) arene with 3.1 equivalents of 1,3-bis (chloromethyl)- 5-(propargyloxy)-benzene under click reaction conditions (see Figure 2.21).

These first generation chlorodendrimers were further treated with NaN<sub>3</sub> to give the corresponding azidodendrimers, which could undergo a second click reaction and azide substitution to yield second generation azidodendrimers. Cholic acid or deoxycholic acid were functionalized by reacting with *para*-toluenesulfonic acid and propargyl bromide, then acylated to afford the protected terminal alkyne steroidal derivatives.

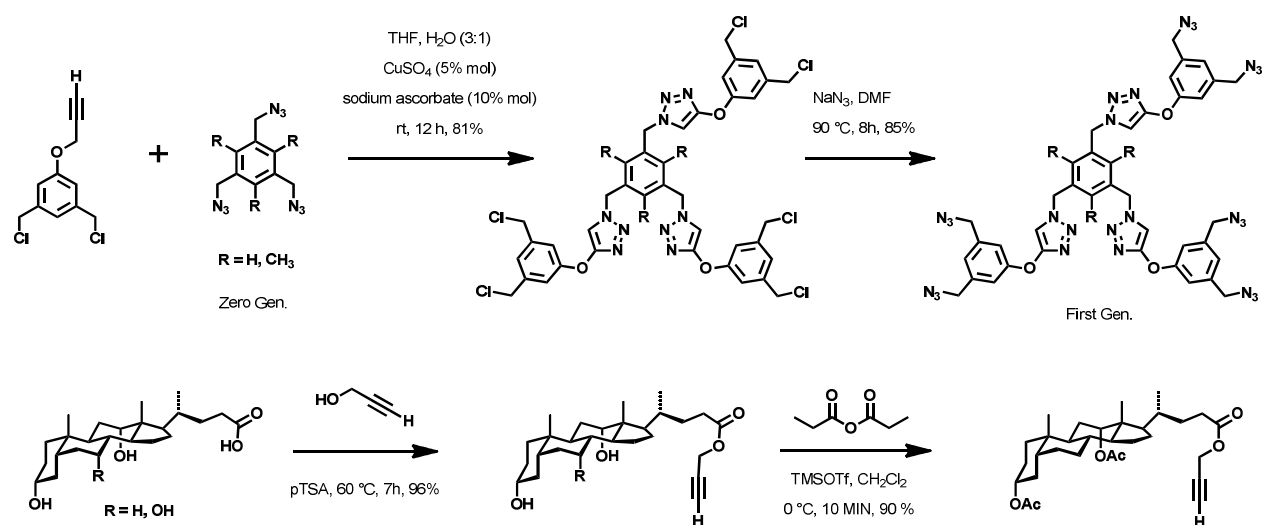


Figure 2.21 Designing Building Blocks for Click Reaction

Construction of steroid functionalized zero, first, and second generation dendrimers proceeded via click conditions, with yields decreasing with increasing generations (*see Figure 2.22*).

Analysis of the anticancer activity of the dendrimers on C6 glioma cell lines by MTT assay showed greatest cytotoxicity for the second generation dendrimers (IC<sub>50</sub> value of 10.48 μM)

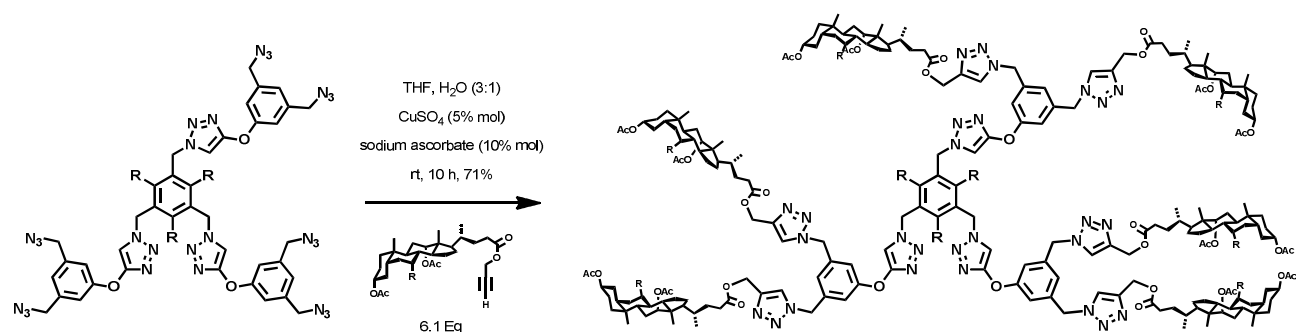


Figure 2.22 BA Functionalized Dendrimers

Pandey reported the synthesis of a bis-1,2,3-triazolium cholaphane using click reaction and the cholaphane's ability to bind anions.<sup>27</sup> Starting from methyl deoxycholate, the 3 $\alpha$  position was propargylated with propargyl bromide in the presence of sodium hydride in THF (*see Figure 2.23*). After refluxing with sulfuric acid in methanol, the monoester was acylated with bromoacetyl bromide in the presence of K<sub>2</sub>CO<sub>3</sub> in CHCl<sub>3</sub>. Treatment with sodium azide in DMF gave its azido derivative, which underwent the click reaction to give the cholaphane in 50% yield. Because previous work determined that the alkyl 1,2,3-triazolium moiety is a better hydrogen bond donor for anion recognition than the 1,2,3-triazole, methylation with methyl iodide was performed, followed by anion exchange with sodium hexafluorophosphate to remove the iodide counterions.

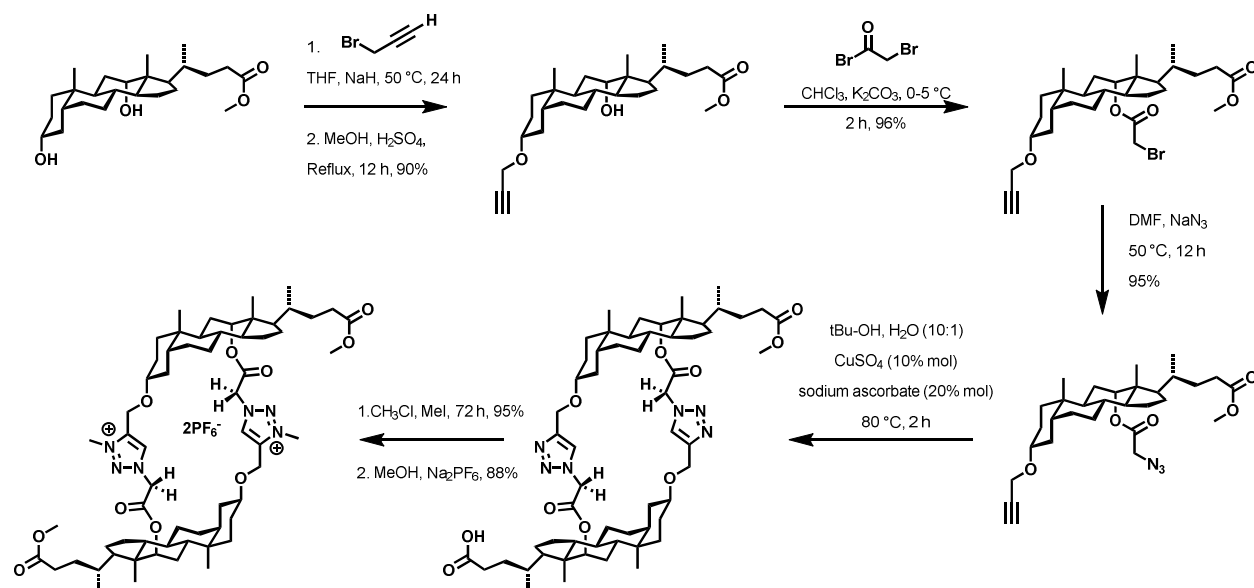


Figure 2.23 Triazole 3-12 Linked Dimers

Anion binding studies of the cholaphane were performed by titrating with  $\text{Bu}_4\text{NX}$  salts in  $\text{CDCl}_3$  and monitoring by  $^1\text{H}$  NMR spectroscopy.<sup>58</sup> It was observed that a downfield shift of the triazolium and acetyl methylene hydrogens occurred upon anion binding (*see Figure 2.24*). The association constants were determined by WinEQNMR software with the binding trend being  $\text{Cl}^- > \text{H}_2\text{SO}_4^{2-} > \text{H}_2\text{PO}_4^{2-} > \text{F}^- > \text{Br}^- > \text{CH}_3\text{COO}^- > \text{I}^-$ . The higher affinity for chloride ions ( $K_a = 3700 \text{ M}^{-1}$ ) was assumed to be because of appropriate cavity size for stronger hydrogen bonding of the anion.

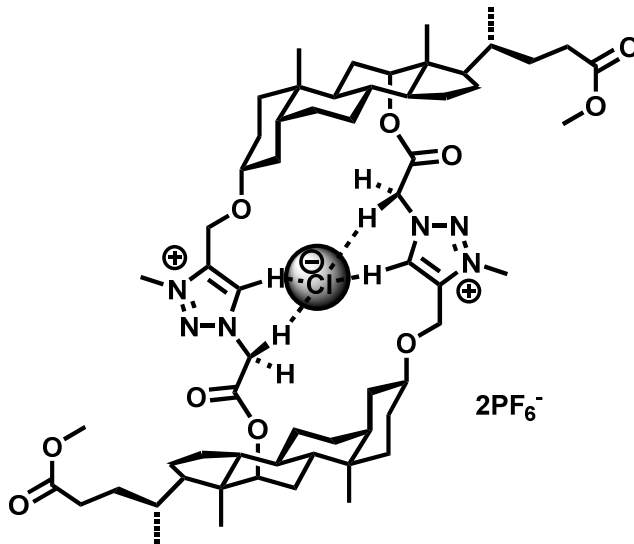


Figure 2.24 Anion Binding

Li reported the synthesis of a similar dimer, this time coupling the acid side chain to the 3-OH position through similar methodologies (*see Figure 2.25*).<sup>59</sup> Proton NMR studies confirmed that the hydroxy protons were not involved in anion binding despite being proton donors (*see Figure 2.26*). The dimer showed high selectivity for  $F^-$  compared to other anions, with binding constants calculated to be  $K_1 = 560 (\pm 8) M^{-1}$  and  $K_2 = 18 (\pm 3) M^{-1}$ . Loss of signal for the aliphatic CH upon addition of TBAF (2 eq.) indicated two strong H-bonding positions in the dimer.

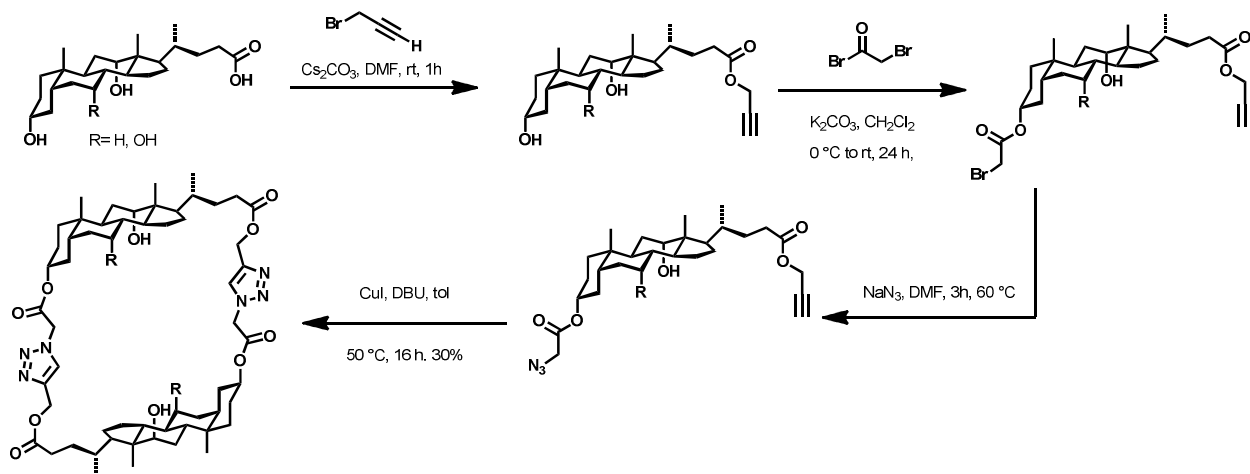


Figure 2.25 Head to Tail Triazole Dimers

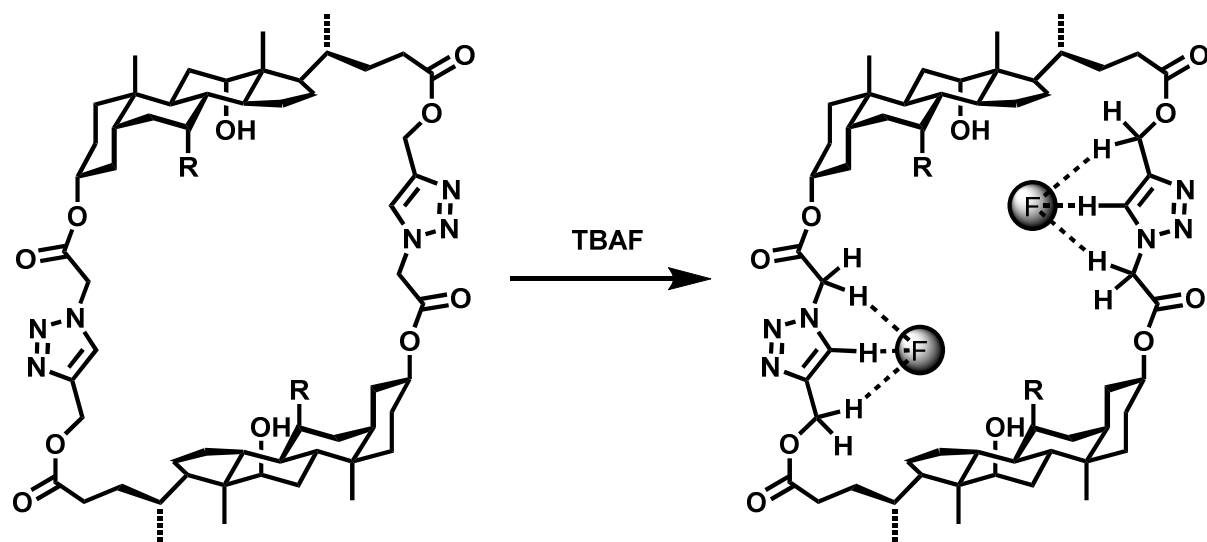


Figure 2.26 Anion Binding

Further work by Li developed cholapods that incorporated colorimetric anion binding structures via the click reaction.<sup>60</sup> These were accessed via similar methods as previous work, but with better yields (>80%) using the click reaction compared to the cholapod synthesis (*see Figure 2.27*). The first compound showed a UV absorption band at 360 nm, which decreased upon addition of  $\text{Bu}_4\text{NH}_2\text{PO}_4$  in  $\text{CHCl}_3$ , giving rise to an absorption band at 400 nm and a distinct yellow solution. Similarly, the second compound showed a decrease at 380 nm and an increase at 600 nm, turning blue in the presence of TBAF,  $\text{Bu}_4\text{NCH}_3\text{CO}_2$ , or  $\text{Bu}_4\text{NH}_2\text{PO}_4$  (*see Figure 2.28*). The increased flexibility of the cholapods was noted as a factor for the selectivity for  $\text{H}_2\text{PO}_4^-$ , as compared to  $\text{Cl}^-$  for the macrocycles.

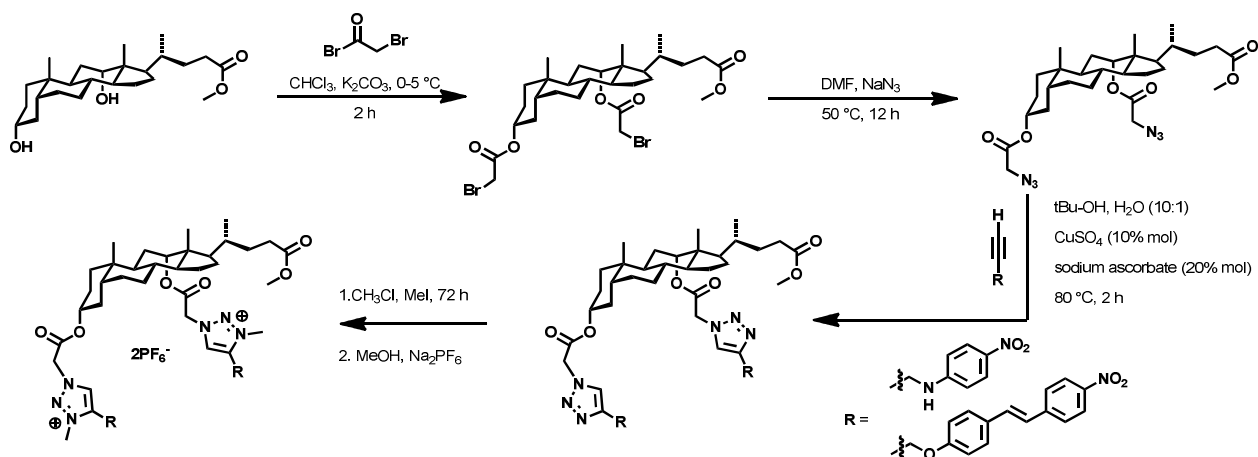


Figure 2.27 Triazole Functionalized Cholapods

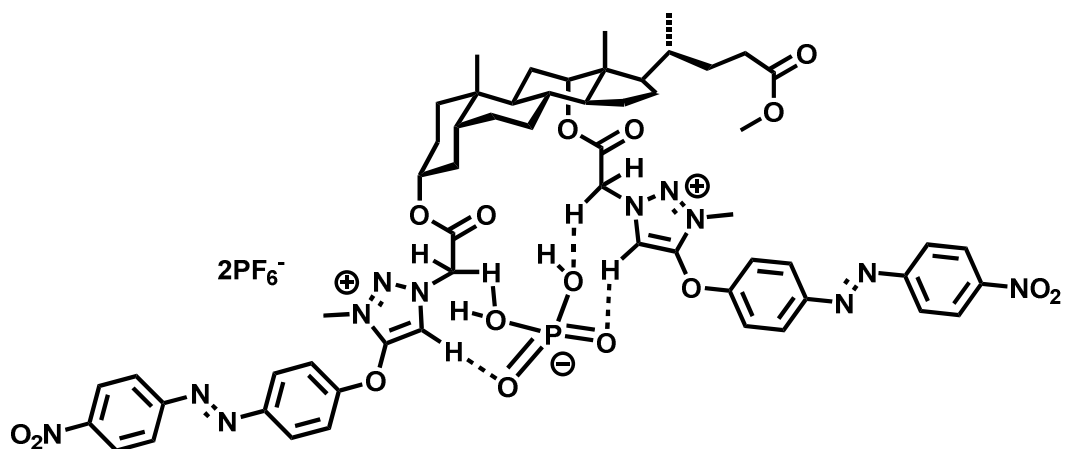


Figure 2.28 Phosphoric Acid Binding

Further development of the click protocol for construction of functionalized BAs led to the construction of BA-calixarene hybrids for anion sensing.<sup>61</sup> Synthesis proceeded as with previous methods to couple the steroid triazide to a propargyl functionalized calixarene (*see Figure 2.29*). Two absorption peaks at 284 nm and 289 nm were seen from the triazole and calixarene ring, respectively. Upon the addition of various metal perchlorates in CH<sub>3</sub>CN these peaks were suppressed and two isosbestic points at 276 nm and 302 nm were observed. Binding studies on the hybrid receptor showed an affinity for mercury ( $K_a = 1.2 \times 10^4 \text{M}^{-1}$ ) with a selectivity order of  $\text{Hg}^{2+} > \text{Cd}^{2+} > \text{Zn}^{2+} > \text{Pb}^{2+} > \text{Li}^+ > \text{Mn}^{2+} > \text{Cu}^{2+}$ .



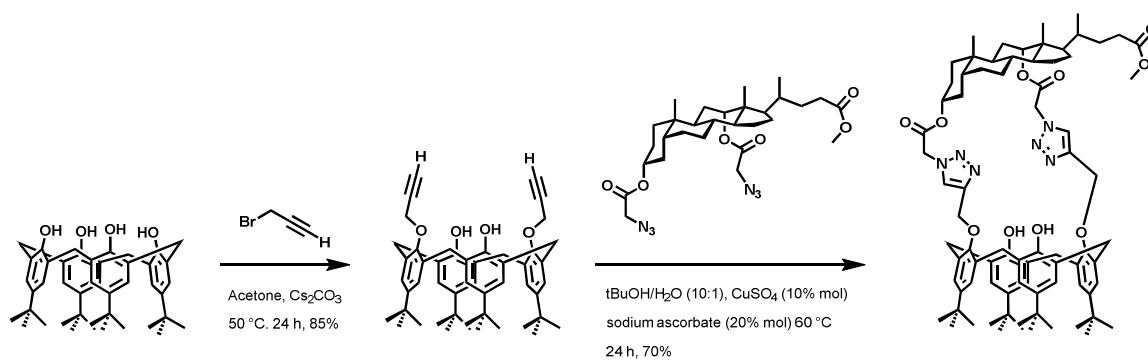


Figure 2.29 Calizarene Hybrids via Sonogashira Coupling

### 2.3.6 Sonogashira Coupling

Ju and Li utilized oligo (*p*-phenyleneethynylene) (OPE) linkers to join various BAs and examined their self-assembly into molecular superstructures (*see Figure 2.30*).<sup>62</sup> The BAs were DCC-coupled to an aryl iodide via the acid side chain, which was Sonogashira-coupled to diethylenebenzene for the BA dimers. Unlike other steroidal dimers, these structures did not exhibit gelling properties, but instead would form distinctive aggregates upon addition of water to a THF solution. The nature of the BA determined the general structure with  $\pi$ - $\pi$  stacking of the spacers thought to contribute to the mechanism of self-assembly, supported by X-ray diffraction studies. Specifically, cholic acid dimers formed spheres and chenodeoxycholic acid dimers formed ribbons, but lithocholic acid dimers failed to aggregate and simply precipitated.

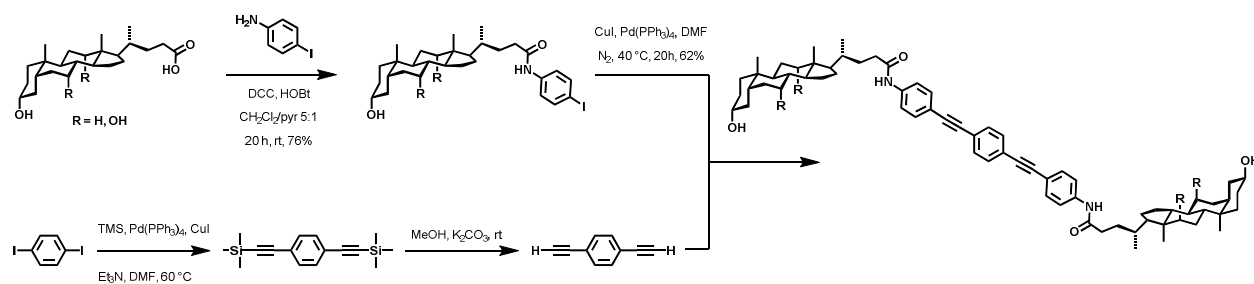


Figure 2.30 OPE Linked BAs

Morzycki, *et al.*, demonstrated the use of Sonogashira coupling to join two androstane steroidal structures into macrocyclic molecular rotors (*see Figure 2.31*).<sup>63</sup> Silyl protection of the alcohol followed by Grignard addition to the ketone afforded the appropriate  $\alpha$ -functionalized structure due to steric hindrance at the  $\beta$  face. Sonogashira coupling under inert atmosphere gave the dimer in acceptable yields, as confirmed by MS and NMR. TBAF deprotection and Mitsunobu addition afforded the butanoic diesters with inversion of stereochemistry into an orientation that favored olefin cross coupling. The length of the sidechain was chosen in order to minimize the strain of the macrocycle as determined by molecular modeling using an MM+ force-field (HyperChem).<sup>63</sup>

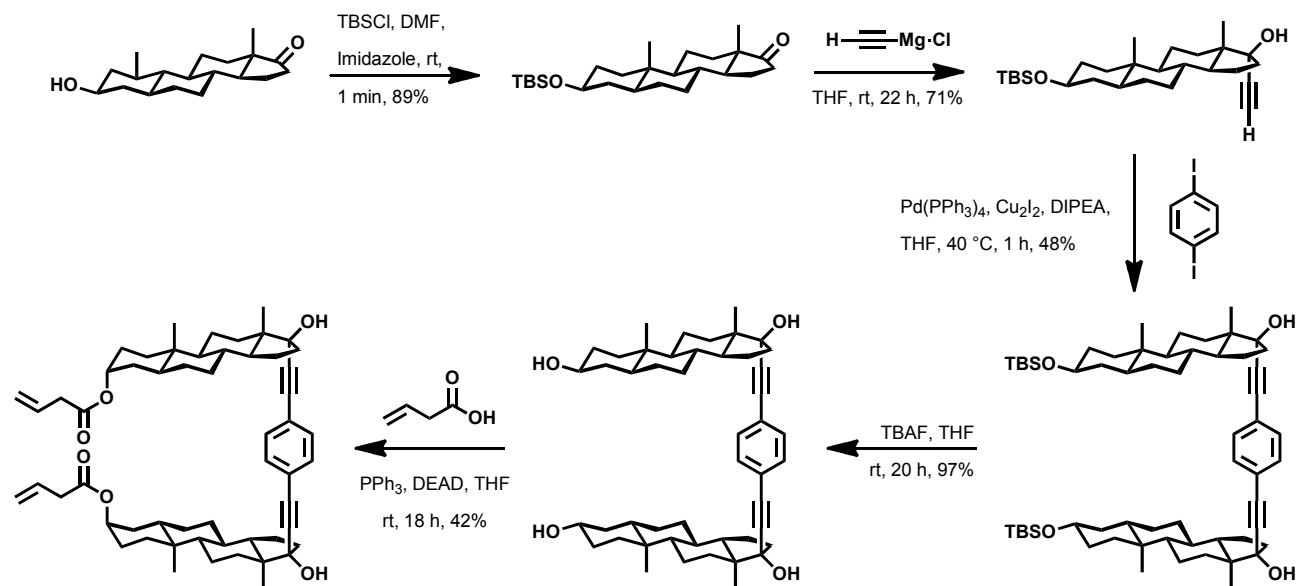


Figure 2.31 Androstane Dimers by Sonogashira Coupling

Olefin metathesis with Grubbs 2<sup>nd</sup> generation catalyst gave the macrocycles in 1:1 *E*:*Z* ratio. X-ray crystal studies determined the 1, 4-diethynylphenyl bridge to be nearly linear in structure (see Figure 2.32). Variable-temperature solid-state <sup>13</sup>C NMR spectroscopy studies showed rotation around the bridge was affected by the stereochemistry of the alkene bond. The 7-(*E*) structure had tighter conformation, while the relatively looser 7-(*Z*) was determined to have a rotational activation barrier of 7.19 kcal/mol and a frequency of 1,000 Hz at 273 K.

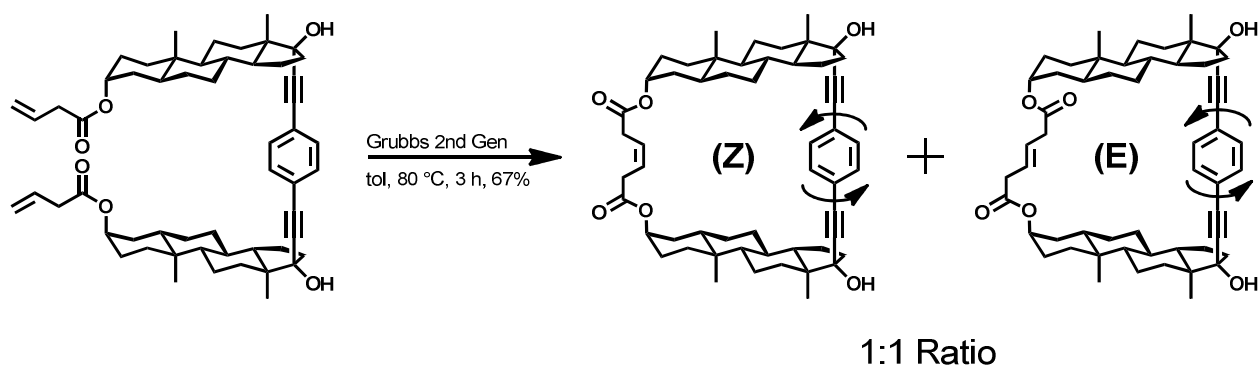


Figure 2.32 Olefin Metathesis Closure of the Macrocycles

Farfán, *et. al.*, developed a similar one-pot asymmetric coupling with triphenylmethyl and triphenylsilylethynyl substituents in an attempt to investigate the properties of asymmetric stators (*see Figure 2.33*).<sup>64</sup> However, X-ray crystallographic analysis of the solid revealed an amorphous nature without long-range chemical order, which prevented further studies of their structures. Substitution of silicon for quaternary carbon yielded similar amorphous results although with an increased solubility of the product in organic solvents.

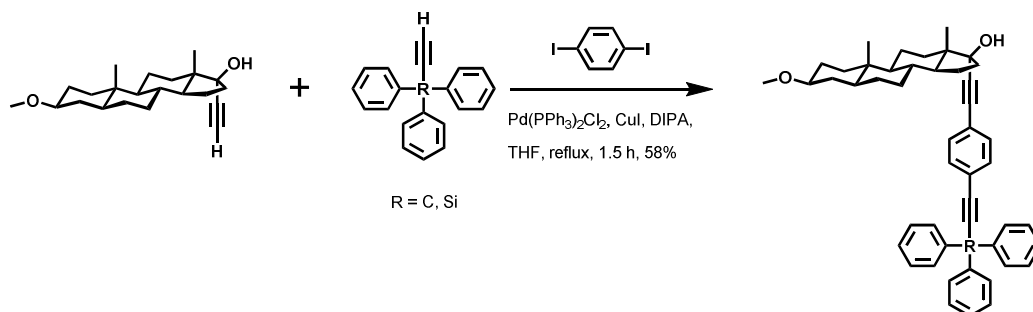


Figure 2.33 One Pot Sonogashira Coupling towards BA Rotors

## 2.4 Conclusion

Bile acids and similar amphiphilic steroids have been demonstrated to be useful building blocks for dimeric structures, macrocycles, and oligomers. Their unique characteristics enable the construction of interesting molecular architectures that have shown application in supramolecular chemistry. Their structures can be functionalized with a variety of moieties, which enable macrocyclization and influence the size and properties of the resulting molecular cavities. Continuous research into methods of functionalizing and coupling steroidal monomers is of great interest in order to expand the scope and application of steroidal macrocycles in supramolecular chemistry.

## CHAPTER 3

### 3. OXA-MICHAEL STRATEGIES TOWARD CDCA DIMERS

#### 3.1 Introduction

The oxa-Michael is a simple and mild coupling reaction that has a long history dating back to its original discovery in 1878.<sup>65</sup> It has been used in a wide range of syntheses from drug-like molecules to natural products.<sup>66</sup> This conjugate addition forms new C-O bonds between an oxygen nucleophile and an electron-deficient Michael accepting moiety, such as a vinyl carbonyl (see Figure 3.1). Other well documented Michael acceptors include the vinyl sulfones and their analogues including sulfonate esters and sulfonamides.<sup>67</sup> Furthermore, it has been demonstrated that in the presence of TBAF, silyl alcohols can both be deprotected and undergo intramolecular oxa-Michael cyclization in a single step.<sup>68</sup> This combination reaction allows the silyl protection of reactive alcohols to enable both functionalization of less reactive sites and cyclization under mild conditions.

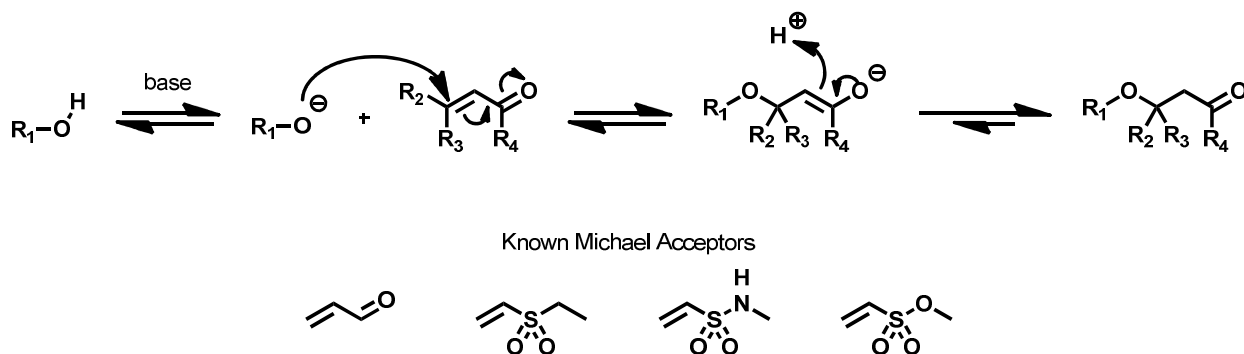


Figure 3.1. The oxa-Michael Reaction

The vinyl sulfonate group is an excellent Michael acceptor which displays high conversion and rapid reactivity rates to couple with nucleophiles, such as thiols, amines, and alcohols. It is easily accessed in high yields through a one-pot sulfonylation and S<sub>N</sub>2 elimination between 2-chloroethanesulfonyl chloride and an alcohol.<sup>68</sup> This, combined with its activity under mild conditions, tolerance to aqueous media, and high atom economy, has led to oxa-Michael reactions with vinyl sulfonates being designated one of the “click” reactions.<sup>69</sup> It has seen use in the synthesis of materials such as dendrimers and polymers,<sup>70</sup> drug-like molecules,<sup>68</sup> and in biochemical modifications.<sup>71</sup> The sulfonate esters are easily cleaved from chemical architectures using nucleophilic or hydrolytic conditions because the conjugate acid has a pK<sub>a</sub> a million times stronger than the corresponding carboxylic acid, and their sensitivity to removal can be modulated through modification of the ester functionality.<sup>72</sup> Thus, sulfonates are important tools for coupling-and-decoupling chemistry, acting as both protecting groups and alkylating agents. The high polarity of sulfonates means that they can be used to impart water solubility in small molecules like dyes and drugs, while larger chemical architectures possessing sulfonate groups have detergent-like properties.<sup>73</sup>

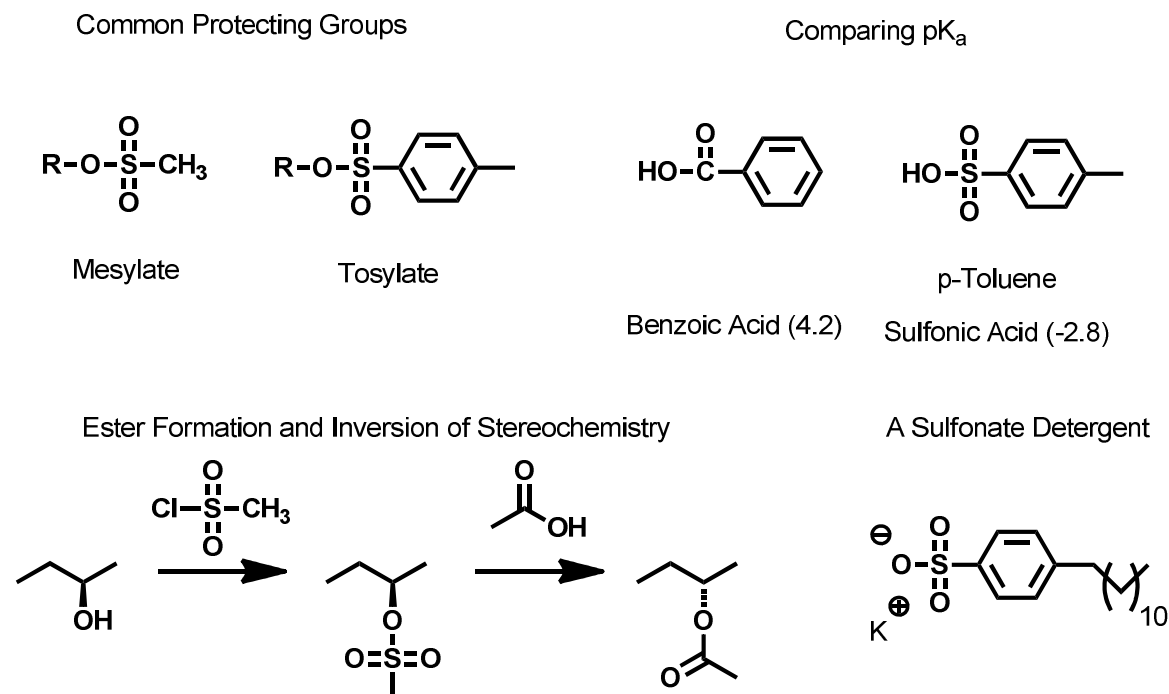


Figure 3.2 Sulfonate Esters in Chemistry

While popular as a protecting group, the sulfonate ester functional group is underrepresented as a linking group in the construction of bile acid macrocycles. In addition to its chemical properties, it has a variety of structural properties, which make it an interesting focus for research. It possesses an achiral, tetrahedral structure with the overall dipole moment orientated in the direction of the two  $sp^2$  hybridized oxygens. In this way, the sulfonate ester can be thought of as an analogue to phosphate esters, naturally occurring structure in DNA and cell membranes.

Because the nature of the linking group can have significant effects on the properties of bile acid scaffolds, this represents unexplored chemical space in this field. We sought to utilize known procedures to functionalize CDCA with the vinyl sulfonate moiety and exploit it in an



intermolecular Michael addition to construct a new class of bile acid macrocycles. The structural and physical properties we wished to investigate include the orientation of the oxygen atoms on the tetrahedral sulfonate ester linkers, the size of the interior cavity, and ability to coordinate to metal cations, the stability of the dimer under acidic conditions, and the solubility of the resulting macrocycle in protic media. We here report our efforts towards these goals.

## 3.2 Results and discussion

### 3.2.1 Synthesis of oxa-Michael Macrocycles

The strategy toward synthesis of CDCA macrocycles by oxa-Michael coupling is as follows. Initially, methyl esterification of the steroidal acid was required in order to prevent cross reactions from the Yamaguchi esterification. Installation of the methyl group was performed by the treatment of an ice-cold solution of CDCA in methanol with acyl chloride. The immediate reaction of the acid chloride and methanol produced an excess of hydrochloric acid. The reaction was run at 0 °C in order to increase the solubility of the acid in solution and prevent evaporation of the solvent due to the exothermic nature of the reaction. This transformation promotes a Fischer esterification with the excess methanol via HCl protonation of the carboxylic acid.

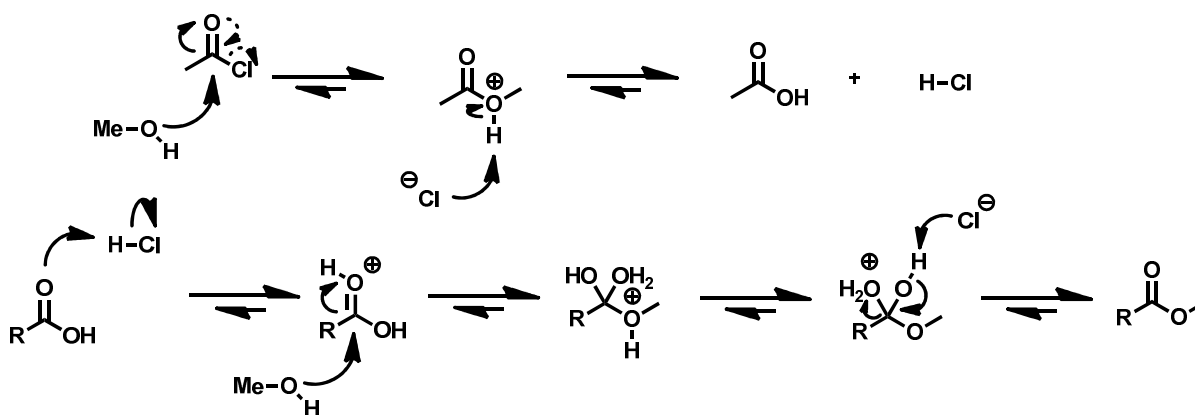


Figure 3.3 Methylation Mechanism

Following methyl esterification of the carboxylic acid, the 3 $\alpha$  hydroxide was protected by reacting the steroid with a silyl chloride and imidazole in THF to produce the 3 $\alpha$ -silyl ether as a viscous, light yellow oil in 91% yield. Both trisopropylsilyl chloride and dimethylisopropylsilyl chloride were chosen over less bulky silyl groups like trimethylsilyl chloride because it was believed that the increased steric bulk would favor reaction at the less hindered 3 $\alpha$  position and prevent formation of the disilylated product. Indeed, no functionalization at the 7 $\alpha$  position was observed as determined by  $^1\text{H}$  NMR spectroscopy.

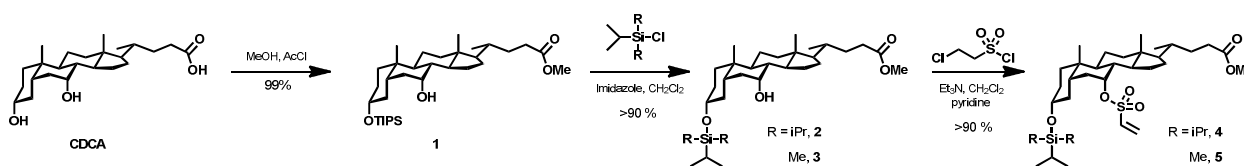


Figure 3.4 Synthesis of oxa-Michael Monomers

Following this reaction, sulfonylation of the 7 $\alpha$  position with 2-chloroethylene sulfonyl chloride was performed. While most reaction conditions proceed forward using only trimethylamine as a base,<sup>74</sup> low conversion to the product was observed under these conditions. Alternatively, use of neat pyridine as both stronger base and solvent caused the sulfonyl chloride to immediately polymerize with itself upon addition, producing a smoking black mass even at lower temperatures. Eventually, the two methods were combined with 3 eq. of trimethylamine in a 1:1 solution of dichloromethane and pyridine to yield the expected product in >90% yields. This was later reduced to a 5:1 ratio of dichloromethane and pyridine with no loss of conversion in order to facilitate easier isolation of the product. The reaction was run with these reagents under nitrogen atmosphere at 0 °C to room temperature over the course of 2 h.

Table 3.1 Sulfonylation Conditions

Conditions	Results
3 eq. Et <sub>3</sub> N in DCM	20% conversion
Pyridine (neat)	Polymerization of reagents
3 eq. Et <sub>3</sub> N in 1:1 DCM: pyridine	>90 % yield
3 eq. Et <sub>3</sub> N in 5:1 DCM: pyridine	>90 % yield

Attempts at purifying the vinyl sulfonate ester via column chromatography resulted in low yields of the product with large amounts of the silylated starting material. It is known that sulfonate esters are sensitive to acidic conditions so alternate methods for purification were investigated. The major contaminant to remove was pyridine, which forms a water-soluble

complex with the copper cations,  $[\text{Cu}_2(\text{pyr})_6](\text{SO}_4)_2$ ,<sup>75</sup> turning the solution from light blue to a dark navy blue. Therefore, pyridine was removed by washing the reaction mixture with 15% w/w  $\text{CuSO}_4$  and extracting it from the organic layer. Washing continued until the aqueous layer no longer turned navy blue, after which a final wash with water was performed to remove any residual copper sulfate. This workup allowed for isolation of the sulfonate ester via simple extraction and eliminating the need for column purification. It was noted at this time that the product had detergent-like properties as seen during extraction, when an emulsion would form during each wash that would take almost an hour to separate.

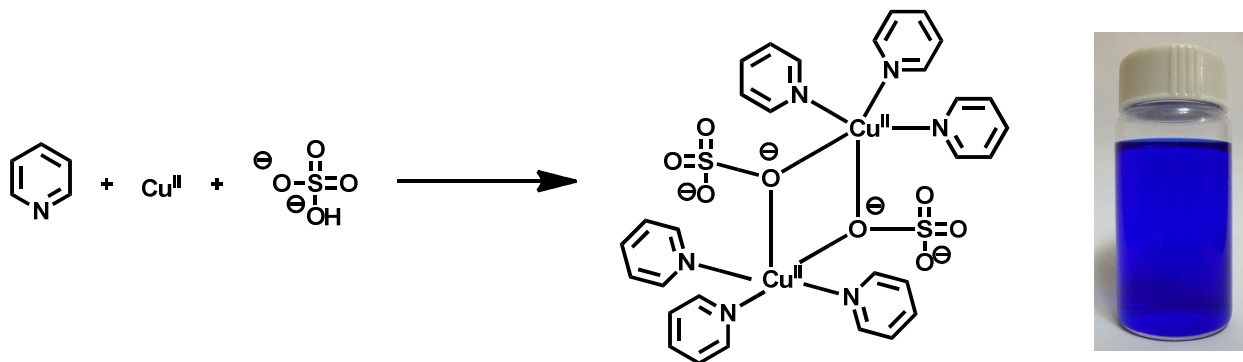


Figure 3.5 Pyridine Complexing with Copper Sulfate,  $[\text{Cu}_2(\text{pyr})_6](\text{SO}_4)_2$

The proposed oxa-Michael coupling would utilize TBAF to deprotect the 3 $\alpha$  oxygen and the resulting alkoxide was expected to Michael into the vinyl sulfoxide (*see Figure 3.6*). The solutions were run at 0.01 M with respect to the monomer in order to prevent polymerization of the monomer. Upon addition of TBAF, the solution darkened in color, however no changes were observed by TLC. Attempts were run with 1, 2, and 3 eq. of 1.0 M TBAF in THF, however  $^1\text{H}$

and  $^{13}\text{C}$  NMR spectroscopic analysis of the resulting products showed that the silyl groups were still present, and a strong silane smell was detectable from the resulting oils upon workup.

Two possibilities for the lack of success in the oxa-Michael coupling are the failure of TBAF to desilylate the alcohol or failure of the resulting alkoxide to undergo Michael addition into the vinyl sulfonate ester, which is likely due to steric congestion around the  $7\alpha$  position. Due to the silyl groups detected in the products following treatment with TBAF, it is likely that desilylation is the issue. Furthermore, a sample of the monomer sent for mass spectra analysis did result in the dimer's expected mass being observed, indicating that dimerization was possible even with the steric bulk around the 7 position. The sample's source was analyzed again to confirm the presence of both the silyl and vinyl sulfonate groups, indicating that the source was still the monomer and something either in transport or ionization caused the desired dimerization.

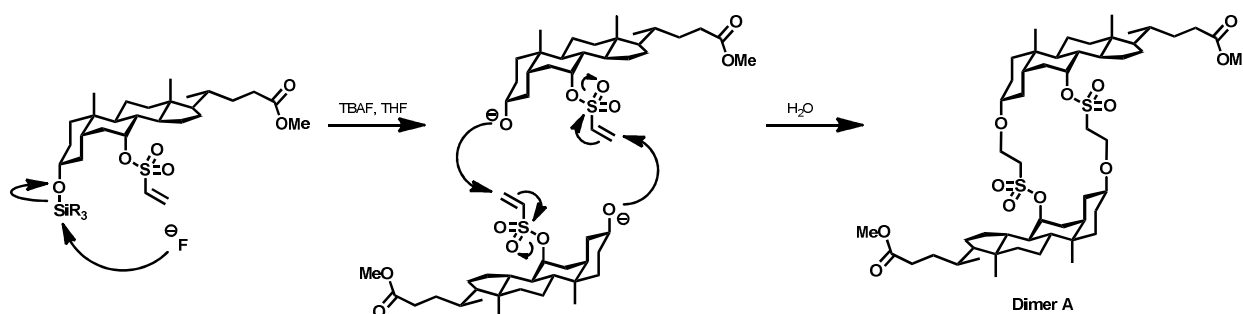


Figure 3.6 Expected Product for oxa-Michael Dimerization

With this in mind, alternate methods for generating the alkoxide under conditions that would be tolerated by the vinyl sulfonate were explored. Previous work in the Dias lab



7 $\alpha$  hydroxide, to yield the respective alkoxides which would then dimerize via oxa-Michael coupling to produce Dimer A or Dimer B, respectively (see Figure 3.8). No product was observed from the 7 $\alpha$  vinyl sulfonate ester although the carbonate was removed. However, the 3 $\alpha$  sulfonate ester showed evidence of dimerization from the shifts in the vinyl peaks in  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. While accessing an alkoxide via removal of the 3 $\alpha$  carbonate should be easier than deprotonation at the 7 $\alpha$  hydroxide, the 3 $\alpha$  vinyl sulfonate ester would be more accessible to attack and cyclization than the 7 $\alpha$  vinyl sulfonate ester.

Interestingly, the methyl peaks from the C-24 methyl ester were present in both samples at  $\sim 3.5$  ppm, indicating that while decarboxylation and/or cyclization occurred, deprotection of the carboxylic acid was not observed. It is known that the carboxylic acid tail of BAs commonly wraps inward towards the hydrophilic  $\alpha$  face of the steroid skeleton, so some interactions with the sulfonate ester may have prevented attack of the carbonate to demethylate the steroid.

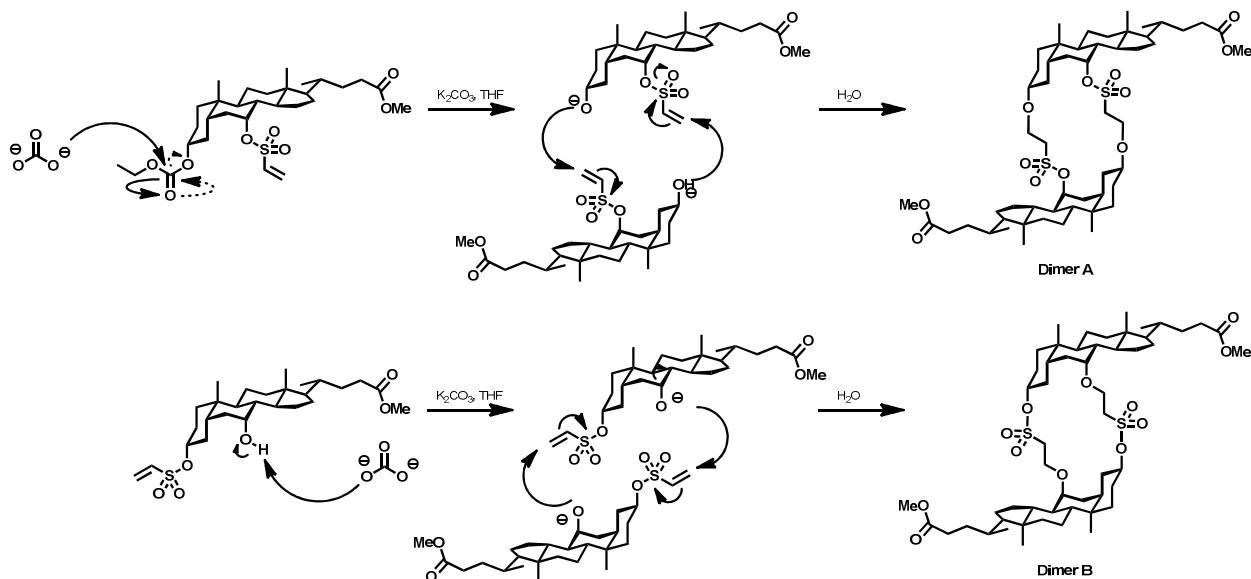


Figure 3.8 Decarboxylation Cyclization Strategy

### 3.2.2 Characterization of Functionalized Bile Acids

#### <sup>1</sup>H-NMR Spectroscopy

The <sup>1</sup>H-NMR spectra of bile acids have a complicated overlap of 25 proton resonances within the limited range of 0.5 – 3.0 ppm. Because of this most protons are not identified in <sup>1</sup>H-NMR spectra, only the characteristic peaks at from the 3 $\beta$ , 7 $\beta$ , and 12 $\beta$  protons, the axial methyl groups C18 and C19, and the methyl C12. Protons from the hydroxide groups are also not identified due to obscuration by other methine and methylene resonances. The 7 $\beta$  and 12 $\beta$  hydrogens present as singlets due to steric isolation of the protons, while 3 $\beta$  proton is a multiplet from coupling to C2-H and C4-H. These protons are located within the range of 3.4 - 3.9 ppm because of the hydroxyl groups and are heavily shifted downfield upon esterification to 5.0 - 4.2 ppm. The C18 and C19 methyl groups are heavily shielded by the steroid skeleton at approximately 0.7 ppm and 0.9 ppm respectively and result in singlets due to their attachment at quaternary carbons. The C21 methyl protons present as a doublet because of spin-spin coupling to the proton at C20. After methylation, a characteristic singlet is also seen around 3.5 ppm from the relatively deshielded methyl group.

The presence of the silyl groups was indicated by the large upfield peaks between 1.0 ppm to 0.0 ppm. Notably the silylation of the 3 $\alpha$  alcohols has little effect on their chemical shift. The vinyl sulfonate presented three separate characteristic resonances from 6.6 to 6.0 ppm. These peaks were shifted more downfield than typical vinyl protons due to the large electron withdrawing effect of the sulfonate. The proton H<sub>A</sub> was the most deshielded due to its proximity to the sulfonate. It was split into a doublet of doublets by the unequal coupling of the two vicinal protons H<sub>B</sub> and H<sub>C</sub> with  $^3J_{AC} > ^3J_{AB}$ . Proton H<sub>B</sub> was next downfield from its *transposition* to the



deshielding sulfonate, split into a doublet from the geminal H<sub>C</sub>. Likewise, H<sub>C</sub> was split into a doublet by H<sub>B</sub> (see Figure 3.9).

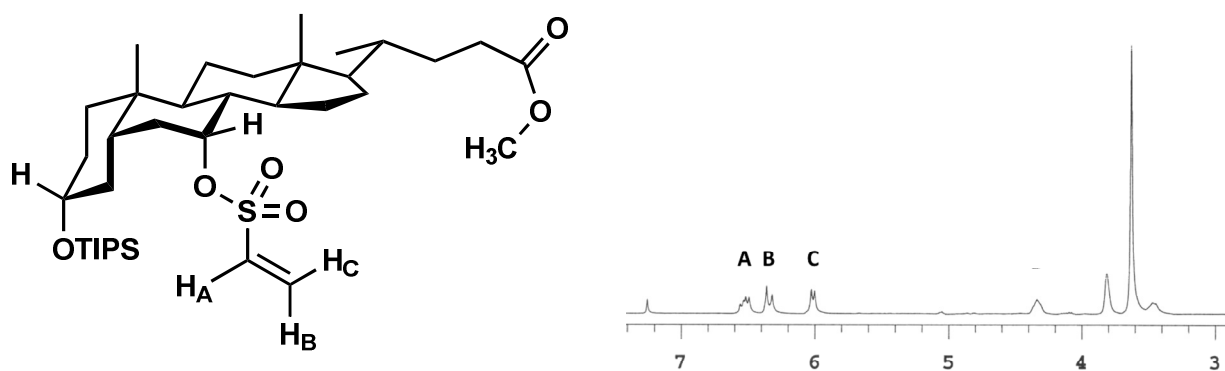


Figure 3.9 Vinyl Sulfonate <sup>1</sup>H NMR

The dimer showed significant changes in the <sup>1</sup>H spectrum from the shift from a highly deshielded vinyl group to relatively deshielded methylene groups.

### <sup>13</sup>C-NMR Spectroscopy

While complicated, the <sup>13</sup>C-NMR spectra of steroid skeletons can be distinguished, although with a few overlapping resonances. Most easily identified is the carboxyl C24 at 175 ppm. The hydroxyl substituted C3 and C7 are next most upfield within the range of 73 – 68 ppm.

These shift upfield upon sulfonylation to 83 – 75 ppm. The bulk of the steroid skeleton presents as single peaks from 50 to 25 ppm. The most downfield peaks are from C18, and C21 at 12 ppm and 18 ppm respectively.

Silylation at the steroid produces large peaks at 0.6, 18, and 32 ppm from the methyl, isopropyl CH<sub>3</sub>, and isopropyl CH, respectively. Sulfonylation gives vinyl peaks at 128 ppm and 134 ppm for the CH<sub>2</sub> and CH carbons respectively. The CH is more heavily deshielded from its position  $\alpha$  to the electron withdrawing sulfone group.

The dimer shifts the linking ethylene carbons to 51 and 60 ppm as the anisotropic effects of the alkene are removed and only the inductive effects of the sulfone and ether linkages remain. Of note is that the 3 $\beta$  and 7 $\beta$  carbon atoms are shifted upfield compared to the monomers. It is likely a shielding effect is occurring from dimerization, slightly offsetting the inductive effects of the sulfonate ester.

## Mass Spectroscopy

### **3 $\alpha$ -Triisopropylsilyloxychenodeoxycholic acid methyl ester.**

The mass spectrum shows the expected mass plus sodium peak at 585.4382 ppm with isotope peak at 586.4412 from both C13 and Si. Also notable is the 631.5 peak resulting from the conjugation of the product with imidazole.

### **Triisopropylsilyloxy-7 $\alpha$ -vinylsulfonyloxychenodeoxycholic acid methyl ester**

The mass spectrum shows the expected mass plus sodium peak at 675.4078 ppm with isotope peaks at 676.2230 from C13 and 677.4986 from S. The main peak at 411.3 is the sodium

conjugated fragment resulting from the loss of the silane at the 3 $\alpha$  position and the sulfonic acid at the 7 $\alpha$  position. The secondary peak at 519.3 is the fragment resulting from the loss of silane at the 3 $\alpha$  position.

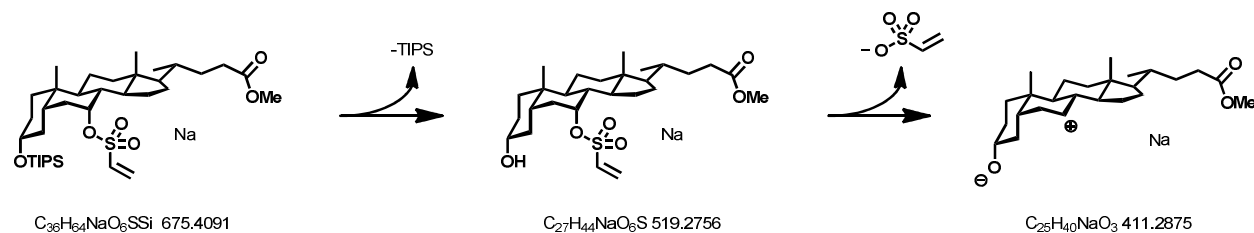


Figure 3.10 Fragmentation of CDCA Vinyl Sulfonate Esters

### 3.3 Conclusion

CDCA was functionalized via selective silylation and sulfonylation of the 3 $\alpha$  and 7 $\alpha$  alcohol groups respectively. Both triisopropyl and dimethylisopropyl silyl chloride produced the silylated products in good yields. The method of sulfonylation to access the desired vinyl sulfonate esters required modification of established procedures, eventually settling on a 5:1 dichloromethane:pyridine solution followed by wash with copper(II) sulfate to cleanly remove the pyridine. This method gave easy access to the desired monomers. While the monomer was isolated in good yields, TBAF deprotection and successive oxa-Michael dimerization was not successful with either silyl group. The desired dimer was detected through MS analysis of a sample of the monomer, indicating that cyclization was possible although not via the expected

desilylation.

Based on previous research, generation of the reactive alkoxide by refluxing in aqueous  $K_2CO_3$  was investigated. Both  $3\alpha$  and  $7\alpha$  vinyl sulfonates of CDCA were synthesized using the developed methods and refluxed under basic conditions. The dimer was produced from the  $7\alpha$  vinyl sulfonate ester of CDCA as detected by  $^1H$  and  $^{13}C$  NMR spectroscopy. It is expected that the reactive alkoxide was formed during the basic decarboxylation and the steric bulk around the  $7\alpha$  position served to protect the sulfonate ester. Further investigation is required to confirm the 3D structure of the dimer as well as its application in hosting guest molecules within its cavity using X-ray crystallography.

### 3.4 Experimental Section

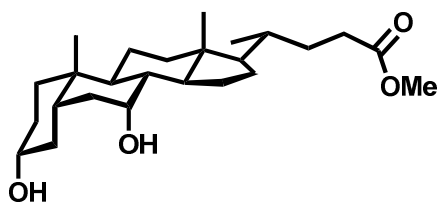
#### 3.4.1 General Methods

**Materials.** Solvents and reagents were purchased from Fischer Scientific unless otherwise noted. Chenodeoxycholic acid and methyl cholate were purchased from Steraloids. Silyl chlorides and 2-chloroethane sulfonyl chloride were purchased from TCI America. Solvents were HPLC grade stored under nitrogen, and used without further purification. Triethylamine ( $Et_3N$ ) was dried over NaOH. Column chromatography was performed on silica gel (MERCK C60) with ethyl acetate:hexane (9:1) as the eluent.

**Instrumentation.**  $^1H$  NMR and  $^{13}C$  NMR spectra were recorded at 400 MHz and 101 MHz, respectively. MSFABspectrometry was performed at University of Kansas Mass Spectrometry center by Lawrence Seib.

### 3.4.2 Experimental Procedures

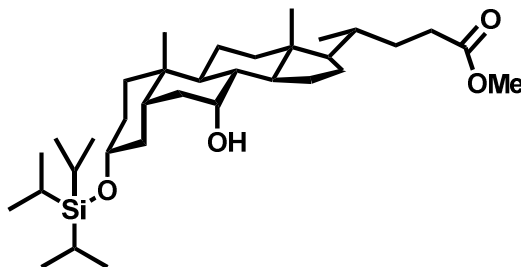
#### Desilylation Oxa-Michael Strategy



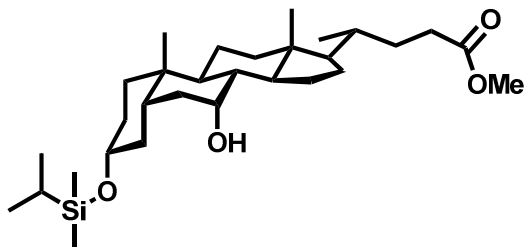
**Chenodeoxycholic acid methyl ester (1).** To a solution of chenodeoxycholic acid (2.0 g, 5.04 mmol) in methanol (20 mL) at 0 °C, acetyl chloride (1.0 mL, 14 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured into ice, extracted with dichloromethane, and dried with sodium sulfate. The solvent was removed by rotary evaporation to yield the product as a white solid (1.924 g, 4.70 mmol, 93.3%)  
 $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.65 (s, 3H, 18- $\text{CH}_3$ ), 0.90 (s, 3H, 19- $\text{CH}_3$ ), 0.92 (d,  $J = 6.4$  Hz, 3H, 21- $\text{CH}_3$ ), 3.40 (m, 1H, 3 $\beta$ -CH), 3.66 (s, 3H, 24-O $\text{CH}_3$ ), 3.8 (s, 1H, 7 $\beta$ -CH) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  12.8 (C18)18.2 (C21), 20.6 (C11), 22.7 (C19), 23.9 (C15), 28.2 (C16), 30.6 (C2), 30.9 (C22, C23), 32.8 (C20), 34.6 (C1), 35.0 (C10), 35.3 (C4, C6), 39.3 (C8), 39.5 (C12), 39.8 (C9), 41.5 (C9), 42.7 (C13), 50.5 (C14), 51.5 (24-O $\text{CH}_3$ ), 55.4 (C17), 68.7 (C7), 73.0 (C3), 174.5 (C24) ppm. 23 of 25 Expected resonances observed. Overlaps at 35.3 and 30.9 ppm.

**General silylation procedure:** To a solution of **1** (1.0 g, 2.46 mmol) and imidazole in tetrahydrofuran (16.0 mL) at room temperature, a solution of the silyl chloride (2.7 mmol) in tetrahydrofuran (5.0 mL) was added dropwise. The reaction was allowed to stir overnight. The

reaction mixture was poured into ice, extracted with dichloromethane, and dried with sodium sulfate. The solvent was removed by rotary evaporation.

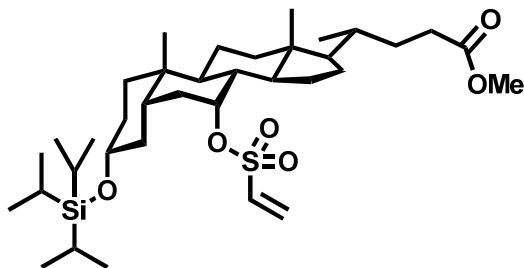


**3 $\alpha$ -Triisopropylsilyloxychenodeoxycholic acid methyl ester (2).** Synthesized according to general silylation procedure and isolated as clear oil (1.37 g, 2.43 mmol, 98.6%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ 0.65 (s, 3H, 18- $\text{CH}_3$ ), 0.90 (s, 3H, 19- $\text{CH}_3$ ), 0.92 (d,  $J = 6.4$  Hz, 3H, 21- $\text{CH}_3$ ), 0.97 (d, 18H, 7 $\alpha$ - $\text{SiCH}(\text{CH}_3)_2$ ), 1.45 (m, 3H, 7 $\alpha$ - $\text{SiCH}(\text{CH}_3)_2$ ), 3.40 (m, 1H, 3 $\beta$ -CH), 3.66 (s, 3H, 24- $\text{OCH}_3$ ), 3.8 (s, 1H, 7 $\beta$ -CH) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$ 11.7 (C18), 18.1 (- $\text{CH}(\text{CH}_3)_2$ ), 18.2 (C21), 20.6 (C11), 22.7 (C19), 23.9 (C15), 28.2 (C16), 30.6 (C2), 30.9 (C22, C23), 32.5 (- $\text{OSiCH}(\text{CH}_3)_2$ ), 32.8 (C20), 34.6 (C1), 35.0 (C10), 35.3 (C4, C6), 39.3 (C8), 39.5 (C12), 39.8 (C9), 41.5 (C9), 42.7 (C13), 50.5 (C14), 51.5 (24- $\text{OCH}_3$ ), 55.4 (C17), 73.0 (C3), 76.0 (C7), 174.8 (C24) ppm. 23 of 25 Expected resonances observed. Overlaps at 35.3 and 30.9 ppm. Calc  $\text{M}+\text{Na} = \text{C}_{34}\text{H}_{63}\text{O}_4\text{SiNa} = 586.4393$ , Found Mass = 586.4412.



**3 $\alpha$ -Isopropylidimethylsilyloxychenodeoxycholic acid methyl ester (3).** Synthesized according to general silylation procedure and isolated as a viscous clear oil. (1.37 g, 2.43 mmol, 98.6%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.21 (s, 6H, 7 $\alpha$ -Si(CH $_3$ ) $_2$ ), 0.65 (s, 3H, 18-CH $_3$ ), 0.90 (s, 3H, 19-CH $_3$ ), 0.92 (d,  $J$  = 6.4 Hz, 3H, 21-CH $_3$ ), 0.97 (d,  $J$  = 6.4 Hz, 6H, 7 $\alpha$ -SiCH(CH $_3$ ) $_2$ ), 1.45 (m, 1H, 7 $\alpha$ -SiCH(CH $_3$ ) $_2$ ), 3.40 (m, 1H, 3 $\beta$ -CH), 3.66 (s, 3H, 24-OCH $_3$ ), 3.8 (s, 1H, 7 $\beta$ -CH) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  0.62 (-OSi(CH $_3$ ) $_2$ ), 11.7 (C18), 18.1 (-CH(CH $_3$ ) $_2$ ), 18.2 (C21), 20.6 (C11), 22.7 (C19), 23.9 (C15), 28.2 (C16), 30.6 (C2), 30.9 (C22, C23), 32.5 (-OSiCH(CH $_3$ ) $_2$ ), 32.8 (C20), 34.6 (C1), 35.0 (C10), 35.3 (C4, C6), 39.3 (C8), 39.5 (C12), 39.8 (C9), 41.5 (C9), 42.7 (C13), 50.5 (C14), 51.5 (24-OCH $_3$ ), 55.4 (C17), 73.0 (C3), 76.0 (C7), 174.8 (C24) ppm. 27 of 27 Expected peaks found.

**General sulfonylation procedure:** To a flame-dried flask under nitrogen the steroid (~1.0 g, 1.77 mmol), triethylamine (1.0 mL), and pyridine (2.0 mL) were added to methylene chloride (6.0 mL). The solution was cooled to 0 °C and 2-chloroethylsulfonyl chloride (0.2 mL, 1.94 mmol) was added dropwise followed by a catalytic amount of dimethylaminopyridine. The reaction was allowed to stir for 2 h while warming to room temperature. The reaction mixture was poured into ice, extracted with dichloromethane, rinsed with 15% (wt/wt) copper (II) sulfate solution and dried with sodium sulfate. The solvent was removed by rotary evaporation.



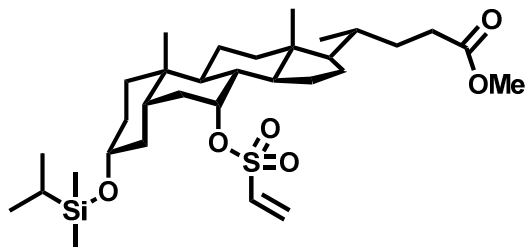
**3 $\alpha$ -Triisopropylsilyloxy-7 $\alpha$ -vinylsulfonyloxychenodeoxycholic acid methyl ester (4).**

Synthesized according to general sulfonylation procedure and isolated as a viscous clear oil (1.09

g, 1.72 mmol, 97.0%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.65 (s, 3H, 18- $\text{CH}_3$ ), 0.90 (s, 3H, 19- $\text{CH}_3$ ), 0.92 (d,  $J = 6.4$  Hz, 3H, 21- $\text{CH}_3$ ), 0.97 (d, 18H, 7 $\alpha$ - $\text{SiCH}(\text{CH}_3)_2$ ), 1.45 (m, 3H, 7 $\alpha$ - $\text{SiCH}(\text{CH}_3)_2$ ), 3.40 (m, 1H, 3 $\alpha$ -CH), 3.66 (s, 3H, 24- $\text{OCH}_3$ ), 3.8 (s, 1H, 7 $\alpha$ -CH), 6.00 (d,  $J = 10$  Hz, 1H, vinyl-CH), 6.34 (d,  $J = 16.8$  Hz, 1H, vinyl-CH), 6.5 (dd,  $J = 10.0, 16.8$ , 1H, vinyl-CH) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  0.62 (- $\text{OSi}(\underline{\text{C}}\text{H}_3)_2$ ), 11.7 (C18), 12.3 (- $\text{OSi}\underline{\text{C}}\text{H}(\text{CH}_3)_2$ ), 18.1 (- $\text{CH}(\underline{\text{C}}\text{H}_3)_2$ ), 18.2 (C21), 20.6 (C11), 22.7 (C19), 23.9 (C15), 28.2 (C16), 30.6 (C2), 30.9 (C22, C23), 32.8 (C20), 34.6 (C1), 35.0 (C10), 35.3 (C4, C6), 39.3 (C8), 39.5 (C12), 39.8 (C9), 41.5 (C9), 42.7 (C13), 50.5 (C14), 51.5 (24- $\text{OCH}_3$ ), 55.4 (C17), 76.0 (C3), 83.0 (C7), 128.7 (Vinyl  $\text{CH}_2$ ), 137.1 (Vinyl CH), 174.5 (C24) ppm. 28 of 30 expected resonances observed.

Overlaps at 35.3 and 30.9 ppm. Mass Spec Calc  $\text{M}+\text{Na} = \text{C}_{36}\text{H}_{64}\text{O}_6\text{SSiNa} = 675.4091$ , Found Mass = 675.4078, 1.9 ppm



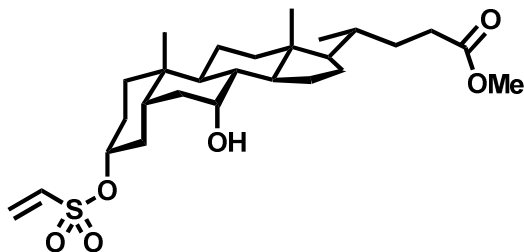


**3 $\alpha$ -Isopropylidimethylsilyloxy-7 $\alpha$ -vinylsulfonyloxychenodeoxycholic acid methyl ester (5).**

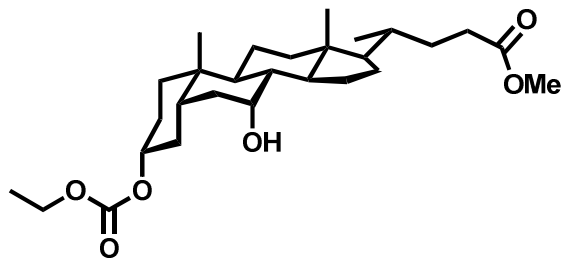
Synthesized according to general sulfonylation procedure and isolated as a viscous clear oil (1.03 g, 1.74 mmol, 98.1%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.21 (s, 6H, 7 $\alpha$ -Si(CH $_3$ ) $_2$ ), 0.65 (s, 3H, 18-CH $_3$ ), 0.90 (s, 3H, 19-CH $_3$ ), 0.92 (d,  $J$  = 6.4 Hz, 3H, 21-CH $_3$ ), 0.97 (d, 6H, 7 $\alpha$ -SiCH(CH $_3$ ) $_2$ ), 1.45 (m, 1H, 7 $\alpha$ -SiCH(CH $_3$ ) $_2$ ), 3.40 (m, 1H, 3 $\beta$ -CH), 3.66 (s, 3H, 24-OCH $_3$ ), 3.8 (s, 1H, 7 $\beta$ -CH), 6.00 (d,  $J$  = 10 Hz, 1H, vinyl-CH), 6.34 (d,  $J$  = 16.8 Hz, 1H, vinyl-CH), 6.5 (dd,  $J$  = 10.0 Hz, 16.8 Hz, 1H, vinyl-CH) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  0.62 (-OSi(CH $_3$ ) $_2$ ), 11.7 (C18), 12.3 (-OSiCH(CH $_3$ ) $_2$ ), 18.1 (-CH(CH $_3$ ) $_2$ ), 18.2 (C21), 20.6 (C11), 22.7 (C19), 23.9 (C15), 28.2 (C16), 30.6 (C2), 30.9 (C22, C23), 32.8 (C20), 34.6 (C1), 35.0 (C10), 35.3 (C4, C6), 39.3 (C8), 39.5 (C12), 39.8 (C9), 41.5 (C9), 42.7 (C13), 50.5 (C14), 51.5 (24-OCH $_3$ ), 55.4 (C17), 76.0 (C3), 83.0 (C7), 128.7 (Vinyl CH $_2$ ), 137.1 (Vinyl CH), 174.5 (C24) ppm. 28 of 30 Expected resonances observed. Overlaps at 35.3 and 30.9 ppm.

**Dimer (A).** Identified by mass spectroscopy from a sample of 3 $\alpha$ -Isopropylidimethylsilyloxy-7 $\alpha$ -vinylsulfonyloxychenodeoxycholic acid methyl ester. Calc M+Na = C $_{54}$ H $_{88}$ O $_{12}$ S $_2$ Na = 1015.5615, Found Mass = 1015.5591, 2.4 ppm

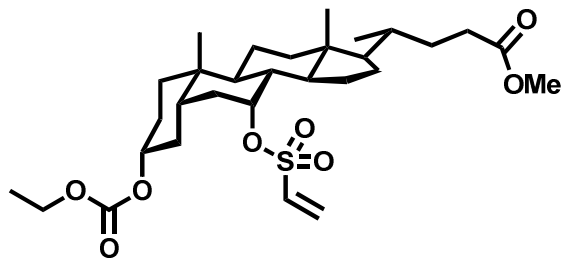
K<sub>2</sub>CO<sub>3</sub> Alkoxide strategy



**Methyl-7α-Hydroxy-3α-vinylsulfonyloxychenodeoxycholate (6).** Synthesized according to general sulfonylation procedure from compound **1** and isolated as a light orange solid. (1.21 g, 1.73 mmol, 97.5%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), δ 0.61 (s, 3H, 18-CH<sub>3</sub>), 0.81 (s, 3H, 19-CH<sub>3</sub>), 0.87 (d, *J* = 7.2 Hz, 3H, 21-CH<sub>3</sub>), 3.62 (s, 3H, 24-OCH<sub>3</sub>), 3.80 (s, 1H, 7β-H), 4.32 (m, 1H, 3β-H), 6.00 (d, *J* = 10 Hz, 1H, CH), 6.34 (d, *J* = 16.8, 1H, CH), 6.5 (dd, *J* = 10.0 Hz, 16.8 Hz, 1H, CH) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 174.8 (C24), 137.1 (Vinyl CH), 128.7 (Vinyl CH<sub>2</sub>), 82.9 (C3), 68.5 (C7), 55.7 (C17), 51.4 (24-OCH<sub>3</sub>), 50.4 (C14), 42.6 (C13), 41.6 (C5), 40.3 (C12), 39.5 (C8), 35.2 (C4), 34.7 (C1, C10), 34.6 (C9), 34.5 (C20), 31.4 (C16), 30.9 (C23), 30.8 (C22), 27.9 (C6), 28.1 (C2), 23.6 (C15), 22.7 (C19), 20.5 (C11), 18.2 (C21), 11.7 (C18) ppm. 26 of 27 Expected resonances observed. Overlap at 34.7 ppm.



**Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -hydroxyl-5 $\beta$ -cholanoate (7).** To a solution of chenodeoxycholic acid methyl ester (10.0 g, 24.6 mmol) in pyridine (20 mL) at -20 °C, ethyl chloroformate (10.8 mL, 113 mmol) was added dropwise. The reaction was allowed to stir for 4 hr while warming up to room temperature. The reaction mixture was poured into ice, extracted with dichloromethane, washed with copper chloride solution (15% wt/wt), and dried with sodium sulfate. The solvent was removed by rotary evaporation to yield the product as a viscous yellow oil (11.4 g, 23.9 mmol, 97%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz),  $\delta$  0.64 (s, 3H, 18-CH<sub>3</sub>), 0.89 (d,  $J$  = 6.4 Hz, 3H, 21-CH<sub>3</sub>),  $\delta$  0.91 (s, 3H, 19-CH<sub>3</sub>),  $\delta$  3.65 (s, 3H, 24-OCH<sub>3</sub>),  $\delta$  3.8 (s, 1H, 7 $\alpha$ -CH),  $\delta$  4.18 (q,  $J$  = 8 Hz, 2H, 3 $\alpha$ -OCOOCH<sub>2</sub>CH<sub>3</sub>),  $\delta$  4.4 (m, 1H, 3 $\alpha$ -CH) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz)  $\delta$  11.7 (C18), 14.2 (3 $\alpha$ -OC(O)OCH<sub>2</sub>CH<sub>3</sub>), 18.1 (C21), 20.5 (C11), 22.6 (C19), 23.6 (C15), 26.5 (C2), 28.0 (C16), 30.8 (C22, 23) 32.6 (C6) 34.3 (C9), 34.8 (C20), 34.9 (C10), 35.0 (C1), 35.2 (C4), 39.3 (C8), 39.5 (C12), 41.1 (C5), 42.5 (C13), 50.2 (C14), 51.1 (24-OCH<sub>3</sub>), 55.6 (C17), 63.3 (3 $\alpha$ -OC(O)OCH<sub>2</sub>CH<sub>3</sub>), 68.0 (C7), 78.0 (C3), 154.6 (3 $\alpha$ -OC(O)OCH<sub>2</sub>CH<sub>3</sub>), 174.5 (C24) ppm. 27 of 28 Expected resonances observed. Overlap at 30.8 ppm. MS Calc M + Na = C<sub>33</sub>H<sub>50</sub>O<sub>7</sub>Na = 581.3454, Found Mass = 581.3427



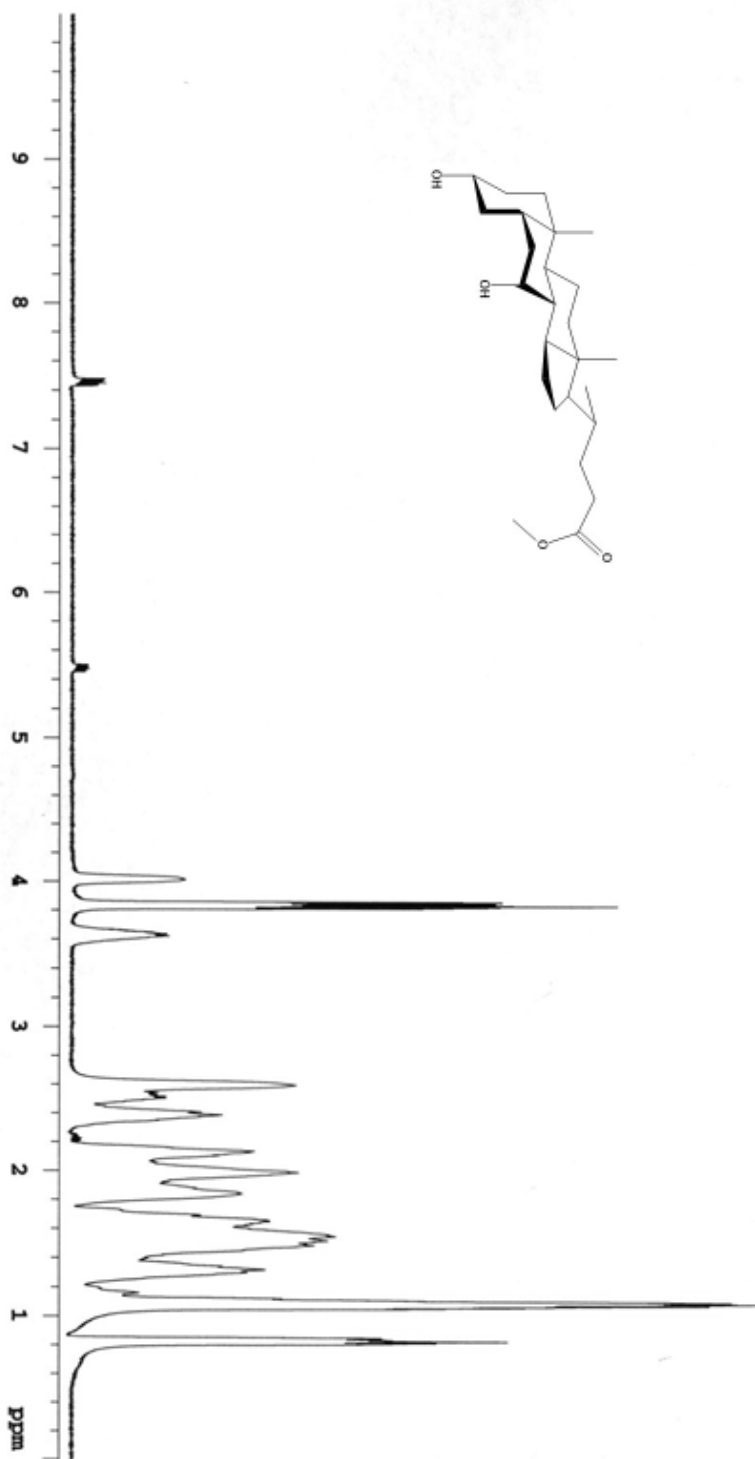
**Methyl-3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -vinylsulfonyloxychenodeoxycholate (8).** Synthesized according to general sulfonylation procedure from compound **4** (1.6 g, 3.34 mmol) and isolated as a light yellow oil (1.62 g, 2.84 mmol, 85%).  $^1\text{H}$  NMR in ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.61 (s, 3H, 18- $\text{CH}_3$ ), 0.88 (m, 6H, 19- $\text{CH}_3$ , 21- $\text{CH}_3$ ), 3.63 (s, 3H, 24- $\text{OCH}_3$ ), 4.14 (q,  $J = 8$  Hz, 2H, 3 $\alpha$ - $\text{OC}(\text{O})\text{OCH}_2\text{CH}_3$ ), 4.41 (m, 1H, 3 $\alpha$ -CH), 4.82 (s, 1H, 7 $\alpha$ -CH), 6.00 (d,  $J = 10$  Hz, 1H, CH), 6.33 (d,  $J = 16.8$  Hz, 1H, CH), 6.54 (dd,  $J = 10.0$  Hz, 16.8 Hz, 1H, CH) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  174.9 (C24), 154.5 (3 $\alpha$ - $\text{OC}(\text{O})\text{OCH}_2\text{CH}_3$ ), 134.9 (Vinyl CH), 128.5 (Vinyl  $\text{CH}_2$ ), 83.2 (C3), 77.6 (C7), 63.8 (3 $\alpha$ - $\text{OC}(\text{O})\text{OCH}_2\text{CH}_3$ ), 55.6 (C17), 51.7 (24- $\text{OCH}_3$ ), 49.9 (C14), 42.9 (C13), 41.1 (C5), 39.2 (C8, C9), 35.5 (C4), 35.4 (C1, C10), 35.0 (C9), 33.5 (C20), 32.1 (C16), 31.2 (C23, C22), 28.2 (C6), 26.9 (C2), 23.6 (C15), 22.8 (C19), 20.6 (C11), 18.5 (C21), 14.5 (3 $\alpha$ - $\text{OC}(\text{O})\text{OCH}_2\text{CH}_3$ ), 12.0 (C18) ppm. 27 of 30 Expected resonances observed. Overlaps at 39.2, 35.4, and 31.2 ppm.

**Dimer (B).** To a solution of **6** (1.02 g, 2.85 mmol) in  $\text{CH}_3\text{OH}$  (15 mL) and THF (15 mL),  $\text{K}_2\text{CO}_3$  (sat, 30 mL) was added. The solution was refluxed overnight. The extra base was neutralized by 3M HCl and the reaction mixture was extracted with EtOAc. The organic layer was dried by  $\text{Na}_2\text{SO}_4$  and solvent was evaporated by rotary vaporization. The crude product was crystallized from acetone as an off-white solid (0.702 g, 80.7%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.59 (s, 3H, 18- $\text{CH}_3$ ), 0.81 (s, 3H, 19- $\text{CH}_3$ ), 0.82 (d,  $J = 7.2$ , 3H, 21- $\text{CH}_3$ ), 3.2 (t, 2H,  $-\text{OCH}_2$ ), 3.72 (s, 3H,

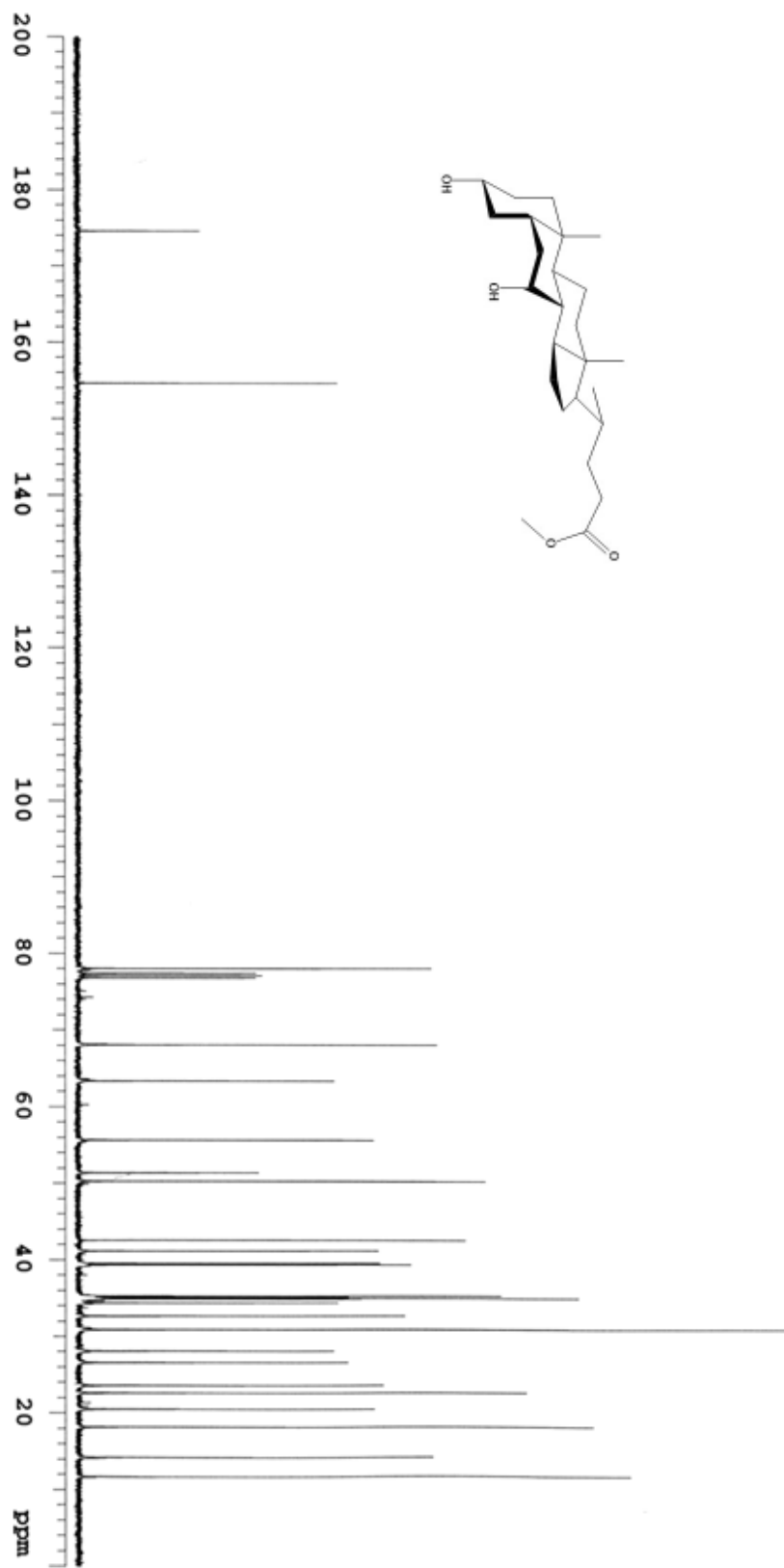
24-OCH<sub>3</sub>), 3.81 (s, 1H, 7 $\alpha$ -CH),  $\delta$  4.11 (t, 2H, -S(O)<sub>2</sub>CH<sub>2</sub>),  $\delta$  4.64 (m, 1H, 3 $\alpha$ -CH) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz)  $\delta$  11.7 (C18), 18.2 (C21), 20.6 (C11), 22.7 (C19), 23.9 (C15), 28.2 (C16), 30.6 (C2), 30.9 (C22, C23), 32.8 (C20), 34.6 (C1), 35.0 (C10), 35.3 (C4, C6), 39.3 (C8), 39.5 (C12), 39.8 (C9), 41.5 (C9), 42.7 (C13), 50.5 (C14), 51.0 (24-OCH<sub>3</sub>), 51.5 (-OS(O)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 55.4 (C17), 60.9 (-OS(O)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 69.0 (C7), 76.0 (C3), 174.5 (C24) ppm. 25 of 27 Expected resonances observed. Overlaps at 35.3, and 30.9 ppm.

### 3.6 Supporting Spectra

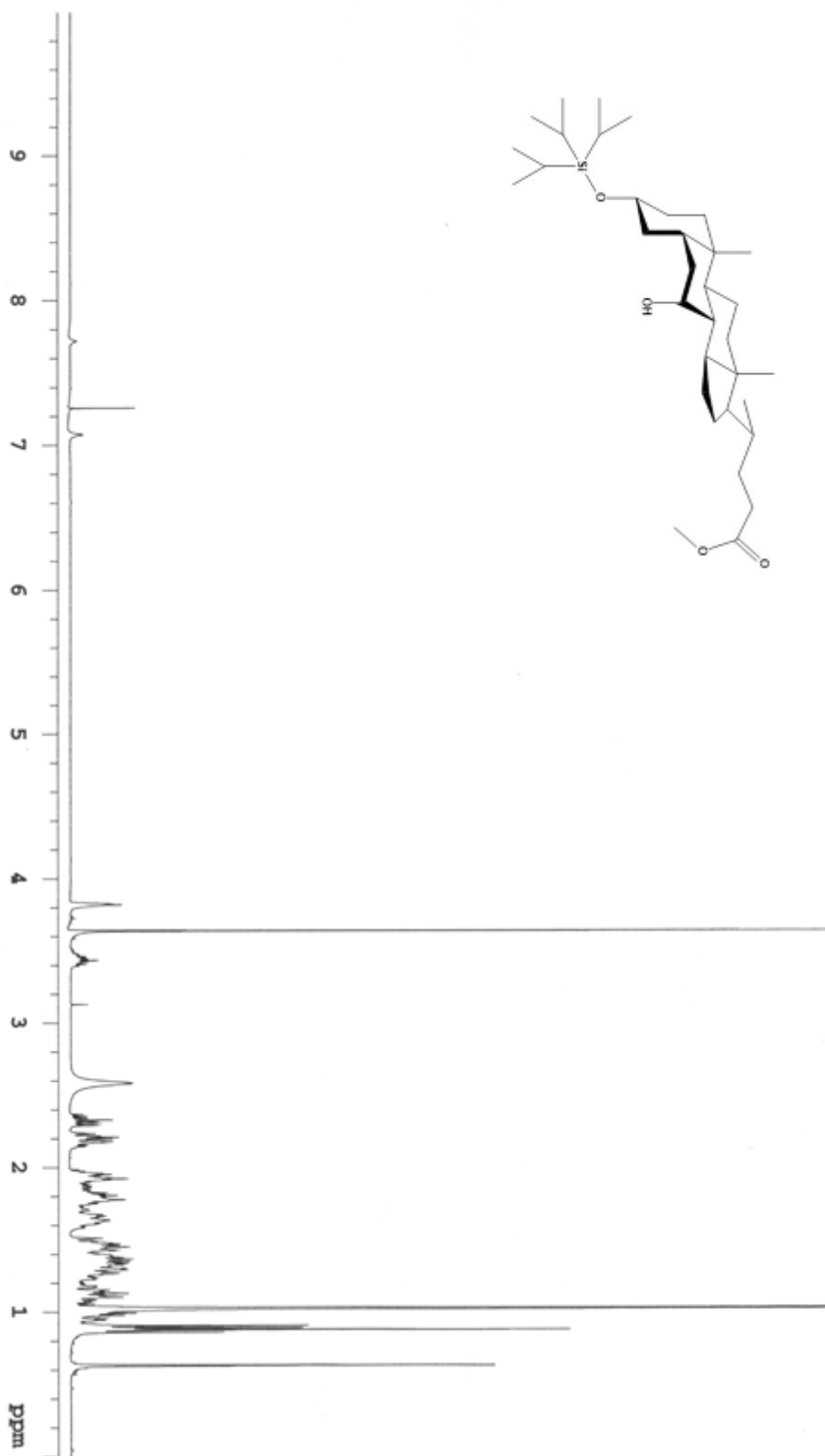
#### Chenodeoxycholic acid methyl ester.



**Chenodeoxycholic acid methyl ester.**

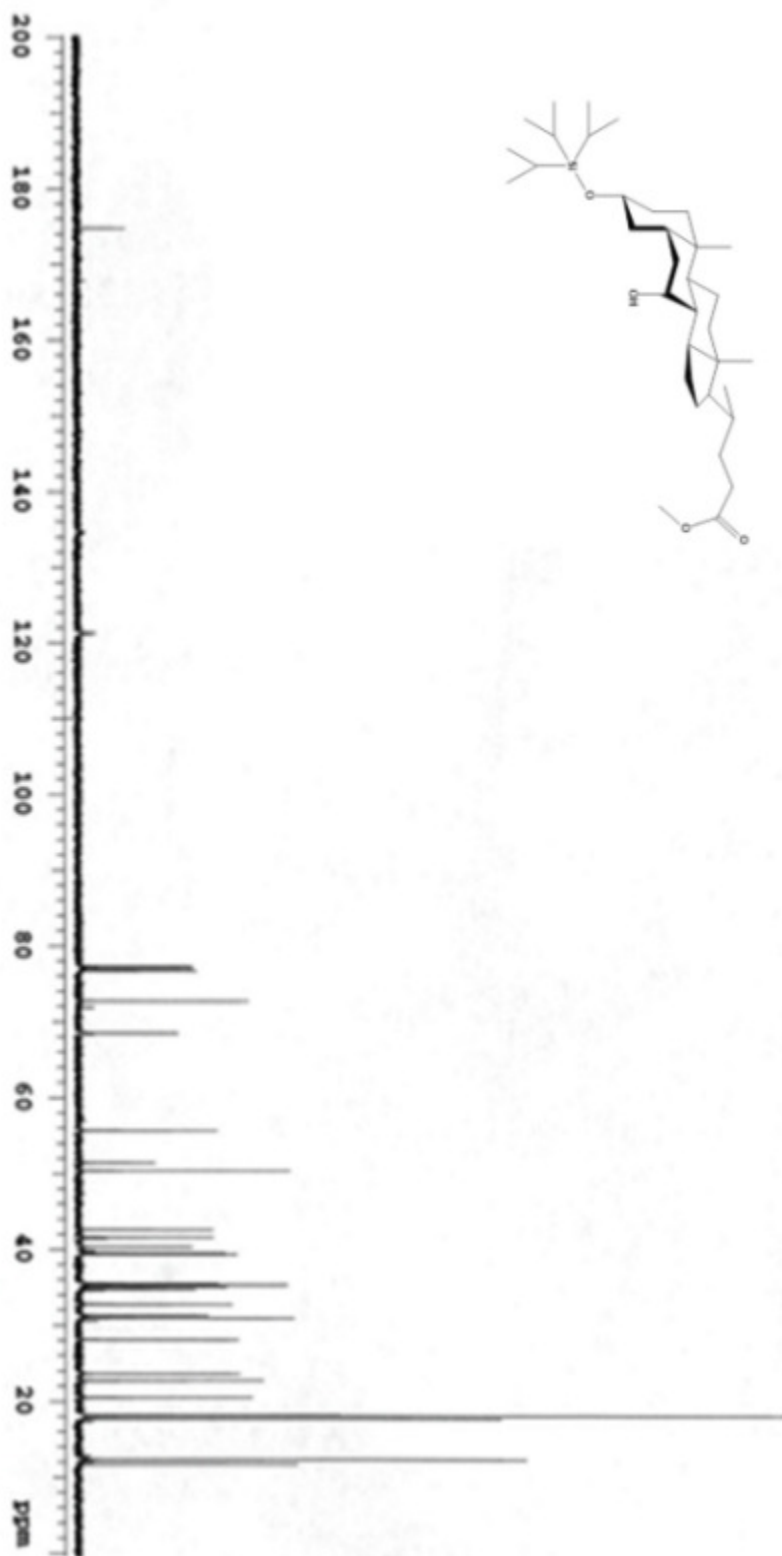


### 3 $\alpha$ -Triisopropylsilyloxychenodeoxycholic acid methyl ester

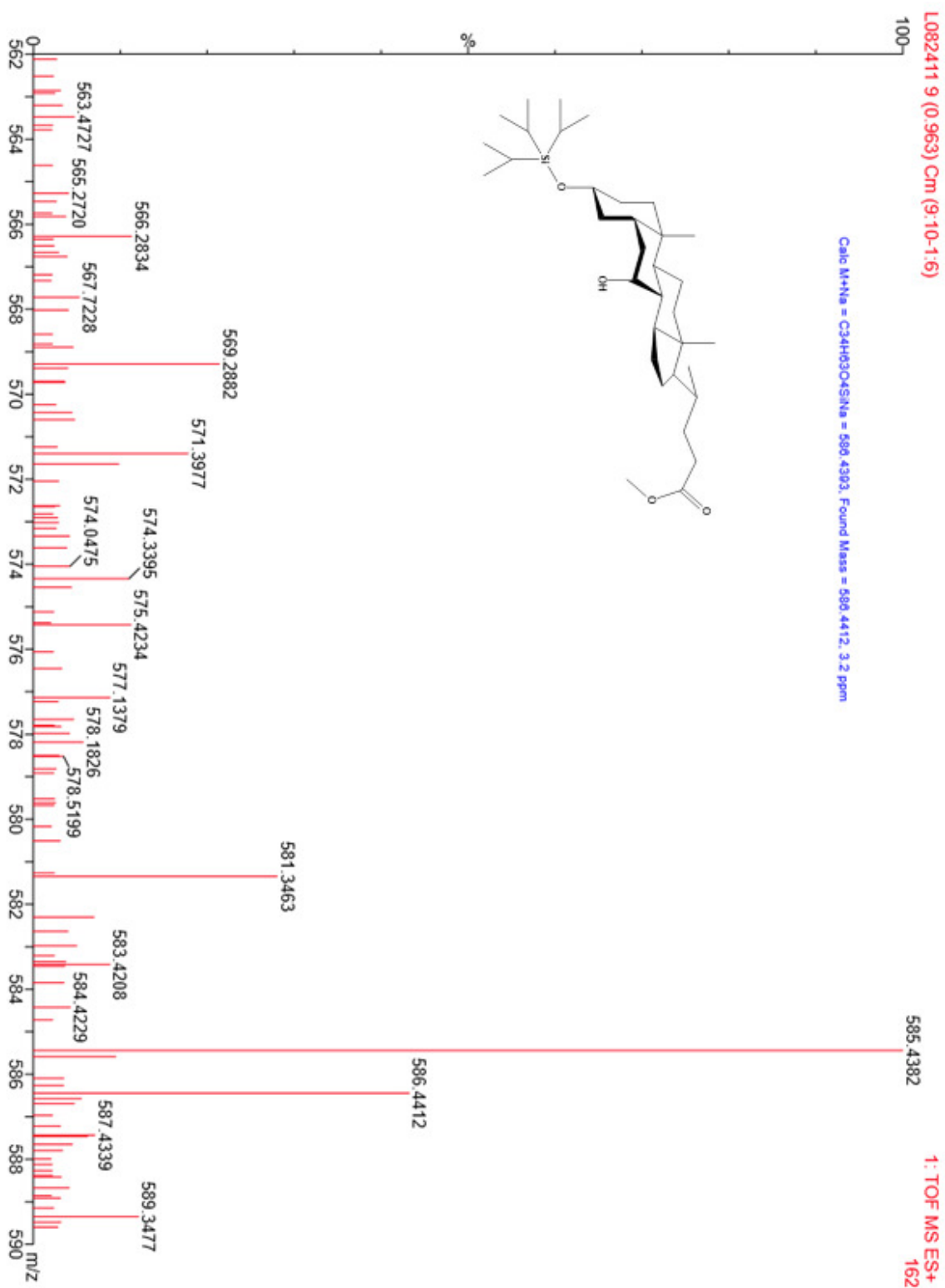




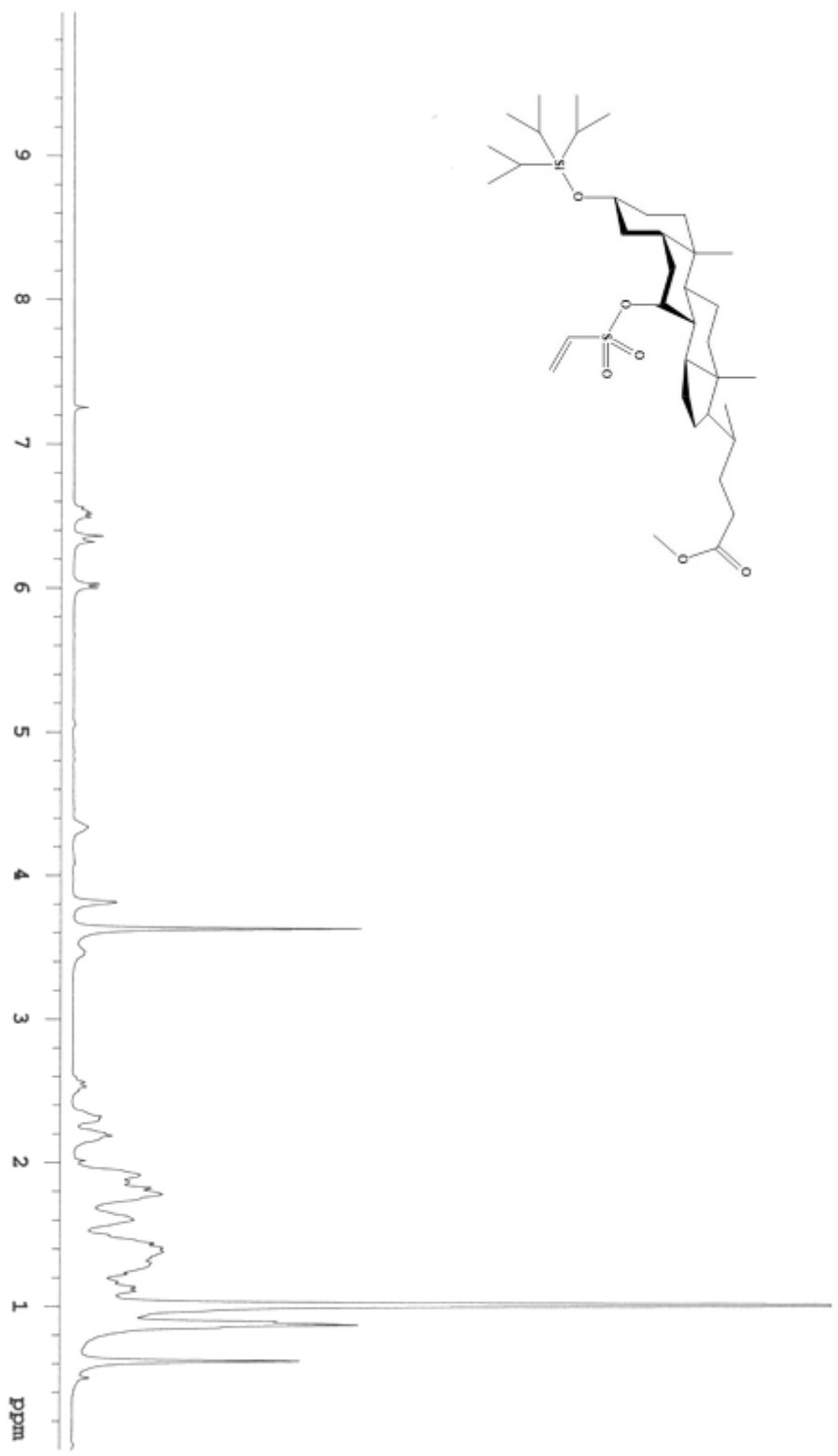
**3 $\alpha$ -Triisopropylsilyloxychenodeoxycholic acid methyl ester**



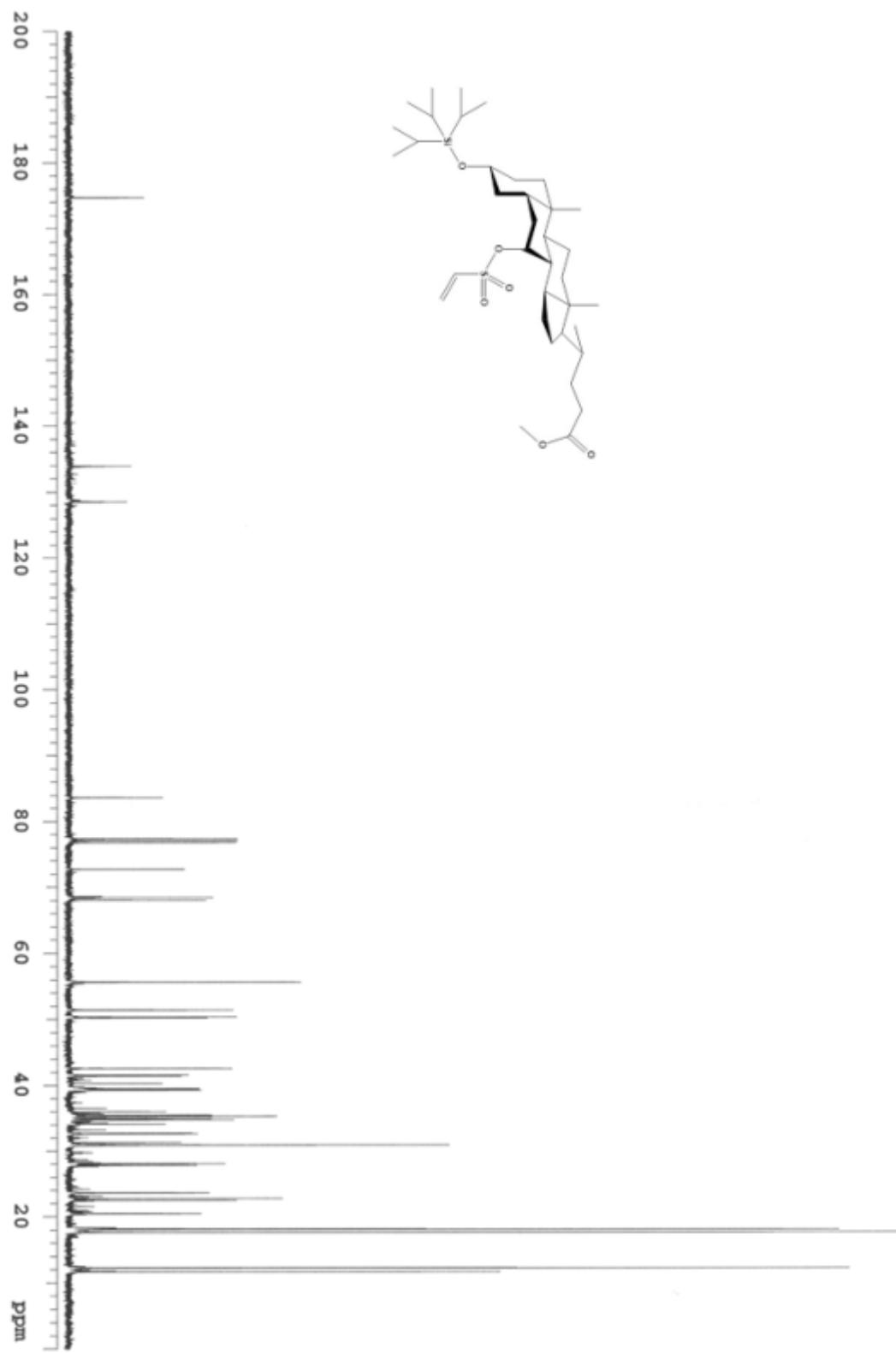
### 3 $\alpha$ -Triisopropylsilyloxychenodeoxycholic acid methyl ester



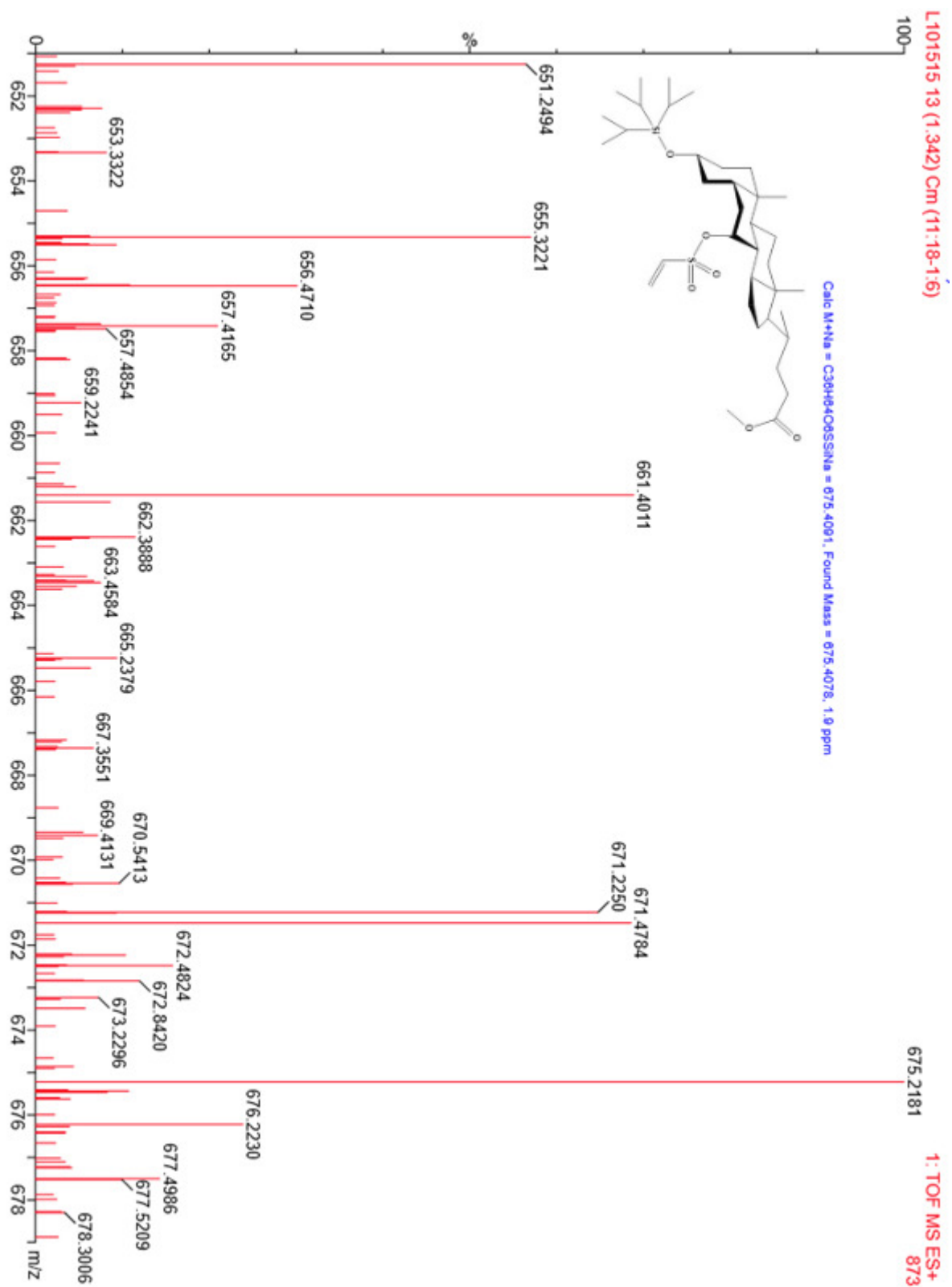
**Triisopropylsilyloxy-7 $\alpha$ -vinylsulfonyloxychenodeoxycholic acid methyl ester.**



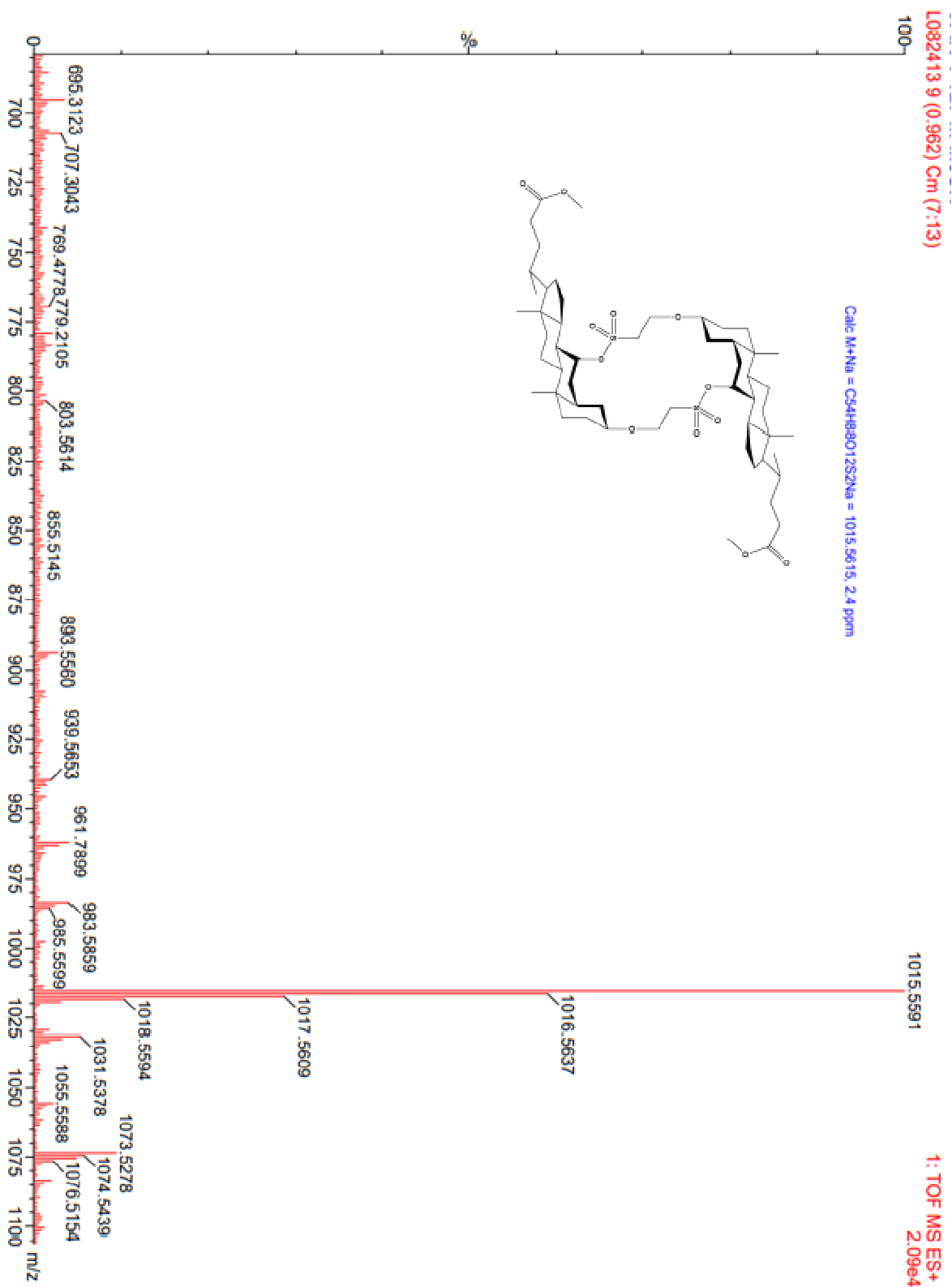
**Triisopropylsilyloxy-7 $\alpha$ -vinylsulfonyloxychenodeoxycholic acid methyl ester.**



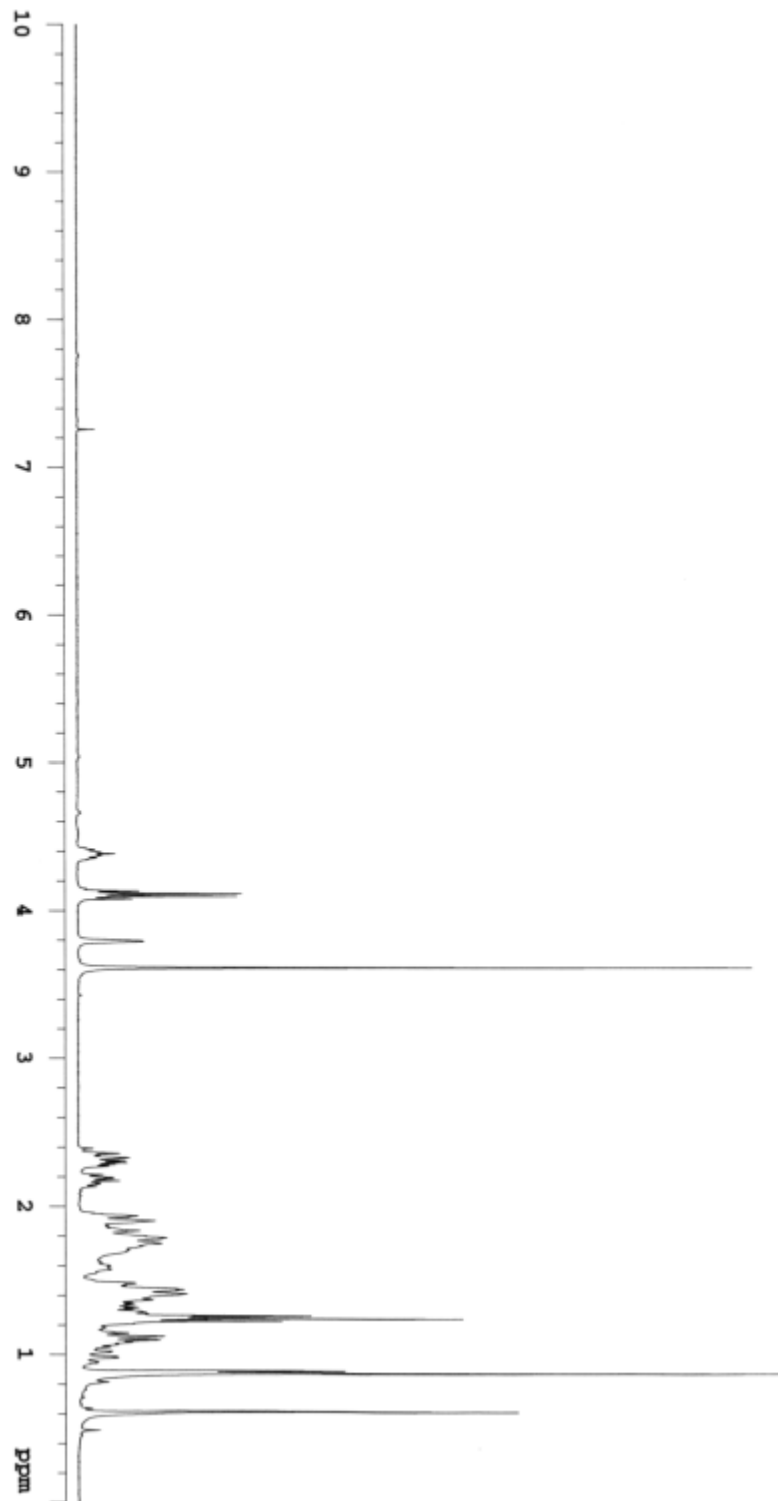
Triisopropylsilyloxy-7 $\alpha$ -vinylsulfonyloxychenodeoxycholic acid methyl ester.



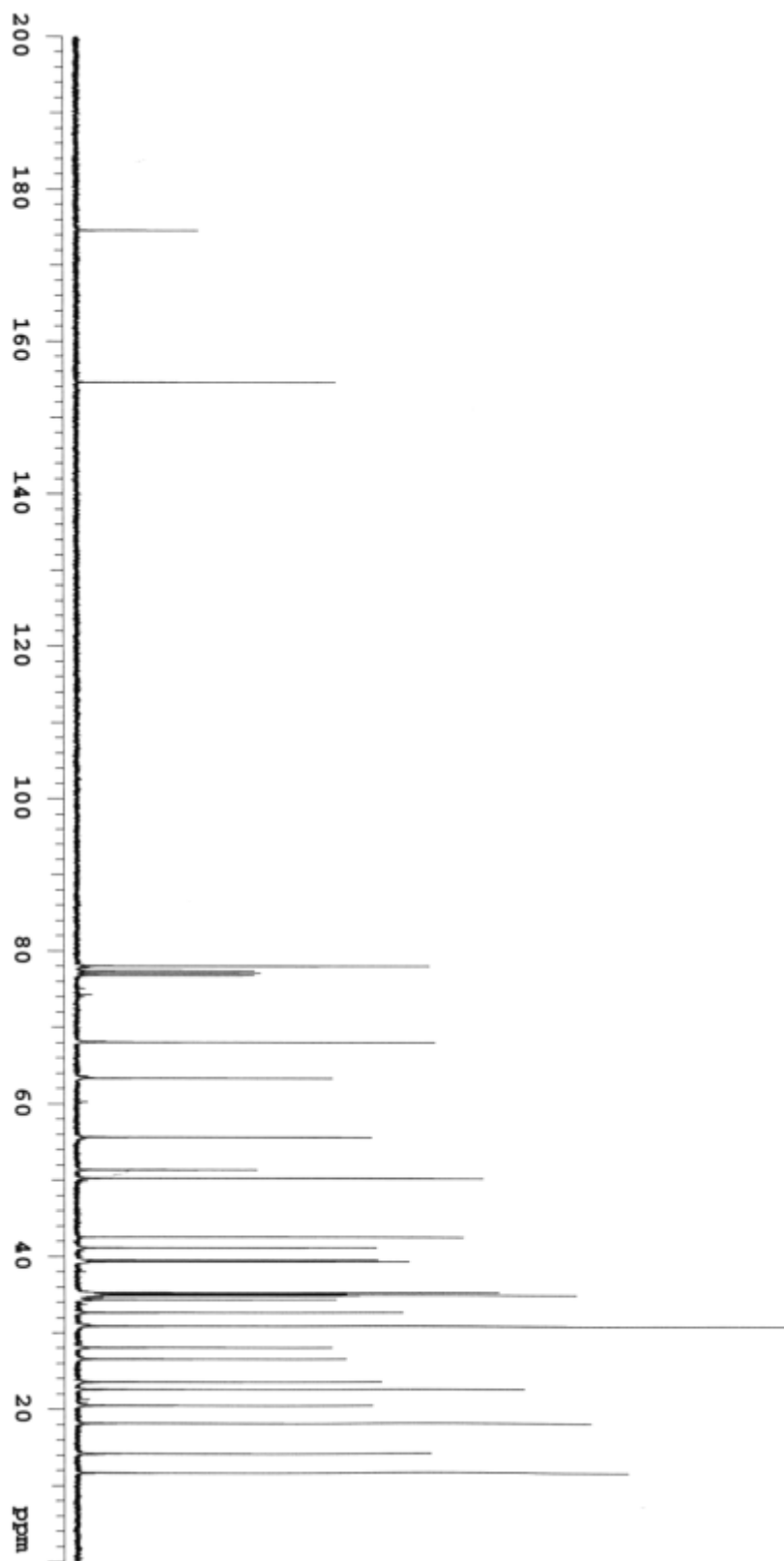
# Dimer (A)



**Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -hydroxyl-5 $\beta$ -cholanoate.**

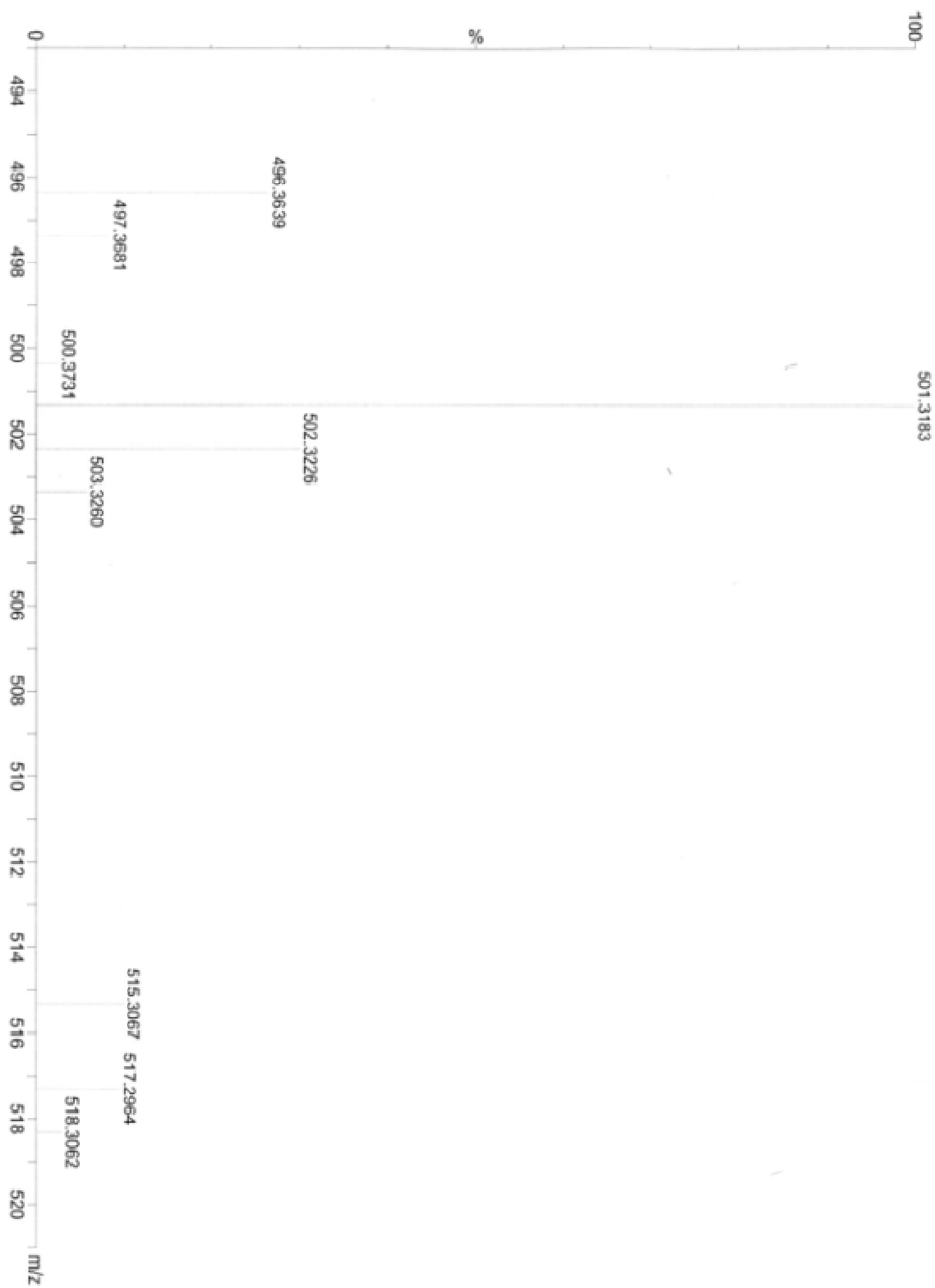


**Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -hydroxyl-5 $\beta$ -cholanoate.**

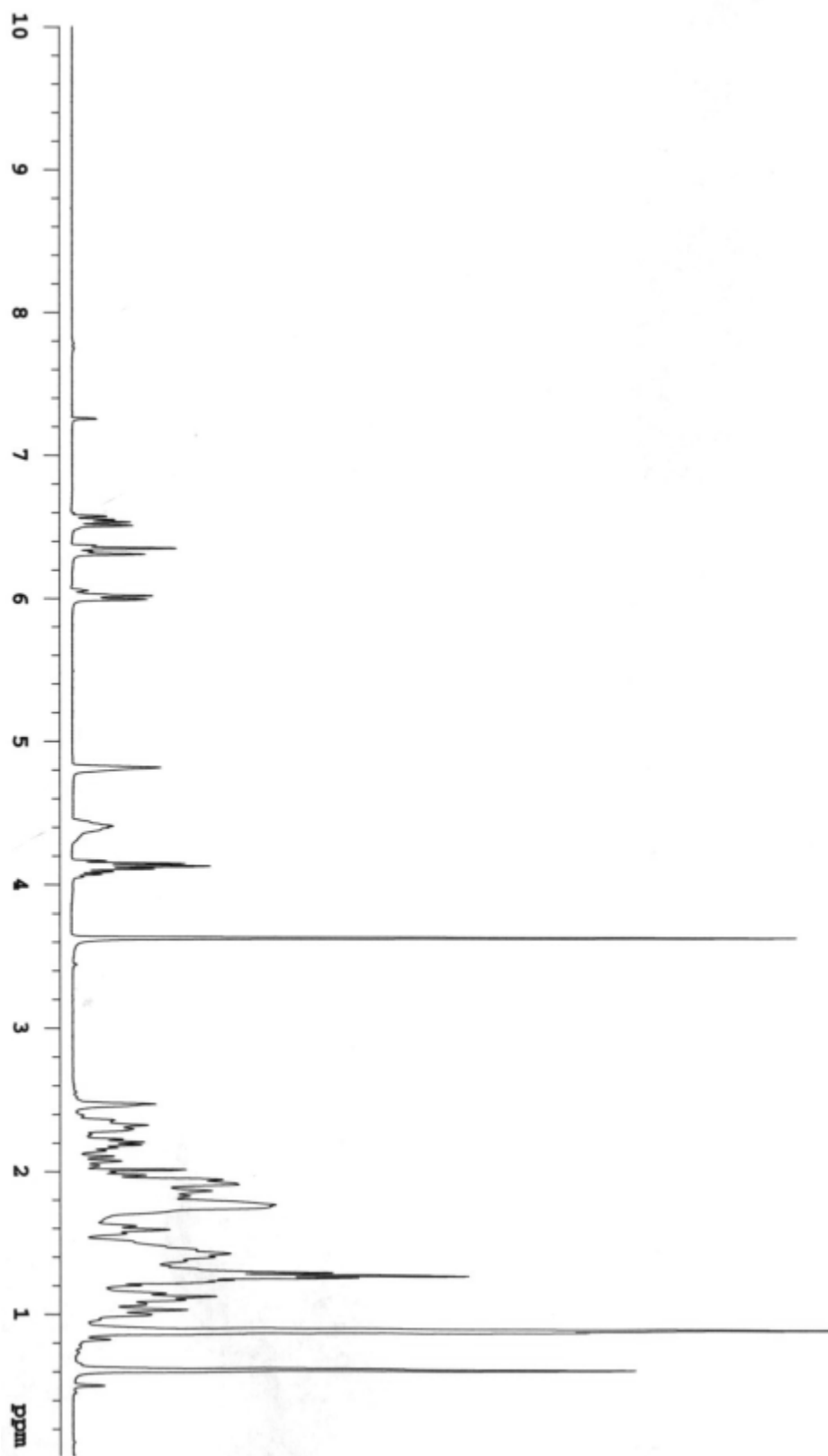




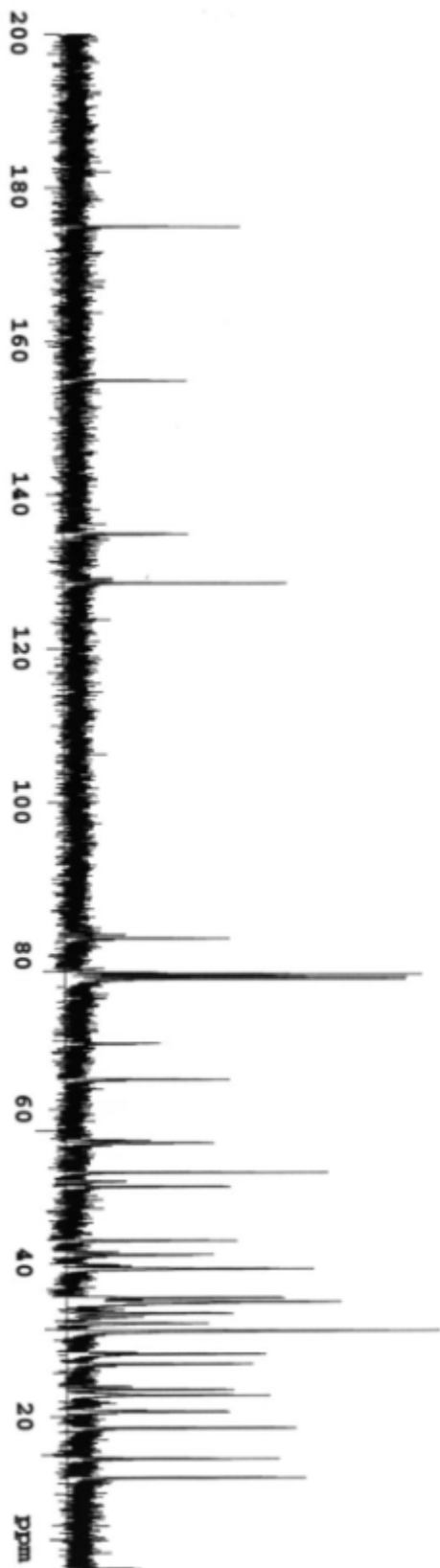
Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -hydroxyl-5 $\beta$ -cholanoate.



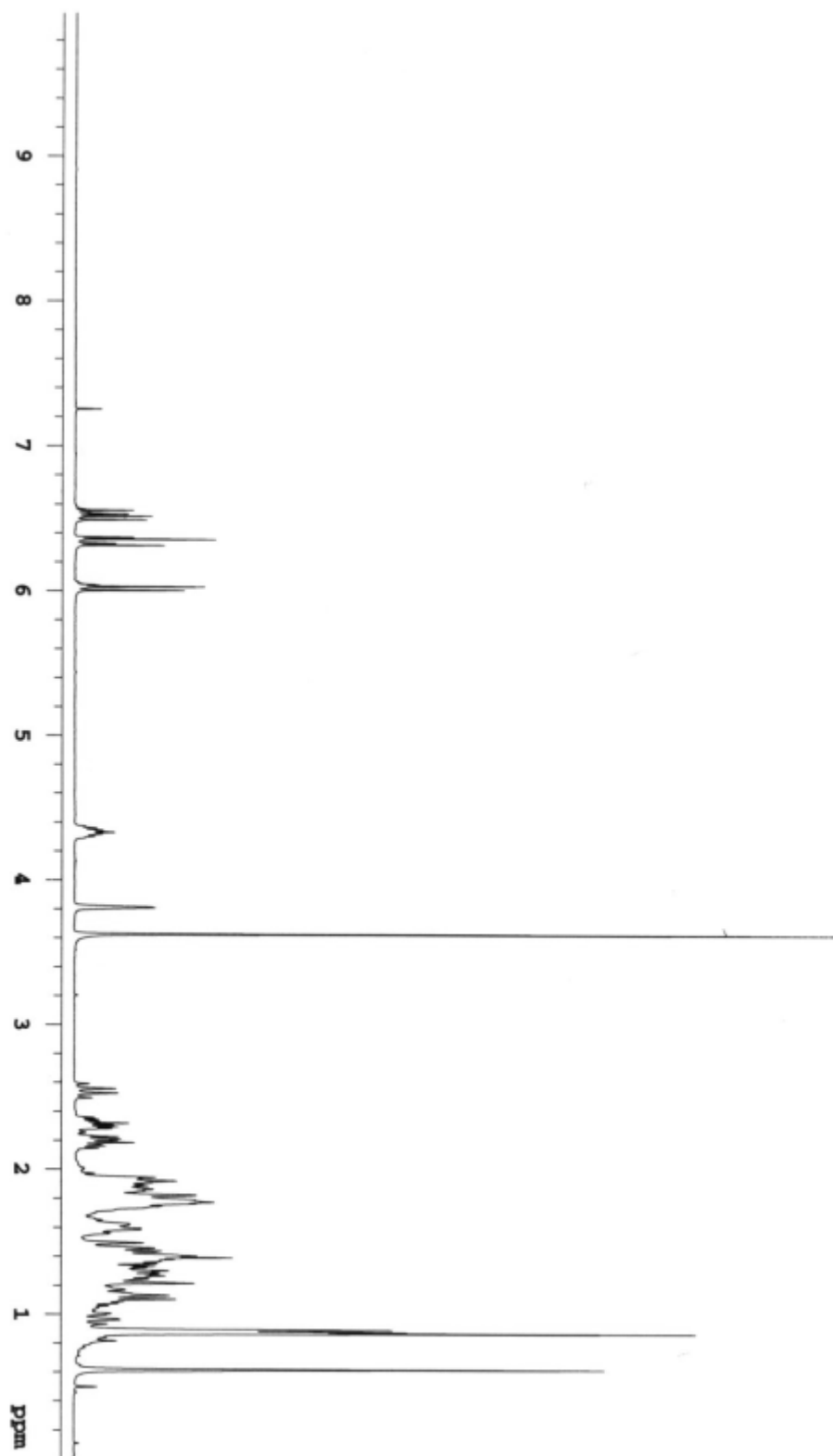
**Methyl-3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -vinylsulfonyloxychenodeoxycholate**



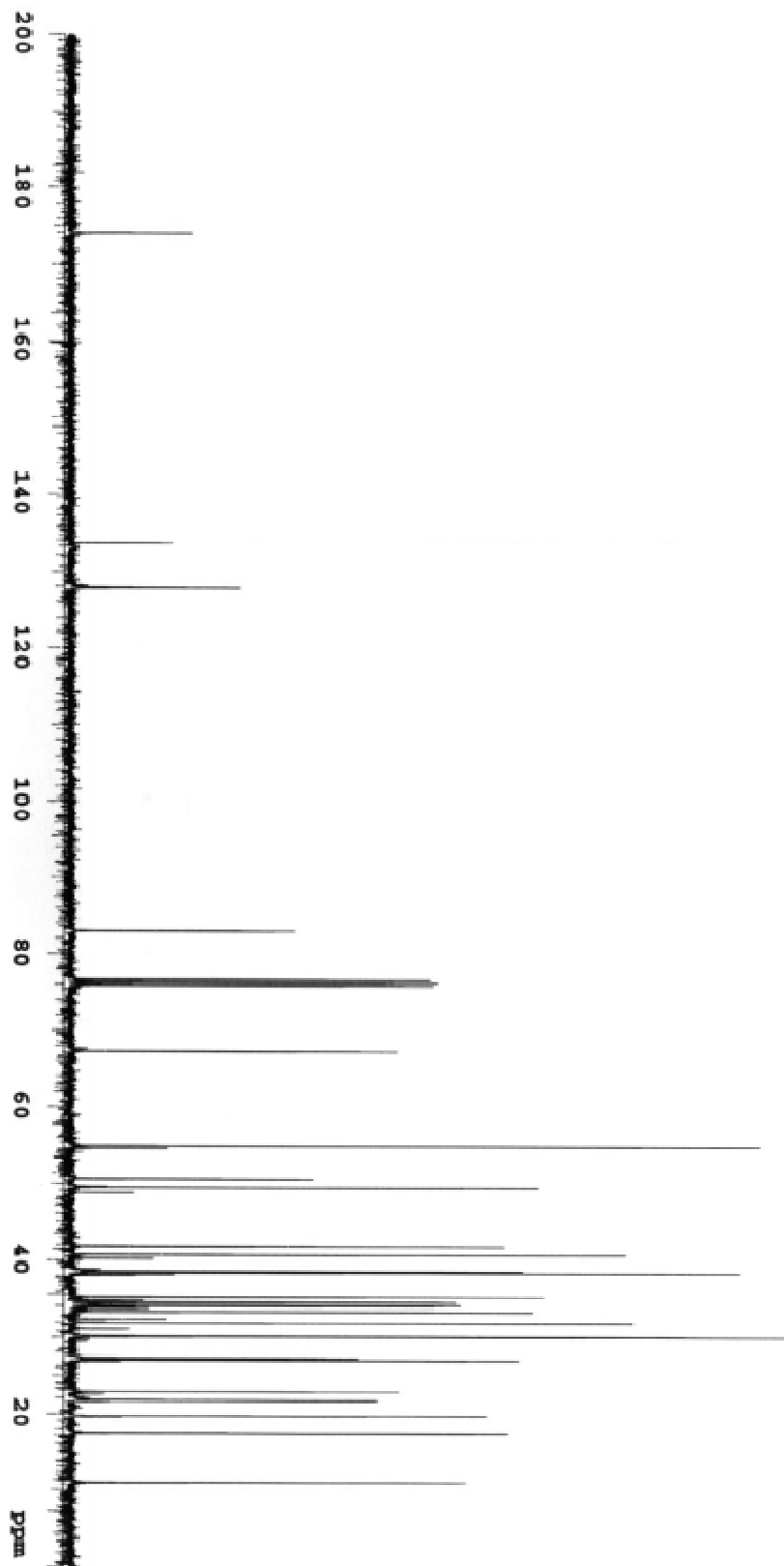
Methyl-3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -vinylsulfonyloxychenodeoxycholate



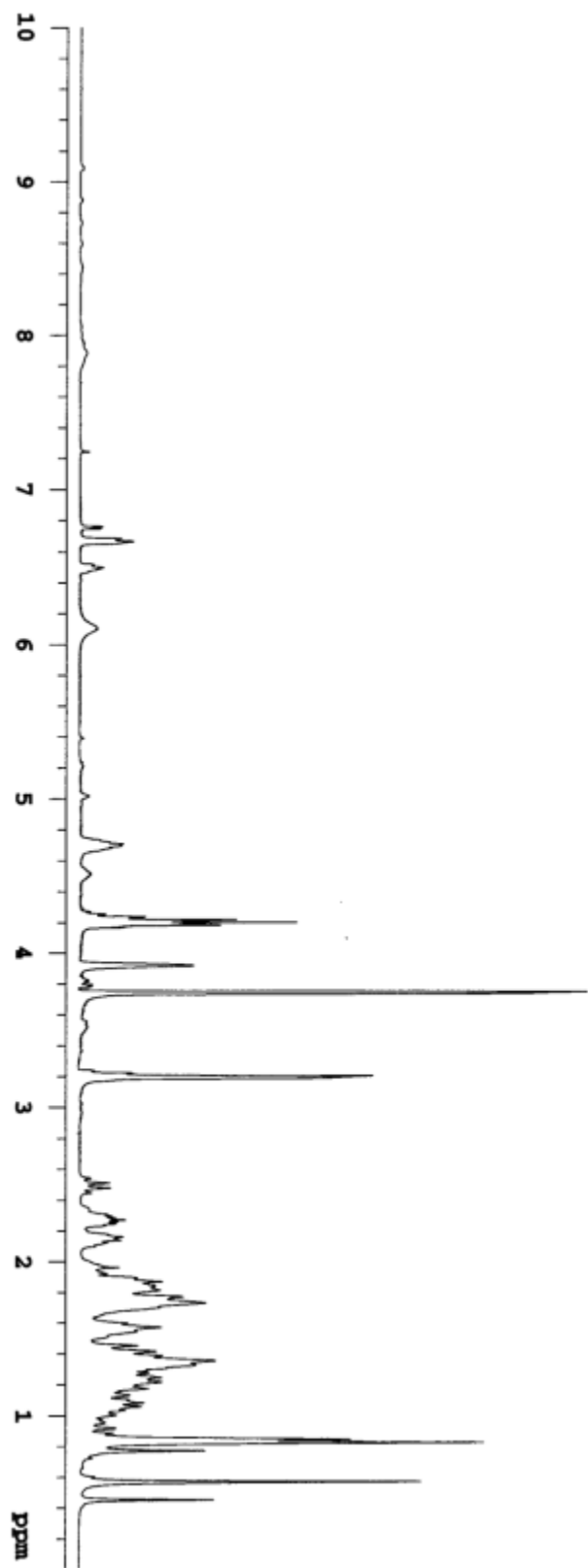
**Methyl-7 $\alpha$ -Hydroxy-3 $\alpha$ -vinylsulfonyloxychenodeoxycholate**



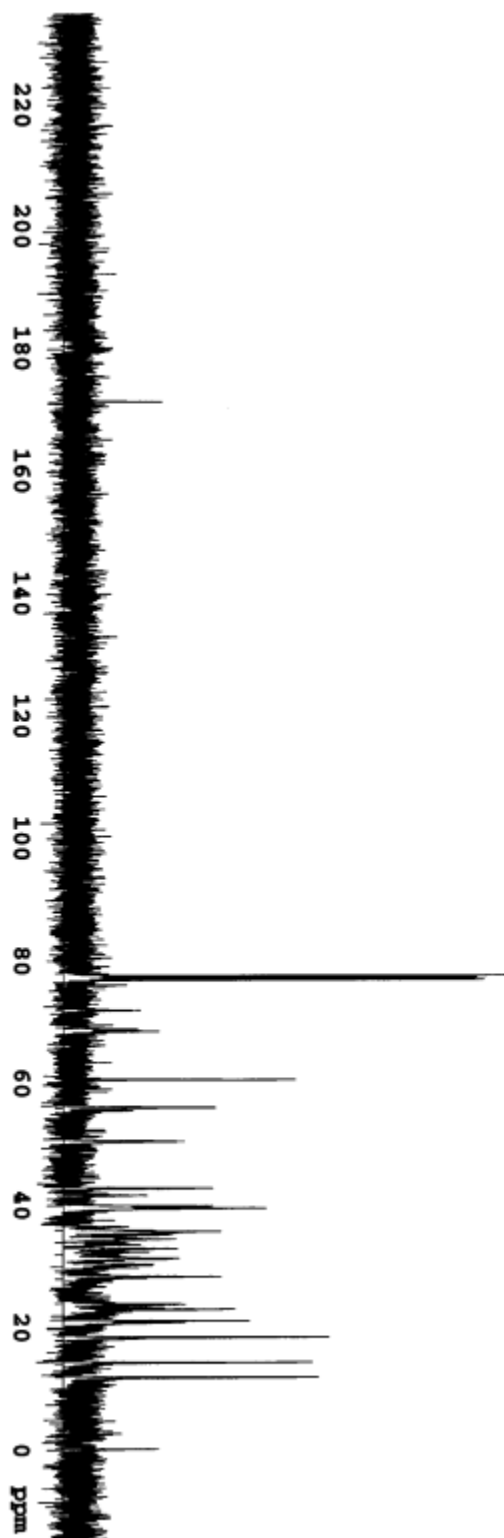
Methyl-7 $\alpha$ -Hydroxy-3 $\alpha$ -vinylsulfonyloxychenodeoxycholate



# Dimer (B)



Dimer (B)



## CHAPTER 4

### 4. SYNTHESIS OF BILE ACIDS DERIVATIVES TOWARDS MACROCYCLE CONSTRUCTION VIA SONOGASHIRA COUPLING

#### 4.1 Introduction

Macrocycles are large molecular structures with twelve or more units (usually atoms) organized in a ring-like arrangement. Due to their size, macrocycles lack the rigidity of smaller ring systems like cyclohexane, and can often take on multiple conformations by rotating around relatively unrestricted chemical bonds. The three-dimensional orientation of macrocycles is important as it affects their properties as ligands,<sup>94</sup> especially in supramolecular chemistry where the size and shape of a cavity within a host molecule determines which guest molecules it can accept. Therefore, the rigidity of macrocycle structures is of consideration when designing these chemical architectures. Strategies to minimize the undesirable conformers of a macrocyclic ring include designing systems which self-assemble into desired structures or ones which have fewer freely rotating bonds. Macrocyclic structures with limited free rotation are most efficiently accessed through the use of conformationally locked building blocks and cyclization methods which introduce in rigid linkers.

For this reason, alkynes are attractive functional groups for introducing into macrocycles. Alkynes have a rigid 180° linear shape across four carbon-carbon bonds which locks structures in specific conformations. They represent an electron rich  $\pi$ -system, which can be conjugated with other unhybridized  $pi$  orbitals to produce conformationally locked extended  $\pi$ -systems. Alkynes also allow for self-assembly of structures through intramolecular forces such as strong  $\pi$ - $\pi$  stacking, van der Waals forces, and hydrophobic interactions.<sup>76</sup> Furthermore, alkynes can under a wide number of further synthetic transformations to access more varied chemical



architectures, including [2+2+2] cyclotrimerization, azide–alkyne [3 + 2] cycloaddition (“click” reactions), and palladium-catalyzed cross coupling. One drawback in the use of alkynes in macrocycle construction are notably lower yields compared to other coupling methods.<sup>95</sup>

Alkynes also have well established coordination properties due to their high electron concentration and have been shown to bind to alkali metal cations for molecular recognition and scavenging purposes. This binding occurs via electron donating of the alkyne into the metal’s empty *d* orbitals while the metal back donates into the alkynes unfilled  $\pi^*$  antibonding orbital according to the Dewar–Chatt–Duncanson model.<sup>77</sup> Alkyne-metal complexes are formed by displacement of a more liable ligand like CO or MeCN and are often involved in catalytic processes to transform alkynes into other functional groups.<sup>78</sup> A wide variety of metals have shown affinity for alkynes as 2- and 4-electron donating ligands including platinum, tungsten, cobalt, molybdenum and chromium in mono-, bis- and tris-coordinated structures.<sup>79</sup> These complexes can be easily identified via IR spectroscopy coordinating to the metal center causes the alkyne substituents to bend away and stretches out the carbon-carbon triple bond, making it more alkene-like and shifting the frequency from 3300 to 1800  $\text{cm}^{-1}$ .

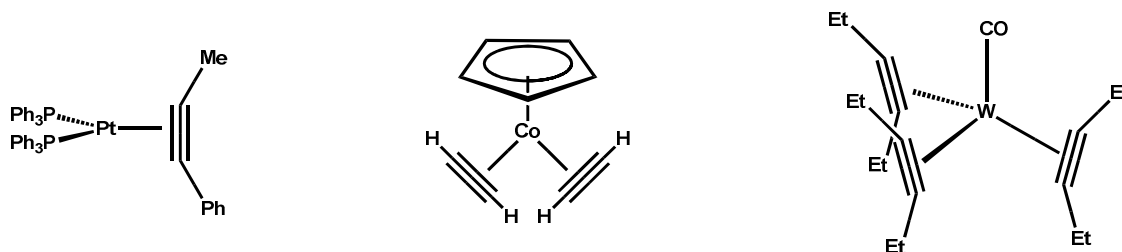


Figure 4.1 Metal-Alkyne Complexes

Alkynes can be employed in synthetic strategies to form new carbon-carbon bonds through transition metal catalyzed reactions like the Sonogashira reaction. This coupling reaction joins terminal alkynes to iodo-substituted aromatic structures, and results in rigid  $\pi$ -conjugated systems. It employs a palladium catalyst alongside a CuI co-catalyst in the presence of triethylamine as a base. A characteristic of the reaction proceeding is the formation of an ammonium iodide side product, which precipitates out of solution as needle-like crystals. An important limitation of the reaction is the requirement to perform it under an inert atmosphere due to the oxygen and water sensitivity of the phosphine ligands and copper co-catalyst, although recent research has developed more robust procedures.

The resulting products are unique aryl-ethynylene groups and are a highly attractive subject for study in the construction of unique molecular architectures. They possess rigid  $\pi$ -conjugated frameworks which can be extended through step-wise reactions. These  $sp$ - $sp^2$  conjugated systems exhibit both electronic and self-assembly properties and have been investigated as supramolecular building blocks, organic electronic materials,<sup>80, 81</sup> and liquid crystals.<sup>82</sup> The properties of the resulting macrocycles can be tuned somewhat by simply varying of the *ortho*, *meta*, or *para* substitutions and the length of the oligomer chain.<sup>83</sup>

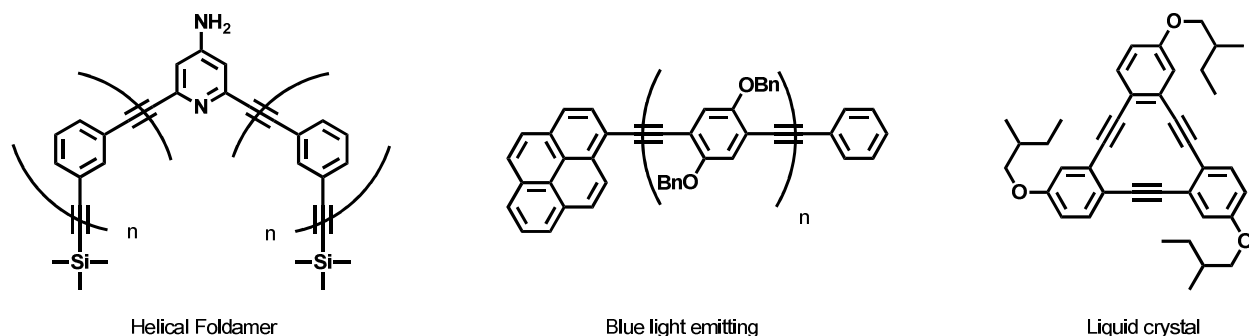


Figure 4.2 Aryl-Ethynylene Structures

Previous work in the Dias lab has made use of chenodeoxycholic acid (CDCA) as a building block to produce  $7\alpha$ -functionalized steroidal macrocycles. Selective functionalization of the  $7\alpha$  position is accomplished by taking advantage of the differential reactivity of the bile acid hydroxyl groups caused by their increasing steric hindrance. By introducing functionality at the  $7\alpha$  position, macrocycles can easily be constructed via head-to-tail linking through the Yamaguchi esterification. The resulting functionalized macrocycles have been shown capable of intramolecular reactions through ruthenium catalyzed olefin metathesis.

Building on this previous work, the combination of the steroidal building blocks along with terminal alkynes and aryl iodine groups is envisioned to access large, constrained macrocycles with functionalities locked in a downward orientation. Structures accessed through palladium catalyzed cross coupling of these macrocycles are envisioned to be highly rigid despite their size due to the resulting aryl-ethynylene linkages, resulting in large barrel-like macrocycles. In this work, we report studies towards the development of these functionalized macrocycles and efforts towards their coupling into large steroid-based ‘barrel’ structures.

## 4.2 Results and Discussion

### 4.2.1 Synthesis of Functionalized Steroid Macrocycles

Four terminal alkynyl carboxylic acids were selected for investigation to produce functionalized BAs with a variety of different length linkers. The shortest 3-butynoic acid was removed from study to it immediately polymerized upon exposure to organic base. It is believed that in the case of 4-butynoic acid, the  $\alpha$  protons are sufficiently acidic to be deprotonated under reaction conditions and undergoes cascading Michael-like additions to form long chain polymers (see Scheme 4.3) The other terminal alkynyl carboxylic acids did not display this issue due to one or more methylene groups separating the  $\alpha$  hydrogens from the alkyne group.

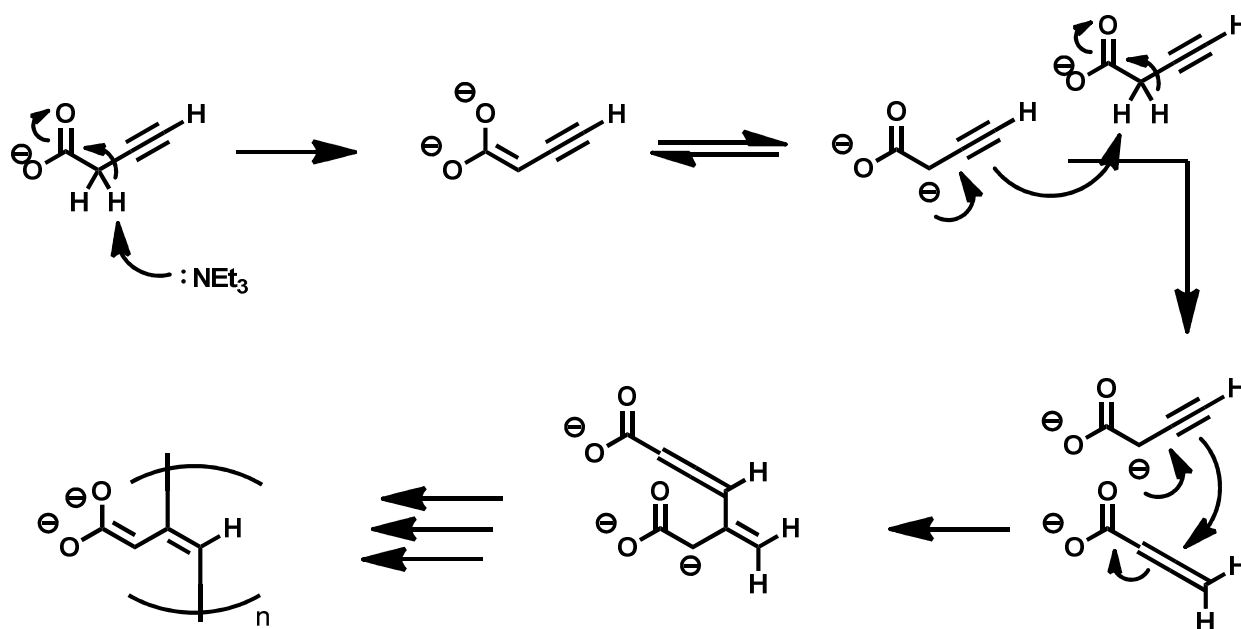


Figure 4.3 Proposed mechanism for the polymerization of 3-butynoic acid

The reactivity of CDCA and cholic acid alcohols towards the proposed coupling methods was examined by running previously described Yamaguchi esterifications on the CDCA and cholic acid methyl esters. While the methyl cholate was commercially available, the CDCA methyl ester was prepared by reacting CDCA with acetyl chloride in the presence of methanol at 0 °C. After extraction and evaporation under reduced pressure, the CDCA methyl ester was isolated in high yield and purity as a white solid.

While Yamaguchi esterification is usually run by refluxing the anhydride intermediate with the coupling alcohol in toluene, the BAs would fortunately couple with the carboxylic acids at room temperature to yield the terminal alkynyl esters. To accomplish this, the carboxylic acids were stirred with 2, 6-dibenzoyl chloride in a solution of THF and triethylamine. This caused a gradual change in color of the solution from colorless to yellow or orange and led to the formation of a precipitate, most likely triethylammonium chloride. Both the CDCA and cholic acid methyl esters saw complete esterification after 24 h at room temperature, yielding the functionalized BAs in good yields as determined by the upfield chemical shift of the  $\beta$  hydrogen atoms in  $^1\text{H}$  NMR spectra. Mono-, di-, and trisubstituted products could be obtained through the same methodology simply by changing the equivalents of the reactants relative to the bile acid. Reactivities of the  $\alpha$  hydroxides followed the expected pattern ( $3 > 12 > 7$ ), with every increase in reactant showing selectivity towards the next reactive hydroxide. There was also a notable trend in the physical appearance of the products, with the  $3\alpha$ -monoesters being white solids, the diesters as off-white semisolids, and the triesters as light yellow oils.

In contrast, 4-iodobenzoic acid displayed different reactivity. While complete esterification of the  $3\alpha$  position could be achieved at room temperature, attempts at the Yamaguchi esterification between CDCA methyl ester and 4-iodobenzoic acid at room

temperature yielded an approximately 50/50 mixture of the 3 $\alpha$  monoester and the 3 $\alpha$ ,7 $\alpha$  diester. Similar reactivity was observed in reactions with cholic acid, with no transformation of the less reactive 12 position. Completion of the Yamaguchi esterification at all positions could be achieved through the traditional method of first forming the acid anhydride through the reaction of 2,6-dichlorobenzoyl chloride to the appropriate carboxylic acid, followed by addition of the acid anhydride to a solution of the BA methyl ester and DMAP in boiling toluene and refluxing for 24 hours. This reactivity was noted as a potential strategy for selective functionalization of the 3 $\alpha$  and 7 $\alpha$  positions without protecting groups.

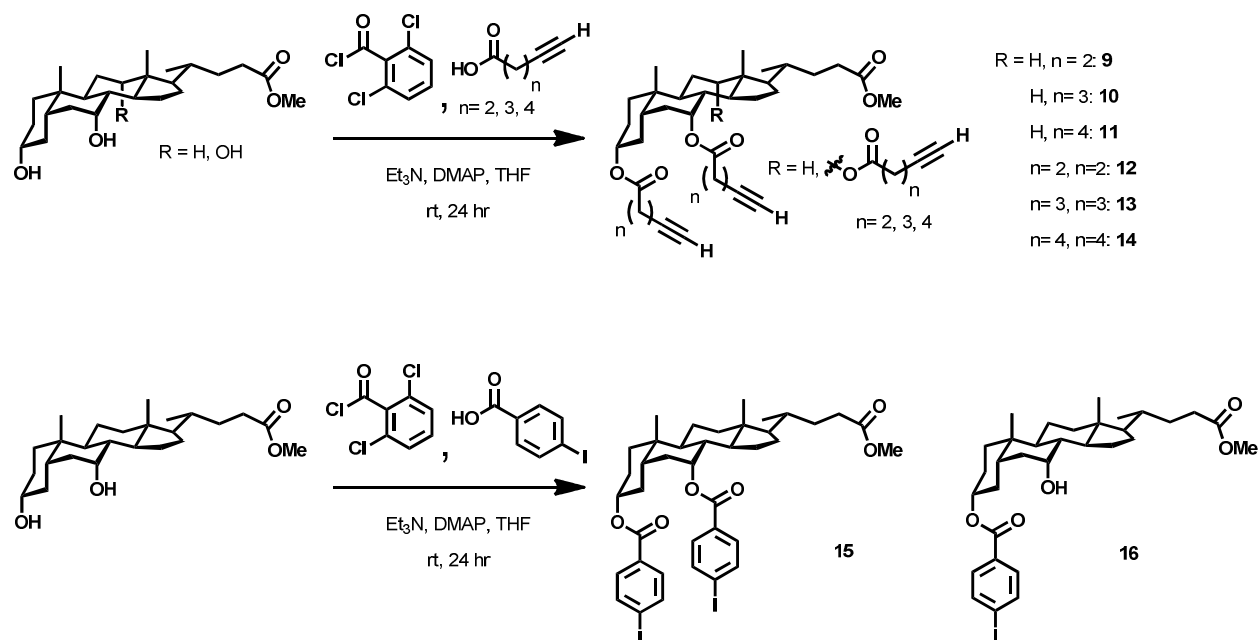


Figure 4.4 Comparison of the hydroxyl reactivities of CDCA

Using a single equivalent of the carboxylic acids, selective functionalization the 3 $\alpha$  position was performed to produce derivatives for testing the Sonogashira coupling of functionalized bile acids. Both the 3 $\alpha$ -hexynoic and 3 $\alpha$ -4-iodobenzoic esters were produced in the respective methods as off-white solids in good yields. Cross coupling was performed utilizing Sonogashira conditions. In a flame-dried flask charged with nitrogen, THF and triethyl amine were introduced and degassed for 10 minutes with nitrogen to remove any dissolved oxygen. To the flask, the functionalized BAs, palladium catalyst, and CuI co-catalyst were added in order. Upon addition of copper, the solution took an immediate green tint which rapidly faded over an hour to yellow. The reaction was allowed to run overnight, at which point it turned golden brown and needle-like crystals precipitated from solution (assumed to be triethylammonium chloride). During evaporation under reduced pressure, the 3 $\alpha$ -bridged CDCA dimer product precipitated out of solution as a golden solid in high yields and high purity (*see Scheme 4.5*).

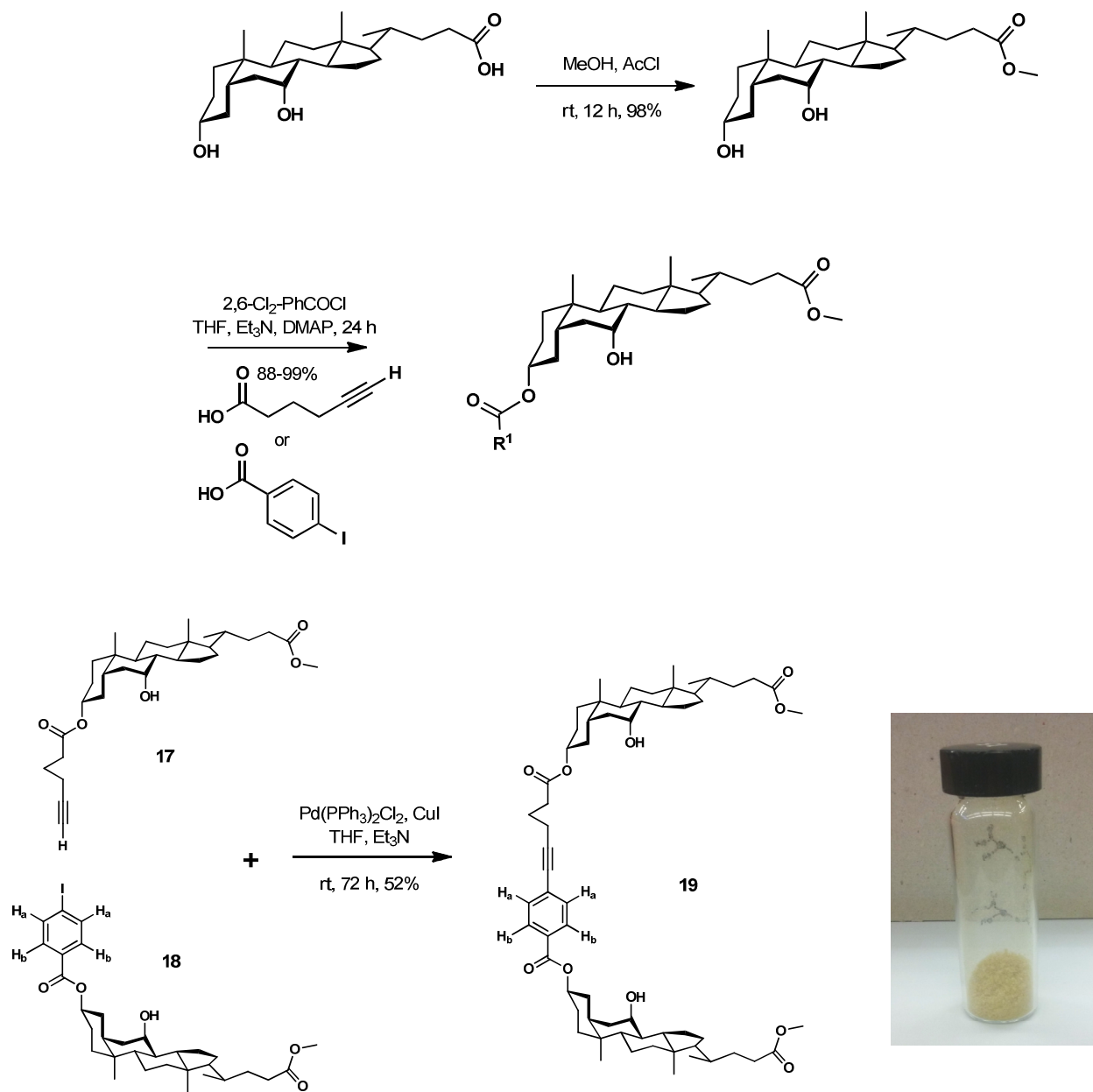


Figure 4.5 Sonogashira dimerization of 3 $\alpha$  substituted CDCA

The 7 $\alpha$  functionalized CDCA derivatives were produced using previously developed methodology in the Dias lab. CDCA was first methylated with acetyl chloride in the presence of methanol to yield the CDCA methyl ester as a white solid. This was treated with excess



ethylchloroformate in pyridine with imidazole at  $-20\text{ }^{\circ}\text{C}$  according to the method developed by Fieser *et. al.*<sup>84</sup> The mixture was washed with a 15% copper sulfate solution to remove pyridine, as previously described, to give the  $3\alpha$  carboxy-protected CDCA methyl ester in good yield. Afterwards, the previous Yamaguchi esterification conditions were applied with the terminal alkynes at room temperature, while the 4-iodobenzoic acid coupling required reflux in toluene. The resulting products were isolated in good yields as viscous yellowish oils. All samples were deprotected by refluxing in the presence of potassium carbonate in methanol and THF as previously described to give the  $7\alpha$  functionalized CDCA derivatives as solids.

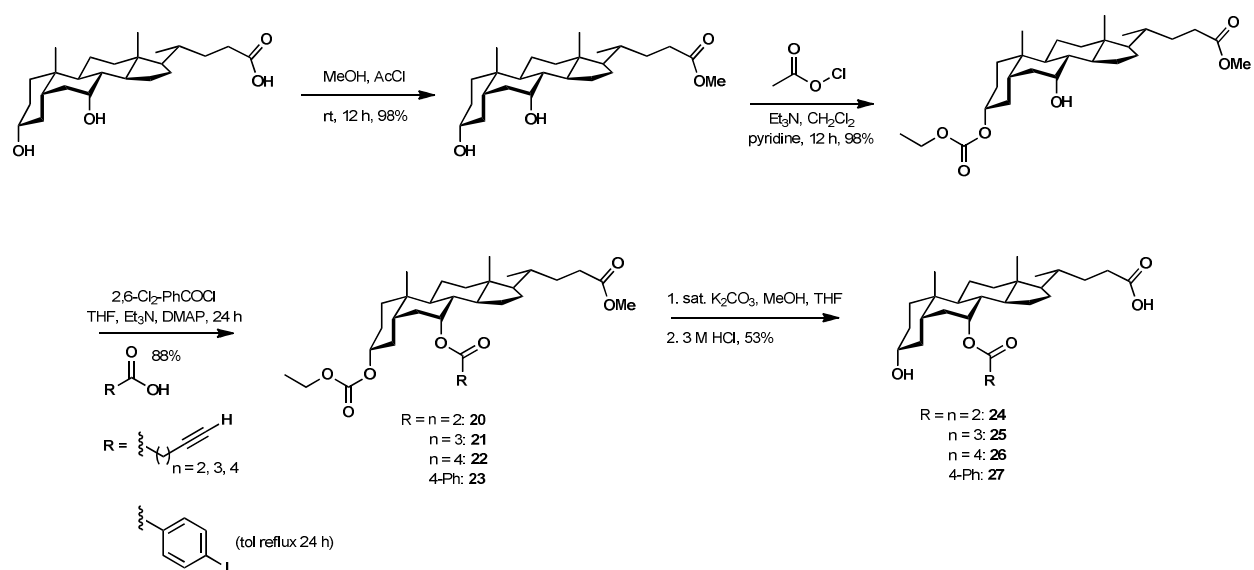


Figure 4.6 Synthesis of  $7\alpha$  Functionalized CDCA Derivatives

Cyclization to the functionalized trimers was performed by previously reported methods. The functionalized CDCA monomers were added to a solution of 2, 6-dichlorobenzoyl chloride in THF, followed by triethylamine. The reaction was allowed to stir at room temperature for an

hour and was then added dropwise to a refluxing solution of DMAP in toluene over 12 hours.

The cooled reaction was then extracted and purified via recrystallization.

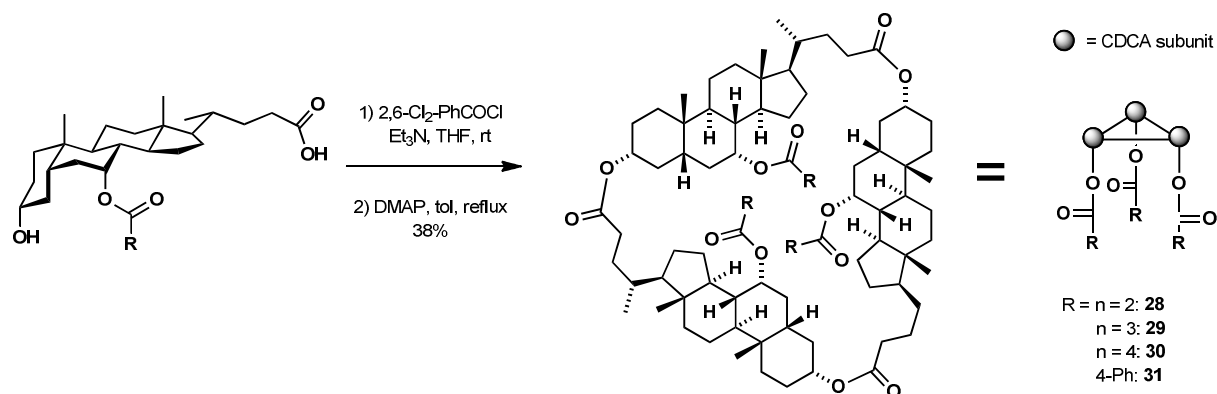


Figure 4.7. Cyclotrimerization

Attempts were made to recrystallize the trimers for X-ray crystallography analysis. Previously reported methods in the literature included recrystallization in acetone and hexane. Both these attempts gave the product as a tacky light brown amorphous solid. Crystals were observed in one sample that was purified by slow evaporation from methylene chloride at room temperature, however these turned out to be the acid anhydride side product. In screening for other solvents, it was noted that the trimers displayed high solubility in chlorinated solvents like methylene chloride and chloroform but unlike the monomers, had a low solubility in ether and methanol. Attempts at a DCM/methanol crystallization again yielded a tacky, amorphous product. The products were then purified by dissolving in a minimal amount of chloroform, which was added dropwise to a boiling solution of diethyl ether. After cooling in an ice bath, the excess liquid was decanted and the resulting solids were washed with ice cold diethyl ether and

allowed to dry at room temperature. This resulted in the products as an amorphous off-white powder. However, large enough crystals for X-ray crystallography could not be isolated.

Table 4.1 Recrystallization Attempts

<b>Solvent</b>	<b>Results</b>
Acetone	Amorphous Tacky Solid
Hexane	Amorphous Tacky Solid
DCM evaporate overnight	Amorphous Tacky Solid
DCM/Methanol	Amorphous Tacky Solid
Chloroform/ Boiling Diethyl Ether	Amorphous White Powder

Sonogashira coupling of the resulting trimers under the previous conditions proved unsuccessful, giving only starting material with no evidence of intermolecular reactions. A range of conditions were then attempted with the hexynoate 4-iodobenzoate substituted derivatives to see if a catalyst or solvent change would improve the results. It was found that the use of THF or neat triethylamine gave no reaction with either catalysts. However, when switching the solvent to dimethylformamide, the reaction had an immediate color change to orange, which gradually faded to yellow over time with formation of a white precipitate. Both catalysts demonstrated similar reactivity, indicating that completion of the reaction was dependent on solvent conditions. Of note is DMF has the highest polarity of the potential solvents. It is believed the higher polarity of the solvent system may either stabilize the polar palladium intermediates or drive the hydrophobic steroidal cyclotrimers together, enabling the Sonogashira cross coupling to

Table 4.2 Sonogashira Reaction Conditions

Catalyst	Solvent	Result
$\text{Pd}(\text{PPh}_3)_4$	THF/ $\text{Et}_3\text{N}$	No reaction
$\text{Pd}(\text{PPh}_3)_4$	DMF/ $\text{Et}_3\text{N}$	New TLC spot detected
$\text{Pd}(\text{PPh}_3)_4$	$\text{Et}_3\text{N}$	No reaction
$\text{Pd}(\text{PPh}_2)_2\text{Cl}_2$	THF/ $\text{Et}_3\text{N}$	No reaction
$\text{Pd}(\text{PPh}_2)_2\text{Cl}_2$	DMF/ $\text{Et}_3\text{N}$	New TLC spot detected
$\text{Pd}(\text{PPh}_2)_2\text{Cl}_2$	$\text{Et}_3\text{N}$	No reaction

take place. Because of examples of the Sonogashira reaction being run in very polar solvents, like water, it is believed that the former explanation is most likely.

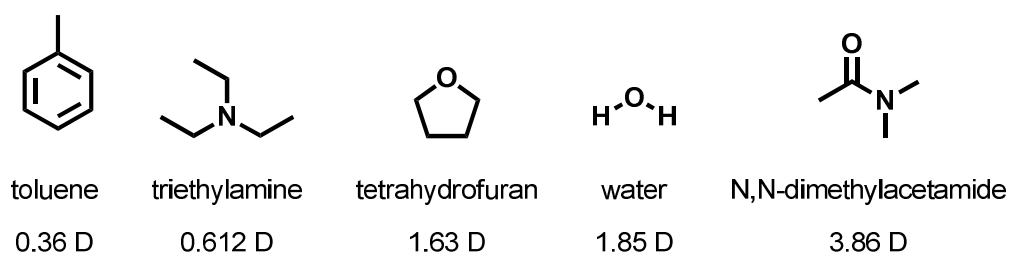


Figure 4.8 Dipole moments of solvents

Sonogashira coupling of the pentyn-, hexyn-, and heptynonate functionalized CDCA cyclotrimers with the 4-iodobenzoate CDCA cyclotrimer were performed under the investigated conditions with  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  as the catalyst and DMF as the solvent. The products were isolated and purified by dissolving in chloroform and dropwise addition to boiling diethyl ether. The products were washed with cold ether and dried to yield the expected ‘barrel’ structures as white powders in low yields.  $^1\text{H}$  NMR spectroscopic analysis of the products indicated completion of the Sonogashira coupling via the characteristic shifts of the aromatic peaks as previously described.

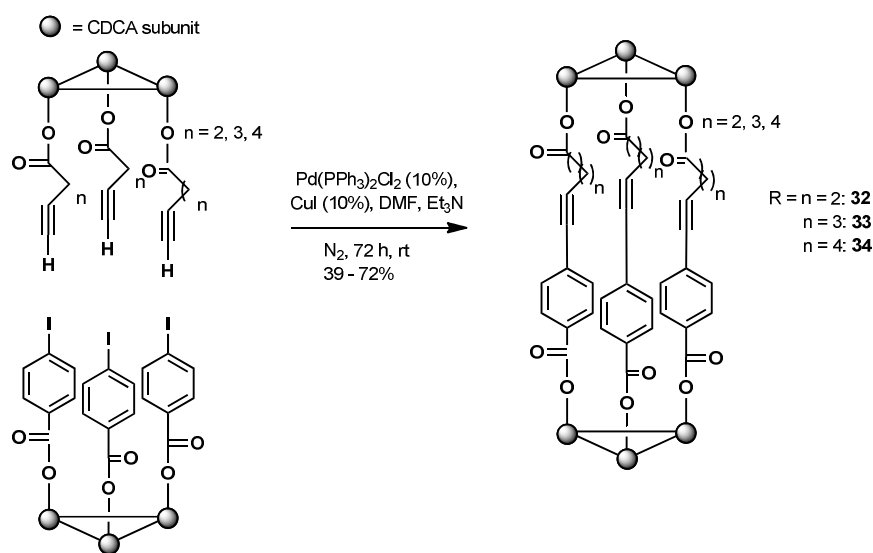


Figure 4.8 Sonogashira coupling to Barrel-like Macrocycles

Mass spectrometric analysis of the products did not show the expected peaks or those coordinated with sodium or HCl ions. The  $7\alpha$ -functionalized starting materials were also not present. Instead all samples showed peaks at 641 m/z. It is believed that the resulting barrel

structures are not stable to the electrospray ionization method and are instead fragmenting into common steroidal subunits.

#### 4.2.2 Characterization of Functionalized Bile Acids.

##### <sup>1</sup>H NMR Spectroscopy

Methylene and methane protons from the terminal alkyne esters are obscured by peaks from the steroid skeleton. The only indication of esterification was the shifts of the  $\beta$  protons. Both the  $7\beta$  and  $12\beta$  (in the case of cholic acid) protons appear as singlets due to their orientation relative to adjacent protons, while the large steric bulk around the  $3\beta$  proton causes splitting into a multiplet. The peaks appear in order  $12\beta$ ,  $7\beta$ , and  $3\beta$  from 3.8 to 3.4 ppm with increasing steric bulk around the protons corresponding to a shielding effect and a general upfield shift. Esterification of the  $\beta$ -hydroxyl groups results in a downfield shift of approximately 1.0 ppm with the general order of the  $\beta$ -protons being conserved. This general trend is seen both in the BA monomers and the cyclized products. Also of note is the slight but noticeable upfield shift of the C21 doublet in the methyl cholate triesters. As these are the only examples where the  $12\alpha$  position is esterified, it is likely that a small shielding effect is being experienced due to the proximity of C21.

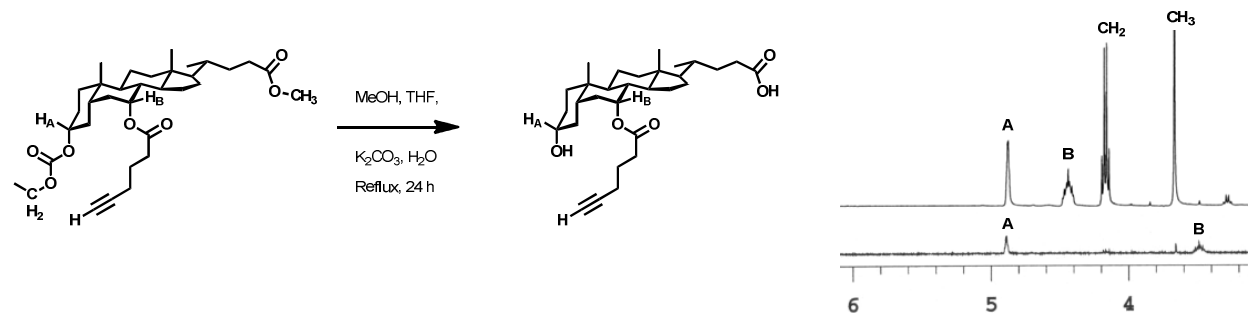


Figure 4.9 <sup>1</sup>H NMR Shifts of β-Protons

The 4-iodobenzoyl ester gave the β hydrogen atom peaks approximately 0.2 ppm downfield from the alkyl esters due to the inductive effect of the benzoyl group. The aromatic peaks were the expected pair of doublets from 8.0 - 7.6 ppm, in agreement with a *para*-substituted aromatic ring with functional groups of differing electron-withdrawing ability. The protons *ortho* to iodine were the most downfield due to its inductive electron withdrawing effects. The splitting of the two doublets increased upon Sonogashira coupling. The conjugated *sp-sp*<sup>2</sup> aryl-ethynylene system increased electron density around the *ortho* protons as the electron-donating alkyne replaces the electron-withdrawing iodine. This also results in a reversal of the positions of the aromatic protons with the protons *ortho* to the ester now more deshielded.

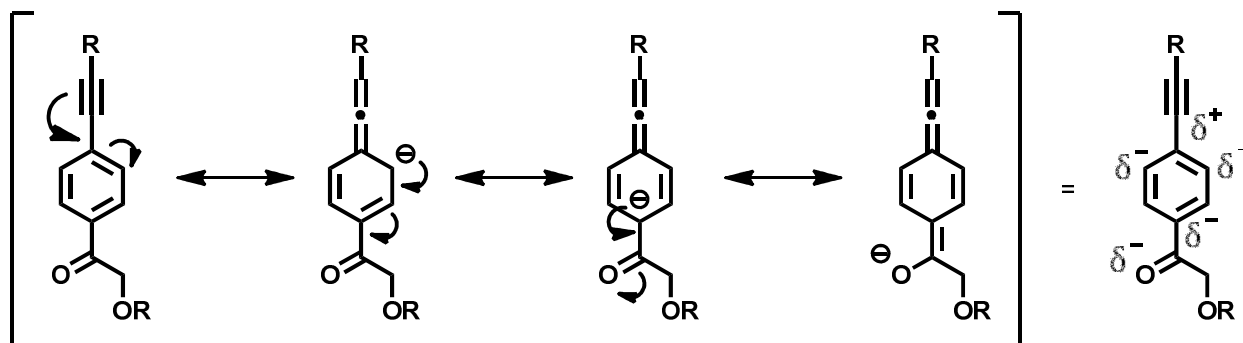


Figure 4.10. Resonance of the conjugate  $sp-sp^2$  conjugated aryl-ethynylene system

### $^{13}\text{C}$ NMR Spectroscopy

The  $^{13}\text{C}$ -NMR spectra allows for identification of the carbons on the alkyl chains of the  $7\alpha$  substituted monoesters. The most characteristic signals are the ester peaks around 170 ppm and the alkynyl C and CH peaks at 83 and 70 ppm, respectively. The carbon atoms of the alkyl chain show a general upfield shift from the methylene  $\alpha$  to the ester at 33 ppm to the methylene  $\alpha$  to the alkyne at 18 ppm.

Peaks for the aromatic protons appear in the expected range with overlaps at 137.9 and 131.5 ppm as expected from an *ortho* substituted ring. The carbonyl substituted carbon atom appears at 130 ppm while the iodo-substituted carbon appears around 100.7 ppm. Upon Sonogashira coupling of the terminal alkyne to the aromatic ring, there is a marked change in the aromatic peaks as the iodine is removed and the electron density around the ring increases. Most notable, there is an upward shift of the *ortho* carbon to 90 ppm, while the other aromatic carbons are drawn closer together to 133 and 131 ppm.



## Mass Spectroscopy

The large barrel-like macrocycles were not detected by MS. However, all samples had common peaks at 609 and 759. These peaks were not present in the trimer macrocycles and represent a new, common fragmentation process throughout all of the barrel-like structures. Future exploration of new methods for ionization are necessary to confirm their structures.

## 4.3 Conclusion

The reactivity of chenodeoxycholic acid and cholic acid hydroxides in Yamaguchi esterification reactions was explored to produce a variety of mono-, di-, and triester derivatives containing both alkyl and aryl functionalities. Reactivity of the alcohols towards esterification followed expected patterns, allowing selective functionalization via variation of the reactant equivalents. It was shown that successful coupling of the carboxylic acids via Yamaguchi esterification was temperature dependant. The alkyl carboxylic acids react at all positions at room temperature, while benzoic acids only couple to the 3 $\alpha$  alcohol at room temperature and required elevated temperatures for the 7 $\alpha$  position. Previously developed methods were utilized for selectively preparing 7 $\alpha$  esters of chenodeoxycholic acid to produce derivatives with terminal alkynyl and iodoaryl moieties. These derivatives were cyclized into cyclotrimers via previous methodologies. Cyclization proved to cause a distinct change in the solubilities of the products, making previous methods for recrystallization and purification unsuccessful. A new recrystallization method of dissolving the product in a minimal amount of chloroform and adding the saturated solution dropwise to boiling ether gave the cyclotrimers as a fine white powder.

Unfortunately X-ray quality crystals could not be obtained. However, the presence of the cyclotrimers were confirmed via high resolution mass spectrometry.

Sonogashira coupling of 3 $\alpha$ -CDCA monoesters possessing terminal alkyne and iodoaryl functionalities was investigated in order to develop a method for coupling the cyclotrimer analogues. It was discovered that longer reaction times (~72 h) were required for full completion of the reaction. This result was likely due to steric interference from the steroid skeleton. Attempts at applying the Sonogashira conditions to the cyclotrimers proved unsuccessful. Upon investigation of different catalyst and solvent conditions, it was found that N,N-dimethylformamide (DMF) was a solvent for the Sonogashira coupling of the cyclotrimers. The cyclotrimers were cross coupled to form steroidal hexamer 'barrels' with aryl alkyne bridges, the structures of which were detected by  $^1\text{H}$  NMR, however there was insufficient material recovered for a clear  $^{13}\text{C}$  NMR and HRMS could not confirm the structure, likely due to fragmentation of the compounds during ionization.

## 4.4 Experimental Section

### 4.4.1 General Methods

**Materials.** Solvents and reagents were purchased from Fischer Scientific unless otherwise noted. Chenodeoxycholic acid and methyl cholate were purchased from Steraloids. Silyl chlorides and 2-chloroethane sulfonyl chloride were purchased from TCI America. Solvents were HPLC grade stored under nitrogen and used without further purification. Triethylamine ( $\text{Et}_3\text{N}$ ) was dried over

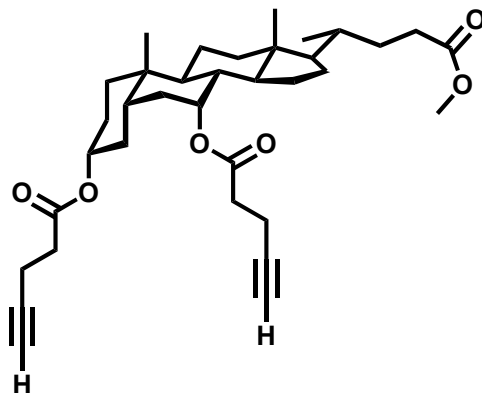
NaOH. Column chromatography was performed on silica gel (MERCK C60) with ethyl acetate:hexane (9:1) as the eluent.

**Instrumentation.**  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded at 400 MHz and 101 MHz, respectively. MSFABspectrometry was performed at University of Kansas Mass Spectrometry center by Lawrence Seib. Single crystal X-ray analysis was performed on a Bruker SMART 1K CCD area detector system at the University of Missouri-Columbia.

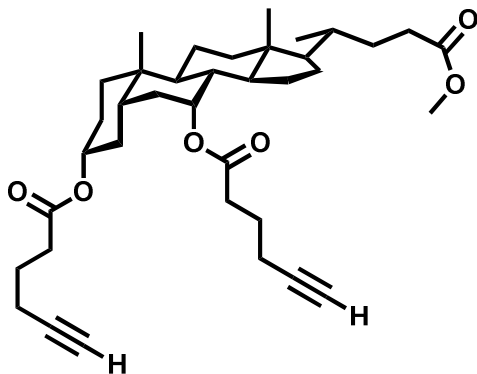
#### 4.4.2 Experimental Procedures

##### 4.4.2.1 Di- and triesters of CDCA and cholic acid methyl esters

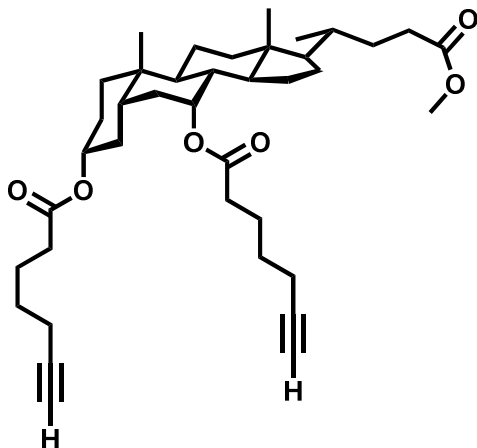
**General procedure for Yamaguchi esterifications.** To a flame-dried flask,  $\text{Et}_3\text{N}$  (2 mL) was added to a mixture of the appropriate acid (2.70 mmol) and 2,6-dichlorobenzoyl chloride (0.525 mL, 3.69 mmol) in 10 mL THF for 1 h, during which a white precipitate formed. The appropriate BA (2.46 mmol) and 5% DMAP (0.03 g) were added to reaction mixture, which was then stirred for 24 h. A yellowish change in color was observed during the reaction. The mixture was extracted with EtOAc, dried over  $\text{Na}_2\text{SO}_4$ , and purified by column chromatography.



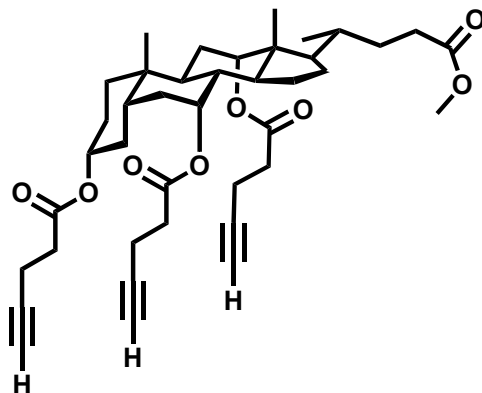
**Methyl 3 $\alpha$ ,7 $\alpha$ -di(4-pentynoyloxy)-5 $\beta$ -cholanoate (9).** It was synthesized according to the standard procedure with 2 eq. of reagents and isolated as a light yellow viscous oil (1.365 g, 2.41 mmol, 98%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.62 (s, 3H, 18- $\text{CH}_3$ ), 0.83 (d,  $J = 8.0$  Hz, 3H, 21- $\text{CH}_3$ ), 0.85 (s, 3H, 19- $\text{CH}_3$ ), 3.61 (s, 3H, 24- $\text{OCH}_3$ ), 4.58 (m, 1H, 3 $\beta$ -H), 4.90 (s, 1H, 7 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  174.3 (C24), 170.9 (C25), 170.6 (C30), 82.2 (C28, C34), 74.1 (C3), 71.4 (C7), 68.9 (C29), 68.7 (C35), 55.4 (C17), 51.2 ( $-\text{OCH}_3$ ), 50.0 (C14), 42.4 (C13), 40.5 (C5), 39.1 (C12), 37.6 (C8), 35.0 (C4), 34.5 (C1), 34.4 (C26, C31), 33.8 (C10), 33.6 (C9), 33.4 (C20), 30.1 (C6), 30.6 (C22, C23), 27.7 (C2), 26.4 (C16), 23.2 (C15), 22.3 (C19), 20.3 (C11), 17.3 (C21), 14.1 (C28, C34) 11.4 (C18) ppm. 32 of 38 Resonances detected. Overlaps at 14.1, 30.6, 34.4, and 82.2 ppm.



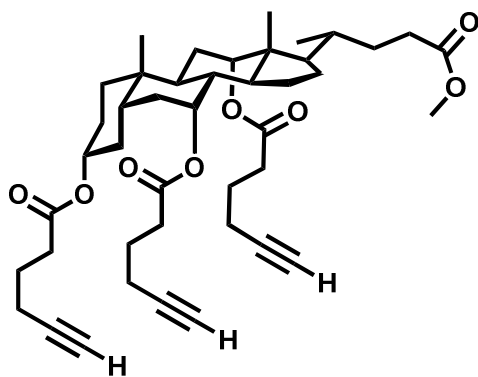
**Methyl 3 $\alpha$ ,7 $\alpha$ -di(5-hexynoxy)-5 $\beta$ -cholanoate (10).** It was synthesized according to the standard procedure with 2 eq. of reagents and isolated as a viscous light yellow oil (1.40 g, 2.36 mmol, 96%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.55 (s, 3H, 18- $\text{CH}_3$ ), 0.83 (d,  $J = 8.0\text{Hz}$ , 3H, 21- $\text{CH}_3$ ), 0.85 (s, 3H, 19- $\text{CH}_3$ ), 3.58 (s, 3H, 24- $\text{OCH}_3$ ), 4.60 (m, 1H, 3 $\beta$ -H), 4.91 (s, 1H, 7 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  172.4 (C24), 172.1 (C25, C31), 83.2 (C35), 83.1 (C29), 74.0 (C3), 71.2 (C7), 69.1 (C30, C36), 55.6 (C17), 51.4 (24- $\text{OCH}_3$ ), 50.3 (C14), 42.7 (C13), 40.8 (C5), 39.4 (C12), 37.8 (C8), 35.2 (C4), 34.8 (C1), 34.7 (C10), 34.0 (C9), 33.3 (C26, C32), 33.2 (C20), 31.3 (C6), 30.9 (C23, C22), 27.9 (C16), 26.7 (C2), 23.5 (C15, C28, C34), 22.6 (C19), 20.6 (C11), 18.2 (C21), 17.7 (C27, C33), 11.7 (C18) ppm. 29 of 36 Resonances detected. Overlaps at 172.1, 69.1, 33.3, 30.9, 23.5 and 17.7 ppm.



**Methyl 3 $\alpha$ ,7 $\alpha$ -di(6-heptynoxy)-5 $\beta$ -cholanoate (11).** It was synthesized according to the standard procedure with 2 eq. of reagents and isolated as a viscous orange oil (1.50 g, 2.41 mmol, 98%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.55 (s, 3H, 18- $\text{CH}_3$ ), 0.83 (d,  $J = 8.0\text{Hz}$ , 3H, 21- $\text{CH}_3$ ), 0.85 (s, 3H, 19- $\text{CH}_3$ ), 3.58 (s, 3H, 24- $\text{OCH}_3$ ), 4.60 (m, 1H, 3 $\beta$ -H), 4.91 (s, 1H, 7 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR in ( $\text{CDCl}_3$ , 101 MHz),  $\delta$  174.5 (C24), 172.7 (C32), 172.7 (C25), 83.8 (C37), 83.7 (C30), 73.9 (C3), 71.0 (C7), 68.7 (C38), 68.5 (C21), 55.7 (C17), 51.4 (24- $\text{OCH}_3$ ), 50.4 (C14), 42.7 (C13), 40.8 (C5), 39.4 (C12), 37.8 (C8), 35.2 (C4), 34.8 (C1), 34.7 (C10, C9), 34.2 (C26, C33), 34.0 (C20), 31.3 (C6), 30.9 (C23, C22), 27.8 (C27, C34), 27.7 (C16), 26.7 (C2), 24.0 (C28, C35), 23.5 (C15), 22.6 (C19), 20.6 (C11), 18.2 (C21), 18.1 (C29, C36), 11.6 (C18) ppm. 24 of 30 Resonances detected. Overlaps at 18.1, 24.0, 27.8, 30.9, 34.2, and 34.7 ppm.

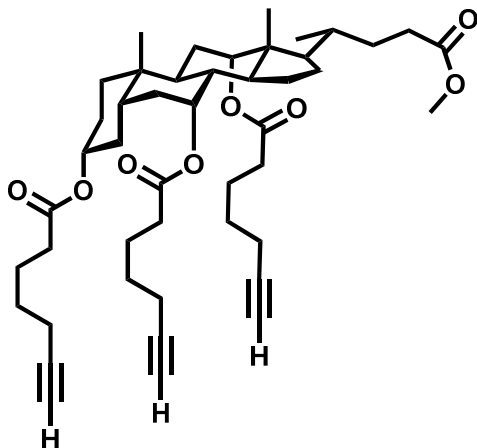


**Methyl 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -tri(4-pentynoyloxy)-5 $\beta$ -choleate (12).** It was synthesized according to the standard procedure with 3 eq. of reagents and isolated as a yellowish oil (1.60 g, 2.41 mmol, 98%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.69 (s, 3H, 18- $\text{CH}_3$ ), 0.78 (d,  $J = 6.8$  Hz, 3H, 21- $\text{CH}_3$ ), 0.88 (s, 3H, 19- $\text{CH}_3$ ), 3.61 (s, 3H, 24- $\text{OCH}_3$ ), 4.56 (m, 1H, 3 $\beta$ -H), 4.91 (s, 1H, 7 $\beta$ -H), 5.08 (s, 1H, 12 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  174.5 (C24), 171.1 (C25), 170.8 (C31, C36), 82.7 (C29), 82.4 (C35, C41), 75.7 (C3), 74.3 (C12) 71.1 (C7), 69.5 (C30), 69.2 (C42), 69.0 (C36), 51.5 (24- $\text{OCH}_3$ ), 47.3 (C14), 45.0 (C17), 43.1 (C13), 40.7 (C5), 37.7 (C8), 34.6 (C4), 34.5 (C26, C32, C38) 34.2 (C1, C10), 34.7 (C10), 33.9 (C9), 33.5 (C20), 31.2 (C6), 30.8 (C22), 30.6 (C23), 28.5 (C16), 27.1 (C2), 26.7 (C11), 25.2 (C15), 22.8 (C27, C39), 22.3 (C33), 17.4 (C21), 14.4 (C28, C34, C40), 14.3 (C19), 12.0 (C18) ppm. 36 of 44 Resonances detected. Overlaps at 170.8, 82.4, 34.5, 34.2, 22.8 and 14.4 ppm.



**Methyl 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -tri(5-hexynoyloxy)-5 $\beta$ -cholate (13).** It was synthesized according to the standard procedure with 3 eq. of reagents and isolated as a yellowish oil (1.71 g, 2.31 mmol, 99%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.73(s, 3H, 18- $\text{CH}_3$ ), 0.81 (d,  $J$  = 6.8 Hz, 3H, 21- $\text{CH}_3$ ), 0.92 (s, 3H, 19- $\text{CH}_3$ ), 3.65 (s, 3H, 24- $\text{OCH}_3$ ), 4.58 (m, 1H, 3 $\beta$ -H), 4.95 (s, 1H, 7 $\beta$ -H), 5.11 (s, 1H, 12 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  172.4 (C24), 172.1 (C25, C31, C37), 83.2 (C29, C41), 83.1 (C35), 74.0 (C3), 73.0 (C12), 71.2 (C7), 69.1 (C30, C36, C42), 55.6 (C17), 51.4 (24- $\text{OCH}_3$ ), 50.3 (C14), 42.7 (C13), 40.8 (C5), 37.8 (C8), 35.2 (C4), 34.8 (C1), 34.7 (C10), 34.0 (C9), 33.3 (C26, C32, C38), 33.2 (C20), 31.3 (C6), 30.9 (C23, C22), 27.9 (C16), 26.7 (C2), 23.5 (C15, C28, C34, C40), 22.6 (C19), 20.6 (C11), 18.2 (C21), 17.7 (C27, C33, C39), 11.7 (C18) ppm. 30 of 40 Resonances detected. Overlaps at 172.1, 83.2, 83.1, 69.1 33.3, 30.9, 23.5, and 17.7 ppm. MS Calc  $\text{M} + \text{Na} = \text{C}_{33}\text{H}_{50}\text{O}_7\text{Na} = 727.4186$ , Found Mass = 727.4199.

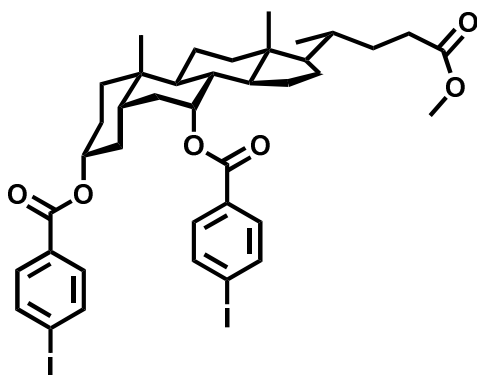




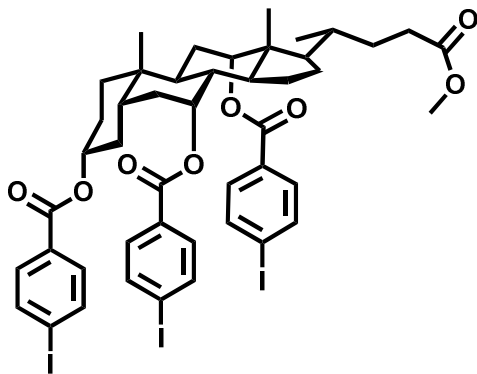
**Methyl 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -tri(6-heptynoyloxy)-5 $\beta$ -choleate (14)** It was synthesized according to the standard procedure with 3 eq. of reagents and isolated as a yellowish oil (1.80 g, 2.31 mmol, 99%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.69 (s, 3H, 18- $\text{CH}_3$ ), 0.78 (d,  $J$  = 6.8 Hz, 3H, 21- $\text{CH}_3$ ), 0.83 (s, 3H, 19- $\text{CH}_3$ ), 3.61 (s, 3H, 24- $\text{OCH}_3$ ), 4.58 (m, 1H, 3 $\beta$ -H), 4.92 (s, 1H, 7 $\beta$ -H), 5.09 (s, 1H, 12 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz),  $\delta$  174.5 (C24), 172.7 (C25, C32, C39), 83.8 (C30, C42), 83.7 (C37), 73.9 (C3), 72.5 (C12) 71.0 (C7), 68.7 (C38), 68.5 (C21), 55.7 (C17), 51.4 (24- $\text{OCH}_3$ ), 50.4 (C14), 42.7 (C13), 40.8 (C5), 37.8 (C8), 35.2 (C4), 34.8 (C1), 34.7 (C10, C9), 34.2 (C26, C33, C40), 34.0 (C20), 31.3 (C6), 30.9 (C23, C22), 27.8 (C27, C34, C41), 27.7 (C16), 26.7 (C2), 24.0 (C28, C35, C42), 23.5 (C15), 22.6 (C19), 20.6 (C11), 18.2 (C21), 18.1 (C29, C36, C43), 11.6 (C18) ppm. 32 of 45 Resonances detected. Overlaps at 172.7, 83.8, 34.2, 30.9, 27.8, 24.0, and 18.1 ppm.

**General procedure for Yamaguchi esterification with 4-Iodobenzoic acid.** To a flame-dried flask,  $\text{Et}_3\text{N}$  (2 mL) was added to a mixture of the appropriate acid (0.0670 g, 2.70 mmol) and 2,6-dichlorobenzoyl chloride (0.525 mL, 3.69 mmol) in 10 mL THF. The reaction was allowed to run for 12 h. The resulting slurry was dissolved in toluene (10 mL) and brought to reflux. A

solution of the appropriate BA (2.46 mmol) and 5% DMAP (0.03 g) in toluene (5 mL) was added dropwise and the reaction was allowed to reflux for 24 h. The mixture was extracted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, and purified by column chromatography.

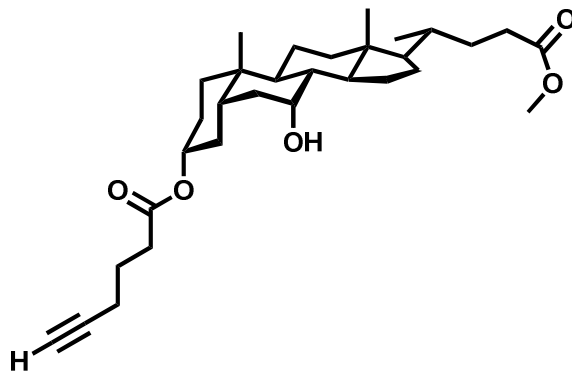


**Methyl 3 $\alpha$ ,7 $\alpha$ -di(4-iodobenzoyloxy)-5 $\beta$ -choleate (15)** It was synthesized according to the standard procedure with 2 eq. of reagents and isolated as a white semisolid (1.90 g, 2.19 mmol, 89%) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  0.64 (s, 3H, 18-CH<sub>3</sub>), 0.90 (d,  $J$  = 6.8 Hz, 3H, 21-CH<sub>3</sub>), 0.92 (s, 3H, 19-CH<sub>3</sub>), 3.65 (s, 3H, 24-OCH<sub>3</sub>), 4.59 (m, 1H, 3 $\beta$ -H), 4.88 (s, 1H, 7 $\beta$ -H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz)  $\delta$  175.0 (C24), 165.3 (C25), 165.2 (C39), 138-137 (C28, C30, C35, C37), 130-132 (C27, C31, C34, C38), 127-128 (C26, C33) 100.9 (C29, C36), 76.5 (C3), 72.1 (C7), 51.4 (24-OCH<sub>3</sub>), 47.8 (C14), 45.9 (C13), 45.4 (C5), 38.2 (C8), 37.8 (C12), 34.7 (C4), 34.6 (C1), 34.5 (C10) 34.3 (C9), 34.2 (C20), 31.3 (C6), 30.9 (C23, C22), 28.7 (C16), 27.2 (C2), 26.3 (C15), 25.0 (C19), 22.3 (C11), 17.5 (C21), 12.2 (C18) ppm. 29 of 38 Resonances detected. Overlaps at 138, 130, 127, 100.9, and 30.9 ppm.

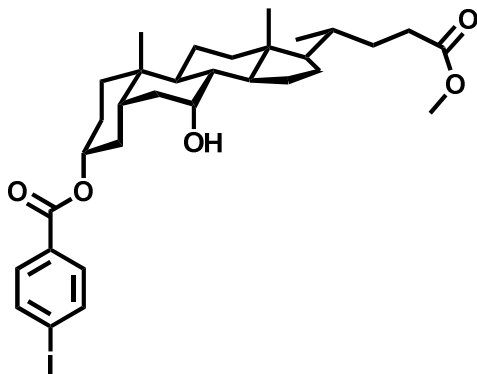


**Methyl 3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -tri(4-iodobenzoyloxy)-5 $\beta$ -choleate (16)** It was synthesized according to the standard procedure with 3 eq. of reagents and isolated as a light orange solid (2.40 g, 2.16 mmol, 88%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.65 (s, 3H, 18- $\text{CH}_3$ ), 0.79 (d,  $J = 6.8$  Hz, 3H, 21- $\text{CH}_3$ ), 0.92 (s, 3H, 19- $\text{CH}_3$ ), 3.59 (s, 3H, 24- $\text{OCH}_3$ ), 4.69 (m, 1H, 3 $\beta$ -H), 5.23 (s, 1H, 7 $\beta$ -H), 5.38 (s, 1H, 12 $\beta$ -H), 7.68 (d,  $J = 8.0$  Hz, 6H, Aromatic H) 7.89 (d,  $J = 8.0$  Hz, 6H, Aromatic H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  175.0 (C24), 165.3 (C25), 165.2 (C39), 138-137 (C28, C30, C35, C37, C42, C44), 130-132 (C27, C31, C34, C38, C41, C45), 127-128 (C26, C33, C40) 100.9 (C29, C36, C43), 76.5 (C3), 74.2 (C12) 72.1 (C7), 51.4 (24- $\text{OCH}_3$ ), 47.8 (C14), 45.9 (C13), 45.4 (C5), 38.2 (C8), 34.7 (C4), 34.6 (C1), 34.5 (C10) 34.3 (C9), 34.2 (C20), 31.3 (C6), 30.9 (C23, C22), 28.7 (C16), 27.2 (C2), 26.3 (C15), 25.0 (C19), 22.3 (C11), 17.5 (C21), 12.2 (C18). 31 of 46 Resonances detected. Overlaps at 138, 130, 127, 100.9, and 30.9 ppm.

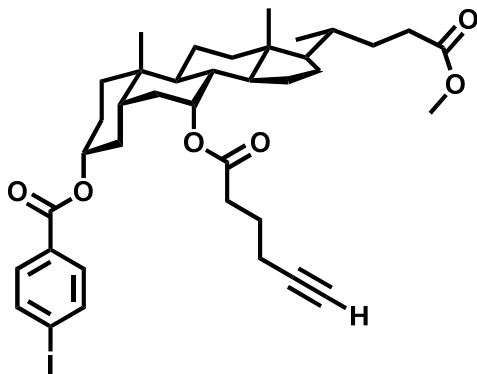
## Synthesis of 3 $\alpha$ Dimers by Sonogashira Coupling



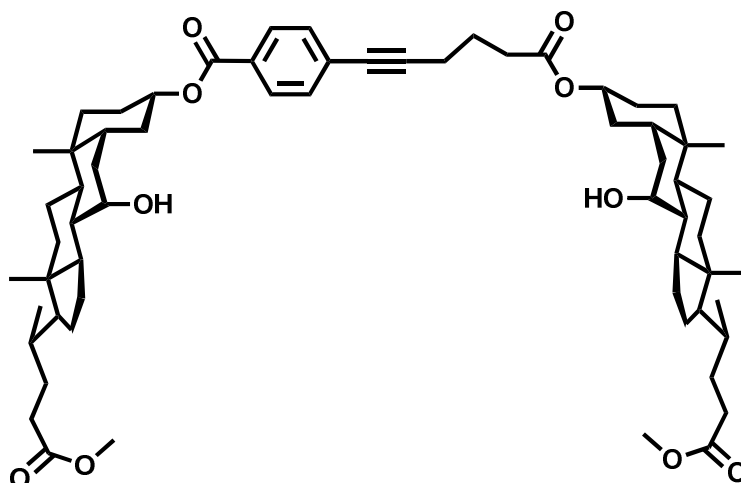
**Methyl 7 $\alpha$ -hydroxy-3 $\alpha$ -(5-hexynoyloxy)-5 $\beta$ -cholanoate (17)** It was synthesized under standard conditions and isolated as a white semisolid (5.918 g, 11.8 mmol, 85%)  $^1\text{H}$  NMR in ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.64 (s, 3H, 18- $\text{CH}_3$ ), 0.92 (d,  $J = 6.0\text{Hz}$ , 3H, 21- $\text{CH}_3$ ), 0.93 (s, 3H, 19- $\text{CH}_3$ ), 3.61 (s, 3H, 24- $\text{OCH}_3$ ), 3.82 (s, 1H, 7 $\beta$ -H) 4.53 (m, 1H, 3 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  11.7 (C18), 17.8 (C28), 18.2 (C21), 20.5 (C11), 22.6 (C19, C27), 22.1 (C15), 27.3 (C2), 26.7 (C16), 30.7 (C22, C23), 30.9 (C6), 33.2 (C6), 33.9 (C20), 34.0 (C26), 34.4 (C9), 34.5(C1, C10), 37.2 (C4), 38.0 (C8), 38.8 (C12), 40.3 (C5), 42.0 (C13), 50.4 (C14), 51.7 (C17), 55.7 (24- $\text{OCH}_3$ ), 68.4 (C7), 69.1 (C30), 74.2 (C7), 83.3 (C29), 172.6 (C25), 174.7 (C24) ppm. 29 of 31 Resonances detected. Overlaps at 30.7 and 34.5 ppm.



**Methyl 7 $\alpha$ -hydroxy-3 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate (18)** It was synthesized under standard conditions and isolated as a white solid (2.70 g, 4.23 mmol, 86%)  $^1\text{H}$  NMR in ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.62 (s, 3H, 18- $\text{CH}_3$ ), 0.89 (d,  $J = 6.8$  Hz, 3H, 21- $\text{CH}_3$ ), 0.90 (s, 3H, 19- $\text{CH}_3$ ), 3.63 (s, 3H, 24- $\text{OCH}_3$ ), 3.84 (s, 1H, 7 $\beta$ -H), 4.79 (m, 1H, 3 $\beta$ -H), 7.77 (d,  $J = 8.4$ , 2H; aromatic H), 7.78 (d,  $J = 8.4$ , 2H; aromatic H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  12.1 (C18), 18.2 (C21), 20.6 (C11), 22.7 (C19), 23.7 (C15), 26.7 (C2), 28.1 (C16), 30.9 (C23, C22), 32.8 (C6), 34.4 (C20), 35.0 (C9), 35.3 (C1, C10), 35.3 (C4), 39.3 (C8), 39.5 (C12), 42.2 (C5), 42.7 (C13), 50.4 (C14), 51.5 (24- $\text{OCH}_3$ ), 55.8 (C17), 68.7 (C7), 75.3 (C3), 100.3 (C29), 130.4 (C26), 131.0 (C27, C31), 137.7 (C28, C30), 165.6 (C25), 174.7 (C24) ppm. 28 Of 32 resonances detected. Overlaps at 30.9, 35.3, 131.0, and 137.7 ppm.

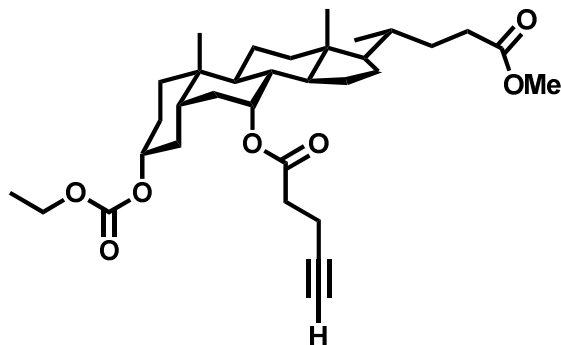


**Methyl 7 $\alpha$ --(5-hexynoyloxy)-3 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate (19)** Isolated as a viscous brown oil (1.60 g, 2.20 mmol 89.0%)  $^1\text{H}$  NMR in ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.59 (s, 3H, 18- $\text{CH}_3$ ), 0.87 (d,  $J = 6.8$  Hz, 3H, 21- $\text{CH}_3$ ), 0.89 (s, 3H, 19- $\text{CH}_3$ ), 3.58 (s, 3H, 24- $\text{OCH}_3$ ), 4.76 (m, 1H, 3 $\beta$ -H), 4.82 (s, 1H, 7 $\beta$ -H), 7.67 (d,  $J = 8.4$ , 2H; aromatic H), 7.77 (d,  $J = 8.4$ , 2H; aromatic H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  11.7 (C18), 17.7 (C35), 18.2 (C21), 20.6 (C11), 22.7 (C19, C34), 23.5 (C15), 26.7 (C2), 27.9 (C16), 30.9 (C23, C22), 31.3 (C6), 33.3 (C20), 34.1 (C9), 34.8 (C1, C10, C33), 35.2 (C4), 37.8 (C8), 39.4 (C12), 40.8 (C5), 42.6 (C13), 50.4 (C14), 51.4 (24- $\text{OCH}_3$ ), 55.7 (C17), 69.1 (C7), 71.2 (C35), 75.3 (C3), 83.0 (C36), 100.4 (C29), 130.3 (C26), 130.9 (C27, C31), 137.7 (C28, C30), 165.4 (C25), 172.1 (C32), 174.58 (C24) ppm. 32 of 38 Resonances detected. Overlaps at 22.7, 30.9, 34.8, 130.9, and 137.7 ppm.



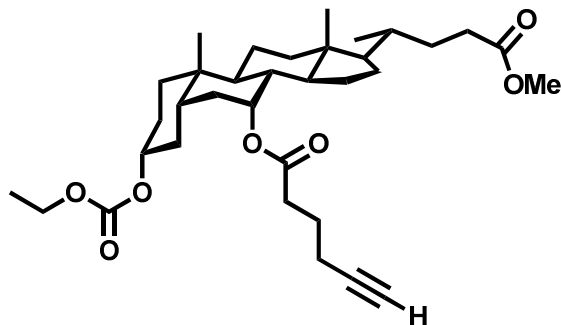
**Dimer (19)** In a flame-dried flask under nitrogen, a solution of Et<sub>3</sub>N (10 mL) and THF (10 mL) was degassed for 10 min by bubbling nitrogen. Compounds **17** (500 mg, 1.0 mmol) and **18** (636 mg, 1.0 mmol) were added followed by CuI (0.010 mg, 0.004 mmol) and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (30 mg, 0.004 mmol) in order. The reaction was allowed to run for 72 h at room temperature. The mixture was extracted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to dryness, upon which the product was isolated as a fine golden powder without further purification (560 mg, 0.554 mmol, 55.4%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.62 (s, 6H, 18-CH<sub>3</sub>), 0.84 (m, 12H, 21-CH<sub>3</sub>, 19-CH<sub>3</sub>), 3.62 (s, 6H, 24-OCH<sub>3</sub>), 4.84 (s, 2H, 7β-H), 4.59 (m, 1H, 3β-H), 4.81 (m, 1H, 3β-H), 7.41 (d, *J* = 8.4, 2H; aromatic H), 7.92 (d, *J* = 8.4, 2H; aromatic H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 11.7 (C18), 17.7 (C35), 18.2 (C21), 20.6 (C11), 22.7 (C19, C34), 23.5 (C15), 26.7 (C2), 27.9 (C16), 30.9 (C23, C22), 31.3 (C6), 33.3 (C20), 34.1 (C9), 34.8 (C1, C10, C33), 35.2 (C4), 37.8 (C8), 39.4 (C12), 40.8 (C5), 42.6 (C13), 50.4 (C14), 51.4 (24-OCH<sub>3</sub>), 55.7 (C17), 69.1 (C7), 71.2 (C35), 75.3 (C3), 83.0 (C36), 92.8 (C29), 130.3 (C26), 131.0 (C28, C30), 133.3 (C27, C31), 165.4 (C25), 172.1 (C32), 174.58 (C24) ppm. 32 Of 38 resonances detected. Overlaps at 22.7, 30.9, 34.8, 130.9, and 137.7 ppm.

## Synthesis of Barrel-like Macrocycles

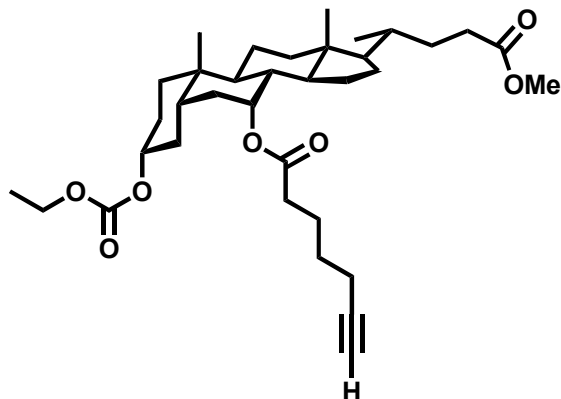


**Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(4-pentynoyloxy)-5 $\beta$ -cholanoate (20).** It was synthesized under standard conditions and isolated as viscous, light yellow oil (1.726 g, 3.04 mmol, 88.0%).  $^1\text{H}$  NMR in ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.55 (s, 3H, 18- $\text{CH}_3$ ), 0.83 (d,  $J = 8.0\text{Hz}$ , 3H, 21- $\text{CH}_3$ ), 0.85 (s, 3H, 19- $\text{CH}_3$ ), 3.58 (s, 3H, 24- $\text{OCH}_3$ ), 4.09 (q,  $J = 8.0\text{Hz}$ , 2H, 3 $\alpha$ -OC(O)OCH $\underline{\text{H}}_2\text{CH}_3$ ), 4.38 (m, 1H, 3 $\beta$ -H), 4.81 (s, 1H, 7 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  11.6 (C18), 14.1 (C27), 14.2 (3 $\alpha$ -OCOOCH $\underline{\text{H}}_2\text{CH}_3$ ), 18.1 (C21), 20.5 (C11), 22.5 (C19), 23.4 (C15), 26.6 (C16), 27.8 (C2), 30.8 (C22, C23), 30.2 (C6), 33.8 (C20), 34.0 (C26), 34.4 (C9), 34.5 (C10), 34.6 (C1), 35.1 (C4), 37.7 (C8), 39.4 (C12), 40.7 (C5), 42.5 (C13), 50.2 (C14), 51.3 (24- $\text{OCH}_3$ ), 55.5 (C17), 63.4 (3 $\alpha$ -OCOOCH $\underline{\text{H}}_2\text{CH}_3$ ), 69.1 (C29), 71.4 (C7), 77.5 (C3), 82.3 (C28), 154.5 (3 $\alpha$ -OC(O)OCH $\underline{\text{H}}_2\text{CH}_3$ ), 170.8 (C25), 174.3 (C24) ppm. 32 Of 33 resonances detected. Overlap at 30.8 ppm. MS Calc M + Na =  $\text{C}_{33}\text{H}_{50}\text{O}_7\text{Na} = 581.3454$ , Found Mass = 581.3427

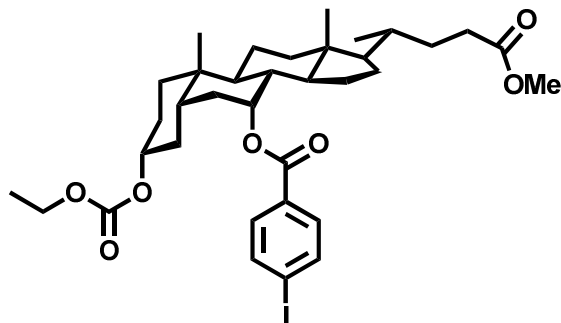




**Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(5-hexynoyloxy)-5 $\beta$ -cholanoate (21).** It was synthesized under standard conditions and isolated as viscous, light yellow oil (1.812 g, 3.13 mmol, 90.6%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.55 (s, 3H, 18- $\text{CH}_3$ ), 0.83 (d,  $J = 8.0\text{Hz}$ , 3H, 21- $\text{CH}_3$ ), 0.85 (s, 3H, 19- $\text{CH}_3$ ), 3.58 (s, 3H, 24- $\text{OCH}_3$ ), 4.09 (q,  $J = 8.0\text{Hz}$ , 2H, 3 $\alpha$ -OC(O)OCH $\underline{2}$ CH $\underline{3}$ ), 4.38 (m, 1H, 3 $\beta$ -H), 4.81 (s, 1H, 7 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  11.6 (C18), 14.2 (3 $\alpha$ -OC(O)OCH $\underline{2}$ CH $\underline{3}$ ), 17.6 (C28), 18.2 (C21), 20.5 (C11), 22.5 (C19), 23.5 (C15, C27), 26.6 (C2), 27.9 (C16), 30.8 (C23, C22), 31.3 (C6), 33.2 (C20), 34.0 (C26), 34.5 (C9), 34.6 (C10), 34.7 (C1), 35.2 (C4), 37.8 (C8), 39.4 (C12), 40.8 (C5), 42.7 (C13), 50.3 (C14), 51.4 (24- $\text{OCH}_3$ ), 55.5 (C17), 63.5 (3 $\alpha$ -OC(O)OCH $\underline{2}$ CH $\underline{3}$ ), 69.3 (C31), 71.0 (C7), 77.7 (C3), 83.0 (C30), 154.5 (3 $\alpha$ -OC(O)OCH $\underline{2}$ CH $\underline{3}$ ), 172.1 (C25), 172.3 (C24) ppm. 30 Of 32 resonances detected. Overlap at 30.8 and 23.5. MS Calc  $\text{M} + \text{Na} = \text{C}_{33}\text{H}_{50}\text{O}_7\text{Na} = 595.3611$ , Found Mass = 581.3427



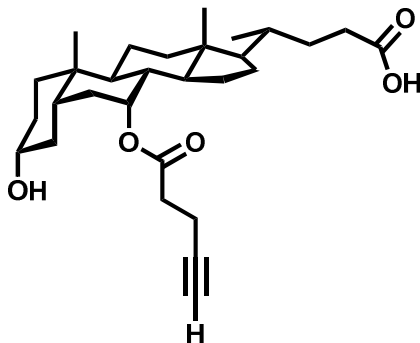
**Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(6-heptynyloxy)-5 $\beta$ -cholanoate (22).** It was synthesized under standard conditions and isolated as viscous, light yellow oil (1.880 g, 3.18 mmol, 91.9%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.55 (s, 3H, 18- $\text{CH}_3$ ), 0.83 (d,  $J = 8.0$  Hz, 3H, 21- $\text{CH}_3$ ), 0.85 (s, 3H, 19- $\text{CH}_3$ ), 3.58 (s, 3H, 24- $\text{OCH}_3$ ), 4.09 (q,  $J = 8.0$  Hz, 2H, 3 $\alpha$ -OC(O)OCH $\underline{\text{H}}_2$ CH $_3$ ), 4.38 (m, 1H, 3 $\beta$ -H), 4.81 (s, 1H, 7 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  11.7 (C18), 14.2 (C29), 14.4 (3 $\alpha$ -OC(O)OCH $\underline{\text{H}}_2$ CH $_3$ ), 18.2 (C21), 20.6 (C11), 22.5 (C19), 23.5 (C15, C27), 26.7 (C2), 28.0 (C16, C28), 30.9 (C22), 31.0 (C23), 31.3 (C6), 33.2 (C20), 34.0 (C26), 34.5 (C9), 34.6 (C10), 34.7 (C1), 35.2 (C4), 37.9 (C8), 39.4 (C12), 40.8 (C5), 42.6 (C13), 50.3 (C14), 51.4 (24- $\text{OCH}_3$ ), 55.6 (C17), 63.6 (3 $\alpha$ -OC(O)OCH $\underline{\text{H}}_2$ CH $_3$ ), 69.1 (C7), 71.6 (C31), 77.8 (C3), 82.5 (C30), 154.6 (3 $\alpha$ -OC(O)OCH $\underline{\text{H}}_2$ CH $_3$ ), 171.1 (C25), 174.3 (C24) ppm. 33 of 35 Resonances detected. Overlaps at 23.5 and 30.9.



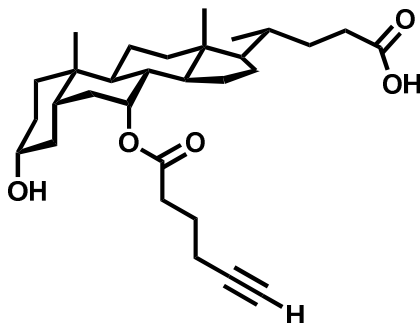
**Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate (23)** Et<sub>3</sub>N (2 mL) was added to a mixture of 4-iodobenzoic acid (1.281 g, 5.16 mmol) and 2,6-dichlorobenzoyl chloride (0.53 mL, 3.7 mmol) in THF for 1 h. The slurry was evaporated to dryness and then added to **1** (2.00 g, 4.18 mmol) and 5% DMAP (0.03 g) in 20 mL of toluene, which was then refluxed for 24 h. The mixture was extracted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, and purified by column chromatography. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  0.60 (s, 3H, 18-CH<sub>3</sub>), 0.85 (d, J = 6.8 Hz, 3H, 21-CH<sub>3</sub>), 0.91 (s, 3H, 19-CH<sub>3</sub>), 3.57 (s, 3H, 24-OCH<sub>3</sub>), 4.08 (q, J = 8.4 Hz, 2H, 3 $\alpha$ -OC(O)OCH<sub>2</sub>CH<sub>3</sub>), 4.37 (m, 1H, 3 $\beta$ -H), 5.08 (s, 1H, 7 $\beta$ -H), 7.68 (d, J = 8.4, 2H; aromatic H), 7.80 (d, J = 8.4, 2H; aromatic H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz)  $\delta$  175.0 (C24), 165.4 (C25), 154.6 (3 $\alpha$ -OC(O)OCH<sub>2</sub>CH<sub>3</sub>), 137.9 (C28, C30), 130.8 (C27, C31) 129.0 (C26), 100.7 (C29), 77.7 (C3), 72.3 (C7), 63.7 (3 $\alpha$ -OCOOCH<sub>2</sub>CH<sub>3</sub>), 55.6 (C17), 51.6 (24-OCH<sub>3</sub>), 50.7 (C14), 42.7 (C13), 40.7 (C5), 39.5 (C12), 38.2 (C8), 35.2 (C4), 34.7 (C1, C10), 34.6 (C9), 34.5 (C20), 31.4 (C6), 30.9 (C23), 30.8 (C22), 27.9 (C16), 26.9 (C2), 23.5 (C15), 22.6 (C19), 20.6 (C11), 18.2 (C21), 14.2 (3 $\alpha$ -OCOOCH<sub>2</sub>CH<sub>3</sub>), 11.7 (C18). 32 of 35 Resonances detected. Overlaps at 137.9, 130.8, and 34.7.

**General procedure for deprotection of CDCA esters.** To a solution of the bile acid (1.0 g, ~2.1 mmol) in CH<sub>3</sub>OH (10 mL) and THF (10 mL), K<sub>2</sub>CO<sub>3</sub> (satd, 20 mL) was added. The

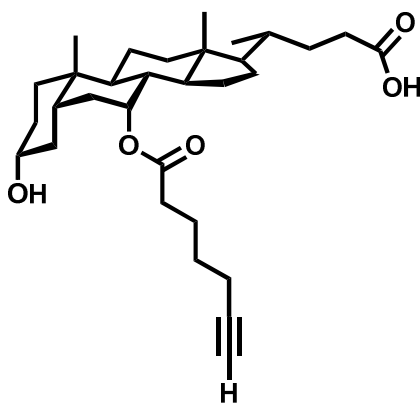
solution was refluxed overnight. The extra base was neutralized by 3M HCl while in the reaction flask. The mixture was poured into water and extracted with EtOAc. The organic layer was dried by  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated by rotary vaporization. The crude product was crystallized from acetone.



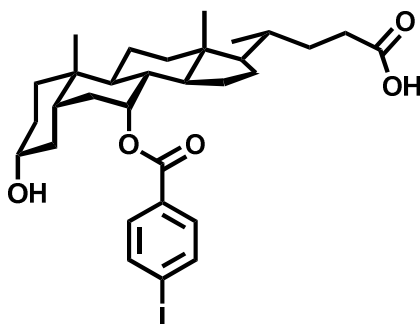
**3 $\alpha$ -Hydroxy-7 $\alpha$ -(4-pentynoyloxy)-5 $\beta$ -cholanoic acid (24).** Isolated as an off-white solid (0.595 g, 1.26 mmol, 60% yield)  $^1\text{H}$  NMR in ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.65 (s, 3H, 18- $\text{CH}_3$ ), 0.90 (d,  $J = 6.0\text{Hz}$ , 3H, 21- $\text{CH}_3$ ), 0.95 (s, 3H, 19- $\text{CH}_3$ ), 3.49 (m, 1H, 3 $\beta$ -H), 5.11 (s, 1H, 7 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR  $\delta$  11.7 (C18), 14.4 (C27), 18.2 (C21), 20.6 (C11), 22.6 (C19), 23.5 (C15), 28.0 (C16), 30.5 (C2), 30.7 (C22), 30.9 (C23), 31.4 (C6), 33.9 (C20), 34.1 (C26), 34.6 (C9), 35.1 (C10), 35.2 (C1), 37.9 (C4), 38.8 (C8), 39.5 (C12), 41.0 (C5), 42.7 (C13), 50.3 (C14), 55.7 (C17), 69.1 (C3), 71.8 (C29, C7), 83.6 (C28), 171.2 (C25) 179.5 (C24) ppm. 29 Of 30 resonances detected. Overlap at 71.8 ppm.



**3 $\alpha$ -Hydroxy-7 $\alpha$ -(5-hexynoyloxy)-5 $\beta$ -cholanoic acid (25).** Isolated as an off-white solid (0.800 mg, 1.64 mmol, 78% yield)  $^1\text{H}$  NMR in ( $\text{CDCl}_3$ , 400 MHz),  $\delta$  0.64 (s, 3H, 18- $\text{CH}_3$ ), 0.92 (d,  $J$  = 6.0Hz, 3H, 21- $\text{CH}_3$ ), 0.93 (s, 3H, 19- $\text{CH}_3$ ), 3.50 (m, 1H, 3 $\beta$ -H), 5.02 (s, 1H, 7 $\beta$ -H)  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz),  $\delta$  11.0 (C18), 13.7 (C28), 17.5 (C21), 19.9 (C11), 22.0 (C19, C27), 22.1 (C15), 27.3 (C2), 29.7 (C16), 30.7 (C22, C23), 30.9 (C6), 33.2 (C6), 33.9 (C20), 34.0 (C26), 34.4 (C9), 34.5(C1, C10), 37.2 (C4), 38.0 (C8), 38.8 (C12), 40.3 (C5), 42.0 (C13), 49.6 (C14), 53.0 (C17), 69.3 (C3), 71.1 (C30, C7), 81.9 (C29), 170.5 (C25) 179.1 (C24) ppm. 27 of 30 Resonances detected. Overlaps at 30.7, 34.5, and 71.1 ppm. MS Calc  $\text{M} + \text{Na} = \text{C}_{30}\text{H}_{46}\text{O}_5\text{Na} = 509.3243$ , Found Mass = 509.3249.



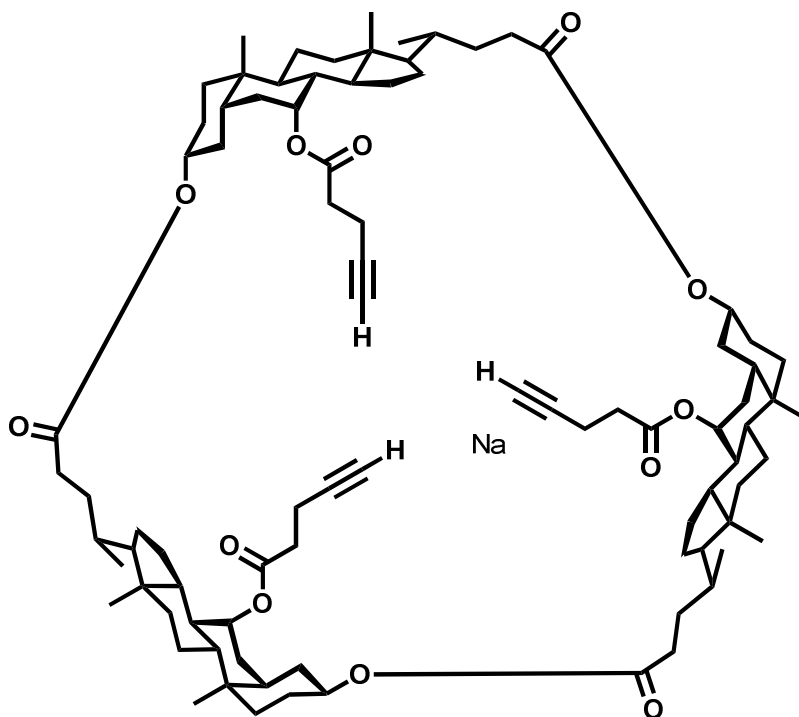
**3 $\alpha$ -Hydroxy-7 $\alpha$ -(6-heptynoyloxy)-5 $\beta$ -cholanoic acid (26).** Isolated as an off-white solid (0.926 mg, 1.85 mmol, 88% yield)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz),  $\delta$  0.65 (s, 3H, 18- $\text{CH}_3$ ), 0.90 (d,  $J$  = 6.0Hz, 3H, 21- $\text{CH}_3$ ), 0.95 (s, 3H, 19- $\text{CH}_3$ ), 3.49 (m, 1H, 3 $\beta$ -H), 5.11 (s, 1H, 7 $\beta$ -H)  $^{13}\text{C}$  NMR  $\delta$  11.7 (C18), 14.4 (C29), 18.2 (C21), 20.6 (C11), 22.6 (C19), 23.5 (C15, C27), 28.0 (C2), 30.5 (C16, 28), 30.7 (C22), 30.9 (C23), 31.4 (C6), 33.9 (C20), 34.1 (C26), 34.6 (C9), 35.1 (C10), 35.2 (C1), 37.9 (C4), 38.8 (C8), 39.5 (C12), 41.0 (C5), 42.7 (C13), 50.3 (C14), 55.7 (C17), 69.1 (C3), 71.8 (C31, C7), 83.6 (C30), 171.2 (C25) 179.5 (C24). 28 of 31 Resonances detected. Overlaps at 23.5, 30.5, and 71.8 ppm.



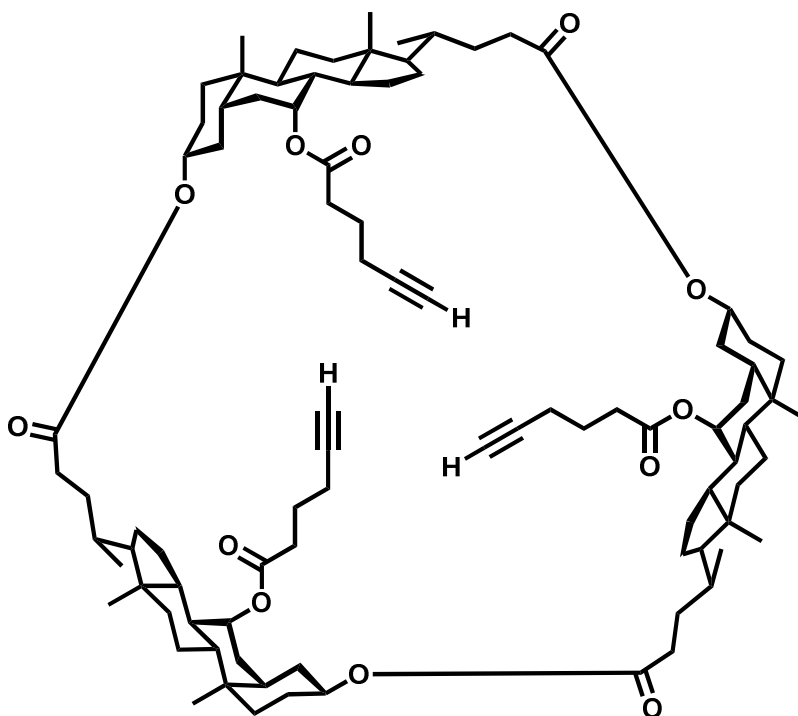
**3 $\alpha$ -Hydroxy-7 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoic Acid (27)** Isolated as an light orange solid (0.693 g, 1.11 mmol, 53% yield)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.65 (s, 3H, 18- $\text{CH}_3$ ), 0.90 (d,  $J$  = 6.0Hz, 3H, 21- $\text{CH}_3$ ), 0.95 (s, 3H, 19- $\text{CH}_3$ ), 3.49 (m, 1H, 3 $\beta$ -H), 5.11 (s, 1H, 7 $\beta$ -H), 7.73 (d,  $J$ =8.0, 2H, Aromatic H), 7.80 (d,  $J$  = 8.0, 2H, Aromatic H) ppm.  $^{13}\text{C}$  NMR in ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  11.7 (C18), 18.2 (C21), 20.6 (C11), 22.7 (C19), 23.5 (C15), 27.8 (C16), 30.0 (C2), 30.5 (C22), 31.5 (C23), 31.6 (C6), 34.5 (C20), 34.7 (C9), 34.7 (C1, C10), 35.2 (C4), 38.2 (C8), 39.5 (C12), 40.7 (C5), 42.8 (C13), 50.7 (C14), 55.6 (C17), 72.3 (C7), 76.6 (C3), 100.7 (C29), 130.9 (C26),

131.5 (C27, C31), 137.9 (C28, C30), 165.4 (C25), 178.4 (C24) ppm. 28 of 31 Resonances detected. Overlaps at 34.7, 131.5, and 137.0 ppm.

**General procedure for cyclotrimerization of 7 $\alpha$ -CDCA esters** Et<sub>3</sub>N (2 mL) was added to a mixture of the 7 $\alpha$ -CDCA monoester (5.16 mmol) and 2,6-dichlorobenzoyl chloride (0.53 mL, 3.7 mmol ) in THF (20 mL) for 1 h. The slurry was evaporated to dryness and suspended in a minimal amount of toluene. The resulting suspension was added dropwise to a refluxing solution of 5% DMAP (0.03 g) in 100 mL of toluene over a period of 1 h, and was then refluxed for 24 h afterward. The mixture was extracted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, and recrystallized by dissolving in chloroform and adding dropwise to refluxing THF.



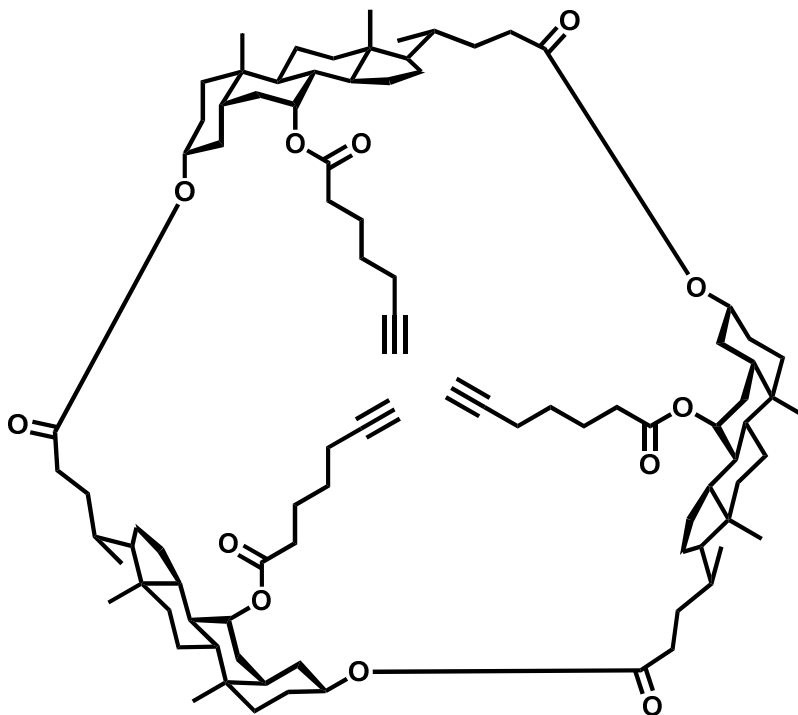
**Cyclotri(chenodeoxycholate)-tripentynoate (29).** It was isolated as white solid (0.502 g, 0.975 mmol, 56.7%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.63 (s, 3H, 18- $\text{CH}_3$ ), 0.93 (m, 6H, 21- $\text{CH}_3$ , 19- $\text{CH}_3$ ), 4.61 (m, 1H, 3 $\beta$ -H), 4.91 (s, 1H, 7 $\beta$ -H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  11.6 (C18), 17.9 (C27) 18.1 (C21), 20.5 (C11), 22.5 (C19), 23.4 (C15), 26.6 (C16), 27.8 (C2), 30.2 (C6), 30.8 (C22, C23), 33.8 (C6), 34.0 (C20), 34.4 (C26), 34.5 (C10), 34.6 (C10), 35.1 (C4), 34.6 (C9), 37.7 (C8), 37.9 (C12), 39.0 (C5), 41.9 (C13), 50.2 (C14), 55.5 (C17), 69.1 (C29), 71.4 (C7), 77.5 (C3), 82.3 (C28), 170.8 (C25), 174.3 (C24) ppm. 28 of 29 Resonances found. Overlap at 30.8 ppm. MS Calc  $\text{M} + \text{Na} = \text{C}_{60}\text{H}_{132}\text{O}_{12}\text{Na} = 1385.9147$ , Found Mass = 1385.9149.



**Cyclotri(chenodeoxycholate)-trihexynoate (30)** It was isolated as white solid (1.02 g, 0.602 mmol, 35.0%)  $^1\text{H}$  NMR in ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.61 (s, 3H, 18- $\text{CH}_3$ ), 0.83 (s, 6H, 21- $\text{CH}_3$ , 19- $\text{CH}_3$ ), 4.55 (s, 1H, 3 $\beta$ -H), 4.87 (s, 1H, 7 $\beta$ -H);  $^{13}\text{C}$  NMR in ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  12.0 (C18), 18.1 (C28), 18.6 (C21), 20.9 (C11), 22.3 (C19), 23.9 (C15, C27), 27.1 (C2), 28.3 (C16), 31.3 (C23,

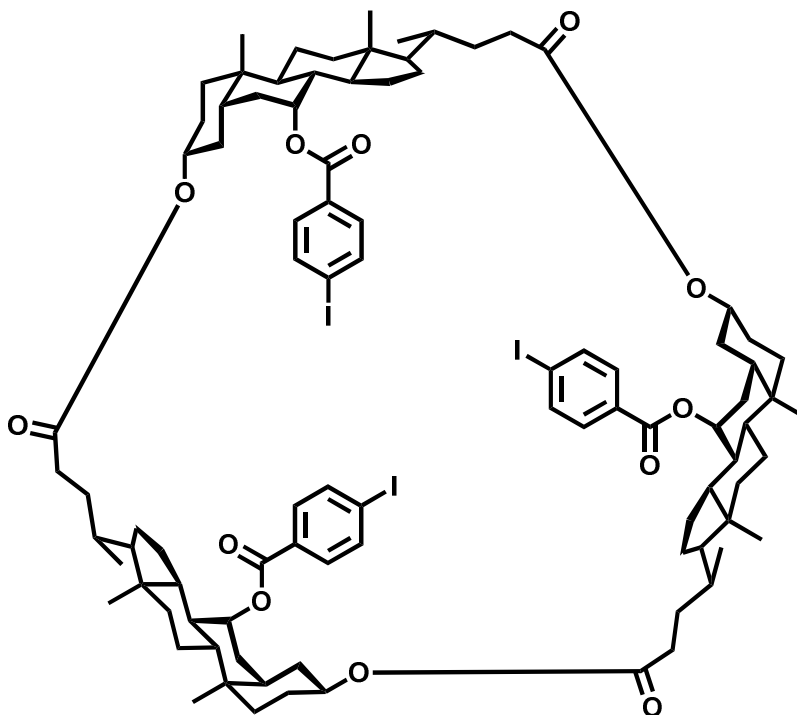


C22), 31.6 (C6), 33.7 (C20), 34.4 (C26), 34.6 (C9), 35.1 (C1, C10), 35.6 (C4), 38.2 (C8), 39.8 (C12), 41.2 (C5), 42.9 (C13), 50.7 (C14), 56.1 (C17), 69.4 (C7), 71.6 (C3), 74.2 (C30), 83.5 (C29), 171.4 (C25), 172.6 (C24) ppm. 27 of 30 Resonances found. Overlaps at 23.9, 31.3, and 35.1 ppm. MS Calc M + Na = C<sub>63</sub>H<sub>138</sub>O<sub>12</sub>Na = 1427.9617, Found Mass = 1427.9253.



**Cyclotri(chenodeoxycholate)-triheptynoate (31)** It was isolated as white solid (1.71 g, 1.07 mmol, 62.0%) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), δ 0.55 (s, 3H, 18-CH<sub>3</sub>), 0.83 (d, *J* = 8.0Hz, 3H, 21-CH<sub>3</sub>), 0.85 (s, 3H, 19-CH<sub>3</sub>), 3.58 (s, 3H, 24-OCH<sub>3</sub>), 4.38 (m, 1H, 3β-H), 4.81 (s, 1H, 7β-H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz), δ 11.7 (C18), 14.2 (C29), 18.2 (C21), 20.6 (C11), 22.5 (C19), 23.5 (C15, C27), 26.7 (C2), 28.0 (C16, C28), 30.9 (C22), 31.0 (C23), 31.3 (C6), 33.2 (C20), 34.0 (C26), 34.5 (C9), 34.6 (C10), 34.7 (C1), 35.2 (C4), 37.9 (C8), 39.4 (C12), 40.8 (C5), 42.6 (C13), 50.3 (C14), 51.4 (24-OCH<sub>3</sub>), 55.6 (C17), 69.1 (C7), 71.6 (C31), 77.8 (C3), 82.5 (C30), 171.1

(C25) 174.3 (C24) ppm. 29 Of 31 resonances detected. Overlaps at 23.5 and 28.0 ppm. MS Calc  
M + Na = C<sub>66</sub>H<sub>142</sub>O<sub>12</sub>Na = 1470.0086, Found Mass = 1470.0240.



**Cyclotri(chenodeoxycholate)-tri-4-iodobenzoate (32)** It was isolated as white solid (0.605 g, 1.22 mmol, 71.1%) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.60 (s, 3H, 18-CH<sub>3</sub>), 0.85 (d, *J* = 6.8 Hz, 3H, 21-CH<sub>3</sub>), 0.91 (s, 3H, 19-CH<sub>3</sub>), 4.37 (m, 1H, 3β-H), 5.08 (s, 1H, 7β-H), 7.68 (d, *J* = 8.4, 2H; aromatic H), 7.80 (d, *J* = 8.4, 2H; aromatic H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 11.7 (C18), 18.2 (C21), 20.6 (C11), 22.6 (C19), 23.5 (C15), 26.9 (C2), 27.9 (C16), 30.8 (C22), 30.9 (C23), 31.4 (C6), 34.5 (C20), 34.6 (C9), 34.7 (C1, C10), 35.2 (C4), 38.2 (C8), 39.5 (C12), 40.7 (C5), 42.7 (C13), 50.7 (C14), 51.6 (24-OCH<sub>3</sub>), 55.6 (C17), 72.3 (C7), 77.7 (C3), 100.7 (C29), 129.0 (C26), 130.8 (C27, C31), 137.9 (C28, C30), 165.4 (C25), 175.0 (C24) ppm. 28 Of 31

resonances detected. Overlaps at 34.7, 130.8, and 137.9 ppm. MS Calc M + Na =  $C_{66}H_{129}O_{12}I_3Cl_2$  = 1871.5212, Found Mass = 1870.80.

**General Sonogashira coupling procedure** In a flame-dried flask under nitrogen, a solution of  $Et_3N$  (3.5 mL) and DMF (3.5 mL) was degassed for 10 min by bubbling nitrogen. The terminal alkyne cyclotrimer (23 mg, ~0.016 mmol) and cyclotri(chenodeoxycholate)-tri-4-iodobenzoate (30 mg, 0.016 mmol) were added followed by CuI (0.311 mg, 0.0016 mmol) and  $Pd(PPh_3)_2Cl_2$  (1.5 mg, 0.00035 mmol) in order. The reaction was allowed to run for 72 h at room temperature. The mixture was extracted with EtOAc, dried over  $Na_2SO_4$ , and evaporated to dryness. The crude product was recrystallized by dissolving in chloroform and adding dropwise to refluxing THF.

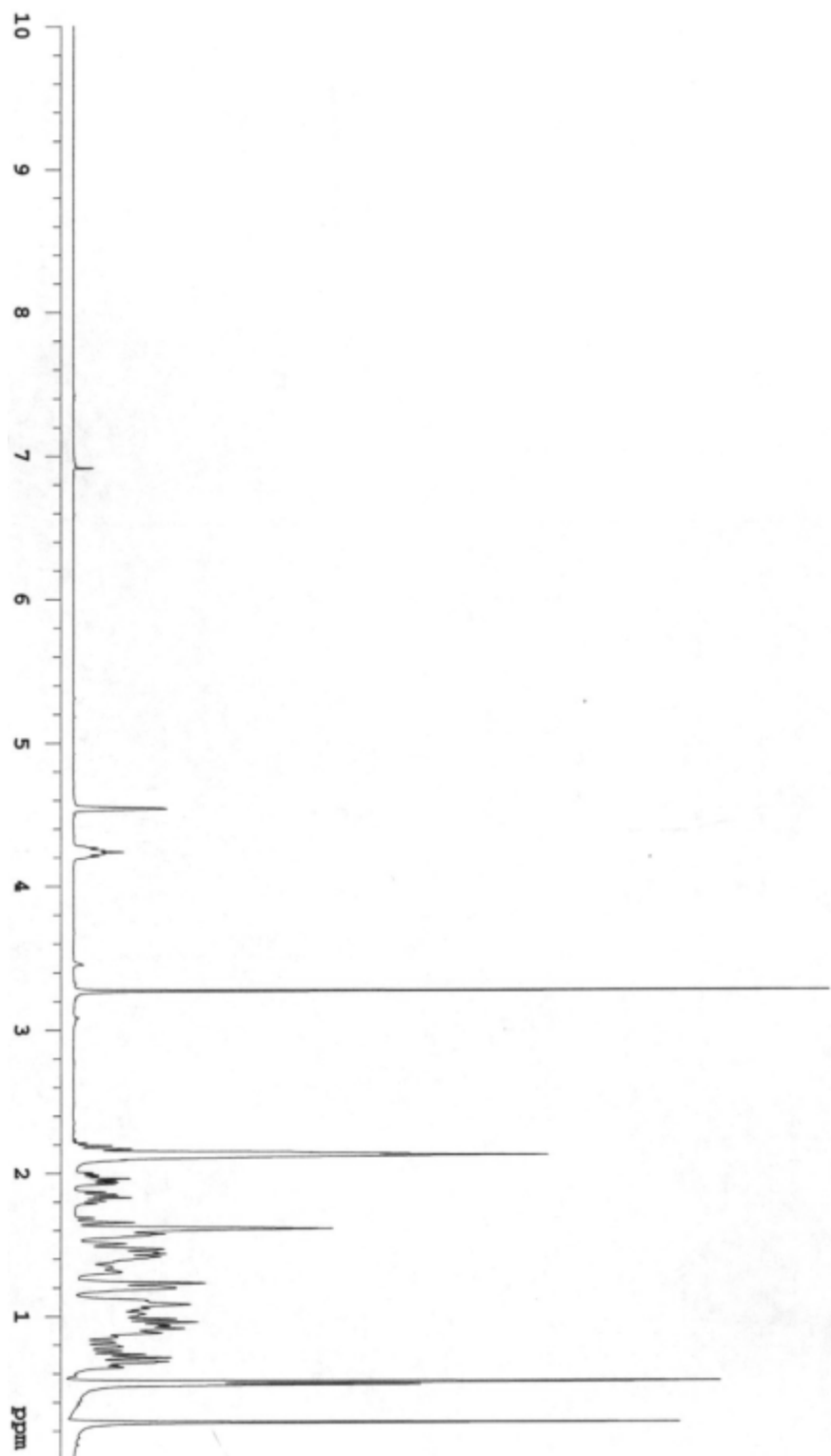
**Bis-Cyclotri(chenodeoxycholate)-tri-4-pentynylbenzoate (33)** It was isolated as white solid (18 mg, 0.00626 mmol, 39.1%)  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  0.61 (s, 6H, 18- $CH_3$ ), 0.88 (m, 12H, 21- $CH_3$ , 19- $CH_3$ ), 4.37 (m, 1H, 3 $\beta$ -H), 4.61 (m, 1H, 3 $\beta$ -H), 4.89 (s, 1H, 7 $\beta$ -H), 5.04 (s, 1H, 7 $\beta$ -H), 7.44 (d,  $J$  = 8.4, 2H; aromatic H), 7.90 (d,  $J$  = 8.4, 2H; aromatic H) ppm.

**Bis-Cyclotri(chenodeoxycholate)-tri-4-hexynylbenzoate (34)** It was isolated as white solid (23 mg, 0.00800 mmol, 50.0%)  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  0.63 (s, 3H, 18- $CH_3$ ), 0.80 (d,  $J$  = 6.8 Hz, 3H, 21- $CH_3$ ), 0.91 (s, 3H, 19- $CH_3$ ), 4.59 (m, 1H, 3 $\beta$ -H), 4.89 (m, 1H, 3 $\beta$ -H), 4.93 (s, 1H, 7 $\beta$ -H), 5.14 (s, 1H, 7 $\beta$ -H), 7.42(d,  $J$  = 8.4, 2H; aromatic H), 7.96 (d,  $J$  = 8.4, 2H; aromatic H) ppm.

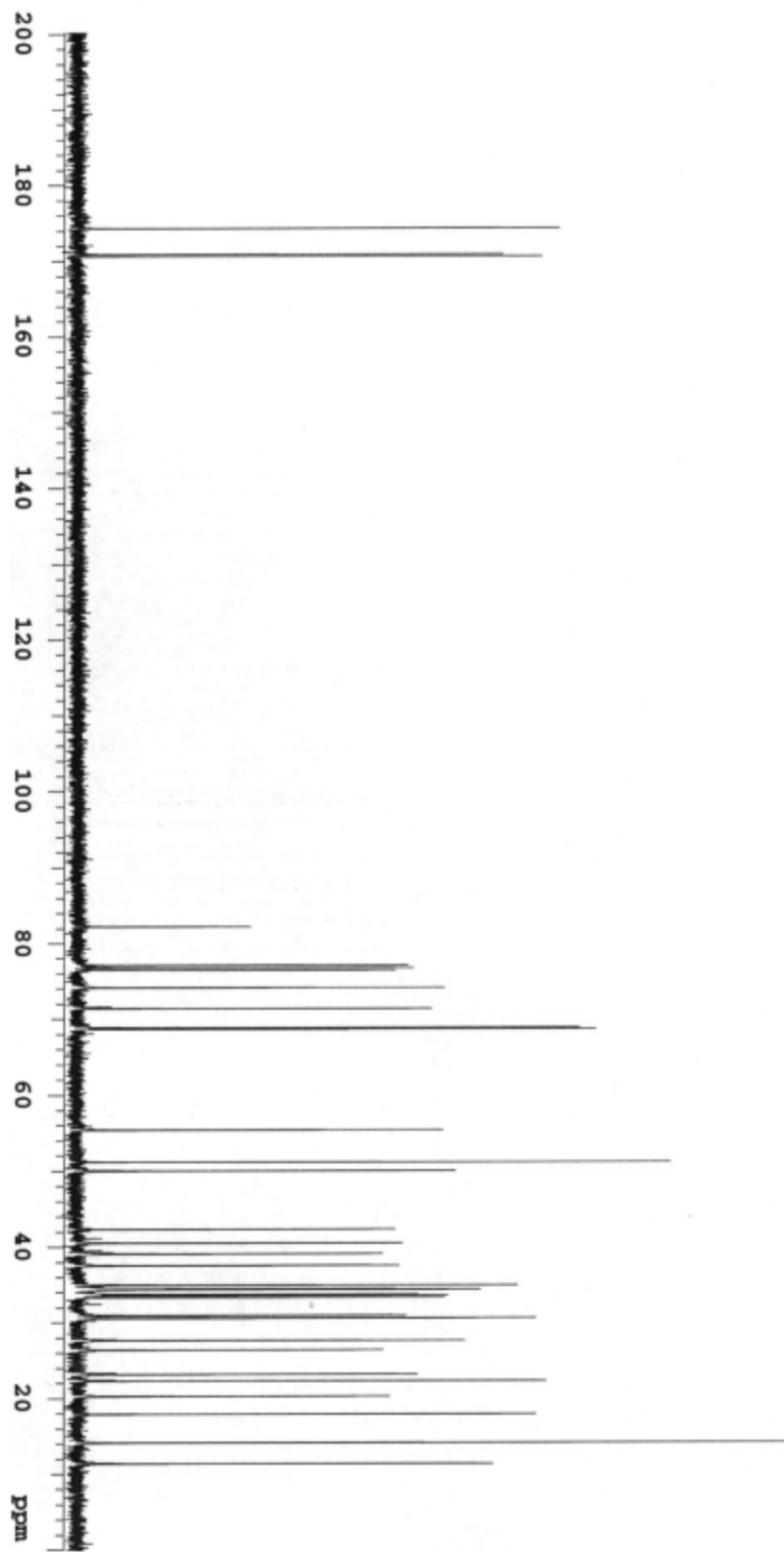
**Bis-Cyclotri(chenodeoxycholate)-tri-4-heptylbenzoate (35)** It was isolated as white solid (33 mg, 0.0114 mmol, 71.8%) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  0.60 (s, 3H, 18-CH<sub>3</sub>), 0.85 (d,  $J$  = 6.8 Hz, 3H, 21-CH<sub>3</sub>), 0.91 (s, 3H, 19-CH<sub>3</sub>), 4.37 (m, 1H, 3 $\beta$ -H), 5.08 (s, 1H, 7 $\beta$ -H), 7.68 (d,  $J$  = 8.4, 2H; aromatic H), 7.80 (d,  $J$  = 8.4, 2H; aromatic H) ppm.

#### 4.4.3 Supporting Spectra

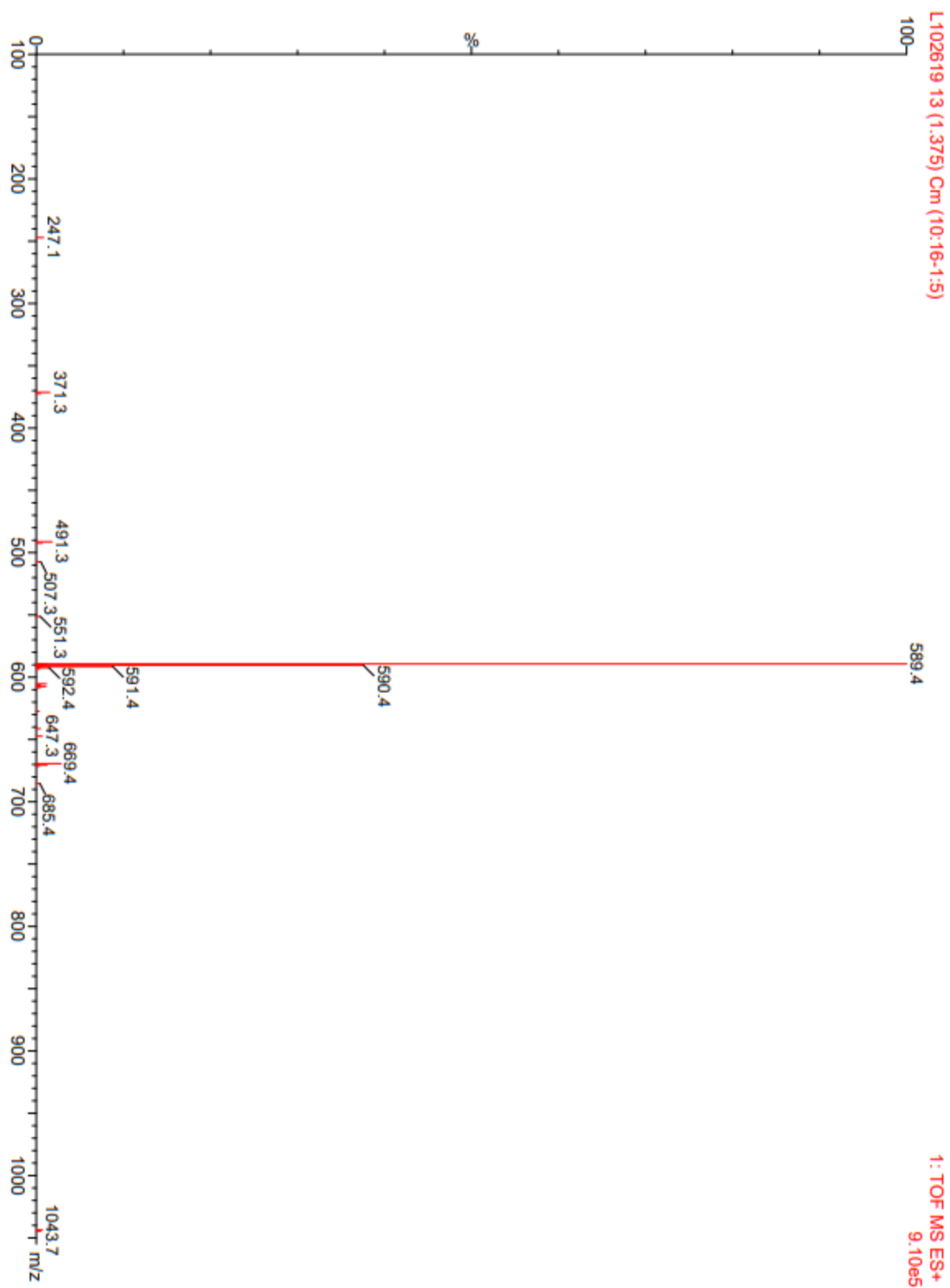
##### Methyl 3 $\alpha$ , 7 $\alpha$ -Di(4-pentynoyloxy)-5 $\beta$ -cholate (9)



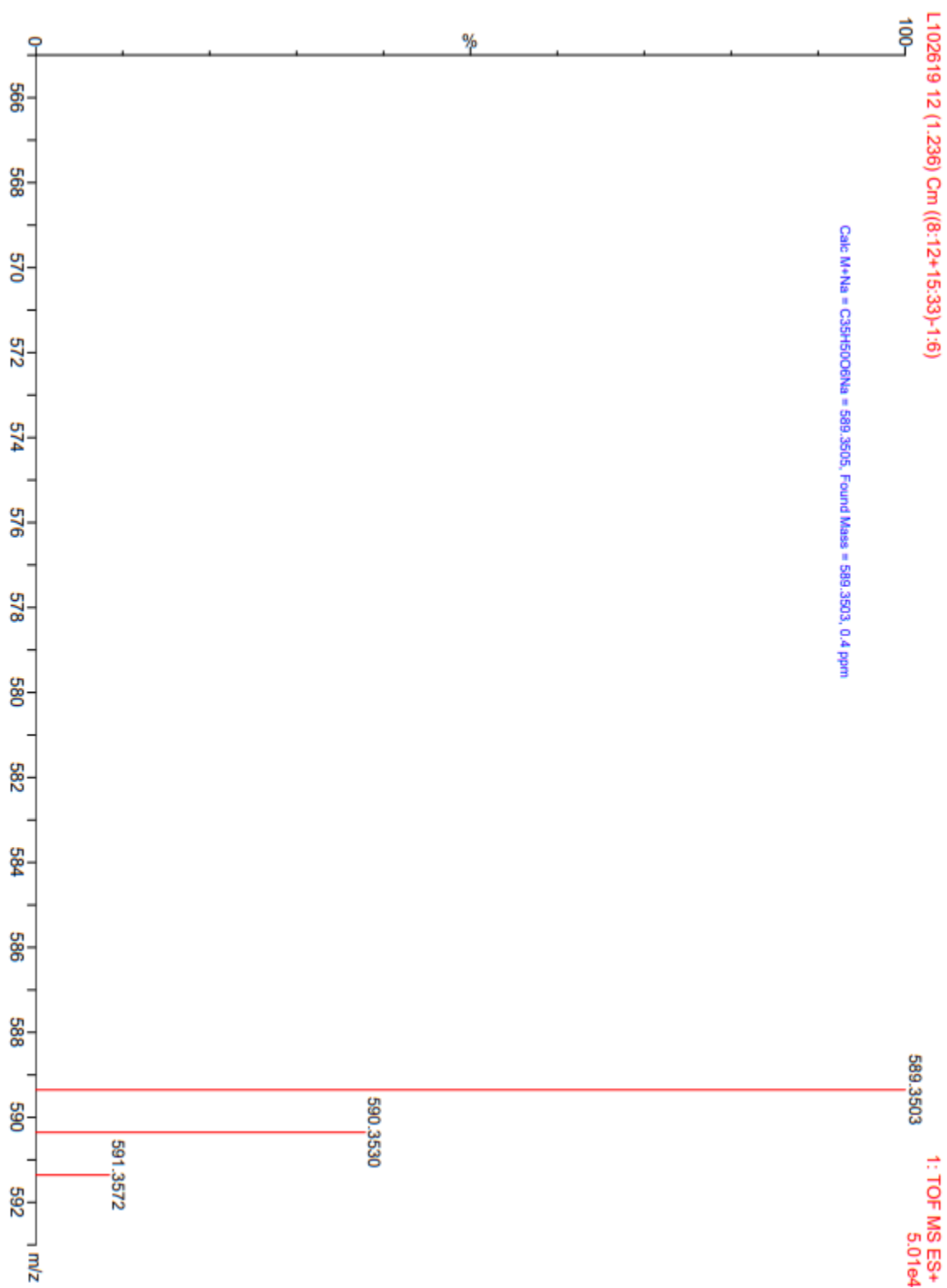
Methyl 3 $\alpha$ , 7 $\alpha$ -Di(4-pentynoyloxy)-5 $\beta$ -cholate (9)



Methyl 3 $\alpha$ , 7 $\alpha$ -Di(4-pentynoyloxy)-5 $\beta$ -cholate (9)

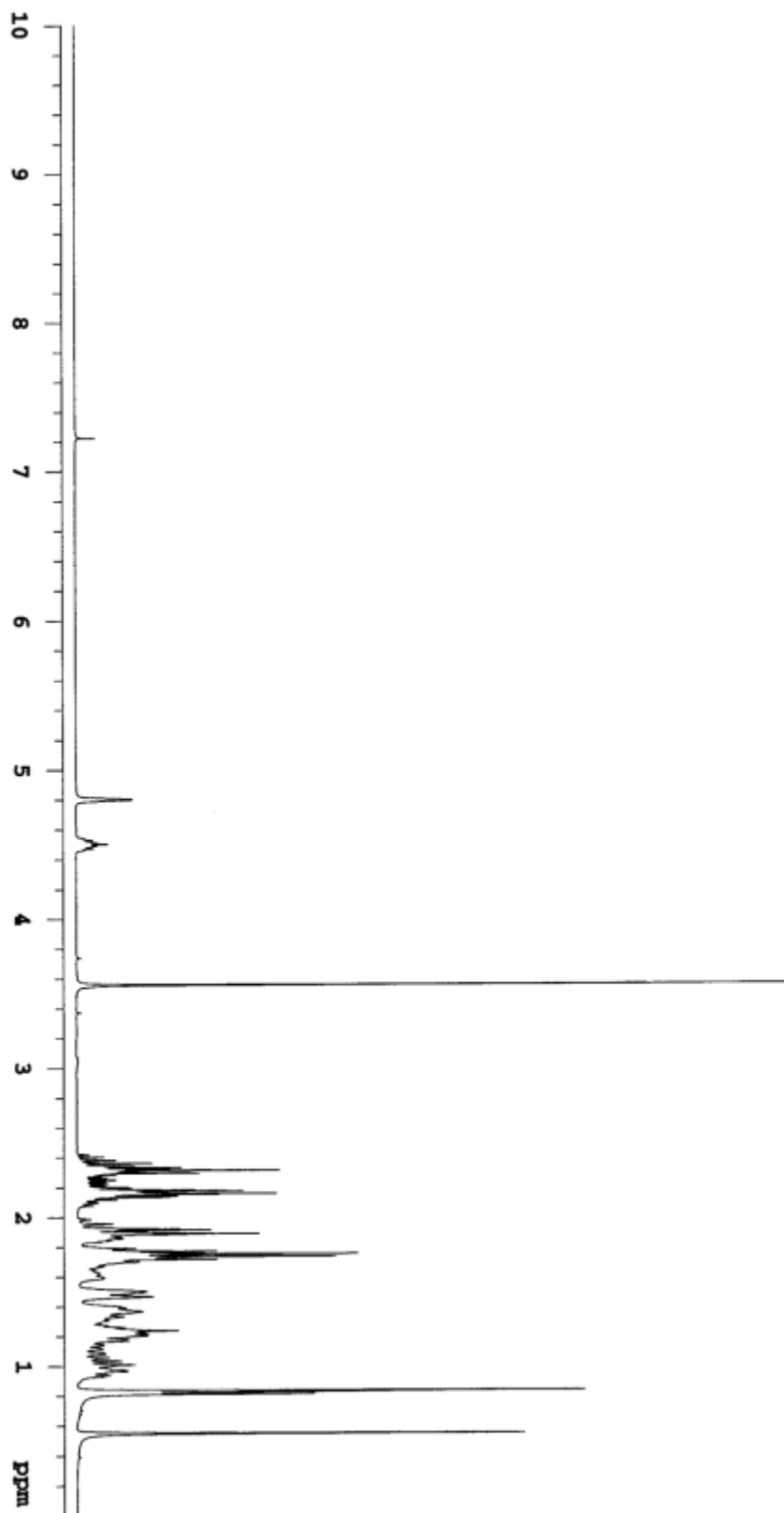


# Methyl 3 $\alpha$ , 7 $\alpha$ -Di(4-pentynoyloxy)-5 $\beta$ -cholate (9)

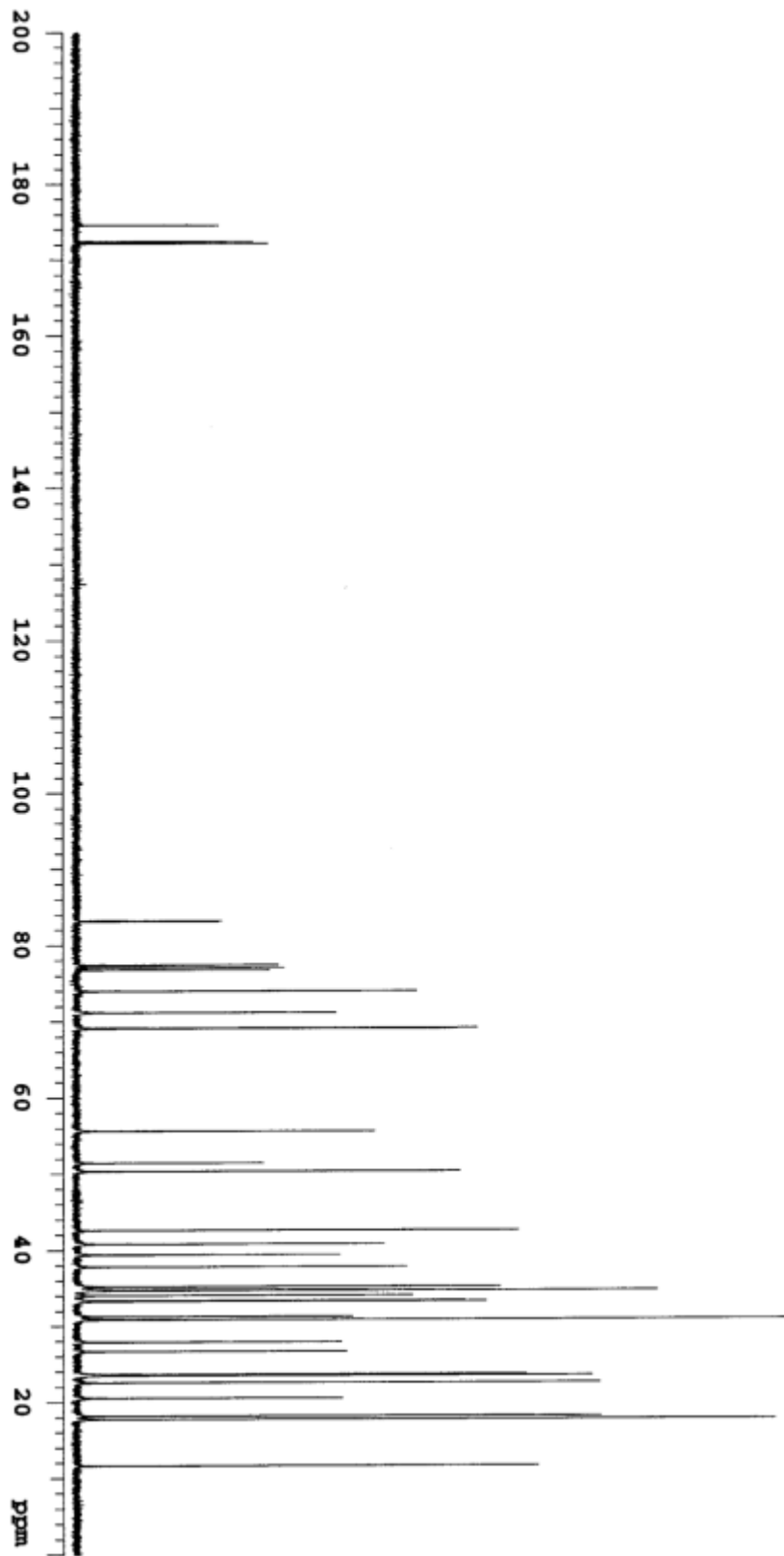




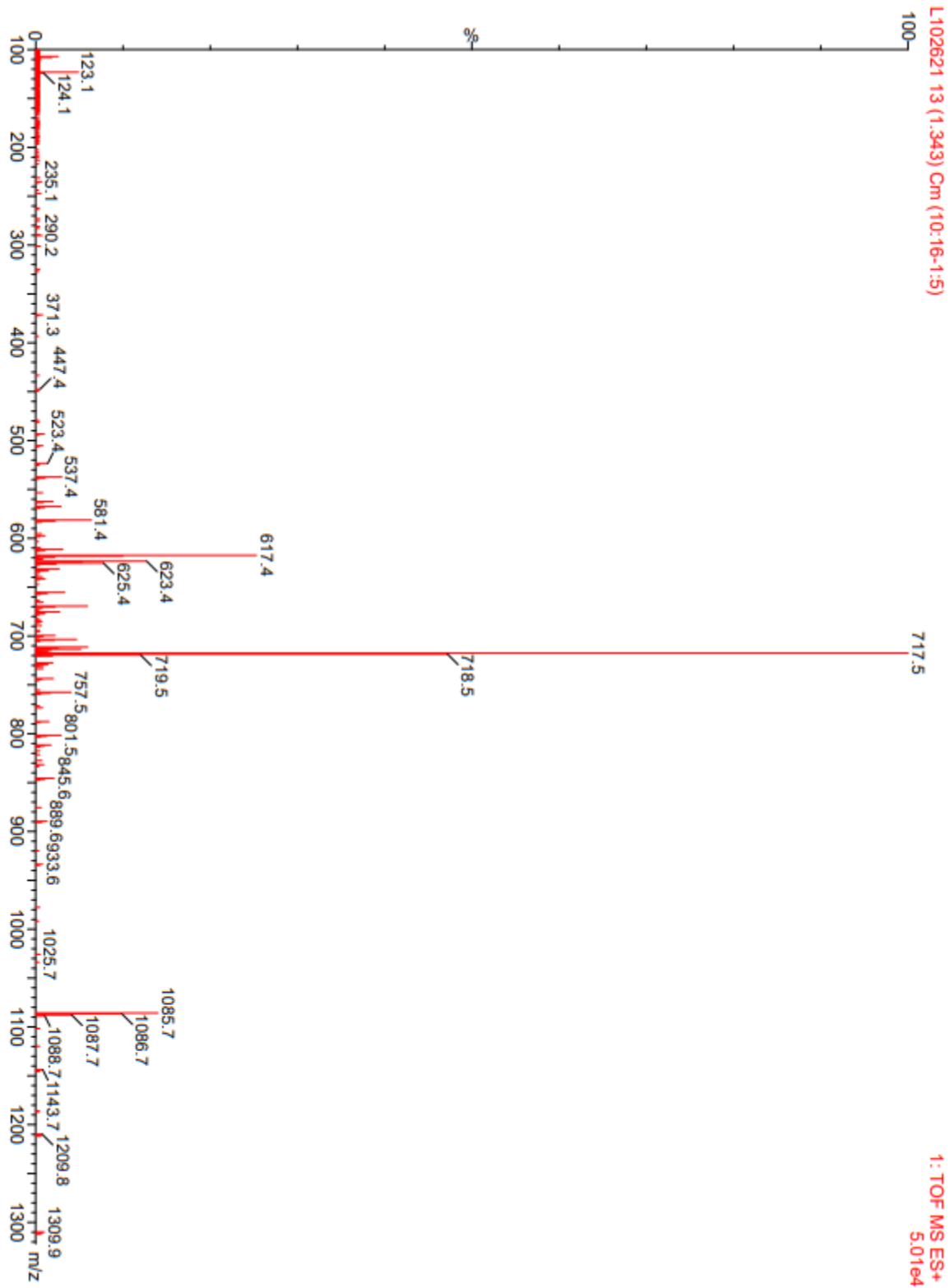
**Methyl 3 $\alpha$ , 7 $\alpha$ -di(5-hexynoxy)-5 $\beta$ -cholate (10)**



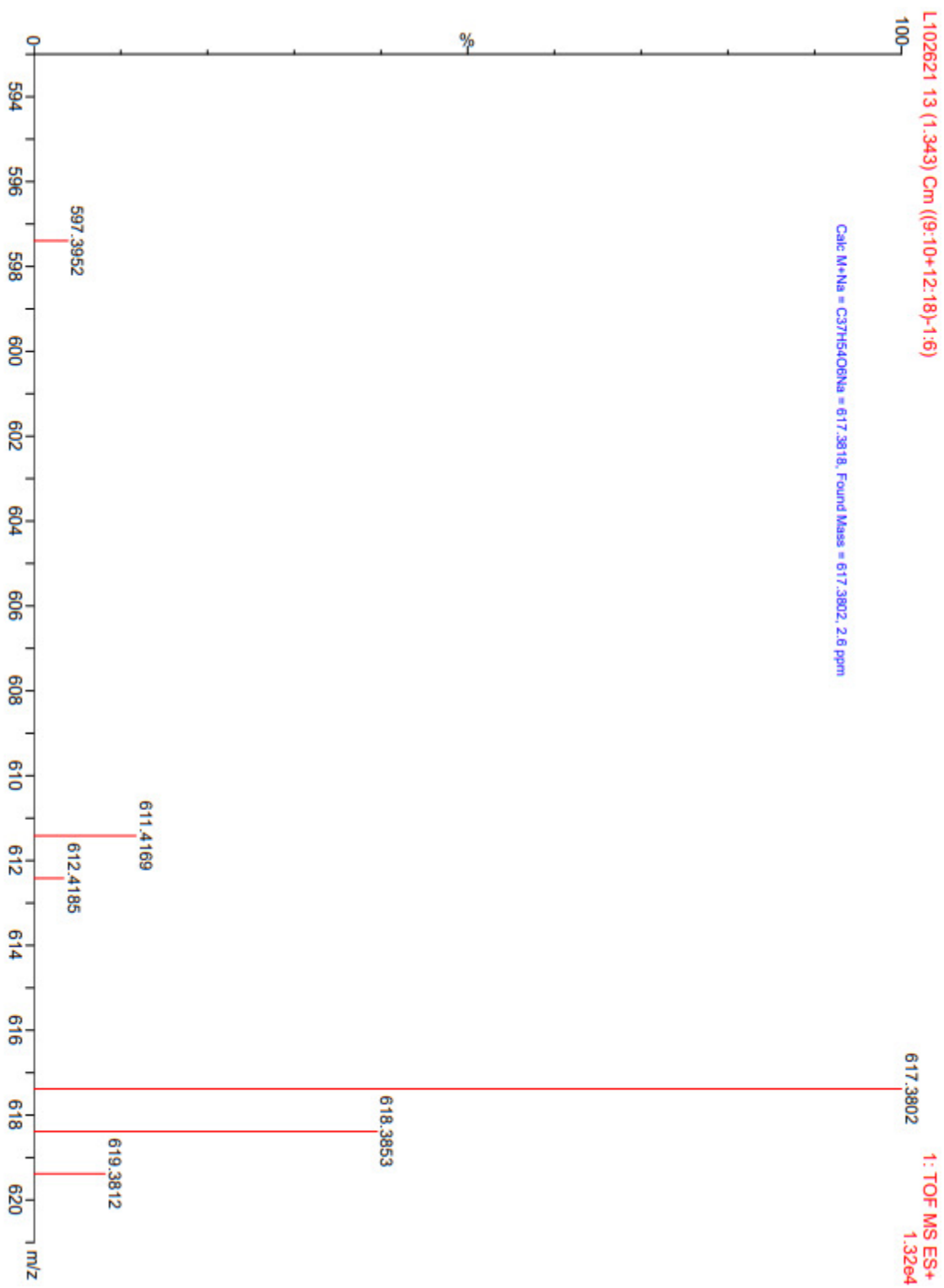
Methyl 3 $\alpha$ , 7 $\alpha$ -di(5-hexynoyloxy)-5 $\beta$ -cholate (10)



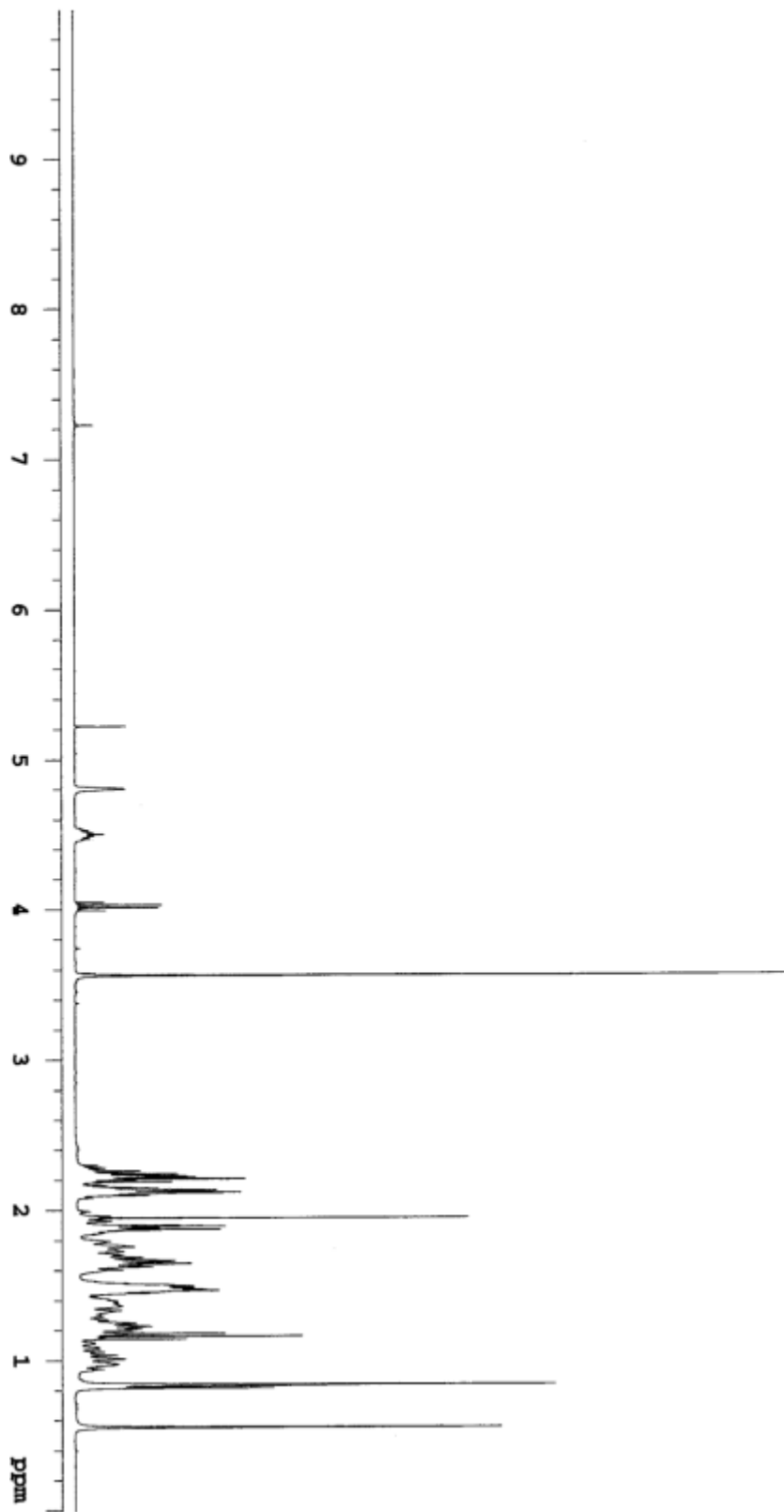
Methyl 3 $\alpha$ , 7 $\alpha$ -di(5-hexynoyloxy)-5 $\beta$ -cholate (10)



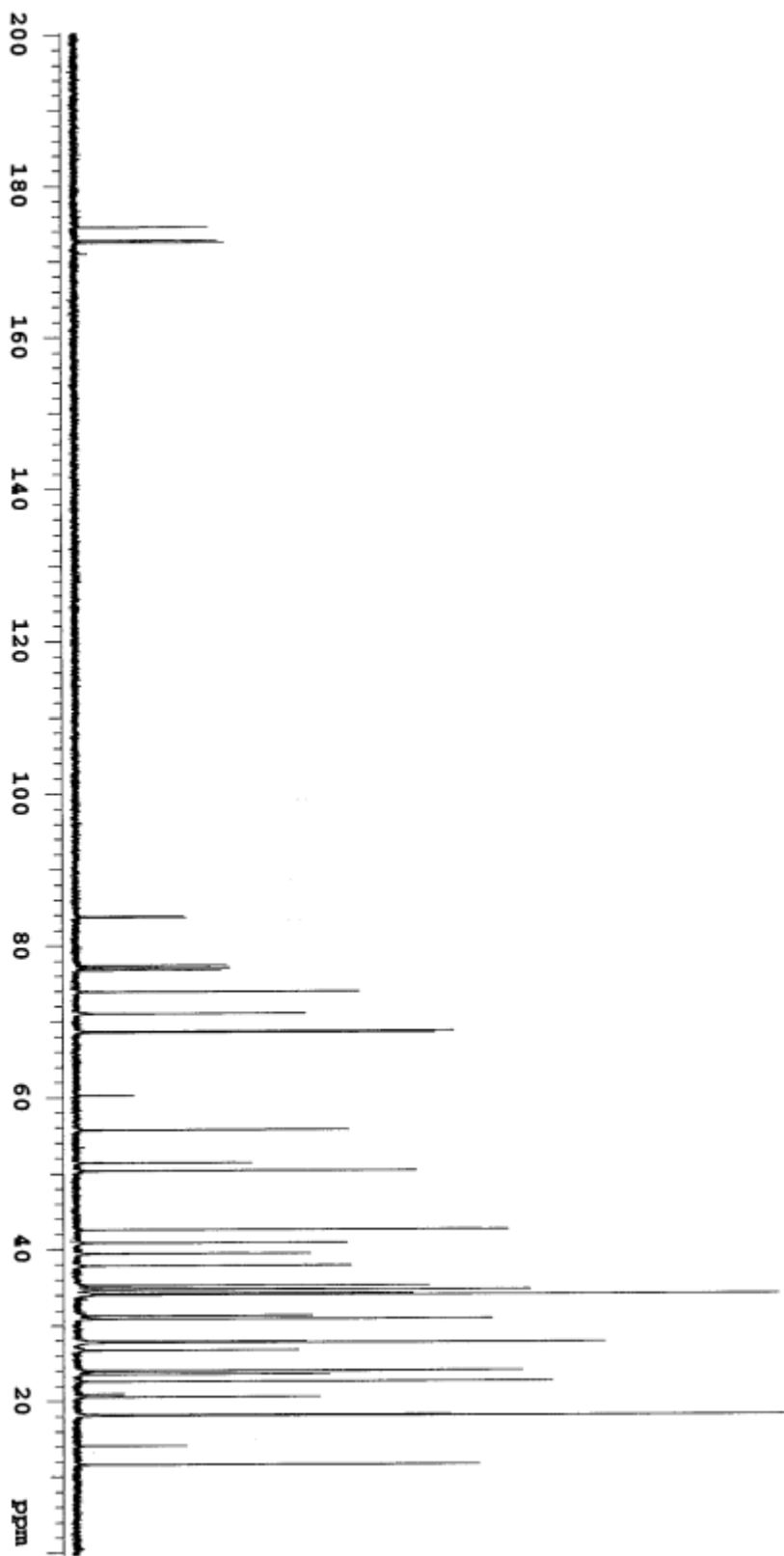
# Methyl 3 $\alpha$ , 7 $\alpha$ -di(5-hexynoyloxy)-5 $\beta$ -cholate (10)



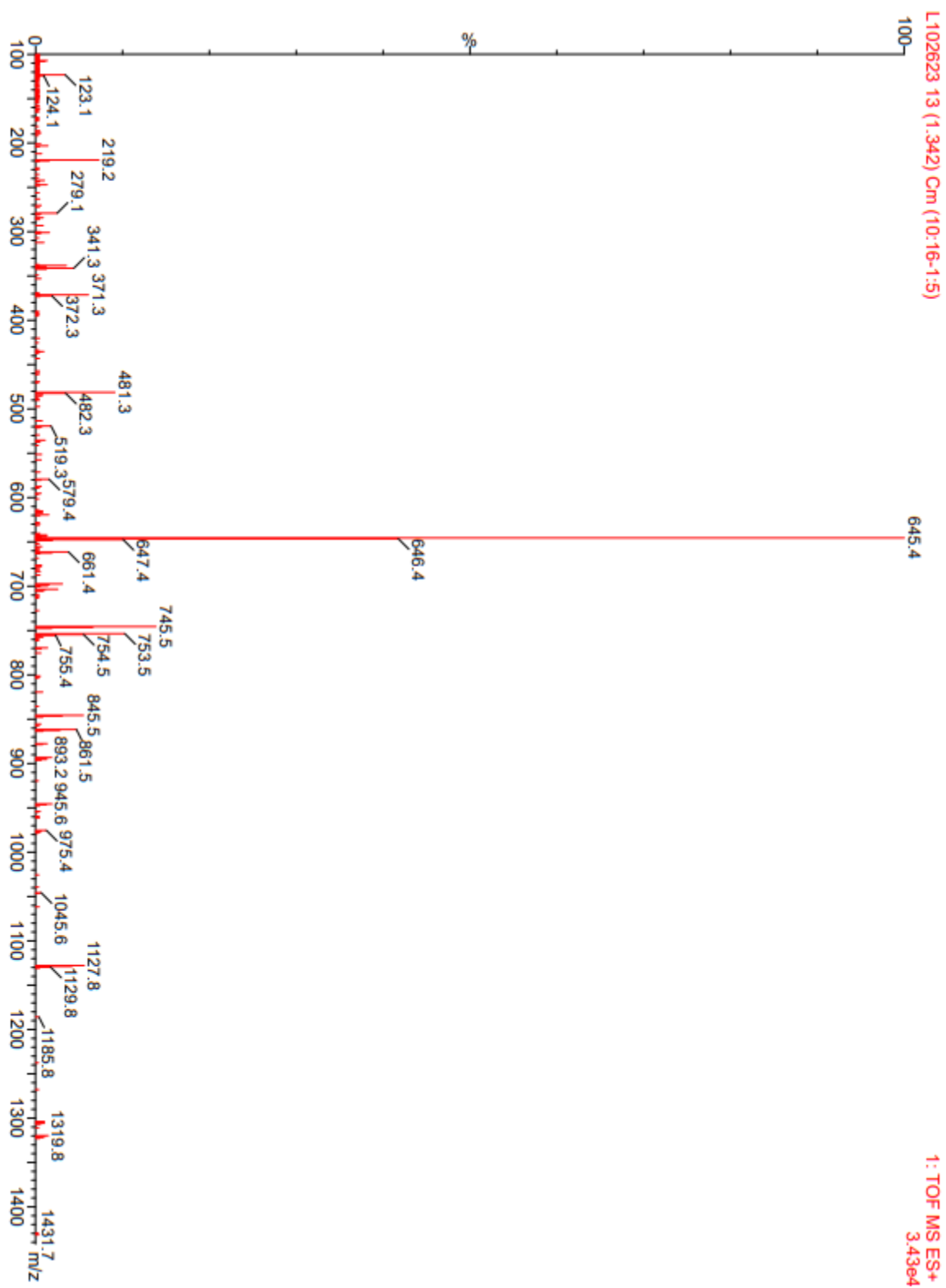
**Methyl 3 $\alpha$ , 7 $\alpha$ -di(6-heptynoxy)-5 $\beta$ -cholate (11)**



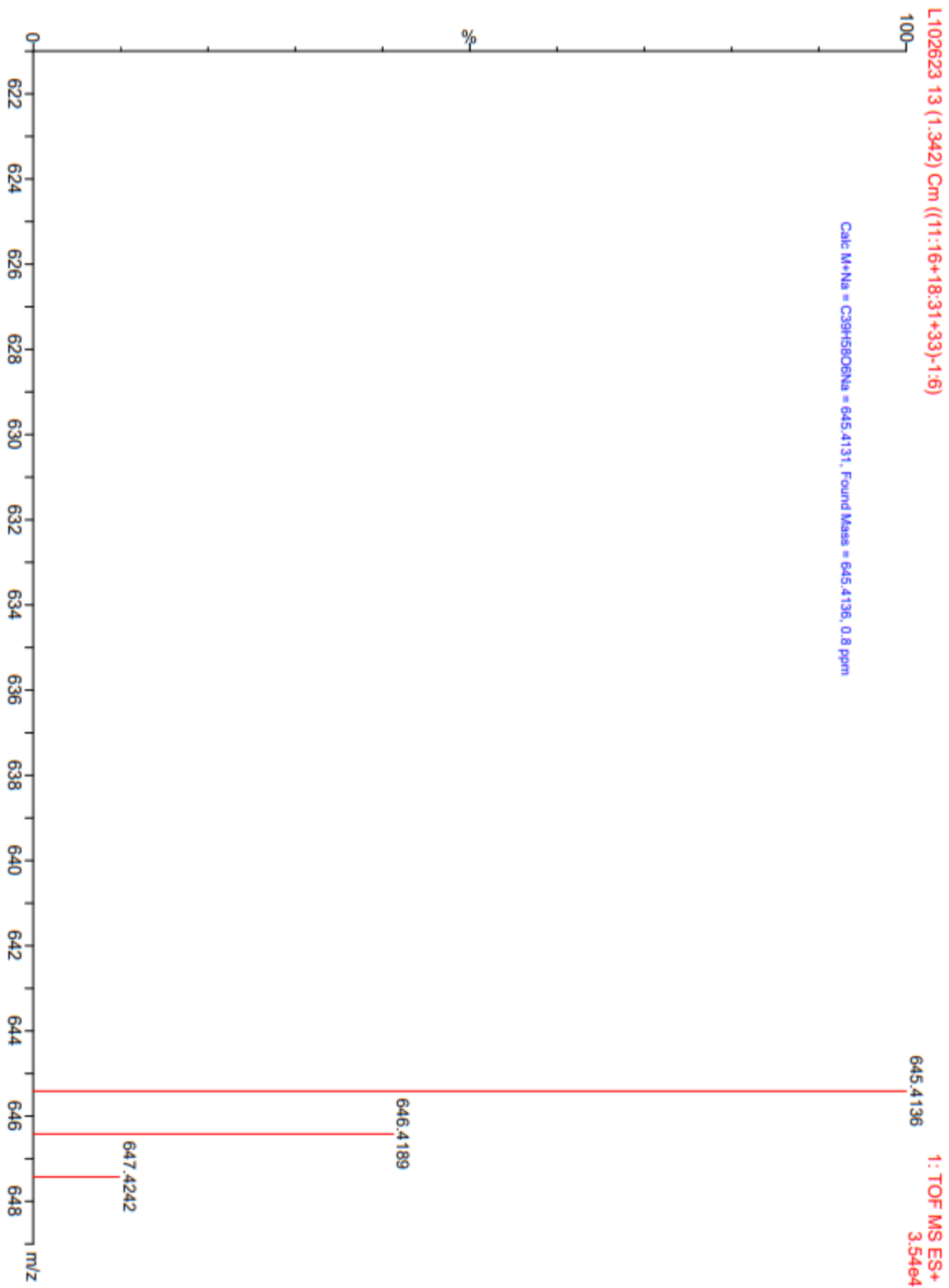
Methyl 3 $\alpha$ , 7 $\alpha$ -di(6-heptynoxy)-5 $\beta$ -cholate (11)



Methyl 3 $\alpha$ , 7 $\alpha$ -di(6-heptynoxy)-5 $\beta$ -cholate (11)

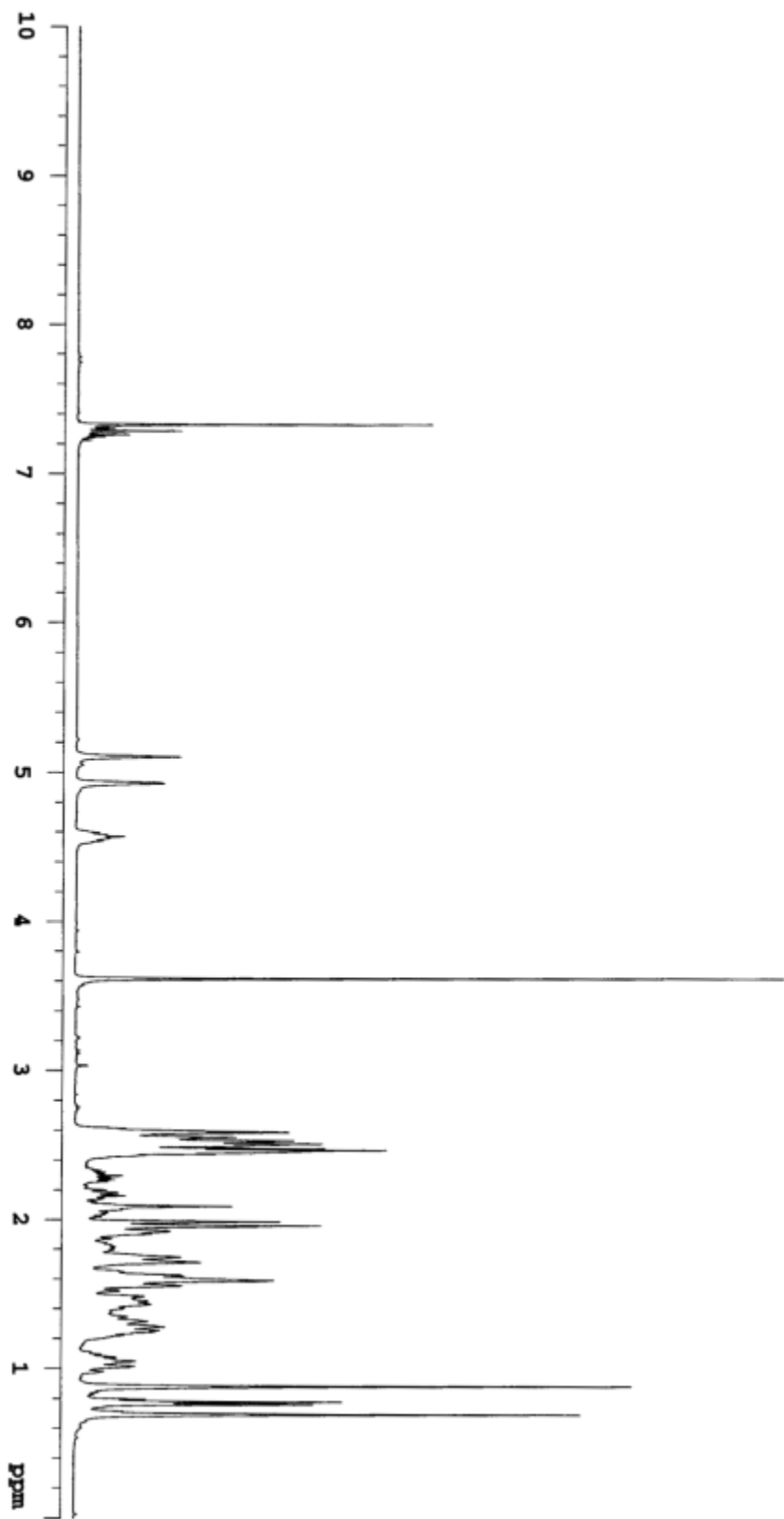


Methyl 3 $\alpha$ , 7 $\alpha$ -di(6-heptynoxy)-5 $\beta$ -cholate (11)

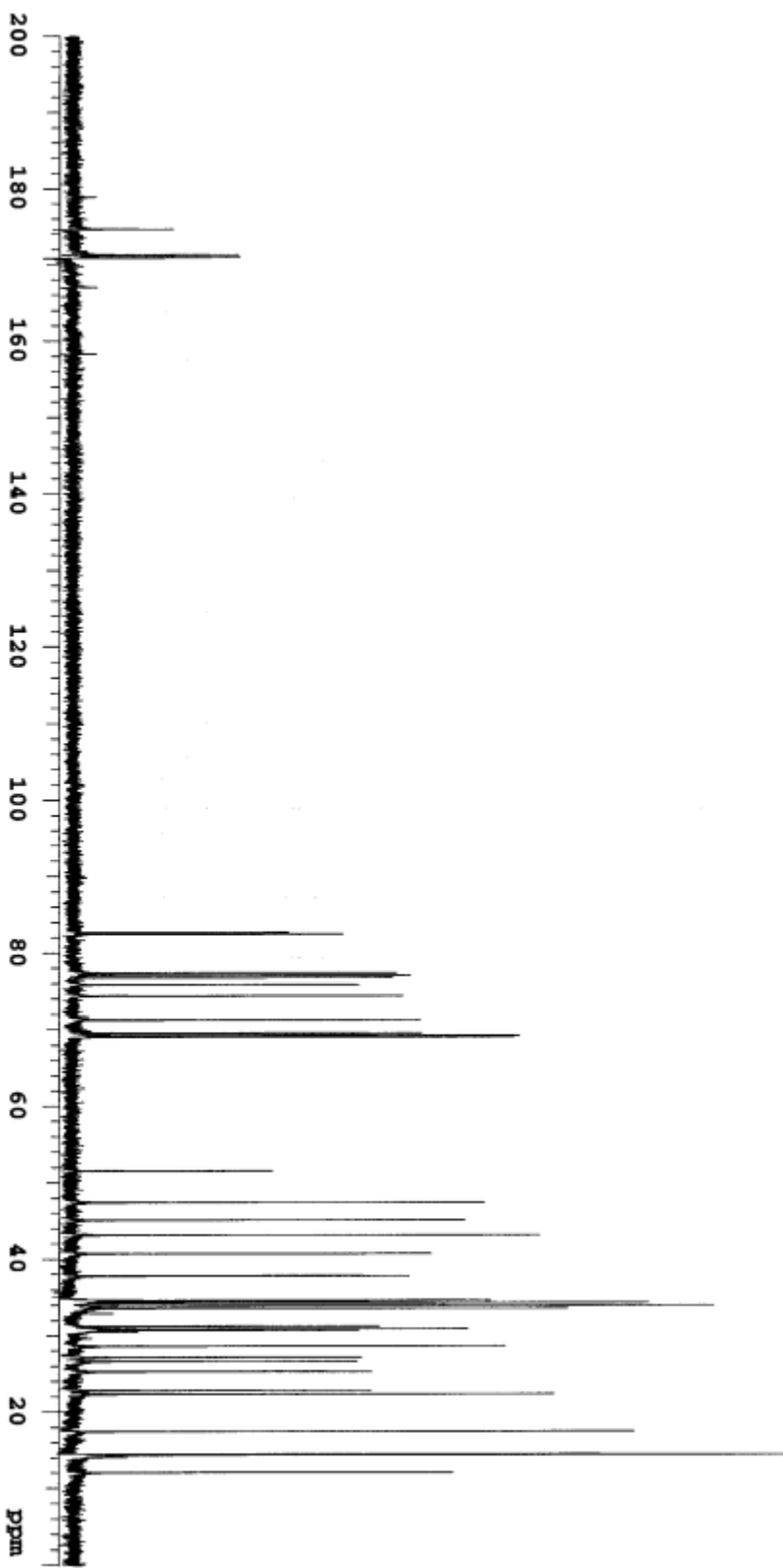




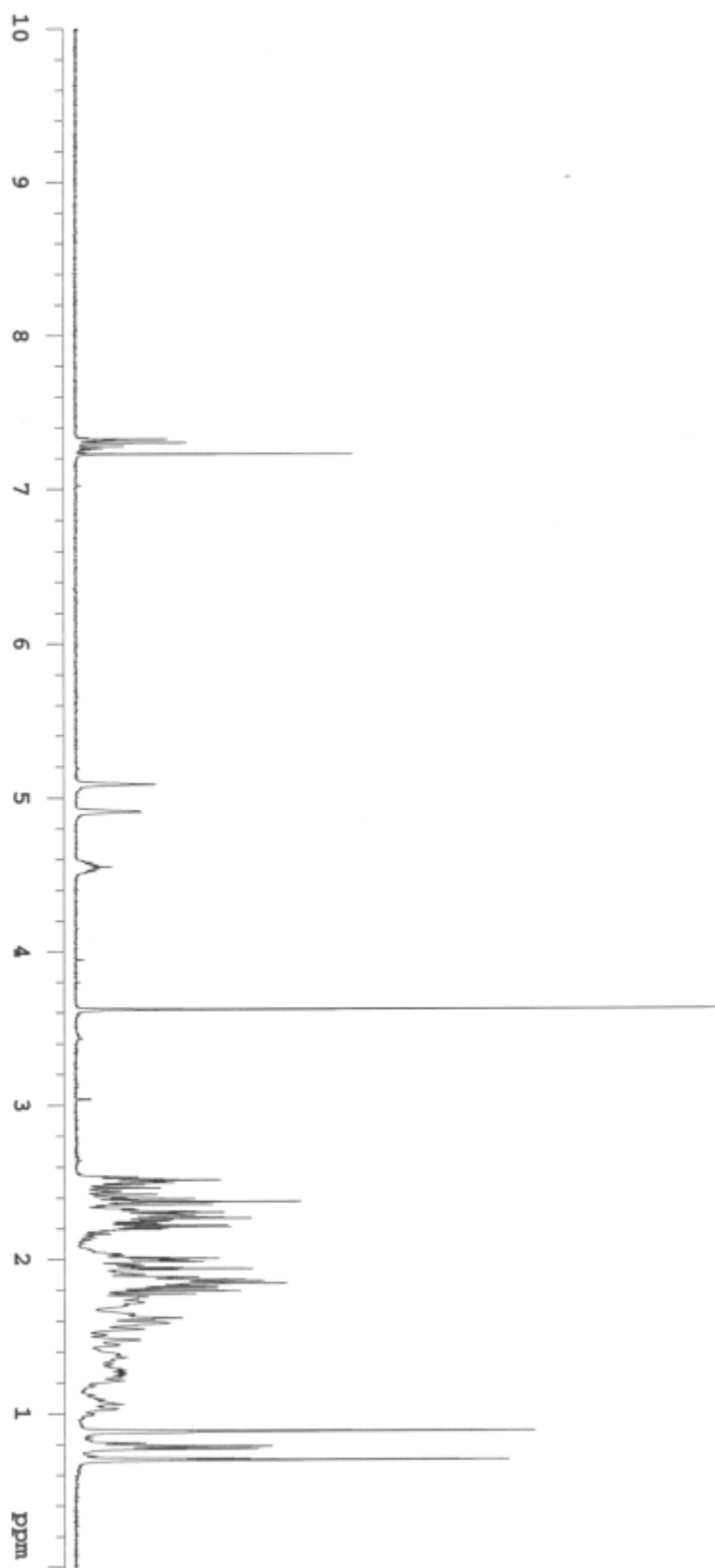
**Methyl 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -tri(4-pentynoyloxy)-5 $\beta$ -cholate (12)**



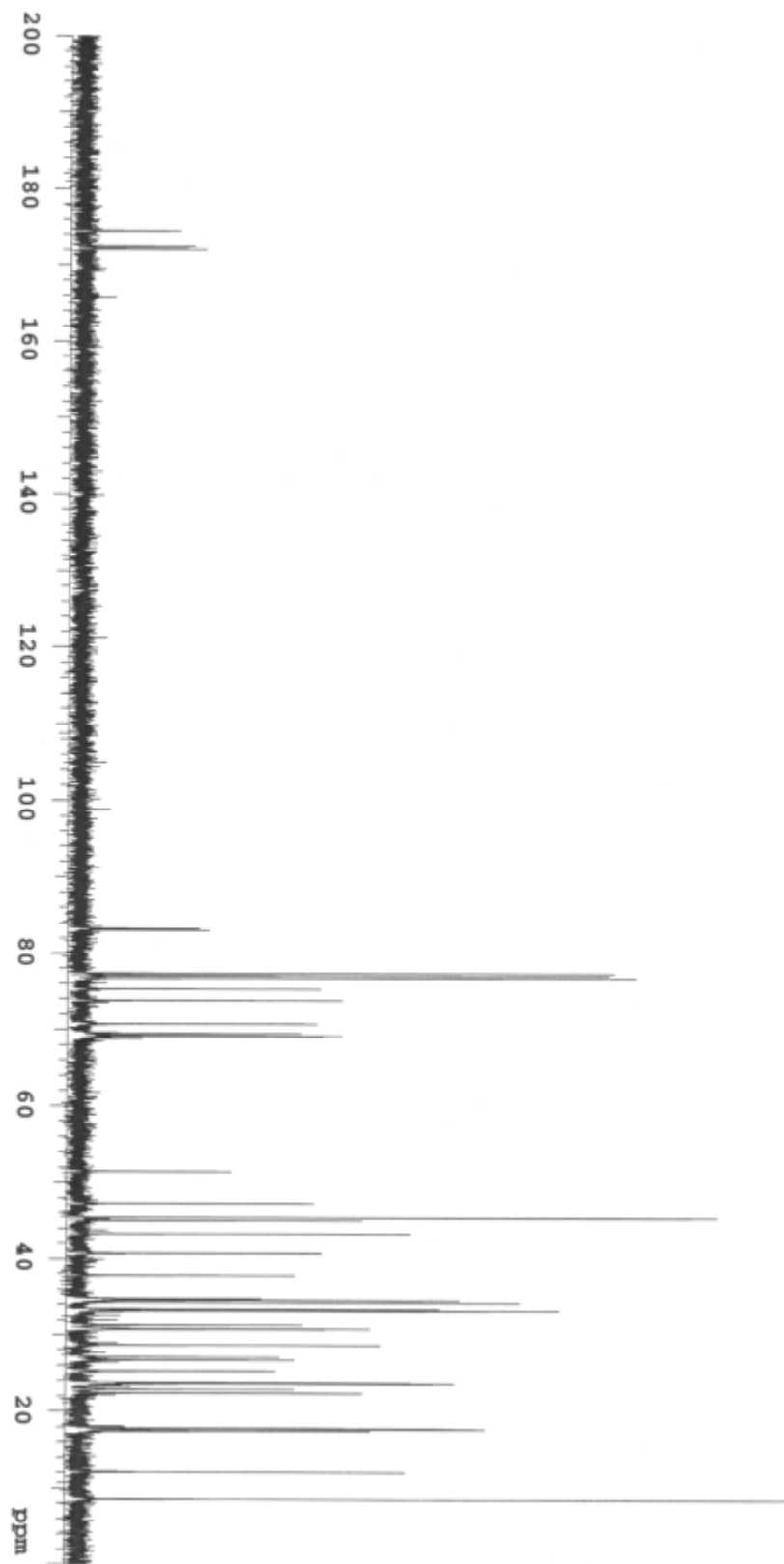
Methyl 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -tri(4-pentynoyloxy)-5 $\beta$ -cholate (12)



**Methyl 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -tri(5-hexynoyloxy)-5 $\beta$ -cholate (13)**



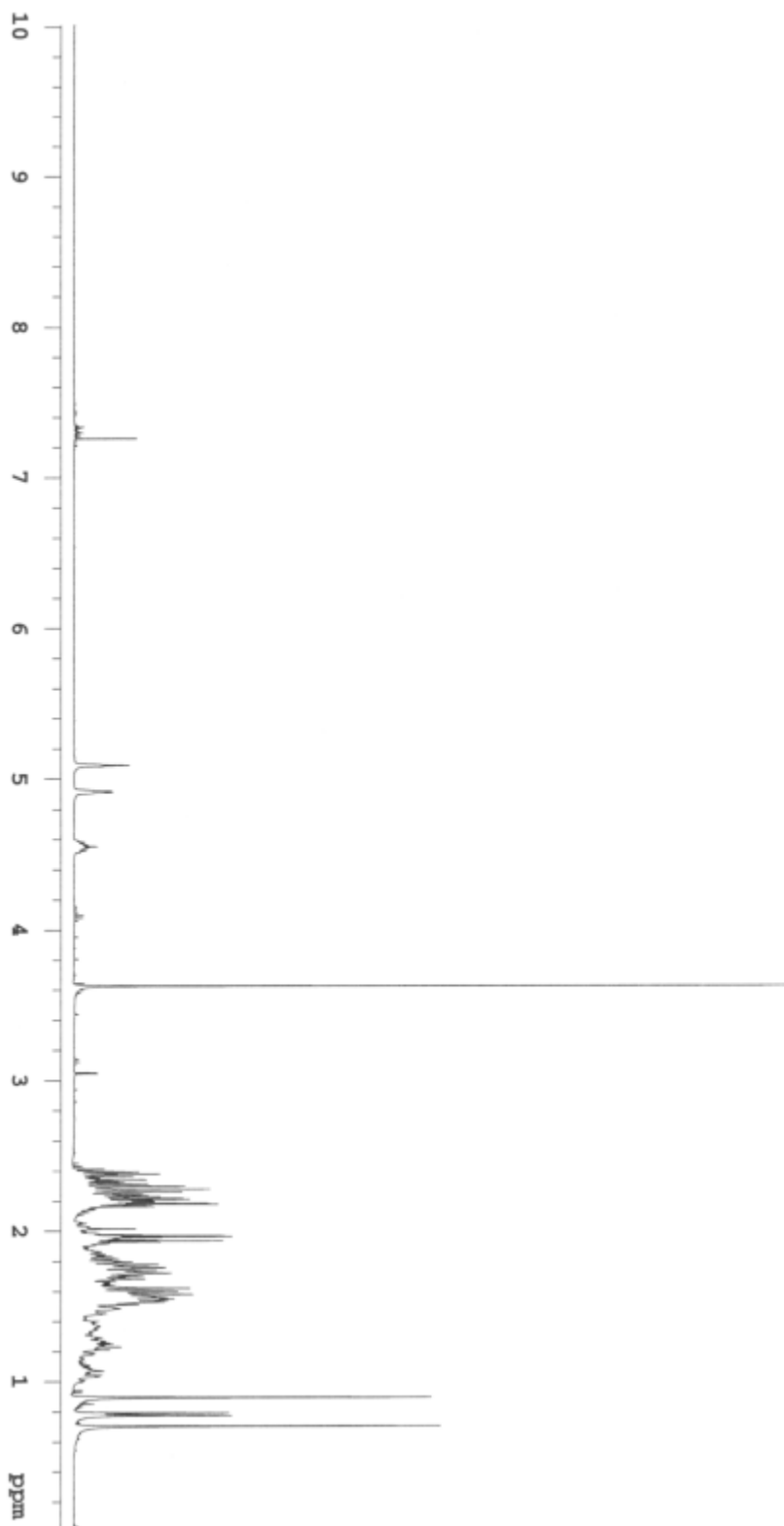
**Methyl 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -tri(5-hexynoyloxy)-5 $\beta$ -cholate (13)**



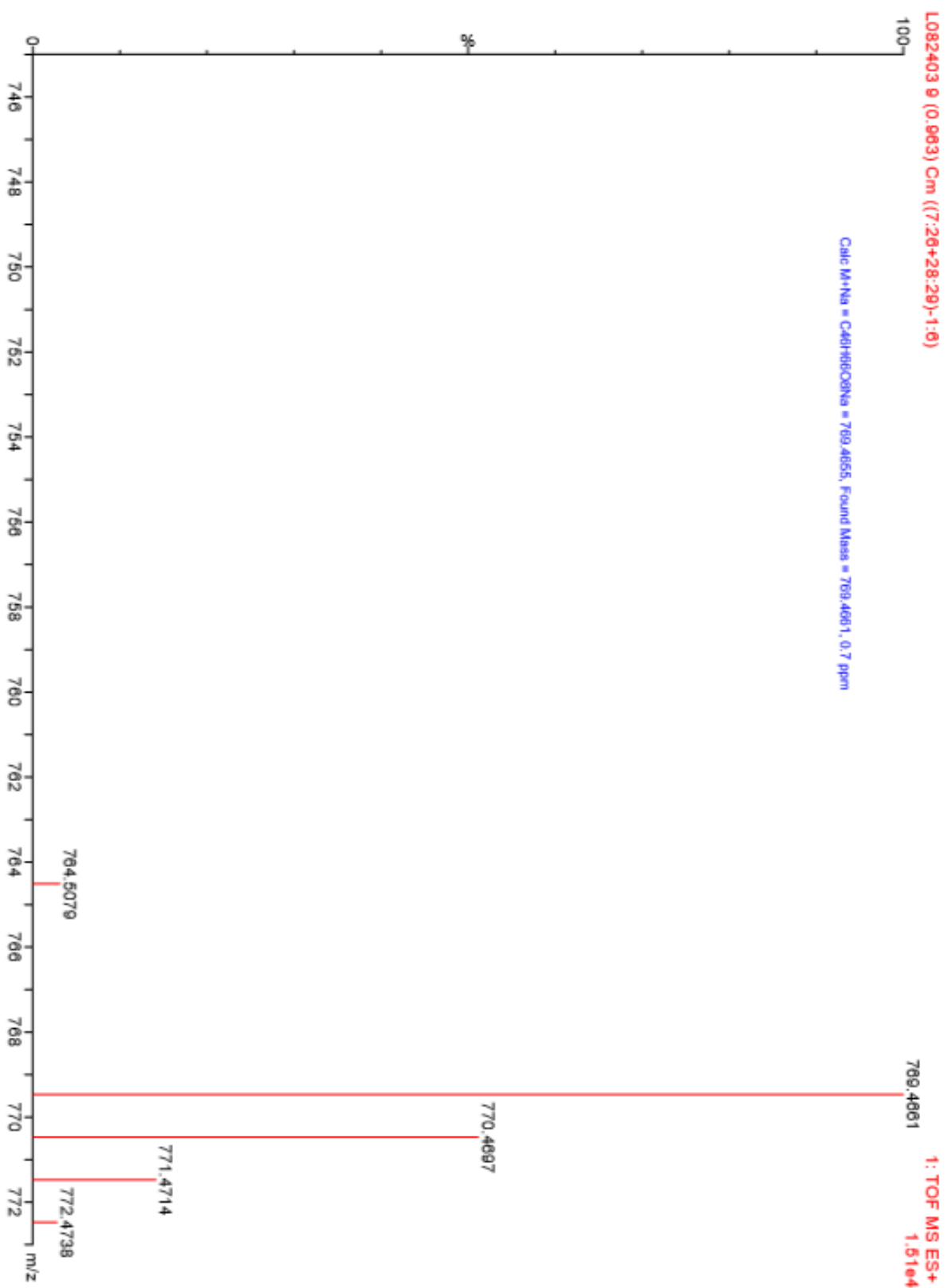
Methyl 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -tri(5-hexynoyloxy)-5 $\beta$ -cholate (13)



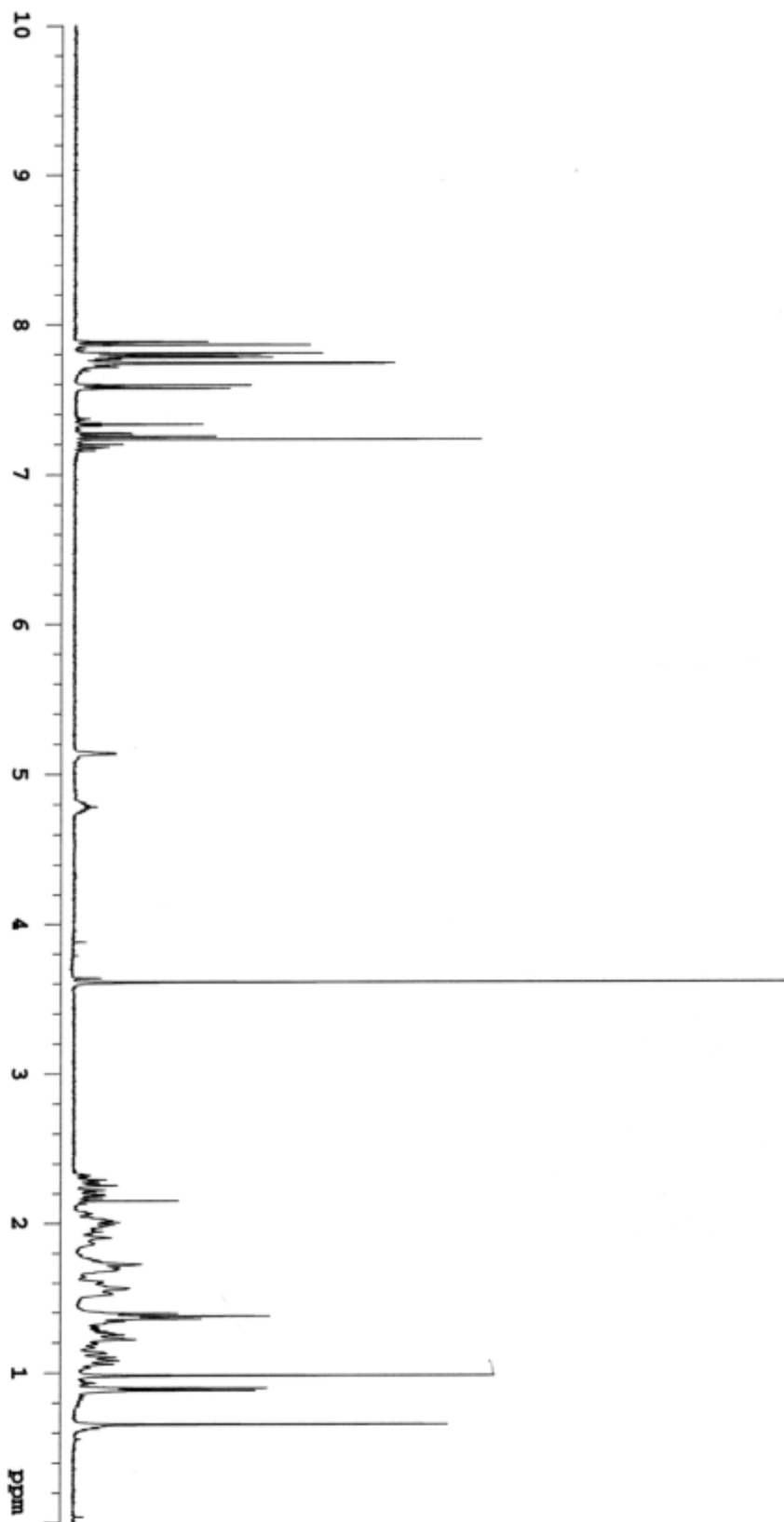
**Methyl 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -tri(6-heptynoxy)-5 $\beta$ -cholate (14)**



Methyl 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -tri(6-heptynoxy)-5 $\beta$ -cholate (14)

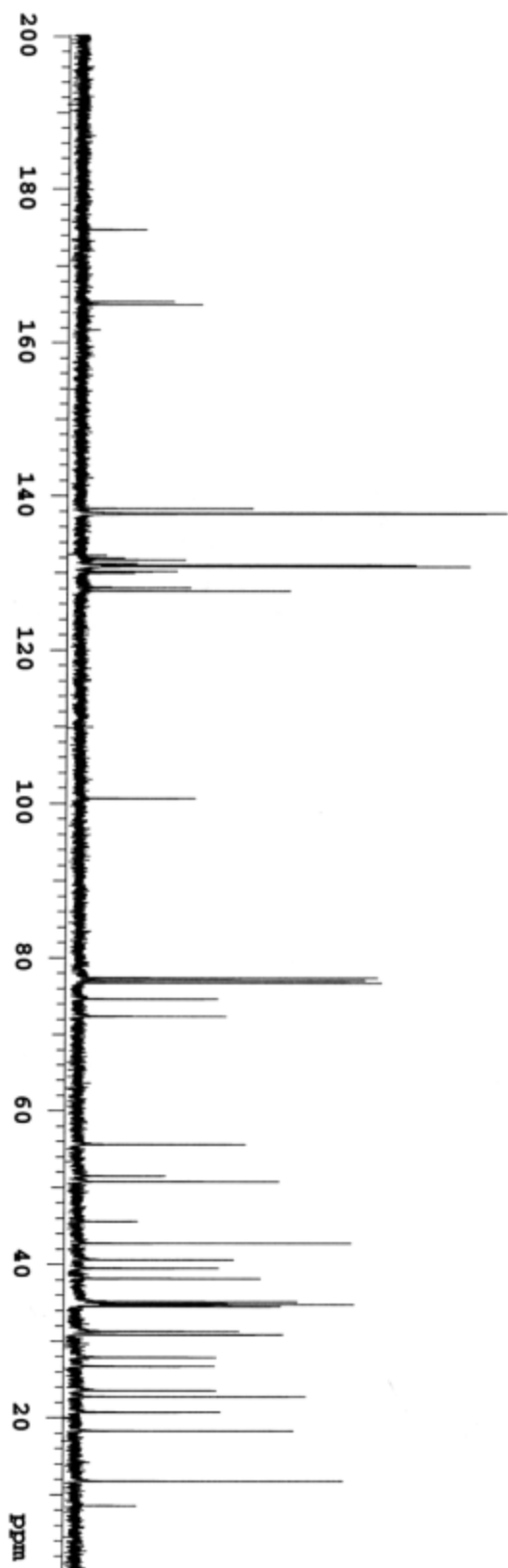


Methyl 3 $\alpha$ , 7 $\alpha$ -Di(4-iodobenzoyloxy)-5 $\beta$ -cholate (15)

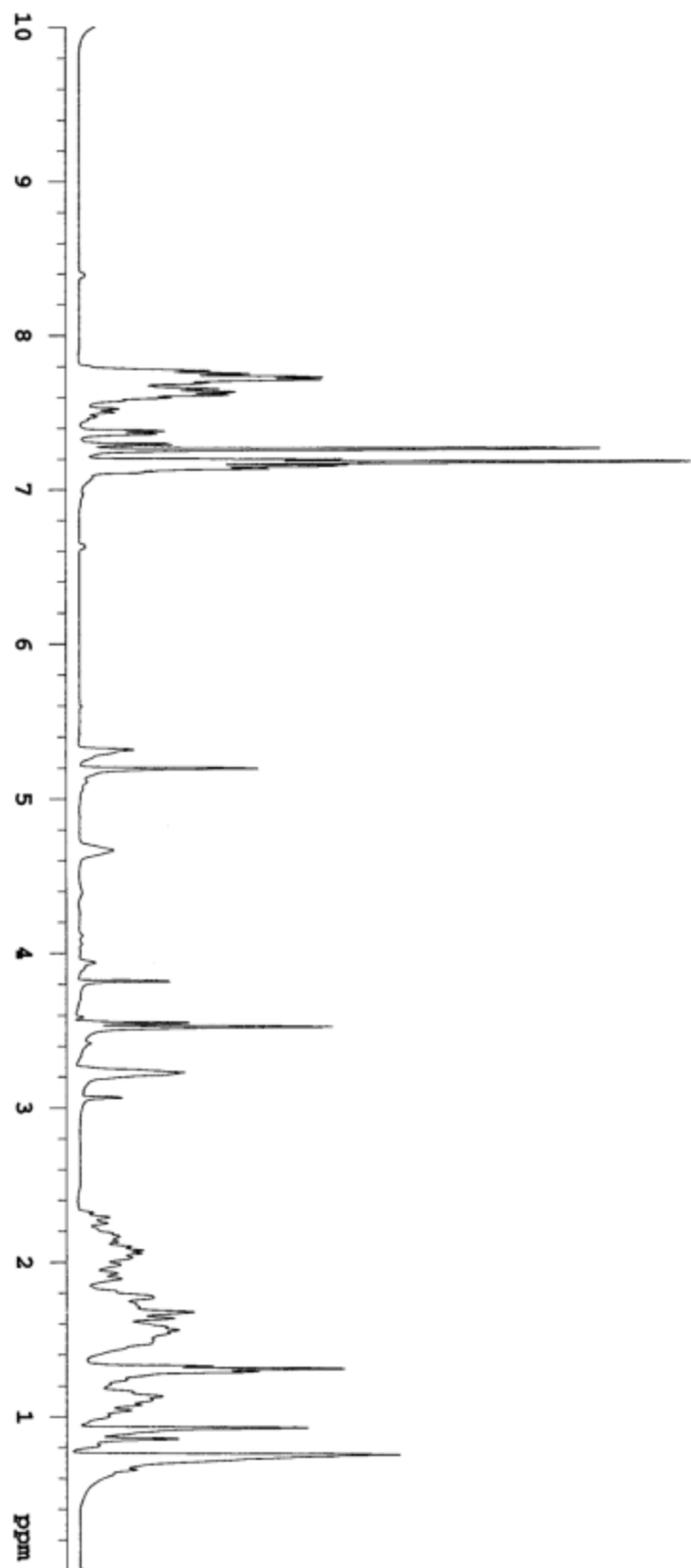




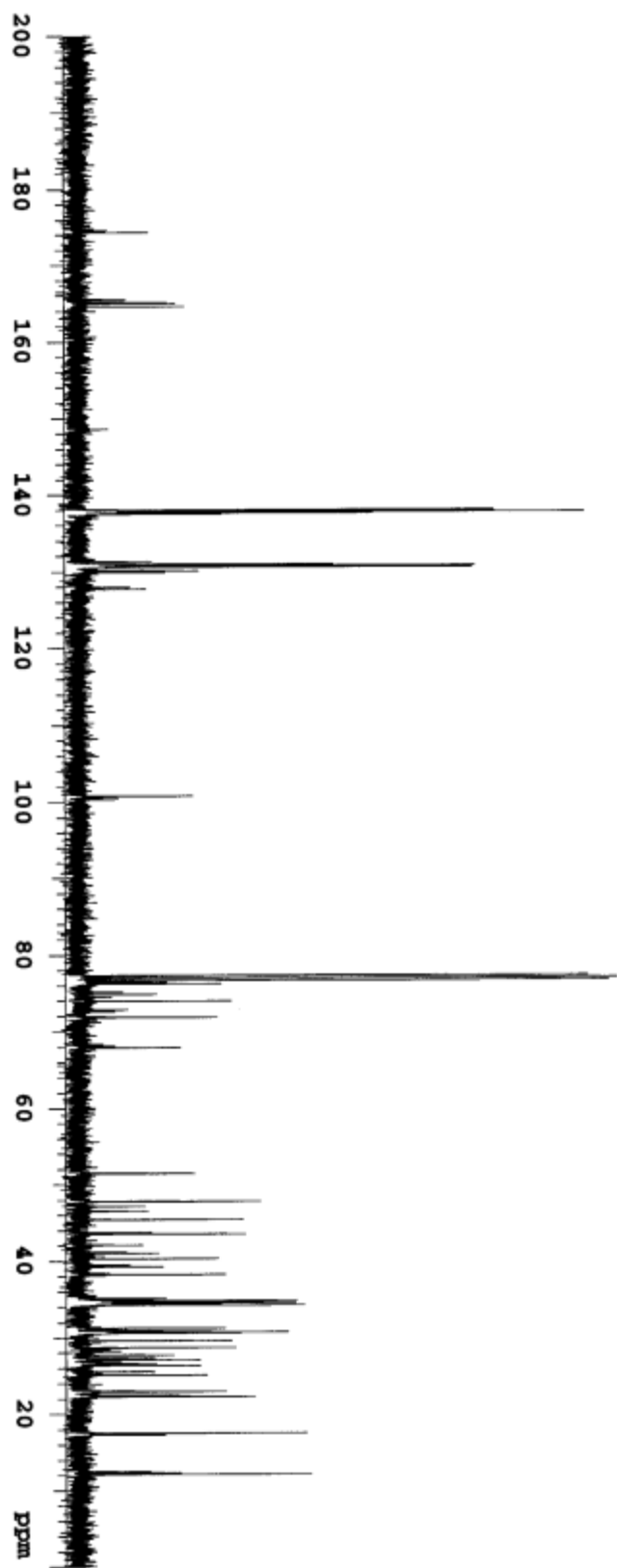
Methyl 3 $\alpha$ , 7 $\alpha$ -Di(4-iodobenzoyloxy)-5 $\beta$ -cholate (15)



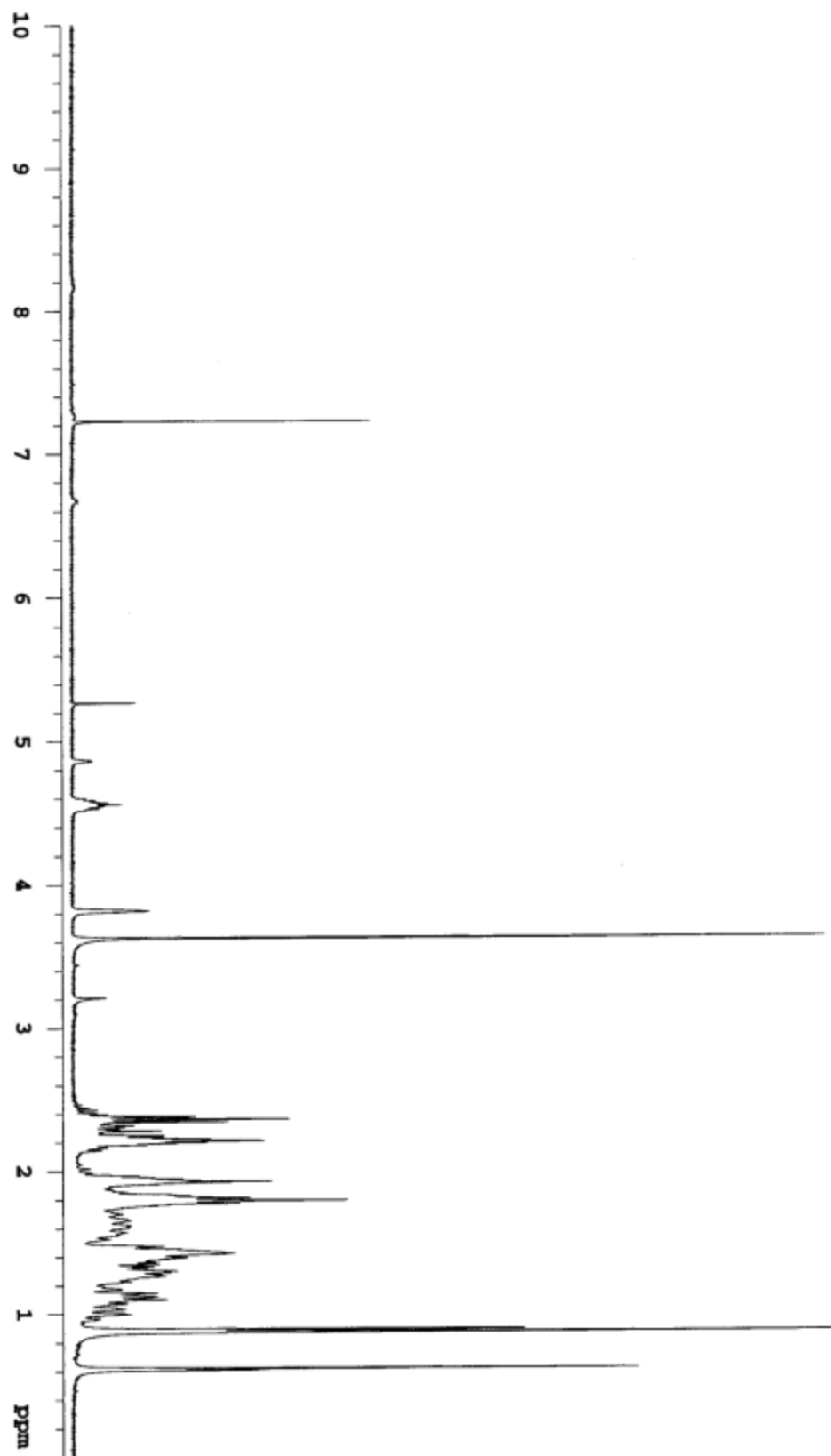
**Methyl 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -tri(4-iodobenzoyloxy)-5 $\beta$ -cholate(16)**



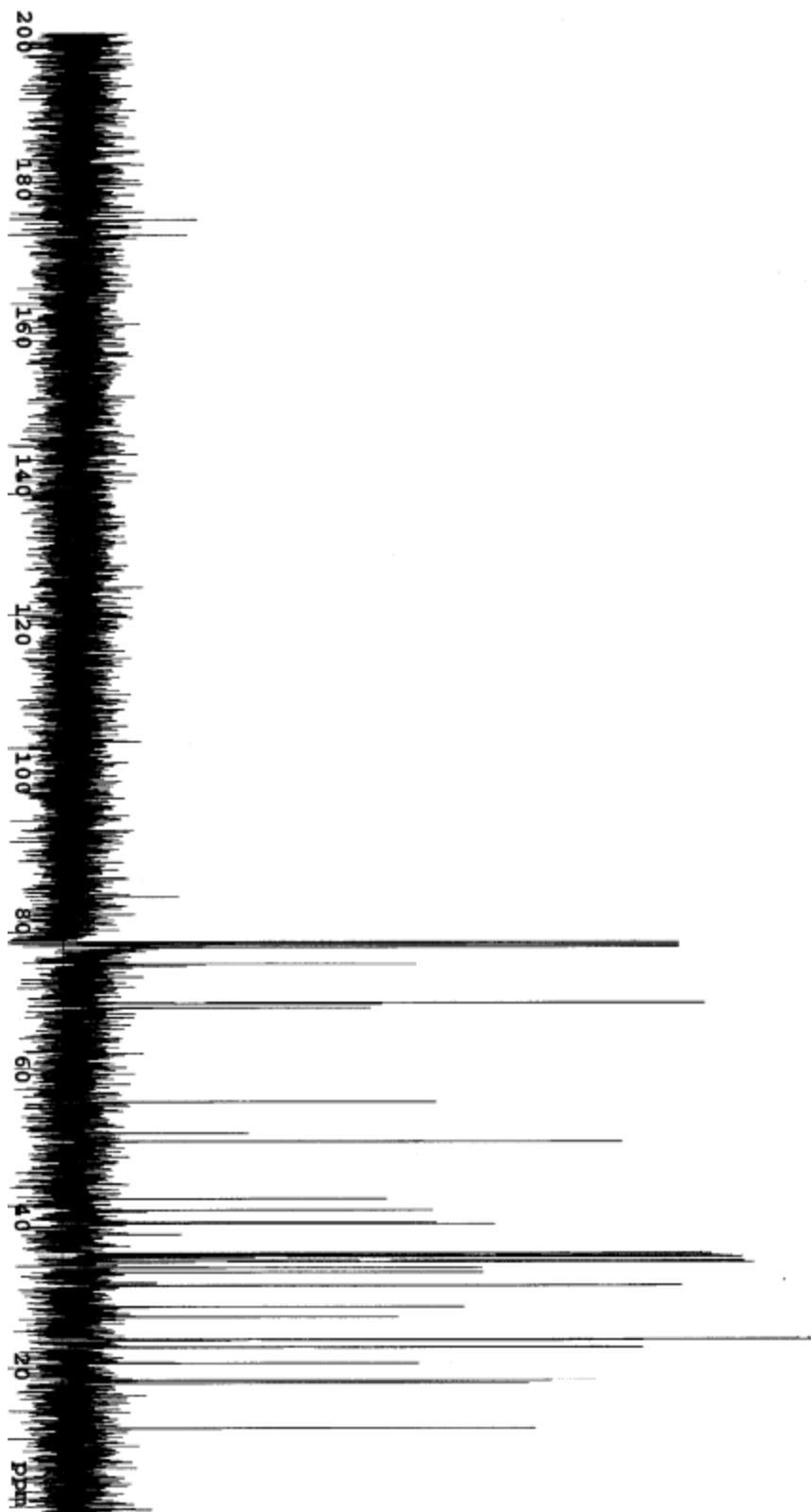
Methyl 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -tri(4-iodobenzoyloxy)-5 $\beta$ -cholate(16)



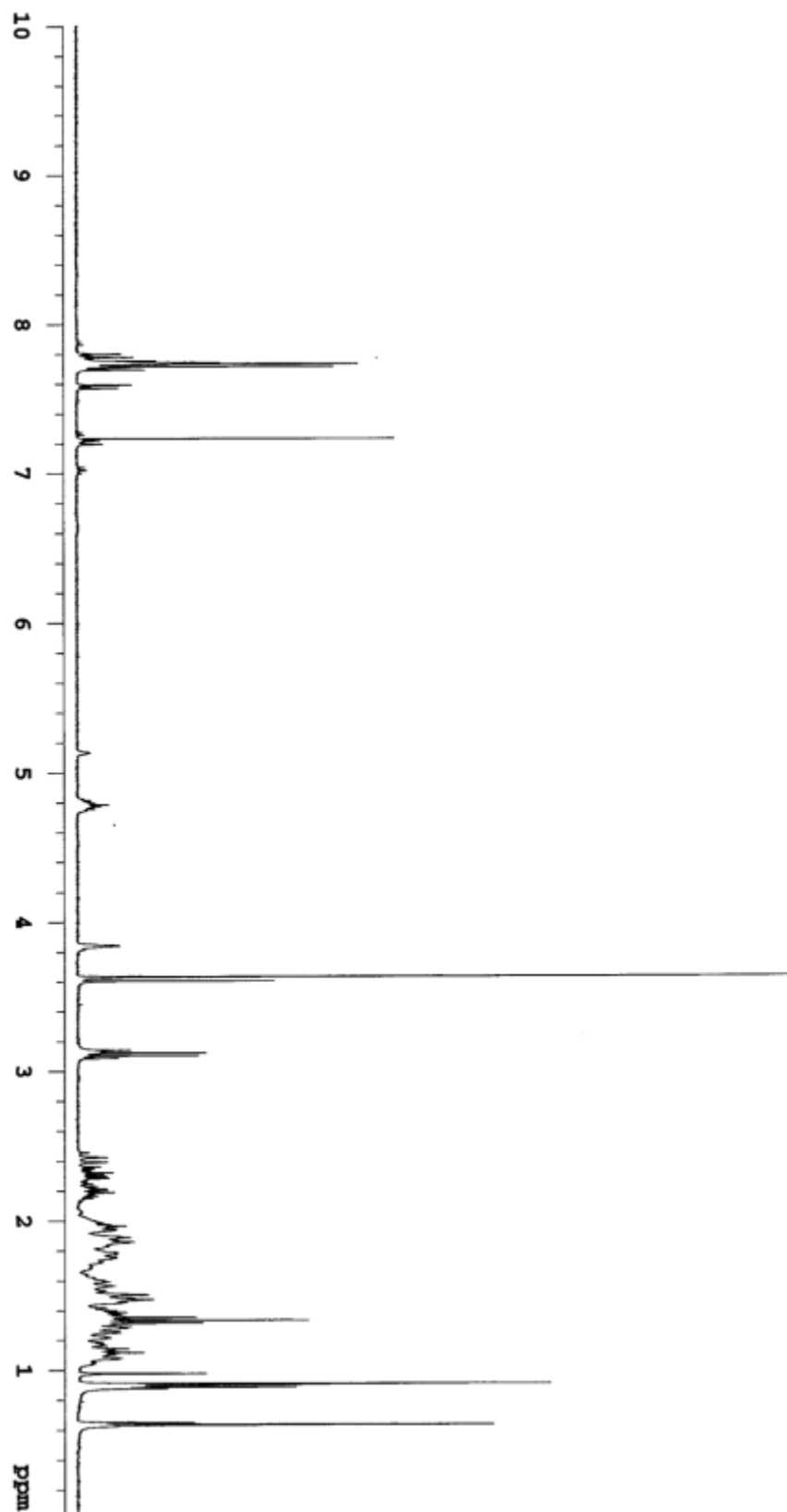
Methyl 7 $\alpha$ -hydroxy-3 $\alpha$ -(5-hexynoyloxy)-5 $\beta$ -cholanoate (17)



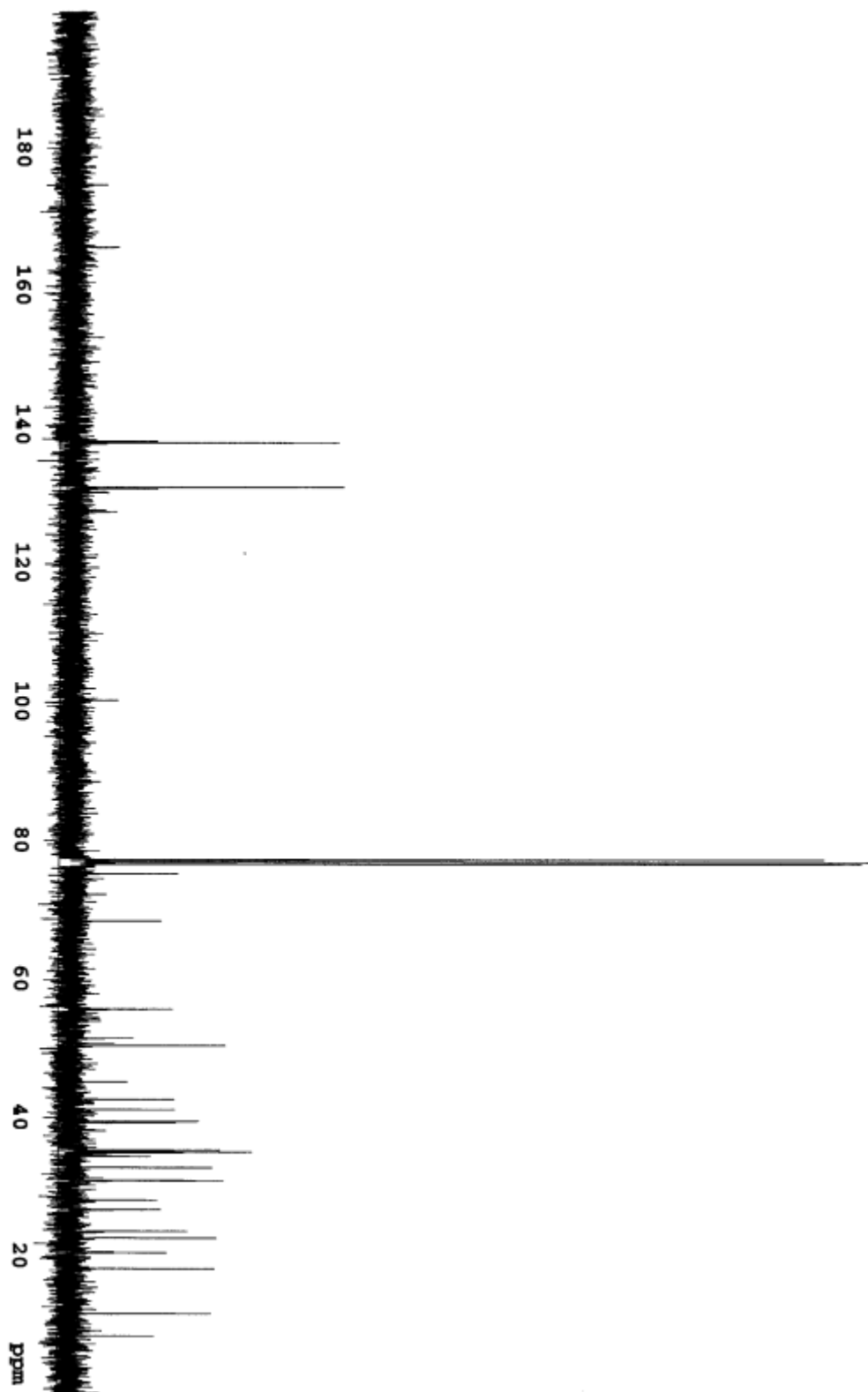
Methyl 7 $\alpha$ -hydroxy-3 $\alpha$ -(5-hexynoyloxy)-5 $\beta$ -cholanoate (17)



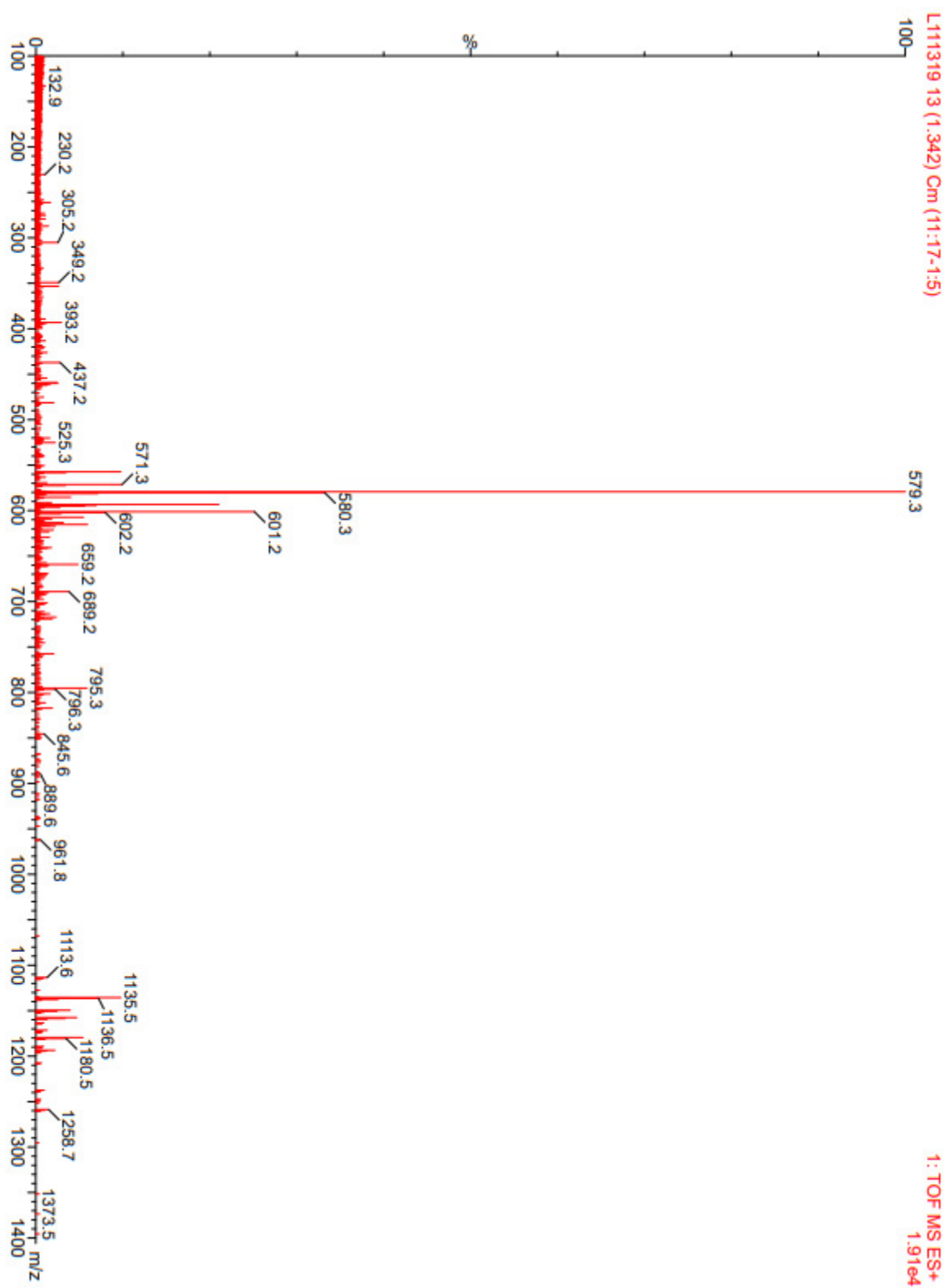
Methyl 7 $\alpha$ -hydroxy-3 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate. (18)



Methyl 7 $\alpha$ -hydroxy-3 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate. (18)

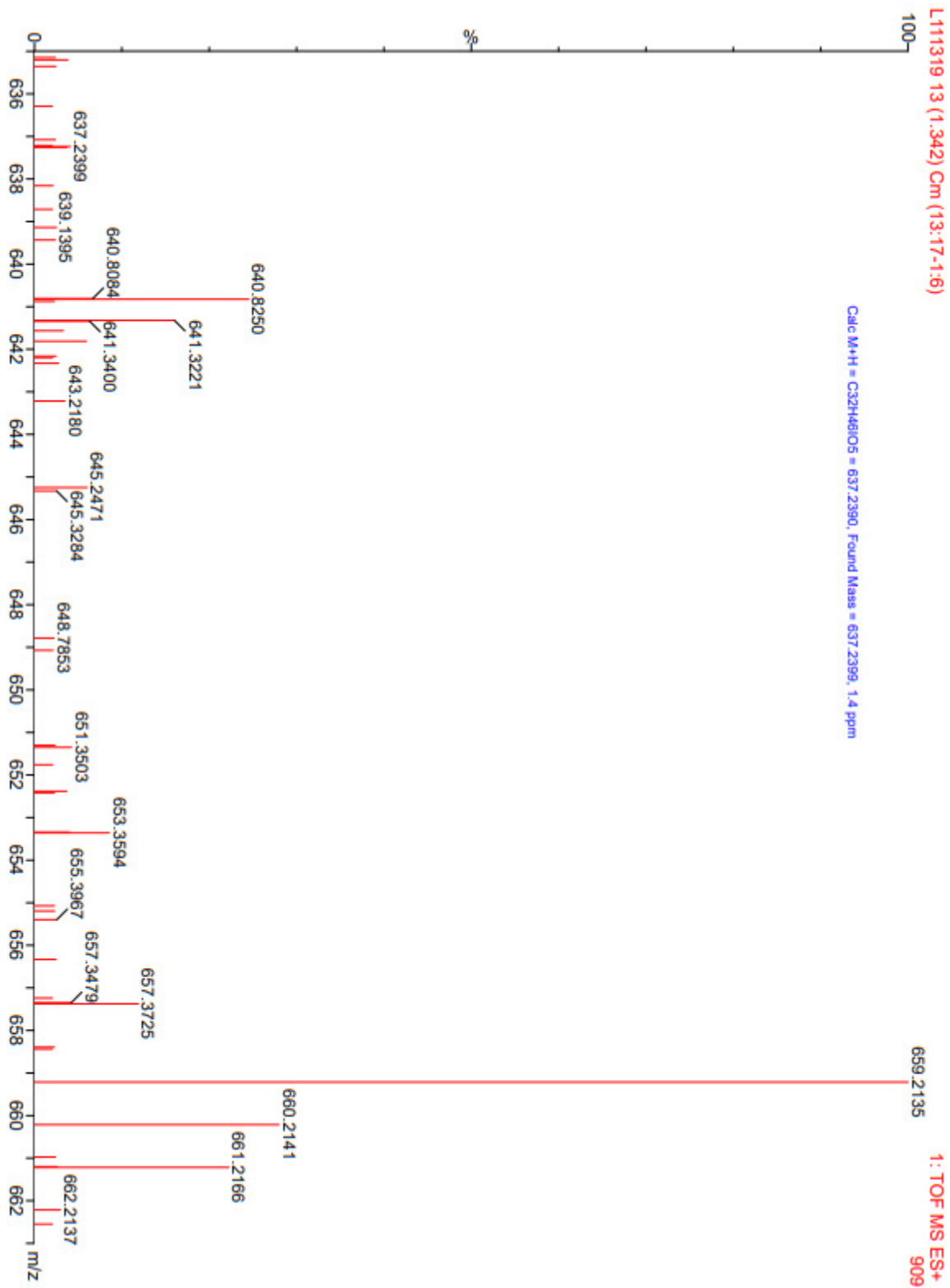


Methyl 7 $\alpha$ -hydroxy-3 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate. (18)

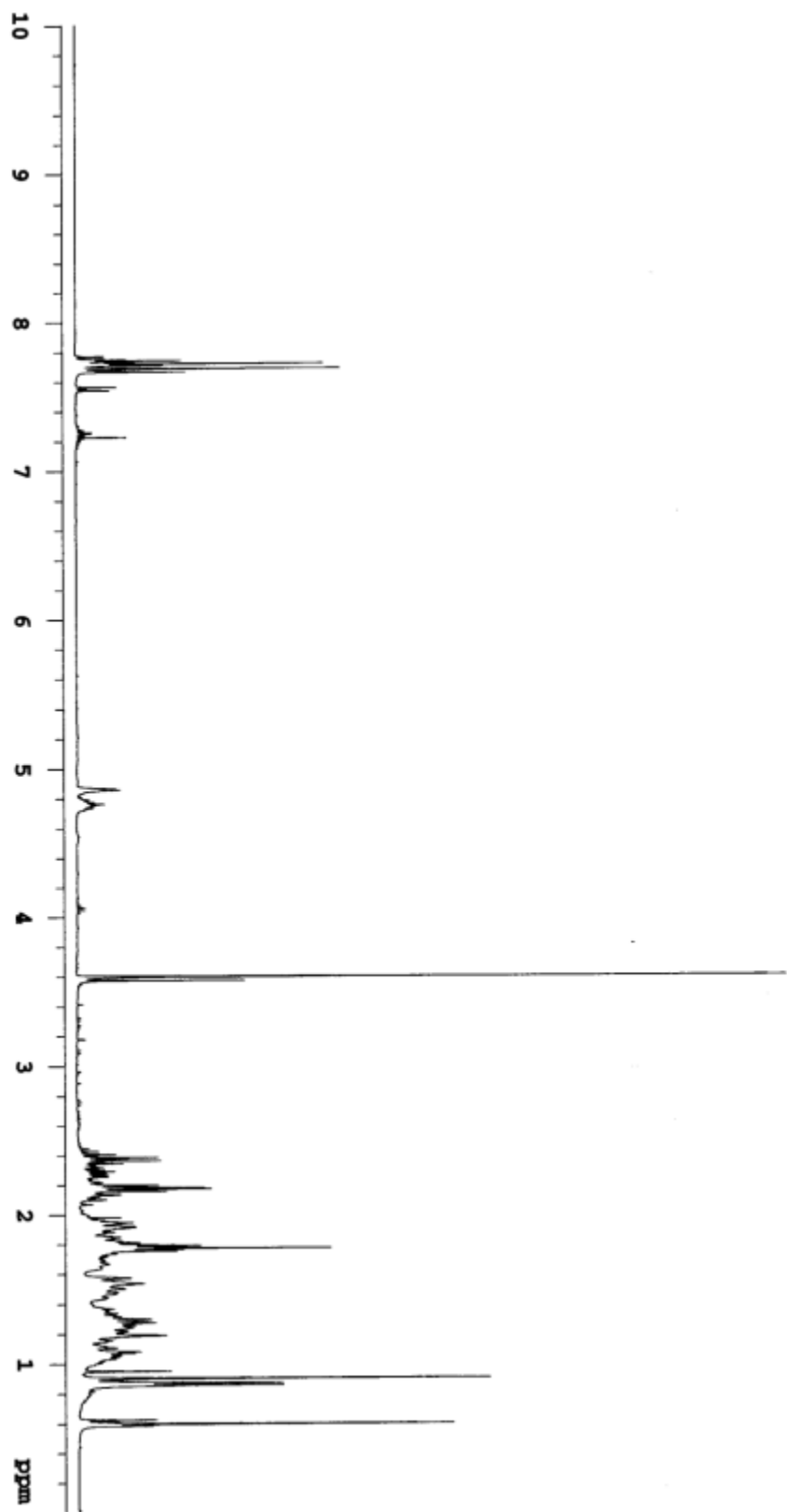




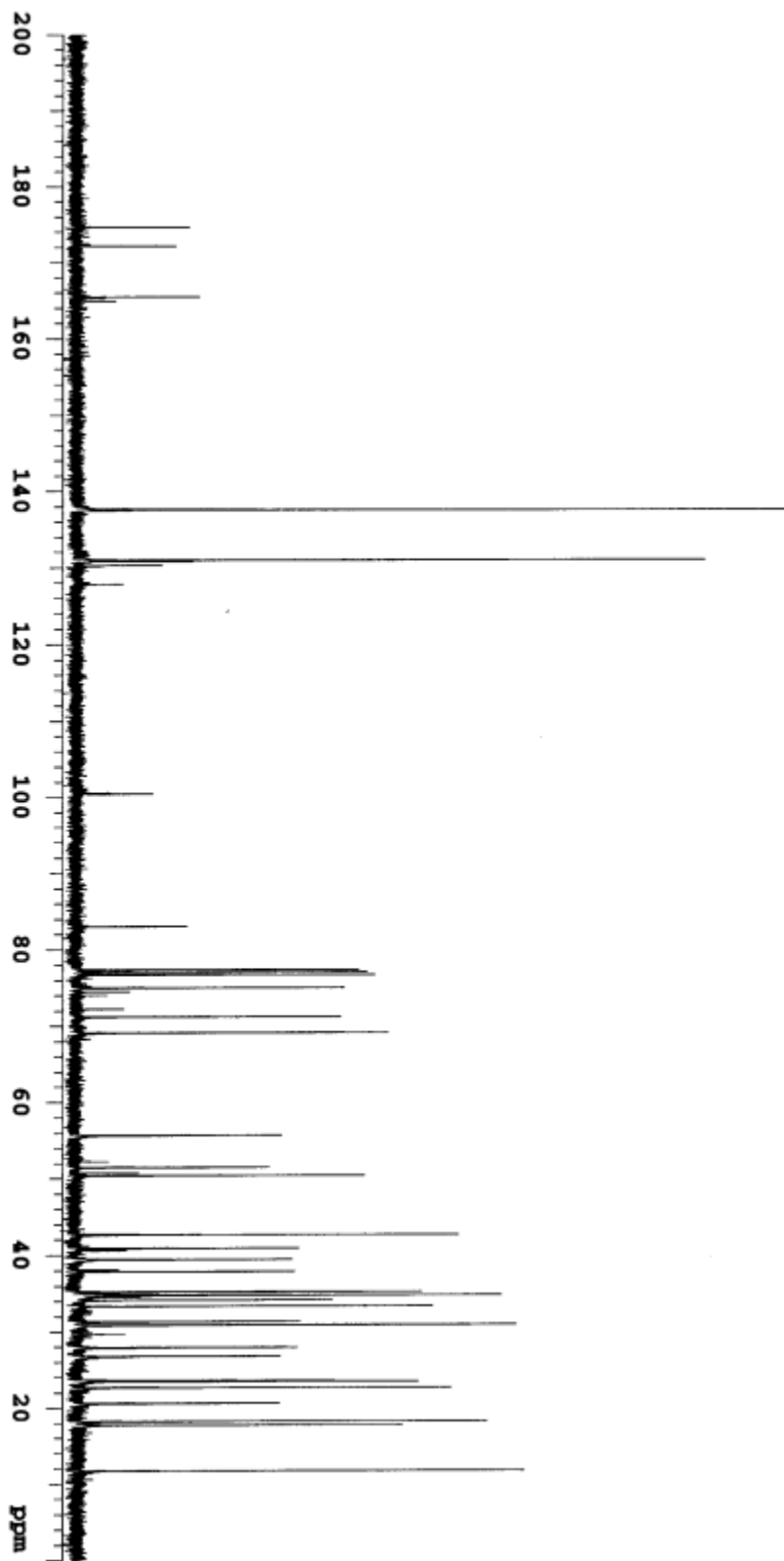
Methyl 7 $\alpha$ -hydroxy-3 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate. (18)



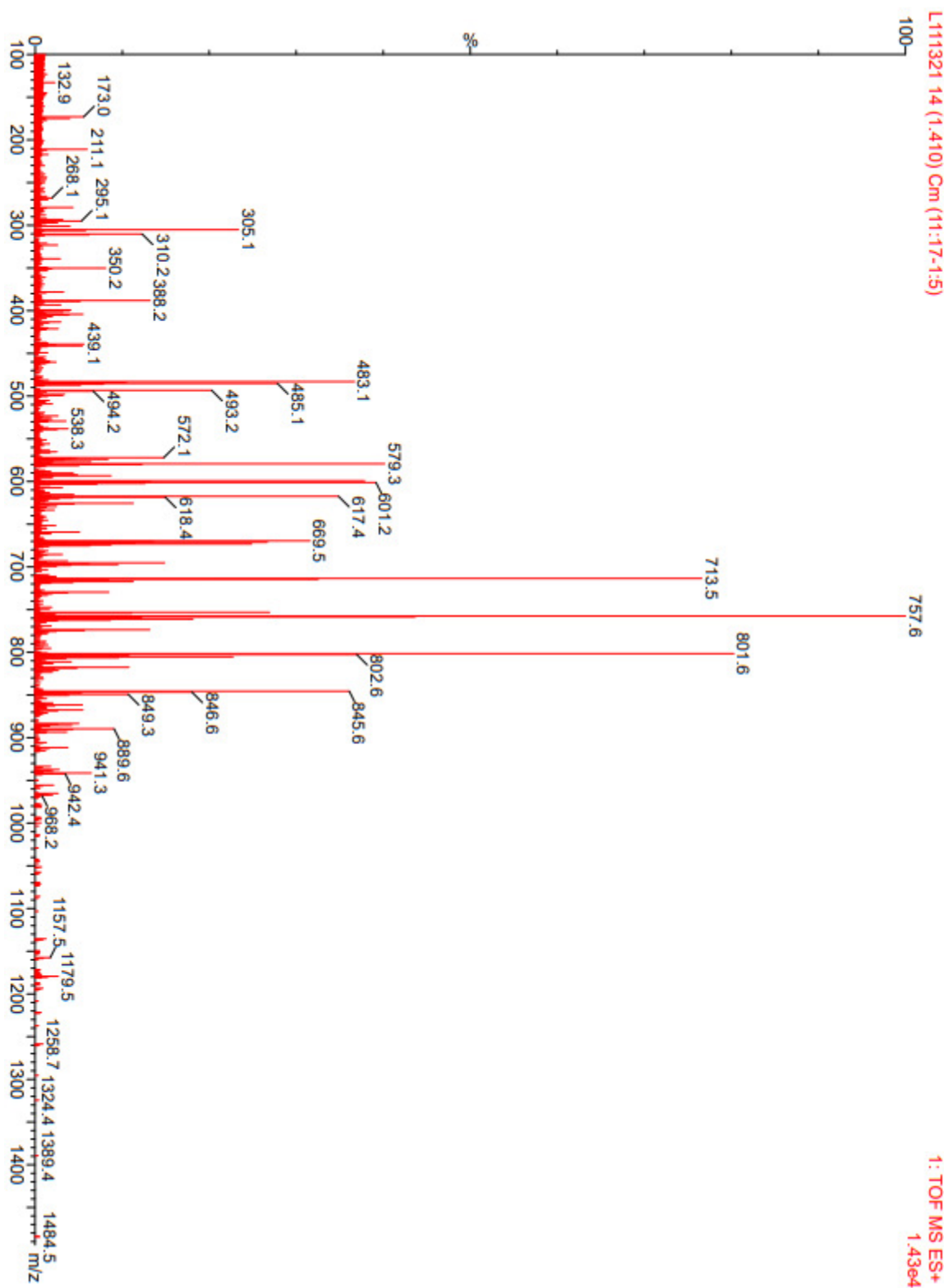
**Methyl 7 $\alpha$ -(5-hexynoyloxy)-3 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate.**



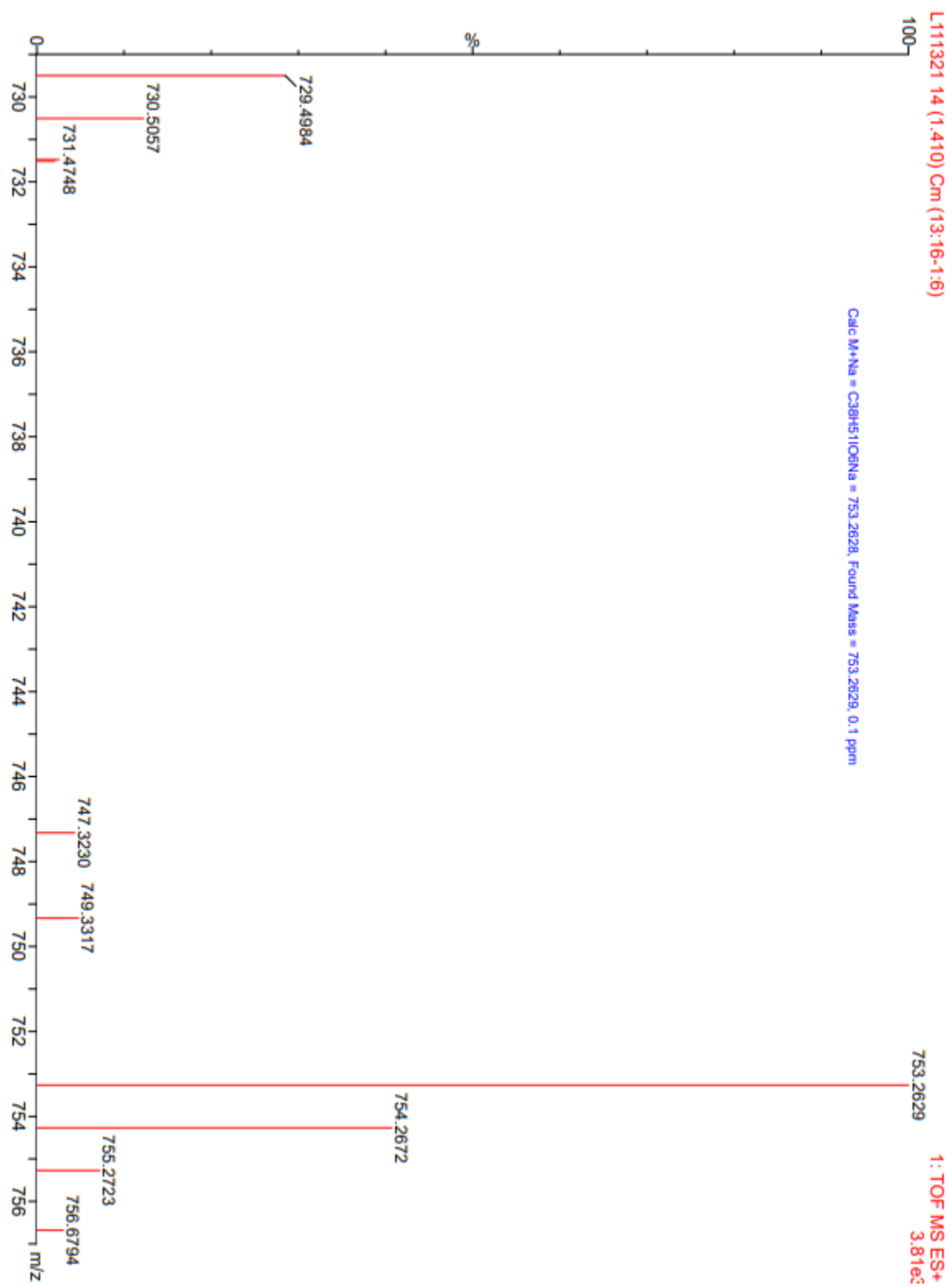
**Methyl 7 $\alpha$ -(5-hexynoyloxy)-3 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate.**



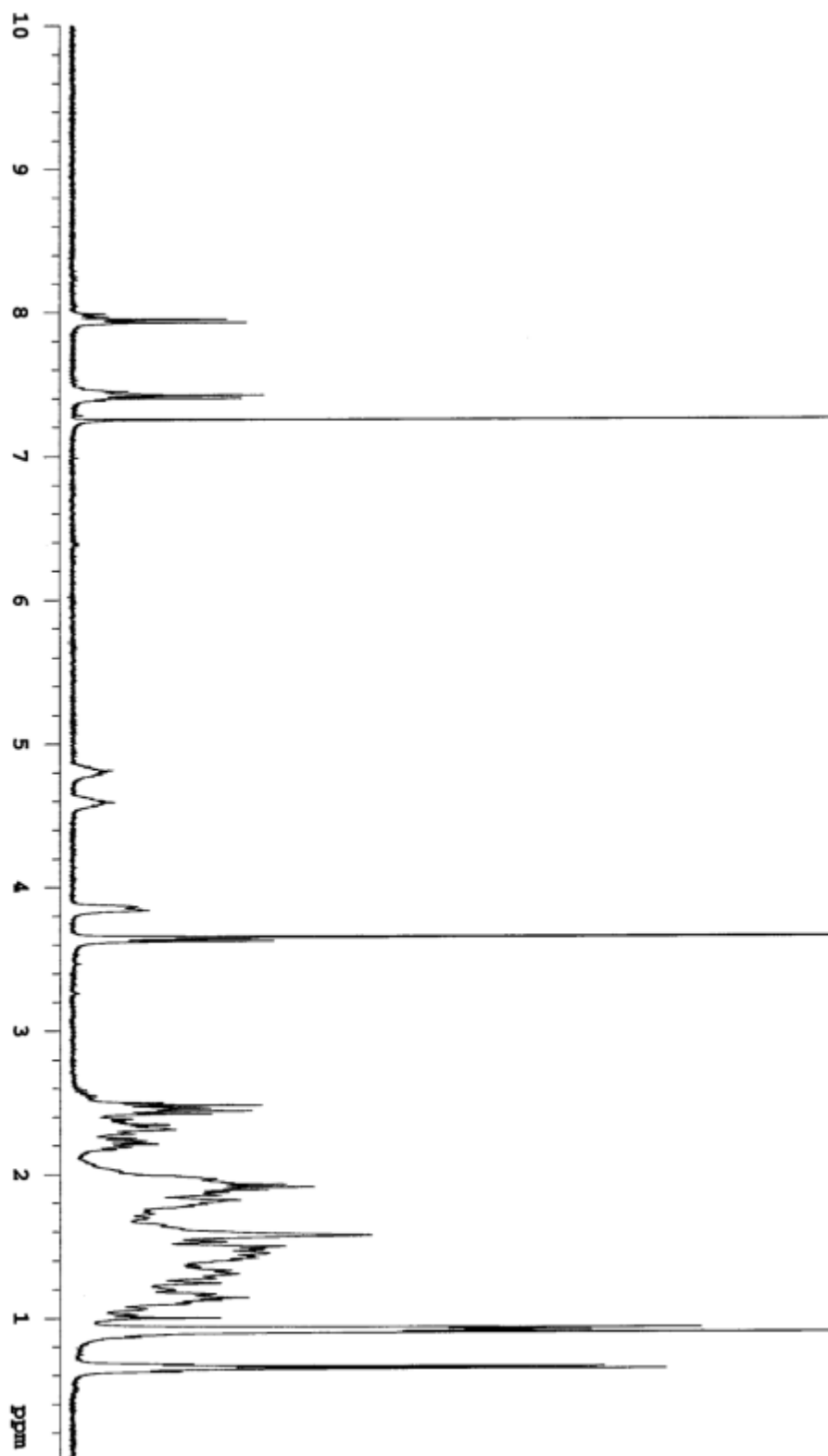
Methyl 7 $\alpha$ -(5-hexynoyloxy)-3 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate.



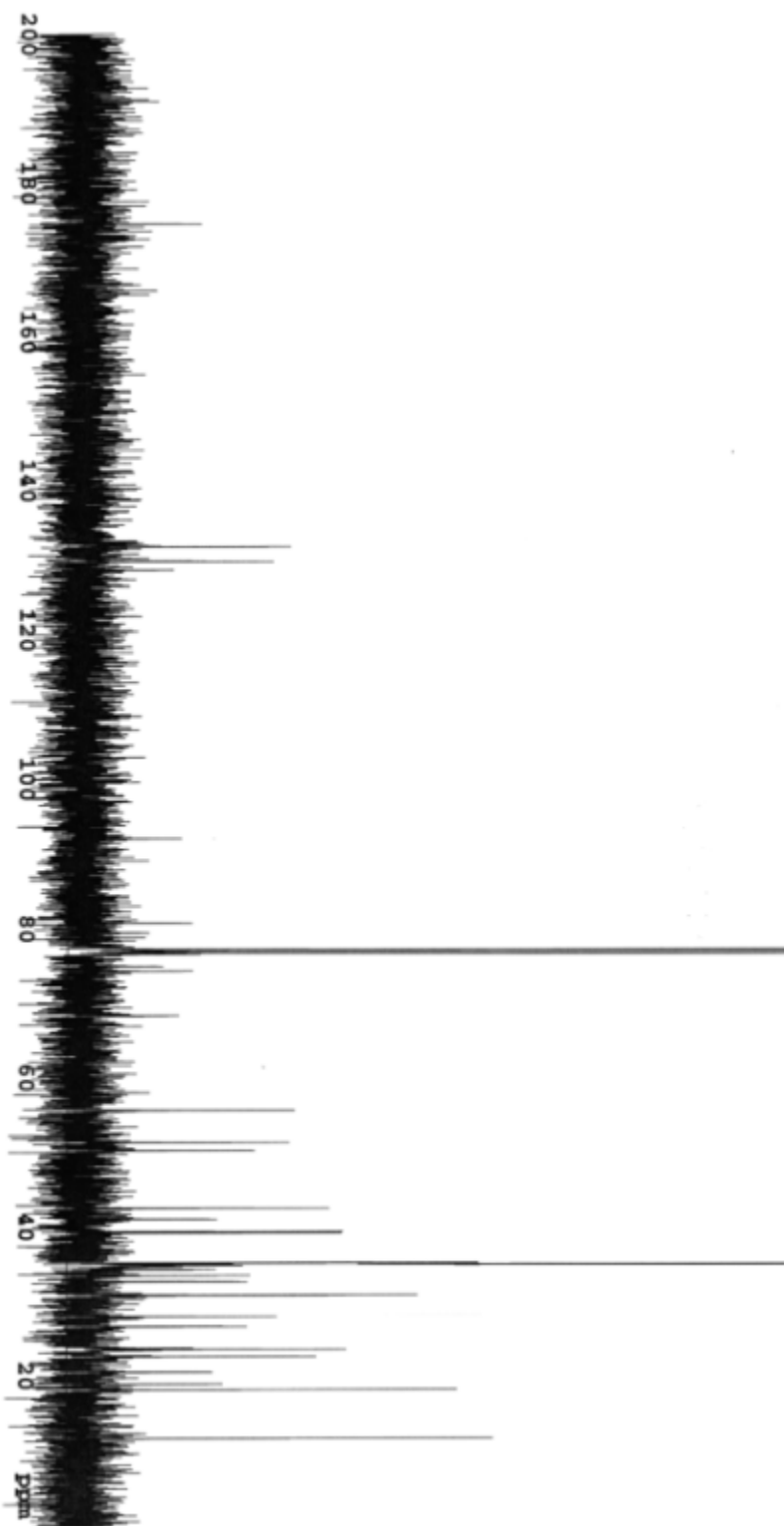
Methyl 7 $\alpha$ -(5-hexynoyloxy)-3 $\alpha$ -(4-iodobenzyloxy)-5 $\beta$ -cholanoate.



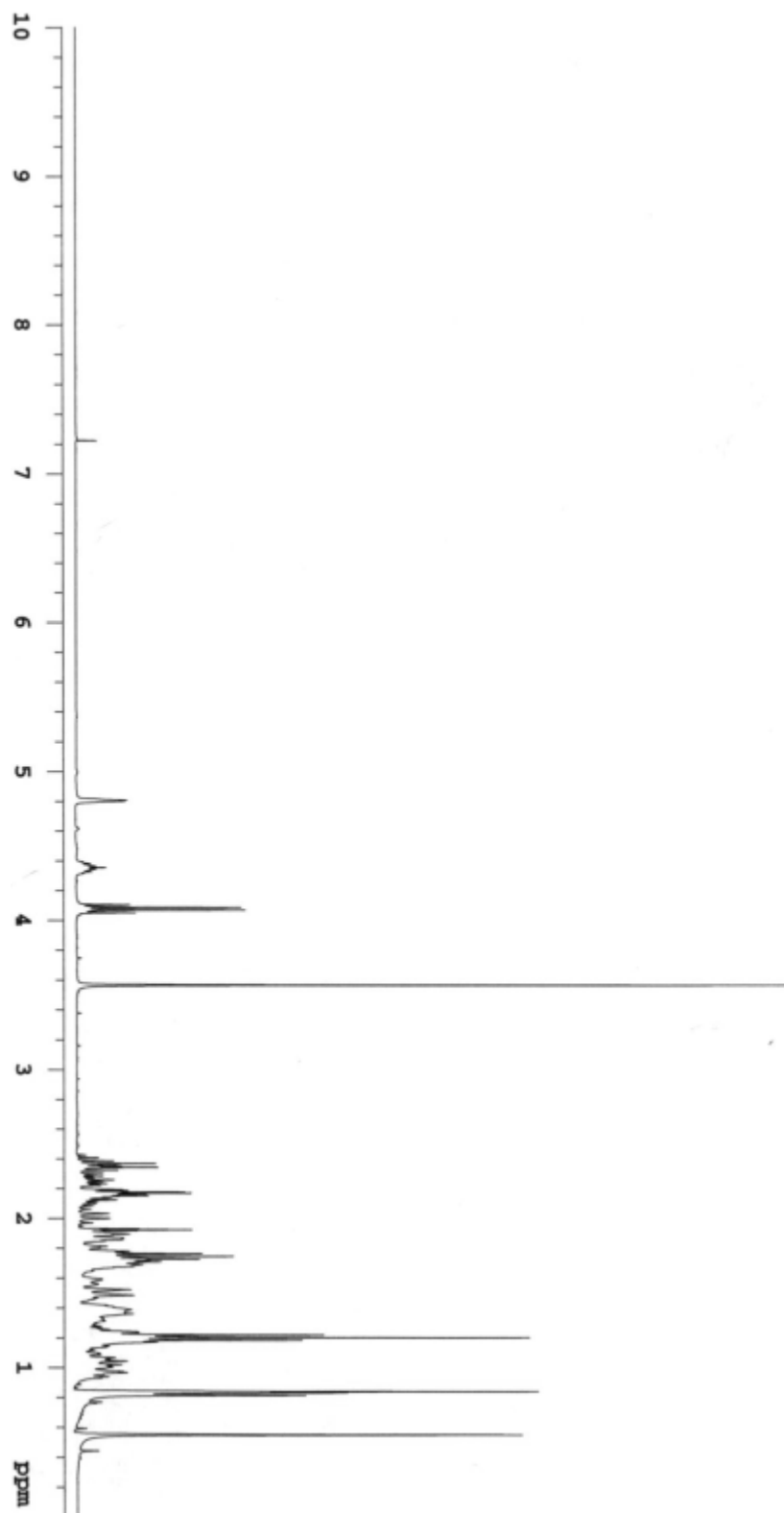
Dimer (19)



# Dimer (19)

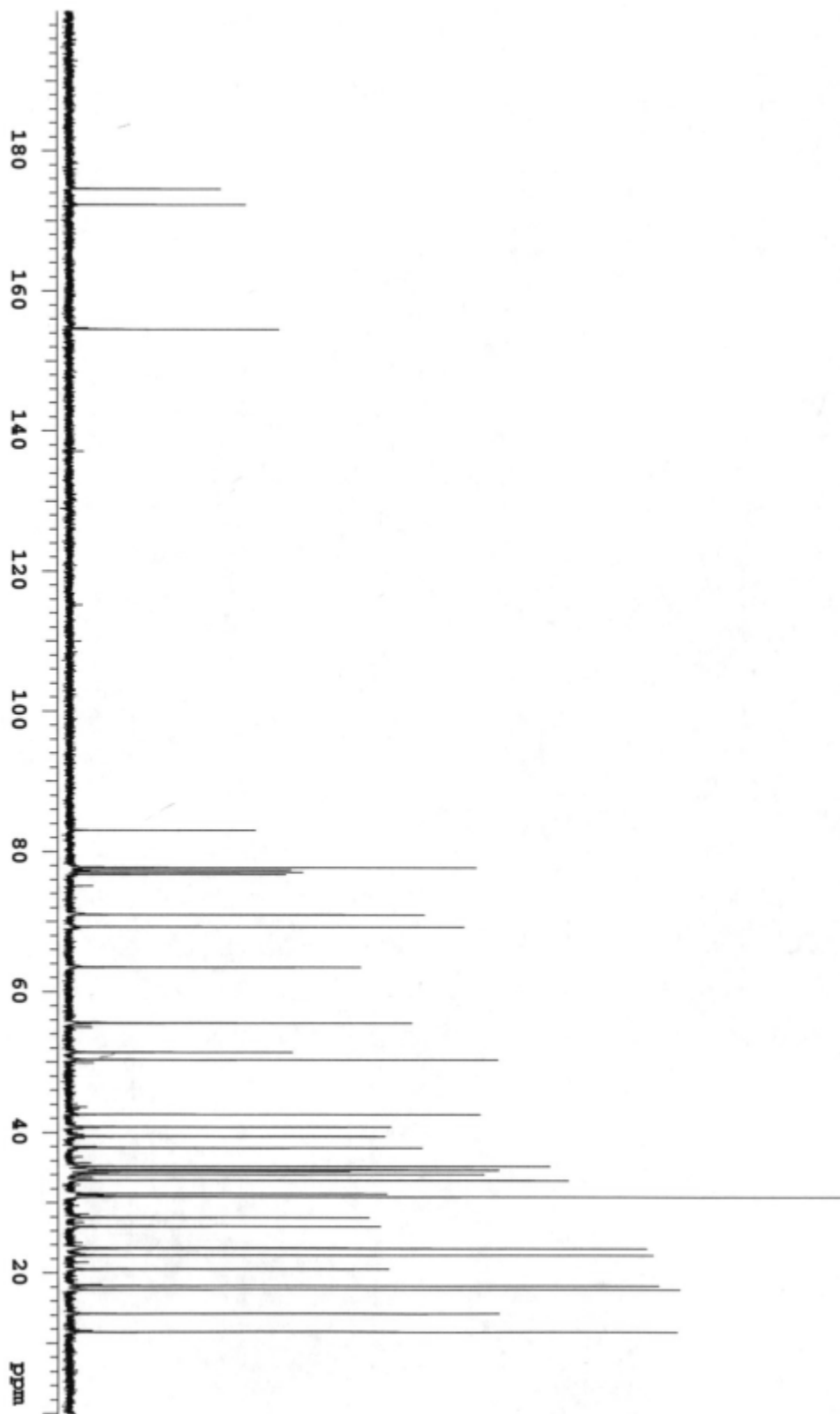


**Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(4-pentynoyloxy)-5 $\beta$ -cholanoate (20)**

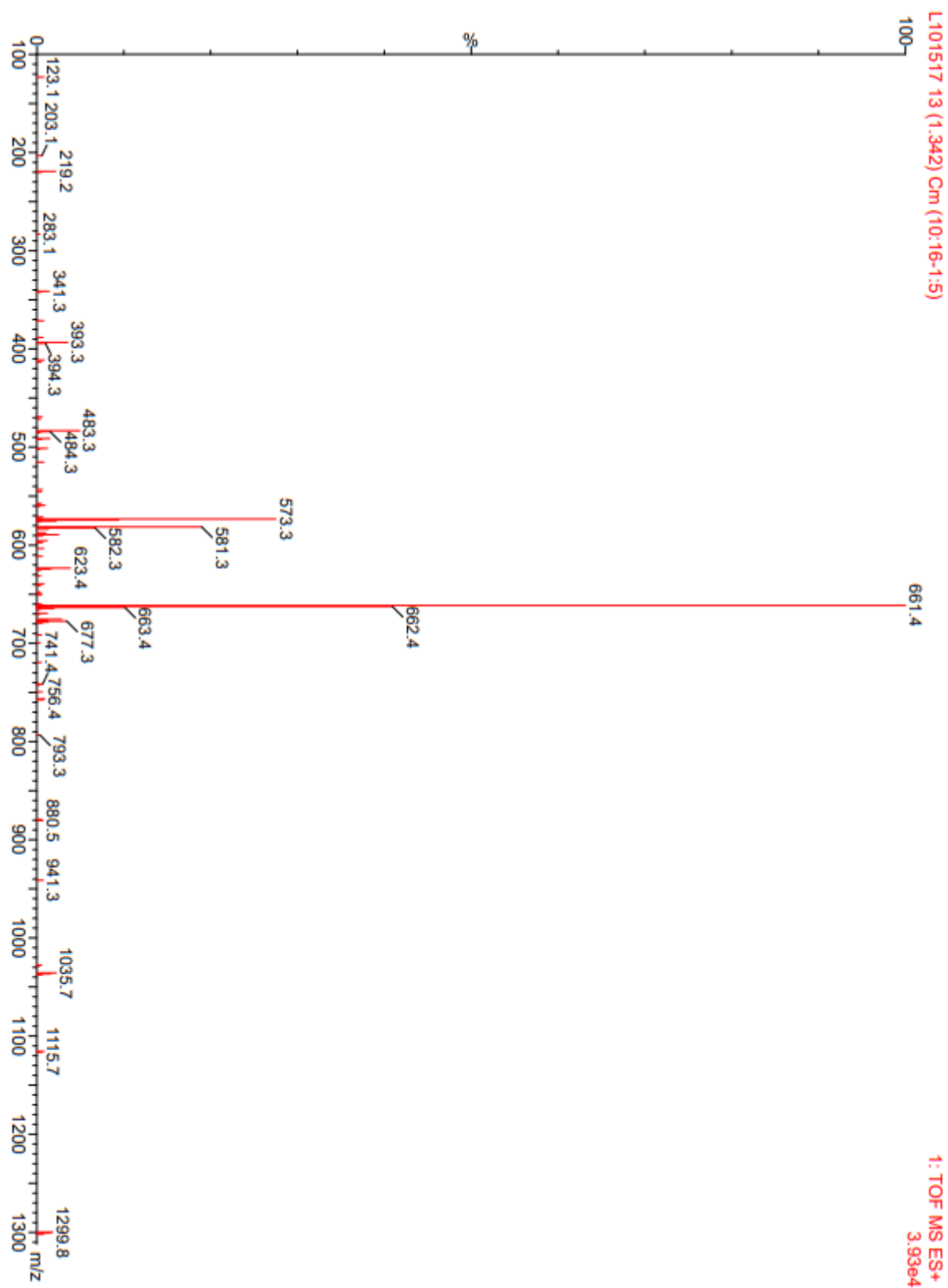




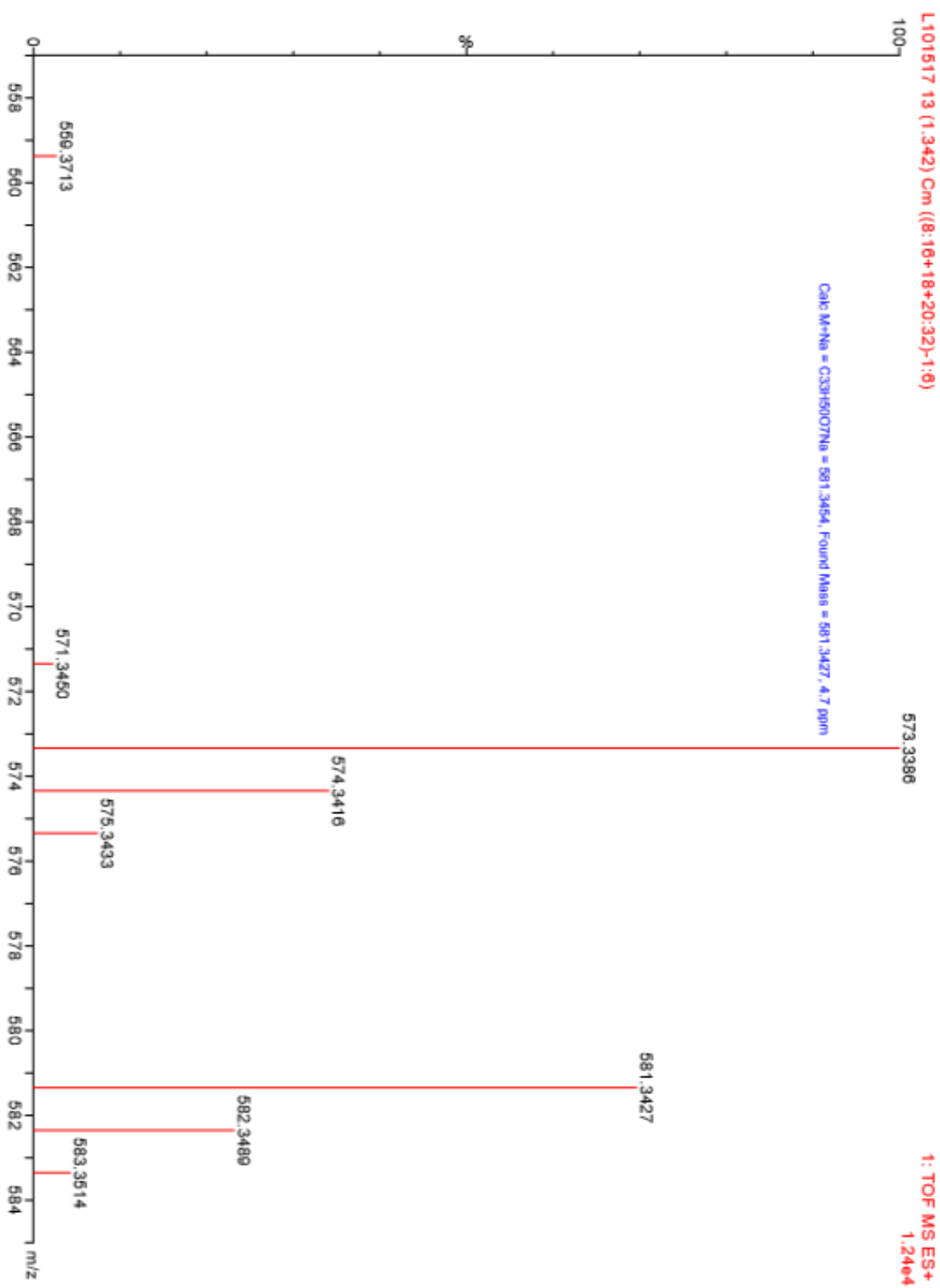
Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(4-pentynoyloxy)-5 $\beta$ -cholanoate (20)



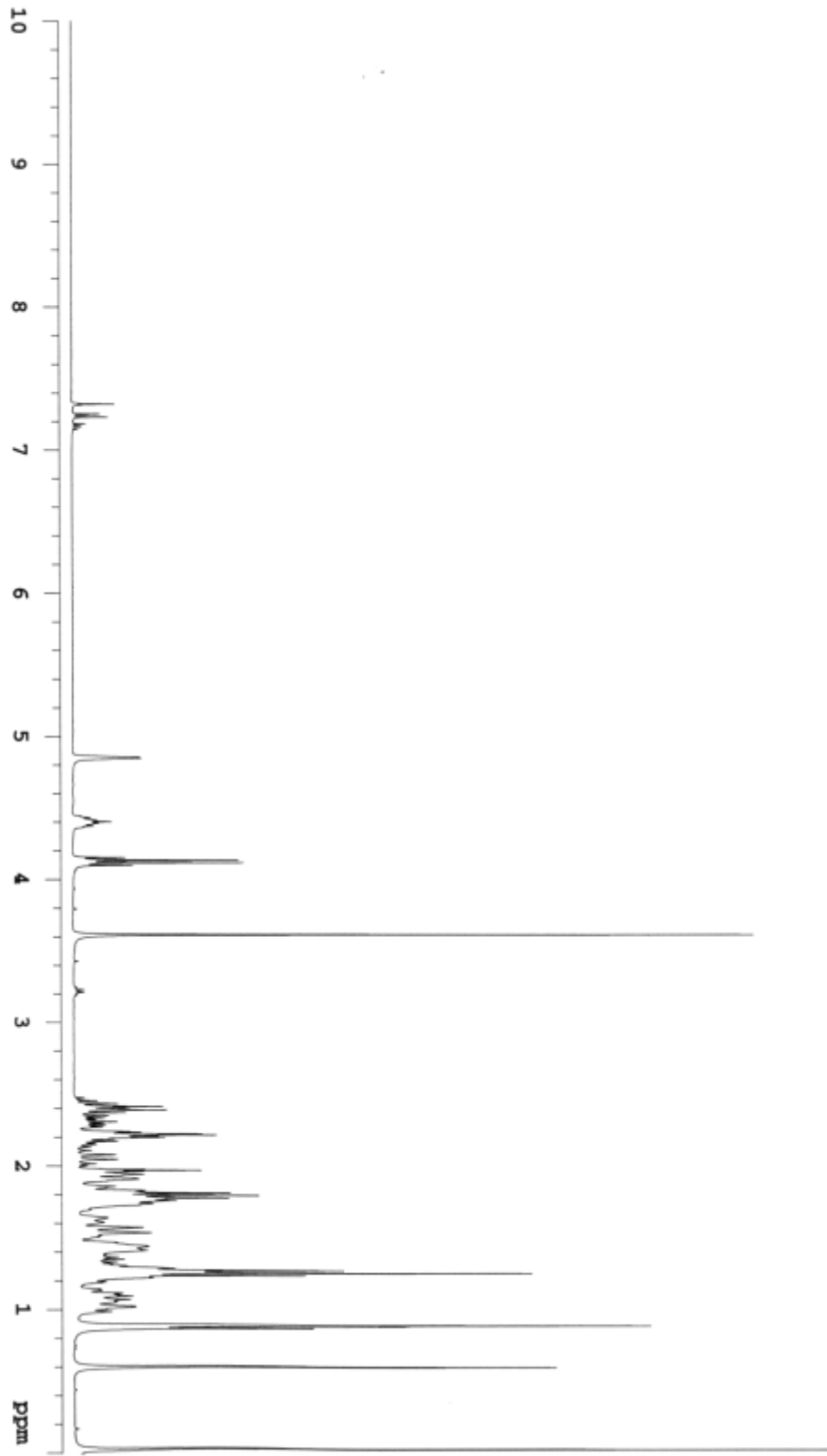
Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(4-pentynoyloxy)-5 $\beta$ -cholanoate (20)



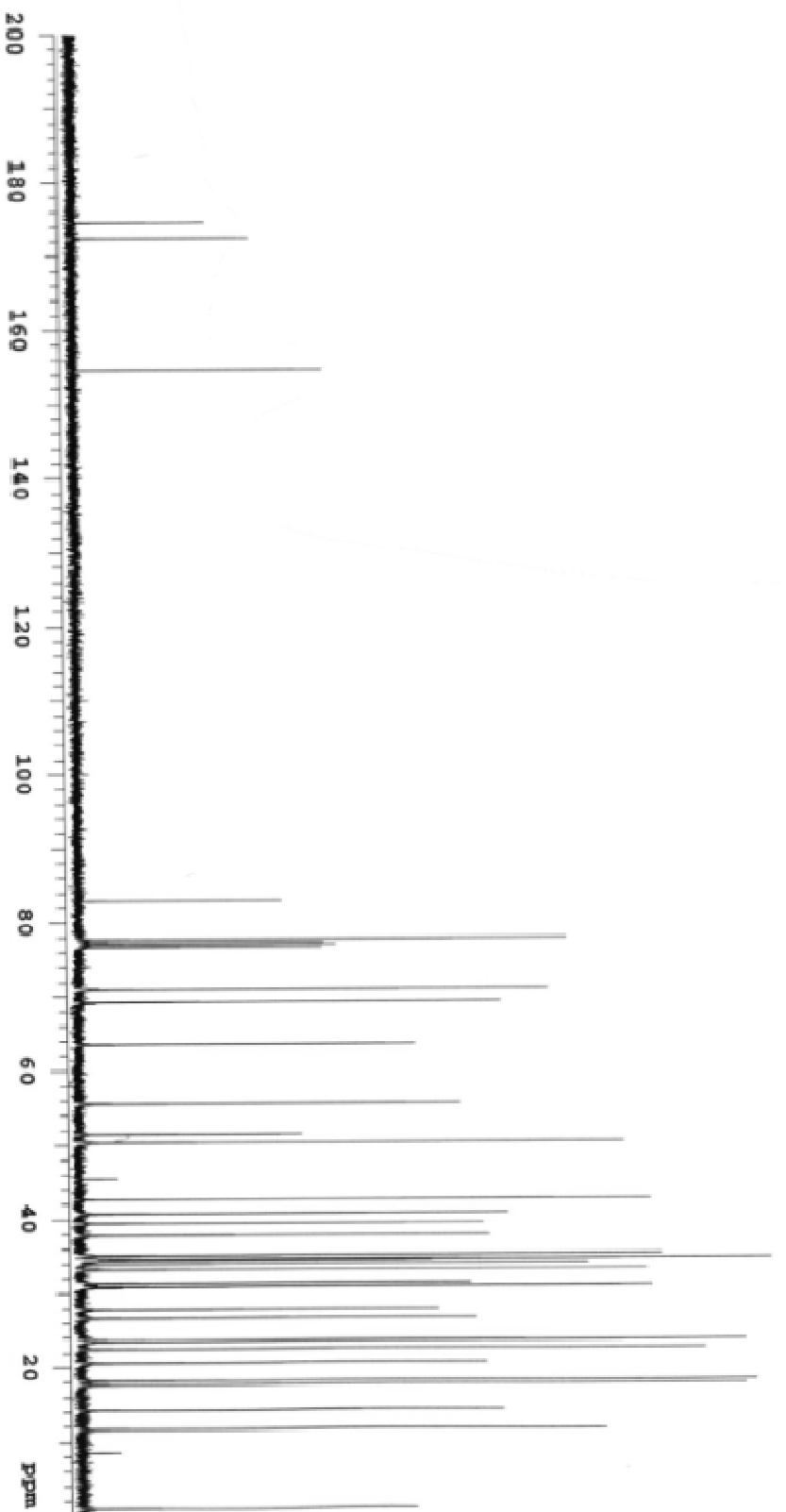
Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(4-pentynoyloxy)-5 $\beta$ -cholanoate (20)



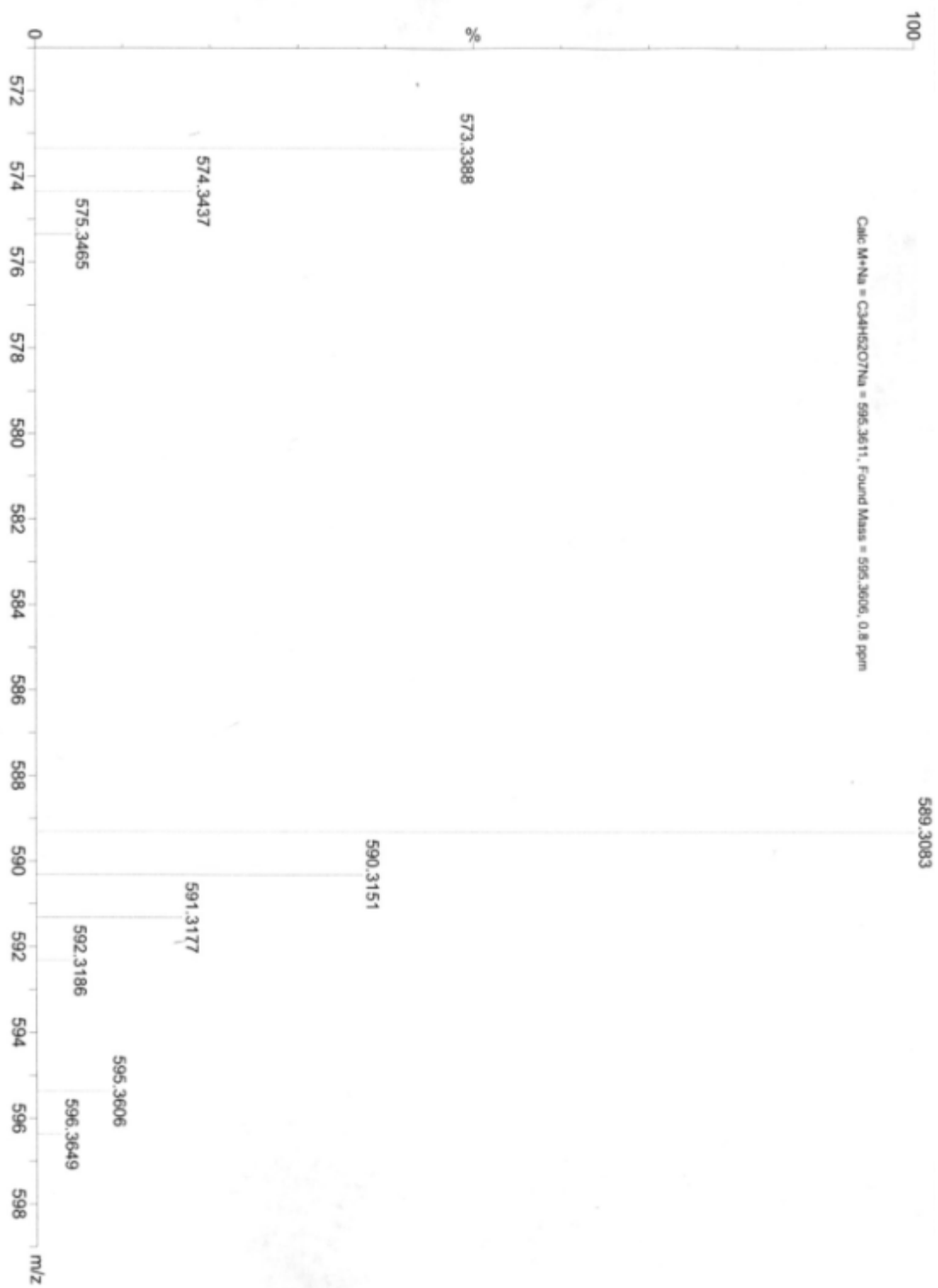
**Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(5-hexynoyloxy)-5 $\beta$ -cholanoate (21)**



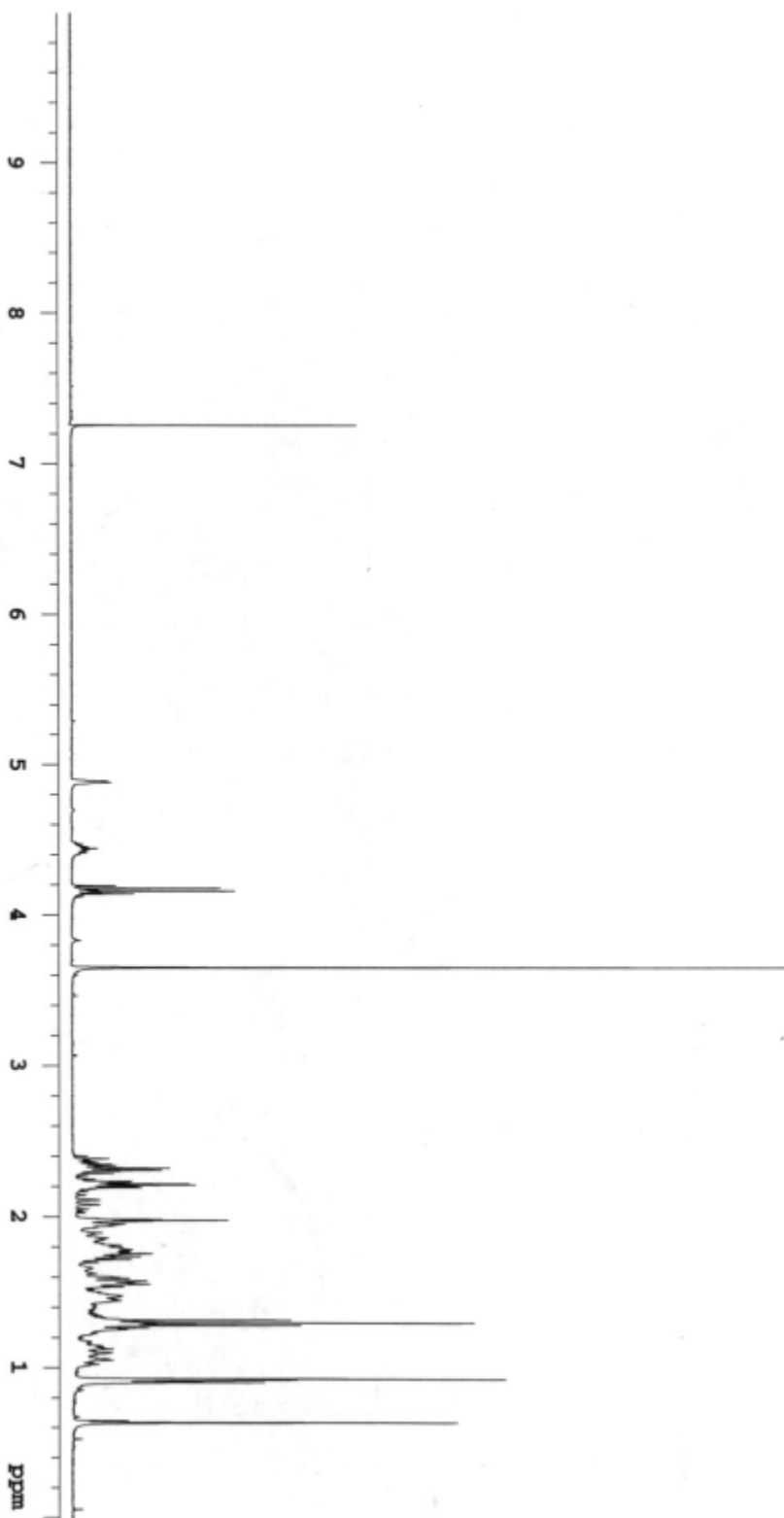
Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(5-hexynoyloxy)-5 $\beta$ -cholanoate (21)



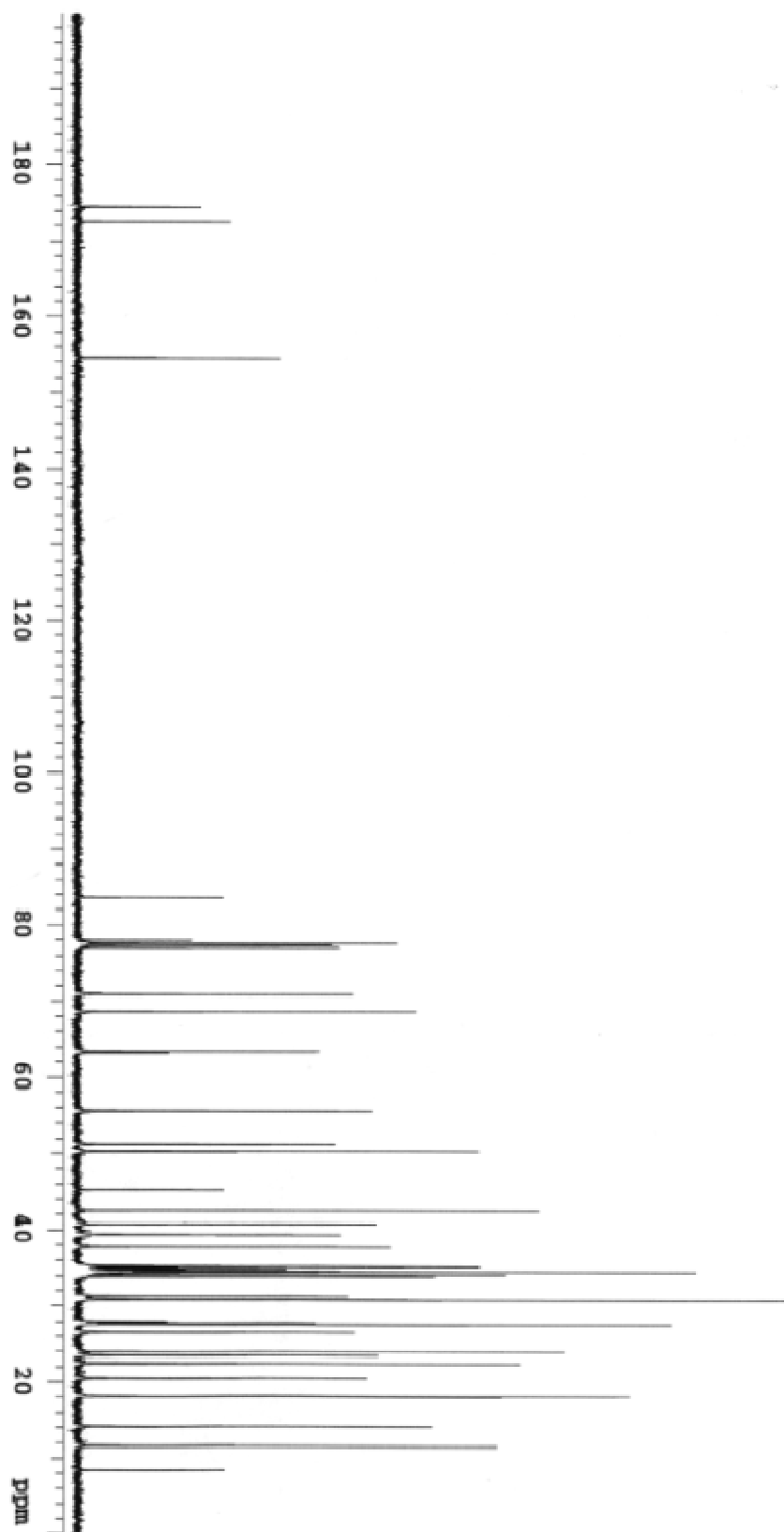
Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(5-hexynoyloxy)-5 $\beta$ -cholanoate (21)



**Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(6-heptynoxy)-5 $\beta$ -cholanoate (22)**

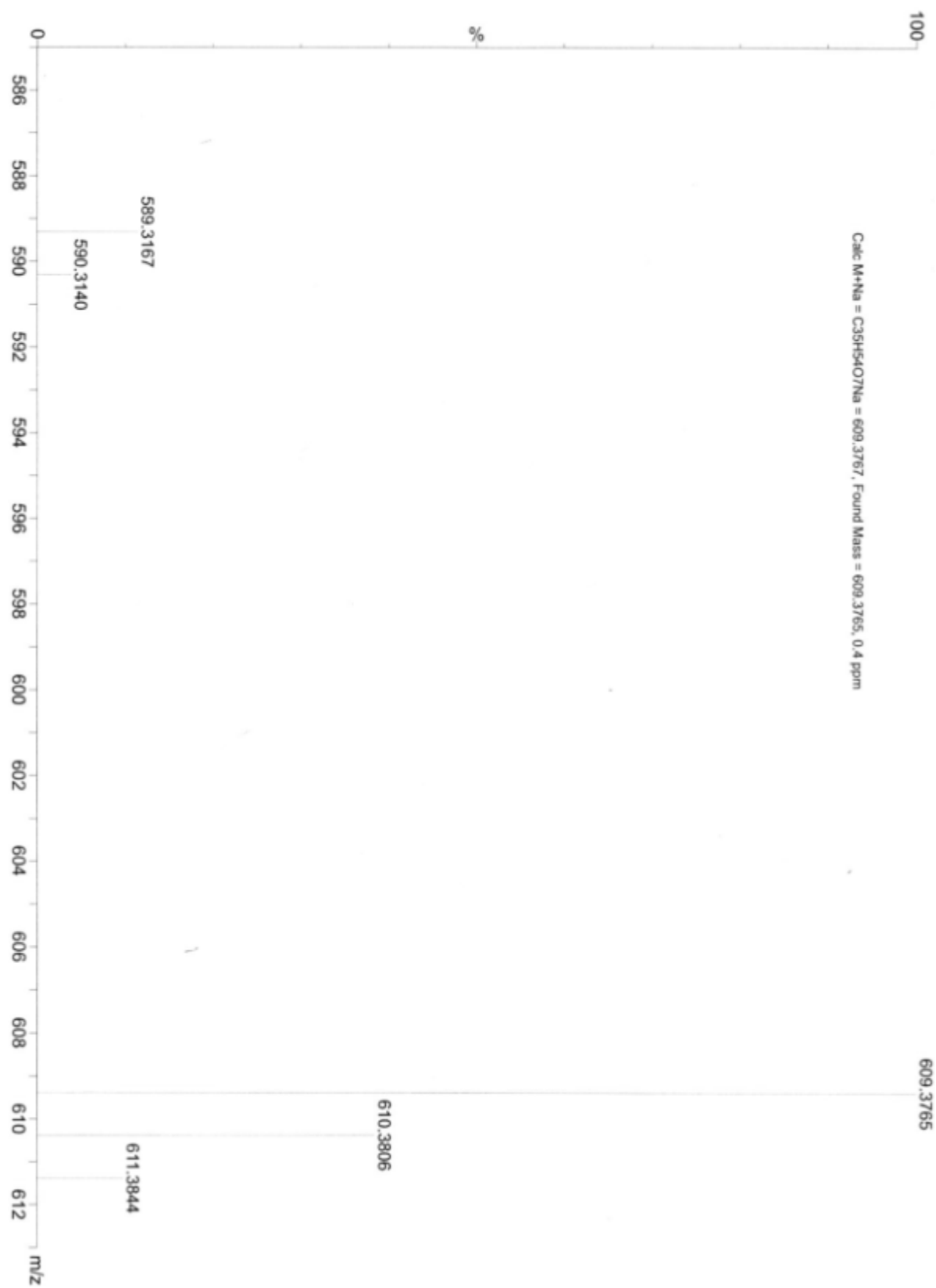


Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(6-heptynoxy)-5 $\beta$ -cholanoate (22)

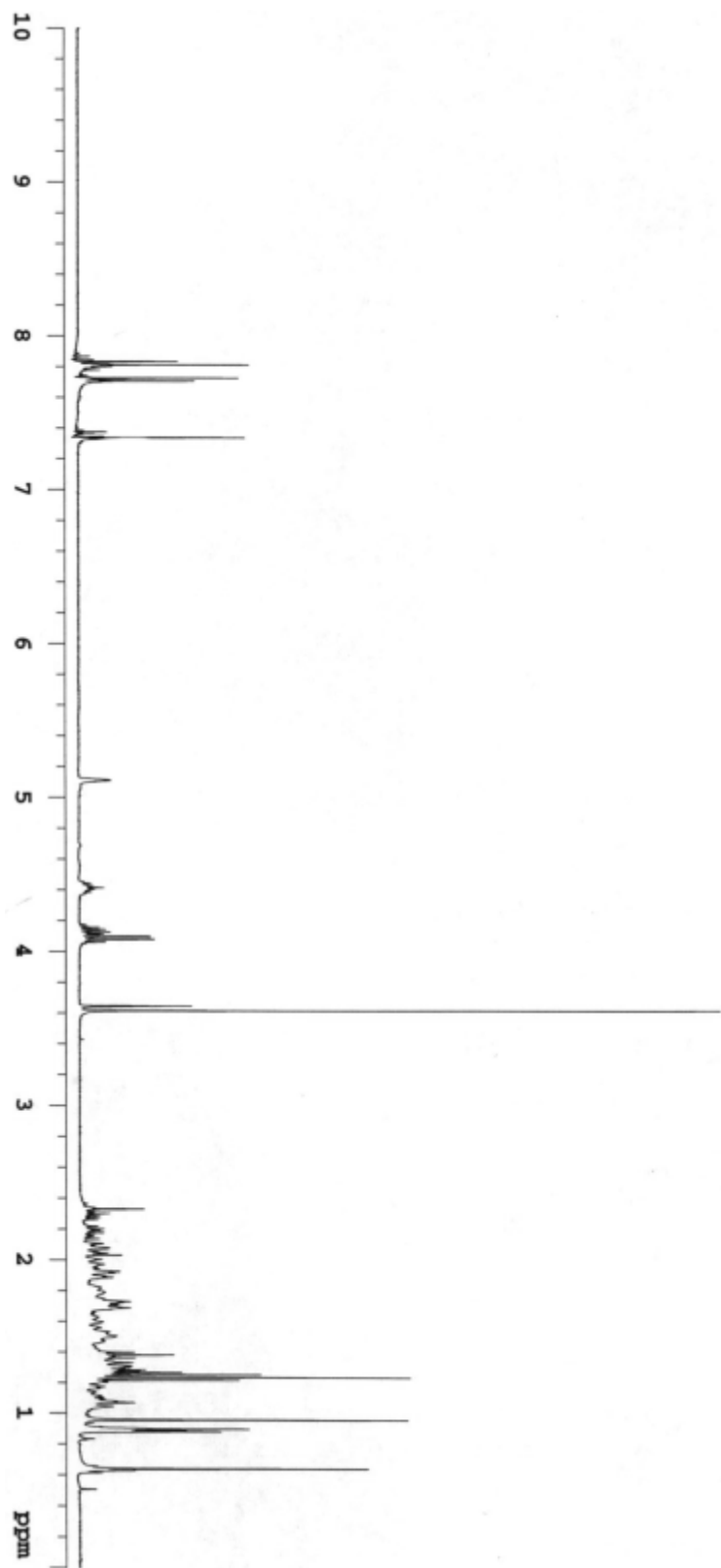




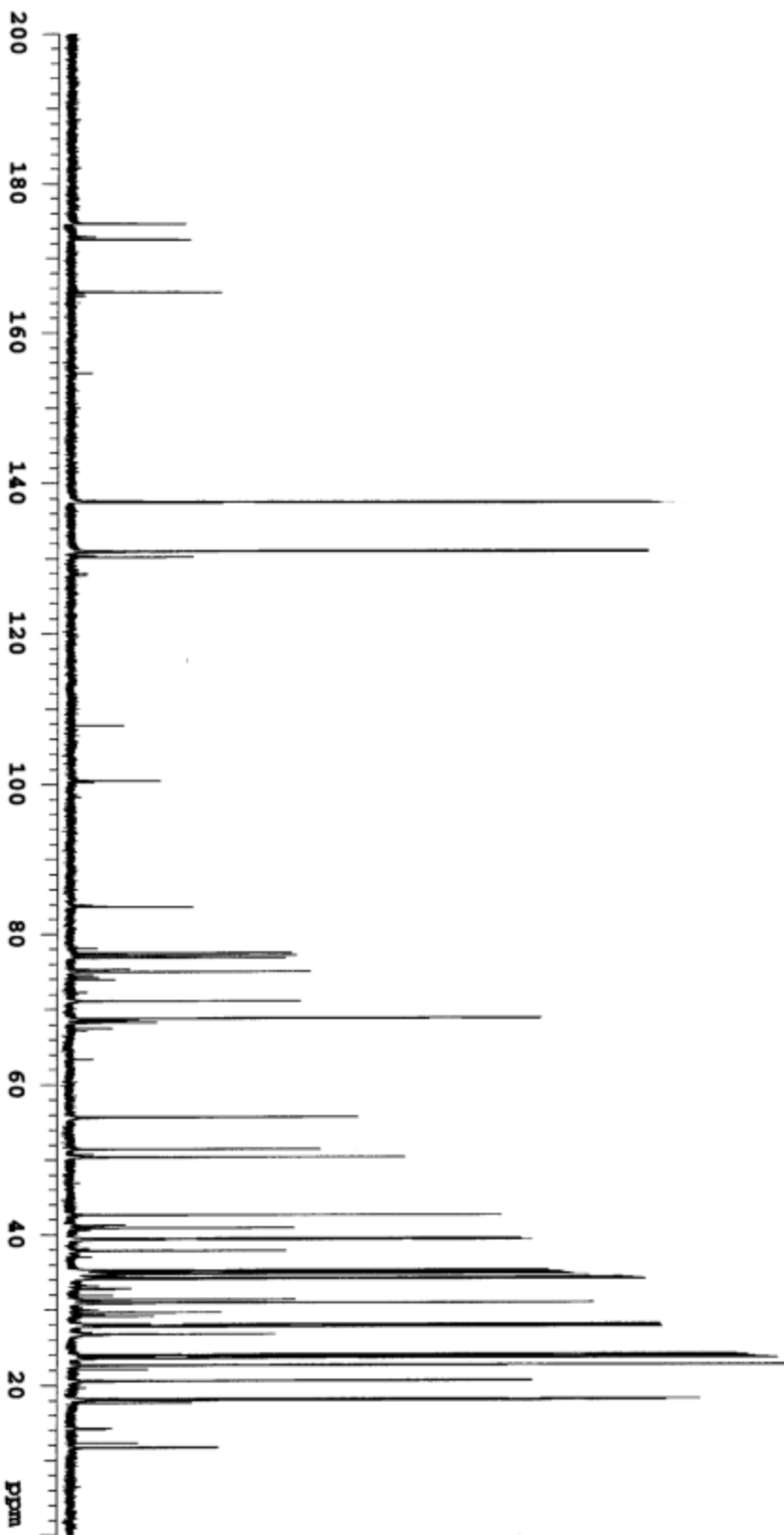
Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(6-heptynoxy)-5 $\beta$ -cholanoate (22)



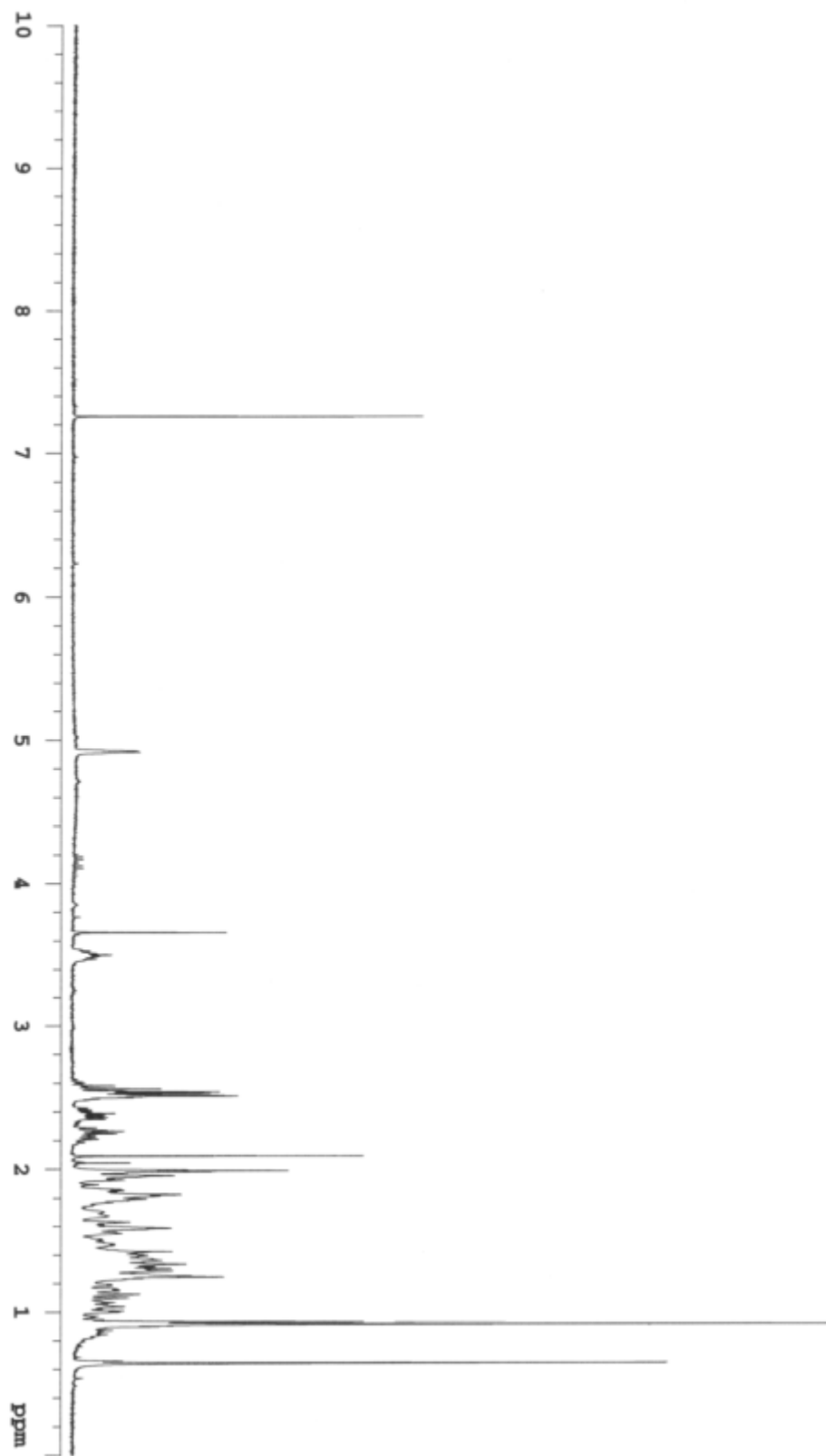
Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate (23)



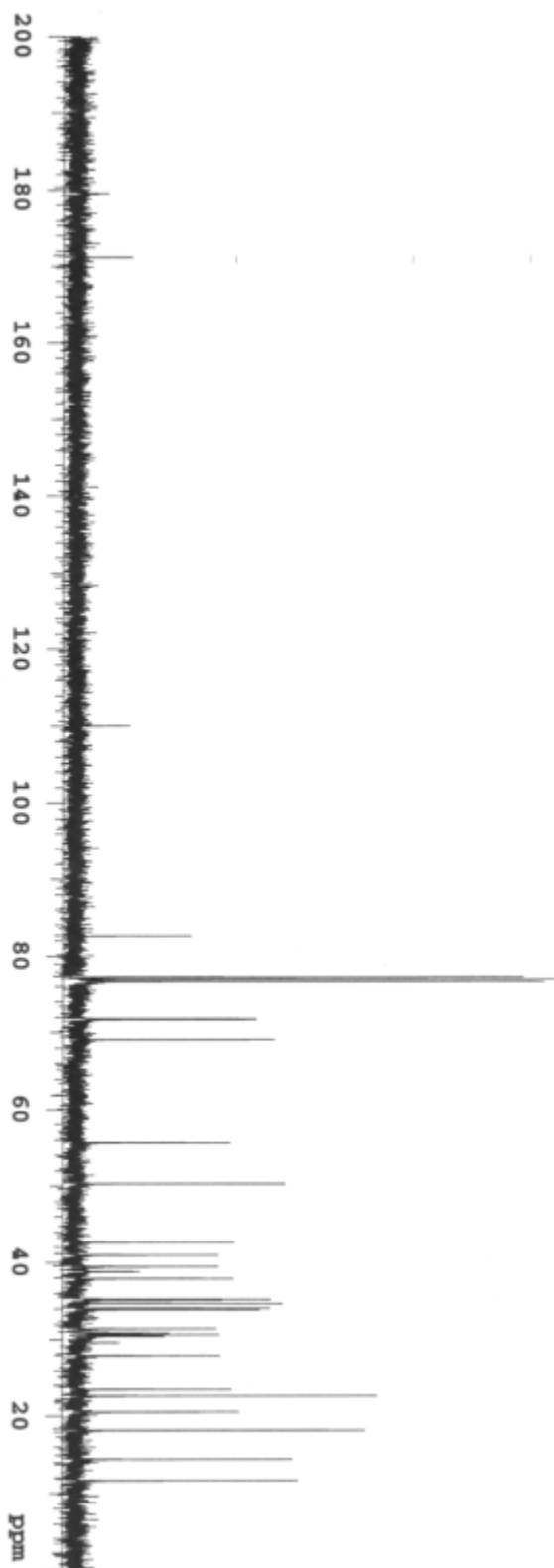
Methyl 3 $\alpha$ -ethoxycarbonyloxy-7 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoate (23)



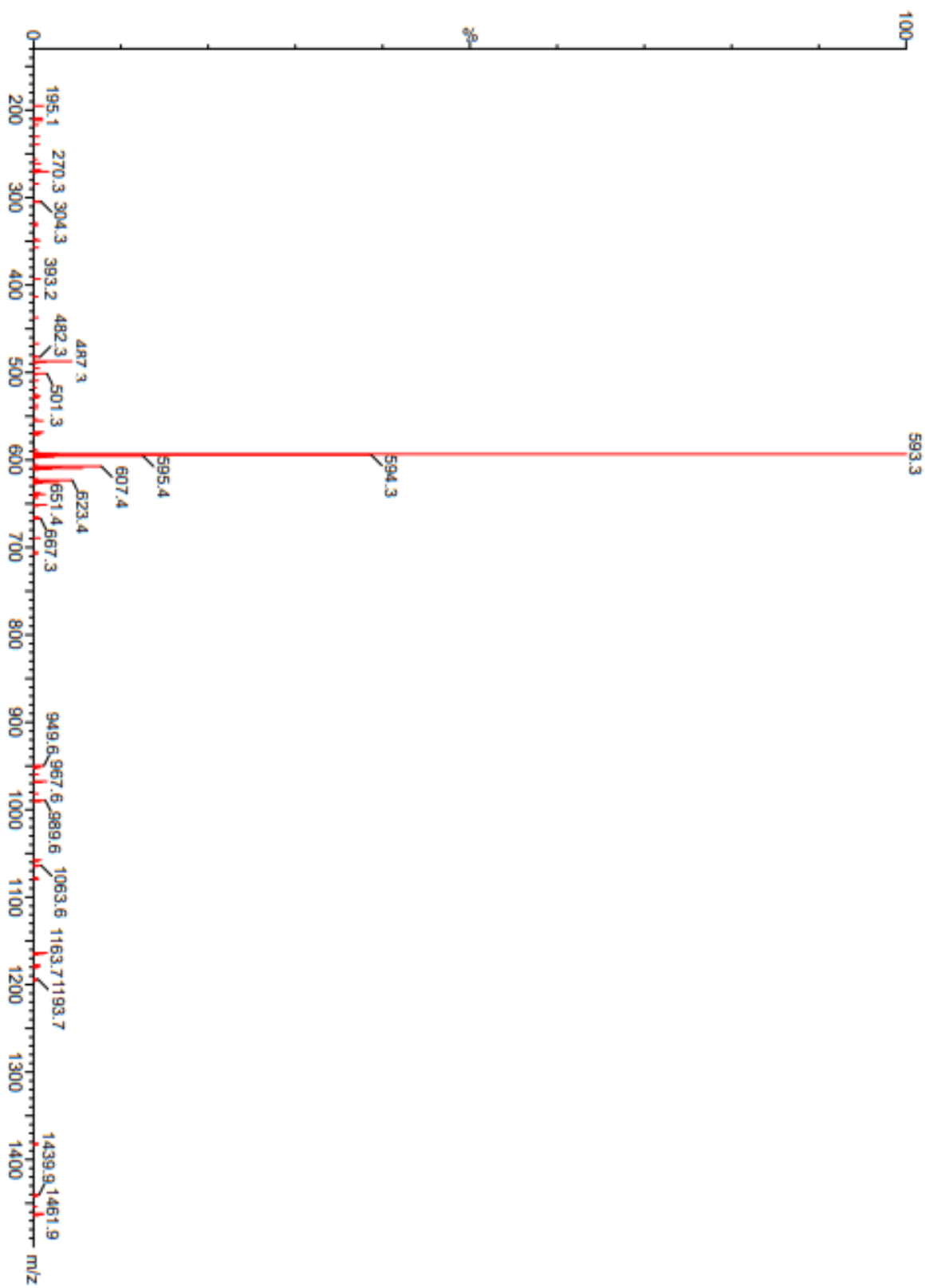
**3 $\alpha$ -Hydroxy-7 $\alpha$ -(4-pentynoyloxy)-5 $\beta$ -cholanoic acid (24)**



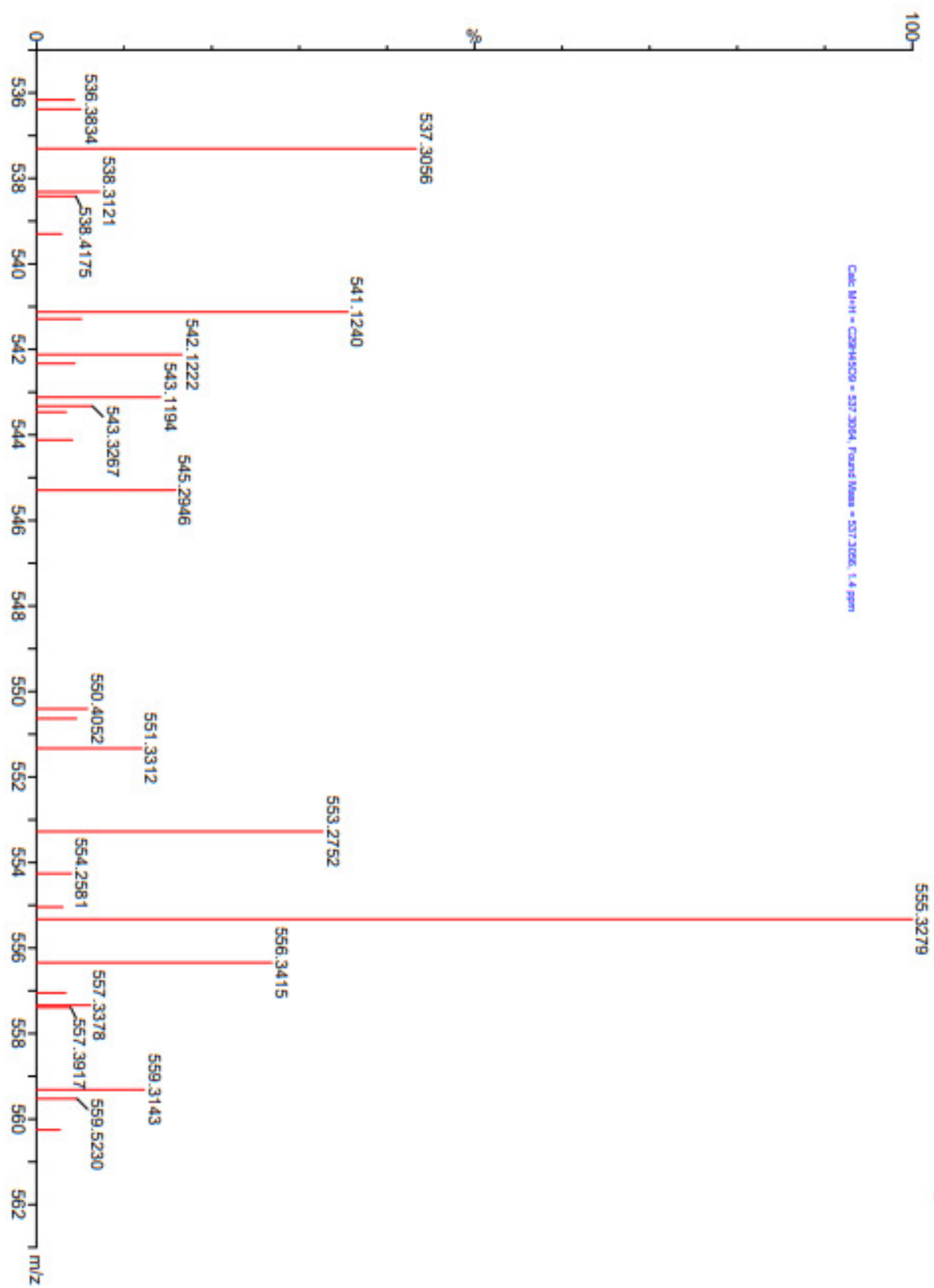
**3 $\alpha$ -Hydroxy-7 $\alpha$ -(4-pentynoyloxy)-5 $\beta$ -cholanoic acid (24)**



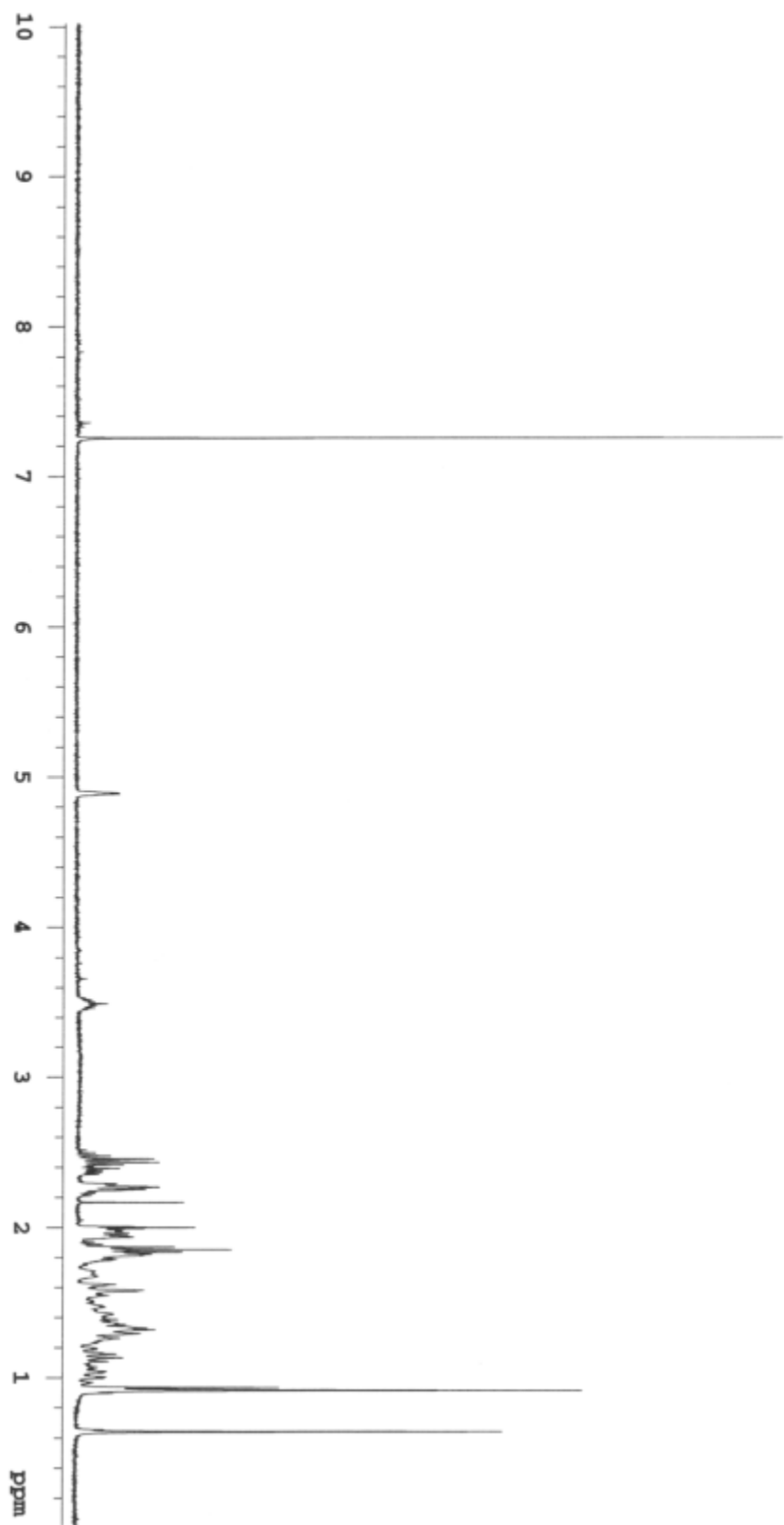
**3 $\alpha$ -Hydroxy-7 $\alpha$ -(4-pentynoyloxy)-5 $\beta$ -cholanoic acid (24)**



### 3 $\alpha$ -Hydroxy-7 $\alpha$ -(4-pentynoyloxy)-5 $\beta$ -cholanoic acid (24)

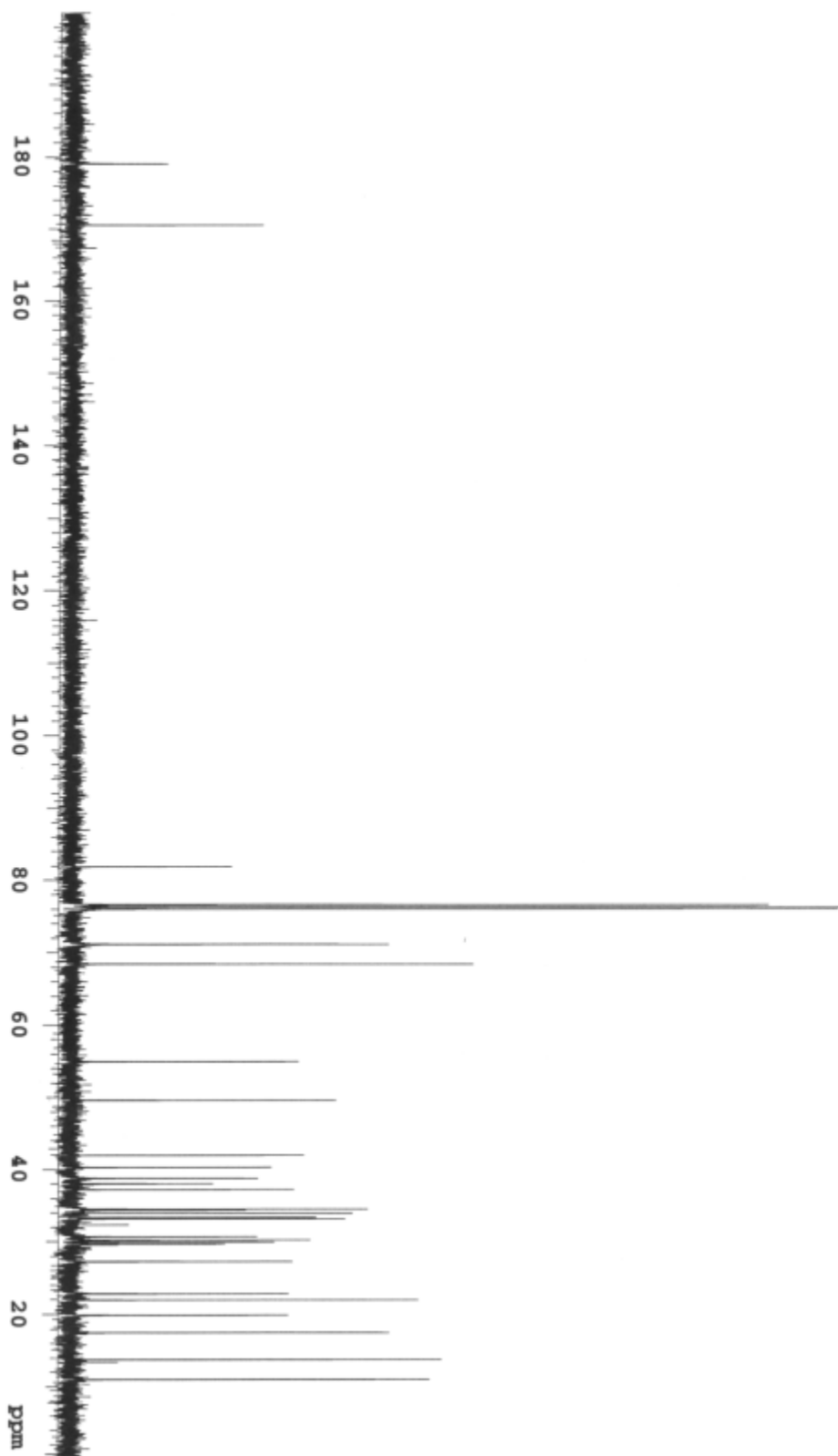


**3 $\alpha$ -Hydroxy-7 $\alpha$ -(5-hexynoyloxy)-5 $\beta$ -cholanoic acid (25)**

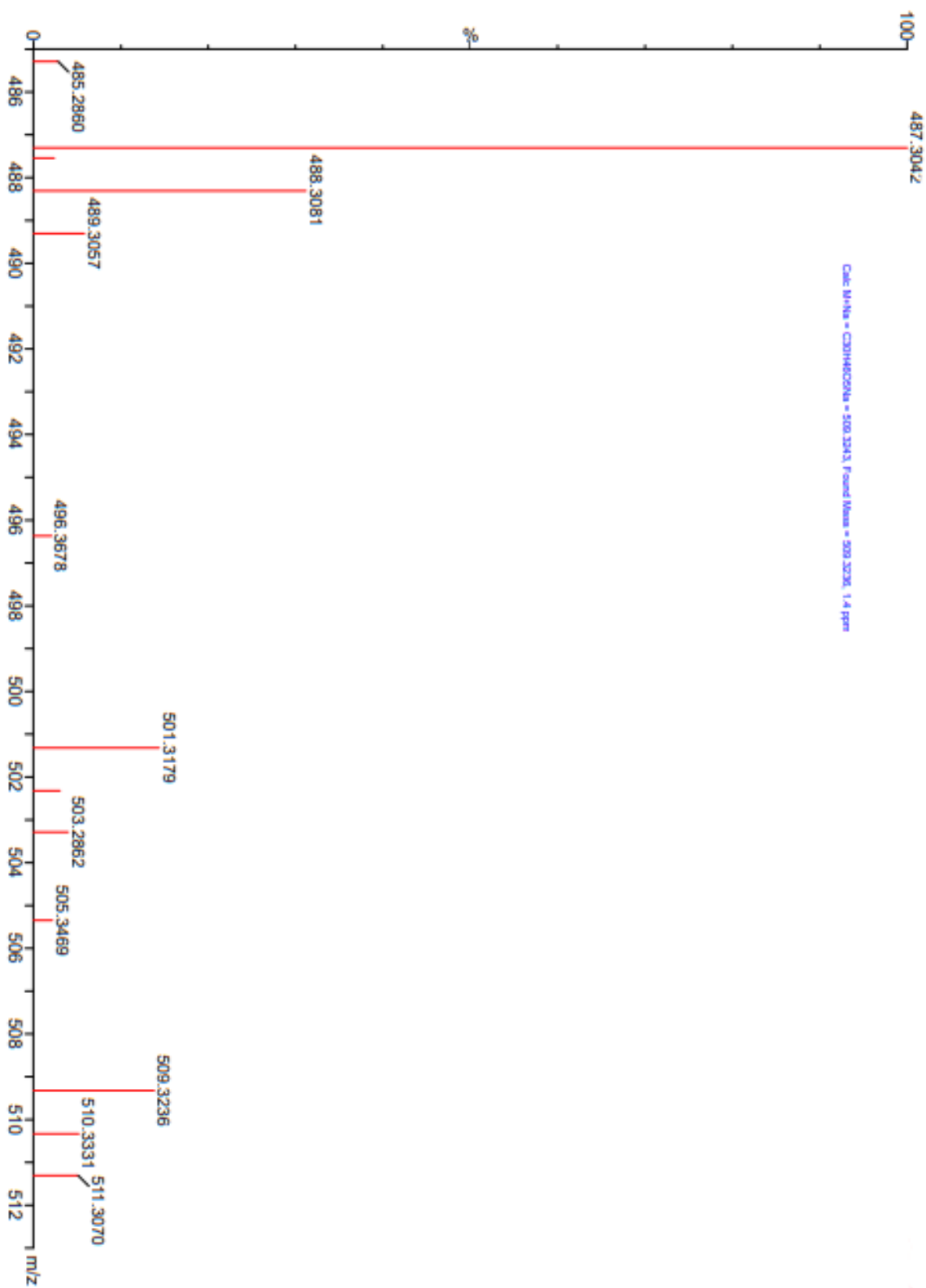




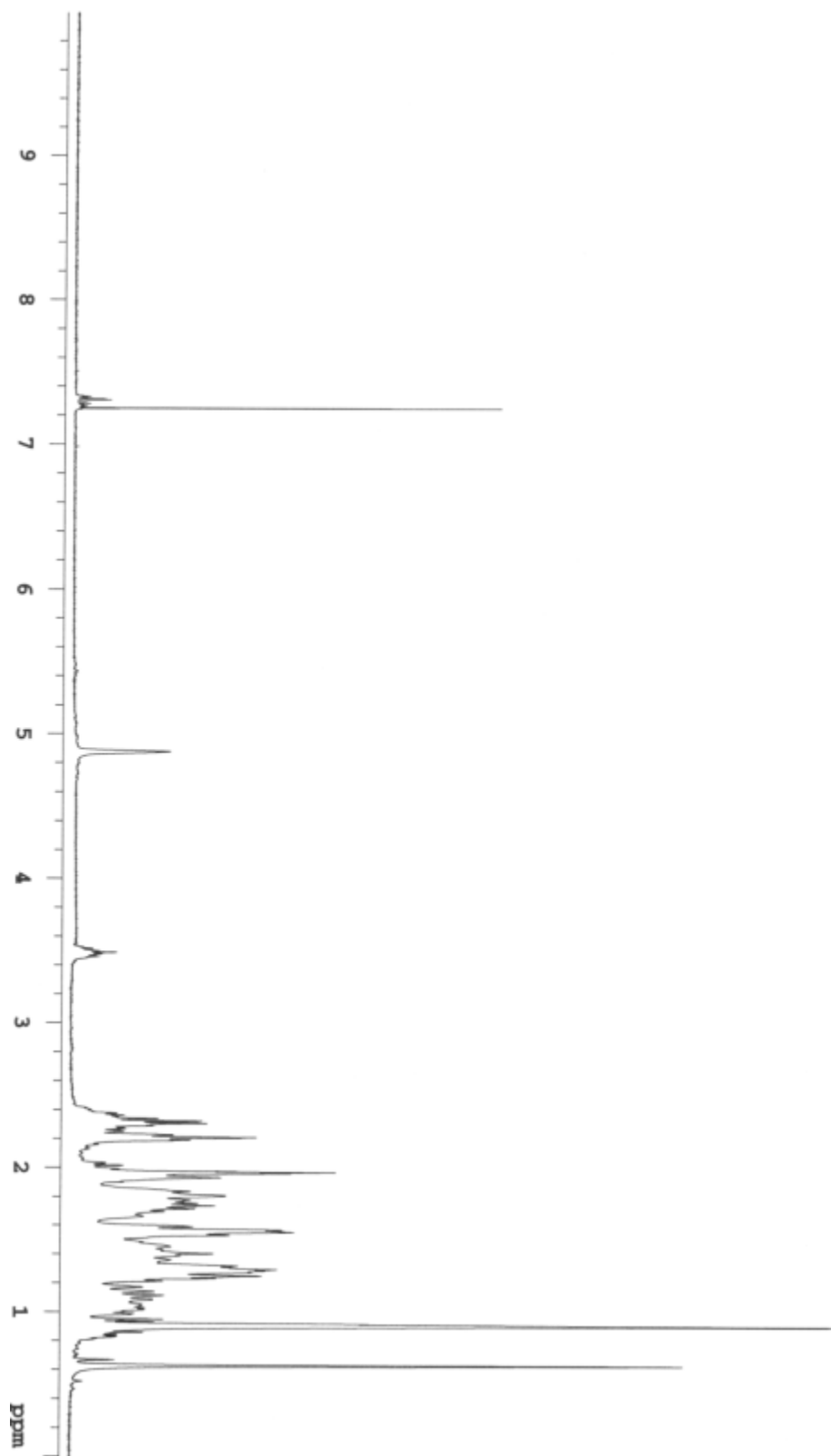
**3 $\alpha$ -Hydroxy-7 $\alpha$ -(5-hexynoyloxy)-5 $\beta$ -cholanoic acid (25)**



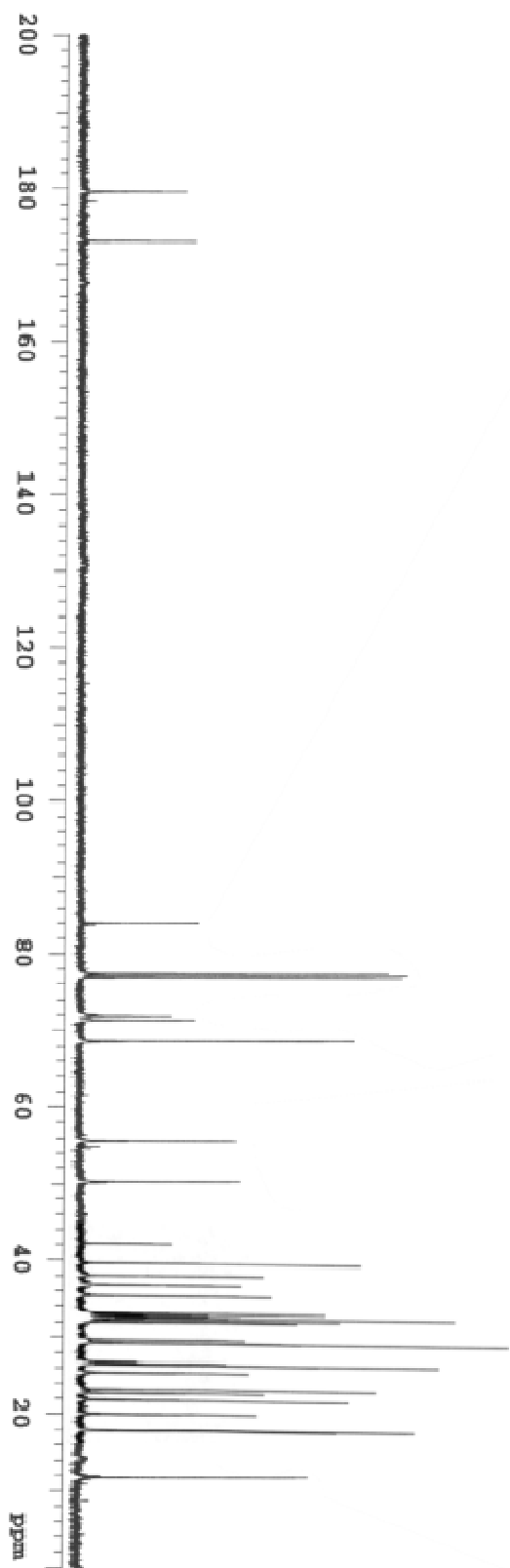
### 3 $\alpha$ -Hydroxy-7 $\alpha$ -(5-hexynoyloxy)-5 $\beta$ -cholanoic acid (25)



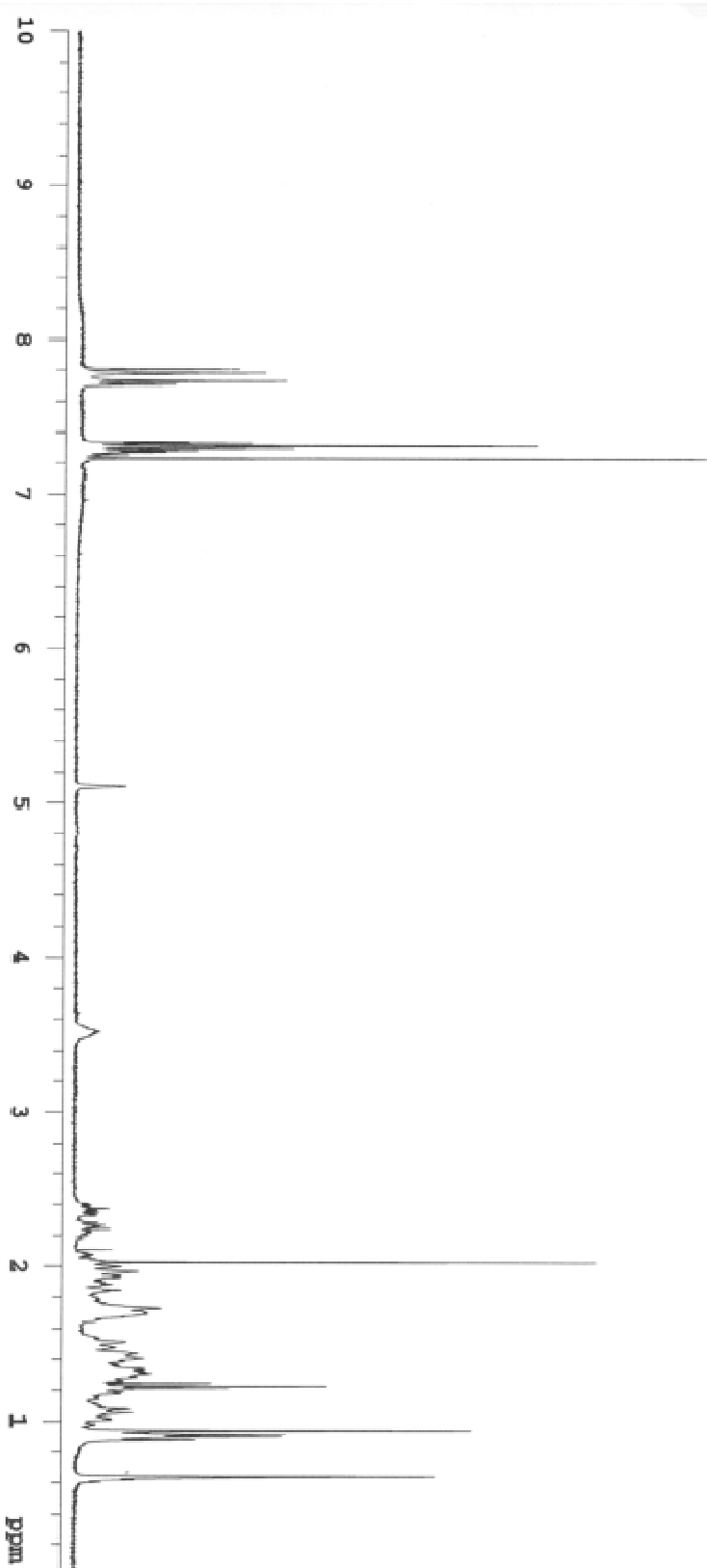
**3 $\alpha$ -Hydroxy-7 $\alpha$ -(6-heptynoyloxy)-5 $\beta$ -cholanoic acid (26)**



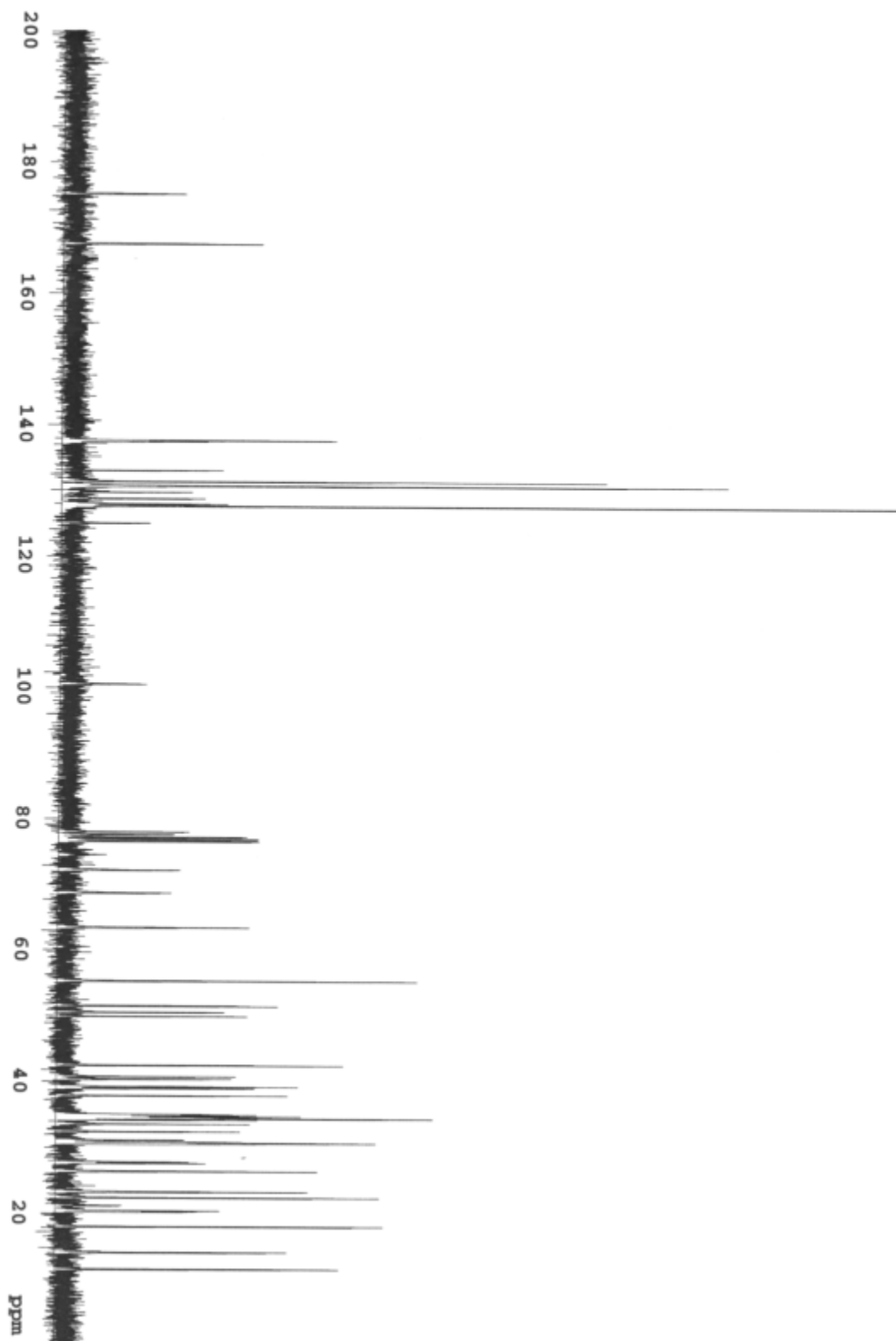
**3 $\alpha$ -Hydroxy-7 $\alpha$ -(6-heptynoxy)-5 $\beta$ -cholanoic acid (26)**



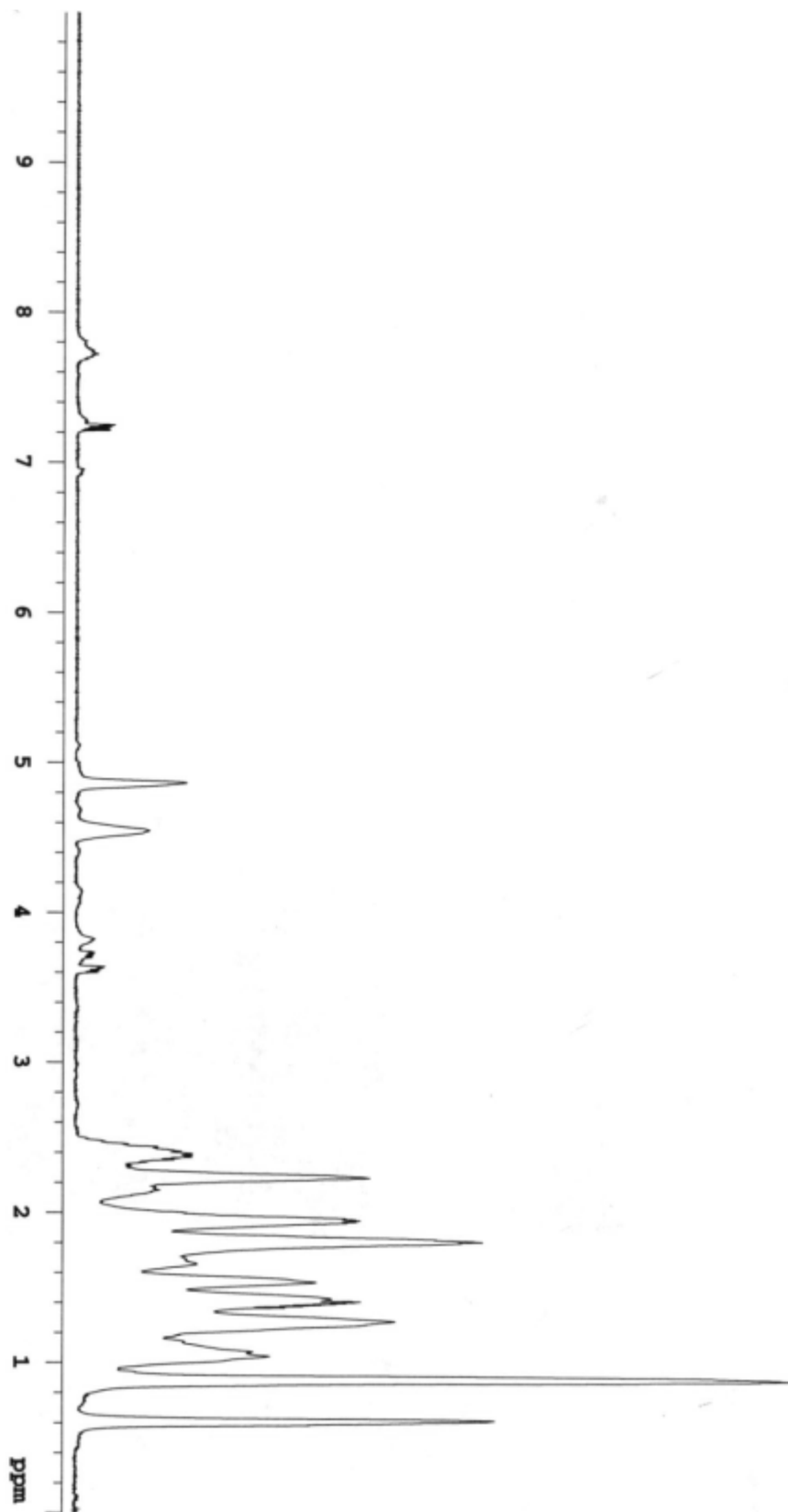
**3 $\alpha$ -Hydroxy-7 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoic Acid (27)**



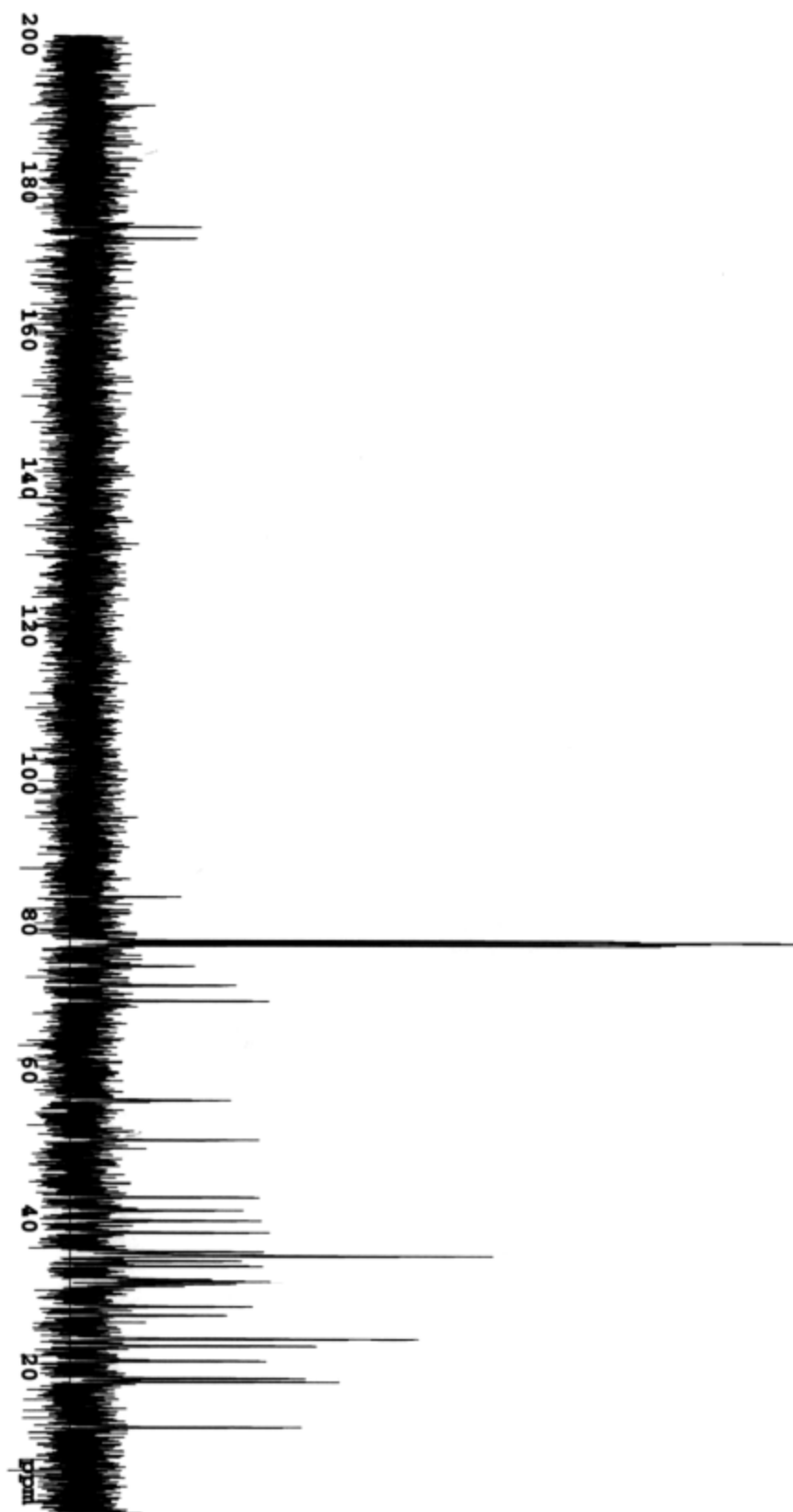
**3 $\alpha$ -Hydroxy-7 $\alpha$ -(4-iodobenzoyloxy)-5 $\beta$ -cholanoic Acid (27)**



Cyclotri(chenodeoxycholate)-tripentynoate (29)

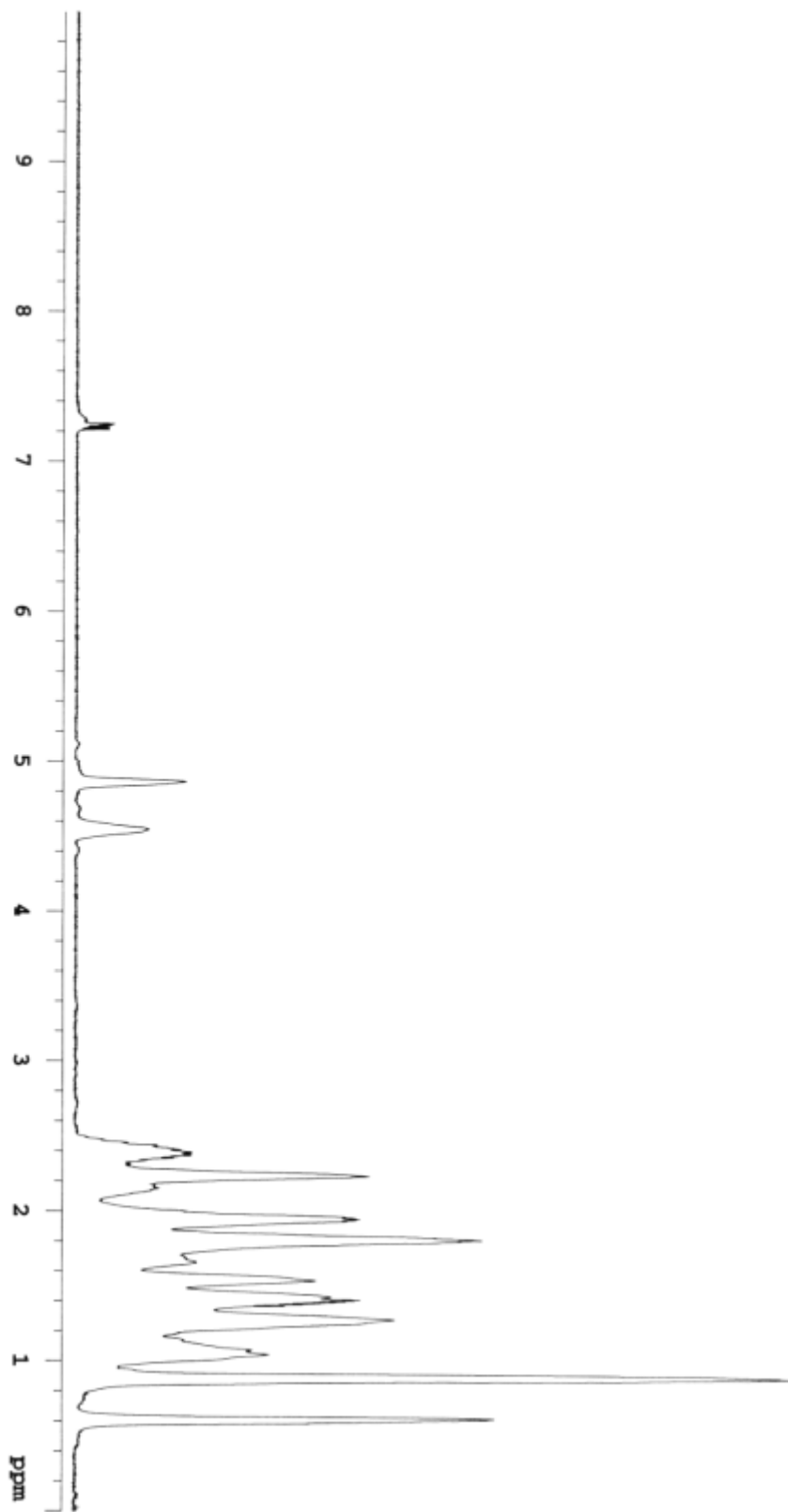


Cyclotri(chenodeoxycholate)-tripentynoate (29)

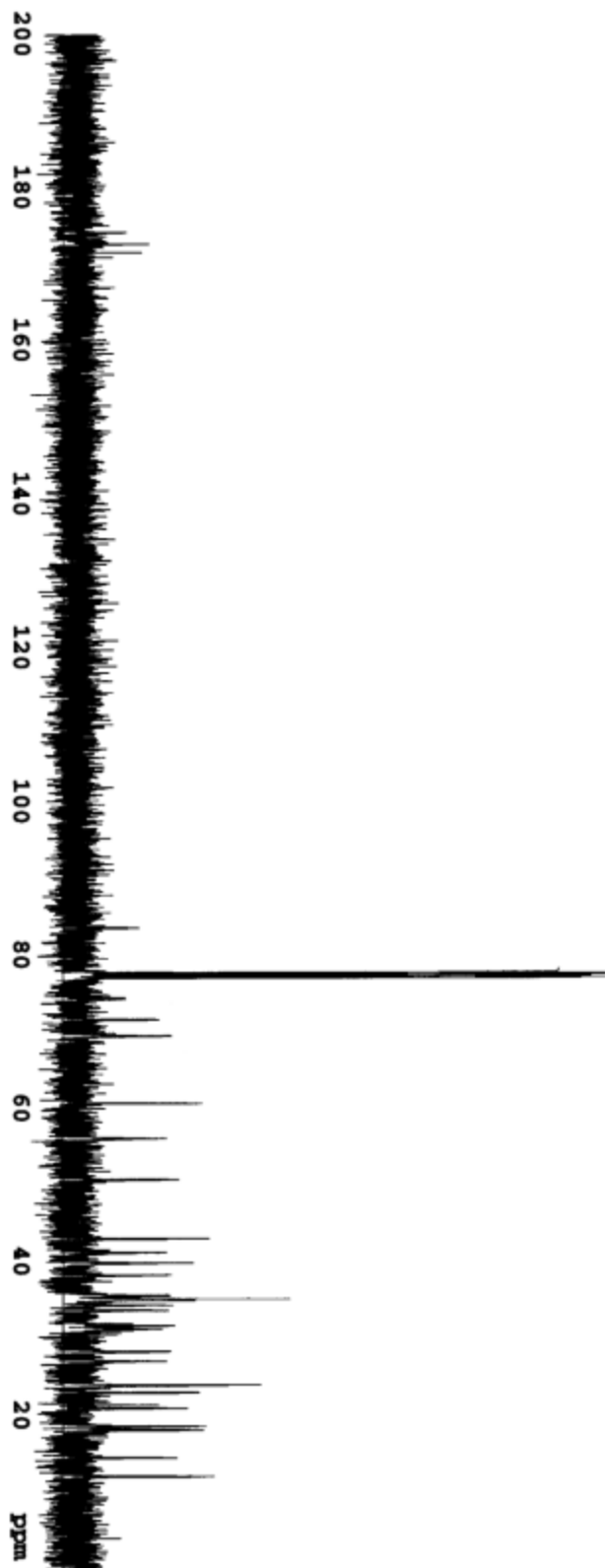




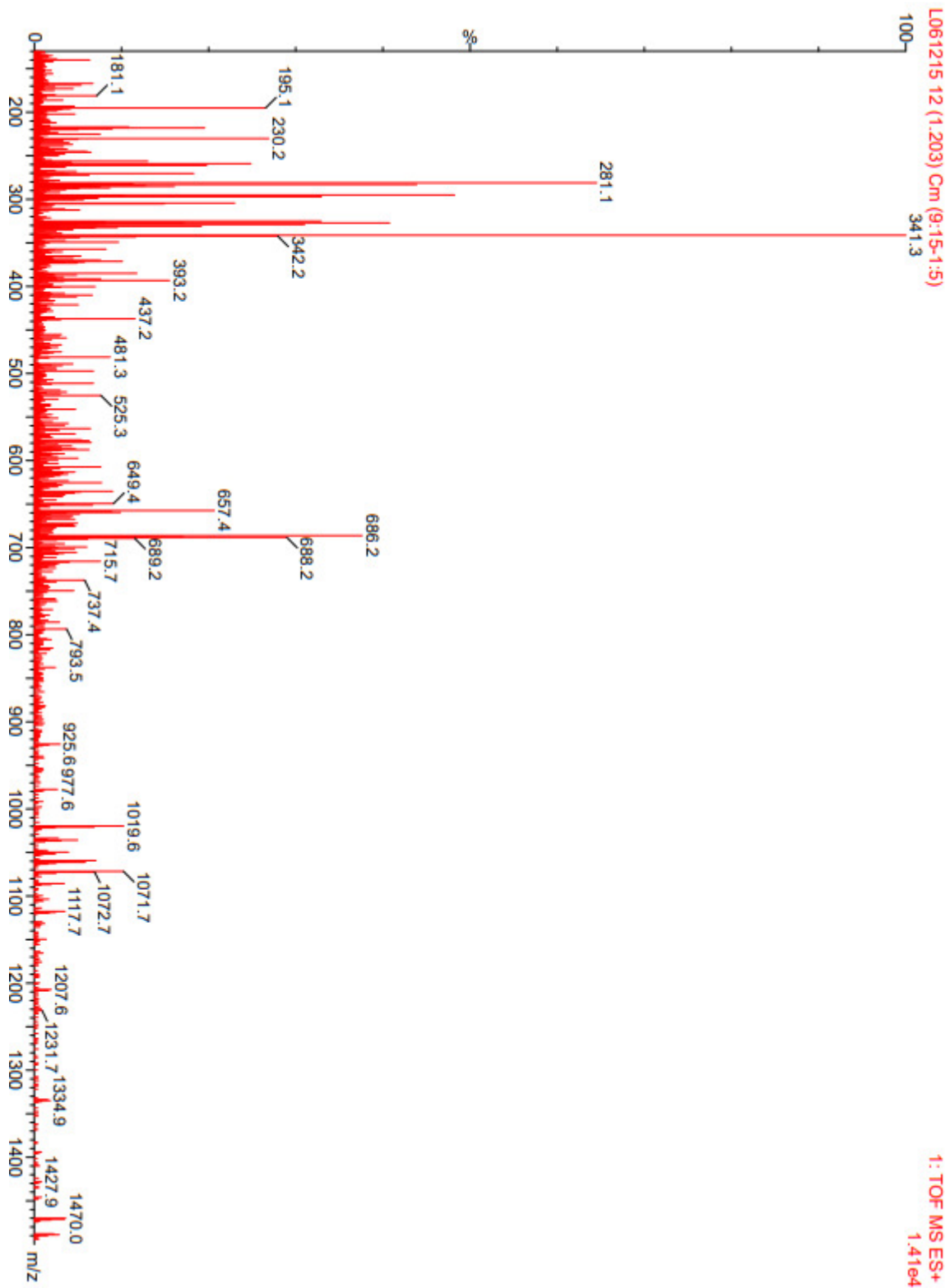
Cyclotri(chenodeoxycholate)-trihexynoate (30)



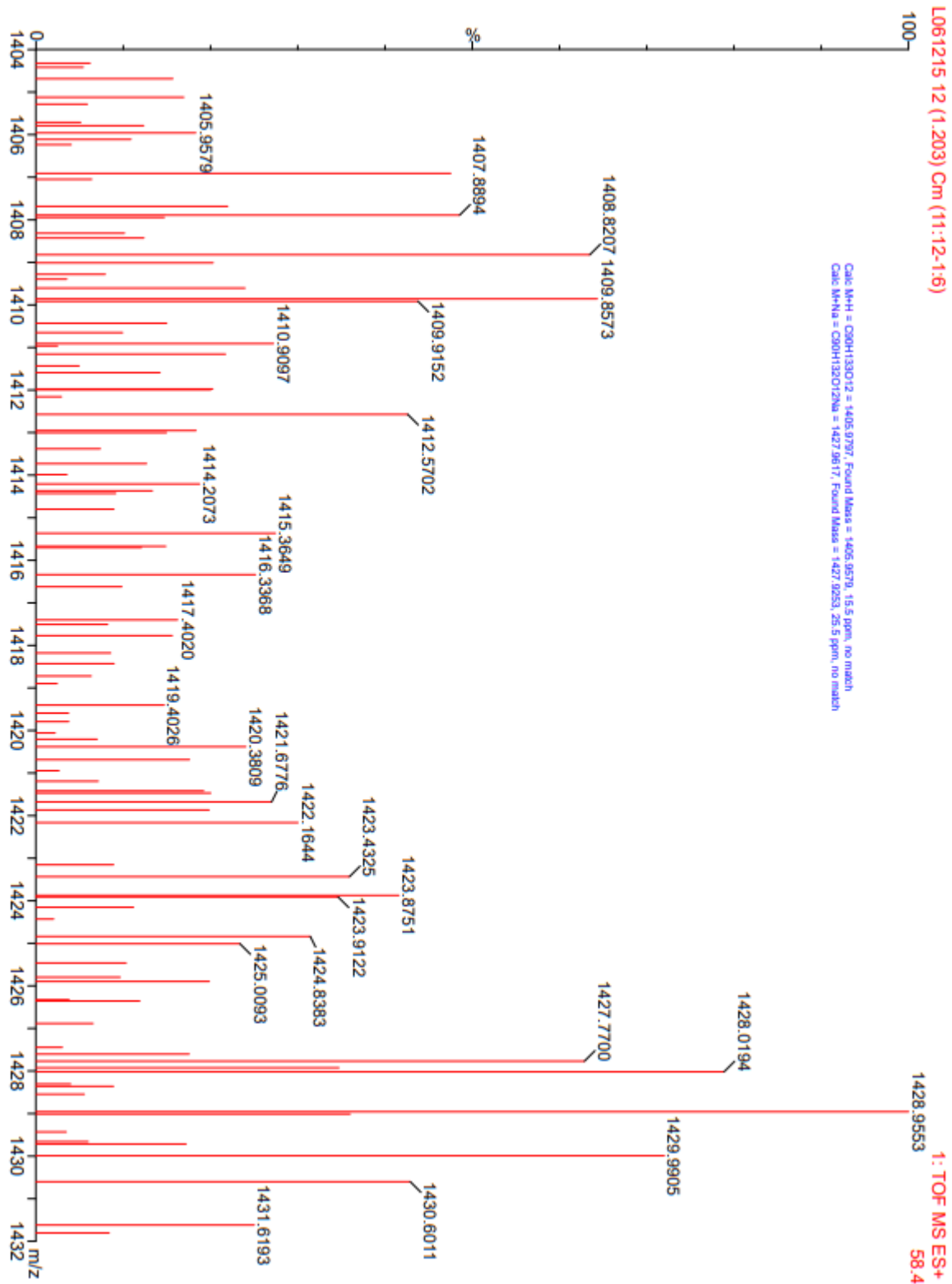
Cyclotri(chenodeoxycholate)-trihexynoate (30)



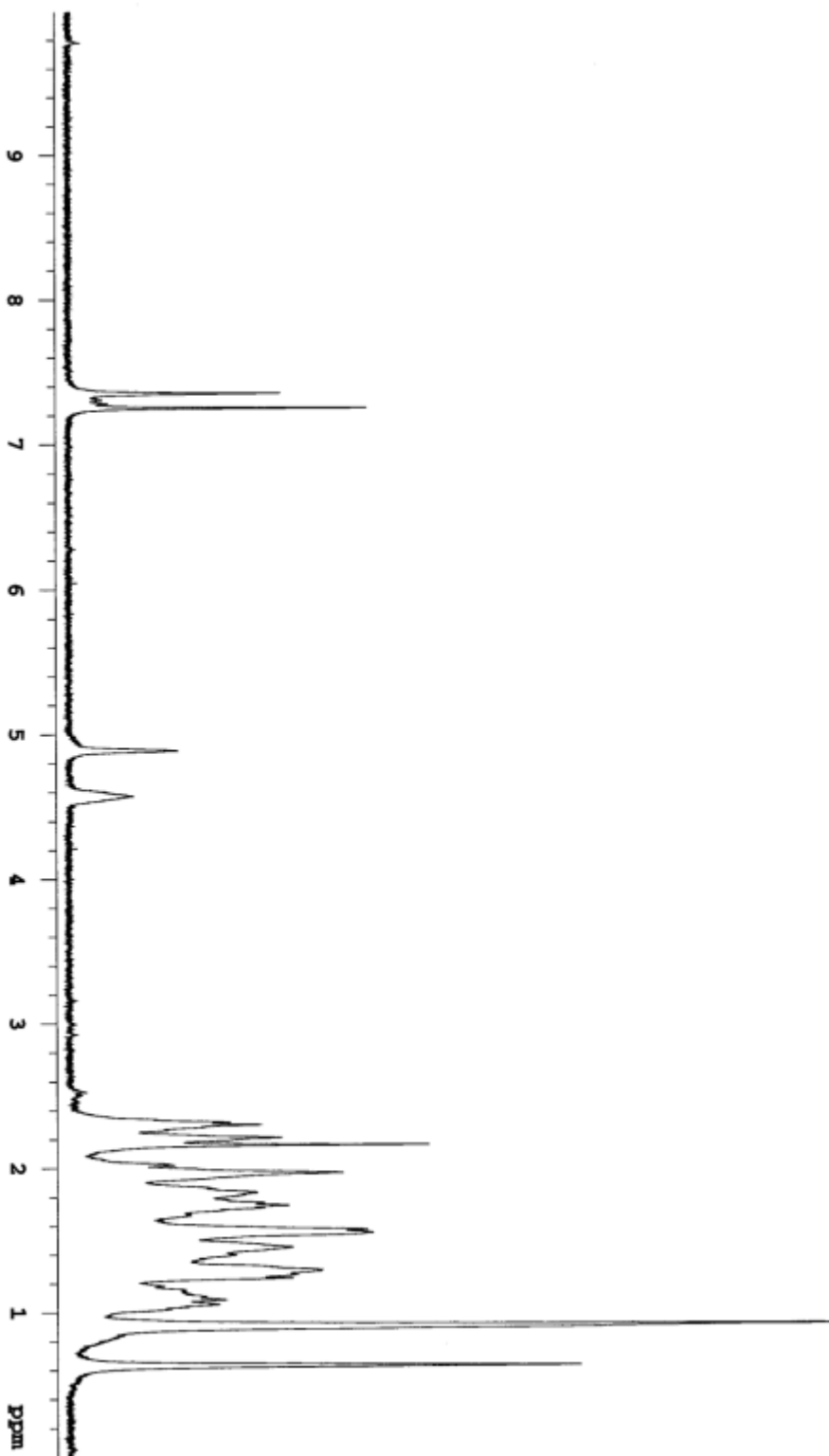
# Cyclotri(chenodeoxycholate)-trihexynoate (30)



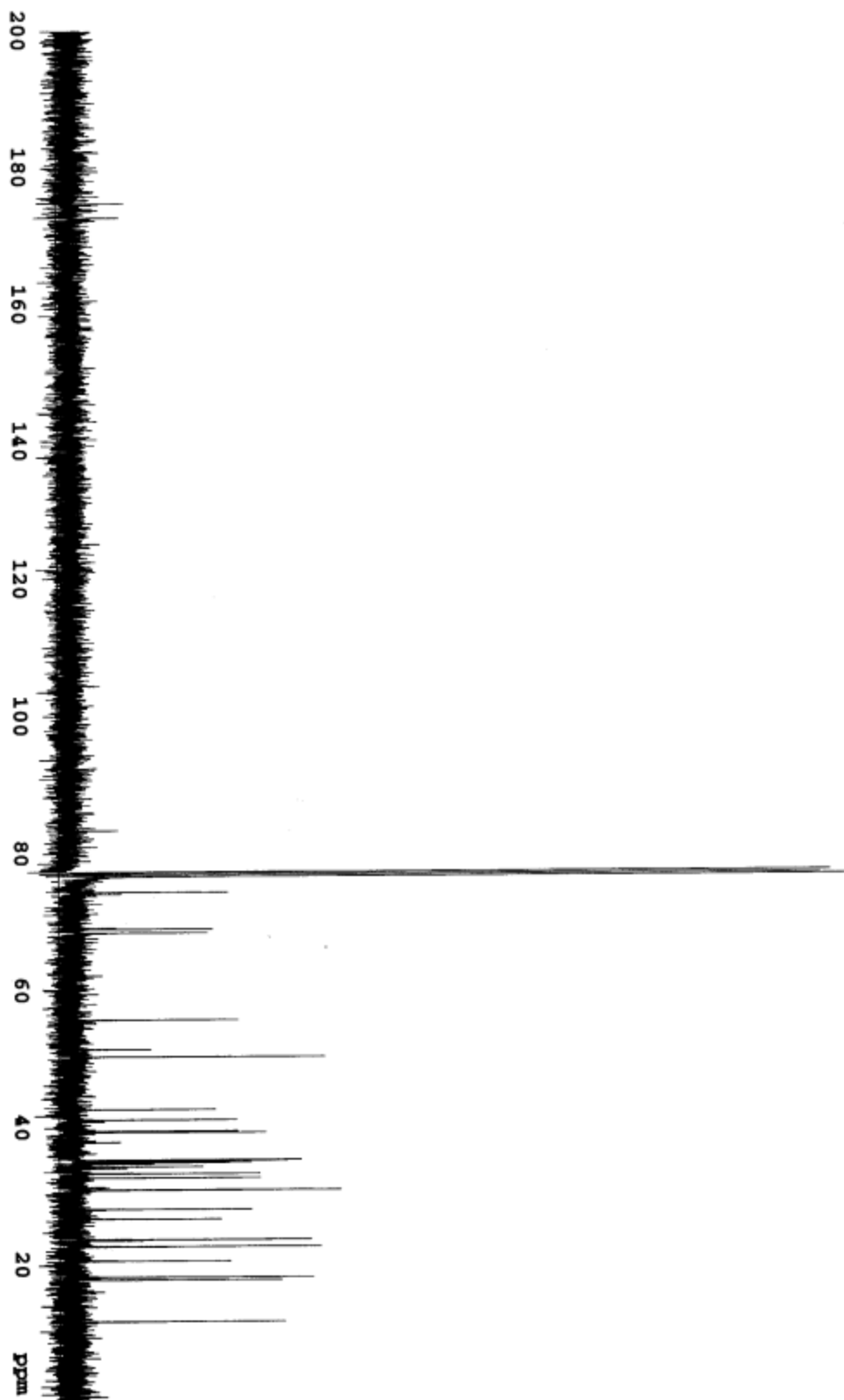
# Cyclotri(chenodeoxycholate)-trihexynoate (30)



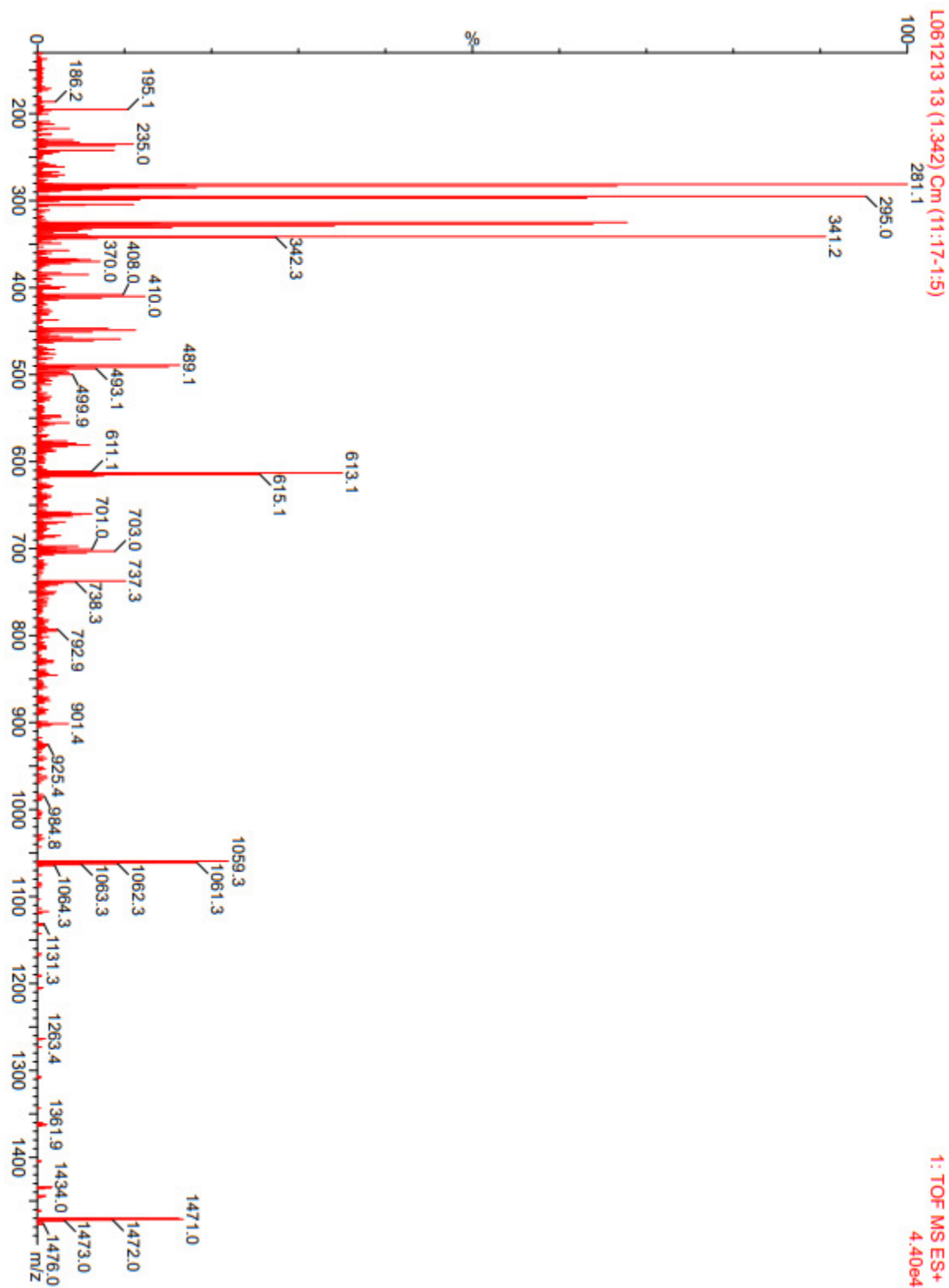
Cyclotri(chenodeoxycholate)-triheptynoate (31)



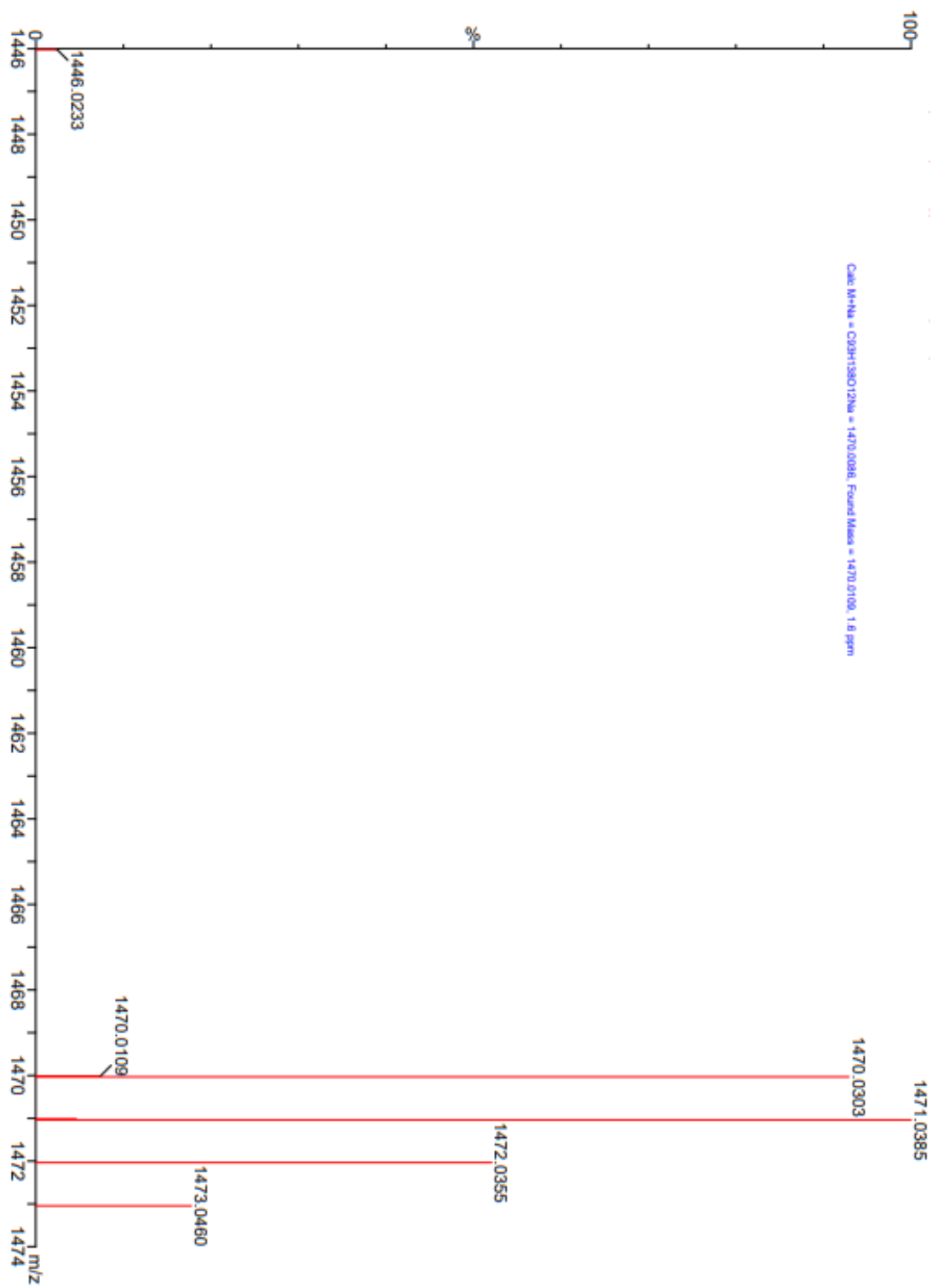
Cyclotri(chenodeoxycholate)-triheptynoate (31)



# Cyclotri(chenodeoxycholate)-triheptynoate (31)

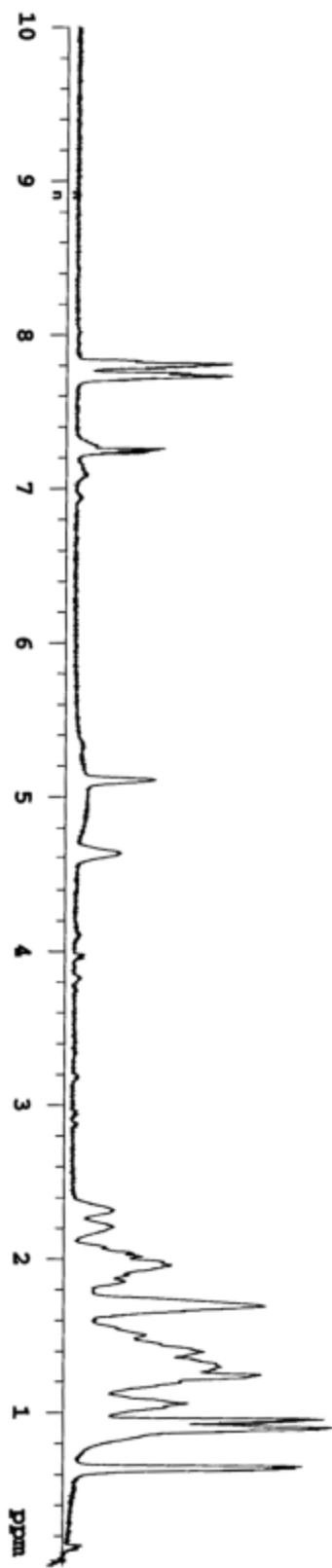


# Cyclotri(chenodeoxycholate)-triheptynoate (31)

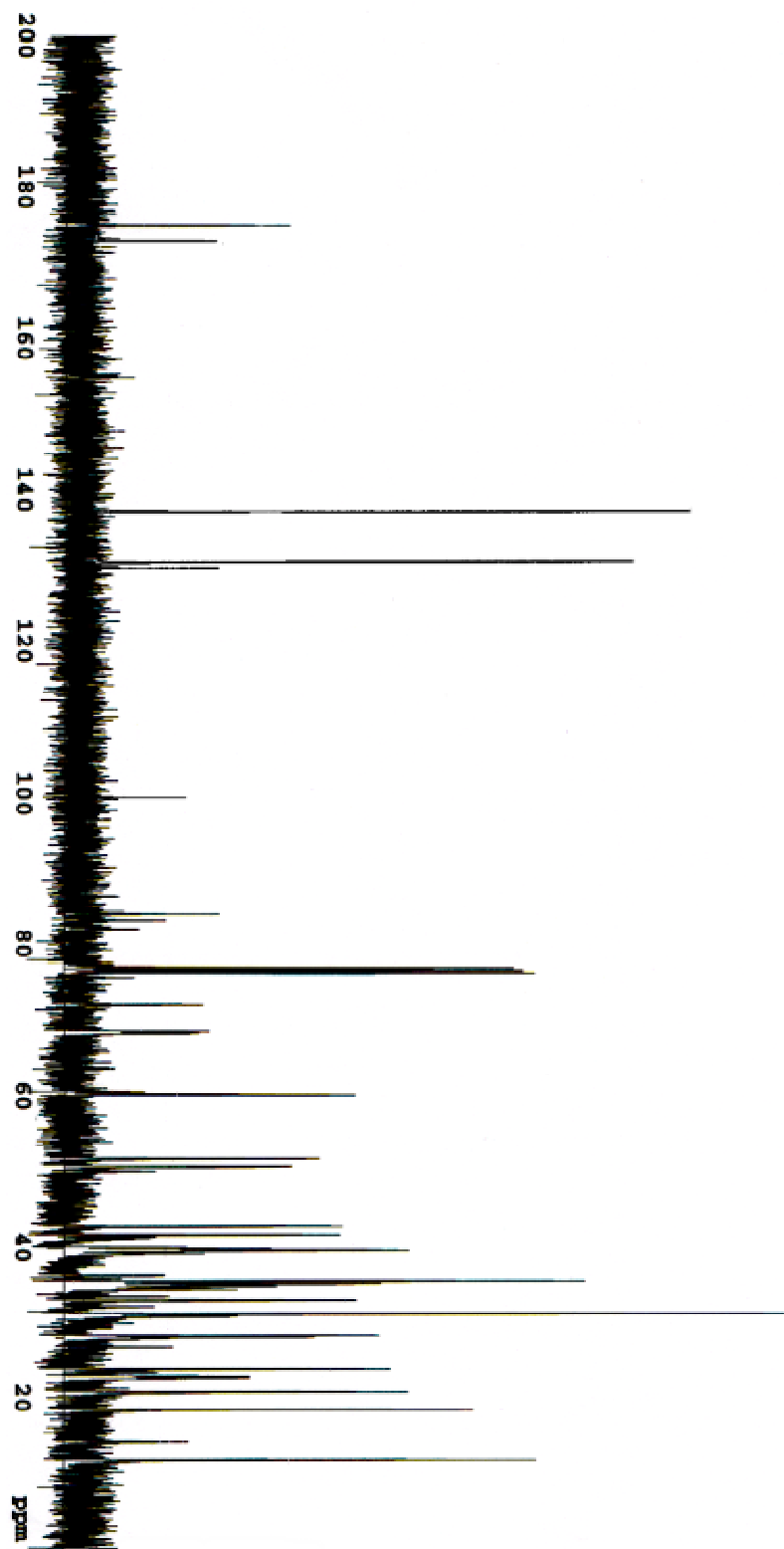




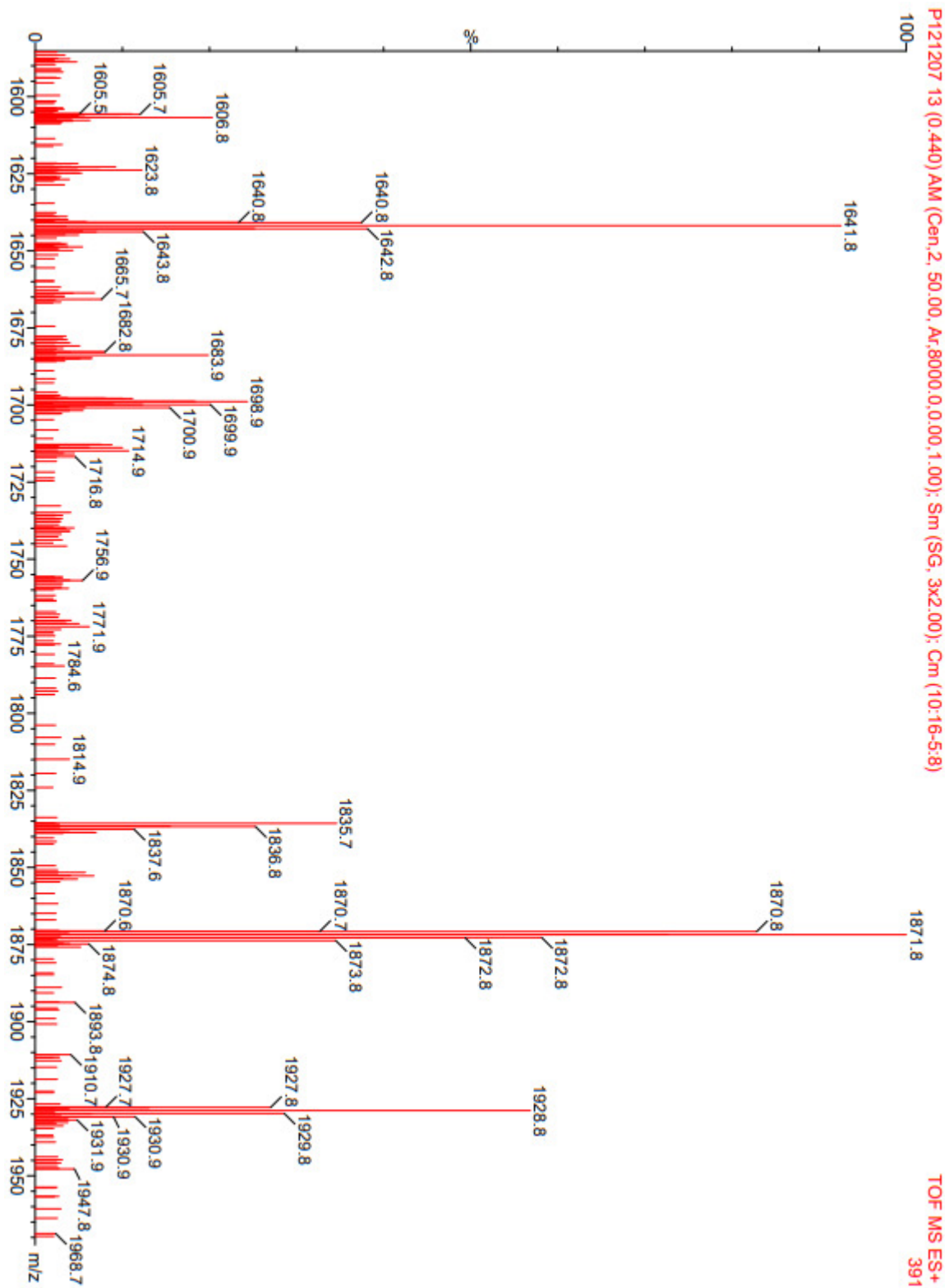
Cyclotri(chenodeoxycholate)-tri-4-iodobenzoate (32)



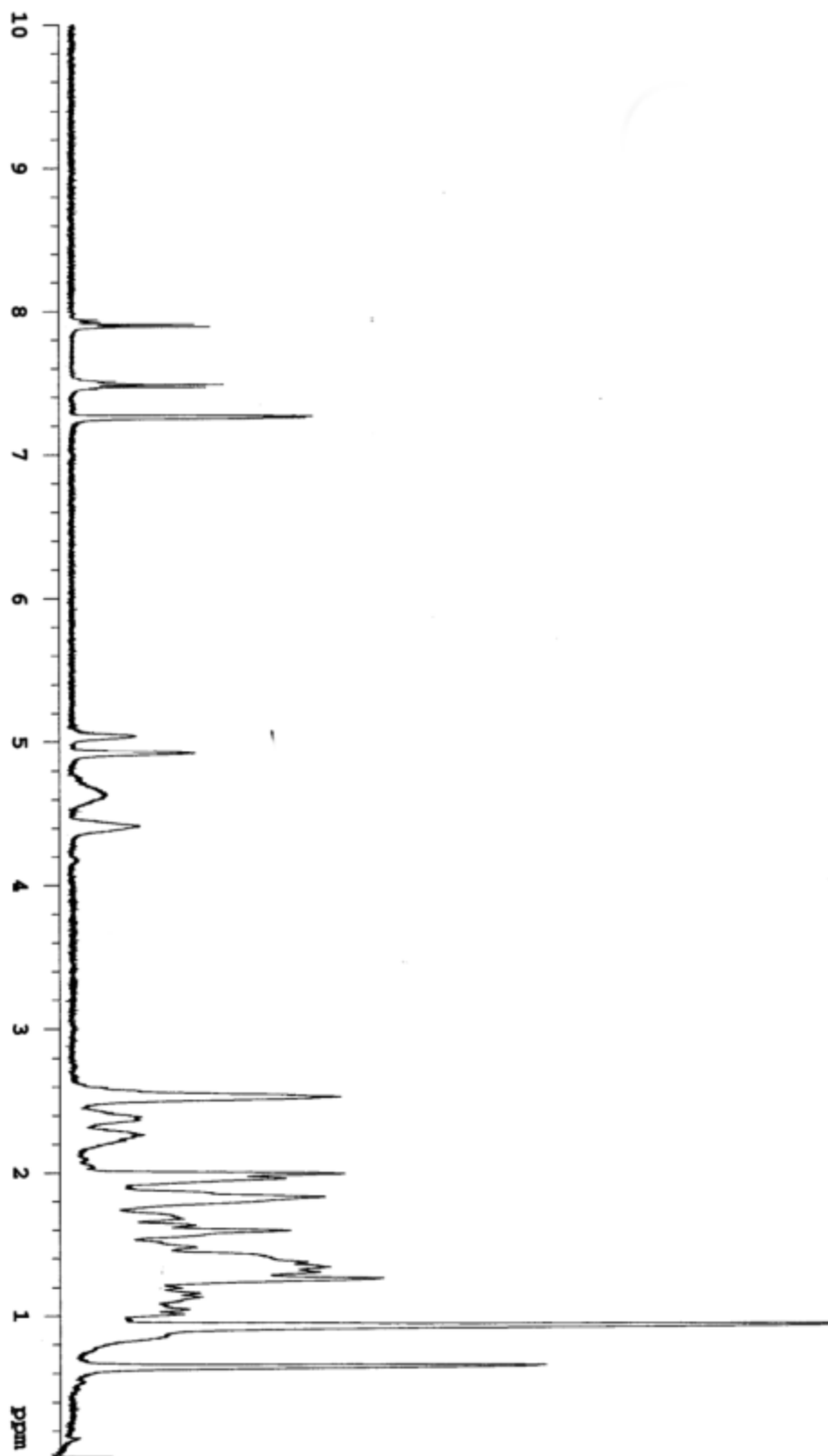
Cyclotri(chenodeoxycholate)-tri-4-iodobenzoate (32)



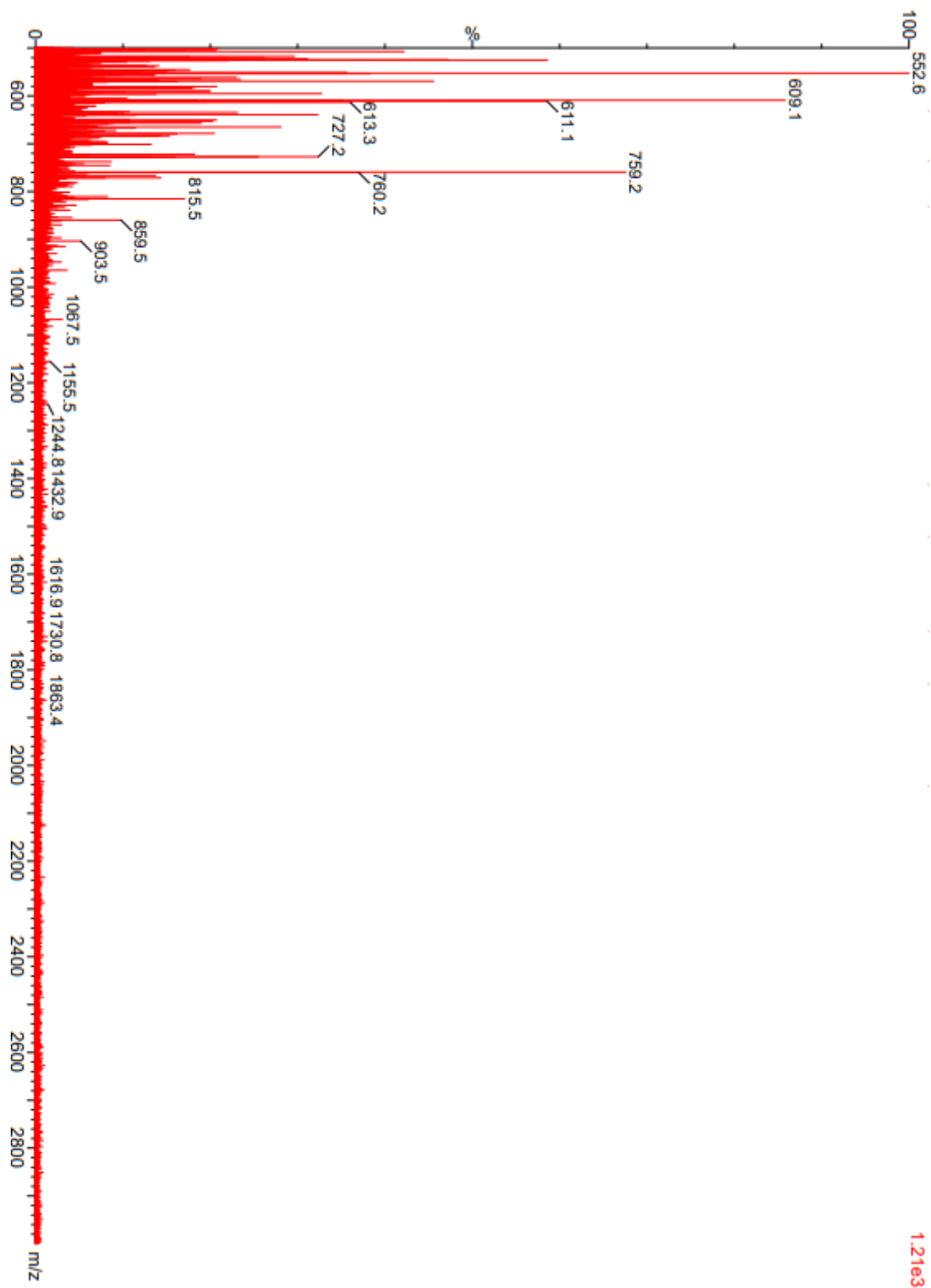
Cyclotri(chenodeoxycholate)-tri-4-iodobenzoate (32)



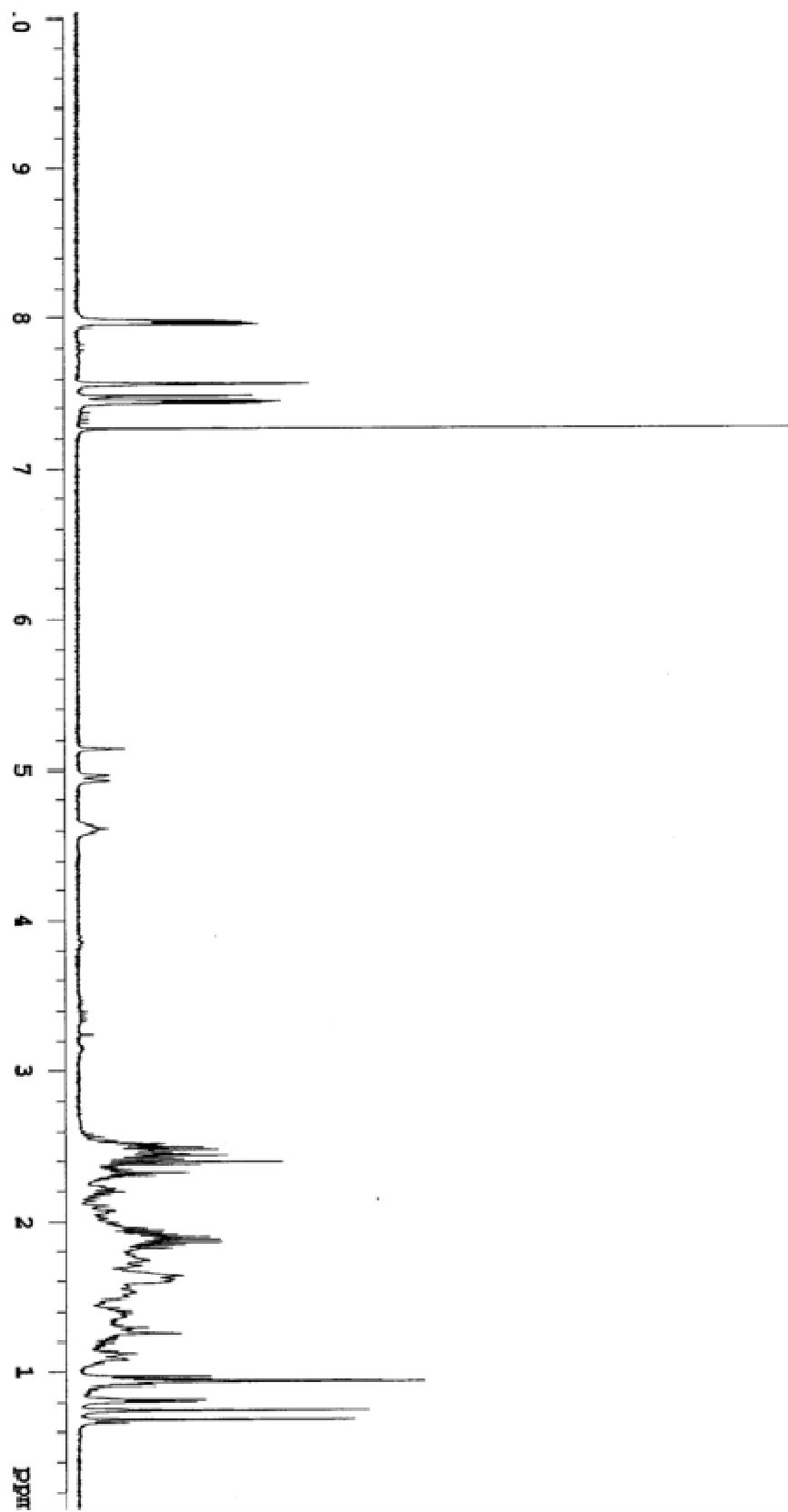
**Bis-Cyclotri(chenodeoxycholate)-tri-4-pentynylbenzoate (33)**



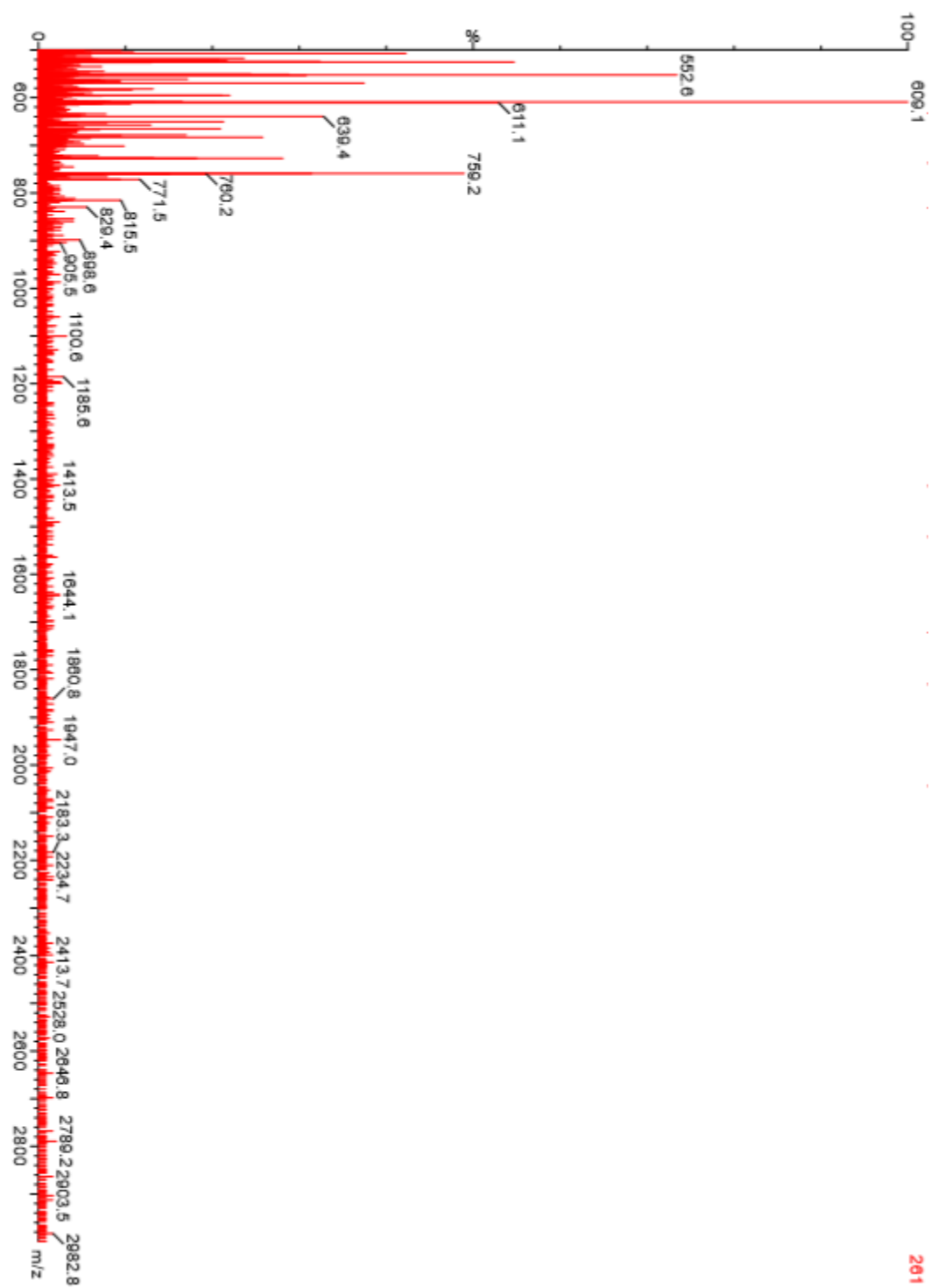
**Bis-Cyclotri(chenodeoxycholate)-tri-4-pentynylbenzoate (33)**



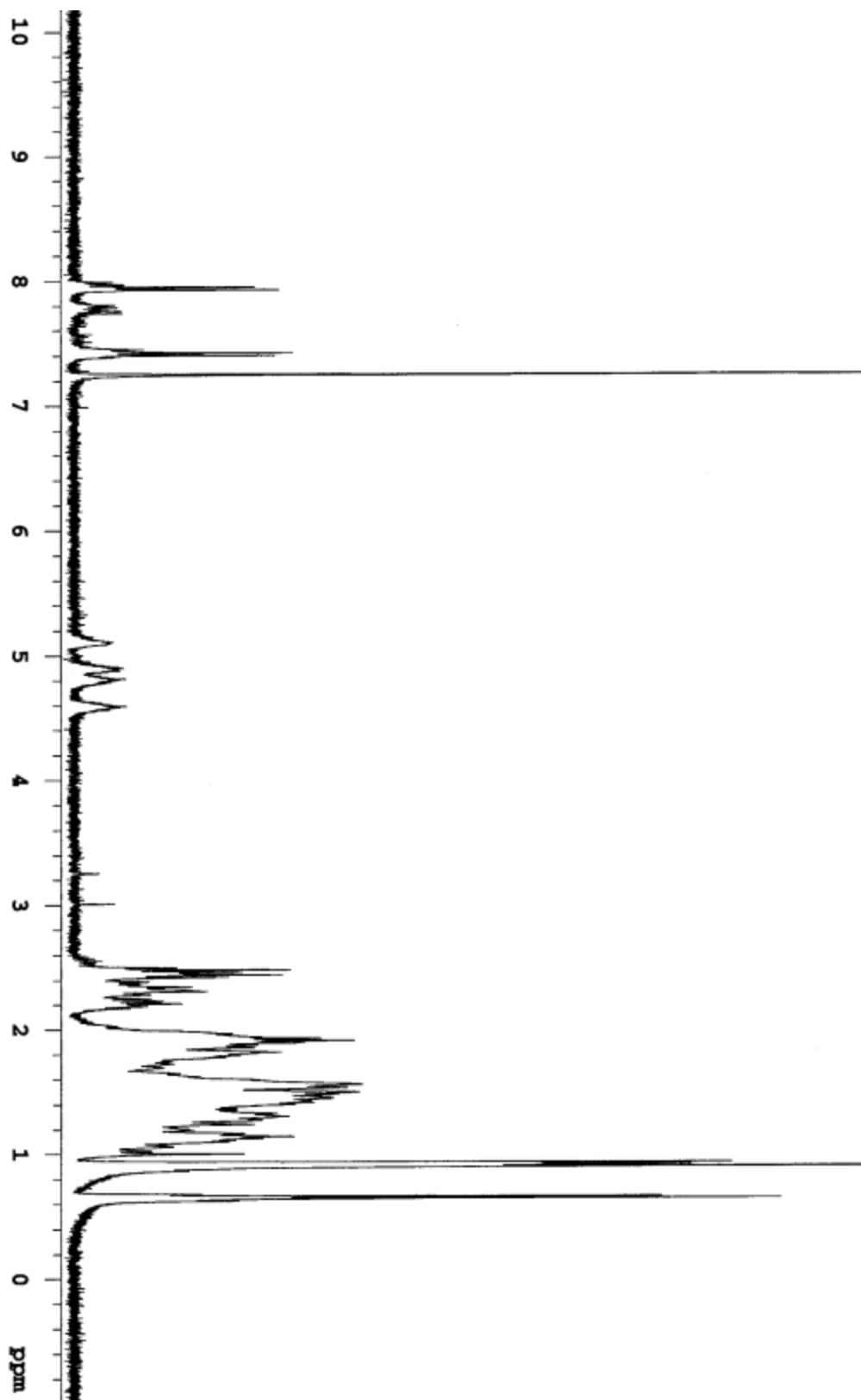
**Bis-Cyclotri(chenodeoxycholate)-tri-4-hexynylbenzoate (34)**



Bis-Cyclotri(chenodeoxycholate)-tri-4-hexynylbenzoate (34)

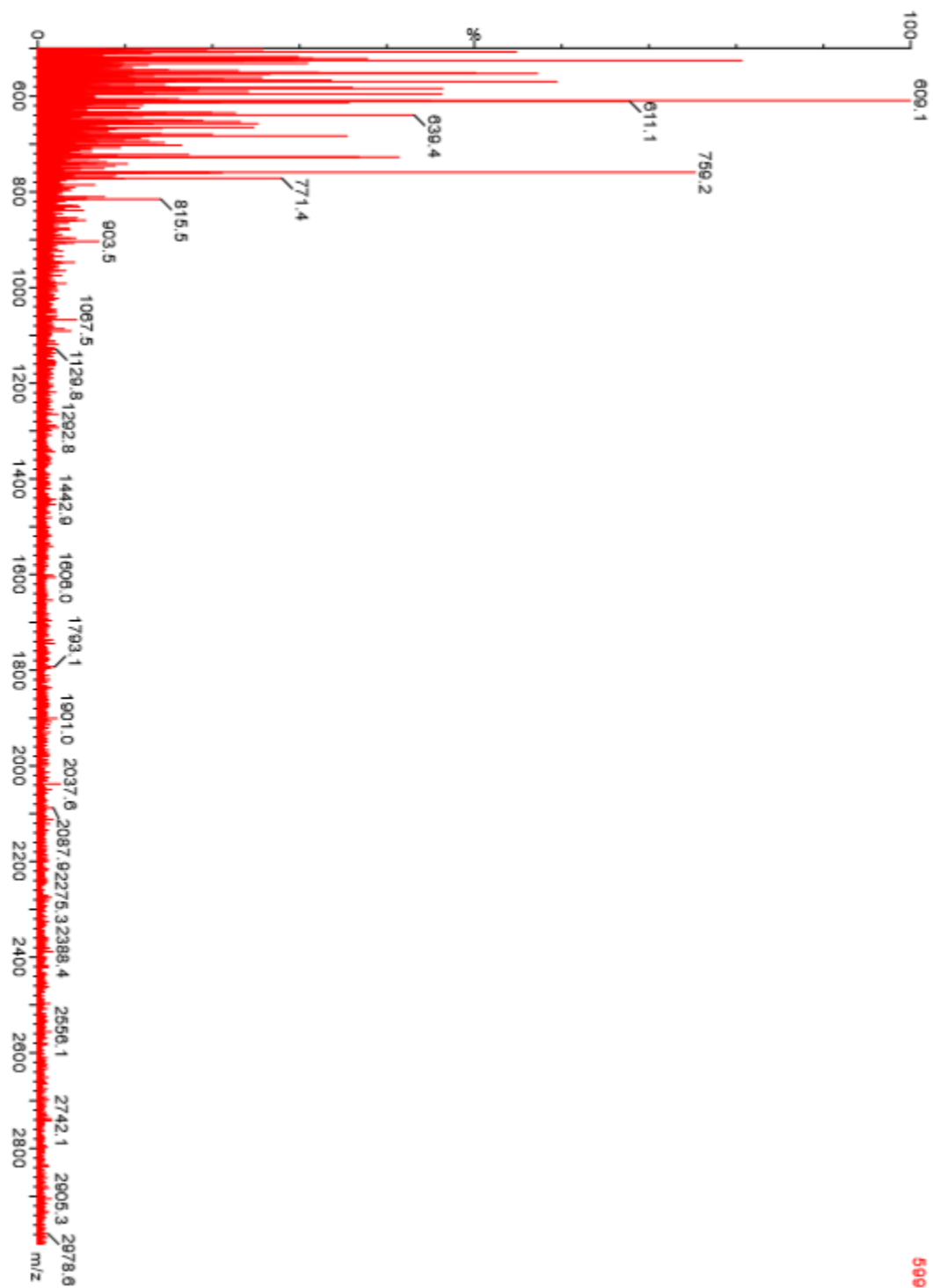


Bis-Cyclotri(chenodeoxycholate)-tri-4-heptylbenzoate (35)





Bis-Cyclotri(chenodeoxycholate)-tri-4-heptylbenzoate (35)



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PART II: EVALUATION AND EXPANSION OF A MODULAR CARD GAME FOR  
TEACHING ORGANIC CHEMISTRY

CHAPTER 5

5. EVALUATION AND EXPANSION OF CHEMKARTA

5.1 Introduction

5.1.1 The Benefits of Educational Gaming

Every year, college students struggle with successful completion of undergraduate organic chemistry courses, courses that are required for STEAM (science, technology, engineering, arts, and mathematics) majors as well as many medical programs. These courses are infamous for high failure with average passing rates around 40-60%.<sup>1-3</sup> Students often find assimilating the breadth and complexity of information in an organic course daunting. Learning is made even more difficult by a negative perception of chemistry courses<sup>3-5</sup> and underdeveloped study skills.<sup>6</sup> A need exists for the development of novel and approachable teaching strategies to address these issues. To this end, a card game “ChemKarta” has been developed for teaching undergraduate organic chemistry.

The use of games in teaching chemistry is an established method of introducing and reinforcing information with students.<sup>7</sup> Educational games are experiential exercises through which students are able to interact with material in a context outside the traditional lecture, homework, and test formats. Advantages of educational games include the presentation of course material in an interesting and enjoyable format, the utilization of knowledge as a strategy for

winning, and the promotion of student discussion during gameplay.<sup>8,9</sup> This approach has been successfully utilized in primary through undergraduate education to teach a wide range of chemistry subjects including chemical formulas, nomenclature, the periodic table, and molecular structures.<sup>10-14</sup>

While successful, previous pedagogical games have often adapted existing properties such as "Go Fish", Taboo<sup>®</sup> and Scrabble<sup>®</sup> to chemistry concepts.<sup>12-14</sup> The most notable advantage of this approach is that students are already familiar with the game and need little instruction to participate. However, by adopting other designs these works are restricted to the assimilated game models, which are not fashioned to incorporate new topics and address new conceptual relationships. It would be more desirable for an educational game to be applicable throughout an entire course rather than a singular topic. To develop such an educational game, a rational design is required rather than a derivative approach.

Building on Gredler's principles for game creation, a rationally designed card game called "ChemKarta" was developed.<sup>15</sup> ChemKarta is a simple, intuitive matching game where players solve questions by pairing them with the appropriate answers. The game's simplicity also allows for customization by adjusting the card content or augmentation of the basic rules through the addition of new cards (e.g. a card that allows a player to draw additional cards). Careful design of these frameworks and the appropriate questions enable the incorporation of new material while preserving the same straightforward matching system.



**Table 5.1 Comparison of Gredler's Principles and ChemKarta's Rationale**

Gredler's Principle	ChemKarta's Rationale
1. Winning should be based on knowledge	Points are scored by pairing correct answers
2. The game should address content, not trivia	Material is taken directly from course material
3. The game should be easy to understand	Matching answers cards is simplistic and intuitive.
4. Students should not lose points for wrong answers	Student do no lose points, but instead discard a card
5. Should not be a zero-sum game with a single winner.	While a single game is a zero-sum activity, points scored through multiple sessions allow students to track improvement

The course material is represented on each card by a structured framework of information from which the student must identify answers called a milieu. Examples of milieus include a molecule with multiple different functional groups or a synthetic route containing a series of chemical reactions. ChemKarta is different from flashcards, another learning technique common in chemistry, by presenting information through a milieu. While flashcard learning is heavily based on memorization (e.g. alcohol = -OH), the milieu adds another layer to studying by requiring students to identify answers within the conceptual framework. Additionally, because the milieu is used to group several pieces of information into a single framework, a single card in

ChemKarta can solve multiple questions within the game. Conversely, a single question can be answered by multiple cards as well. This downplays memorization of answers and instead promotes problems solving. The combination of these layers of learning provides a more in-depth method of learning than traditional flashcards.

An initial card set has been described to teach functional groups<sup>16</sup>, a subject ubiquitous throughout organic courses. This ChemKarta set addressed 22 functional groups in the context of 100 organic molecules (for simplicity, the guanidine group is treated as an imine and two amines), as well as 8 heterocyclic structures. Herein additional work is described, including evaluation of ChemKarta in a classroom setting and demonstration of the modular nature of the game through the development of additional cards for the functional group set, as well as additional sets utilizing the same rationally designed game framework.

## 5.2 Results and Discussion

### 5.2.1 Design and Set-up

The initial ChemKarta set used multiple decks of cards: Solution, Problem, and Bonus cards. Solution cards make up a player's hand, and all players draw from a common Solution deck. A separate Problem deck contains questions that students must solve to earn points (point values are printed on the Problem cards). Finally, a Bonus deck of eight cards is available that addresses advanced material that had not yet been covered in class. In the case of the functional group set, these cards include heterocyclic structures like pyridine, furan, and indole rings. Cards

can be drawn on blank notecards or printed out on cardstock. A list of the cards in each deck is provided in the Appendix.

ChemKarta is designed to work outside of class in short, informal sessions of 4-8 players per session, with a teacher acting as a moderator or referee. Groups of greater than eight students are assigned to teams to play (up to 16 can play in 8 teams of 2). Sessions last 30 minutes regardless of the number of games completed. Initially, students struggled to complete a single game; however, with increased study and experience, students later completed multiple games in a single sitting. Students are allowed and encouraged to take notes during sessions, but outside references are discouraged.

### 5.2.2 Basic Rules

At the beginning of the game, the eight Bonus cards are laid out in the middle of the playing table face-up. The Solution and Problem decks are shuffled and each player is dealt six Solution cards face-up. The Solution and Problem decks are then placed face-down within reach of all players (the decks may be split to accomplish this) as shown in Figure 6.1. Players then have the opportunity to discard and replace any cards they do not like. The game proceeds in a turn-wise fashion beginning with the player on the moderator's left.

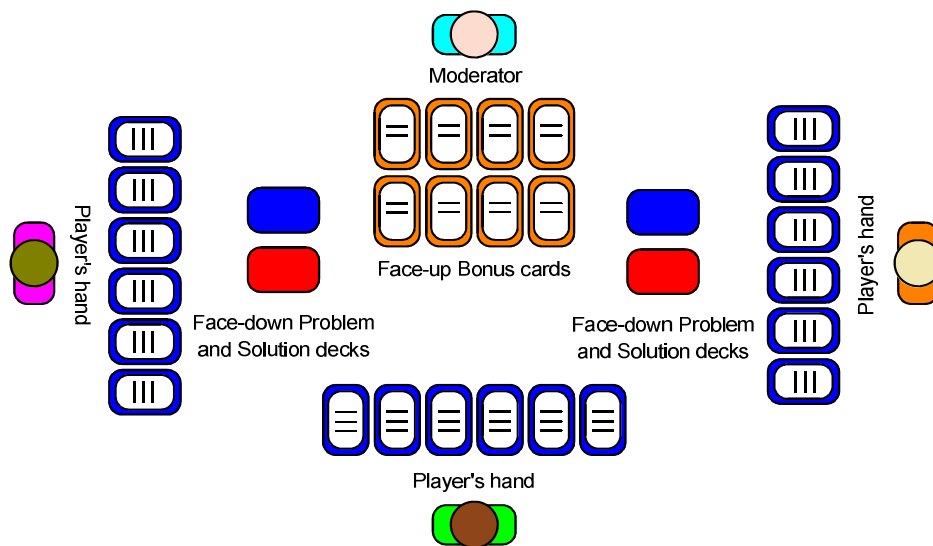


Figure 5.1 Game Setup

On a player's turn, he or she turns over the top card of the Problem deck, which asks that player to identify a functional group. The player may attempt to identify the functional group from the molecules present on his or her Solution cards. To correctly answer a Problem card, a player must say the name of the Solution card and indicate on the molecule where the functional group is. If the player correctly solves the Problem, that player removes the Solution card from his or her hand, pairs the Solution with the Problem card, and scores the number of points printed on the Problem card.

Some cards have "Honors" questions that can be answered for additional points. These are printed on the opposite end on the Problem card and have a higher point value than the regular question. If a player can answer the Honors question in addition to the initial question, that player scores the higher point value. However, if the player incorrectly answers the Honors question, the player just scores the normal points.

For example, it is Ella's turn and her Problem is an alcohol (requiring identification of an alcohol group). She chooses a Solution card with the molecule Cyanoketone and identifies the

alcohol. The Honors question asks if the alcohol is 1°, 2°, 3°, or aryl. She chooses 2°, which is incorrect. She scores the normal 5 points instead of the Honors 10.

If a player is unable to solve a Problem card or answers incorrectly, he or she cannot attempt another answer and must discard the Solution card (in the case of an incorrect answer). Now, other players in the group may attempt to answer the Problem card and score the points instead, effectively “stealing” the player’s turn. That player chooses who may answer the Problem card first if multiple players believe they have the solution. Again, if other players are incorrect in their answers, they must discard their Solution card and cannot attempt another answer this turn. Attempts to solve the Problem card may continue until it is solved or no one can answer, at which point the card is discarded and the turn ends.

At the end of the turn, the player may discard any number of cards and draw back up to six Solution cards. Players may only refill their hands at the end of their turn. Answering multiple Problem cards during others’ turns will reduce a player’s hand so fewer Solution cards are available on that player’s turn.

Additionally, eight Bonus cards are available in the middle of the table. If at any time a player answers with a Solution that corresponds to an appropriate Bonus, he or she may collect that card and add the points to that player’s score. Bonus cards are not refilled during the game.

For another example, on his turn Jacob reveals an amide Problem (requiring identification of an amide group). He plays the card Raspberry Ketone and incorrectly chooses a ketone. He discards his card and asks if any other players want to answer. Both Courtney and Lucas want to answer. Jacob chooses Lucas to answer. Lucas chooses the Solution card Stepronin, identifies the amide, and then also collects the Bonus card Thiofuran for playing a

card with a thiofuran group, for a total of 25 points. At the end of his turn, Jacob draws a card to replace the one he lost (see Figure 5.2).

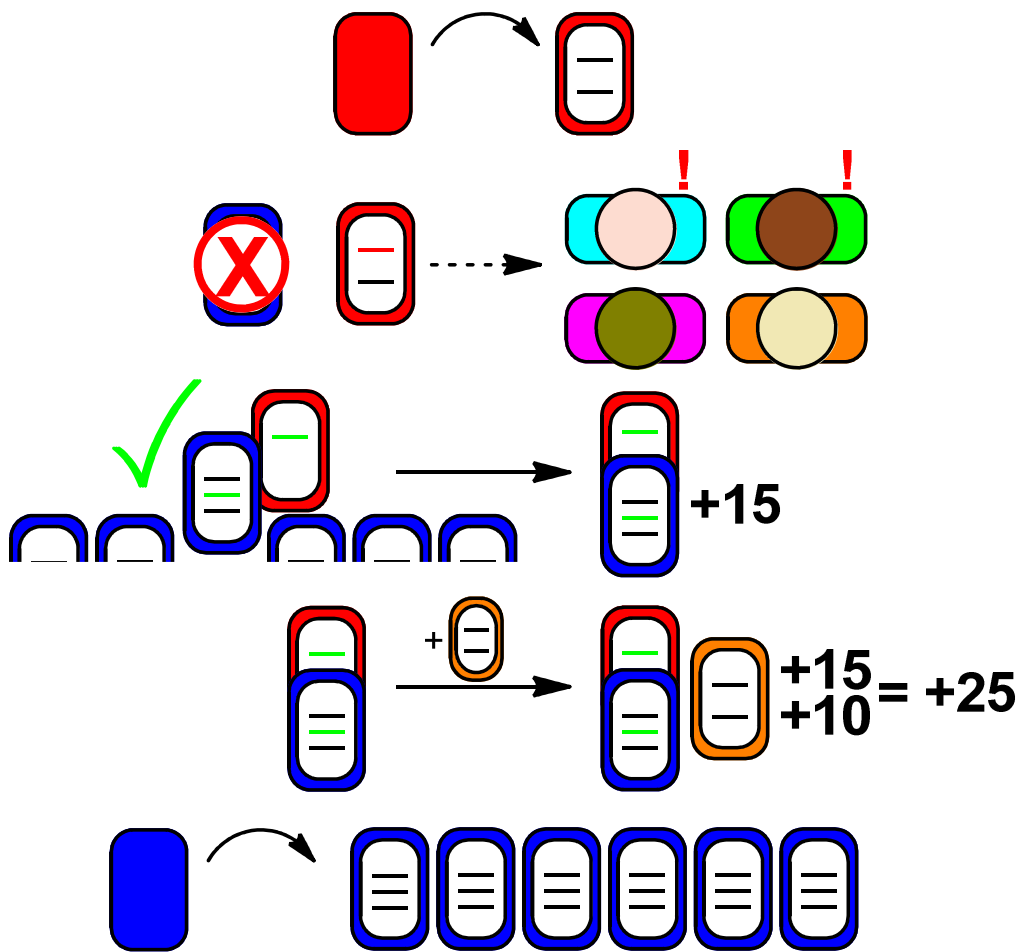


Figure 5.2 An Example of a Turn.

Play continues until a player reaches 100 points, at which point a player is declared the winner.

### 5.2.3 Evaluation

During game development, students responded favorably toward the game as a learning tool. The game had a very low learning curve, enabling students to learn the game through playing rather than through instruction. New students were assigned to take their turn last and were consistently able to play by simply watching other players. Students found the game to be constantly engaging due to the possibility of “stealing” another player’s points. During each player’s turn, all students were looking through their Solution cards to try to solve the Problem card in case that player couldn’t. Students thought the game was an enjoyable study tool because of its novelty, its informal nature, the ability to answer Problems with different Solutions, and the ease of play.

Early in game development, ChemKarta was played like poker, with students keeping their hands secret and competition was encouraged. However, students stated that the focus on winning made the game unenjoyable because they felt like they were being encouraged to beat their classmates (See Gredler’s Principle #5). To address this, students were allowed to play with their hands face up and encouraged to discuss among themselves, both to solve Problems and to aid other students who were struggling. This produced a more student-centered supportive learning environment where students acted as leaders in peer-to-peer learning. As a result, students were more willing to attempt to work out problems, were less afraid to make mistakes, and would develop their own mnemonic devices and learning techniques. Previous game sessions and information from Solution cards not in play were regularly referenced, indicating retention of information. Group cooperation was regularly observed at the beginning of the game, but as the game progressed, students who were winning would receive less help.

Ultimately, in order to win, students' peers required them to learn to solve problems on their own.

In addition, there appeared to be a direct correlation between how much students participated with other players verbally during the game and their performance in class. High performing students would take the lead in peer learning while low performing students would simply play the game with little verbal interaction. Encouraging social interaction, not simply relying on gameplay, may offer the best improvement in student performance. It is hoped the promotion of this behavior may strengthen students' self-sufficiency to the point of eliminating the need for the presence of a teacher thus allowing students to play independently.

The card sets were exploited as a resource for classroom discussion and exam questions. With 100 cards in the set, it was impossible for students to memorize answers, thus requiring them to learn how to work through problems. Students found it easier to address questions on molecules they were familiar with from playing ChemKarta. These molecules could then be utilized as recognizable examples in later chapters of the course.

Evaluation of the ChemKarta functional group module was performed in the Organic Chemistry I class at Johnson County Community College in collaboration with Dr. Faith Jacobsen (number of students  $N = 23$ ). The course was a three-credit course, which met 3 h per week. A total of 4 games were played over a week's time according to the basic gameplay rules. Students were given an initial survey to judge their views towards organic chemistry and took a similar final survey which asked the same questions as well as their opinions of ChemKarta as a teaching tool. The responses were graded according to the following: (0 = strongly disagree, 5 = neutral, 10 = strongly agree).



**Table 5.2 JCCC Initial Class Results**

	High	Low	Mean	Median	Mode	SD
Can ID FG	7	0	3.78	4	4	2.32
Familiar with organic molecules	8	0	3.26	3	3	2.30
Learning OC is difficult	10	0	4.87	5	5	2.80
Interest in OC	10	5	8.08	8	10	2.09

**Table 5.3 JCCC Final Class Results**

	High	Low	Mean	Median	Mode	SD
Can ID FG	9	0	5.21	5	7	2.21
Familiar with organic molecules	8	0	4.31	4	4	2.47
Learning OC is difficult	10	2	7.73	8	10	2.20
ChemKarta is effective	10	0	6.65	7	6	2.57
ChemKarta is easy	10	4	8.08	8	10	1.68
ChemKarta is fun	10	3	6.60	7	8	2.55
ChemKarta > Flash Cards	10	3	6.78	7	8	2.47
Want more card sets	10	4	7.08	7	5	2.09
Want electronic app	10	4	8.08	9	10	2.21

A student's t-test was performed to determine if before (1) and after (2) populations were different concerning their perceived ability to identify functional groups (a), familiarity with organic molecules (b) and perceived difficulty of organic chemistry (c).

$$a) \frac{(5.21 - 3.78)}{\sqrt{\frac{2.32^2}{23^2} + \frac{2.21^2}{23^2}}} = 2.21 \quad b) \frac{(3.41 - 3.26)}{\sqrt{\frac{2.30^2}{23^2} + \frac{2.47^2}{23^2}}} = 1.23 \quad c) \frac{(7.73 - 4.87)}{\sqrt{\frac{2.80^2}{23^2} + \frac{2.20^2}{23^2}}} = 3.86$$

Figure 5.3 t-Tests

**Table 5.4 JCCC Results Analysis**

	t stat	t critical	Conclusion
Can ID FG	2.14	2.01	Populations are significant
Familiar with organic molecules	1.23	2.01	No change
Learning OC is difficult	3.86	2.01	Populations are significant

The initial student population was unfamiliar with functional groups and organic molecules from their scores in the 3-4 range. They had a neutral attitude close to 5 towards the difficulty of learning, but were highly interested in organic chemistry with a very positive score of 8.08. This indicated a student population that is highly interested in the subject matter, but with low familiarity with it. After playing ChemKarta, students expressed an increase in their perceived understanding of the material leaning toward a neutral attitude (3.78 to 5.21), little change in their negative familiarity of the subject (3.26 to 3.41), and an increased perception in the difficulty of learning (4.87 to 7.73). Students t-tests confirmed that the change in understanding and perceived difficulty were significant ( $t_{\text{stat}} > t_{\text{crit}}$ ), but there was no change in the familiarity with the subject matter ( $t_{\text{stat}} < t_{\text{crit}}$ ).

By using ChemKarta as a teaching tool, students were able to practice identifying functional groups. Increased practice is the expected cause for in higher confidence in performance as students had more opportunities to evaluate their performances. However, it is disappointing that increased exposure to relevant molecules did not lead to an increase in familiarity. Simply presenting molecules in the game format is therefore not sufficient for familiarizing students with organic molecules and increased instruction toward the subjects is therefore required. Furthermore, playing ChemKarta led to an increased perception in the difficulty of organic chemistry among. While the intent of play was to make students familiar with chemical structures, the large card set was likely overwhelming for many. This is a challenge in implementing ChemKarta because it may increase a negative perception of the subject matter. It is therefore essential for an educator to work to maintain a positive teaching environment during play in order to prevent a negative association with the game or teaching material.

Concerning playing ChemKarta, students responded slightly favorable toward the game (6.60), its ease of play (8.08) , its efficacy as a learning tool (6.60), and their preference towards it as a learning tool compared to flash card (6.78) There was a wide range of answers for the effectiveness of ChemKarta indicating that although the majority of the classroom population liked learning through this method, there were certain students who did not enjoy the use of a competitive game as a learning tool (one student mentioned this in notes). For this reason, ChemKarta is not recommended to be a required activity for learning a subject matter, but rather a supplemental tool to aid students who may respond better to alternative learning methods. There was also a strong preference towards an electronic version as opposed to a physical game. Students' preference towards an electronic app may indicate a desired to play on their own and

on their own time rather than in group settings. While an electronic option may increase students' access to ChemKarta, it may do so at the cost of losing the interpersonal learning experiences of a social environment.

#### 5.2.4 Modular Development

In order to demonstrate the flexibility of ChemKarta's game design and introduce more complexity into the game for more experienced players, two additional types of cards have been developed: Technique and Victory cards. Should students be interested in additional challenges, more cards can be added to the basic game. These Technique and Victory cards can be seamlessly added to the basic game without greatly modifying the rules, allowing players to quickly learn how to use them. Technique cards are shuffled into the Solutions deck, so a player may draw them in addition to Solution cards. Technique cards are played from the hand when designated on the card in order to affect the game. These effects include drawing additional cards, preventing other players from solving a Problem, or discarding a Problem card for another.

Victory cards make winning more challenging by place additional restrictions on players. At the beginning of the game each player is dealt a Victory card face-down. Instead of automatically winning at 100 points, at the beginning of their turn, if a player has 100 points or more, they flip over their Victory card and attempt to meet the conditions on the card in order to win. If a player cannot meet the conditions, they have to wait for their next turn to try again. Play continues until a player meets the requirements on their Victory card, at which point a player is declared the winner. Players who have turned over their Victory cards may not play any more

Technique cards or steal Solutions from other players in order to let them catch up (except in the case of the 200 point card).

An example of a complex turn incorporating Technique and Victory cards would be as follows. On his turn, Isabella reveals an Aldehyde Problem (requiring identification of an aldehyde group). She plays the card Raspberry Ketone and correctly chooses the aldehyde. However, Chen has the Technique card Hydrogenation, which can be played during Isabella's turn and prevents her from scoring with Vanillin (since reducing the aldehyde would make it an alcohol, an invalid answer). She then discards Vanillin and asks if anyone else wants to try to answer. Both Chen and Amy want to answer. Isabella chooses Amy to answer. Amy chooses the Solution card Elenoic Acid and identifies the aldehyde. This raises Amy's score to 100 points, but she has a face down Victory card and does not win immediately. Isabella draws a card to replace the one she lost and passes her turn.

At the beginning of Amy's turn, she flips over the Victory card to see how she is to win. She has the Victory card Multiple Solutions, which requires her to draw 6 Solution cards and identify a different functional group on each one. She correctly identifies only 5 of the 6 functional groups. Therefore, she discards those cards and waits for her next turn to try again. (*see Figure 6.3*).

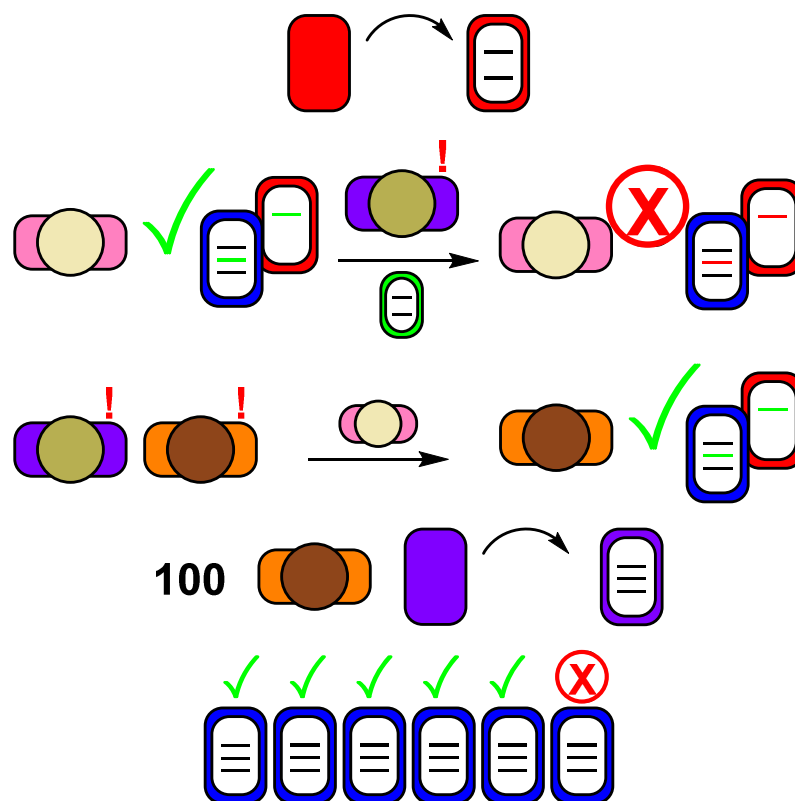


Figure 5.3 An Example of an Advanced Turn.

The addition of these new types of cards without the need to change rules demonstrates ChemKarta as a flexible game system rather than a static teaching game. While the Technique cards are easy to understand, they introduce a level of strategy to the game which requires thought and analysis of the cards and the game board. For example, would it be best to use an Oxidation card now to prevent a player from getting ahead or later to stop a high scoring player from reaching 100 points? The effects of technique cards also relate back to concepts they're named after thus reinforcing these concepts and their application in student thought experiential learning.

Further exploration into the modular nature of ChemKarta's game design involved the

development of new sets of cards to teach different subjects in chemistry. The same basic rules structure was preserved: a matching game with Problem, Solution, and Bonus cards. The only change is the material on the cards and the representative milieus. Two more modules have been developed: one to teach structure and bonding, and an advances module for graduate students to teach name reactions.

Table 5.5 Subjects Addressed in Attached Modules

		Structure and Bonding		Functional Groups			Name Reaction		
Number of Subjects	Subject	Number of cards/ Points		Subject	Number of cards/ Points		Subject	Number of cards/ Points	
1	C $sp^3$ orbital	58	5	Acid Chloride	6	30	Michael Addition	14	15
2	C $sp^2$ orbital	40	5	Alcohol	32	10	Dess-Martin Oxidation	16	15
3	C $sp$ orbital	10	15	Aldehyde	13	20	Olefin Metathesis	14	15
4	C $\sigma$ bond	77	5	Alkene	34	10	Diels Alder Reaction	14	15
5	C $\pi$ bond	23	10	Alkyne	8	20	Heck Reaction	11	15
6	N $sp^3$ orbital	10	10	Amide	24	15	Friedal Crafts Alkylation	6	25
7	N $sp^2$ orbital	20	5	Amine	32	10	Wittig Reaction	23	10
8	N $sp$ orbital	9	15	Arene	48	5	Aldol Addition	17	15
9	N $\sigma$ bond	35	5	Carboxylic Acid	27	10	Aldol Condensation	16	15
10	N $\pi$ bond	21	10	Disulfide	7	25	Mitsunobu Reaction	16	15
11	O $sp^3$ orbital	30	5	Diphosphate	6	30	Birch Reduction	11	15
12	O $sp^2$ orbital	31	5	Ester	16	15	Claisen Rearrangement	14	15
13	O $\sigma$ bond	50	5	Ether	24	15	Dieckmann Condensation	8	20
14	O $\pi$ bond	30	10	Halide	14	15	Horner-Wadsworth-Emmons	13	15
15	S $sp^3$ orbital	7	15	Imine	9	25	Swern Oxidation	17	15
16	S $sp^2$ orbital	4	20	Ketone	13	20	Grignard Reaction	16	15



17	S $\sigma$ bond	11	10	Nitrile	11	20	Baeyer-Villiger Oxidation	7	20
18	S $\pi$ bond	4	20	Phosphate	12	20	Stille Coupling	10	20
19	Hal $\sigma$ bond	19	10	Sulfide	11	20	Williamson Ether Synthesis	16	15
20	B/Al $sp^2$ orbital	8	15	Sulfoxide	7	25	Jones Oxidation	16	15
21	B/Al $\sigma$ bond	8	15	Thioester	9	20	Fischer Esterification	6	25
22	Metal ionic bond	10	15	Thiol	10	20	Friedel Crafts Acylation	9	20
23							Wolff-Kishner Reduction	6	25
24							Hofmann Elimination	9	20
25							Claisen Condensation	9	20

The structure and bonding module used a nearly identical milieu as Functional groups with molecules being the solution cards. These were drawn with lone pairs as this module was envisioned to be utilized before Functional Groups where students are just becoming familiar with Lewis structures. There are 100 Solution cards just like the Function Groups module. The molecules chosen were common reagents, solvents, and other molecules of interest that may be discussed or used in an organic chemistry class. The problems focus on identifying the structural characteristics of the molecules like sigma and pi bonds, hybridization ( $sp^3$ ,  $sp^2$ ,  $sp$ ), and dipole moments. Overall there are 22 structure and bonding concepts addressed in the Problem deck, with Honors questions addressing dipole moments and bond polarity. All of these characteristics are present in a single molecule, thus allowing multiple answers for a single card exactly how the

Functional Groups cards were structured. Bonus cards dealt with the subject of formal charges, which would have to be reasoned from the cards' structures. Gameplay proceeds exactly as in the Functional Group module where a player has a hand of Solution cards, reveals a Problem card on their turn, and attempts to match the appropriate Problem and Solution cards, collecting Bonus cards where appropriate.

The Name Reaction module was envisioned to apply ChemKarta to graduate learning. Name reactions are a common introductory subject in graduate organic classes and must be learned to develop a base set of knowledge, similar to how functional groups are learned in undergraduate organic chemistry. The milieu chosen to address name reactions were notable synthetic routes to organic molecules which had the selected reactions in them. While the basic Problem cards looked for identification of the name reaction, Honors questions were then awarded if a player could correctly identify the synthetic route the displayed. Problem cards therefore provided an incentive for player to familiarize themselves with these syntheses in order to be more successful in the game. Bonus cards focused on the researchers who published the synthetic routes used, promoting students' knowledge of notable chemists and how they've applied name reactions in their work. Overall the Name Reaction module addresses 25 name reactions within the context of 16 different synthetic targets representing the works of 15 notable researchers.

Table 5.6 Name Reactions Module

	Researcher	Number of syntheses	Total cards	Synthetic target	Number of syntheses	Total cards
1	John Wood	1	5	Ingenol	2	10
2	Larry Overman	2	8	Alkaloid 251F	1	5
3	Jeff Aube	1	5	Quinine	1	4
4	Steven Welch	1	5	Prostaglandin F2a	1	4
5	Isao Kuwajima	1	5	Sarain A	1	4
6	David Evans	1	5	Morphine	2	10
7	E. J. Corey	2	14	Zaragonzic Acid	1	5
8	Barry Trost	1	5	Azadirachtin	1	10
9	Gilbert Stork	1	5	Gymnomoritol	2	9
10	Dale Boger	1	5	Fredericamycin A	1	5
11	Steven Ley	1	10	Bikavaren	1	4
12	Leo A Paquette	2	8	Retigeranic Acid	2	14
13	James D White	1	4	pupukeanone	1	4
14	Robert B Woodward	3	12	Illudinine	1	4
15	Derek Barton	1	4	Guanacastepone	1	4
16				Chlorophyll A	1	4
	15 Researchers	20 syntheses	100 cards	16 Targets	20 syntheses	100 cards

While in previous modules the Problem cards would ask to identify a named concept on a Solution card, this was not possible with name reactions since there was not enough room on a single card to draw multiple synthetic steps. Instead the matching scheme was swapped and the names of the name reactions were included on the Solution cards, while the Problem cards displayed a name reaction to be identified. Even though there was an inversion of the matching convention, the nature of the matching game was preserved and gameplay proceeded according to the previously described rules.

## 5.3 Conclusion

### 5.3.1 Conclusion

ChemKarta represents a fun and educational way to get students to interact with chemistry information. In general, students found the game simple to learn. However, it is not universally accepted by students and should only be used as a supplemental teaching tool rather than a basis for a teaching. ChemKarta exposed students to the wide amount of information present in chemistry subjects, resulting in increased awareness of the difficulty of the subject matter. The game demonstrated a modular design with its ability to have additional types of cards inserted or removed and to incorporate different subjects without modifying the core game structure. To the author's knowledge, this is the only example of a modular educational game in chemistry that can be adapted in this way.

### 5.3.2 Future Work

Several more sets of ChemKarta are being developed to continuously expand the game to address the material of a complete undergraduate organic chemistry course, as well as graduate level information. The information from each card set is being catalogued to produce a searchable data set from which examples, homework, quizzes and exams may be derived.

More comparative studies of this method versus traditional teaching techniques are still required to evaluate the overall performance of this game method as a learning tool. A larger dataset of students is necessary to accurately determine the effectiveness of ChemKarta. In

addition, there are logistical challenges in implementing such an interactive learning method in larger (>100 students) class sizes. It is envisioned that the use of teaching assistants running multiple sessions during a week would be required to address this need.

Development of an electronic version of ChemKarta has been highly desired by students in surveys. The use of an electronic version of ChemKarta that could be played on a smartphone-like device would possibly address the issues of access to the game, enabling student to play on their own time. However, there are concerns that electronic media used as an individual may not have the benefits of learning in a group setting. Development of an electronic application and its comparison to the effectiveness of the paper version are still being explored.

The current card sets are continuously being reevaluated and modified to address shortcoming in the card sets and more relevant examples as they are discovered. One notable issue with the Name Reactions module is the overrepresentation of white, male researchers. Refinement of the Name Reactions module should attempt to address this issue by including more women and people of color in the module.

## 5.4 Experimental

### 5.4.1 JCCC Evaluation Forms

Initial evaluation:

On the following scale indicate how much you agree with the following statements.

(0 = strongly disagree, 5= neutral, 10 = strongly agree)

**Q1** I know all of and can readily identify the organic chemistry functional groups.

0    1    2    3    4    5    6    7    8    9    10

**Q2** I am familiar with medically, commercially, or historically important organic molecules.

0    1    2    3    4    5    6    7    8    9    10

**Q3** I think learning organic chemistry functional groups will be difficult.

0    1    2    3    4    5    6    7    8    9    10

**Q4** I am interested in learning organic chemistry.

0    1    2    3    4    5    6    7    8    9    10

What methods have you used for studying chemistry before?

Final evaluation:

On the following scale indicate how much you agree with the following statements.

(0 = strongly disagree, 5= neutral, 10 = strongly agree)

**Q1** I can readily identify the organic chemistry functional groups.

0 1 2 3 4 5 6 7 8 9 10

**Q2** I am familiar with medically, commercially, or historically important organic molecules.

0 1 2 3 4 5 6 7 8 9 10

**Q3** I am interested in learning organic chemistry.

0 1 2 3 4 5 6 7 8 9 10

**Q4** The ChemKarta game was effective in helping me learn functional groups.

0 1 2 3 4 5 6 7 8 9 10

**Q5** The ChemKarta game was easy to learn to play.

0 1 2 3 4 5 6 7 8 9 10

**Q6** The ChemKarta game was fun to play

0 1 2 3 4 5 6 7 8 9 10

**Q7** I would prefer studying via ChemKarta instead of flash cards.

0 1 2 3 4 5 6 7 8 9 10

**Q8** I would like to have ChemKarta sets for additional subjects in organic chemistry.

0 1 2 3 4 5 6 7 8 9 10

**Q9** I would prefer ChemKarta as an electronic app I could play on my own as opposed to a card game I would play with other students.

0 1 2 3 4 5 6 7 8 9 10

Are there any molecules you found of particular interest? If possible, list their names, use, and any functional groups present.

Any additional comments?

#### 5.4.2 JCCC Survey Results

##### Initial

<b>Q1</b>	4	7	1	4	3	6	3	5	6	3	4	6	0	0	0	7	5	6	0	4	6	2	4
<b>Q2</b>	7	3	0	7	0	3	4	4	3	4	2	4	0	4	0	3	6	8	0	4	3	4	3
<b>Q3</b>	0	6	7	2	5	8	9	5	2	6	8	3	0	3	4	5	6	3	5	10	2	9	4
<b>Q4</b>	10	5	9	10	10	8	5	7	7	9	8	8	10	10	5	10	8	10	8	10	10	3	6

##### Final

<b>Q1</b>	4	4	5	6	9	2	0	3	3	3	8	6	5	7	5	7	5	6	3	7	8	7	7
<b>Q2</b>	4	4	0	4	8	3	0	4	4	8	8	7	1	5	7	6	2	4	0	4	4	5	3
<b>Q3</b>	6	10	10	2	10	10	10	6	5	5	10	10	7	6	9	9	8	7	10	7	7	8	6
<b>Q4</b>	7	4	10	6	10	5	0	3	6	6	8	8	8	6	2	8	7	6	10	9	9	8	7
<b>Q5</b>	6	7	10	8	10	4	10	6	8	7	10	8	5	9	9	8	9	7	10	9	10	8	7
<b>Q6</b>	8	4	10	7	10	3	0	6	8	10	10	8	4	7	5	8	6	5	5	9	8	6	5
<b>Q7</b>	9	3	8	5	7	6	5	6	6	10	10	8	5	8	0	9	9	8	7	9	7	8	3
<b>Q8</b>	8	5	10	5	10	5	5	6	8	10	10	8	8	7	4	9	9	4	5	9	6	7	5
<b>Q9</b>	7	10	5	10	8	5	10	5	4	10	10	10	10	10	10	8	5	7	10	9	8	10	5



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## 6. CONCLUSION

The field of chemistry challenges its practitioners both in its application and communication of results. In synthesis, chemists attempt to apply the wide array of chemical reactions available to discover routes through which their starting materials can be transformed into their target molecules. Although there are many reactions and routes to choose from not all of them are applicable to each starting material. The process of research often ends in a few successes after a multitude of failures, however the information gathered from these failures is often as important as from successes. After the challenge of performing research, there comes the challenge of presenting and articulating the information not just to colleagues, but also to the professionals in other fields, the general public, and upcoming students seeking to further their education. After all, the word ‘doctor’ in Latin means ‘teacher,’ denoting not only a learned person but also one who passes on their knowledge. In this work we have studied the use of BAs as scaffold for constructing new molecular architectures as a demonstration of aptitude in chemical research and investigated the use of games for teaching undergraduate organic chemistry as a demonstration of introducing chemistry topics to students.

The functionalization of BAs often requires unique reaction conditions due to the steric environment of the steroid skeleton. This results in chemically distinct hydroxyl groups with varying degrees of reactivity. Their relative reactivity is distinct enough that selective functionalization of the alcohols can be achieved via esterification, carbonylation, silylation, and sulfonylation. In the case of sulfonylation, we’ve demonstrated the installation of a new functionality, the vinyl sulfonate ester, to the CDCA scaffold as a linker for forming new BA dimers. The reported literature methods for forming sulfonate esters from the sulfonyl chloride were not successful and a new method using pyridine diluted in dichloromethane was developed.

While a single pot desilylation-oxa-Michael reaction was expected to yield the desired dimer, this was not observed, although the dimer was detected by MS from a sample of the monomer, indicating that alkoxide generation not cyclization was the inhibiting factor. From this information refluxing the vinyl sulfonate ester in aqueous potassium carbonate was attempted to generate the desired alkoxide and oxa-Michael dimer.

The Yamaguchi esterification is a mild esterification procedure which has been shown to couple carboxylic acids to the CDCA scaffold. Exploration of the reactivity of CDCA and cholic acid towards Yamaguchi esterification showed that mono-, di-, and trimer of primary carboxylic acids can be achieved at room temperature simply by varying the ratios of the reagents. However, in the case of benzoic acids, only the least sterically hindered  $3\alpha$  position can be accessed at room temperature, while esterifying the  $7\alpha$  position required refluxing in toluene. This allowed for sequential functionalization of CDCA with 4-iodobenzoic acid and terminal alkynyl carboxylic acids to produce monomers designed for Sonogashira coupling to steroidal macrocycles. Sonogashira coupling was carried out between  $3\alpha$  substituted CDCA derivatives and it was found that an extended period of time (72 h) was required for completion of the reaction.

Building on previous work a strategy to use Sonogashira coupling to link functionalized CDCA macrocycles was developed. This employed previous methylation and carbonylation reactions to protect the carboxylic acid and  $3\alpha$  alcohol respectively, followed by functionalization at the  $7\alpha$  position by Yamaguchi esterification. As described previous, primary carboxylic acids gave high yields at room temperature, but 4-iodobenzoic acid required refluxing in toluene to proceed. Deprotection by refluxing in aqueous potassium carbonate yielded the  $7\alpha$  monoesters which were then cyclized into CDCA-based cyclotrimers via Yamaguchi

esterification. Employing the previous methods for Sonogashira coupling gave no results, however a change in solvent from THF to DMF gave the expected barrel-like structures in moderate yields.

In the case of ChemKarta, the card game has been further evaluated and expanded upon after its initial card set. Work with Dr Faith Johnson of JCCC further enforced that students found the game easy to learn and relatively enjoyable to play. Evaluation of student's perception of organic chemistry was performed before and after playing 5 sessions of ChemKarta over a week period. The evaluations demonstrated that after playing students became more confident in their ability to identify functional groups. At the same time there was no change in their familiarity with the material and they had an increase in their perceived difficulty of organic chemistry. This is evidence that ChemKarta alone is better as a supplement, not a replacement for traditional teaching techniques and careful implementation needs to be taken when introducing students to ChemKarta as the large card set can overwhelm student and give them a negative perception of the subject matter.

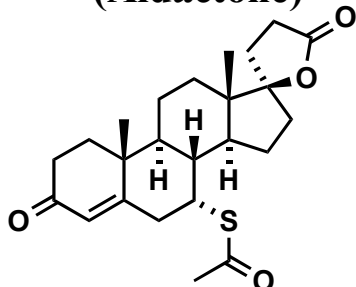
One of the main aspects of ChemKarta's design is that it was envisioned as a game system that can be adapted to teach multiple subjects. This can be by either adding cards to expand the current set, or developing new decks which utilize the same rules. While teachers can modify the cards in a single card set, by swapping new Problem/Solution/Bonus cards in and out, the development of new Technique and Victory cards adds new elements to the game to keep more experienced students engaged. Furthermore, the core gameplay can be utilized to develop modules to teach different subjects without substantial change. Here two addition modules were shown which utilize the same rules as the Functional Groups module: Structure and Bonding and

Name Reactions. These use ChemKarta's same matching system with new decks of over 200 cards in each module.

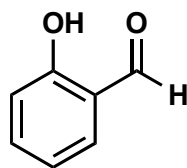
APPENDIX CHEMKARTA CARDSETS

Appendix A. Functional Groups

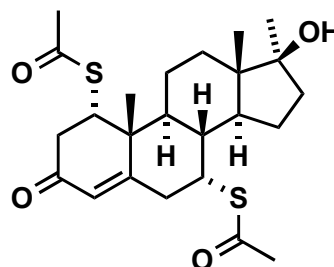
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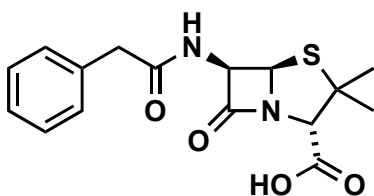
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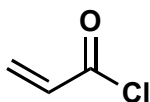
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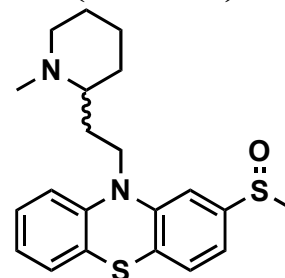
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(Penicillin G)**



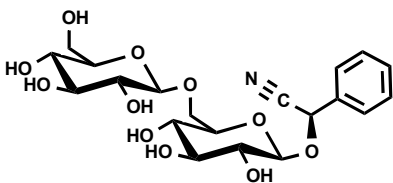
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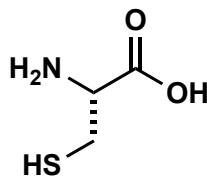
**Mesoridazine  
(Serentil)**



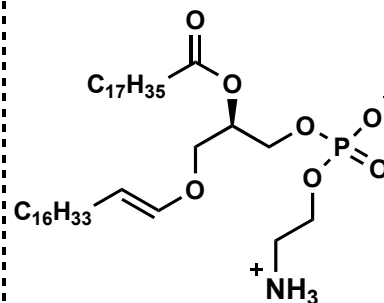
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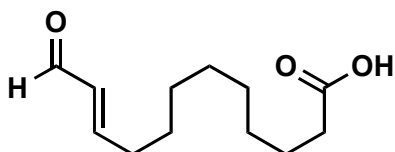
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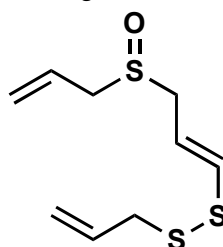
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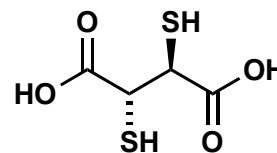
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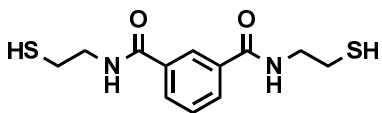
**Ajoene**



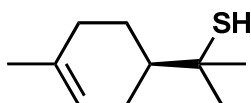
**Dimercaptosuccinic  
Acid**



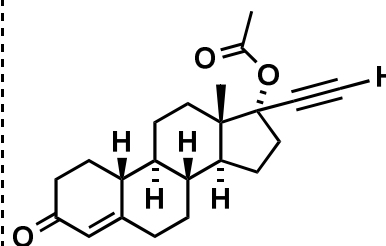
**BDTH2  
(OSR#1)**



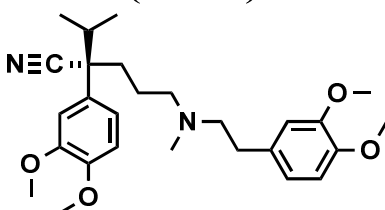
**Grapefruit  
Mercaptan**



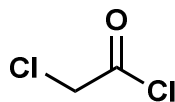
**Norethisterone  
Acetate  
(Aygestin)**



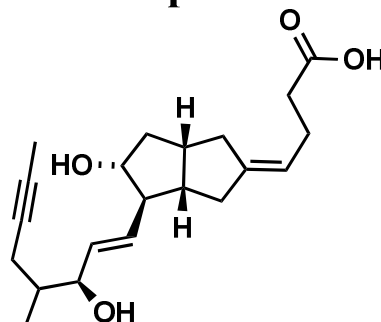
**Verapamil  
(Calan)**



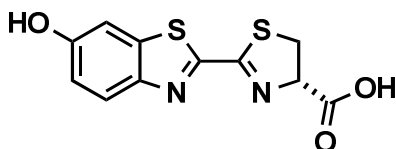
**Chloroacetyl  
Chloride**



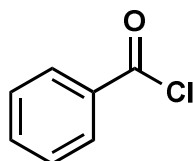
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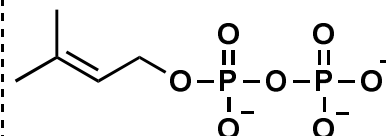
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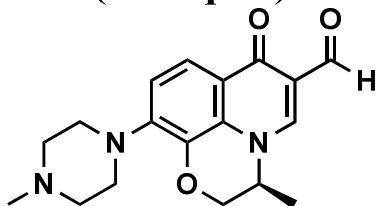
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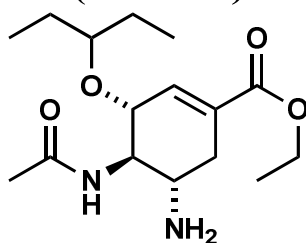
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Pyrophosphate  
(DMAPP)**



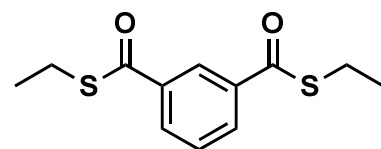
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**Oseltamivir  
(Tamiflu)**



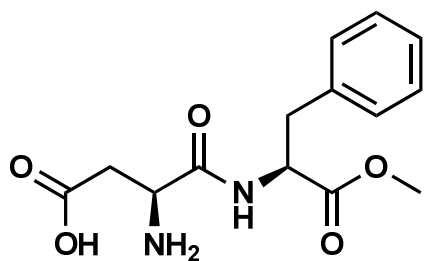
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(Etisul)**



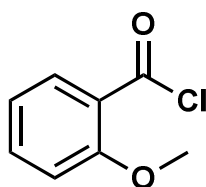




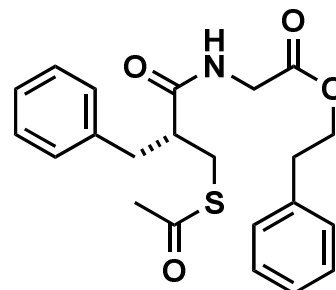
**Aspartame  
(NutriSweet)**



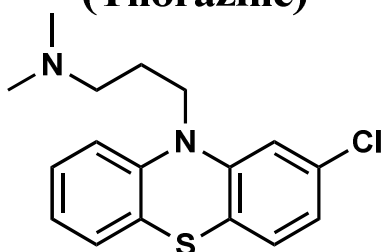
***o*-Anisoyl Chloride**



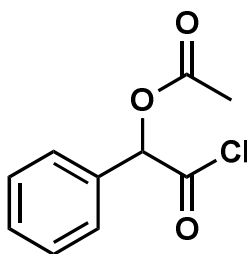
**Racecadotril  
(Tiorfan)**



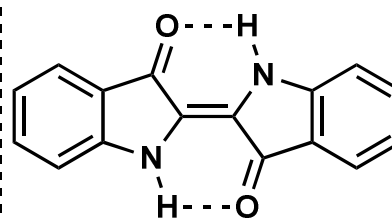
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(Thorazine)**



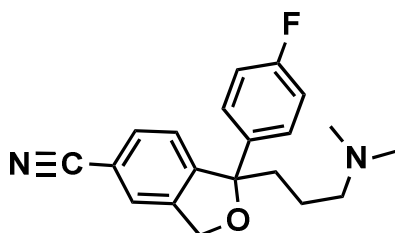
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Acid Chloride**



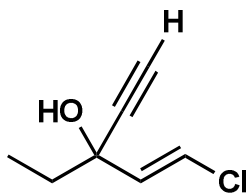
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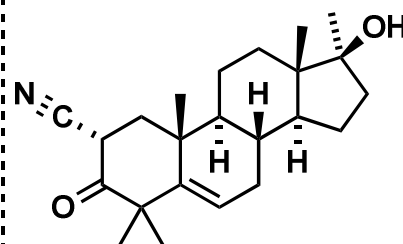
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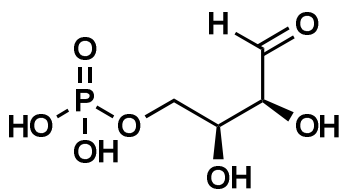
**Ethchlorvynol  
(Placidyl)**



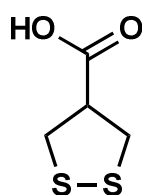
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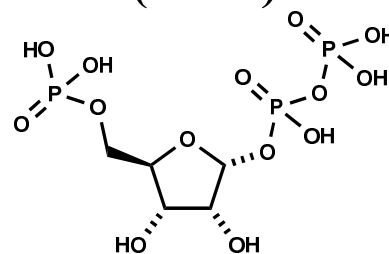
**Erythrose  
4-Phosphate**



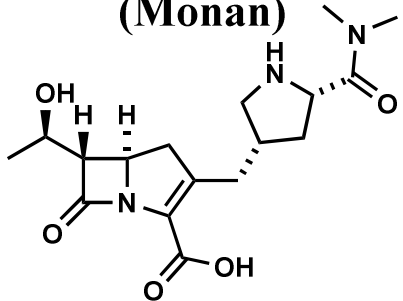
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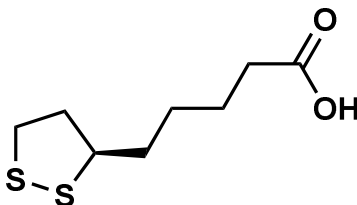
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Pyrophosphate  
(PRPP)**



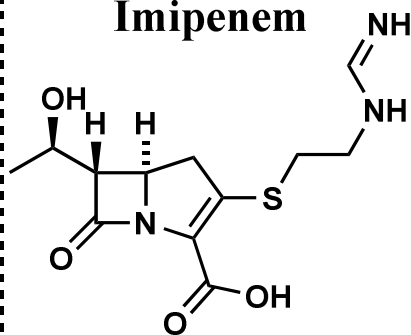
**Meropenem  
(Monan)**



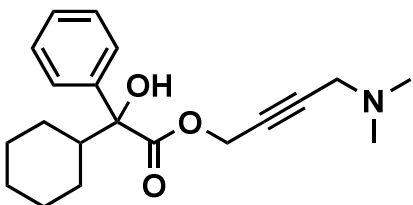
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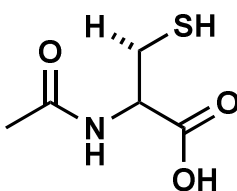
**Imipenem**



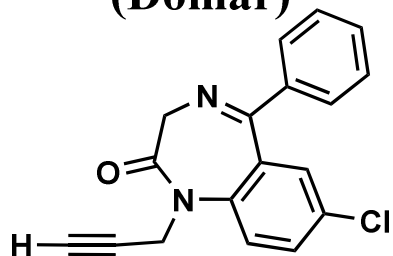
**Oxybutynin  
(Ditropan)**



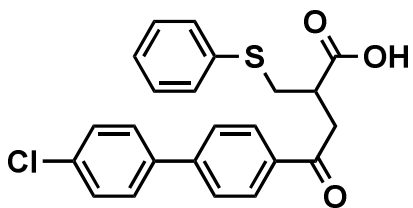
**Acetylcysteine**



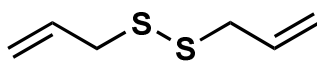
**Pinazepam  
(Domar)**



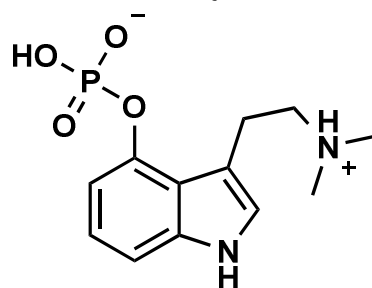
**Tanomastat**



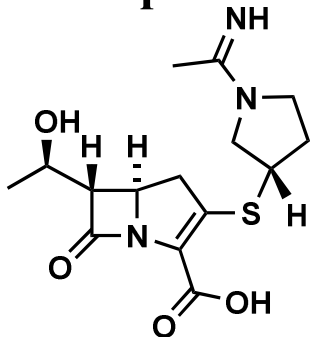
**Diallyl Disulfide**



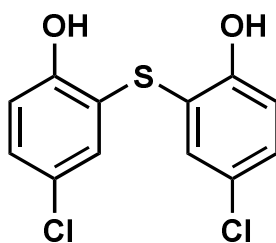
**Psilocybin**



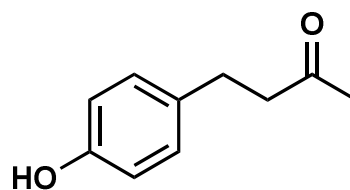
**Panipenem**



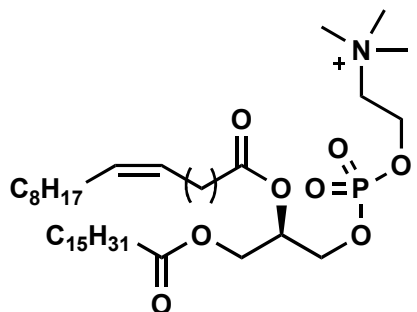
**Fenticlor**



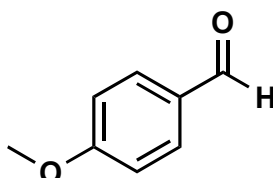
**Raspberry Ketone**



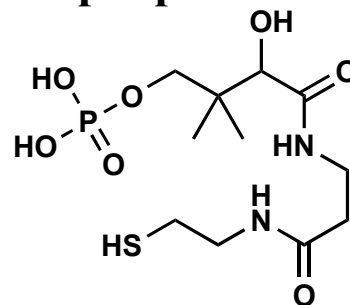
**Phosphatidylcholine**



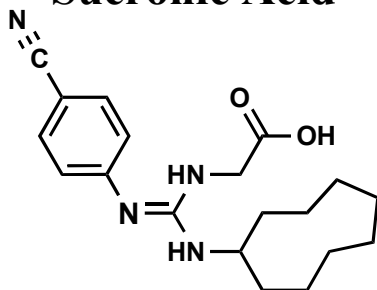
***p*-Anisaldehyde**



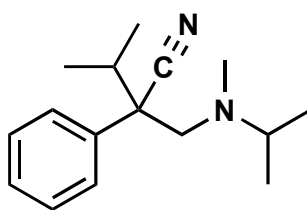
**Phosphopantetheine**



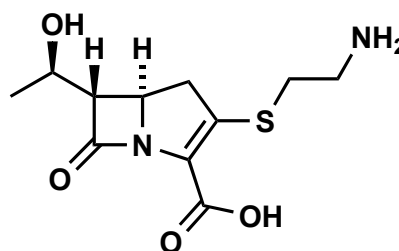
**Sucronic Acid**



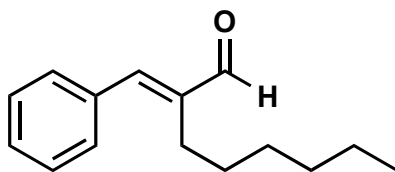
**Isoaminile  
(Pericon)**



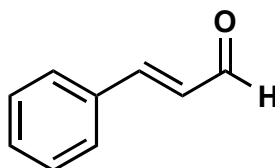
**Thienamycin**



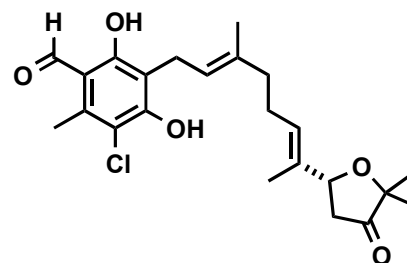
**Hexyl  
Cinnamaldehyde**



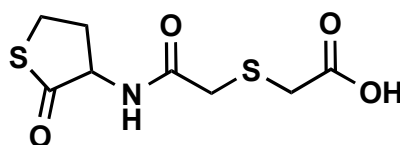
**Cinnamaldehyde**



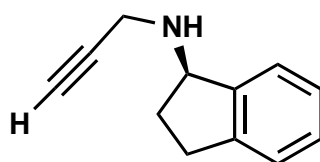
**Ascofuranone**



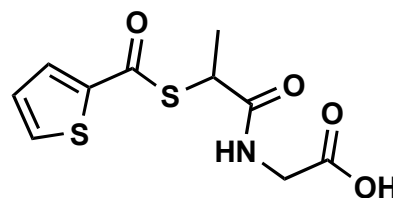
**Erdosteine**



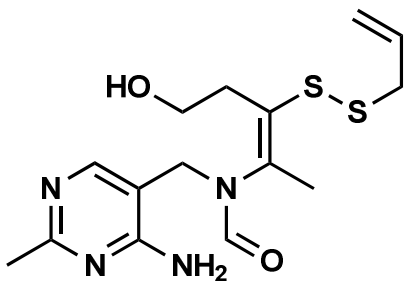
**Rasagiline  
(Azilect)**



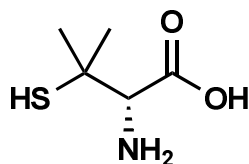
**Stepronin**



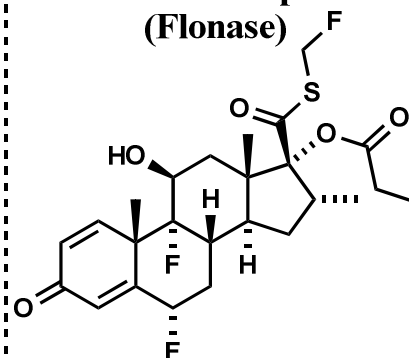
**Allithamine**



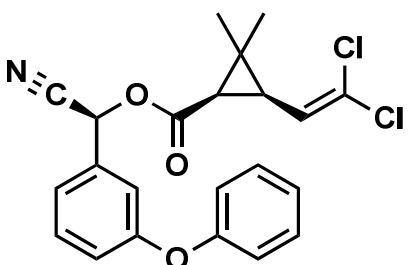
**Penicillamine**



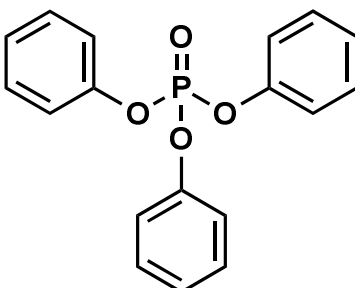
**Fluticasone Propionate (Flonase)**



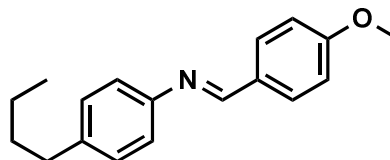
**Cypermethrin**



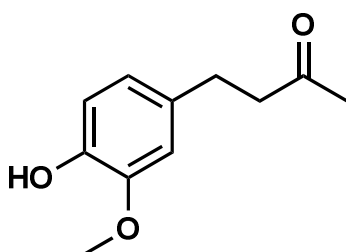
**Triphenyl Phosphate**



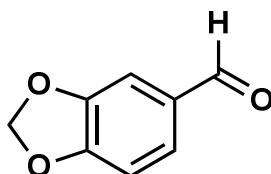
**MBBA**



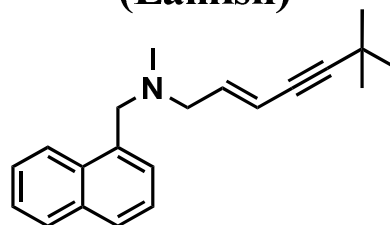
**Zingerone**



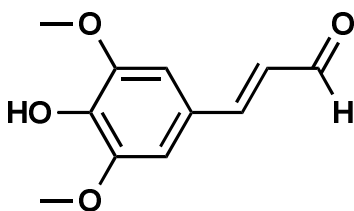
**Piperonal (Heliotropin)**



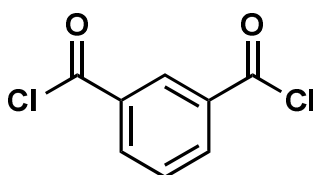
**Terbinafine (Lamisil)**



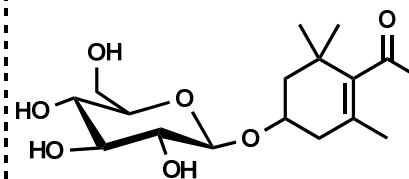
**Sinapaldehyde**



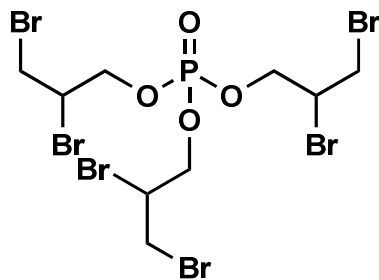
**Terephthaloyl Chloride**



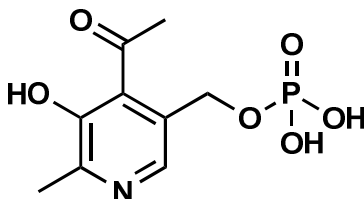
**Picrocrocin**



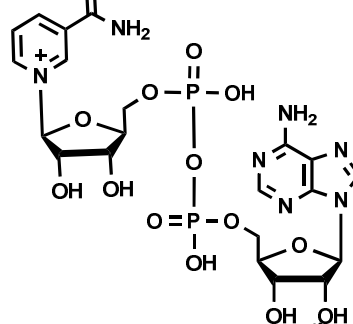
**Tris**



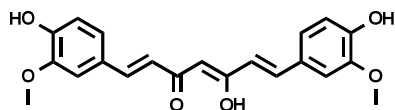
**Pyridoxal Phosphate (P5P)**



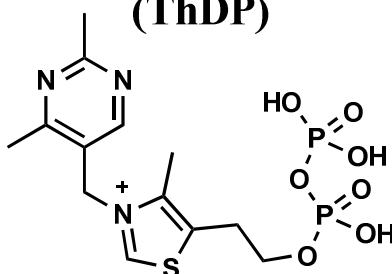
**NADH**



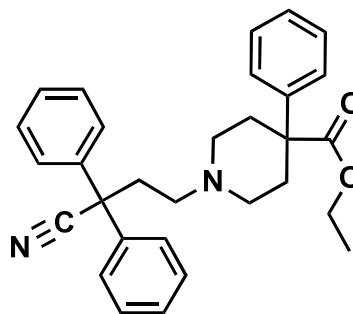
**Curcumin**



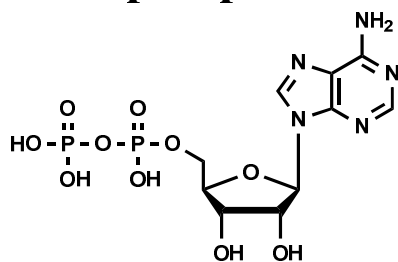
**Thiamine Diphosphate (ThDP)**



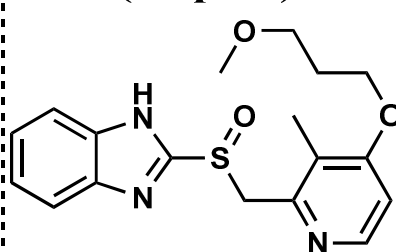
**Diphenoxylate**



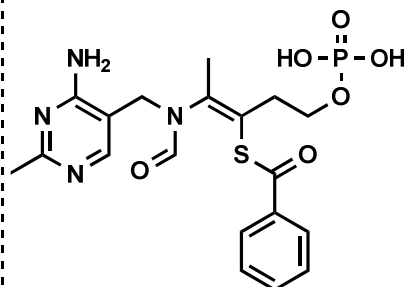
**Adenosine Diphosphate**



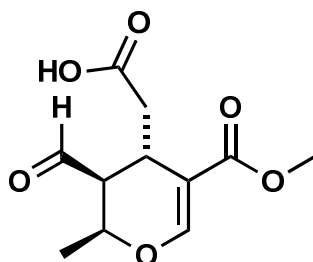
**Rabeprazole (Aciphex)**



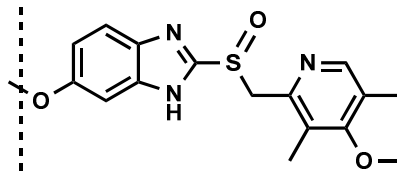
**Benfotiamine**



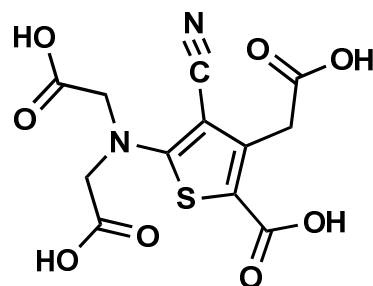
**Elenolic Acid**



**Esomeprazole (Nexium)**



**Ranelic Acid**





Problem

**Alkene**

**10**

Problem

**Alkene**

**10**

Problem

**Aldehyde**

**15**

Problem

**Aldehyde**

**15**

Problem

**Ketone**

**15**

Problem

**Ketone**

**15**

Problem

**Arene**

**5**

Problem

**Arene**

**5**

Problem

**Acid Chloride**

**25**



Problem <b>Alkyne</b> <b>15</b> <b>20</b> <b>Terminal or</b> <b>Internal</b> <b>Alkyne Honors</b>	Problem <b>Alkyne</b> <b>15</b> <b>20</b> <b>Terminal or</b> <b>Internal</b> <b>Alkyne Honors</b>	Problem <b>Halide</b> <b>15</b>
Problem <b>Halide</b> <b>15</b>	Problem <b>Amine</b> <b>5</b> <b>10</b> <b>1° 2° 3° or</b> <b>quaternary?</b> <b>Amine Honors</b>	Problem <b>Amine</b> <b>5</b> <b>10</b> <b>1° 2° 3° or</b> <b>quaternary?</b> <b>Amine Honors</b>
Problem <b>Imine</b> <b>20</b>	Problem <b>Imine</b> <b>5</b>	Problem <b>Acid Chloride</b> <b>25</b>

Problem <b>Alkyne</b> <b>15</b> <b>20</b> <b>Terminal or Internal</b> <b>Alkyne Honors</b>	Problem <b>Alkyne</b> <b>15</b> <b>20</b> <b>Terminal or Internal</b> <b>Alkyne Honors</b>	Problem <b>Nitrile</b> <b>15</b>
Problem <b>Nitrile</b> <b>15</b>	Problem <b>Amide</b> <b>10</b> <b>15</b> <b>Cyclic or Linear?</b> <b>Amide Honors</b>	Problem <b>Amide</b> <b>10</b> <b>15</b> <b>Cyclic or Linear?</b> <b>Amide Honors</b>
Problem <b>Carboxylic Acid</b> <b>10</b>	Problem <b>Carboxylic Acid</b> <b>10</b>	Problem <b>Ester</b> <b>10</b> <b>15</b> <b>Cyclic or Linear?</b> <b>Ester Honors</b>

Problem <b>Alcohol</b> <b>5</b> <b>10</b> 1° 2° 3° or aryl Alcohol Honors	Problem <b>Alcohol</b> <b>5</b> <b>10</b> 1° 2° 3° or aryl Alcohol Honors	Problem <b>Disulfide</b> <b>20</b>
Problem <b>Disulfide</b> <b>20</b>	Problem <b>Ether</b> <b>5</b> <b>10</b> Cyclic or Linear? Ether Honors	Problem <b>Ether</b> <b>5</b> <b>15</b> Cyclic or Linear? Ether Honors
Problem <b>Diphosphate</b> <b>25</b>	Problem <b>Diphosphate</b> <b>25</b>	Problem <b>Ester</b> <b>10</b> <b>15</b> Cyclic or Linear? Ester Honors

Problem <b>Thiol</b> <b>15</b> <b>20</b> Iyr jo or aryl I 2 3 0 I	Problem <b>Thiol</b> <b>15</b> <b>20</b> Iyr jo or aryl I 2 3 0 I	Problem <b>Thioester</b> <b>20</b>
Thiol Honors	Thiol Honors	
Problem <b>Thioester</b> <b>20</b>	Problem <b>Sulfide</b> <b>10</b> <b>15</b> Cyclic or Linear? Sulfide Honors	Problem <b>Sulfide</b> <b>10</b> <b>15</b> Cyclic or Linear? Sulfide Honors
Problem <b>Phosphate</b> <b>15</b>	Problem <b>Phosphate</b> <b>15</b>	<b>Special Problem</b> <b>Complete Solution</b> Name all the functional groups on any 1 <b>Solution</b> card. 10 pts for each correctly named functional group.

Special Problem

Special Problem

Special Problem

**Complete Solution**

Name all the functional groups on any 1 **Solution** card. 10 pts for each correctly named functional group.

**10**

**20**

**30**

**40**

**Complete Solution**

Name all the functional groups on any 1 **Solution** card. 10 pts for each correctly named functional group.

**10**

**20**

**30**

**40**

**Complete Solution**

Name all the functional groups on any 1 **Solution** card. 10 pts for each correctly named functional group.

**10**

**20**

**30**

**40**

Problem

Problem

Problem

Problem

Problem

Problem

Bonus

**Furan**

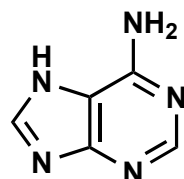
**+10**



Bonus

**Adenine**

**+10**

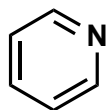


Bonus

Bonus

**Pyridine**

**+10**



Bonus

**Thiofuran**

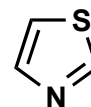
**+10**



Bonus

**Thiazole**

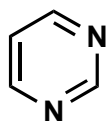
**+10**



Bonus

**Pyrimidine**

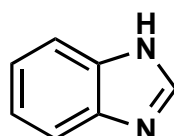
**+10**



Bonus

**Benzimidazole**

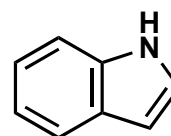
**+10**



Bonus

**Indole**

**+10**



Appendix B. Functional Groups Victory and Technique Cards

<p style="text-align: center;"><b>Victory</b></p> <p><b>Complete Solution</b></p> <p>Reveal the top 3 cards from the <b>Solution</b> deck. Choose 2 of them. Identify all functional groups on those 2 cards.</p> <p>Only reveal if you have 100 or more points.</p>	<p style="text-align: center;"><b>Victory</b></p> <p><b>Auto-Win</b></p> <p>You automatically win the game</p> <p>Only reveal if you have 100 or more points.</p>	<p style="text-align: center;"><b>Victory</b></p> <p><b>Multiple Solutions</b></p> <p>Reveal the top 6 cards from the <b>Solution</b> deck. Identify a different functional group on each card.</p> <p>Only reveal if you have 100 or more points.</p>
<p style="text-align: center;"><b>Victory</b></p> <p><b>Complete Solution</b></p> <p>Reveal the top 3 cards from the <b>Solution</b> deck. Choose 2 of them. Identify all functional groups on those 2 cards.</p> <p>Only reveal if you have 100 or more points.</p>	<p style="text-align: center;"><b>Victory</b></p> <p><b>Fill in the Blanks</b></p> <p>On each <b>Solution</b> card you have scored with, identify a functional group other than the one on the matching <b>Problem</b>. You must identify a different functional group each time if possible.</p> <p>Only reveal if you have 100 or more points.</p>	<p style="text-align: center;"><b>Victory</b></p> <p><b>200 Points</b></p> <p>Continue playing as normal. You win when you reach 200 points (you may win on another player's turn).</p> <p>Only reveal if you have 100 or more points.</p>
<p style="text-align: center;"><b>Victory</b></p> <p><b>Multiple Solutions</b></p> <p>Reveal the top 6 cards from the <b>Solution</b> deck. Identify a different functional group on each card.</p> <p>Only reveal if you have 100 or more points.</p>	<p style="text-align: center;"><b>Victory</b></p> <p><b>Fill in the Blanks</b></p> <p>On each <b>Solution</b> card you have scored with, identify a functional group other than the one on the matching <b>Problem</b>. You must identify a different functional group each time if possible.</p> <p>Only reveal if you have 100 or more points.</p>	

## Technique

### Hydrogenation

Prevent any 1 Player from answering a **Problem** that has a double or triple bond. That player discards his/her **Solution** and cannot attempt another answer.

Play on another Player's turn

## Technique

### Hydrogenation

Prevent any 1 Player from answering a **Problem** that has a double or triple bond. That player discards his/her **Solution** and cannot attempt another answer.

Play on another Player's turn

## Technique

### Hydrogenation

Prevent any 1 Player from answering a **Problem** that has a double or triple bond. That player discards his/her **Solution** and cannot attempt another answer.

Play on another Player's turn

## Technique

### Oxidation

Prevent any 1 Player from answering an Alcohol, Amine, or Thiol **Problem**. That player discards his/her **Solution** and cannot attempt another answer.

Play on another Player's turn

## Technique

### Oxidation

Prevent any 1 Player from answering an Alcohol, Amine, or Thiol **Problem**. That player discards his/her **Solution** and cannot attempt another answer.

Play on another Player's turn

## Technique

### Oxidation

Prevent any 1 Player from answering an Alcohol, Amine, or Thiol **Problem**. That player discards his/her **Solution** and cannot attempt another answer.

Play on another Player's turn

## Technique

### Diversification

Reveal the top 5 cards of the **Problem** deck. Choose 1 of those cards to answer and discard the rest.

Play on your turn before a **Problem** is revealed.

## Technique

### Diversification

Reveal the top 5 cards of the **Problem** deck. Choose 1 of those cards to answer and discard the rest.

Play on your turn before a **Problem** is revealed.

## Technique

### Diversification

Reveal the top 5 cards of the **Problem** deck. Choose 1 of those cards to answer and discard the rest.

Play on your turn before a **Problem** is revealed.



## Technique

### Hydrogenation

Prevent any 1 Player from answering a **Problem** that has a double or triple bond. That player discards his/her **Solution** and cannot attempt another answer.

Play on another Player's turn

## Technique

### Synthesis

Reveal the top 3 cards of the **Solutions** deck and put two of those cards into your hand. Discard the rest.

Play on your turn

## Technique

### Synthesis

Reveal the top 3 cards of the **Solutions** deck and put two of those cards into your hand. Discard the rest.

Play on your turn

## Technique

### Oxidation

Prevent any 1 Player from answering an Alcohol, Amine, or Thiol **Problem**. That player discards his/her **Solution** and cannot attempt another answer.

Play on another Player's turn

## Technique

### Synthesis

Reveal the top 3 cards of the **Solutions** deck and put two of those cards into your hand. Discard the rest.

Play on your turn

## Technique

### Synthesis

Reveal the top 3 cards of the **Solutions** deck and put two of those cards into your hand. Discard the rest.

Play on your turn

## Technique

### Diversification

Reveal the top 5 cards of the **Problem** deck. Choose 1 of those cards to answer and discard the rest.

Play on your turn before a **Problem** is revealed.

## Technique

### Diversification

Reveal the top 5 cards of the **Problem** deck. Choose 1 of those cards to answer and discard the rest.

Play on your turn before a **Problem** is revealed.

## Technique

### Synthesis

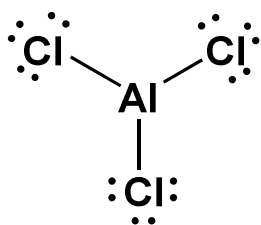
Reveal the top 3 cards of the **Solutions** deck and put two of those cards into your hand. Discard the rest.

Play on your turn

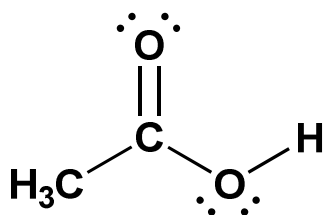
6.5.3

Appendix C. Structure and Bonding

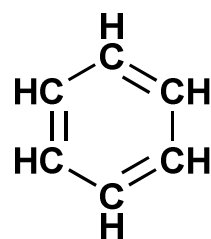
**Aluminum Trichloride**



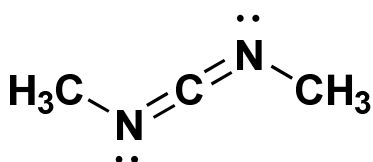
**Acetic Acid**



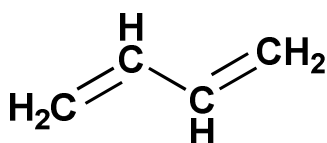
**Benzene**



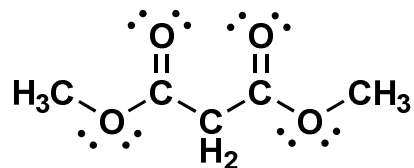
**Dimethyl Carbodimide**



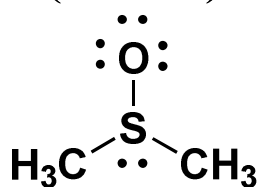
**Butadiene**



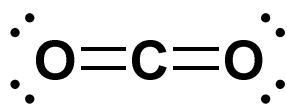
**Dimethyl Malonate**



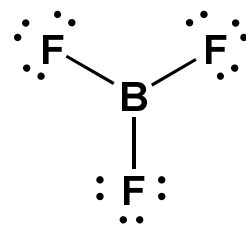
**Dimethylsulfoxide (DMSO)**



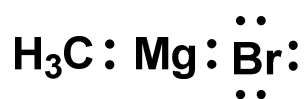
**Carbon Dioxide**



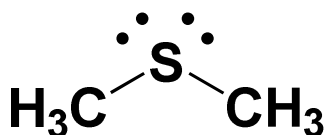
**Boron Trifluoride**



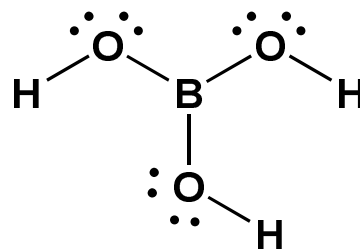
**Methyl Magnesium Bromide**



**Dimethyl Sulfide**



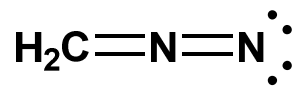
**Boric Acid**



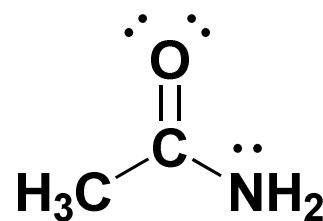
**Methyl Lithium**



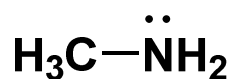
**Diazomethane**



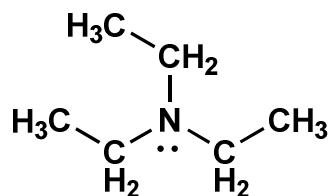
**Acetamide**



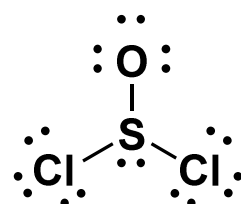
**Methylamine**



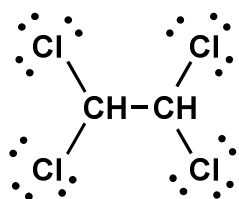
**Triethylamine**



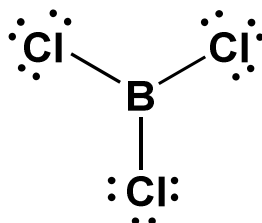
**Thionyl Chloride**



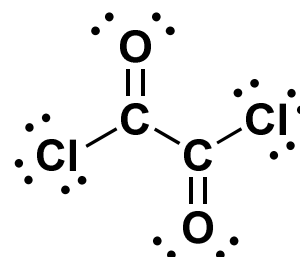
**Tetrachloroethylene**



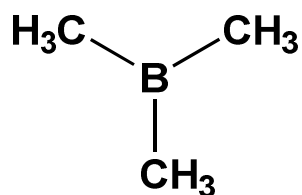
**Boron Trichloride**



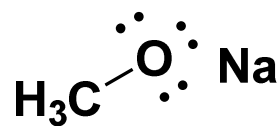
**Oxalyl Chloride**



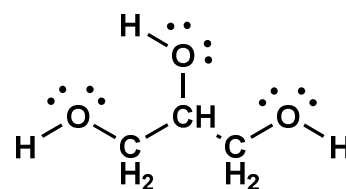
**Trimethylborane**



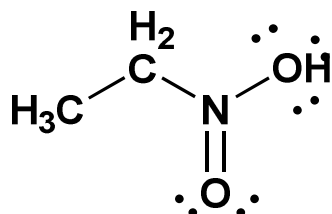
**Sodium Methoxide**



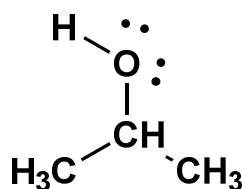
**Glycerine**



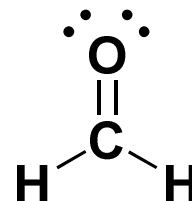
**Nitroethane**



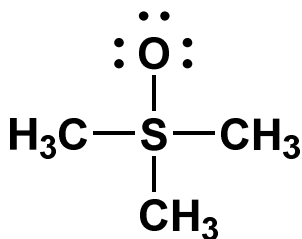
**Isopropyl Alcohol**



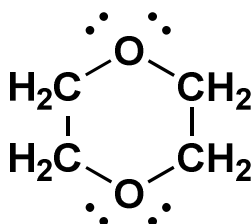
**Formaldehyde**



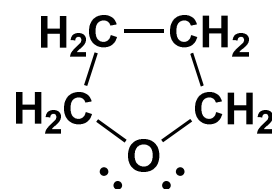
**Trimethyl-  
oxasulfonium**



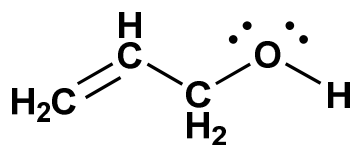
**Dioxane**



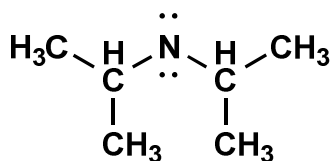
**Tetrahydrofuran  
(THF)**



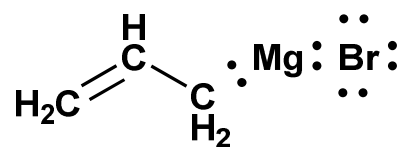
**Allyl Alcohol**



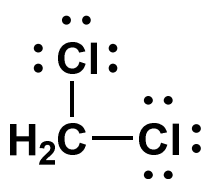
**Lithium Diisopropyl  
Amine (LDA)**



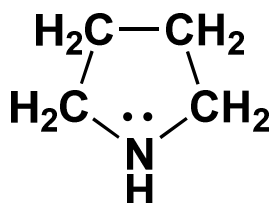
**Vinyl Magnesium  
Bromide**



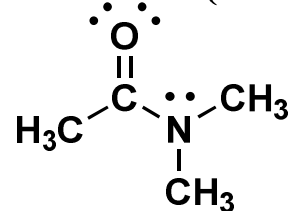
**Dichloromethane  
(DCM)**



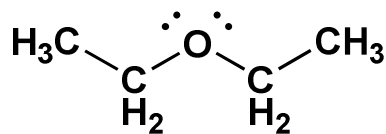
**Pyrrolidine**



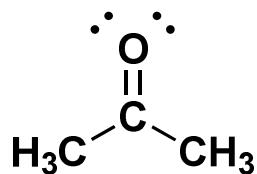
**N,N-Dimethyl  
Formamide (DMF)**



**Diethyl Ether**



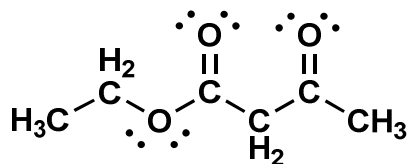
**Acetone**



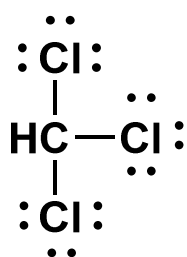
**Methyl Isocyanide**



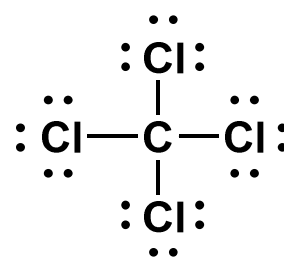
**Ethyl Acetoacetate**



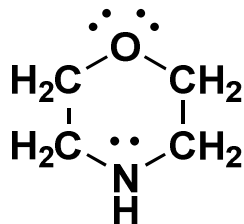
**Chloroform**



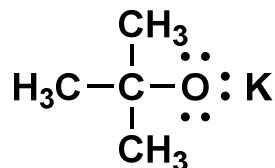
**Carbon Tetrachloride**



**Morpholine**



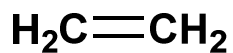
**Potassium  
t-Butoxide**



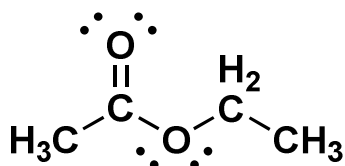
**Acetylene**



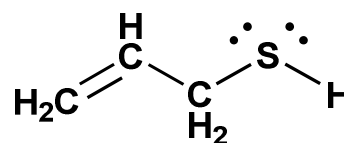
**Ethylene**



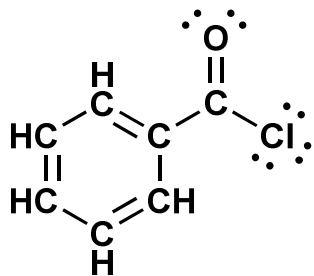
**Ethyl Acetate**



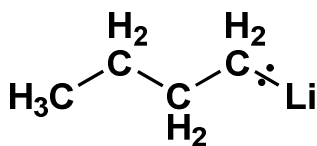
**Allyl Mercaptan**



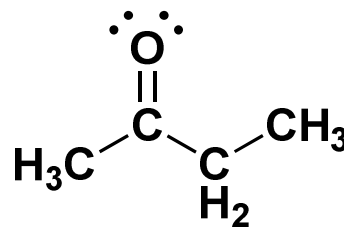
**Benzoyl Chloride**



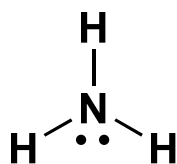
**n-Butyl Lithium**



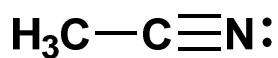
**Methyl Ethyl Ketone**



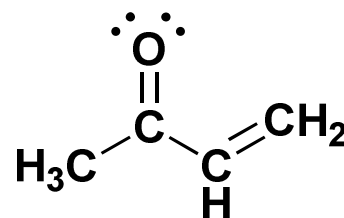
**Ammonia**



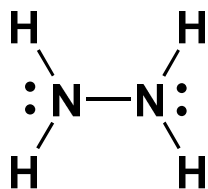
**Acetonitrile**



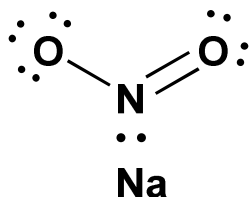
**Methyl Vinyl Ketone**



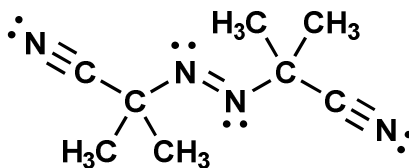
**Hydrazine**



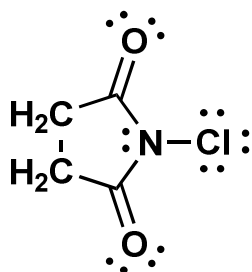
**Sodium Nitrite**



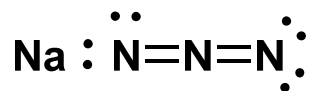
**AIBN**



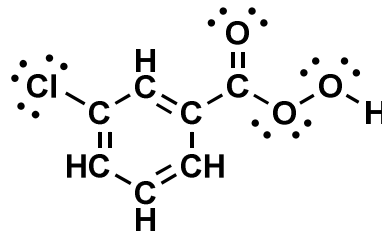
**N-Chloro Succinimide**



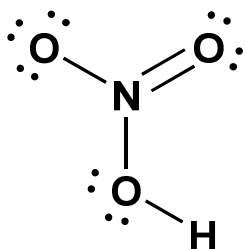
**Sodium Azide**



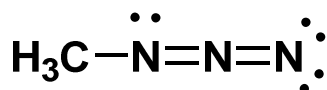
***m*-Chloro Peroxybenzoic Acid (mCBPA)**



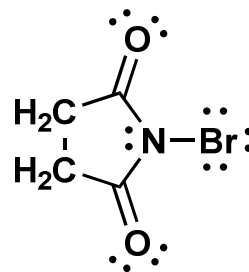
**Nitric Acid**



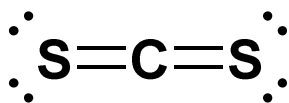
**Methyl Azide**



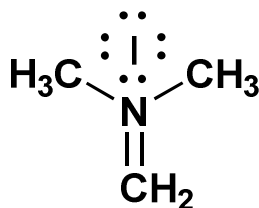
**N-Bromo Succinimide**



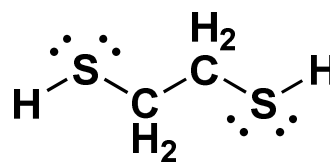
**Carbon Disulfide**



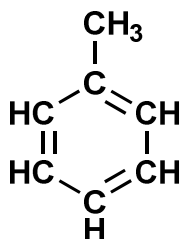
**Eshenmosher's Salt**



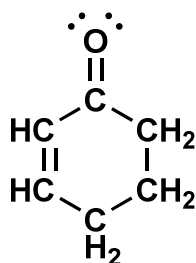
**Dimercaptoethane**



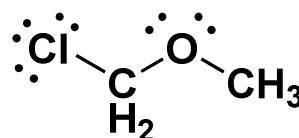
**Toluene**



**Cyclohexenone**



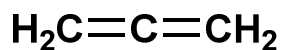
**Chloromethyl Methyl Ether (MOMCl)**



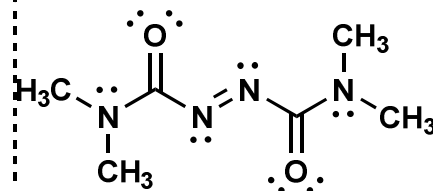
**Sodium Amide**



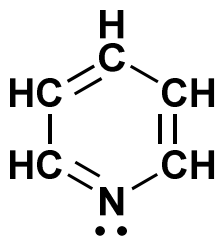
**Allene**



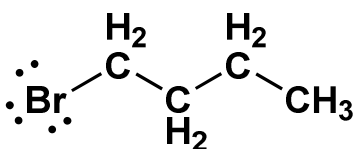
**Tetramethylazo-dicarboxamide (TMAD)**



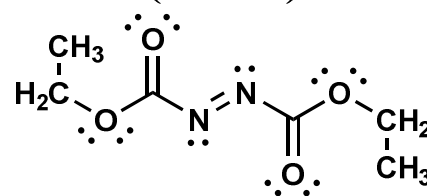
**Pyridine**



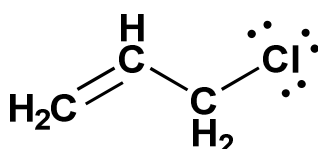
**1-Bromobutane**



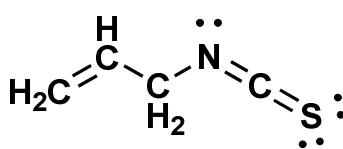
**Diethylazo-dicarboxamide (DEAD)**



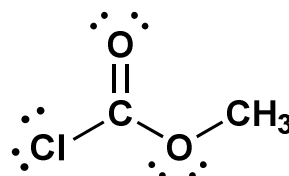
**Vinyl Chloride**



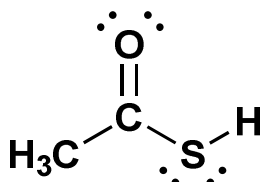
**Allyl Isothiocyanate**



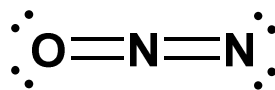
**Methylchloroformate**



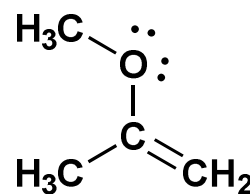
**Thioacetic Acid**



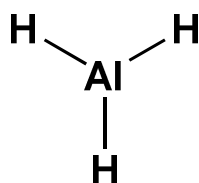
**Nitrous Oxide**



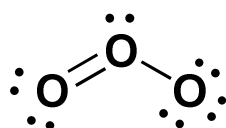
**2-Methoxypropene**



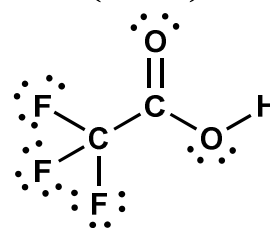
**Alane**



**Ozone**

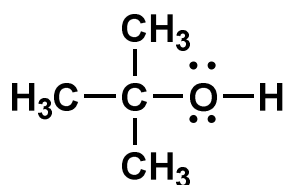


**Trifluoroacetic Acid (TFA)**

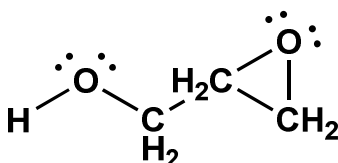




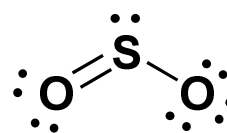
**t-Butyl Alcohol**



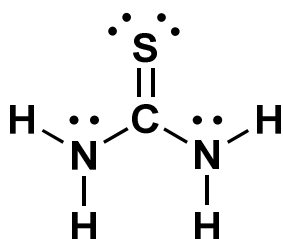
**Glycidol**



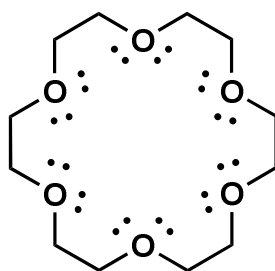
**Sulfur Dioxide**



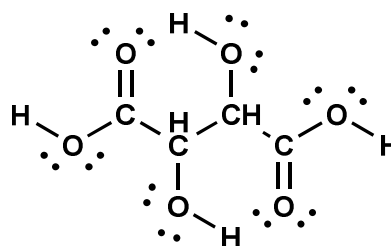
**Thiourea**



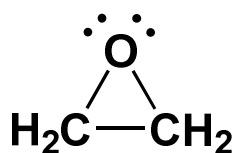
**18-Crown-6**



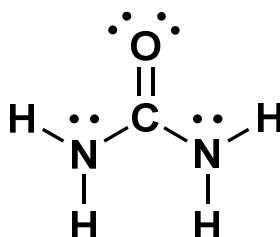
**Tartaric Acid**



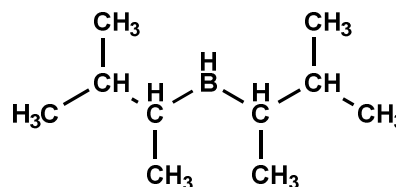
**Ethylene Oxide**



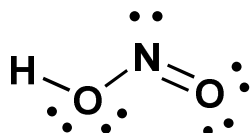
**Urea**



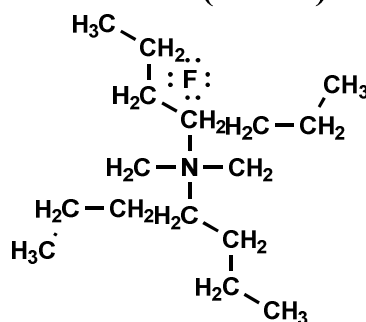
**Disiamylborane**



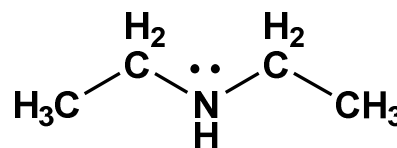
**Nitrous Acid**



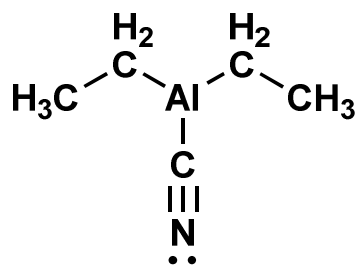
**Tetrabutylammonium  
Fluoride (TBAF)**



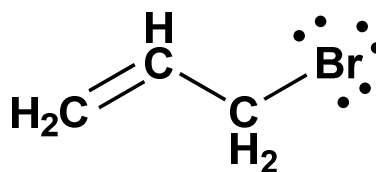
**Diethylamine (DEA)**



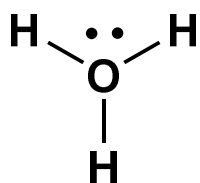
### Diethylaluminum Cyanide



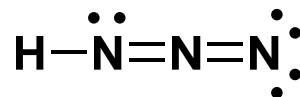
### Allyl Bromide



### Hydronium



### Hydrogen Azide



Problem <b>Carbon <math>sp^3</math></b> <b>5</b> <b>10</b> Give the bond polarity C $sp^3$ HONORS	Problem <b>Carbon <math>sp^3</math></b> <b>5</b> <b>10</b> Give the bond polarity C $sp^3$ HONORS	Problem <b>Carbon <math>sp^2</math></b> <b>5</b> <b>10</b> Give the bond polarity C $sp^2$ HONORS
Problem <b>Carbon <math>sp^2</math></b> <b>5</b> <b>10</b> Give the bond polarity C $sp^2$ HONORS	Problem <b>Nitrogen <math>sp^2</math></b> <b>5</b> <b>15</b> Give the bond polarity N $sp^2$ HONORS	Problem <b>Oxygen <math>sp^3</math></b> <b>5</b> <b>10</b> Give the bond polarity O $sp^3$ HONORS
Problem <b>Nitrogen <math>sp^3</math></b> <b>10</b> <b>20</b> Give the bond polarity N $sp^3$ HONORS	Problem <b>Nitrogen <math>sp^3</math></b> <b>10</b> <b>20</b> Give the bond polarity N $sp^3$ HONORS	Problem <b>Nitrogen <math>sp^2</math></b> <b>5</b> <b>15</b> Give the bond polarity N $sp^2$ HONORS

Problem <b>Oxygen <math>sp^3</math></b> <b>5</b> <b>10</b> Give the bond polarity	Problem <b>Oxygen <math>sp^2</math></b> <b>5</b> <b>10</b> Give the bond polarity	Problem <b>Oxygen <math>sp^2</math></b> <b>5</b> <b>10</b> Give the bond polarity
O $sp^3$ Honors	O $sp^2$ Honors	O $sp^2$ Honors
Problem <b>Sulfur <math>sp^3</math></b> <b>15</b> <b>25</b> Give the bond polarity	Problem <b>Sulfur <math>sp^2</math></b> <b>20</b> <b>30</b> Give the bond polarity	Problem <b>Sulfur <math>sp^2</math></b> <b>20</b> <b>30</b> Give the bond polarity
S $sp^3$ Honors	S $sp^2$ Honors	S $sp^2$ Honors
Problem <b>Sulfur <math>sp^3</math></b> <b>15</b> <b>25</b> Give the bond polarity	Problem <b>C sigma Bond</b> <b>5</b> <b>10</b> Give dipole direction	Problem <b>C sigma Bond</b> <b>5</b> <b>10</b> Give dipole direction
S $sp^3$ Honors	C sigma Honors	C sigma Honors

Problem <b>N sigma Bond</b> <b>5</b> <b>15</b> Give dipole direction N sigma Honors	Problem <b>N sigma Bond</b> <b>5</b> <b>15</b> Give dipole direction N sigma Honors	Problem <b>O sigma Bond</b> <b>5</b> <b>10</b> Give dipole direction O sigma Honors
Problem <b>O sigma Bond</b> <b>5</b> <b>10</b> Give dipole direction O sigma Honors	Problem <b>S sigma Bond</b> <b>10</b> <b>20</b> Give dipole direction S sigma Honors	Problem <b>S sigma Bond</b> <b>10</b> <b>20</b> Give dipole direction S sigma Honors
Problem <b>Al/B sigma Bond</b> <b>15</b> <b>25</b> Give dipole direction Al/B sigma Honors	Problem <b>Al/B sigma Bond</b> <b>15</b> <b>25</b> Give dipole direction Al/B sigma Honors	Problem <b>Hal sigma Bond</b> <b>10</b> <b>15</b> Give dipole direction Hal sigma Honors

Problem <b>Hal sigma Bond</b> <b>10</b> <b>15</b> Give dipole direction <b>Hal sigma Honors</b>	Problem <b>A / B <math>sp^2</math></b> <b>15</b> <b>25</b> Give the bond polarity <b>A / B <math>sp^2</math> Honors</b>	Problem <b>A / B <math>sp^2</math></b> <b>15</b> <b>25</b> Give the bond polarity <b>A / B <math>sp^2</math> Honors</b>
Problem <b>Nitrogen <math>sp</math></b> <b>15</b> <b>20</b> Give the bond polarity <b>N <math>sp</math> Honors</b>	Problem <b>Nitrogen <math>sp</math></b> <b>15</b> <b>20</b> Give the bond polarity <b>N <math>sp</math> Honors</b>	Problem <b>Carbon pi Bond</b> <b>10</b> <b>15</b> Give dipole direction <b>C pi Honors</b>
Problem <b>Carbon <math>sp</math></b> <b>15</b> <b>20</b> Give the bond polarity <b>C <math>sp</math> Honors</b>	Problem <b>Carbon <math>sp</math></b> <b>15</b> <b>20</b> Give the bond polarity <b>C <math>sp</math> Honors</b>	Problem <b>Carbon pi Bond</b> <b>10</b> <b>15</b> Give dipole direction <b>C pi Honors</b>

### Special Problem

#### Intermolecular Interactions

Name all the intermolecular interactions for any 1 **Solution** card. 10 pts for each correctly named interaction.

10  
20  
30  
40

### Special Problem

#### Intermolecular Interactions

Name all the intermolecular interactions for any 1 **Solution** card. 10 pts for each correctly named interaction.

10  
20  
30  
40

### Special Problem

#### Acid/Base Reaction

Choose any 2 **Solution** cards with a pKa. Identify which acid would be favored in equilibrium.

20

### Special Problem

#### Acid/Base Reaction

Choose any 2 **Solution** cards with a pKa. Identify which acid would be favored in equilibrium.

20

### Special Problem

#### Resonance

Choose any 1 **Solution** card which can undergo resonance. Identify the number of possible resonance forms. 10 pts for each resonance form.

10  
20  
30  
40

### Special Problem

#### Resonance

Choose any 1 **Solution** card which can undergo resonance. Identify the number of possible resonance forms. 10 pts for each resonance form.

10  
20  
30  
40

### Problem

#### Nitrogen pi Bond

10

15

N pi BONDS  
Give dipole  
direction

### Problem

#### Nitrogen pi Bond

10

15

N pi BONDS  
Give dipole  
direction

### Problem

#### Oxygen pi Bond

10

15

O pi BONDS  
Give dipole  
direction

Special Problem

**Intermolecular Interactions**

Name all the intermolecular interactions for any 1 **Solution** card. 10 pts for each correctly named interaction.

10  
20  
30  
40

Problem

**Sulphur pi Bond**

25

30

Give dipole direction

S pi Honors

Special Problem

**Acid/Base Reaction**

Choose any 2 **Solution** cards with a pKa. Identify which acid would be favored in equilibrium.

20

Special Problem

**Intermolecular Interactions**

Name all the intermolecular interactions for any 1 **Solution** card. 10 pts for each correctly named interaction.

10  
20  
30  
40

Special Problem

**Resonance**

Choose any 1 **Solution** card which can undergo resonance. Identify the number of possible resonance forms. 10 pts for each resonance form.

10  
20  
30  
40

Problem

**Sulphur pi Bond**

25

30

Give dipole direction

S pi Honors

Problem

**Metal Ionic Bond**

15

20

Assign bond polarity

Metal ionic Honors

Problem

**Metal Ionic Bond**

15

20

Assign bond polarity

Metal ionic Honors

Problem

**Oxygen pi Bond**

10

15

Give dipole direction

O pi Honors



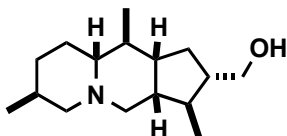
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<b>Formal Charge</b>	<b>Formal Charge</b>	<b>Formal Charge</b>
<b>+10</b>	<b>+10</b>	<b>+10</b>
<b>O<sup>[-1]</sup></b>	<b>N<sup>[+1]</sup></b>	<b>C<sup>[-1]</sup></b>

Bonus	Bonus	Bonus
<b>Formal Charge</b>	<b>Formal Charge</b>	<b>Formal Charge</b>
<b>+10</b>	<b>+10</b>	<b>+10</b>
<b>O<sup>[+1]</sup></b>	<b>S<sup>[+1]</sup></b>	<b>N<sup>[-1]</sup></b>

Bonus	Bonus	Bonus
<b>Formal Charge</b>	<b>Formal Charge</b>	
<b>+10</b>	<b>+10</b>	
<b>Halide<sup>[-1]</sup></b>	<b>N<sup>[+1]</sup></b>	

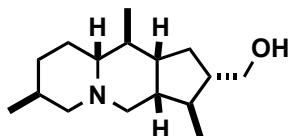
Appendix D. Name Reactions

**Alkaloid 251F**



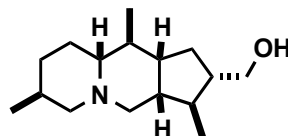
Olefin Metathesis  
Aldol Condensation  
Birch Reduction  
\*Jeff Aubè\*

**Alkaloid 251F**



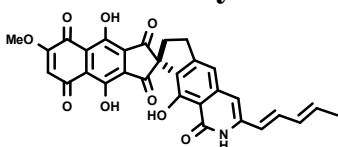
Michael Addition  
Aldol Condensation  
Birch Reduction  
\*Jeff Aubè\*

**Alkaloid 251F**



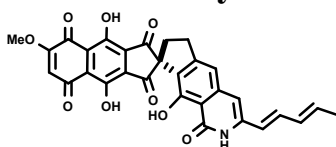
Olefin Metathesis  
Michael Addition  
Aldol Condensation  
\*Jeff Aubè\*

**Fredericamycin A**



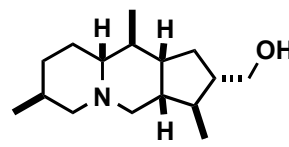
Baeyer-Villiger Oxidation  
Wittig Reaction  
Aldol Addition  
\*Dale Boger\*

**Fredericamycin A**



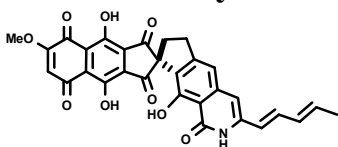
Dieckmann Condensation  
Wittig Reaction  
Aldol Addition  
\*Dale Boger\*

**Alkaloid 251F**



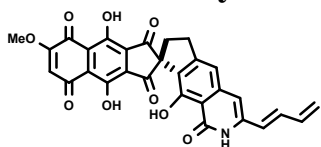
Olefin Metathesis  
Michael Addition  
Birch Reduction  
\*Jeff Aubè\*

**Fredericamycin A**



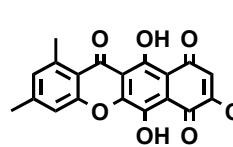
Baeyer-Villiger Oxidation  
Dieckmann Condensation  
Wittig Reaction  
\*Dale Boger\*

**Fredericamycin A**



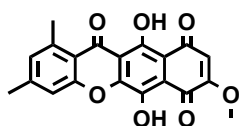
Baeyer-Villiger Oxidation  
Dieckmann Condensation  
Aldol Addition  
\*Dale Boger\*

**Bikaverin**



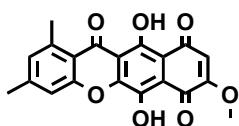
Aldol Condensation  
Claisen Condensation  
Friedel-Crafts Acylation  
\*Derek Barton\*

**Bikaverin**



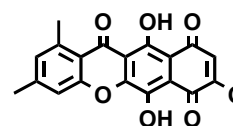
Aldol Condensation  
Williamson Ether Synthesis  
Friedel-Crafts Acylation  
\*Derek Barton\*

**Bikaverin**



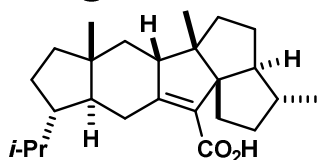
Claisen Condensation  
Williamson Ether Synthesis  
Friedel-Crafts Acylation  
\*Derek Barton\*

**Bikaverin**



Aldol Condensation  
Claisen Condensation  
Williamson Ether Synthesis  
\*Derek Barton\*

### Retigeranic Acid



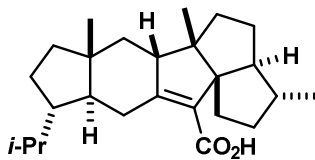
Mitsunobu Reaction

Gringard Reaction

Wittig Reaction

\*E. J. Corey\*

### Retigeranic Acid



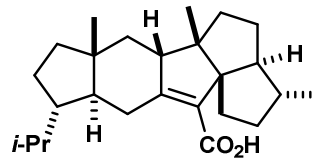
Mitsunobu Reaction

Gringard Reaction

Diels-Alder Reaction

\*E. J. Corey\*

### Retigeranic Acid



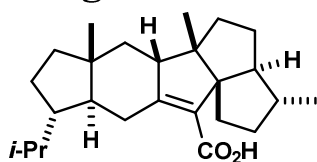
Mitsunobu Reaction

Gringard Reaction

Aldol Condensation

\*E. J. Corey\*

### Retigeranic Acid



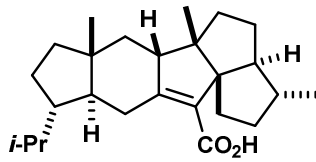
Mitsunobu Reaction

Diels-Alder Reaction

Wittig Reaction

\*E. J. Corey\*

### Retigeranic Acid



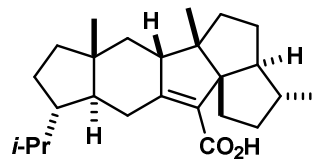
Mitsunobu Reaction

Wittig Reaction

Aldol Condensation

\*E. J. Corey\*

### Retigeranic Acid



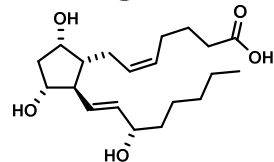
Mitsunobu Reaction

Diels-Alder Reaction

Aldol Condensation

\*E. J. Corey\*

### Prostaglandin F2a



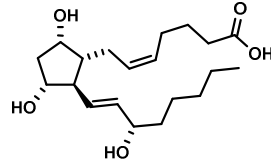
Diels-Alder Reaction

Baeyer-Villiger Oxidation

Horner-Wadsworth-Emmons

\*E. J. Corey\*

### Prostaglandin F2a



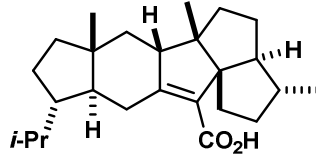
Diels-Alder Reaction

Baeyer-Villiger Oxidation

Wittig Reaction

\*E. J. Corey\*

### Retigeranic Acid



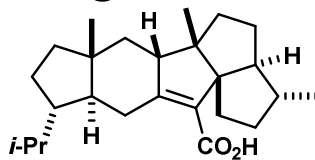
Gringard Reaction

Wittig Reaction

Diels-Alder Reaction

\*E. J. Corey\*

### Retigeranic Acid



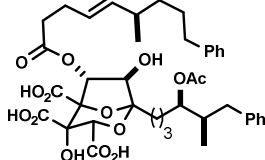
Gringard Reaction

Wittig Reaction

Aldol Condensation

\*E. J. Corey\*

### Zaragozic Acid C



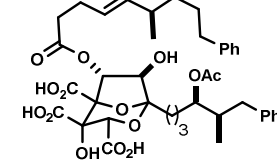
Swern Oxidation

Birch Reduction

Dess-Martin Oxidation

\*David Evans\*

### Zaragozic Acid C



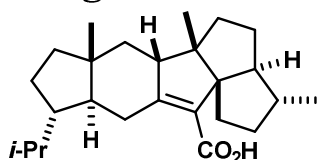
Swern Oxidation

Birch Reduction

Grignard Reaction

\*David Evans\*

### Retigeranic Acid



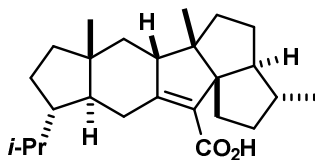
Grignard Reaction

Diels-Alder Reaction

Aldol Condensation

\*E. J. Corey\*

### Retigeranic Acid



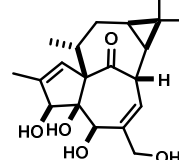
Diels-Alder Reaction

Wittig Reaction

Aldol Condensation

\*E. J. Corey\*

### Ingenol



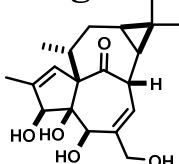
Claisen Rearrangement

Aldol Addition

Horner-Wadsworth-Emmons

\*Isao Kuwajima\*

### Ingenol



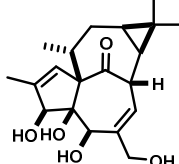
Claisen Rearrangement

Aldol Addition

Swern Oxidation

\*Isao Kuwajima\*

### Ingenol



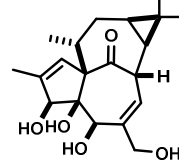
Claisen Rearrangement

Horner-Wadsworth-Emmons

Swern Oxidation

\*E. J. Corey\*

### Ingenol



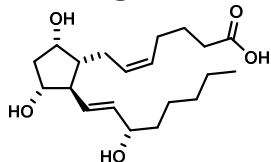
Aldol Addition

Horner-Wadsworth-Emmons

Swern Oxidation

\*E. J. Corey\*

### Prostaglandin F2a



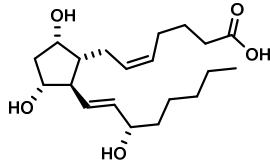
Diels-Alder Reaction

Horner-Wadsworth-Emmons

Wittig Reaction

\*E. J. Corey\*

### Prostaglandin F2a



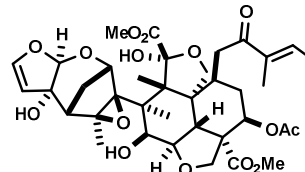
Baeyer-Villiger Oxidation

Horner-Wadsworth-Emmons

Wittig Reaction

\*E. J. Corey\*

### Azadirachtin



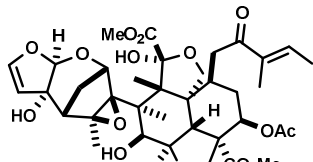
Claisen Rearrangement

Wittig Reaction

Swern Oxidation

\*Steven Ley\*

### Azadirachtin



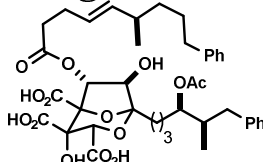
Claisen Rearrangement

Wittig Reaction

Horner-Wadsworth-Emmons

\*Steven Ley\*

### Zaragozic Acid C



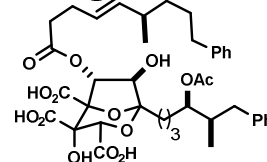
Swern Oxidation

Dess-Martin Oxidation

Grignard Reaction

\*David Evans\*

### Zaragozic Acid C



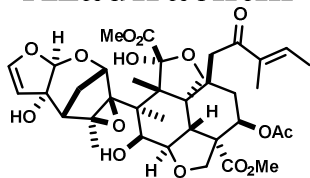
Birch Reduction

Dess-Martin Oxidation

Grignard Reaction

\*David Evans\*

### Azadirachtin



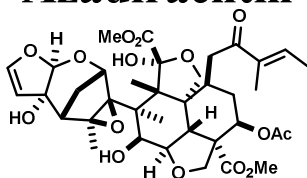
Claisen Rearrangement

Swern Oxidation

Horner-Wadsworth-Emmons

\*Steven Ley\*

### Azadirachtin



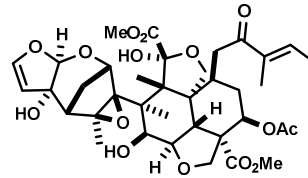
Wittig Reaction

Swern Oxidation

Horner-Wadsworth-Emmons

\*Steven Ley\*

### Azadirachtin



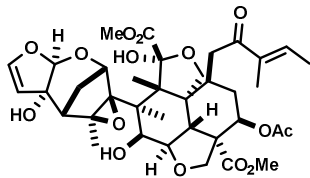
Williamson Ether Synthesis

Claisen Rearrangement

Horner-Wadsworth-Emmons

\*Steven Ley\*

### Azadirachtin



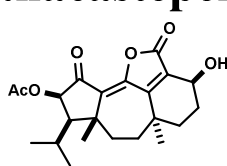
Williamson Ether Synthesis

Wittig Reaction

Swern Oxidation

\*Steven Ley\*

### Guanacastepene N



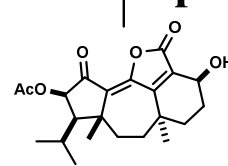
Hofmann Elimination

Claisen Condensation

Heck Reaction

\*Larry Overman\*

### Guanacastepene N



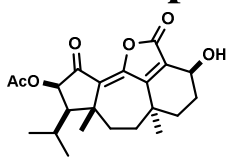
Hofmann Elimination

Claisen Condensation

Michael Addition

\*Larry Overman\*

### Guanacastepene N



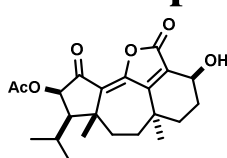
Hofmann Elimination

Heck Coupling

Michael Addition

\*Larry Overman\*

### Guanacastepene N



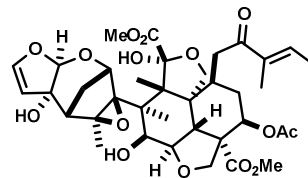
Claisen Condensation

Heck Coupling

Michael Addition

\*Larry Overman\*

### Azadirachtin



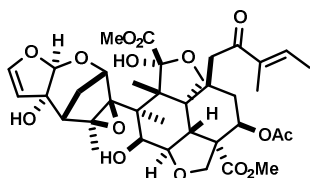
Williamson Ether Synthesis

Wittig Reaction

Horner-Wadsworth-Emmons

\*Steven Ley\*

### Azadirachtin



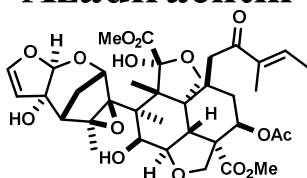
Williamson Ether Synthesis

Claisen Rearrangement

Swern Oxidation

\*Steven Ley\*

### Azadirachtin



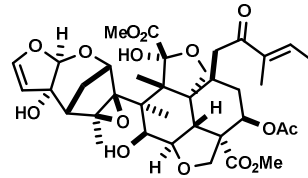
Williamson Ether Synthesis

Swern Oxidation

Horner-Wadsworth-Emmons

\*Steven Ley\*

### Azadirachtin



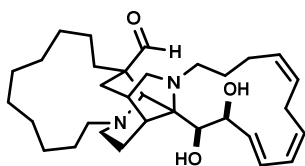
Birch Reduction

Dess-Martin Oxidation

Grignard Reaction

\*Steven Ley\*

### Sarain A



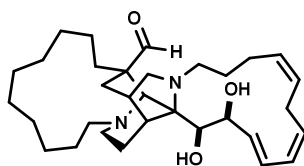
Mitsunobu Reaction

Swern Oxidation

Olefin Metathesis

\*Larry Overman\*

### Sarain A



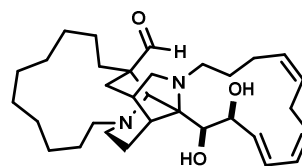
Mitsunobu Reaction

Swern Oxidation

Stille Coupling

\*Larry Overman\*

### Sarain A



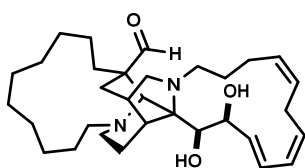
Mitsunobu Reaction

Olefin Metathesis

Stille Coupling

\*Larry Overman\*

### Sarain A



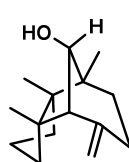
Swern Oxidation

Olefin Metathesis

Stille Coupling

\*Larry Overman\*

### Gymnomitrol



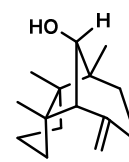
Wolff-Kishner Reduction

Michael Reaction

Aldol Addition

\*Leo A Paquette\*

### Gymnomitrol



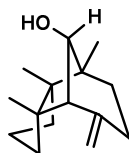
Wolff-Kishner Reduction

Michael Reaction

Jones Oxidation

\*Leo A Paquette\*

### Gymnomitrol



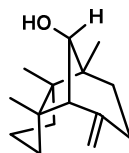
Wolff-Kishner Reduction

Aldol Addition

Jones Oxidation

\*Steven Welch\*

### Gymnomitrol



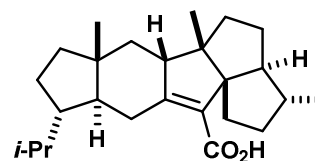
Michael Reaction

Aldol Addition

Jones Oxidation

\*Steven Welch\*

### Retigeranic Acid



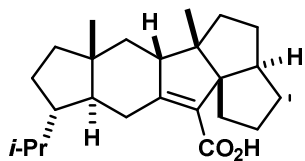
Aldol Addition

Wolff-Kishner Reduction

Mitsunobu Reaction

\*Steven Ley\*

### Retigeranic Acid



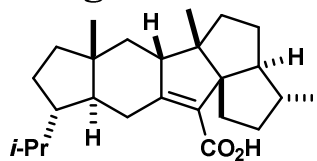
Aldol Condensation

Wolff-Kishner Reduction

Mitsunobu Reaction

\*Steven Ley\*

### Retigeranic Acid



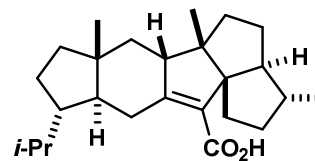
Aldol Condensation

Aldol Addition

Mitsunobu Reaction

\*Leo A Paquette\*

### Retigeranic Acid



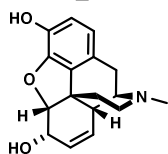
Aldol Condensation

Aldol Addition

Wolff-Kishner Reduction

\*Leo A Paquette\*

## Morphine



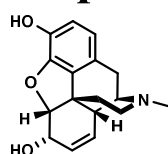
Wittig Reaction

Diels-Alder Reaction

Dess-Martin Oxidation

\*Gilbert Stork\*

## Morphine



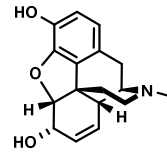
Heck Coupling

Diels-Alder Reaction

Dess-Martin Oxidation

\*Gilbert Stork\*

## Morphine



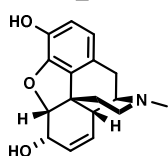
Mitsunobu Reaction

Heck Coupling

Stille Coupling

\*Barry Trost\*

## Morphine



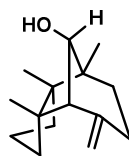
Mitsunobu Reaction

Heck Coupling

Dess-Martin Oxidation

\*Barry Trost\*

## Gymnomitrol



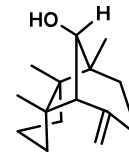
Williamson Ether Synthesis

Claisen Rearrangement

Jones Oxidation

\*Steven Welch\*

## Gymnomitrol



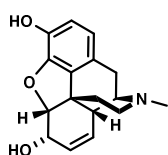
Williamson Ether Synthesis

Claisen Rearrangement

Dieckmann Condensation

\*Steven Welch\*

## Morphine



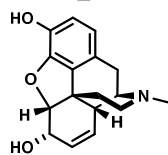
Mitsunobu Coupling

Stille Coupling

Dess-Martin Oxidation

\*Barry Trost\*

## Morphine



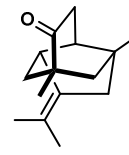
Heck Coupling

Stille Coupling

Dess-Martin Oxidation

\*Barry Trost\*

## Pupukeanone



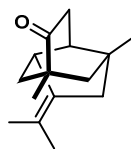
Fischer Esterfication

Grignard Reaction

Diels-Alder Reaction

\*James D White\*

## Pupukeanone



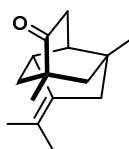
Birch Reduction

Grignard Reaction

Diels-Alder Reaction

\*James D White\*

## Pupukeanone



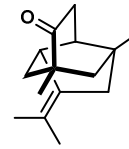
Birch Reduction

Fischer Esterfication

Diels-Alder Reaction

\*James D White\*

## Pupukeanone



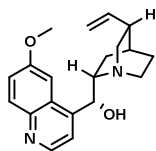
Birch Reduction

Fischer Esterfication

Grignard Reaction

\*James D White\*

## Quinine



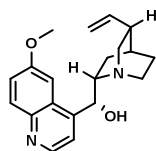
Jones Oxidation

Hofmann Elimination

Fischer Esterification

\*Robert B. Woodward\*

## Quinine



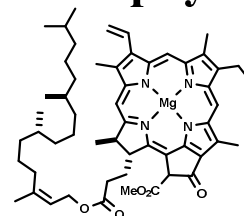
Jones Oxidation

Hofmann Elimination

Claisen Condensation

\*Robert B. Woodward\*

## Chlorophyll A

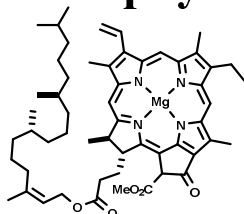


Friedel-Crafts Alkylation

Hofmann Elimination

\*Robert B Woodward

## Chlorophyll A

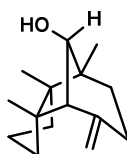


Friedel-Crafts Alkylation

Hofmann Elimination

\*Robert B Woodward

## Gymnomitrol



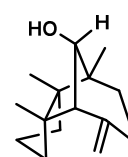
Williamson Ether Synthesis

Jones Oxidation

Dieckmann Condensation

\*Steven Welch\*

## Gymnomitrol



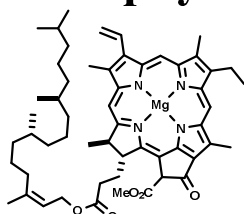
Claisen Rearrangement

Jones Oxidation

Dieckmann Condensation

\*Steven Welch\*

## Chlorophyll A

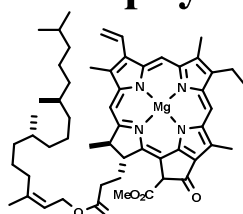


Hofmann Elimination

Friedel-Crafts Acylation

\*Robert B Woodward

## Chlorophyll A

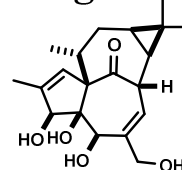


Friedel-Crafts Alkylation

Friedel-Crafts Acylation

\*Robert B Woodward

## Ingenol



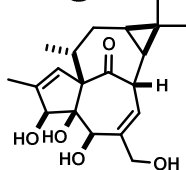
Diels-Alder Reaction

Olefin Metathesis

Dess-Martin Oxidation

\*John Wood\*

## Ingenol



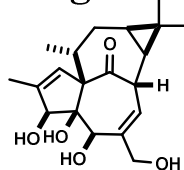
Michael Addition

Olefin Metathesis

Dess-Martin Oxidation

\*John Wood\*

## Ingenol



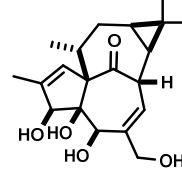
Michael Addition

Diels-Alder Reaction

Dess-Martin Oxidation

\*John Wood\*

## Ingenol



Michael Addition

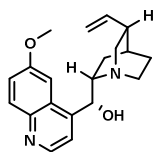
Diels-Alder Reaction

Olefin Metathesis

\*John Wood\*



## Quinine



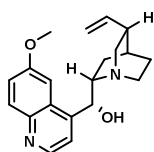
Jones Oxidation

Fischer Esterification

Claisen Condensation

\*Robert B. Woodward\*

## Quinine



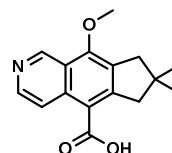
Hofmann Elimination

Fischer Esterification

Claisen Condensation

\*Robert B. Woodward\*

## Illudinine



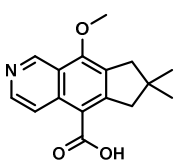
Friedel-Crafts Acylation

Friedel-Crafts Alkylation

Grignard Reaction

\*Robert B Woodward\*

## Illudinine



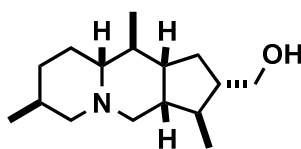
Friedel-Crafts Acylation

Friedel-Crafts Alkylation

Williamson Ether Synthesis

\*Robert B Woodward\*

## Alkaloid 251F



Olefin Metathesis

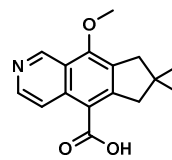
Michael Addition

Aldol Condensation

Dess-Martin Oxidation

\*Jeff Aubè\*

## Illudinine



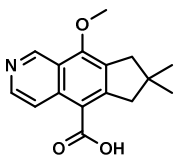
Friedel-Crafts Acylation

Williamson Ether Synthesis

Grignard Reaction

\*Robert B Woodward\*

## Illudinine



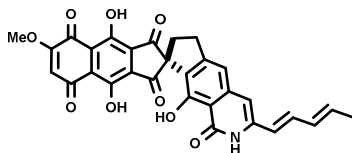
Friedel-Crafts Alkylation

Williamson Ether Synthesis

Grignard Reaction

\*Robert B Woodward\*

## Fredericamycin A



Dieckmann Cyclization

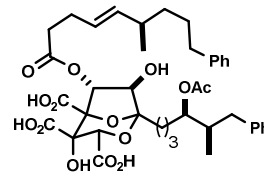
Baeyer-Villiger Oxidation

Wittig Reaction

Aldol Addition

\*Dale Boger\*

## Zaragonzic Acid C



Swern Oxidation

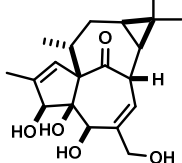
Birch Reduction

Dess-Martin Oxidation

Grignard Reaction

\*Dave Evans\*

## Ingenol



Claisen Rearrangement

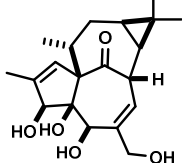
Aldol Addition

Horner-Wadsworth-Emmons

Swern Oxidation

\*Isao Kuwajima\*

## Ingenol



Michael Addition

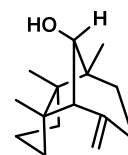
Diels-Alder Reaction

Olefin Metathesis

Dess-Martin Oxidation

\*John Wood\*

## Gymnomitrol



Williamson Ether Synthesis

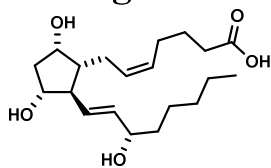
Claisen Rearrangement

Jones Oxidation

Dieckmann Cyclization

\*Steven Welch\*

### Prostaglandin F2a



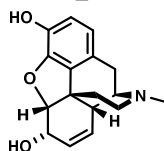
Diels-Alder Reaction

Horner-Wadsworth-Emmons

Wittig Reaction

\*E. J. Corey\*

### Morphine



Wittig Reaction

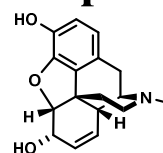
Diels-Alder Reaction

Des-Martin Oxidation

Heck Coupling

\*Gilbert Stork\*

### Morphine



Mitsunobu Reaction

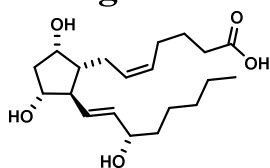
Heck Coupling

Stille Coupling

Des-Martin Oxidation

\*Barry Trost\*

### Prostaglandin F2a



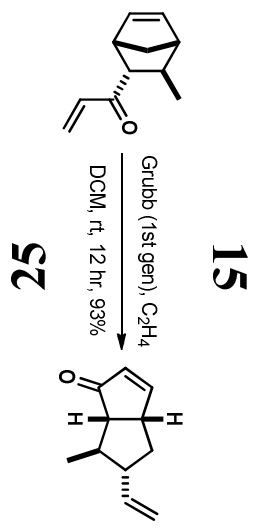
Baeyer-Villiger Oxidation

Horner-Wadsworth-Emmons

Wittig Reaction

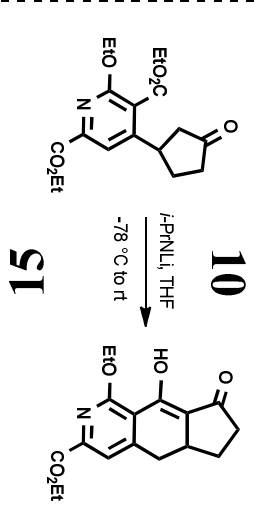
\*E. J. Corey\*

Honors - ID Synthetic Target



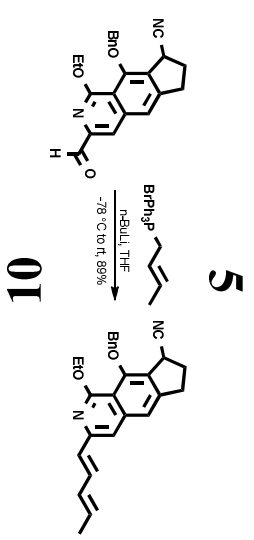
Problem

Honors - ID Synthetic Target



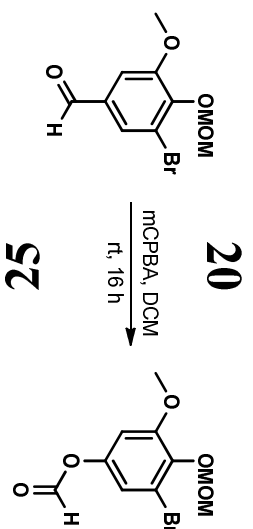
Problem

Honors - ID Synthetic Target



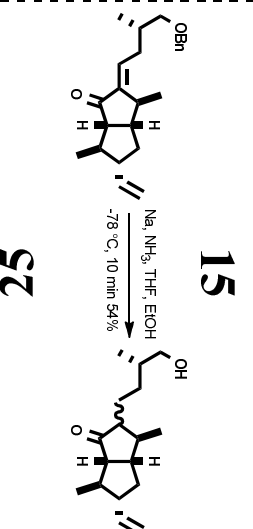
Problem

Honors - ID Synthetic Target



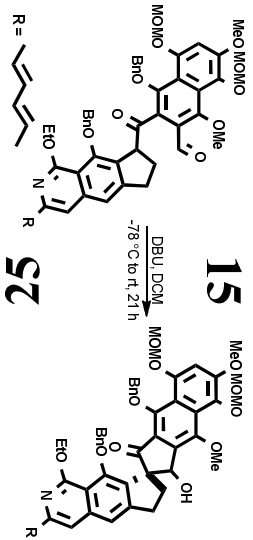
Problem

Honors - ID Synthetic Target



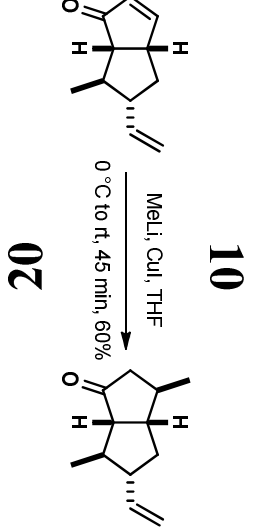
Problem

Honors - ID Synthetic Target



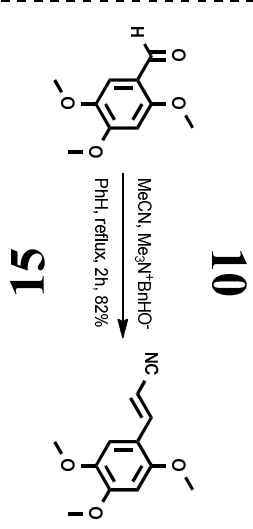
Problem

Honors - ID Synthetic Target



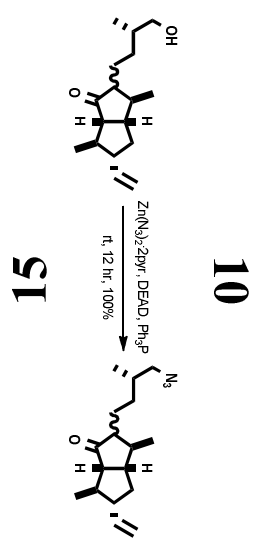
Problem

Honors - ID Synthetic Target



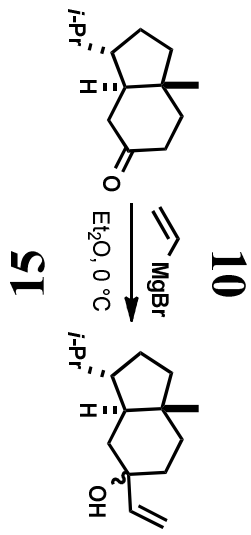
Problem

Honors - ID Synthetic Target



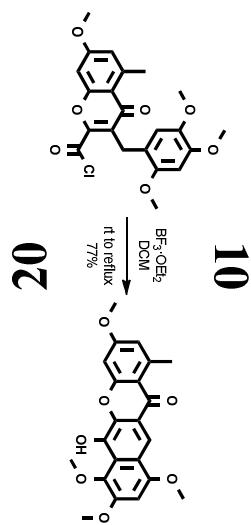
Problem

Honors - ID Synthetic Target



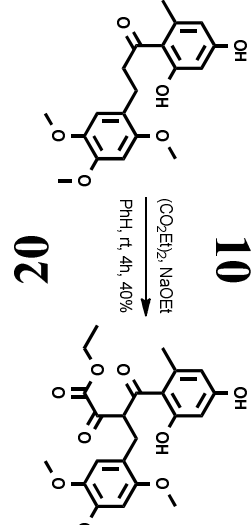
Problem

Honors - ID Synthetic Target



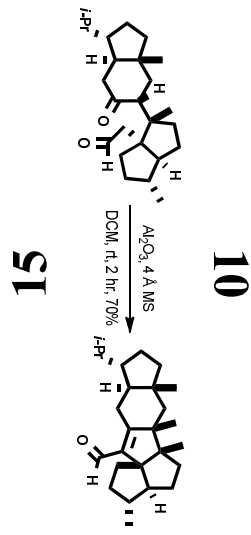
Problem

Honors - ID Synthetic Target



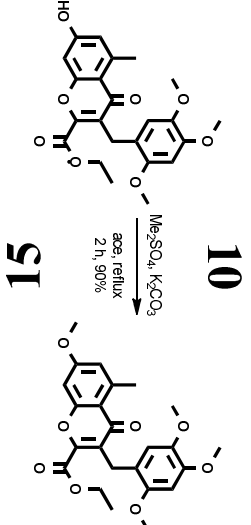
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Honors - ID Synthetic Target



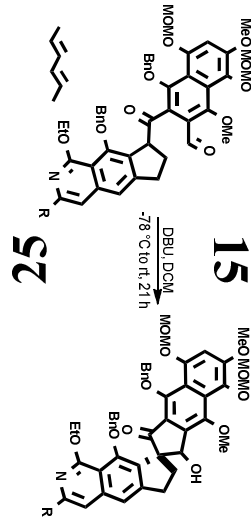
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Honors - ID Synthetic Target



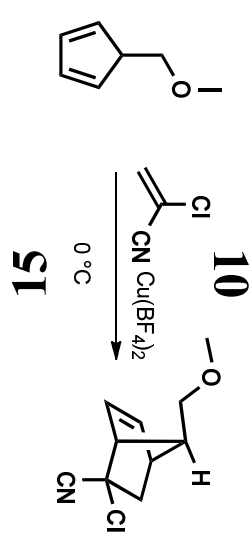
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Honors - ID Synthetic Target



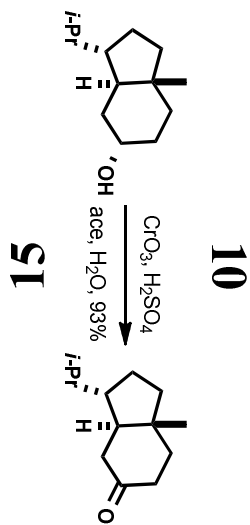
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Honors - ID Synthetic Target



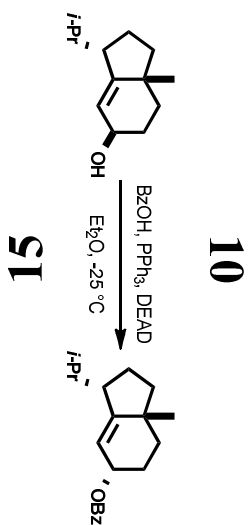
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Honors - ID Synthetic Target



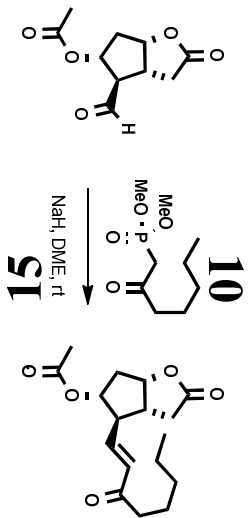
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Honors - ID Synthetic Target



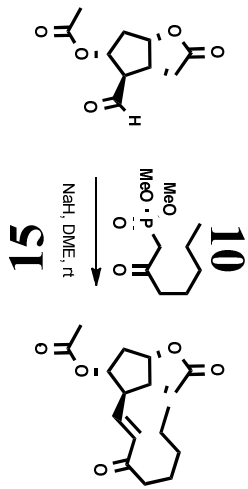
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Honors - ID Synthetic Target



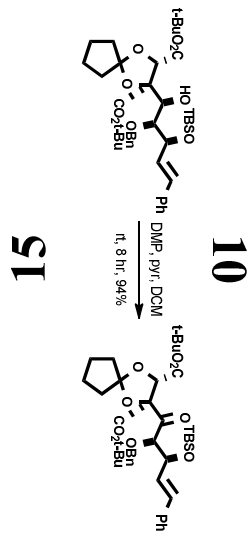
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Honors - ID Synthetic Target



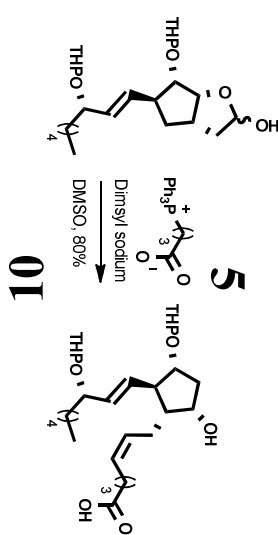
Problem

Honors - ID Synthetic Target



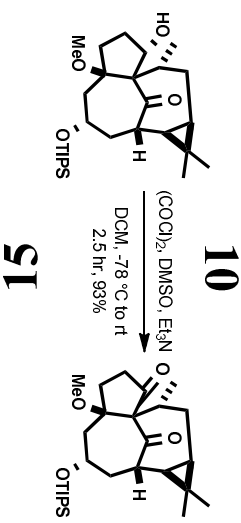
Problem

Honors - ID Synthetic Target



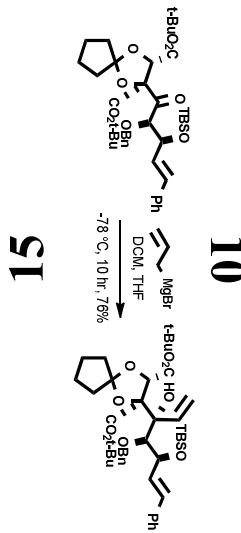
Problem

Honors - ID Synthetic Target



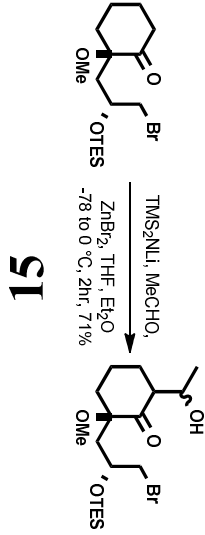
Problem

Honors - ID Synthetic Target



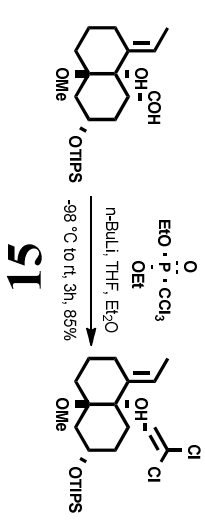
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Honors - ID Synthetic Target



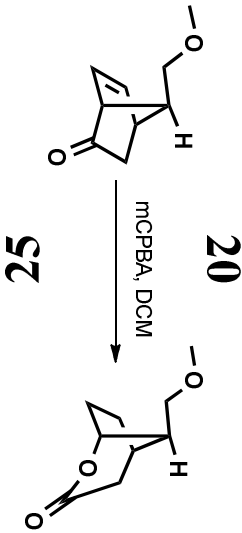
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Honors - ID Synthetic Target



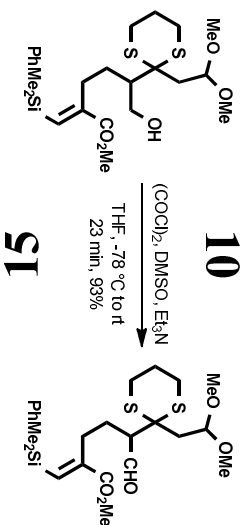
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Honors - ID Synthetic Target



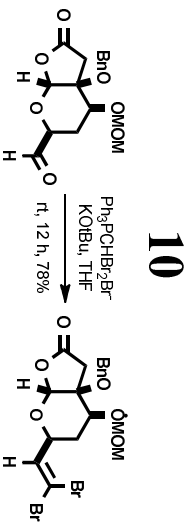
Problem

Problem



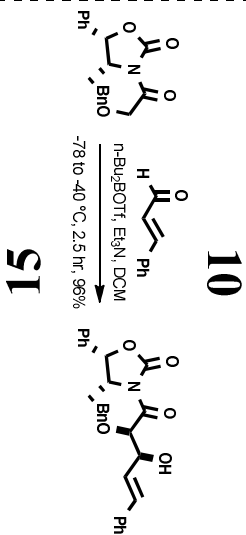
Honors - ID Synthetic Target

Problem



Honors - ID Synthetic Target

Problem



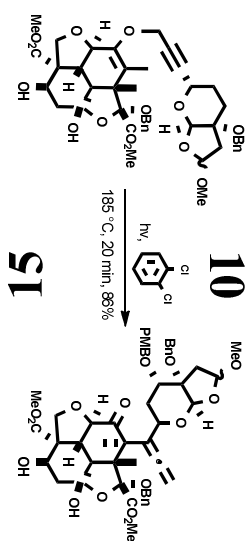
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Problem



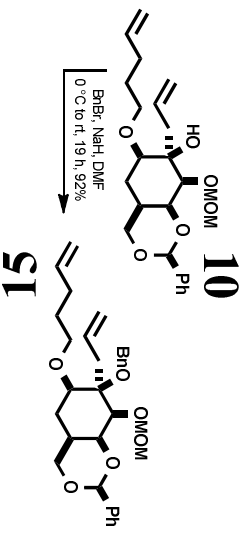
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Problem



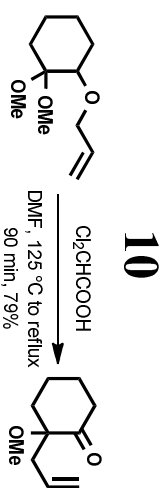
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Problem



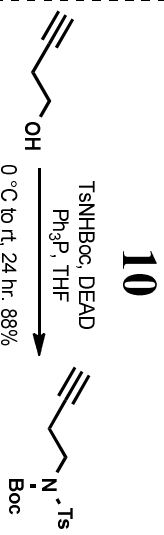
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Problem



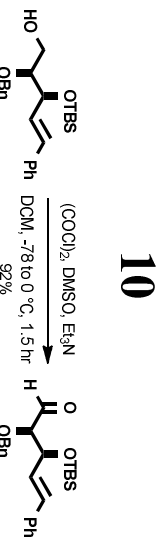
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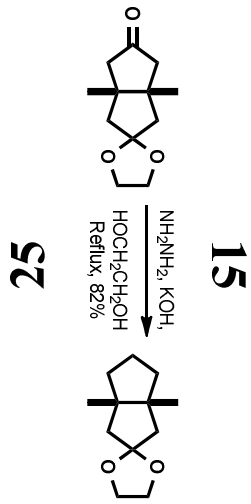
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Problem



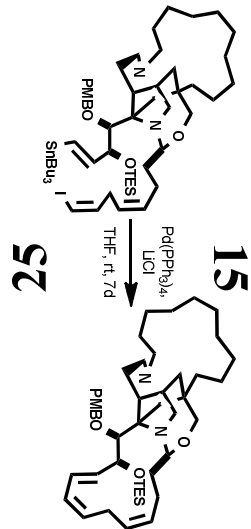
Honors - ID Synthetic Target

Honors - ID Synthetic Target



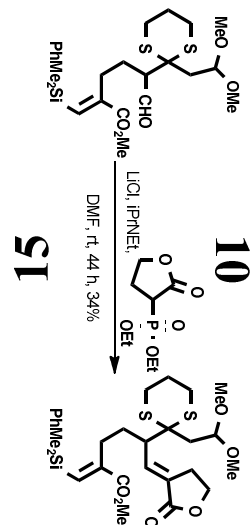
Problem

Honors - ID Synthetic Target



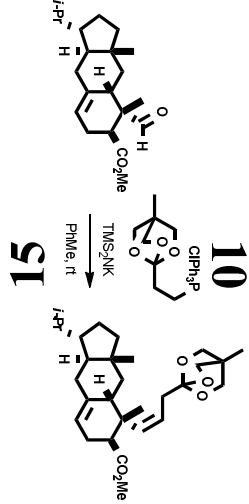
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Honors - ID Synthetic Target



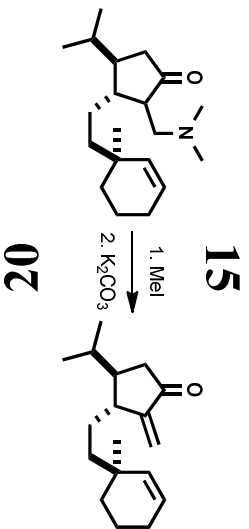
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Honors - ID Synthetic Target



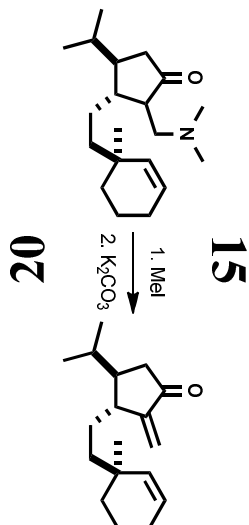
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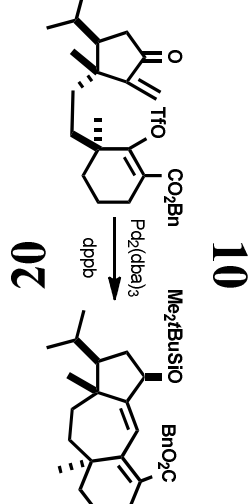
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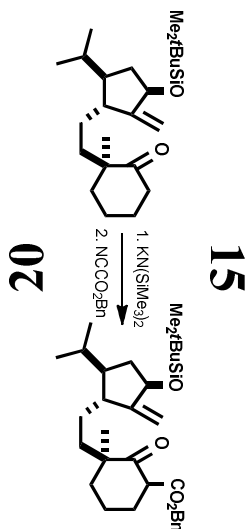
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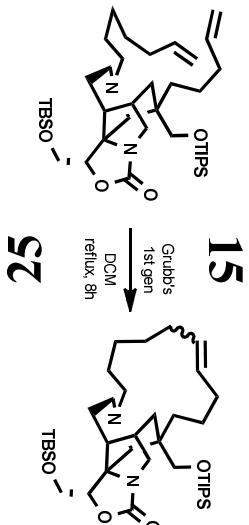
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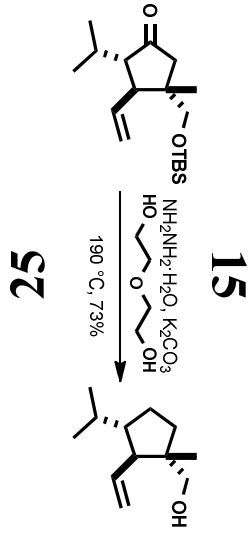
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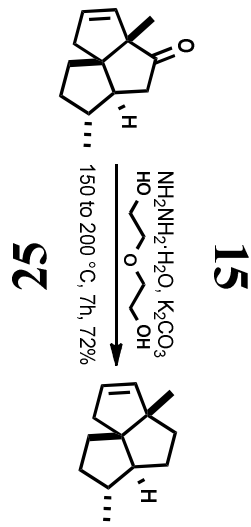
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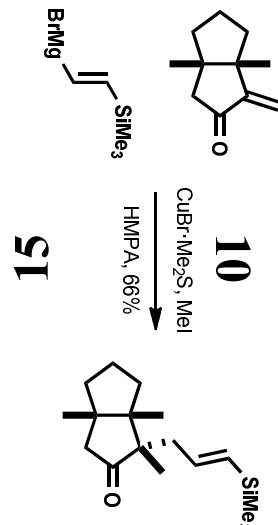
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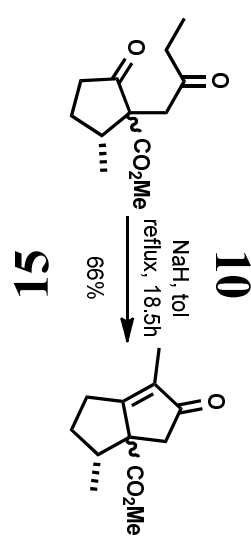
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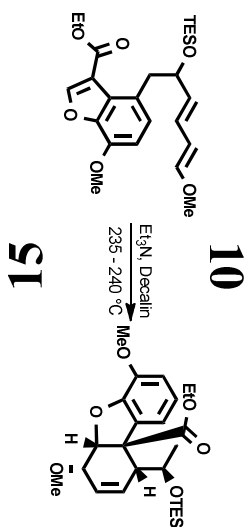
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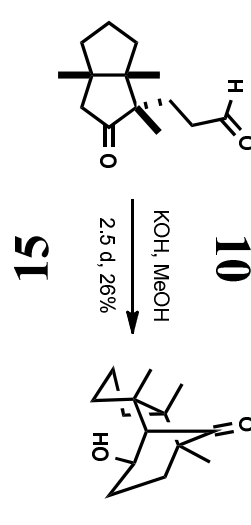
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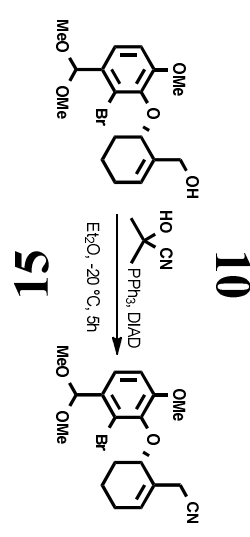
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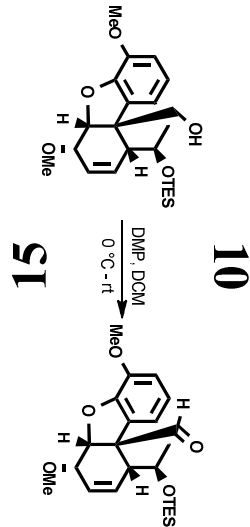
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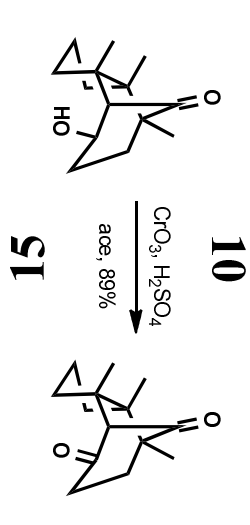
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Problem

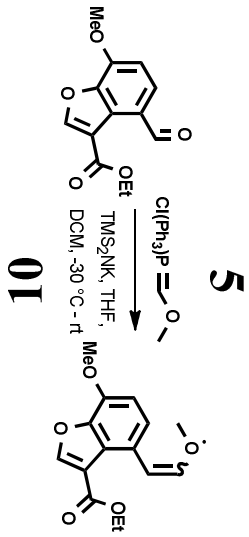
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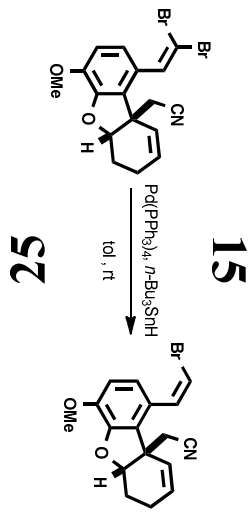


Honors - ID Synthetic Target



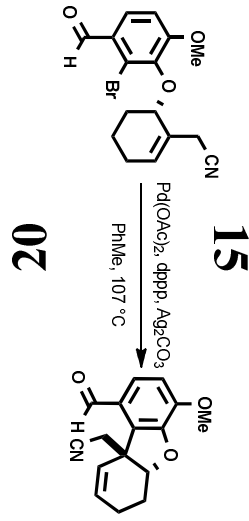
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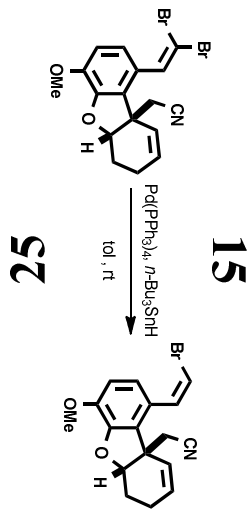
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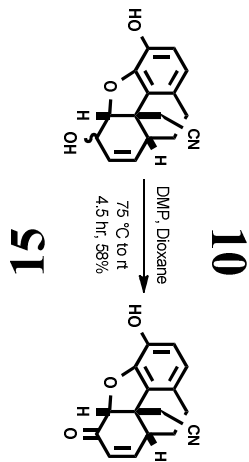
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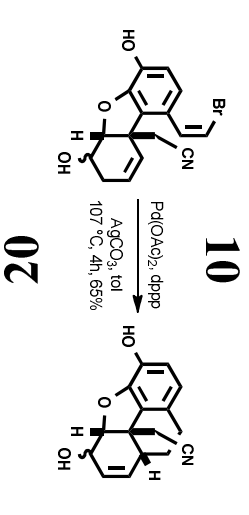
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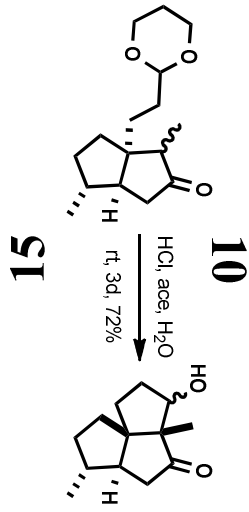
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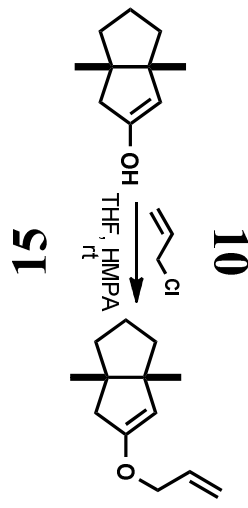
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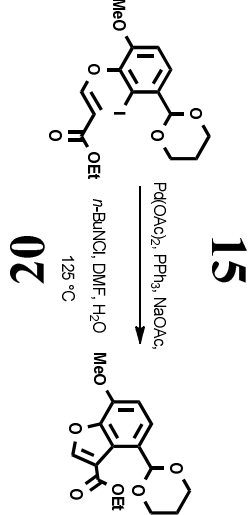
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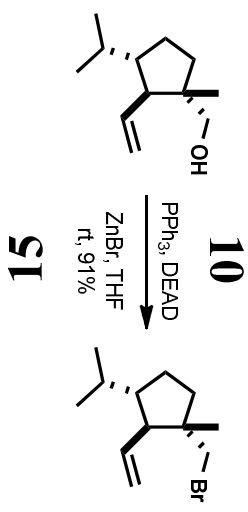
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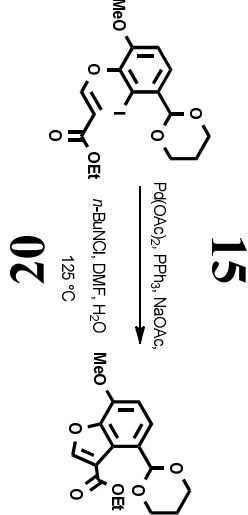
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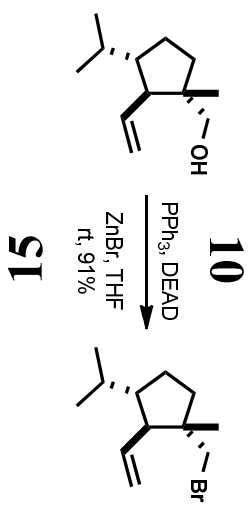
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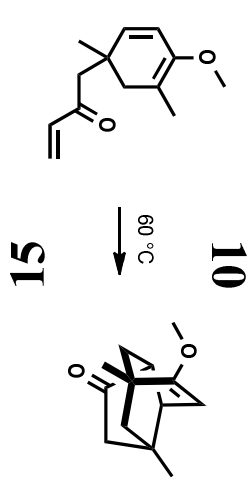
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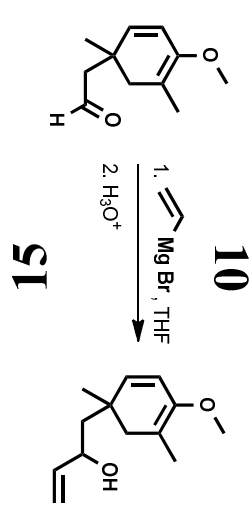
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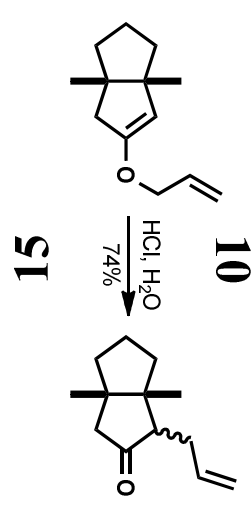
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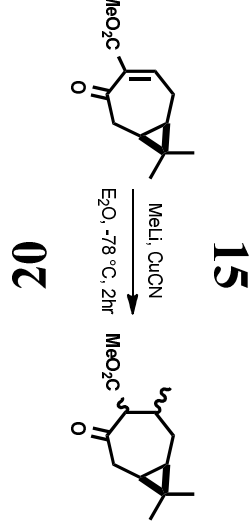
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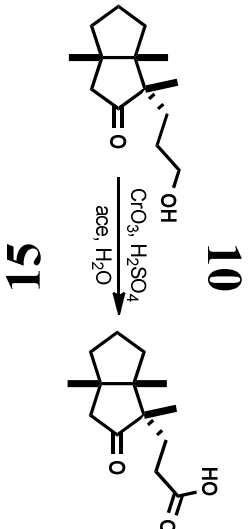
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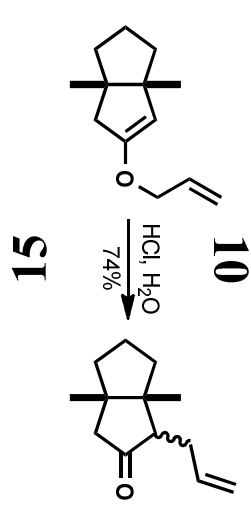
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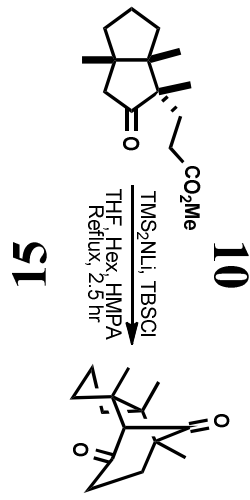
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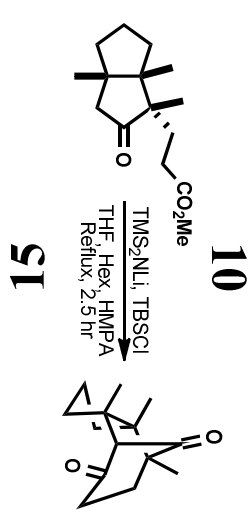
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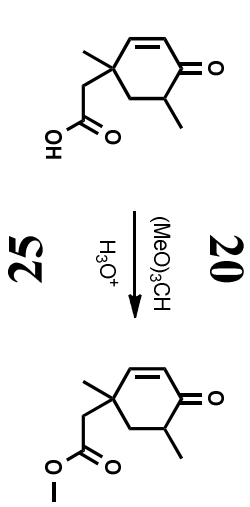
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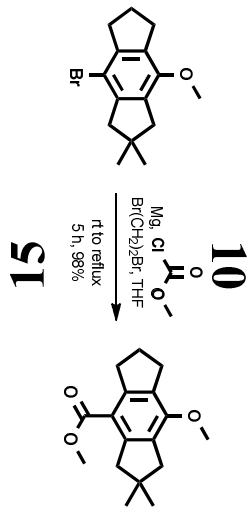
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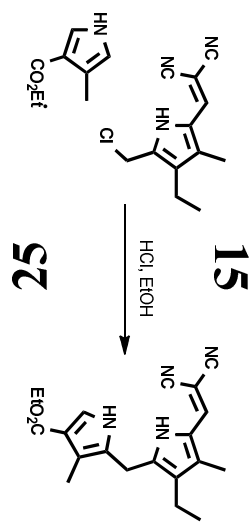
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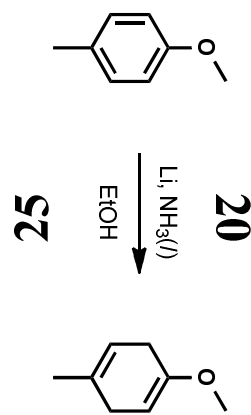
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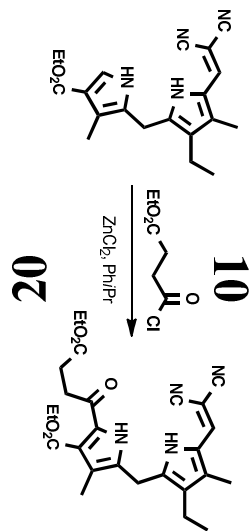
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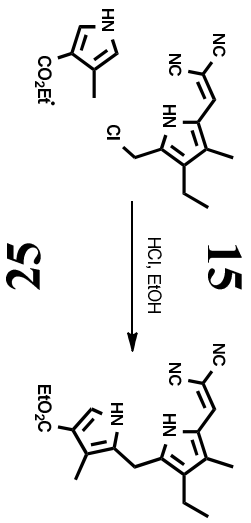
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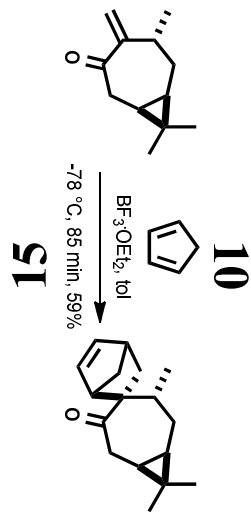
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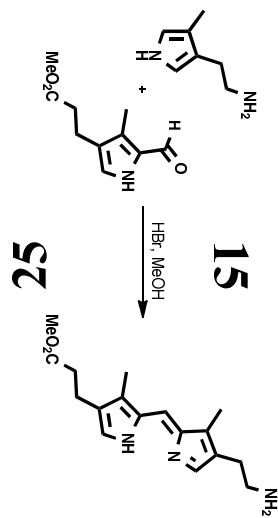
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Honors - ID Synthetic Target



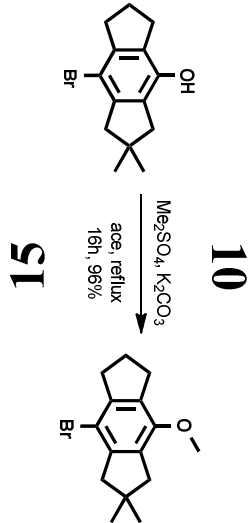
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Honors - ID Synthetic Target



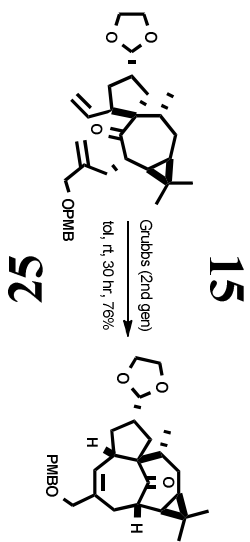
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Honors - ID Synthetic Target



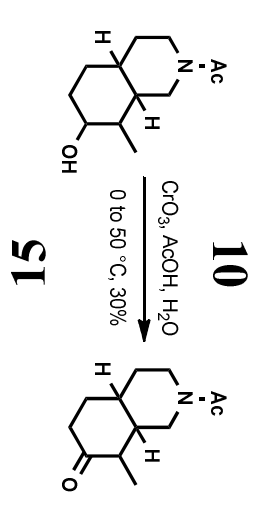
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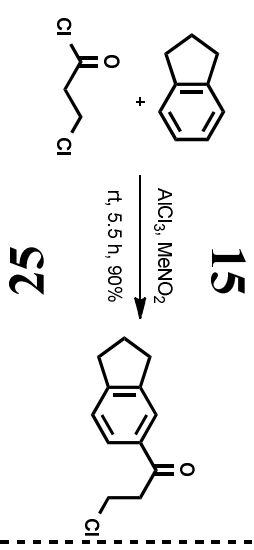
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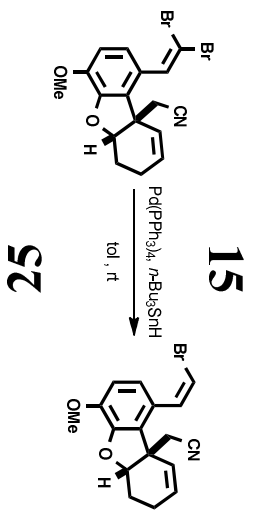
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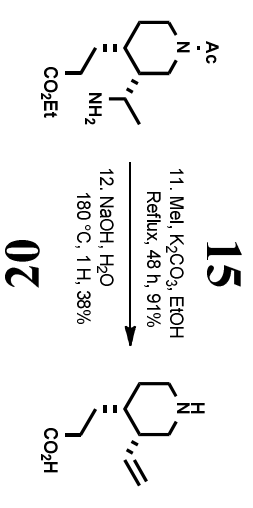
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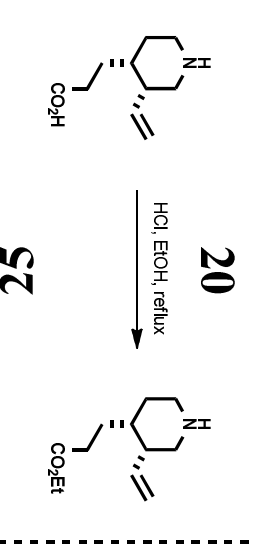
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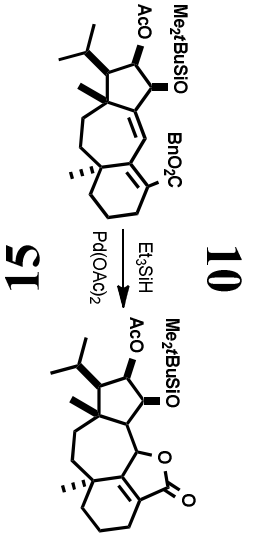
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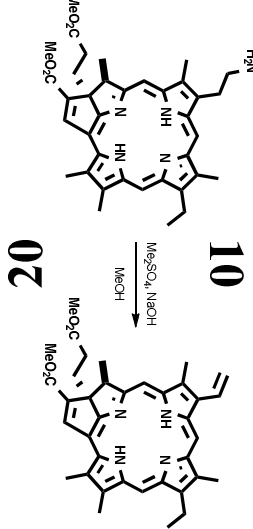
Problem

Honors - ID Synthetic Target



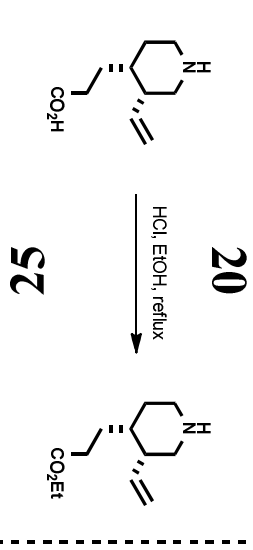
Problem

Honors - ID Synthetic Target



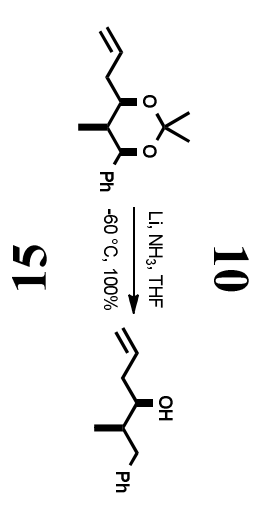
Problem

Honors - ID Synthetic Target



Problem

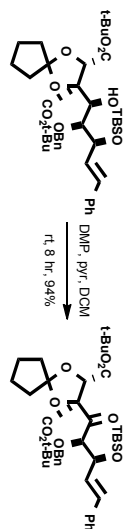
Honors - ID Synthetic Target



Problem

Honors - ID Synthetic Target

15



10

Problem

Bonus

**E. J Corey**

**+10**

Bonus

**Robert B.  
Woodward**

**+10**

Bonus

**Larry Overman**

**+10**

Bonus

**Jeff Aube**

**+10**

Bonus

**David Evans**

**+ 10**

Bonus

**Barry Trost**

**+10**

Bonus

**Leo Paquette**

**+10**

Bonus

**James D. White**

**+10**

Bonus  
**Gilbert Stork**

**+10**

Bonus  
**Dale Boger**

**+10**

Bonus  
**Derek Barton**

**+10**

Bonus  
**Steven Ley**

**+10**

Bonus  
**John L. Wood**

**+10**

Bonus  
**Steven Welch**

**+ 10**

Bonus  
**Isao Kuwajima**

**+10**

Bonus

Bonus

## VITA - CHRISTOPHER KNUDTSON

Christopher Knudtson was born on January 28, 1982 in Omaha, Nebraska. He earned his Bachelor of Science degree in Chemistry from Saint Louis University in 2004 and his Master of Science degree in Chemistry from University of Kansas in 2011. After two years teaching as an adjunct instructor at Midland University and The College of Saint Mary, he entered the University of Missouri - Kansas City (UMKC) Interdisciplinary Doctoral program to pursue his Ph.D. degree in Organic Chemistry with a co-discipline of Pharmaceutical Sciences. He worked on the synthesis of novel bile acid-based derivatives in Dr. Dias's group. He also worked on developing educational resources for undergraduate labs in the form of online videos. In addition to chemistry, he personally enjoys fencing, art, and board games.

### AWARDS & DISTINCTIONS

<b>School of Graduate Studies Research Grant</b>	UMKC	April 2015
<b>Best Graduate Research Poster</b>	Spencer Award Ceremony	Oct 2015
<b>Preparing Future Faculty Scholarship</b>	UMKC	May 2014
<b>Mr. &amp; Mrs. Fong Wu Chen Scholarship</b>	UMKC	May 2014
<b>Best Physical Science Poster</b>	UMKC	May 2014
<b>Dr. &amp; Mrs. Jean Grad. Student Scholarship</b>	UMKC	Aug 2012

### PATENTS AND COPYRIGHTS

Educational Card Game-Functional Groups      #VAu001137709      Oct 2012

### Service

**PUBLICATIONS**

- **Knudtson, C. A.**; Dias, J. R. Recent Methods for Diversification of Bile Acids and Related Steroids towards Supramolecular. *Steroids*. **2019**, *151*, 108442-108445.
- **Knudtson, C. A.** ChemKarta: A Card Game for Teaching Functional Groups in Undergraduate Organic Chemistry. *J. Chem. Educ.* **2015**. *92*, 1514–1517.
- Zang, Q.; Javed, S.; Zhou, A.; **Knudtson, C. A.**; Bi, D.; Basha, F. Z.; Hanson, P. R. Synthesis of a Library of 1,5,2-dithiazepine-1,1-dioxides. Part 2: Routes to Bicyclic Sultams. *Heterocycles* **2012**, *86*, 1675-1688.
- Zang, Q.; Zhou, A.; Javed, S.; Bi, D.; Marity, P.; **Knudtson, C. A.**; Hastings, J. J.; Basha, F. Z.; Hanson, P. R. Synthesis of 1, 5, 2-Dithiazepine-1, 1-dioxide Library Part1: A One-Pot Sulfonylation/thia-Michael (“Cy-Click”) Protocol. *Heterocycles* **2012**, *86*, 1661-1674.
- Ullah, F.; Zang, Q.; Javed, S.; Zhou, A.; **Knudtson, C. A.**; Bi, D.; Hanson, P. R.; Organ, M. G. Synthesis of 1,2,5-thidiazepane 1,1-dioxide Library Utilizing One-Pot Elimination and Inter-/Intramolecular Double aza-Michael Addition Via Microwave-Assisted Continuous Flow Organic Synthesis (MACOS) *J. Flow Chem.* **2012**, *2*, 118-123.
- Zang, Q.; Javed, S.; Ullah, F.; Zhou, A.; **Knudtson, C. A.**; Bi, D.; Basha, F. Z.; Organ, M. G.; Hanson, P. R. Application of a Double aza-Michael Reaction in a



“Click, Click, Cy-Click” Strategy: From Bench to Flow. *Synthesis* **2011**, *17*, 2753-2750.

- **Knudtson, C. A.**; Hanson, P. R. Synthesis of heterocyclic systems by transition-metal-catalyzed cyclization-migration reactions: a diversity-oriented strategy for the construction of spirocyclic 3(2H)-furanones and 3-pyrrolones. *Chemtracts* **2007**, *20*, 469-471.

### **MEMBERSHIPS**

**American Chemical Society**, *Organic Division*

2004 - present

**USA Fencing**, *St Louis Fencing*, St Louis

Epee C 2007, Foil C 2007

**Boy Scouts of America**, *Troop 570*, Omaha NE

Eagle Scout, 2000