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THE TOTAL SYNTHESIS OF MYCOTHIOIOL AND NEW INHIBITORS OF
CARBOHYDRATE PROCESSING ENZYMES

by

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ABSTRACT OF THE DISSERTATION

The Total Synthesis of Mycothiol and New Inhibitors of Carbohydrate

Processing Enzymes

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Professor Spencer Knapp

The work described in this dissertation covers a wide range of disciplines within organic chemistry, with the common goal of obtaining more information about various carbohydrate-processing enzymes. Carbohydrate-processing enzymes are garnering an increasing amount of attention relative to their more well-studied protein-processing counterparts, as they are ubiquitous and implicated in various regulatory, signaling and metabolic processes in eukaryotic cells.

Chapter 1 involves the synthesis of anomeric phosphothioates as possible O-GlcNAc transferase inhibitors, and a mechanistic study on the anomeric Pudovik rearrangement of thiophosphites to thiophosphonates is described.

Chapter 2 is an account of the development of a facile method for functionalizing 2-methyl thiazoline rings, and several selective GlcNAc-thiazoline-based *O*-GlcNAcase inhibitors were synthesized by this method. Chapter 3 details the 16-step total synthesis of the *M. tuberculosis* antioxidant carbohydrate mycothiol by a new intramolecular glycosylation method. The method is amenable to glycosylations of 2-deoxy-2-aminoglycosides, a unique aspect among such reactions. The efficiency of the synthetic route to mycothiol makes it attractive as a template from which to design analogs as potential inhibitors of enzymes involved in the biosynthesis of mycothiol. An apparently unprecedented 1,9-hydride shift is also described in the third chapter.

Chapter 4 describes a tripartate prolonged-release drug delivery system, in which the drug of interest (ethynyl estradiol in this study) is coupled, through a variable linker, to another carrier drug with a long half-life and a relatively high inhibitory concentration. The effect of steric bulk on the *in vitro* release of ethynyl estradiol was evaluated, showing a direct relationship between steric bulk around the ester linkage and ethynyl estradiol release time. *In vivo* data from pigs also seemed to point to an increase in drug bioavailability with the 3-part system. Finally, chapter 5 describes early efforts to synthesize boronic acid analogs of folic acid and antifolates.

Dedication

To my loving parents, David and Josephine Ajayi.

Acknowledgements

The last several years have encompassed an absolutely critical and irreplaceable learning and growing experience for me, and I thank my advisor, Prof. Spencer Knapp, for that experience. Thanks to your guidance and patience, I know how to conduct meaningful and effective scientific research, and I can promise you that I will continue to put those newly-acquired skills to great use. I also thank my thesis committee members, Prof. Lawrence Williams, Prof. Daniel Seidel, and Dr. Agis Kydonieus for invaluable discussions, both scientific and otherwise.

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List of abbreviations

| | |
|----------------|---------------------------------------------------------------------------------------|
| Ac | Acetyl |
| ADME | Absorption, distribution, metabolism, and excretion |
| BEMP | 2- <i>tert</i> -Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine |
| BHT | Butylated hydroxytoluene |
| Bn | Benzyl |
| BNCT | Boron neutron capture therapy |
| BSA | <i>N,O</i> -Bis(trimethylsilyl)acetamide |
| Bt | Benzotriazole |
| COSY | Correlation spectroscopy |
| <i>m</i> -CPBA | 3-Chloroperbenzoic acid |
| DBU | 1,8-Diazabicycloundec-7-ene |
| DMAP | 4-Dimethylaminopyridine |
| DMF | Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| DMTSF | Dimethyl(methylthio)sulfonium tetrafluoroborate |
| EDCI | 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide |
| EE | Ethynyl estradiol |
| FPGS | Folyl- γ -polyglutamate synthetase |
| GlcNAc | <i>N</i> -acetyl glucosamine |

| | |
|--------------|---------------------------------------------------------------------------------------------|
| HATU | <i>O</i> -(7-Azabenotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate |
| HMDS | Hexamethyldisilazane |
| HMPA | Hexamethylphosphoramide |
| HMQC | Heteronuclear multiple quantum coherence |
| IAD | Intramolecular aglycon delivery |
| Ipc | Isopinocampheyl |
| Me | Methyl |
| MS | Molecular sieves |
| MSH | Mycothiol |
| MSSM | Mycothione |
| MTM | Methylthiomethyl |
| NBS | <i>N</i> -bromosuccinimide |
| NMR | Nuclear magnetic resonance |
| OGA | <i>O</i> -GlcNAcase |
| OGT | <i>O</i> -GlcNAc transferase |
| ORTEP | Oak Ridge thermal ellipsoid plot program |
| Pyr | Pyridine |
| <i>t</i> -Bu | <i>tert</i> -butyl |
| TB | Tuberculosis |
| Tf | Trifluoromethanesulfonyl |
| TFA | Trifluoroacetic acid |

| | |
|------|---------------------------|
| TFAA | Trifluoroacetic anhydride |
| THF | Tetrahydrofuran |
| TLC | Thin-layer chromatography |
| TMS | Trimethylsilyl |
| UDP | Uridine diphosphate |
| UV | Ultraviolet |

Chapter 1. Biomimetic phosphothioates

1.1. Biomimetics and bioisosterism

Medicinal chemists employ many different techniques in their quest for new therapeutic agents. One such technique, termed rational drug design, involves the strategic modification of a lead compound with the purpose of increasing *in vivo* activity, decreasing undesired interactions, increasing bioavailability, and/or increasing or decreasing stability.¹ Such modifications usually involve substitution of one atom, or group of atoms, for another atom, or *isostere*, with similar structural or electronic properties (Figure 1.1). *Bioisosteres* are isosteres that also confer similar biochemical properties to the modified substrates.² Compounds that mimic the biochemical function of natural substrates are described as *biomimetic*, and the most straightforward method for designing biomimetic compounds is through isosteric replacement of molecular groups on the natural substrate of interest. In this project, we intended to evaluate the phosphothioate group (Figure 1.1, dashed box) as a bioisosteric replacement for phosphate groups on the anomeric position of some natural glycoconjugates (Figure 1.2), as phosphates often exhibit poor bioavailability and enzymatic lability,³ and thioglycosides often exhibit increased resistance to enzymatic processing.^{4,5}

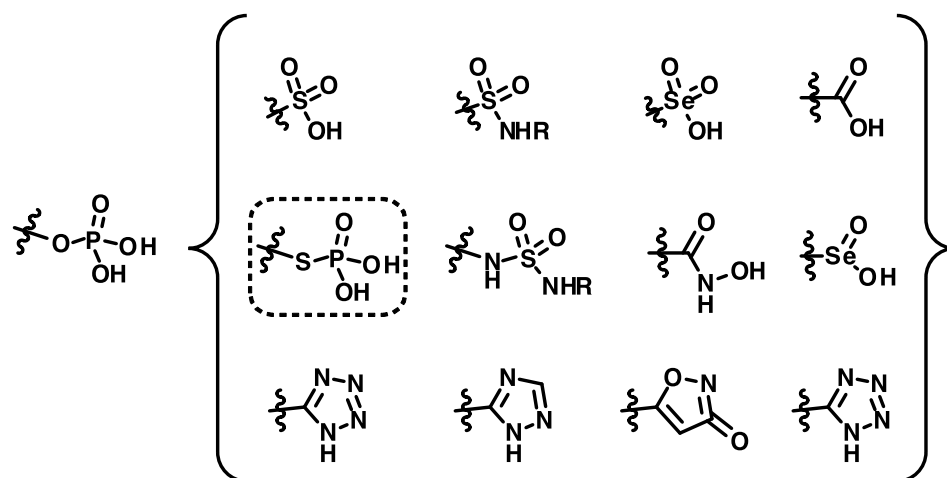


Figure 1.1. Some classical and non-classical bioisosteres

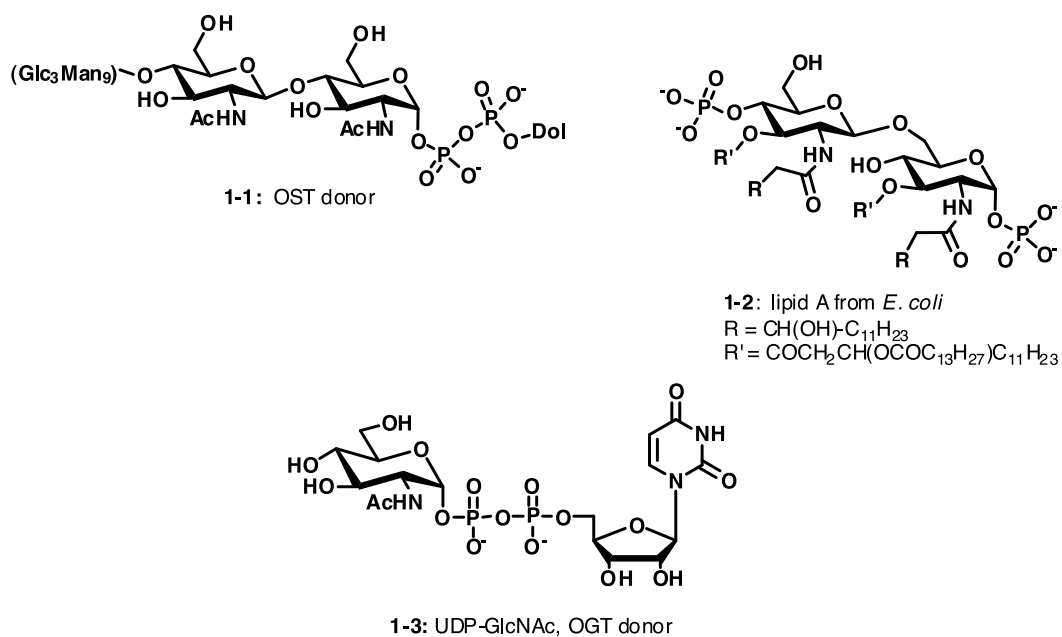


Figure 1.2. Natural glycosyl phosphates

O-GlcNAc transferase (OGT) is a biologically ubiquitous enzyme that promotes the 2-acetamido-2-deoxy- β -D-glucosylation of serine and threonine residues (**1-4**) of a wide variety of nuclear and cytoplasmic proteins (Figure 1.3).^{6,7} Despite the importance of OGT in myriad biological processes and disease states, there is a dearth of OGT inhibitors for use as probes of its action and effects. Many of the known glycosyltransferase inhibitors were created by modifying their endogenous substrates; for OGT, that substrate is uridine diphosphate *N*-acetyl glucosamine (UDP-GlcNAc, **1-3**). UDP-GlcNAc is therefore a sensible target for bioisosteric modification to phosphothioate **1-6**, and many other research groups have made modifications to this molecule with varying results.⁸⁻¹³

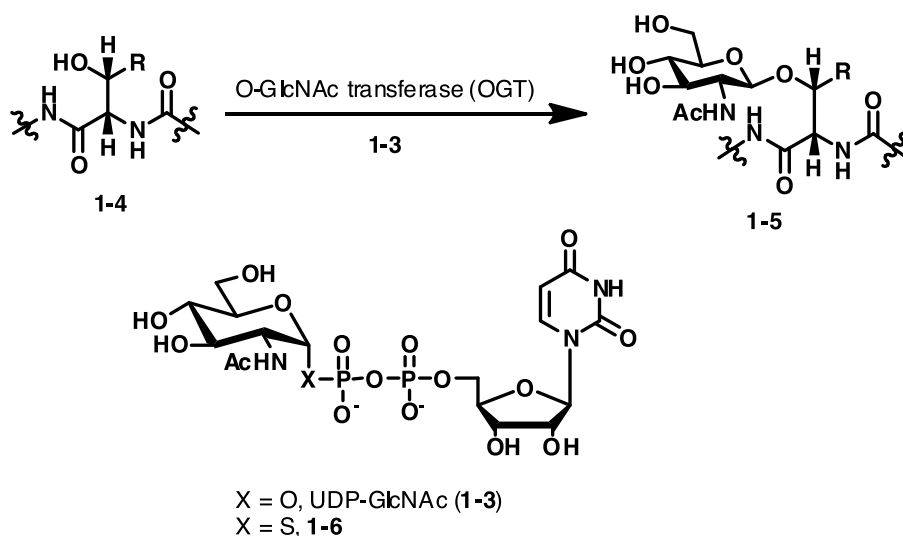
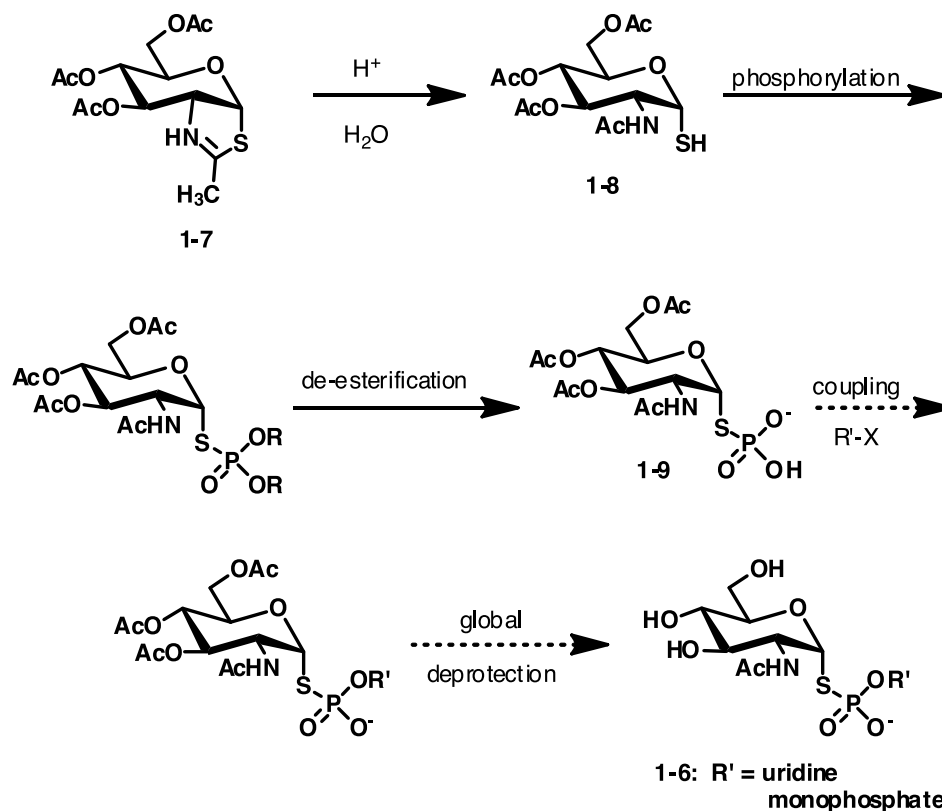


Figure 1.3. OGT mechanism

1.3. Early synthetic studies of anomeric phosphothioates

Reports of *S*-glycopyranosyl phosphothioates are known, but GlcNAc phosphothioates are, as of this writing, exclusive to the Knapp laboratories.^{14–16} Most of the other known syntheses of anomeric phosphothioates are limited in scope and/or efficiency.^{17,18} The targeted biomimetic compounds could all be synthesized using 1,2-*cis*-fused GlcNAc thiazoline **1-7**¹⁹ as the starting material (Scheme 1.1). Acid hydrolysis of **1-7** gives alpha GlcNAc mercaptan **1-8**,^{15,16} which can be phosphorylated using various methods. Subsequent deesterification to **1-9** and coupling with the appropriate partner would produce the desired biomimics such as UDP-GlcNAc mimic **1-6**.



Scheme 1.1. Synthetic route to phosphothioates

The reactions of **1-8** with *O,O*-dialkyl (*N,N*-diisopropyl)phosphoramidites under acidic activation with tetrazole (Table 1.1), followed by oxidation with tert-butylhydroperoxide,^{15–18} gave good to poor yields of the desired *O,O*-dialkyl-*S*-glycosylphosphothioates **1-10–1-12**, as a function of the *O*-alkyl substituent (allyl, methyl, or benzyl, respectively). These products were characterized by their mass, ^1H NMR ($J_{\text{H-1/H-2}} \sim 5$ Hz), ^{13}C NMR, and ^{31}P NMR (diagnostic signal near 24 ppm) spectra. In addition, **1-10–1-12** were accompanied by varying amounts of the rearranged *O,O*-dialkyl-*P*-glycosylthiophosphonates **1-13–1-15** (Table 1.1, entries 1–3).

These products were characterized by their mass, ^1H NMR, ^{13}C NMR, and ^{31}P NMR (diagnostic signal near 88 ppm) spectra. The alpha configurations of **1-13–1-15** were indicated by their large trans-diaxial H-2/P couplings (e.g., 31 Hz for **1-15**, whereas the beta isomer should show 10 Hz).²⁰

Table 1.1. S-phosphorylations with *O,O*-dialkyl *N,N*-diisopropylphosphoramidites

1-8

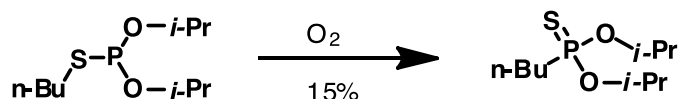
1-10: R = allyl
1-11: R = Me
1-12: R = Bn

1-13: R = allyl
1-14: R = Me
1-15: R = Bn

| Entry | R | Acid promotor | [O] | Yield of <i>S</i> -glycosides | Yield of <i>P</i> -glycosides |
|-------|--------|-----------------|------------------------|-------------------------------|-------------------------------|
| 1 | Allyl | Tetrazole | <i>t</i> -BuOOH | 62% (1-10) | — |
| 2 | Methyl | Tetrazole | <i>t</i> -BuOOH | 5% (1-11) | 45% (1-14) |
| 3 | Benzyl | Tetrazole | <i>t</i> -BuOOH | — | 48% (1-15) |
| 4 | Benzyl | Tetrazole + BHT | <i>t</i> -BuOOH | 41% (1-12) | 13% (1-15) |
| 5 | Benzyl | Tetrazole, 0 °C | Et ₃ B, air | <1% | 79% (1-15) |
| 6 | Benzyl | NMB-HOTf | <i>m</i> -CPBA | 72% (1-12) | — |

1.4. The anomeric Pudovik rearrangement

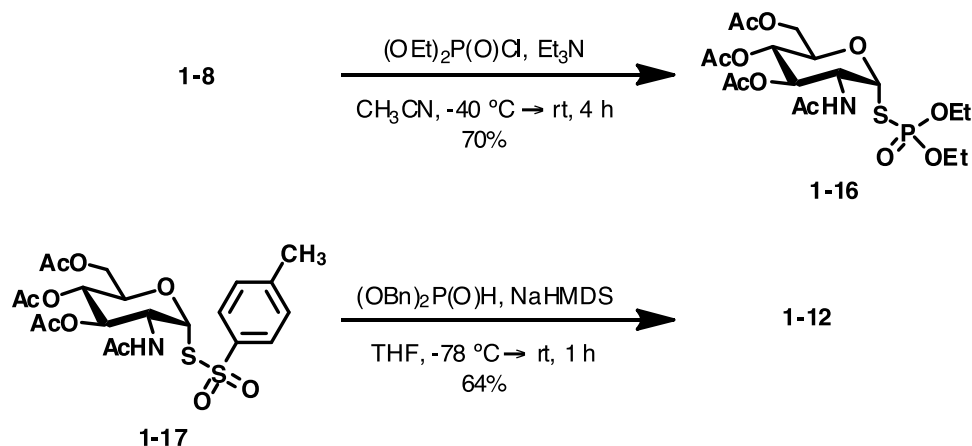
Products **1-13–1-15** reflect a Pudovik rearrangement (Scheme 1.2), wherein the thiophosphite *S*-substituent (here, glucopyranosyl) has migrated to phosphorus. This reaction, which may be viewed as a version of the Arbuzov rearrangement, has been previously studied by Pudovik and Pudovik and their co-workers,^{21–28} as well as by others.^{29–32} The Arbuzov rearrangement³³ itself encompasses a broad family of phosphite to phosphonate transformations initiated variously by alkylation, heat, light, or radicals.



Scheme 1.2. A prototypal Pudovik rearrangement

Most prior examples of the Pudovik rearrangement occur upon exposure of the thiophosphite to oxygen or air, and are postulated to be radical processes.²⁷ Accordingly, the reaction of **1-8** with *O,O*-dibenzyl(*N,N*-diisopropyl)phosphoamidite was repeated, but with the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT) added during the oxidation step. The result (entry 4) was an increase in the percentage of phosphothioate **1-12**, and less rearrangement to **1-15**. Very likely the *O*-allyl substituents in entry 1 also inhibit radical propagation, accounting for the preferred formation of **1-10**. In contrast, the Pudovik rearrangement product **1-15** was formed almost exclusively when the oxidation was promoted by the radical initiator combination³⁴ of triethylborane and air (entry 5). Modifications in the promoter³⁵ and the oxidation conditions allowed the isolation of the phosphorylation product **1-12** in good yield to the exclusion of the rearrangement (entry 6, NMB = *N*-methylbenzimidazole). The oxidant *m*-chloroperbenzoic acid probably operates by a polar mechanism, minimizing the formation of **1-15**. Alternatively, the *S*-glycosylphosphothioate product **1-16** was prepared without oxidation by treating **1** directly with base and diethyl chlorophosphate (Scheme 1.3). The latter reaction failed in the *O,O*-dibenzyl version; instead, benzyl

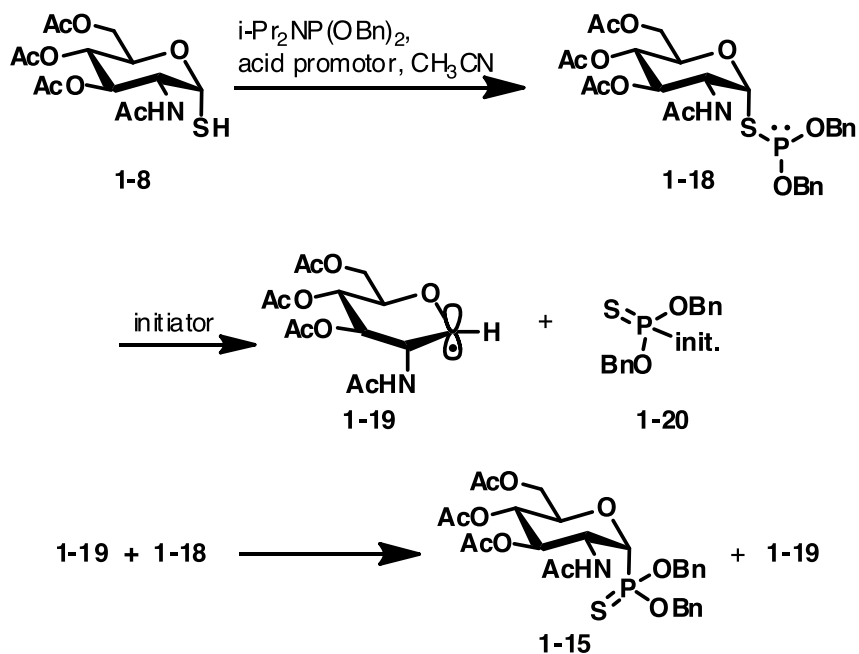
3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-1-thio-*alpha*-D-glucopyranoside was formed in 27% yield as the result of thiolate *S*-benzylation. The phosphothioate product could also be formed by treating an *S*-glycosylthiosulfonate³⁶, such as **1-17**, with the desired trialkyl phosphite or a dialkyl phosphite and a strong base.³⁷



Scheme 1.3. Direct phosphorylation of mercaptan **1-8**

The formation of thiophosphonates **1-13–1-15** can be accommodated by the radical chain process shown in [Scheme 1.4](#). Initial *S*-phosphitylation of **1-8** to give the intermediate thiophosphite **1-18** is followed, upon addition of initiator, by a radical initiation step consisting of the removal of the phosphothiyl fragment **1-20** and formation of the 3,4,5-*O*-triacetyl-2-acetamido-2-deoxy-D-glucopyranosyl anomeric radical **1-19**.³⁸ Subsequent and analogous reaction of **1-19** with **1-18** in a propagation step provides product **1-15** and regenerates **1-19**. The *alpha* anomeric stereochemistry of **1-15** reflects the tendency (with ample precedent) of

D-glucopyranosyl anomeric radicals such as **1-19** to react with almost exclusive *alpha* stereoselectivity.³⁹

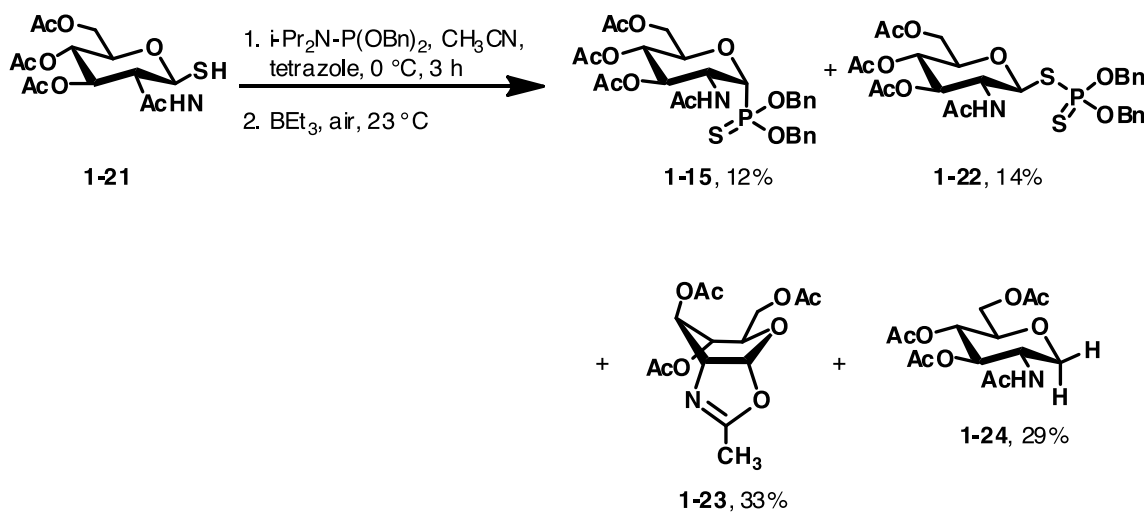


Scheme 1.4. Radical chain mechanism for the Pudovik rearrangement of **1-18**

1.5. Pudovik rearrangement of *beta* thiophosphites

A radical fragmentation/recombination mechanism has been advanced for the Pudovik rearrangement,²⁷ to our knowledge the stereochemical consequences at the migrating carbon have not previously been investigated. Application of the reaction conditions of entry 5 (Table 1.1) to the phosphorylation/oxidation of the corresponding *beta* anomeric mercaptan **1-21** led,

after chromatography, to the array of products shown in [Scheme 1.5](#). The alpha thiophosphonate **1-15** matched the compound obtained from **1-8**. The corresponding *beta* thiophosphonate, which if formed should have eluted near **1-15**, was neither isolated nor detected by ^{31}P or ^1H NMR analysis of the crude reaction mixture or chromatography fractions. The *beta* phosphodithioate **1-22** was characterized by its ^1H (with COSY analysis), ^{13}C , ^{31}P , and mass spectra.⁴⁰ Its *beta* configuration was established by the large H-1/ H-2 coupling (10 Hz). The oxazoline **1-23** and 3,4,5-tri-*O*-acetyl-2-acetamido-1,5-anhydro-2-deoxy-D-glucitol **1-24** were identified by spectroscopic comparison with the known compounds.

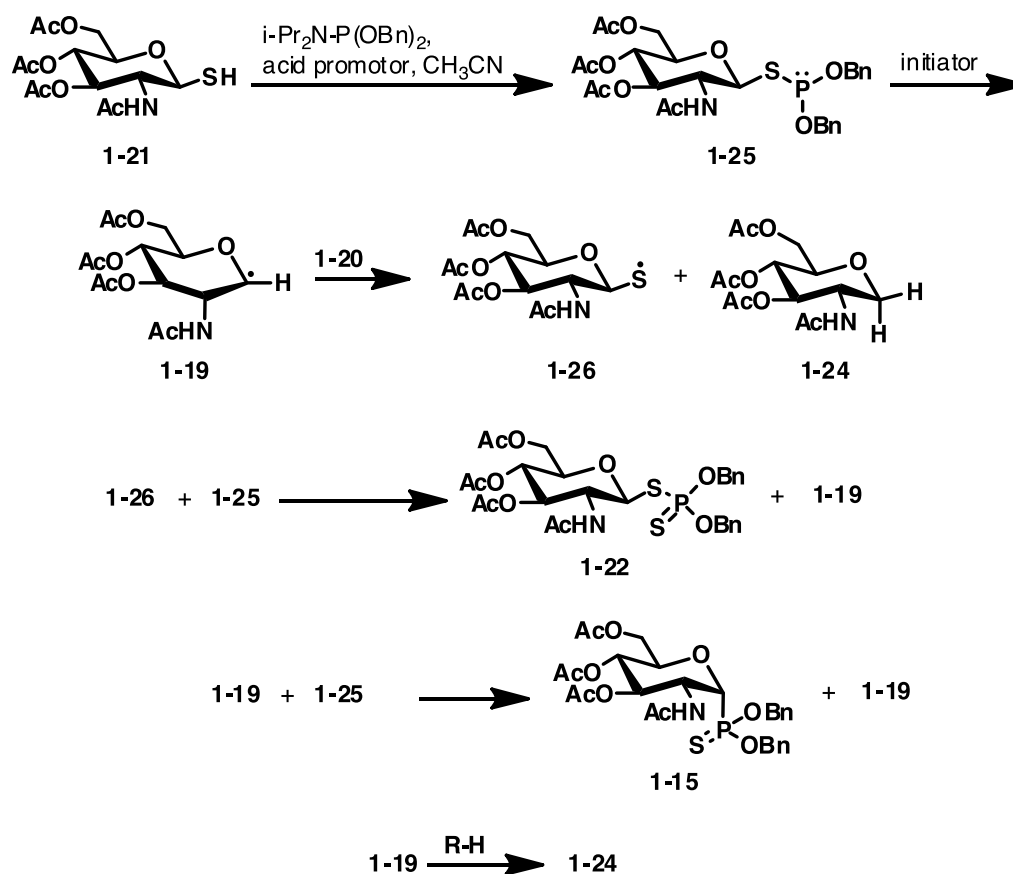


Scheme 1.5. Phosphitylation/oxidation/rearrangement of the *beta* mercaptan

1-21

[Scheme 1.6](#) shows pathways that rationalize the formation of **1-15**, **1-22**, **1-23**, and **1-24** from **1-21**. Following phosphitylation of **1-21** analogous to that of **1-8**, the thiophosphite **1-25** reacts with the radical initiator to produce the same

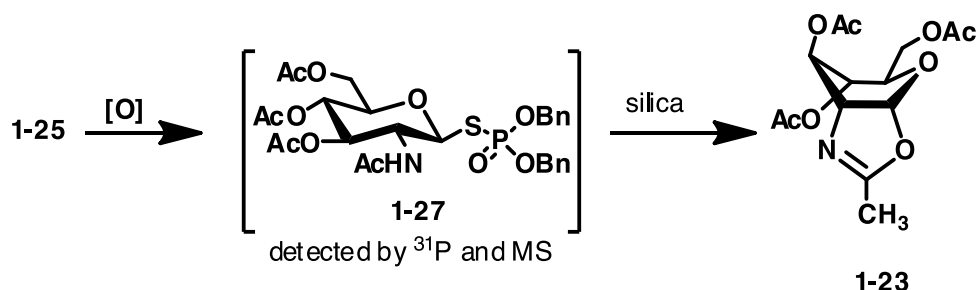
3,4,5-*O*-triacetyl-2-acetamido-2-deoxy-D-glucopyranosyl anomeric radical **1-19**. The analogous chain propagation step involving **1-19** and **1-25** likewise produces the alpha thiophosphonate **1-15** (the Pudovik rearrangement product). To the extent that starting mercaptan **1-21** remains, reaction of **1-19** with **1-21** gives thiyl radical **1-26** by hydrogen atom transfer, and a chain propagation step involving **1-26** and **1-25** leads to the phosphodithioate **1-22**. Dithio products analogous to **1-22** have been isolated previously from the Pudovik rearrangement reaction mixtures, particularly when excess mercaptan is present.^{17,25} The other (reduced) product from the latter process has not been reported, but in this case can be isolated in the form of tri-*O*-acetyl-2-acetamido-1,5-anhydro-2-deoxy-D-glucitol **1-24**. While **1-22** can come from unreacted **1-21**, an additional reductive pathway (e.g., **1-19** → **1-24**) is likely present to account for the fact that there is formed more **1-24** than **1-22**.



Scheme 1.6. Proposed pathways for the *beta* mercaptan phosphitylation/oxidation

Some of the (*P*-oxidized) phosphothioate **1-27** (Scheme 1.7) probably formed in competition with **1-15**, as has been noted in other systems,^{17,25,32} and in the entries in Table 1.1. Circumstantial evidence for **1-27** was found in the crude reaction mixture: ^{31}P NMR analysis showed a phosphothioate peak at 25.1 ppm (compare **1-12** at 24.4), and the mass spectrum featured a prominent signal at m/z 646, which corresponds to $[\text{MNa}]^+$ for **1-27**. Instead of **1-27**, however, oxazoline **1-23** was isolated in significant amounts, even though it was not present

in the crude product mixture (e.g., no H-4 of **1-23** at or near 4.81 ppm). Oxazoline **1-23** could be formed by acid-promoted cyclization of **1-27** during chromatography.



Scheme 1.7. Pathway for formation of oxazoline **1-23**

The formation of **1-15**, independent of the stereochemistry of the precursor thiophosphite (**1-18** or **1-25**) and to the apparent exclusion of the *beta* stereoisomer, provides strong evidence that the same anomeric radical (**1-19**) is the intermediate in both reactions. Formation of the reduction product **1-24** is also rationalized by invoking **1-19** as the intermediate.

The differences in the phosphitylation/oxidation reactions of **1-8** and **1-21** merit comment. Although the reaction conditions are very similar, the relative rates of initial phosphitylation differ, with *alpha* mercaptan **1-8** being qualitatively more reactive according to TLC analysis. The relative rates of conversion of the thiophosphites **1-18** and **1-25** to the anomeric radical **1-19** may also differ, although the related 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl anomeric radical is formed from both the *alpha* and *beta* anomeric chloride precursors at about the

same rate (Cl abstraction by tributyltin radical).⁴¹ Finally, autooxidation at phosphorus⁴² of **1-18** and **1-25** to the respective phosphothioates **1-12** and **1-27** (competing with formation of **1-19**) may occur at different rates. A faster rate of oxidation of **1-25** would account for the formation of more oxidized product **1-27** (and hence **1-23**) compared with **1-12** under these conditions.

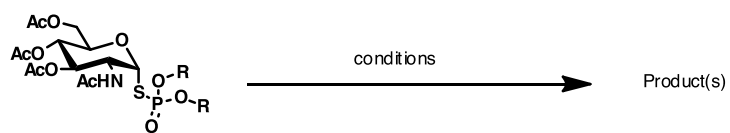
1.6. Phosphothioate deesterification and future direction

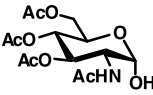
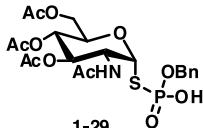
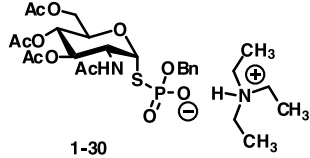
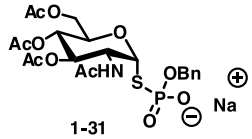
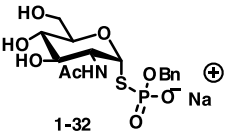
With a reliable synthesis of *S*-glycopyranosyl phosphothioates available, we examined methods for unmasking the free, dibasic phosphothioate **1-37**, and the results are summarized in Table 1.2. Dialkyl phosphates are often removed under acidic conditions in a polar solvent with a trimethylsilyl halide,^{43,44} but application of these conditions to the dimethyl- and diethylphosphothioates was not fruitful. Those conditions produced varying amounts of the reducing sugar **1-28** (entry 3), and when 2,6-lutidine was added as a buffer (entries 1 and 2),⁸ no reaction occurred. Diethyl phosphothioate **1-16** was exposed to DBU at elevated temperatures but, unlike with the ethyl ester of a glycosyl sulfonate,⁴⁵ no deesterification occurred (entry 4).

Benzyl esters are popular protecting groups, mainly because of their facile removal with palladium supported on carbon. When dibenzyl phosphothioate **1-12** was subjected to typical hydrogenation conditions, only one benzyl group was removed to form **1-29** (entry 5), characterized by an upfield shift of .

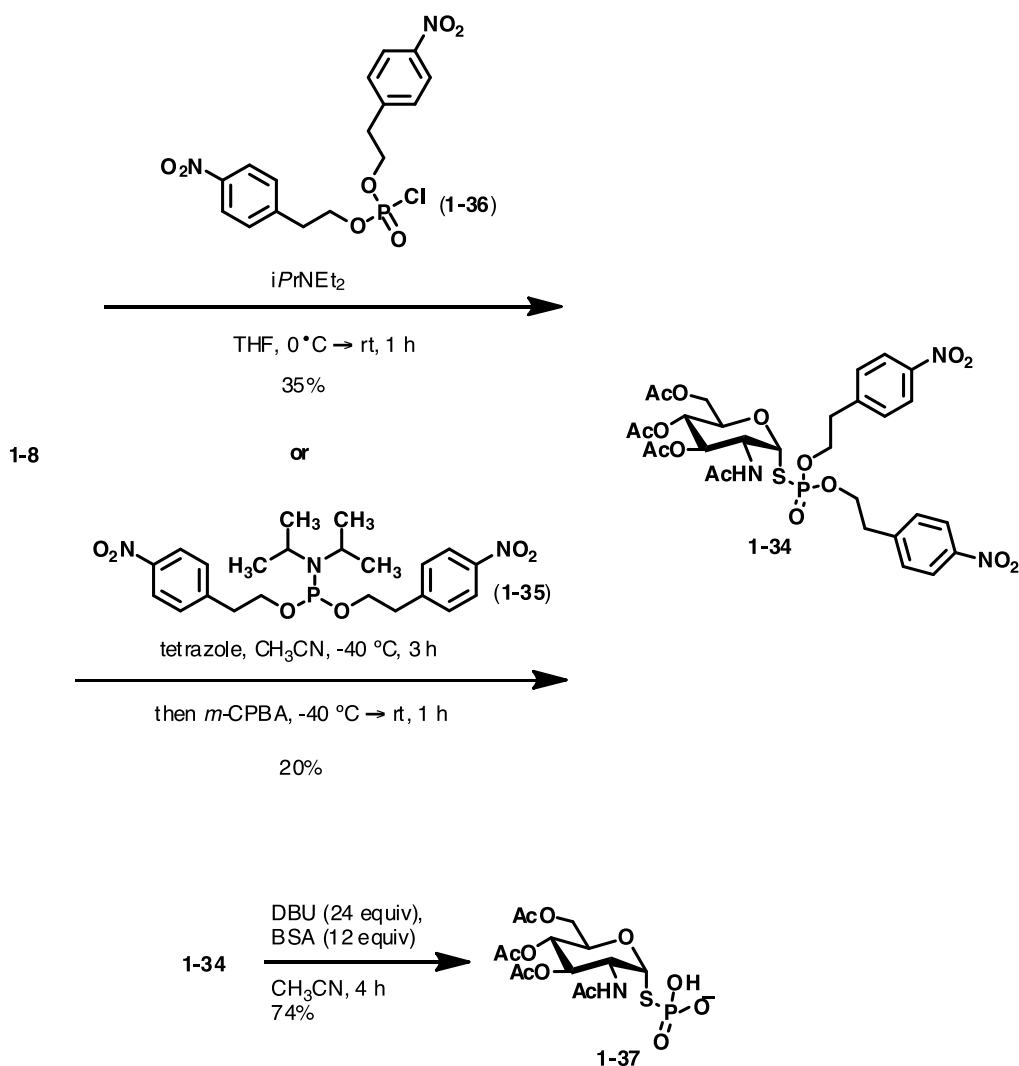
Apparently, the increased electron density that results from monodebenzylation poisoned the catalyst and prevented further hydrogenation. Charging the flask with additional catalyst eventually effects reduction at the anomeric carbon to produce glucitol **1-24**. Use of triethylamine to buffer any acidic intermediates did not improve the reaction (entry 6), and use of a pH 4 carbonate buffer was likewise ineffective (entry 7). When the hydrogenolysis was carried out in a pH 2 chloride buffer, several phosphorus-free products were produced, including **1-28** (entry 8). Anomeric phosphate benzyl esters of an acid-sensitive sugar were reportedly hydrogenated in the presence of sodium bicarbonate,⁴⁶ but those conditions failed to give the desired dibasic phosphothioate, instead giving monobasic triol **1-32** after 8 hours (entry 9). Diphenyl phosphothioate **1-33** was subjected to hydrogenation conditions using platinum oxide as the catalyst, but no reaction took place (entry 10). These results caused us to, with great reluctance, try less popular ester groups.

Table 1.2. Attempted phosphothioate deesterification



| Entry | R | Conditions | Product(s) |
|-------|----|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| 1 | Et | TMS-Br, 2,6-lutidine CH ₃ CN | no reaction |
| 2 | Et | TMS-I, 2,6-lutidine CH ₃ CN | no reaction |
| 3 | Et | TMS-I, CH ₃ CN |  1-28 |
| 4 | Et | DBU, toluene, 65 °C | no reaction |
| 5 | Bn | H ₂ , Pd/C THF |  1-29 + 1-24 |
| 6 | Bn | H ₂ , Pd/C, Et ₃ N CH ₃ OH, CH ₂ Cl ₂ |  1-30 |
| 7 | Bn | H ₂ , Pd/C CH ₃ OH, pH 4 buffer |  1-31 |
| 8 | Bn | H ₂ , Pd/C CH ₃ OH, pH 2 buffer | 1-28 |
| 9 | Bn | H ₂ , Pd/C, aq NaHCO ₃ CH ₃ OH |  1-32 |
| 10 | Ph | H ₂ , PtO ₂ , EtOH | no reaction |

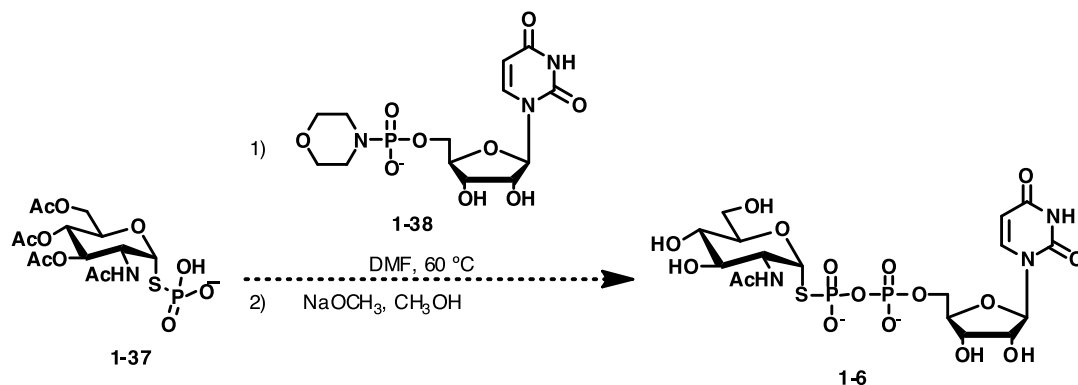
Phosphothioate **1-12** seemed to be unstable to acidic conditions, and the carbon-sulfur bond appeared to be reductively labile to an appreciable extent. We thought it was possible that when **1-16** was treated with iodotrimethylsilane, the ethyl groups may have been removed, leaving behind a phosphorothioic acid that was unstable to the acidic conditions. If that hypothesis is correct, then using base-labile protecting groups may be a viable solution. After trying a few such groups (cyanoethyl, fluorenylmethyl) we eventually found some success with the 2-(4-nitrophenyl)ethyl group^{47,48}, which can be installed onto **1-8** using either the phosphoramidite method with phosphoramidite **1-35**,⁴⁹ or with the chlorophosphate **1-36**, prepared by a literature procedure.⁵⁰ Unoptimized runs of both methods yielded **1-34** in 20% and 35% yields, respectively (Scheme 1.8). As Pudovik rearrangement occurs at temperatures as low as -40 °C, circumvention of the thiophosphite intermediate is most wise. Upon treatment with excess DBU for 30 minutes, one of the nitrophenethyl groups of phosphothioate **1-34** was removed. The other group is expected to leave under prolonged (>24 hours) exposure to DBU,⁵⁰ but addition of excess *N,O*-bis(trimethylsilyl)acetamide to the reaction⁵¹ caused the dibasic phosphothioate **1-37** to form in 74% yield after 4 hours at room temperature and a silica gel column with triethylamine in the eluent.



Scheme 1.8. Synthesis and deesterification of phosphothioate 1-34

With phosphothioate **1-37** in hand, we can now attempt couplings with suitable reagents. To obtain UDP-GlcNAc mimic **1-6**, **1-37** can be coupled to a uridine monophosphate derivative that can be activated under the reaction conditions (Scheme 1.9). Morpholidate **1-38** is usually activated by a mild acid, like tetrazole, though it was found that the starting anomeric phosphate is

sufficiently acidic to effect this coupling.⁵² Deacetylation of the coupled product would give **1-6**.



Scheme 1.9. Synthetic route to **1-6**

1.7. References

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Chapter 2. Tautomeric Modification of Glc-NAc Thiazoline

2.1. *O*-GlcNAcase as a therapeutic target

A wide variety of nuclear and cytoplasmic proteins are modified on serine and threonine residues by the dynamic addition and removal of *O*-GlcNAc units.¹⁻³ These diverse targets mediate important biological processes that may in turn be regulated by the β -*O*-GlcNAc cycling. *O*-GlcNAc addition and removal are catalyzed, respectively, by *O*-GlcNAc transferase (OGT) and *O*-GlcNAcase (OGA, Figure 2.1), the study of which has acquired urgency as the importance of the *O*-GlcNAc modification to processes such as cellular signaling and regulation⁴ and to disease states such as type II diabetes,⁵ cancer,⁶ and Alzheimer's⁷ has become clear.

2.2. GlcNAc 1,2-*cis*-fused thiazolines as OGA inhibitors

To help sort out the mechanisms and effects of protein "*O*-GlcNAc-ylation," a significant effort has been directed toward the development of inhibitors of OGA that do not simultaneously inhibit the mechanistically related human *N*-acetylhexosaminidases HexA and HexB. In comparison to the latter, OGA tolerates inhibitor groups larger than acetamido -CH₃, or its equivalent, in the acetamido binding pocket and thus provides an avenue for potential optimization of inhibitor selectivity, efficacy, solubility, transport, and metabolic stability.

GlcNAc-thiazoline⁸ (**2-2**, Figure 2.1) is a nanomolar but nonselective inhibitor of OGA, HexA,⁹ and HexB by virtue of its resemblance to the transition state leading to the enzyme-bound intermediate, oxazolinium ion **2-1**.^{10,11} By increasing the size of the thiazoline ring substituent from methyl to ethyl, propyl, and isopropyl, Vocadlo and coworkers were able to increase the selectivity for inhibition of OGA (see **2-3–2-5**).^{12,13} Analogous steric-based selectivity improvements to other OGA inhibitors have also been realized.^{13–20} On the other hand, inhibitors that possess *functionalized* acetamido mimics could provide an expanded array of options for biochemical and medicinal chemistry studies.²¹ We have now prepared a new series of methyl- modified GlcNAc-thiazolines **2-6** by exploiting the previously unrecognized propensity of GlcNAc-thiazolines to undergo buffer- and acylation-induced imine-to-enamine conversion.

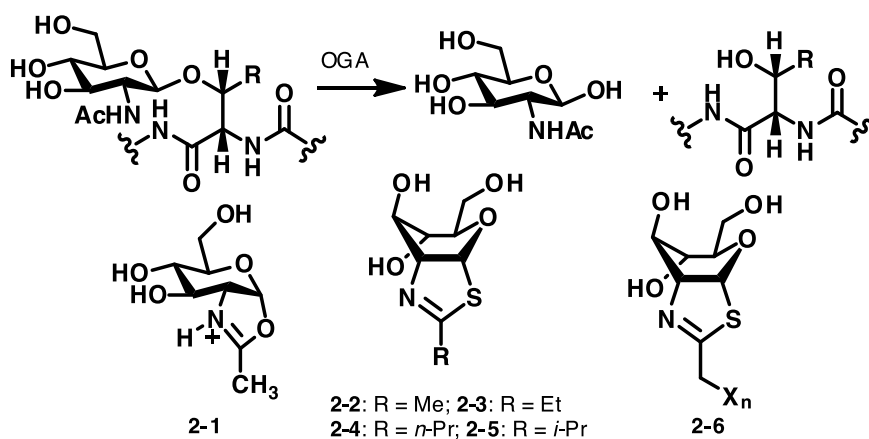
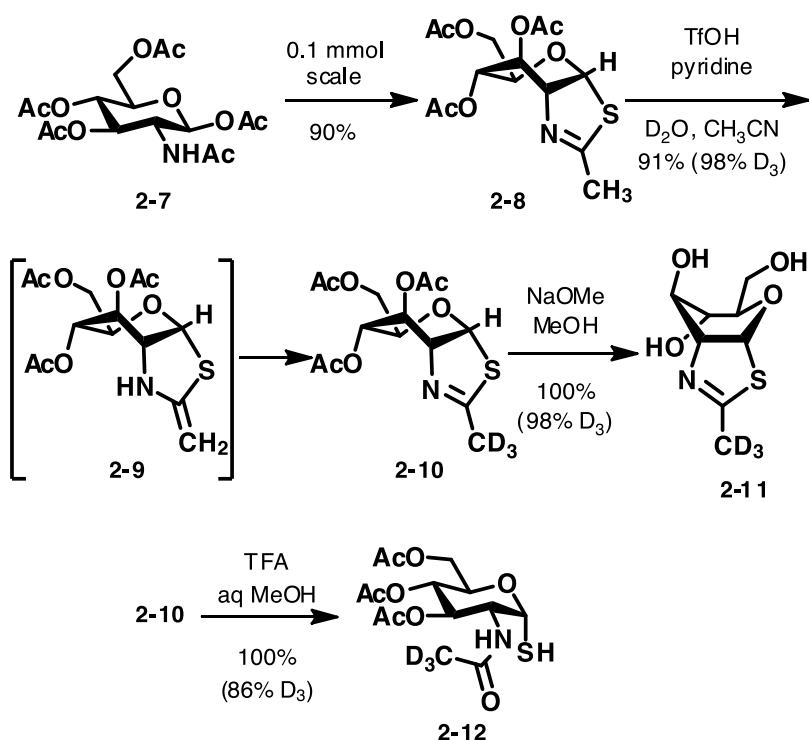


Figure 2.1. OGA-catalyzed reaction, intermediate, and OGA inhibitors

2.3. Tautomeric modification of 2-methyl thiazolines

The GlcNAc-thiazoline triacetate **2-8** is available on a multigram scale by treatment of commercial glucosamine pentaacetate **2-7** with P_4S_{10} (Scheme 2.1).²² Whereas **2-2** binds in enzyme active sites in an apparent *pseudo-chair* (4C_1) pyranose conformation,^{23–26} GlcNAc-thiazoline triacetates such as **2-8** exist principally in a twist boat (0S_2) in $CDCl_3$ solution.²⁷ In the solid state, the 2,4-dinitrobenzenesulfonic acid salt of **2-8** also exhibits the 0S_2 pyranose conformation (Figure 2.2). The corresponding thiazoline triols (e.g., **2-2**) exist in a dynamic equilibrium ($^4C_1 \rightleftharpoons ^0S_2 \rightleftharpoons ^1S_3$).²⁸



Scheme 2.1. Tautomeric deuteration of GlcNAc-thiazoline

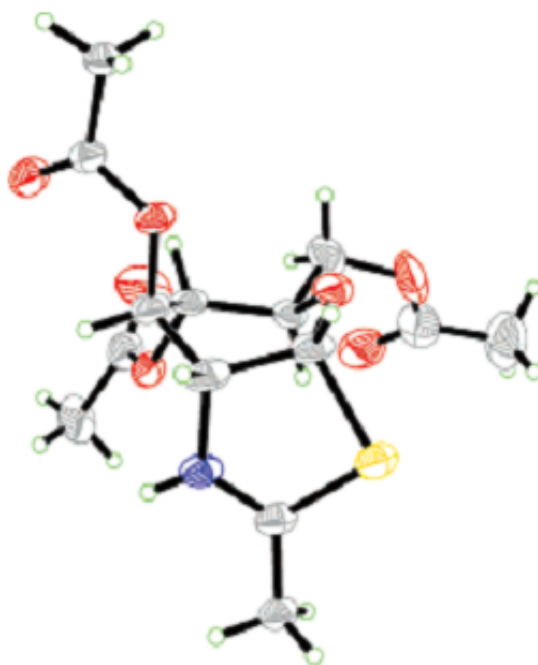


Figure 2.2. ORTEP view of one cation of the salt $8 \cdot \text{HO}_3\text{SAr}$ (Ar = 2,4-dinitrophenyl), showing the $^{\circ}\text{S}_2$ pyranose conformation.

The methyl protons of **2-8** exchange with deuterium in certain solvents in the presence of acid. As this reaction could also be used to prepare tritiated **2-2**, the deuteration was optimized as follows. Treatment of **2-8** with 2.4 equiv of pyridine, 1.2 equiv of triflic acid, and 100 equiv of D_2O in acetonitrile solution for 8 h at 23 °C and then extractive workup gave the trideuterated GlcNAc-thiazoline **2-10**. No C-deuteration was detected in the absence of the buffer components pyridine and triflic acid. Standard deacetylation then led to the corresponding triol **2-11** without significant loss of deuterium, according to integration of the methyl signal in the ^1H NMR spectrum. Alternatively, triol **2-2** was directly trideuterated by treatment with the same buffer system, and **2-11** was separated from the buffer

components by partitioning between 1-butanol and saturated aqueous sodium bicarbonate (93% yield, 95% D₃). In polar solvents at acidic pH, **2-8** hydrolyzes to the acetamido mercaptan, and thioconjugates can then be prepared by various *S*-alkylation and arylation reactions.²⁹ Hydrolysis of **2-10** led analogously to the trideuteroacetamido mercaptan **2-12**; however, ~5% of the deuterium was lost in the process. The transformations in Scheme 2.1 are consistent with acid-promoted tautomerization of **2-8** to give the enamine **2-9**; reprotonation leads to sequential replacement of all three methyl H's.

Would other electrophiles react with **2-9**? Treatment of **2-8** with the same buffer but in the presence of 3.2 equiv of *N*-bromosuccinimide gave the tribromide **2-14** (Figure 2.3). The dibromide **2-13** could be obtained (along with **2-14**) by reducing the amount of NBS to 2.2 equiv. The monobromide could not be prepared selectively, evidently because the second and third brominations are faster than the first. Fluorination, however, could be effectively stopped after one substitution: exposure of **8** to buffer and 1.5 equiv of Selectfluor³⁰ gave **2-15** in high yield. Standard deacetylation led to the fluoro thiazoline triol **2-16**.

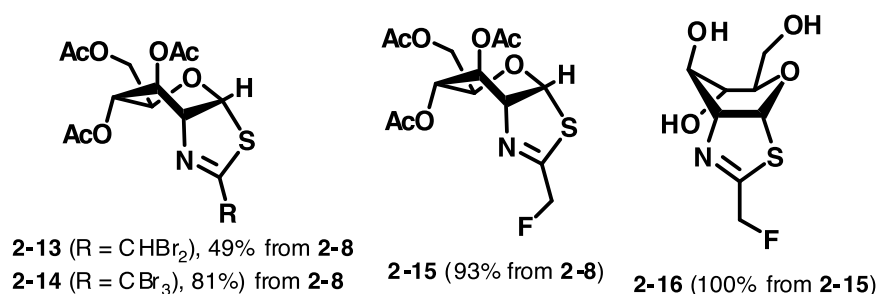
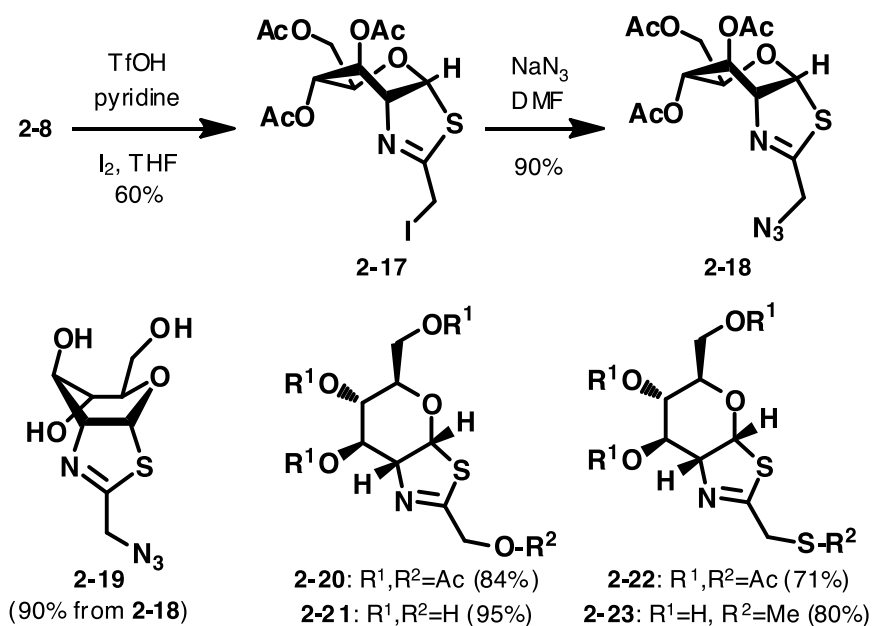


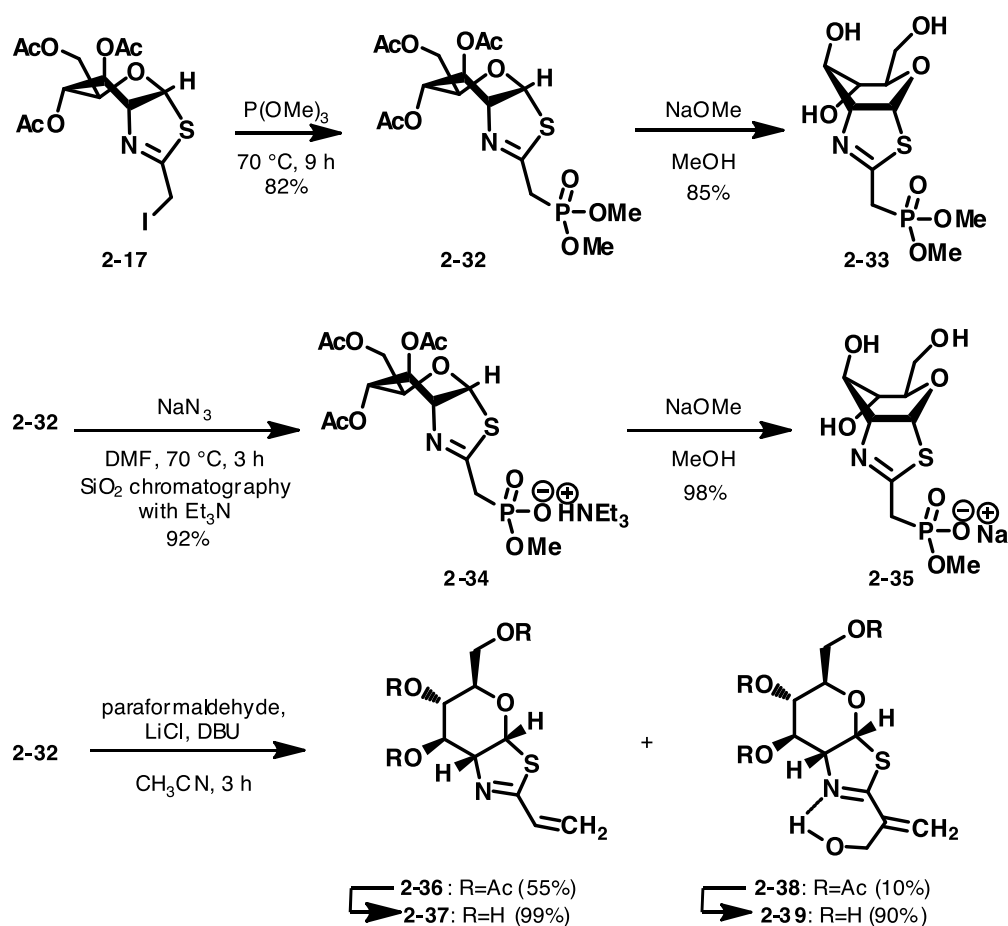
Figure 2.3. Tautomeric halogenation of GlcNAc-thiazoline

Iodination of **2-8** could also be stopped after a monosubstitution (Scheme 2.2). The product **2-17** proved to be unstable to storage but could be isolated, characterized, and subsequently treated with nucleophiles. Thus, substitution of iodo by azido led to **2-18** and, following deacetylation, to **2-19**. Replacement of iodo with acetoxy and *S*-acetylthio was also successful, and the resulting thiazolines **2-20** and **2-22** were deacetylated (the latter in the presence of iodomethane) to afford **2-21** and **2-23**, respectively.



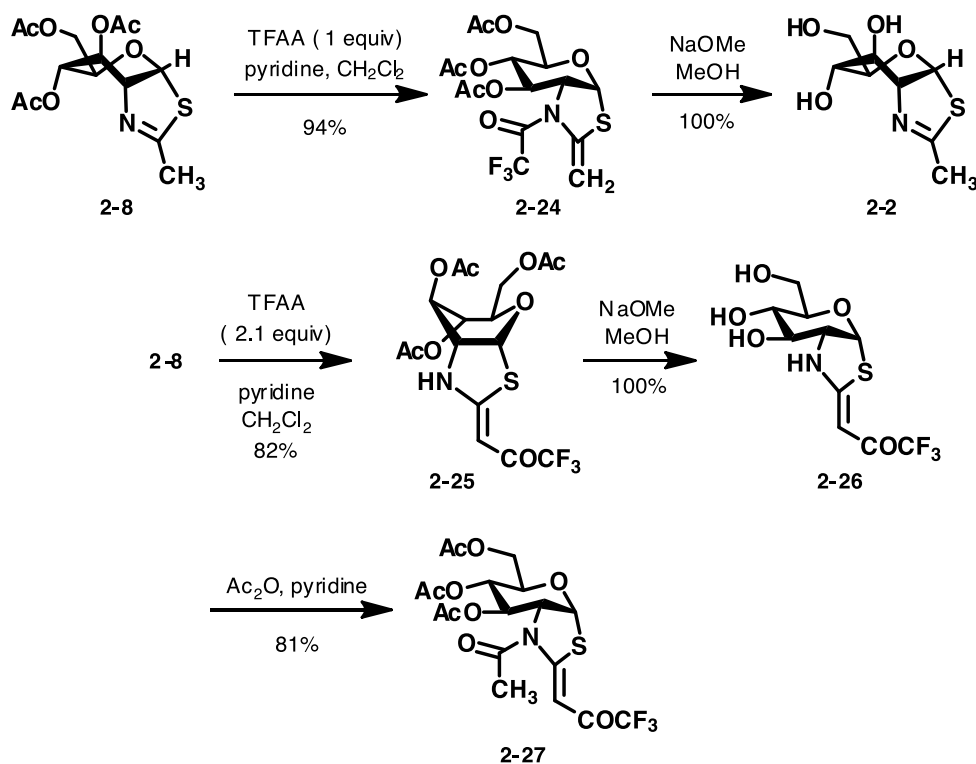
Scheme 2.2. Tautomeric iodination and displacement reactions

Iodide **2-17** was also converted to the dimethylphosphonate **2-32**, which served as the starting point for four other derivatives (Scheme 2.3): phosphonate diester **2-33**, monobasic phosphonate **2-35** (from treatment with sodium azide), vinyl thiazoline **2-37** (a Horner-Wadsworth-Emmons olefination product³¹), and enol **2-39** (from double addition of formaldehyde during HWE olefination). Derivatives **2-37** and **2-39** might serve as competent active site nucleophile traps.



Scheme 2.3. New analogs from phosphonate **2-32**

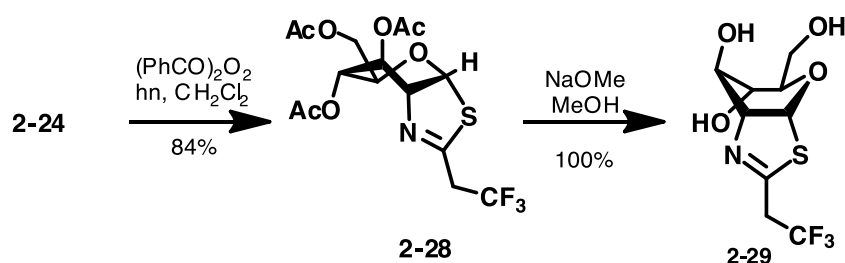
The ease of tautomerization of **2-8** suggested that an *N*-acyl enamine might also be accessible (Scheme 2.4).³² Reaction of **2-8** with 1 equiv of TFAA (courtesy of Mohannad Abdo) indeed gave the enamine **2-24**. In methanol solution, **2-24** reverted to **2-8**, and when treated with methoxide, **2-24** gave **2-2**. Upon acylation of **2-8** with 2.1 equiv of TFAA, the *C*-acylated product **25** formed in good yield, presumably through **2-24** as an intermediate. Deacetylation gave keto triol **2-26**, as confirmed by peracetylation to **2-27**. Both **2-24** and **2-27** exist as *pseudo*-chair conformers in solution, according to the vicinal proton *J* values.



Scheme 2.4. Thiazoline acylations

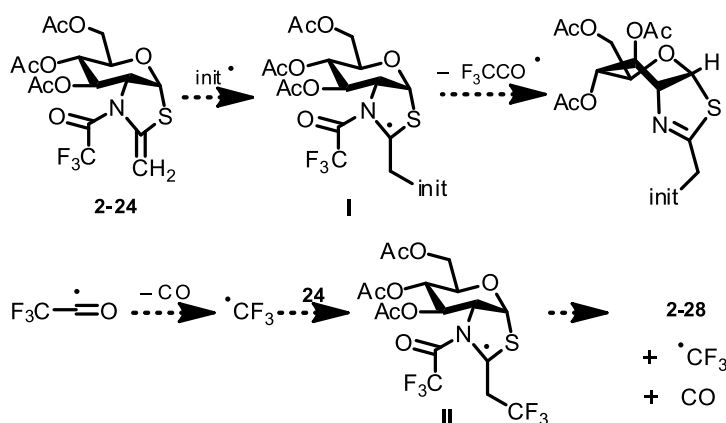
2.4. Radical trifluoromethylation of 2-methyl thiazolines

During attempts to brominate **2-24**, we discovered a new trifluoromethylation reaction. Treatment of **2-24** with benzoyl peroxide and a low power UV light source gave the 2, 2, 2-trifluoroethyl thiazoline **2-28** (Scheme 2.5). This product shows the diagnostic five-bond coupling³³ between the thiazoline methylene H's and the pyranose H-2. ¹⁹F NMR analysis (*J* -63.9, *t*, *J*) 10.3 Hz) supports this structure, as do the spectra of the deacetylated product **2-29**.



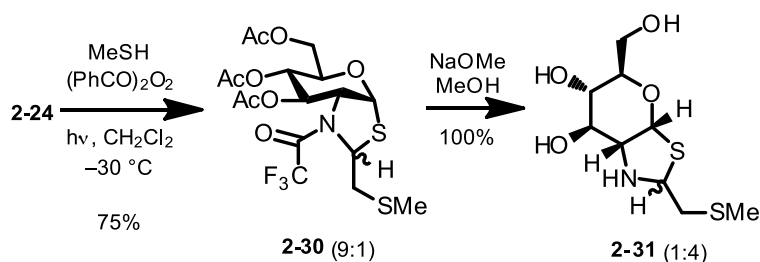
Scheme 2.5. Radical trifluoromethylation

A radical chain mechanism (Scheme 2.6) accounts for the formation of **2-28**. The initiating radical can add to the $\text{C}=\text{C}$ of **2-24**, leading to a tertiary thiazolidine radical **I**, fragmentation of which would give the trifluoroacetyl radical and a thiazoline product. The trifluoroacetyl radical likely fragments further to provide carbon monoxide and the trifluoromethyl radical.³⁴ Addition of trifluoromethyl radical to **2-24** again leads to a thiazolidinyl radical (**II**), and then the chain is propagated by another fragmentation, giving **2-28** as well as more trifluoromethyl radical.³⁵



Scheme 2.6. Proposed mechanism for radical trifluoromethylation

This mechanism is supported by the successful trapping of the thiazolidine radical by methyl mercaptan (Scheme 2.7). Exposure of **2-24** to the radical initiating conditions, but in the presence of excess mercaptan, led to the formation of thioether adduct **2-30** as an inseparable 9:1 mixture of stereoisomers (respective anomeric H's at 5.94 and 6.21 ppm). Kinetic hydrogen atom abstraction likely occurs preferentially from the less hindered β face³⁶ and is faster than loss of $\text{CF}_3\text{CO}^\bullet$, accounting for the formation of product still bearing this group. Deacetylation of **2-30** gave triol **2-31**, but as a 1:4 mixture of isomers (respective H-1's at 5.77 and 5.98 ppm). The change in isomeric composition upon basic hydrolysis³⁷ reflects thiazolidine ring opening to an imine mercaptide intermediate, which recloses to give the thermodynamic mixture of isomers of **2-31**.



Scheme 2.7. Radical addition of CH_3SH

2.5. Biochemical evaluation of modified thiazolines

Figure 2.4 shows the selective inhibition of human recombinant *O*-GlcNAcase by the new modified GlcNAc- thiazolines, relative to their inhibition of human placental β -hexosaminidase.³⁸ While all seven new compounds show somewhat reduced inhibition relative to the parent **2-2**, the azide **2-19** and the fluoride **2-16** exhibit excellent selectivity for the *O*-GlcNAcase, and **2-19** retains nearly all of the inhibitory activity of **2-2**. These two highly selective and potent GlcNAc- thiazolines differ significantly from previously characterized selective *O*-GlcNAcase inhibitors. The fluorine and azide derivatives may prove useful for developing reagents for imaging, labeling, and interfering with *O*-GlcNAc cycling in living cells and tissues.

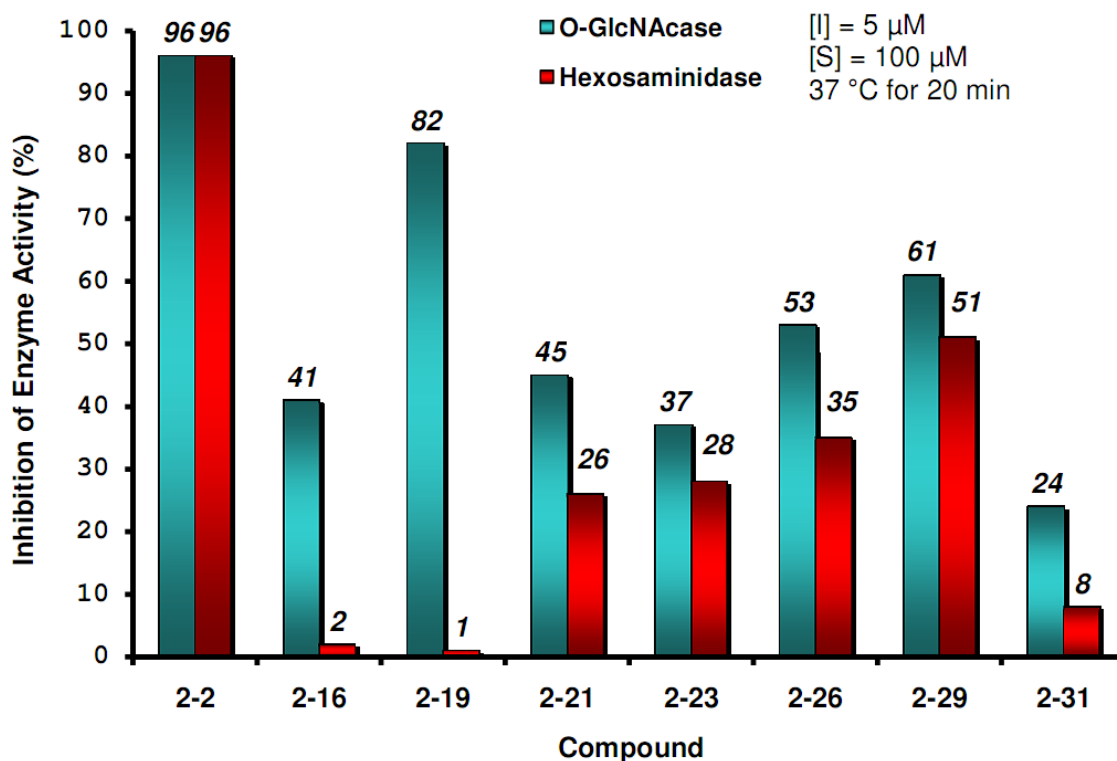
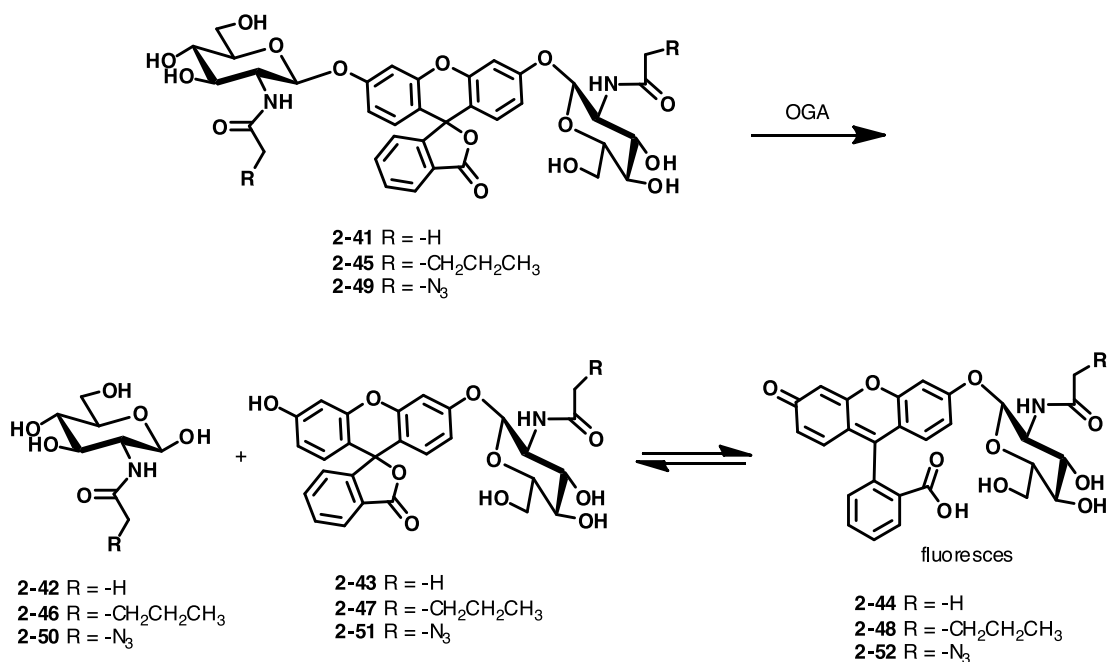


Figure 2.4. Inhibition by modified GlcNAc-thiazolines of *O*-GlcNAcase in comparison to human placental *beta*-hexosaminidase

2.6. Design of a probe for OGA assay with improved sensitivity

The method devised by Hanover and coworkers for the high-throughput screening of OGA inhibitors³⁸ is based on the reactivity of **2-40** with OGA (Scheme 2.8). When one of the glycosyl bonds is cleaved by the action of OGA, it produces phenol **2-42**, which tautomerizes into fluorescent carboxylate **2-43**. The measured amount of fluorescence is then used to calculate the inhibitory activity of a particular substrate. The assay performs admirably, but the results from this

assay do not address concerns that the phenotypic changes in an organism treated with an OGA inhibitor may not be solely due to OGA inhibition. To address this concern, an OGA-specific probe had to be developed.

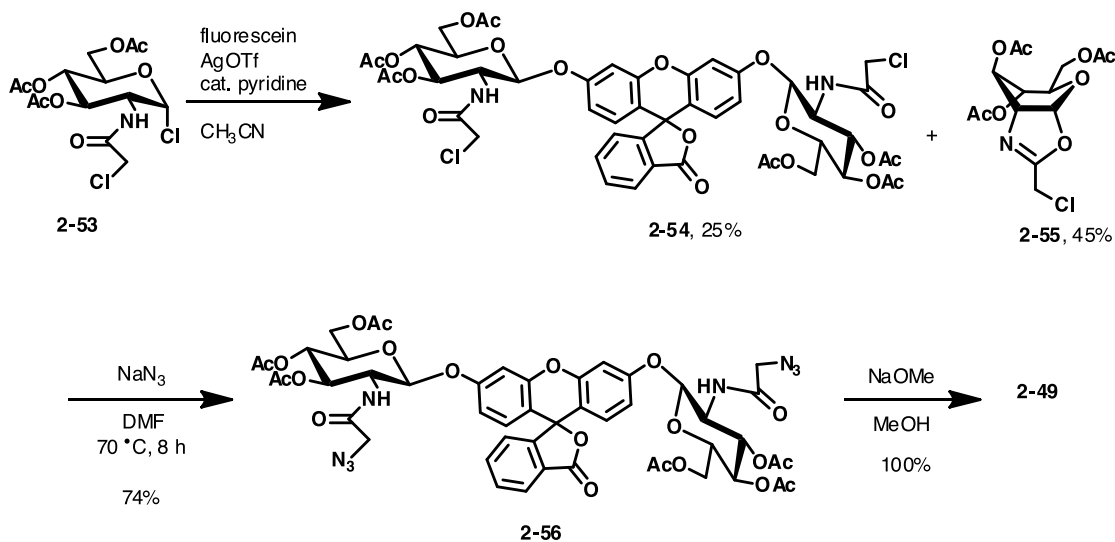


Scheme 2.8. OGA assay method

Vocadlo's work on selective OGA inhibitors inspired the synthesis of (bis)pentanamide **2-45**, with the (substantiated) thought that the same substitutions made for the selective OGA inhibitors could confer the same selectivity (and same loss of potency) to the probe.¹⁵ Likewise, we expect that, based on the information shown in Figure 2.4, azido analog **2-49** will exhibit an even higher degree of selectivity and a minimal loss of activity relative to **2-41**. Coupling of chloride **2-53**³⁹ (Scheme 2.9) with fluorescein gave diether **2-54** in

poor yield, along with significant amounts of chloromethyl oxazoline **2-55**.

Substitution with sodium azide followed by Zemplén deacetylation gave **2-49**.



Scheme 2.9. Synthesis of azido fluorescein analog **2-49**

2.7. References

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(3a*R*,5*R*,6*S*,7*R*,7a*R*)-6,7-dihydroxy-5-hydroxy-methyl-2-methyl-5,6,7,7a-tetrahydro-3a*H*-pyrano[3,2-*d*]thiazole.
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27. Vicinal proton coupling constants for **2-8**: $J_{1,2} = 7$, $J_{2,3} = 3$, $J_{3,4} = 1.5$, and $J_{4,5} = 9$ Hz. See also: Foces-Foces, C.; Cano, F. H.; Bernabe, M.; Penades, S.; Martin-Lomas, M. *Carbohydr. Res.* **1984**, *135*, 1–11.
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Chapter 3. Total synthesis of mycothiol via intramolecular aglycon delivery

3.1. Mycothiol structure, biosynthesis, and function

Tuberculosis (TB) is a very serious disease that, according to the World Health Organization, kills 2 million people worldwide annually, and an estimated 8 million people develop the active form of TB in the same time frame. Because *Mycobacterium tuberculosis*, the causative agent of the disease, has recently been gaining resistance to most known treatments, and those treatments are largely ineffective against the bacteria in the dormant (non-proliferative) state,^{1,2} efforts to understand the underlying defense mechanisms are underway. Mycothiol (MSH, **3-1**, Figure 3.1) is the low-molecular weight thiol used by mycobacteria as their main line of defense against foreign electrophilic agents (radicals, reactive oxygen, drugs, etc.), which is analogous to the role of glutathione in eukaryotes.³

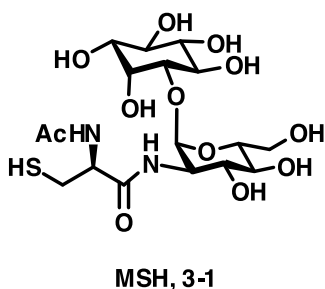
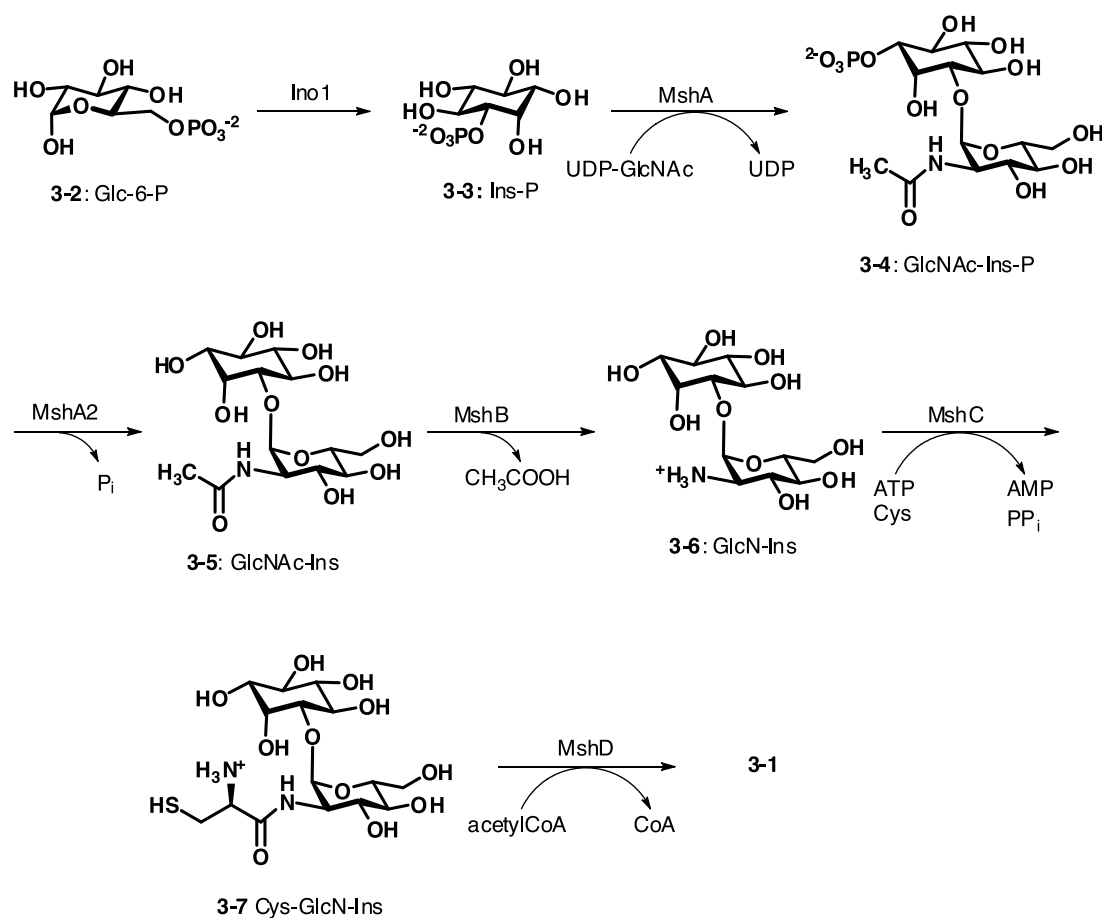


Figure 3.1. Structure of mycothiol

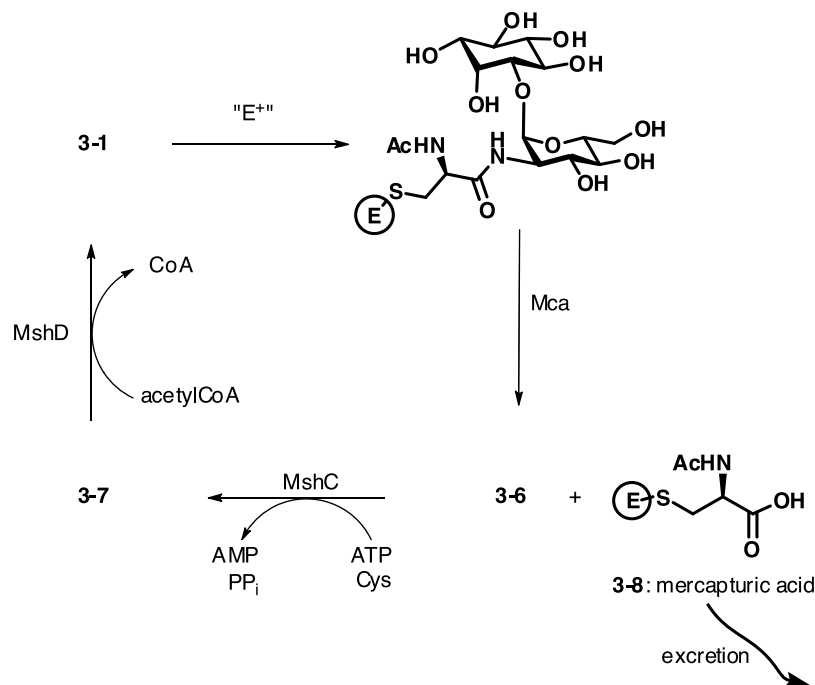
Mycothiols were first isolated and characterized in 1994 from *Streptomyces* sp. AJ 9463⁴ and *Mycobacterium bovis*.⁵ Disruption of MSH production has been shown to be fatal to *M. tuberculosis* cultures, so the biosynthetic pathways involved in that process have been studied in great detail, with the information obtained through these studies being used to develop new anti-tubercular drugs.⁶ The currently accepted biosynthetic pathway to mycothiol is shown in Scheme 3.1⁷⁻¹² as a five-step process. Rearrangement of glucose-6-phosphate **3-2** to *myo*-inositol phosphate **3-3** is catalyzed by *myo*-inositol-1-phosphate synthetase. Phosphate **3-3** then undergoes MSH glycosyltransferase-catalyzed glycosylation by UDP-GlcNAc to form disaccharide **3-4**, which is dephosphorylated and deacetylated by the actions of MSH phosphatase and MSH deacetylase, respectively, forming aminooctol **3-6**. MSH ligase catalyzes the ATP-mediated coupling of **3-6** to cysteine to give then cysteine conjugate **3-7**. Finally, MSH acetyltransferase-catalyzed acetylation with acetylCoA gives the final product.



Scheme 3.1. Biosynthesis of mycothiol

The mechanism of mycothiol-mediated detoxification is also a subject of intense research efforts. The currently accepted mode of action is depicted in Scheme 3.2.^{13–15} When a foreign agent enters the bacterial cell, MSH attaches itself to the agent through the sulfur atom to form a stable conjugate. MSH *S*-conjugate amidase catalyses deacylation of the newly formed conjugate to produce GlcN-Ins and *N*-acetylcysteine **3-8** conjugated to the foreign invader. The cysteine derivative is then pumped out of the cell, and the remaining GlcN-Ins is recycled for MSH synthesis. Examples of drug metabolites that seem to

confirm this detoxification mechanism include those that stem from the antibiotics granaticin A¹⁶ and naphthomycin A.¹⁷ MSH apparently causes these drugs to be excreted from the bacterial cell as their much-less-potent mercapturic acid derivatives, which is analogous to the action of glutathione in mammalian cells.



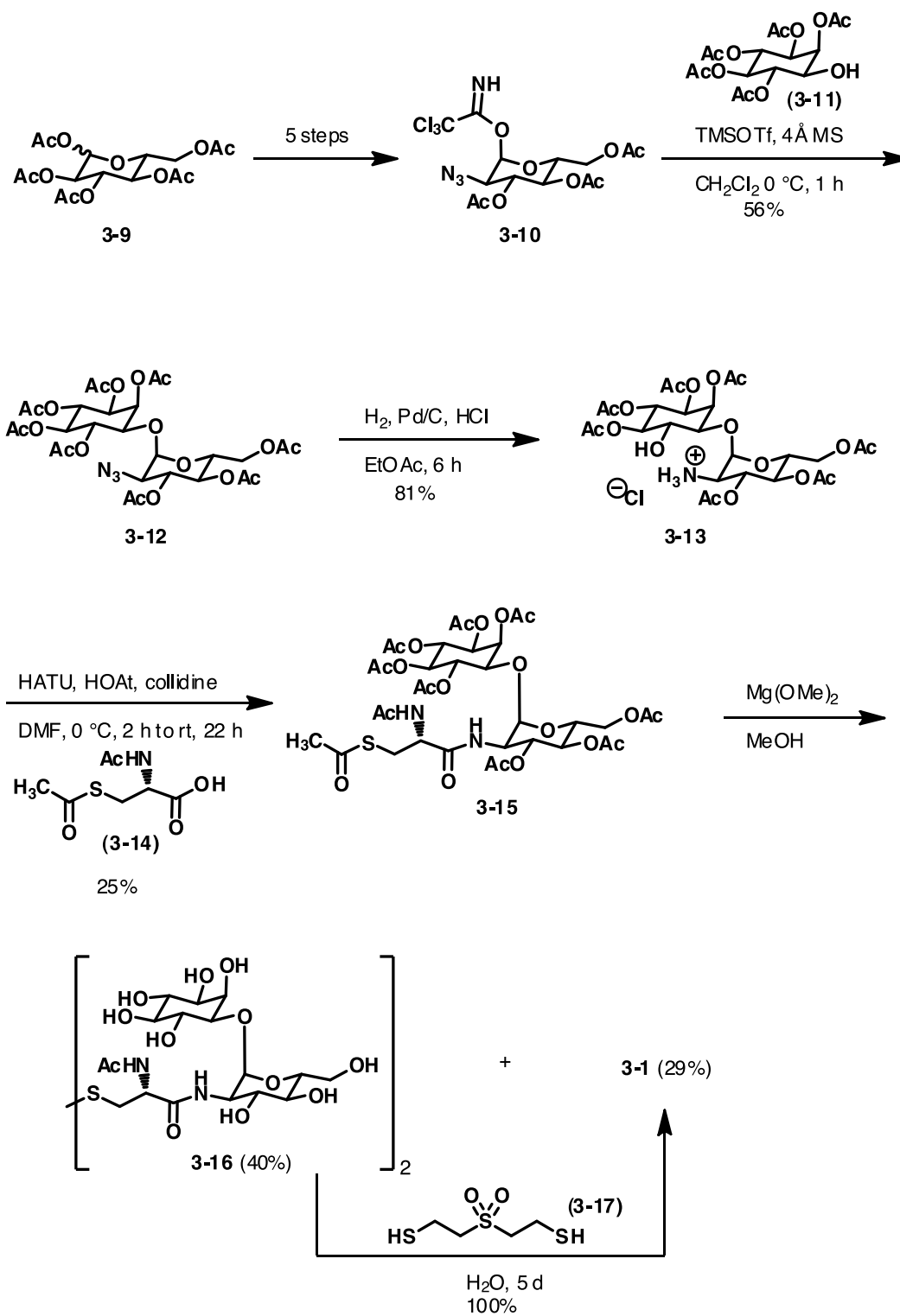
Scheme 3.2 MSH-mediated detoxification pathway

Efforts to study the metabolic pathway(s) of MSH have been hampered by its lack of availability through either isolation or total synthesis. Several of the enzymes in the biosynthetic pathway shown in Schemes 3.1 and 3.2 are thought to be promising drug targets, especially **MshC**. Furthermore, it has been shown that some of those enzymes are non-essential for MSH biosynthesis (**MshD**),¹⁸ and the importance of certain other enzymes for MSH are still debatable (**MshA**).¹⁹ Many groups have therefore pursued synthetic methods and isolation methods to

increase the scant availability of MSH and, consequently, gain better insight into the biosynthetic and metabolic pathways and receptors involved. The remainder of this chapter describes some of those efforts, and details our own efforts to develop an efficient, scalable synthesis of MSH.

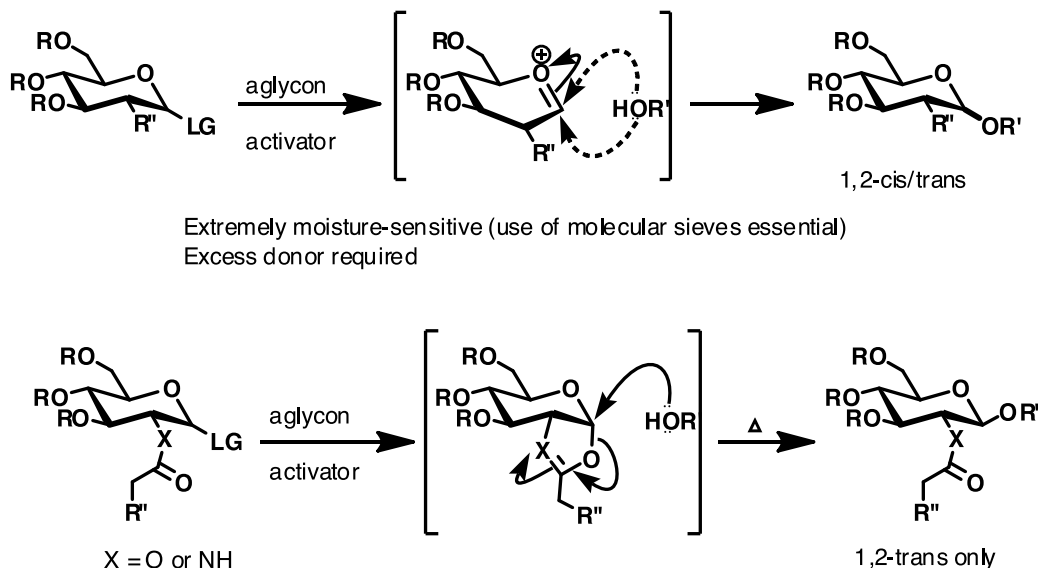
3.2. Previous synthetic studies in the literature

There are a few synthetic studies on MSH^{20,21} and MSH analogs^{22–26} in the literature, but only one synthesis of mycothiol is currently known²⁷. The only existing synthesis of mycothiol (Scheme 3.3), from the Rosazza group out of the University of Iowa, has a few shortcomings, not least of which is the relatively inefficient glycosylation of inositol pentaacetate **3-11** with 2-deoxy-2-azidoglucosyl trichloroacetimidate **3-10** to form 1,2-*cis* glucoside **3-12** with a 56% yield, along with a 9% yield of the *beta* anomer. A slight excess of acceptor was required to achieve this modest yield, and the overall yield of **3-1** from **3-10** was only 7%. A similar limitation was encountered during Bewley's (National Institutes of Health) efforts to synthesize the well-known bimanane conjugate of MSH²¹. As both donor and acceptor are expensive intermediates in those particular glycosylations, efficient coupling is of paramount importance. Any proposed MSH synthesis will have to address the problem of achieving stereospecific *alpha*-glycosylation of a 2-deoxy-2-aminoglucose derivative.



Scheme 3.3 Rosazza's synthesis of MSH

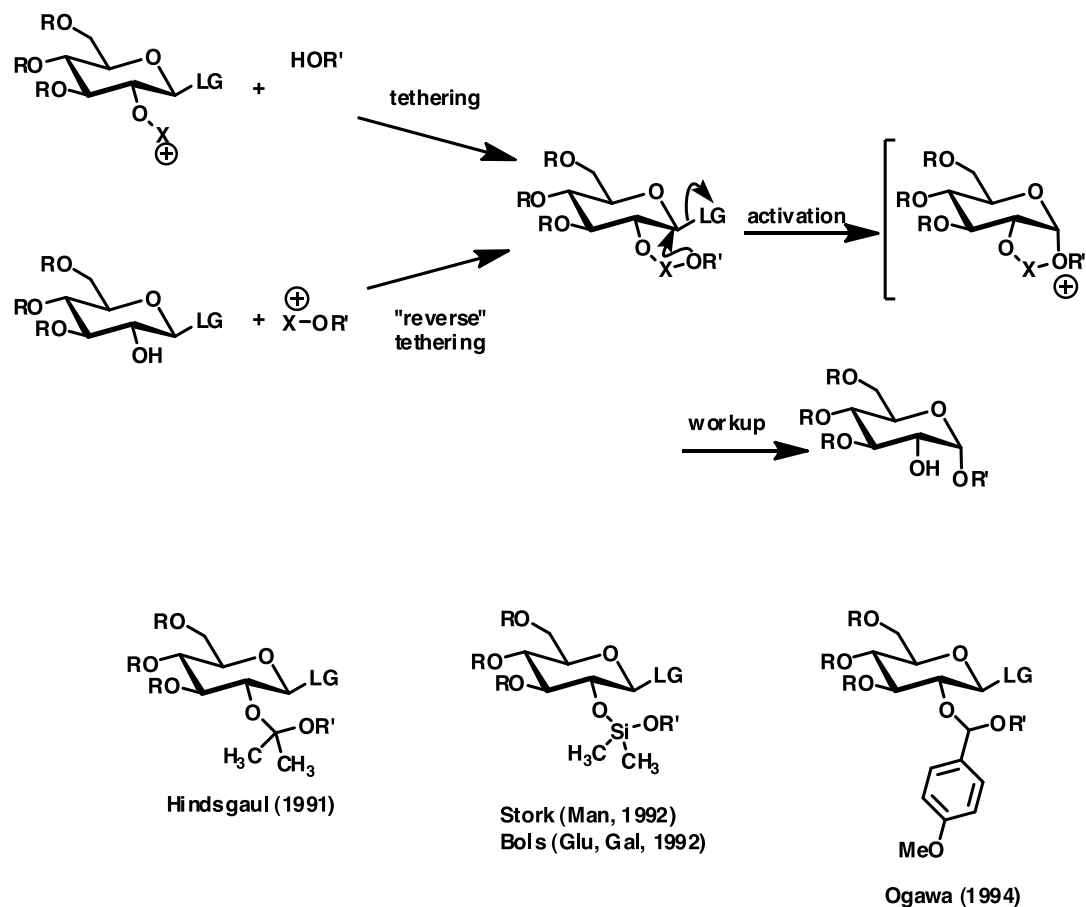
Glycosylation reactions (Scheme 3.4) generally suffer from a number of issues, including high water sensitivity, which necessitates the use of excess donors that are often expensive. Anomer selectivity is always an issue, particularly when using 2-acetamidoglucose derivatives as donors, as the intermediate oxazolinium ion formed effectively blocks the *alpha* face of the sugar, and is also resistant to nucleophilic attack.²⁸⁻³¹ Therefore, non-participating amide precursors must be used to achieve the desired diastereoselectivity, and even under those conditions, the degree of diastereoselectivity conferred is mostly substrate-dependent. The most common masked amine used for this purpose is the azide group, due to its small size. 2-Deoxy-2-azidoglucosides can come from addition across the double bond of a glucal,^{32,33} which is a reaction that itself is plagued with regio- and stereoselectivity problems, as well as modest efficiency. Treatment of glucosamine with triflyl azide can give the desired azide with greater efficiency,³⁴ but the dangerous diazo transfer reagent must be synthesized. Bulkier glycosyl acceptors tend to give less of the desired 1,2-*cis* products. Methods to achieve efficient, 1,2-*cis* selective glycosylations are therefore still highly sought after and desirable.



Scheme 3.4. Chemical glycosylation mechanisms

3.3. Intramolecular aglycon delivery

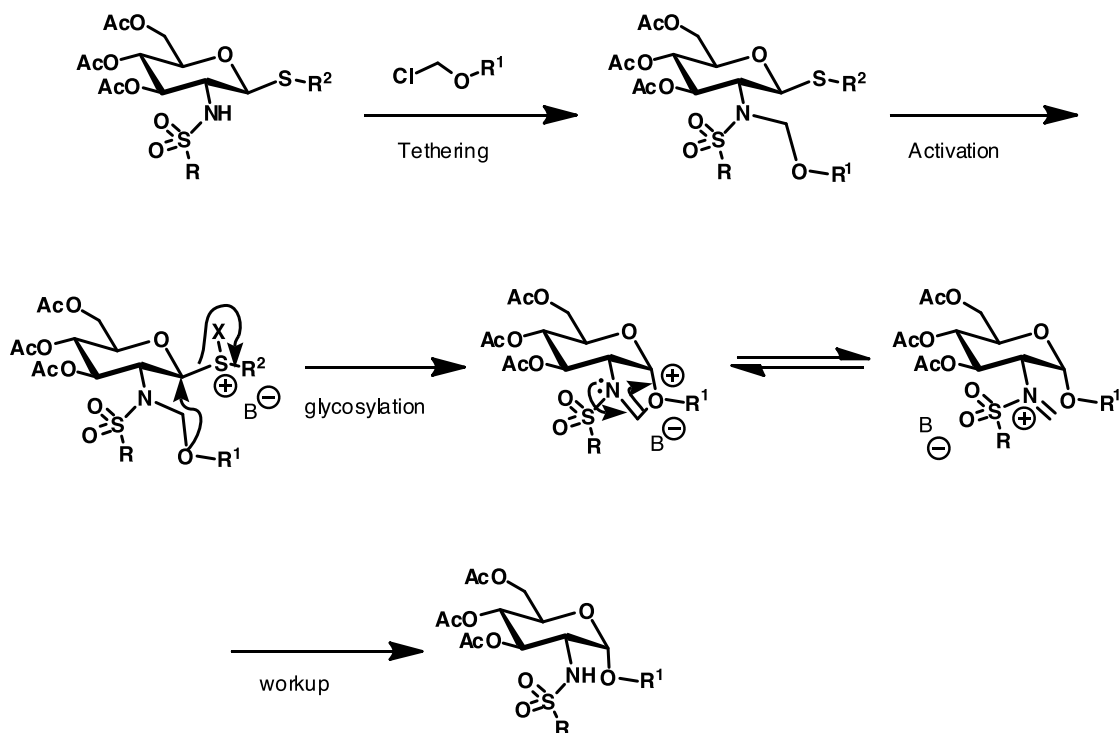
One method, termed intramolecular aglycon delivery (IAD), became important in the early 1990s as a method for the stereospecific formation of 1,2-*cis* glucosides. A natural progression from the phenomenon of participation in typical glycosylations, IAD involves the tethering of the desired aglycon, through a removable bridge, to a group in the sugar that can deliver the aglycon to the desired face. The generalized 2-step process is shown in Scheme 3.5. A few IAD methods have been developed by the Hindsgaul³⁵, Stork,³⁶ Bols,³⁷ and Ogawa³⁸ groups, with good success. A couple of useful reviews have been published on IAD.^{39,40} As useful as these methods are, however, they cannot be used to synthesize *alpha*-2-deoxy-2-aminosugars such as MSH.



Scheme 3.5. Intramolecular aglycon delivery (IAD) methods

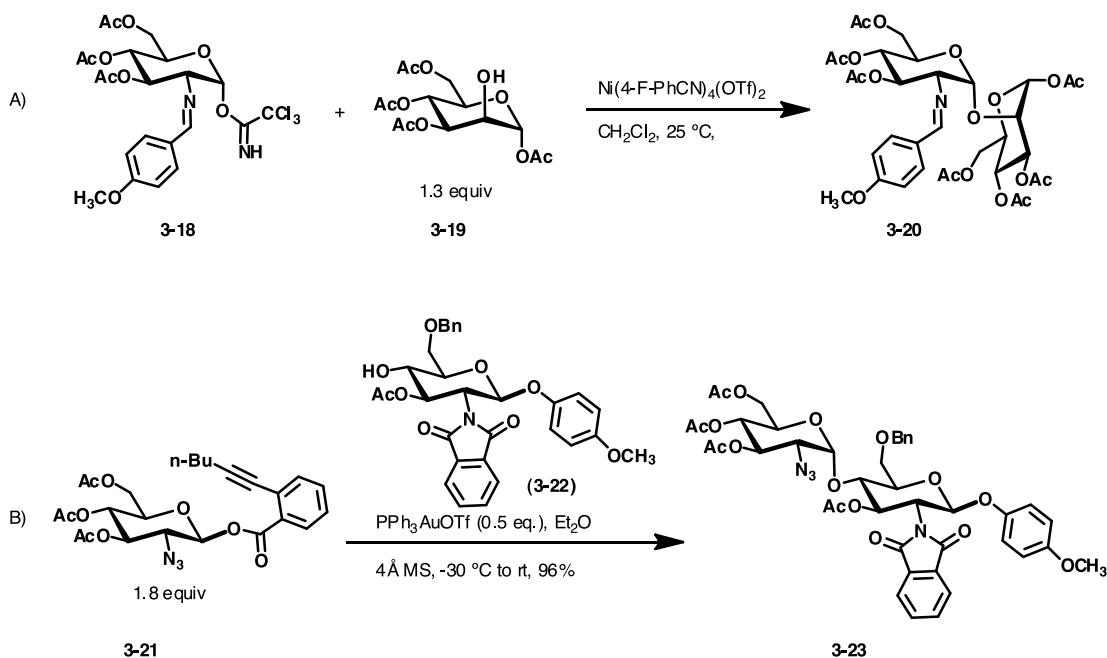
The first intramolecular aglycon delivery method for 2-deoxy-2-amino sugars was recently developed in the Knapp laboratories to solve this problem (Scheme 3.6). In this system, the aglycon is tethered to a sulfonamide group on the 2-position of a thioglycoside. The thioether group, upon activation, is displaced by the aglycon, which forms the desired 1,2-*cis* aminoglycoside after basic workup, along with an equivalent of formaldehyde. This IAD method was shown to be efficient (no excess of donor or acceptor required), completely

stereospecific, performed with readily available glycosyl donors, and accommodating of bulky glycosyl acceptors without sacrificing stereoselectivity.



Scheme 3.6. IAD of 2-deoxy-2-aminoglucose derivatives

In the past year, two other methods that can accomplish the same goal have been published. Nguyen's Ni(II)-catalyzed method (Scheme 3.7A) is high-yielding, but requires excess of the glycosyl acceptor, unstable benzylidene donors like **3-18**, and a non-commercial catalyst.⁴¹ Yu's Au(III)-catalyzed method (Scheme 3.7B) is very high-yielding and was shown to be efficient in the synthesis of a complex tetrasaccharide.⁴² However, it does have some of the same drawbacks as Nguyen's method, and diethyl ether is required as a solvent to attain *alpha* selectivity with 2-deoxy-2-azidosugars like **3-21**.⁴³



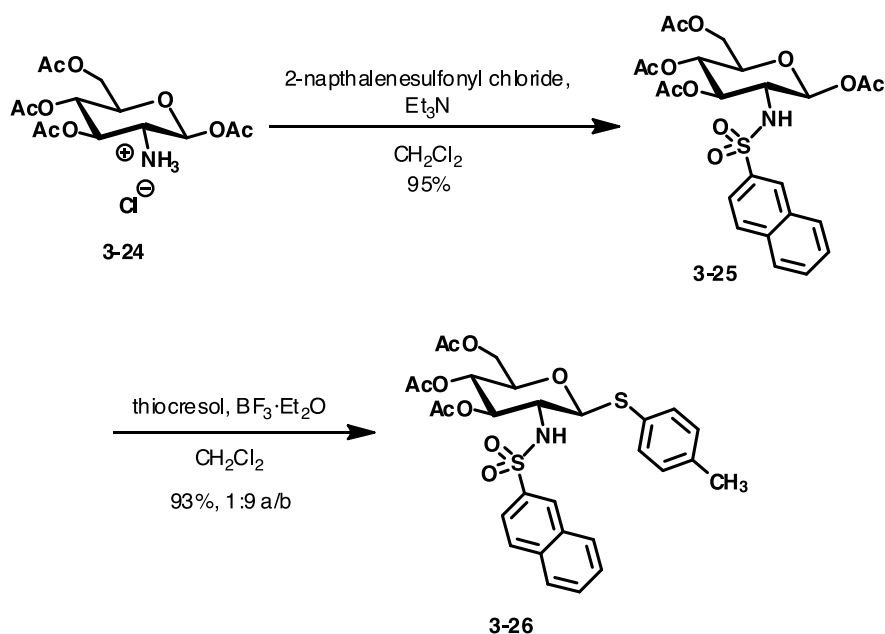
Scheme 3.7. Efficient 1,2-cis glycosylations in the recent literature

3.4. Model studies

Using our IAD method, we set out on a total synthesis of mycothiol. Previous studies had focused on toluenesulfonamide as a tethering anchor. Glycosylation using dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)⁴⁴ as the activator was successful. However, when the time came to remove the sulfonamide, the harsh conditions necessary for such a removal made it impossible to recover the desired product. Fukuyama's 4-nitrobenzenesulfonyl group⁴⁵ can be removed under mild conditions that would not interfere with the benzyl and acetyl protecting groups. The 2,4-dinitro analog can even be transformed into an amide directly,^{46,47} which would be useful in a synthetic route

to MSH. Unfortunately, the electron-poor nature of the 4-nitrobenzenesulfonyl group necessitated somewhat forcing conditions for an efficient glycosylation (~95% conversion after 2 days at 75 °C using DMTSF). We eventually decided to utilize the naphthalenesulfonyl group as the *N*-protecting group. Due to its higher (less negative) reduction potential relative to toluenesulfonamide,⁴⁸ we believed that conditions exist for its selective removal in the presence of benzyl ethers.

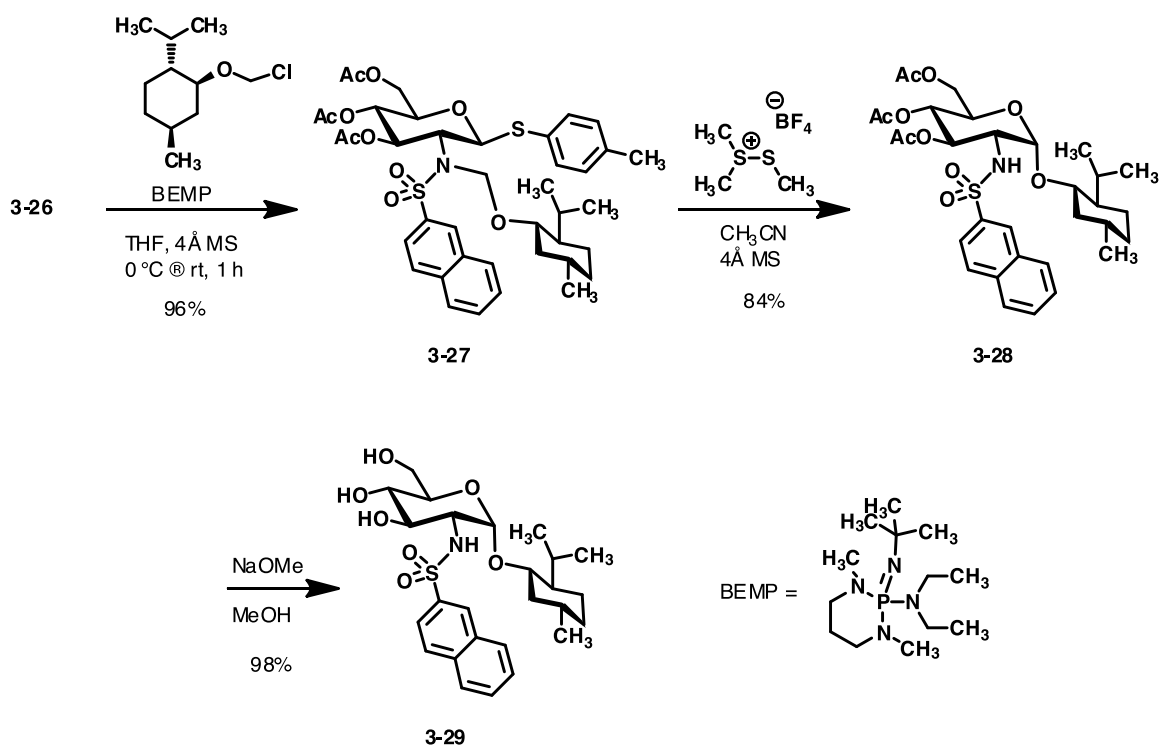
Because of the expense of the required glycosyl acceptor and the possibility of undesired reactivity with the naphthalenesulfonyl group, we elected to work with menthol as a model acceptor. Synthesis of thioglucoside 3-26 from glucosamine tetraacetate 3-24 (3 steps from glucosamine hydrochloride⁴⁹) was straightforward, with sulfonylation occurring in 95% yield and a boron trifluoride-mediated glycosylation of thiocresol occurring in 93% yield as a separable mixture of anomers (Scheme 3.8).



Scheme 3.8. IAD donor preparation

Treatment of 3-26 with chloromethyl menthyl ether in the presence of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) gave the tethered aglycon 3-27 in nearly quantitative yield (Scheme 3.9). Use of other bases such as sodium hexamethyldisilazide gave multiple products and cut the yield down to 71%. Use of molecular sieves is critical for the success of the tethering step, as the product is sensitive to aqueous conditions. The key glycosylation step was then performed. Previous attempts at this reaction showed that traditional thioglycoside activators such as N-iodosuccinimide/catalytic triflic acid effected glycosylation, but could not furnish the desired secondary sulfonamide after workup, instead forming a stable N-sulfonyl-N'-succinyl aminal. The sulfenylating agent DMTSF effectively promoted glycosylation to 3-28 with a yield of 84%. This glycosylation reaction

must be quenched under somewhat basic conditions, such as aqueous sodium bicarbonate, as quenching with aqueous ammonium chloride had produced the *N*-hydroxymethyl derivative of 3-28 in previous experiments. After quantitative deacetylation, we turned our attention to determining conditions for selective removal of the naphthalenesulfonyl group.

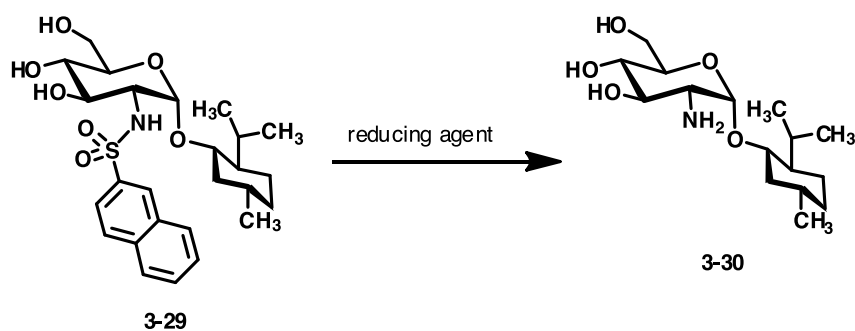


Scheme 3.9. Model IAD reaction with naphthalenesulfonamide 3-27

A short screening of reduction methods was performed on 3-29, and the results are shown in Table 3.1. A literature survey revealed the use of magnesium metal and ammonium chloride in methanol as a mild reducing agent for unmasking sulfonyl-protected amines.⁵⁰ Adoption of those conditions to 3-29

gave the amine in very low yield, whether the reaction was sonicated or refluxed, so a stronger reductant was needed. Samarium iodide has been shown in the literature to be a competent reducing agent for various functional groups, including epoxides,⁵¹ halides,⁵² and sulfonamides,⁵³ and the inertness of benzyl ethers towards this reagent has also been demonstrated in the context of complex carbohydrates.⁵⁴ Indeed, treatment of **3-29** with samarium iodide and HMPA in THF produced the free amine in 57% yield after refluxing for 18 hours. Appreciative of, but unsatisfied with, those results, we again moved up higher in reduction power. Sodium amalgam and dibasic potassium phosphate in methanol represent well-known conditions for desulfurization.⁵⁵ Using those reagents, we were pleased to obtain **3-30** in 79% yield from **3-29** after refluxing for 1 h. With efficient *alpha*-glycosylation and selective sulfonamide reduction methods in hand, we tackled the synthesis of MSH.

Table 3.1. Screening of naphthalenesulfonamide reduction reagents

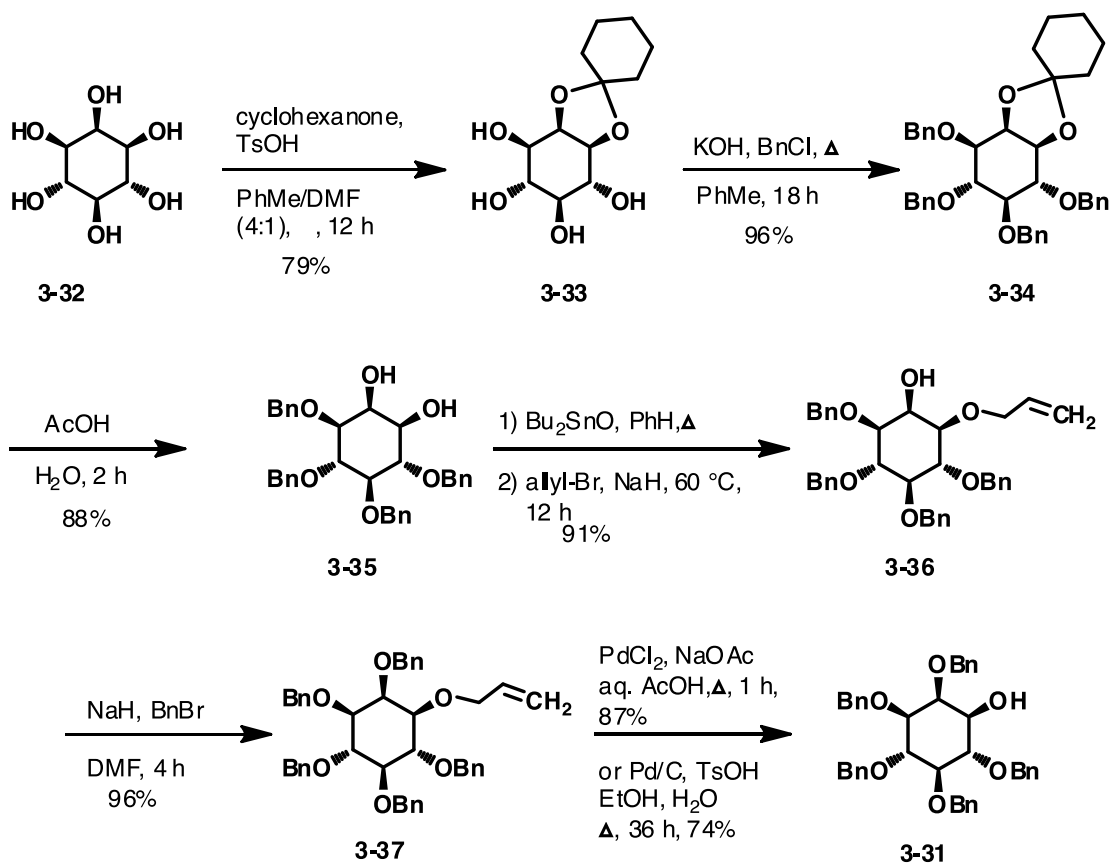


| Reagent/Solvent | Conditions | Product Yield |
|---------------------------------------------------------------------|-----------------|---------------|
| Mg (50 equiv), NH ₄ Cl (20 equiv), MeOH | sonication, 2 h | 6% |
| " | reflux, 24 h | 11% |
| SmI ₂ (25 equiv), HMPA (4.5 equiv), THF | reflux, 18 h | 57% |
| Na(Hg) (15 equiv), Na ₂ HPO ₄ (8 equiv), MeOH | reflux, 1 h | 79% |

3.5. Synthetic route

Before applying the model conditions to the desired substrates, we had to synthesize the required chloromethyl ether derivative of a suitably protected inositol such as **3-31**. The route taken to produce racemic **3-31** is shown in Scheme 3.10.^{56,57} Notable transformations include a selective monoallylation of diol **3-35** mediated by a cyclic dibutylstannylidene and a large-scale deallylation of **3-37** using palladium (0) and toluenesulfonic acid in refluxing ethanol/water. Use of palladium (II) chloride gives a cleaner, faster, and more efficient reaction, but the reaction requires a superstoichiometric amount of “catalyst,” making its use

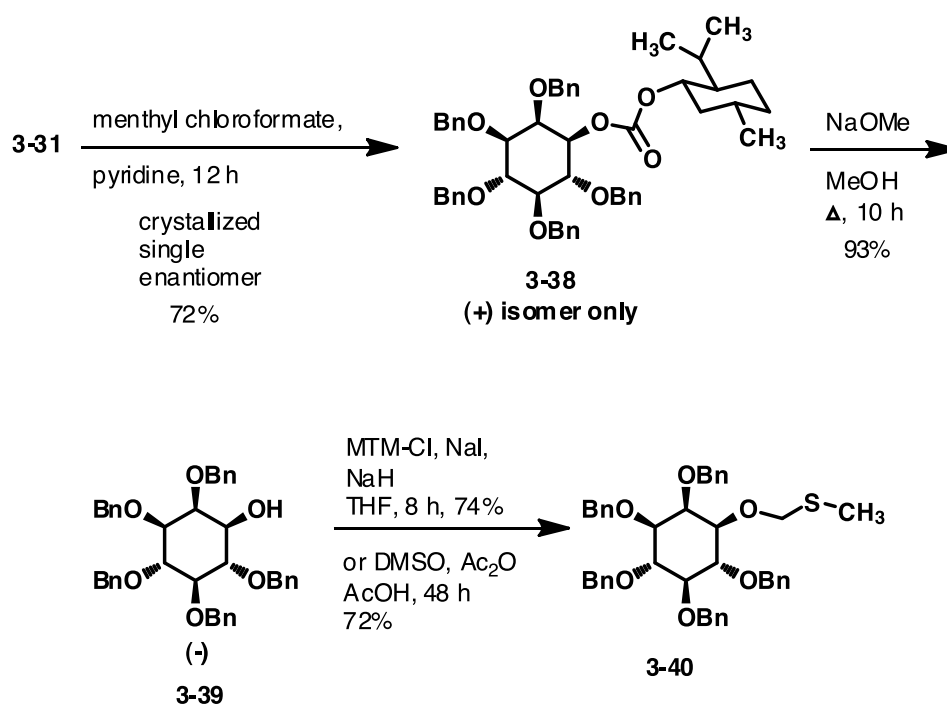
cost-prohibitive on a 20-gram scale. Racemic pentabenzylated inositol **3-31** was obtained in six steps with a 51% overall yield from commercially available *myo*-inositol **3-32**.



Scheme 3.10. Synthesis of protected inositol 3-31

The racemate was then resolved by crystallization of the appropriate menthyl carbonate derivative⁵⁸ from hexanes and subsequent methanolysis to give (-)-**3-39** in 66% yield over two steps (Scheme 3.11). An x-ray crystal structure of the resolved inositol was obtained as proof of stereochemistry (Figure 3.2). Direct chloromethylation of alcohols is known to be an inefficient and unreliable process,

so we decided to use *O,S*-acetal **X** as the precursor to our desired chloride. Unfortunately, installing a methylthiomethyl (MTM) group onto a hindered, secondary alcohol proved problematic. Direct installation with MTM-Cl/NaH/NaI gave variable yields and varying amounts of unreacted alcohol, but DMSO/acetic acid/acetic anhydride slowly formed the desired thioether **3-40** through a Pummerer rearrangement process, consistently with a ~70% yield. A balance between reaction time and undesired ketone formation can be achieved by controlling the amount of acetic acid used.



Scheme 3.11. Synthesis of thioether **3-40**

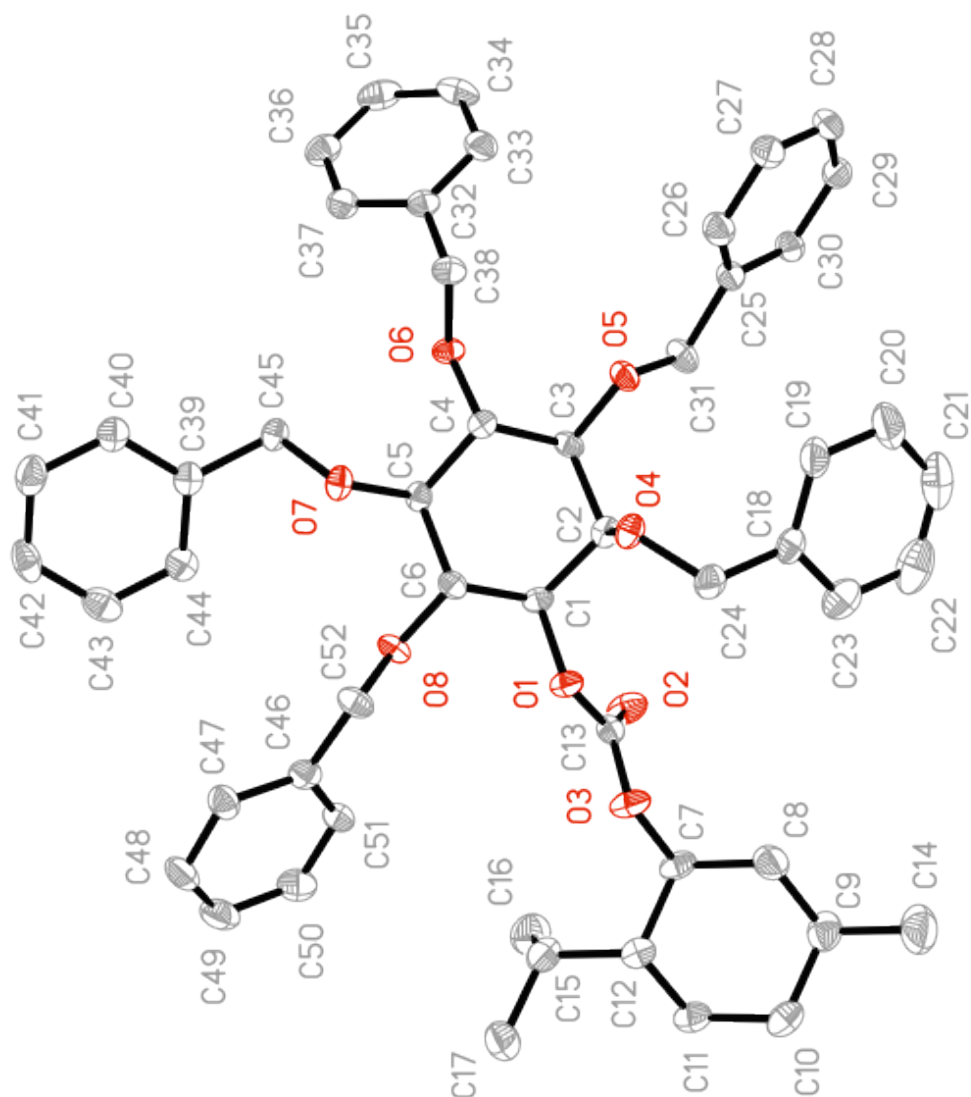
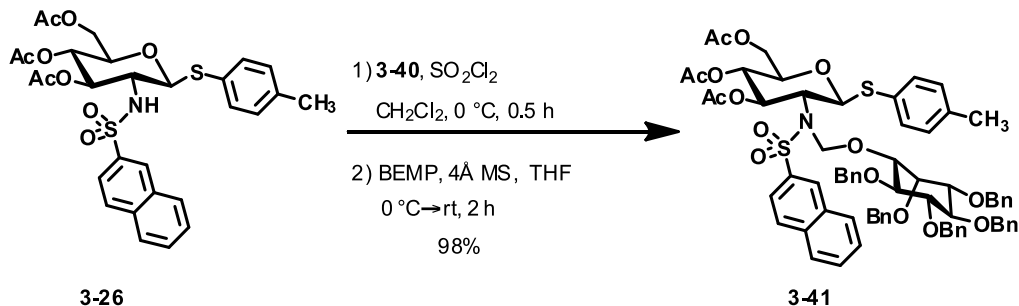


Figure 3.2. X-ray structure of pentabenzyl inositol 3-39

Treatment of thioether **3-40** with a slight excess of sulfuryl chloride produced the chloromethyl ether, which was immediately tethered to thioglycoside **3-26** (Scheme 3.12) with BEMP in overall 98% yield, setting the stage for the key glycosylation step.

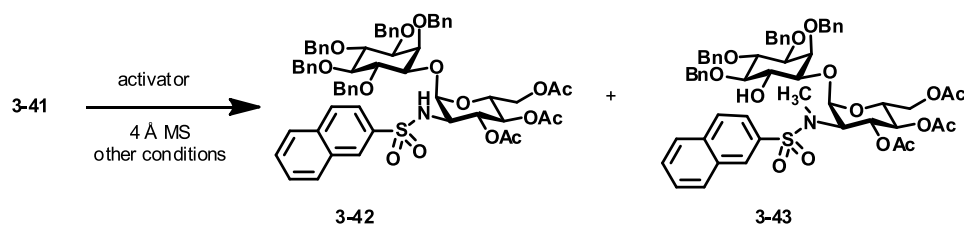


Scheme 3.12. Tethering of aglycon **3-40** to sulfonamide

3.6. Unexpected hydride shift during attempted IAD

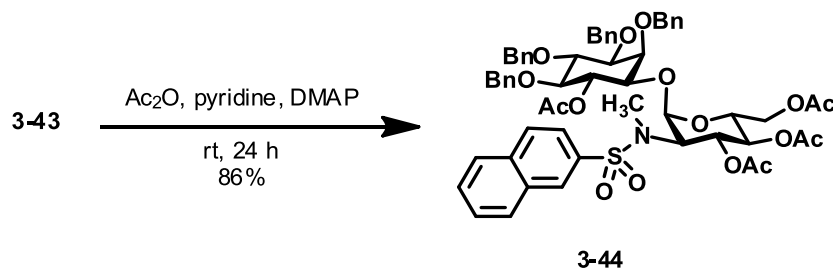
Unfortunately, the DMTSF-mediated glycosylation in this system was much more problematic than in the model system. Though yields of **3-42** as high as 91% had been obtained when the activator was added as a solution in acetonitrile at 0 °C, a more typical result involved the formation of varying amounts of *N*-methyl sulfonamide **3-43**, which is described in more detail below. We therefore had to modify the conditions and, eventually, use a more reactive activator system, phenylsulfenyl chloride/silver triflate,⁵⁹ at a lower temperature to produce an efficient glycosylation. Some of the tested modulations are listed in Table 3.2.

Table 3.2. Screened glycosylation conditions for donor/acceptor 3-41



| entry | activator (equiv.) | other conditions | yield of 3-41 | yield of 3-42 | yield of 3-43 |
|-------|----------------------------------------|------------------------------------------------------------------------------------------------------------------|---------------|---------------|---------------|
| 1 | DMTSF (5.0) | CH ₃ CN 0 \rightarrow 50 °C, 5 h | — | 33 | 48 |
| 2 | DMTSF (10.0) | CH ₃ CN 50 °C, 1 h | — | — | 96 |
| 3 | DMTSF (1.2) | CH ₃ CN 0 \rightarrow 50 °C, 8 h | 45 | 28 | 10 |
| 4 | DMTSF (3.0) | CH ₃ CN 0 °C \rightarrow rt, 6 h | 62 | — | 16 |
| 5 | DMTSF (3.0) | (CH ₃) ₂ S (10 equiv.) CH ₃ CN 0 °C \rightarrow rt, 12 h | 100 | — | — |
| 6 | PhSCI (2.0) AgOTf (4.0) | CH ₂ Cl ₂ /CH ₃ CN (2:1) -78 \rightarrow -20 °C, 1 h | — | — | 91 |
| 7 | PhSCI (1.5) AgOTf (1.5) | CH ₂ Cl ₂ /CH ₃ CN (2:1) -78 \rightarrow -20 °C, 1 h | — | 56 | 31 |
| 8 | PhSCI (3.0) AgOTf (0.4) | CH ₂ Cl ₂ /CH ₃ CN (2:1) -78 \rightarrow -20 °C, 1 h | — | 79 | 9 |
| 9 | PhSCI (3.0) AgOTf (0.1) | CH ₂ Cl ₂ /CH ₃ CN (2:1) -78 \rightarrow -20 °C, 2 h | — | 93 | <1 |
| 10 | PhSCI (1.5) AgOTf (1.5) | DTBMP (1.8 equiv.) CH ₂ Cl ₂ /CH ₃ CN (2:1) -78 \rightarrow -20 °C, 1 h | — | — | 91 |
| 11 | PhSCI (3.0) | CH ₂ Cl ₂ /CH ₃ CN (2:1) -78 \rightarrow -20 °C, 3 h | 100 | — | — |
| 12 | PhSCI (3.0) AgNO ₃ (0.4) | CH ₂ Cl ₂ /CH ₃ CN (2:1) -78 \rightarrow -20 °C, 1 h | 100 | — | — |

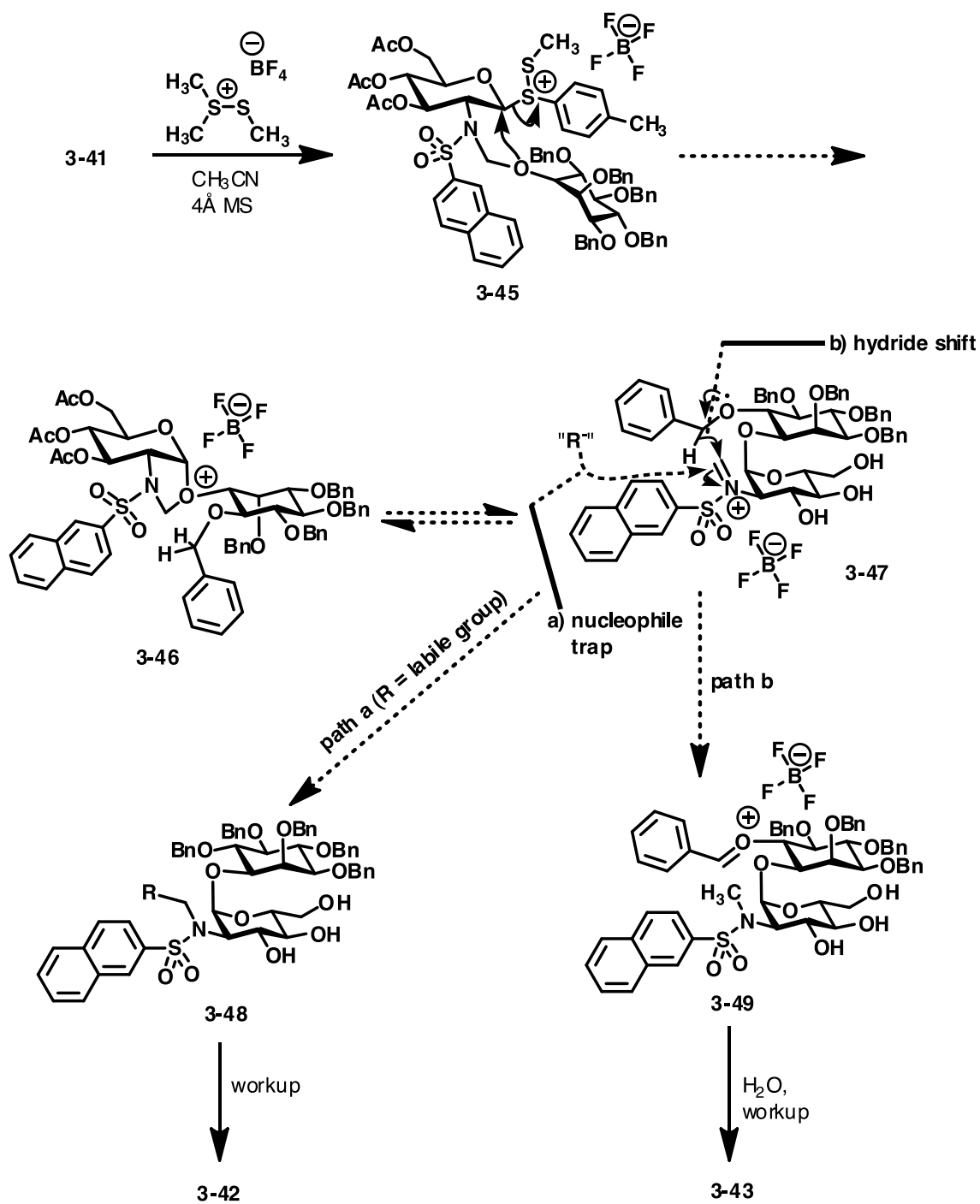
The process that transforms **3-41** to **3-43** represents a formal 1,9-hydride shift of a benzylic hydride to an *N*-sulfonyl iminium ion, with subsequent hydrolysis of a benzyl group from the C-2 oxygen atom. An unexpected 1,5-benzylic hydride shift to a Lewis acid-induced iminium ion was observed by Tietze *et al.* during efforts to synthesize functionalized steroid derivatives as potential enzyme inhibitors.^{60,61} Tietze's report, to the best of our knowledge, describes the only known example of this particular kind of hydride shift, albeit over five bonds. Hydride shifts over seven bonds are much less common, but known.⁶² A hydride shift over *nine* bonds is, to the best of our knowledge, unprecedented. Sulfonamide **3-43** and its acetate derivative **3-44** (Scheme 3.13) was characterized by ¹H, ¹³C, COSY and HMQC NMR.



Scheme 3.13. Acetylation of hydride shift product

Proposed mechanisms for the formation of **3-42** and **3-43** are shown in Scheme 3.14. Upon activation of thioglucoside **3-41**, the tethered aglycon attacks the anomeric center, creating oxazolidinium ion **3-46** in equilibrium with *N*-sulfonyl iminium ion **3-47**. To obtain the desired glycoside **3-42**, a nucleophile that can trap the equilibrated cation irreversibly (path a), yet create a labile intermediate,

like **3-48**, to be converted to **3-42** upon workup, is needed. Using the phenylsulfenyl chloride/silver triflate activator system (Table 3.2, entries 6-12), a chloride ion is available to form an *N*-chloromethylsulfonamide (**3-48**, R = Cl), which breaks down into the desired product during silica gel chromatography. The chloromethyl group could also be removed by treatment with aqueous sodium hydroxide,⁶³ which would presumably remove the acetate groups and give triol **3-50** in one pot, but application of these conditions produced a complex mixture that included **3-50**.



Scheme 3.14. Proposed mechanisms for glycosylation and hydride shift

Such a nucleophile (i.e. one that will not render “path a” reversible) is usually absent when using DMTSF as the activator (Table 3.2, entries 1-5); the dimethylsulfide byproduct can only add reversibly to the cation, if at all. Stoichiometric amounts of AgOTf (in the PhSCI/AgOTf activator system) will also reverse the aforementioned chloride trap,⁶⁴ affording “path b” an opportunity to occur. The oxidation potential of the cation is apparently high enough to remove a hydride from the C-2 benzyloxy group to form *N*-methyl sulfonamide **3-48**, leaving a stabilized oxonium ion on C-2 to be quenched upon workup. This shift even occurs at low temperatures (entries 4, 6 and 10). The cases where any amount of **3-42** is formed in this system (entries 1 and 3) can possibly be attributed to the varied amounts of fluoride ion in different reaction runs (often a source of frustration⁶⁵). A rough molecular mechanics energy minimization of **3-47** puts the C-2 benzyl hydrogens in very close proximity to the iminium carbon (nitrogen shown in blue), facilitating the hydride shift (Figure 3.3).

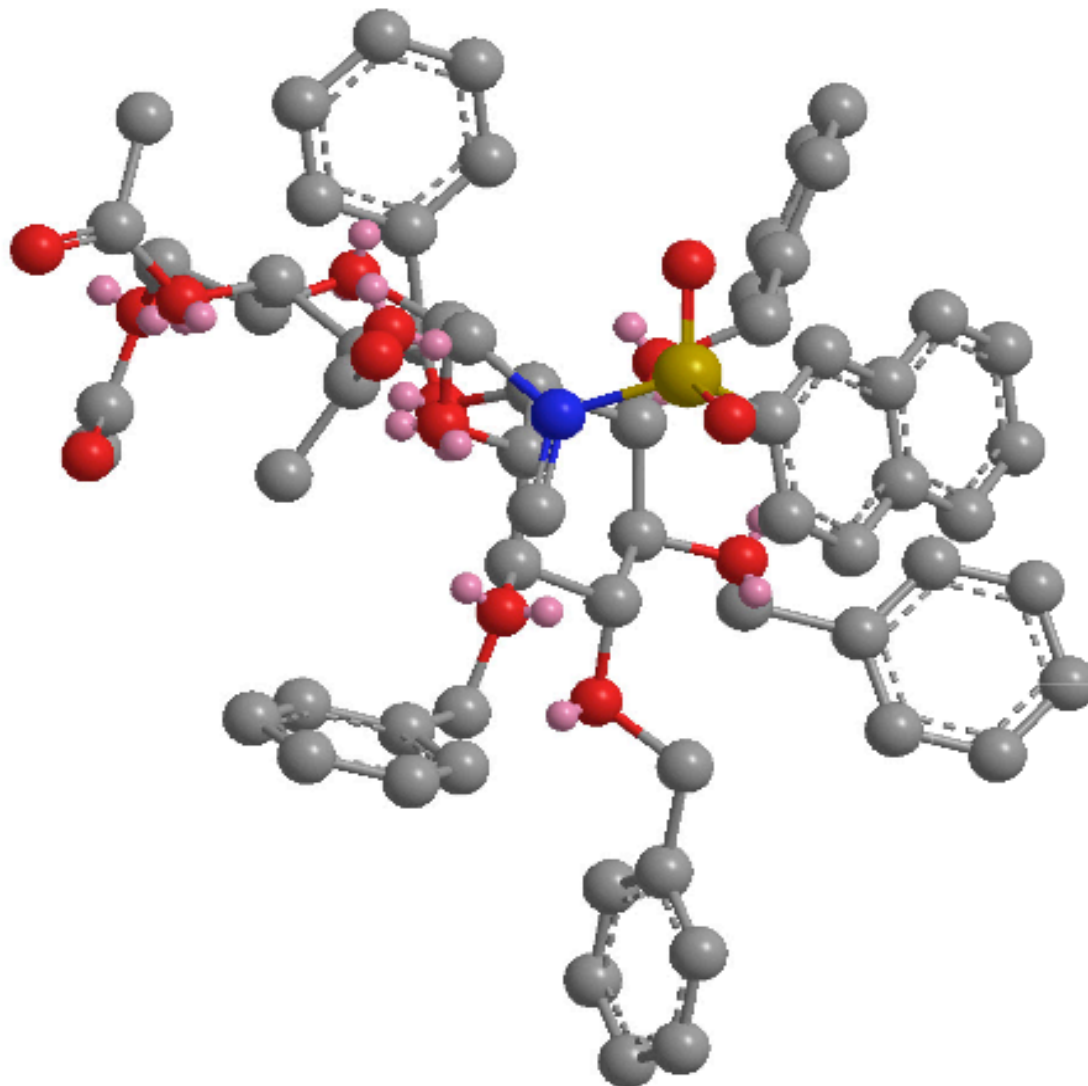
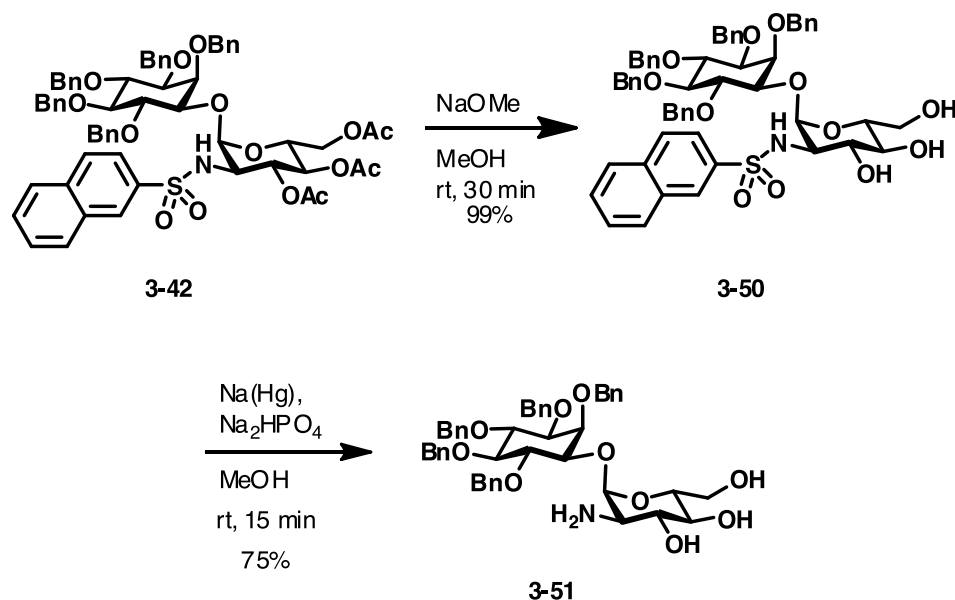


Figure 3.3. Energy-minimized 3-D structure of 3-46.

3.7. Endgame

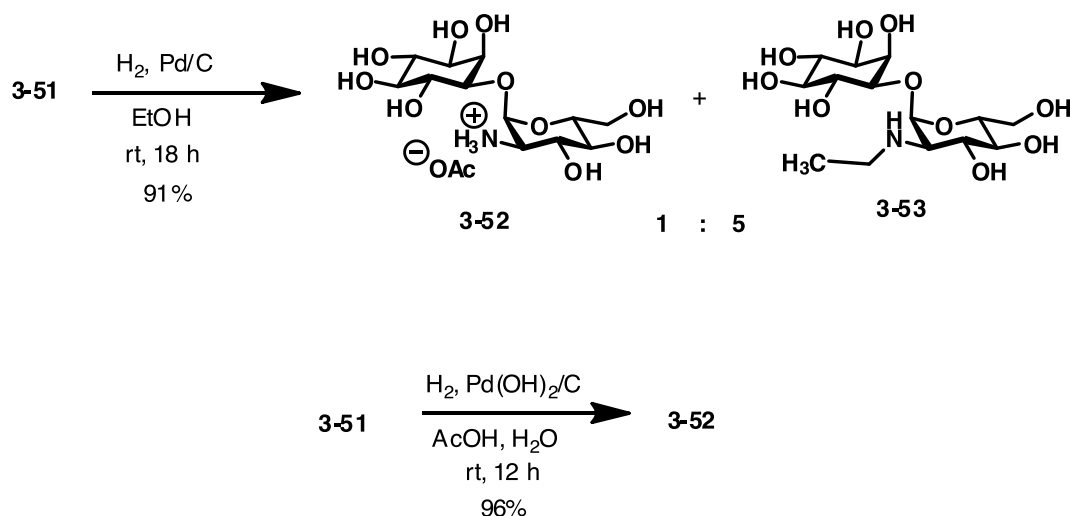
Zemplén deacetylation on **3-42** was quantitative. Application of the sulfonamide reduction conditions determined in the model study to triol **3-50** gave the desired aminotriol **3-51** in good yield after only 15 minutes at room

temperature, with the benzyl groups intact (Scheme 3.15). At 0 °C, sodium amalgam effected only ~40% conversion of **3-51** by TLC after 1 hour.



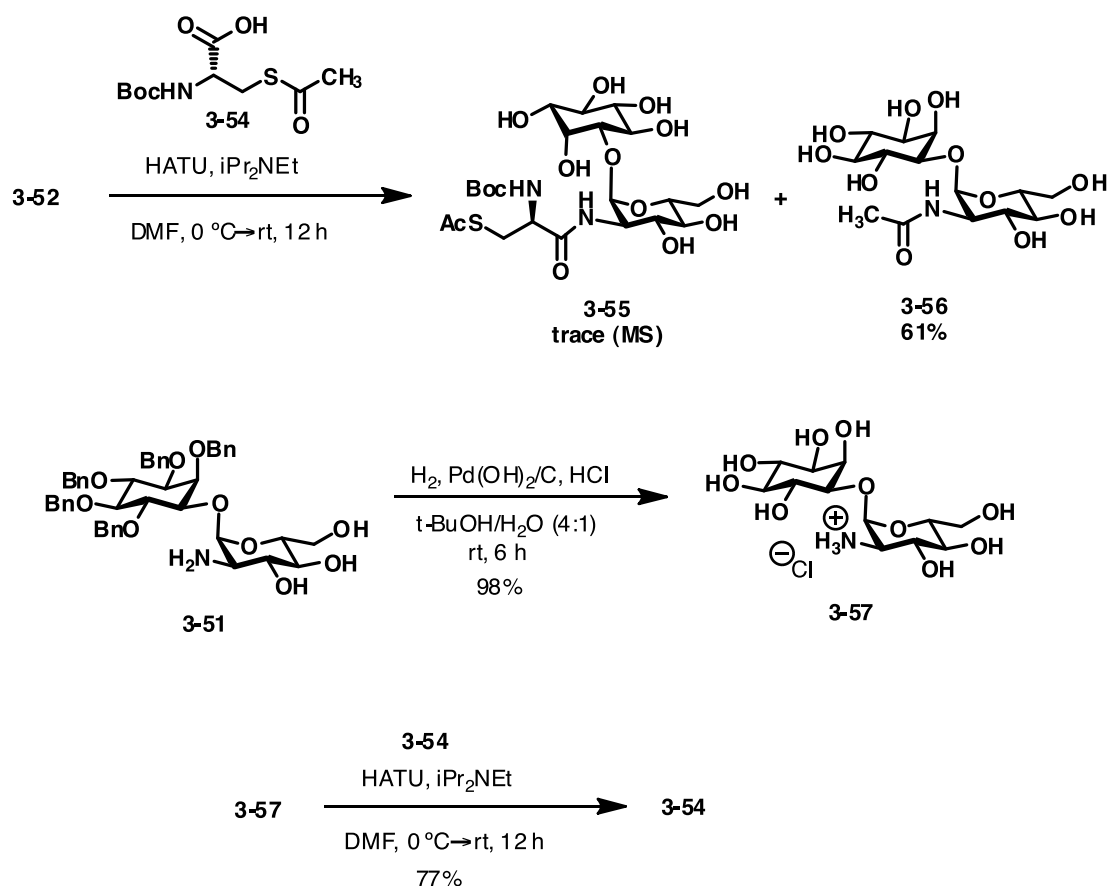
Scheme 3.15. Synthesis of aminotriol **3-51**

Hydrogenolysis of the five benzyl ether groups under standard Pd(0)/C/hydrogen gas/ethanol conditions gave the desired aminooctol **3-52** as a minor product, with the major product being the *N*-ethyl aminooctol derivative **3-53** (Scheme 3.16). That product presumably arose from acetaldehyde found in absolute ethanol, or from dehydrogenation of ethanol in the presence of palladium. At any rate, the *N*-ethylation problem was solved by using 1:1 acetic acid/water as the solvent, giving **3-52** as an acetate salt in 96% yield.



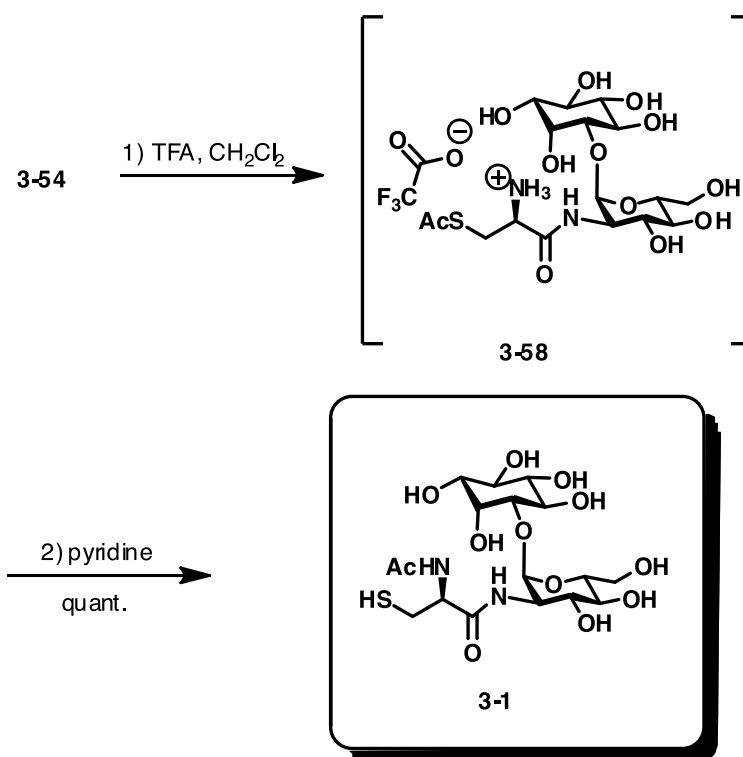
Scheme 3.16. Hydrogenolysis of 3-51

With aminooctol **3-52** in hand, we set out to perform the final 2 steps. We elected to install the cysteine group as the *N*-Boc-*S*-acetyl derivate **3-54** (Scheme 3.17, prepared in 2 steps from *N*-Boc cystine²²). The coupling conditions, HATU and Hünig's base in DMF, were first developed with glucosamine hydrochloride as a model substrate. The acetate ion from **3-52**, however, was able to effectively compete for the coupling reagent, producing *N*-acetyl octol **3-56** and only a trace amount of the desired product, peptide **3-55**. Changing the counterion to chloride prevented formation of **3-56** and gave **3-55** in 77% yield.



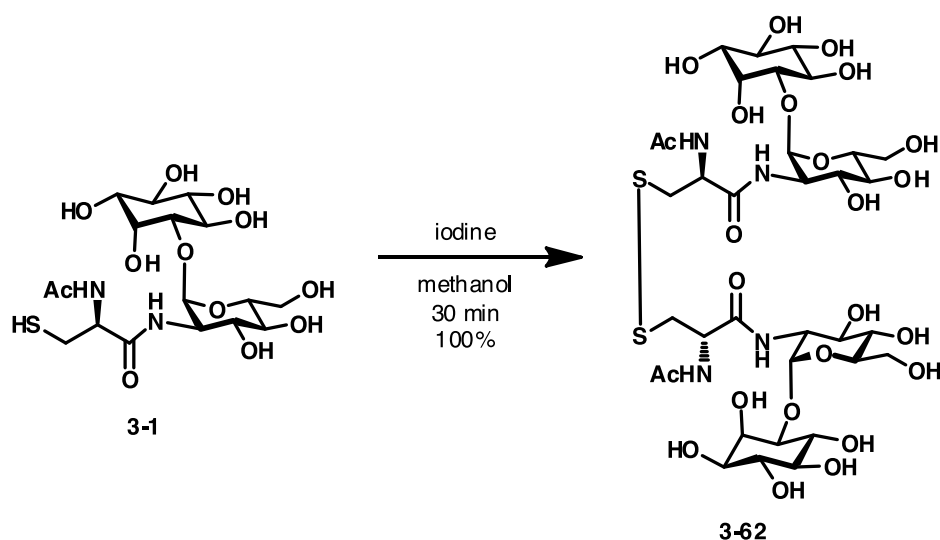
Scheme 3.17. Peptide coupling to GlcN-Ins

The final step, thankfully, worked as described previously.^{22,23} Removal of the Boc group gave ammonium ion **3-58** that, upon neutralization with pyridine, underwent acetyl migration from sulfur in quantitative fashion (Scheme 3.18), leaving free mycothiol **3-1** in an overall process of 16 steps. The yield from glycosyl donor **3-26** was 51%, which represents an over 7-fold improvement over the previous synthesis from a similar starting point.



Scheme 3.18. Migration of acetyl group from sulfur to nitrogen

As further support for the successful synthesis of **3-1**, the product was subject to iodine in methanol to form the natural mycothiol disulfide (MSSM, **3-62**, Scheme 3.19), with spectra matching previously reported spectra.²⁷



Scheme 3.19. Synthesis of MSSM

3.8. References

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Chapter 4. Sustained release of ethynyl estradiol from carrier-linked prodrugs

4.1. Introduction to prodrugs

There are several obstacles to drug development that are not directly related to the potency of a given drug candidate. Drugs often fail in the pipeline due to issues such as low aqueous solubility, low bioavailability, chemical and/or physical instability, rapid *in vivo* metabolism prior to fulfilling their purpose, toxicity, and even subjective unpleasantness that adversely affects patient compliance. A given drug can often be administered as an inactive derivative that lacks some undesired trait that the parent drug possesses, and then converted, either chemically or enzymatically, into the active drug *in vivo* after the need for the derivative has been satisfied. The inactive derivative is called a *prodrug*.¹ To the synthetic chemist, prodrugs can be thought of as molecules that bear biochemically labile protecting groups, many of which are also chemically labile and thus familiar. Though prodrugs have been in use for a couple of decades now, they have been growing in popularity in recent years. Prodrugs can be further differentiated as *bipartate* or *tripartate* prodrugs. Bipartate prodrugs are ones in which the carrier is connected directly to the parent, whereas tripartate prodrugs have the parent drug and the carrier separated by a spacer, or *linker*.²

4.2. Ethynyl estradiol use and limitations

Ethynyl estradiol (EE, **4-1**, Figure 4.2) is the first known orally available synthetic steroidal estrogen. It is indicated for a wide variety of conditions and purposes, pregnancy prevention being chief among them. EE has been used successfully as a contraceptive for more than 60 years, though it has some limitations. The one relevant to this project is its relatively short half-life in humans. Norethindrone, another popular steroidal contraceptive, was modified to become a slow-release drug by converting the 17-hydroxyl group into a carbonate, with good success.³ Though **4-1** is itself a longer-lasting derivative of the hormone estradiol, it still requires daily administration to be effective.

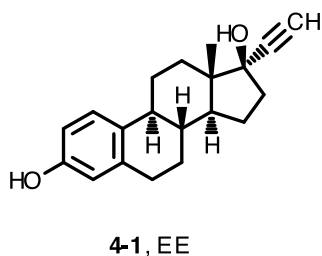
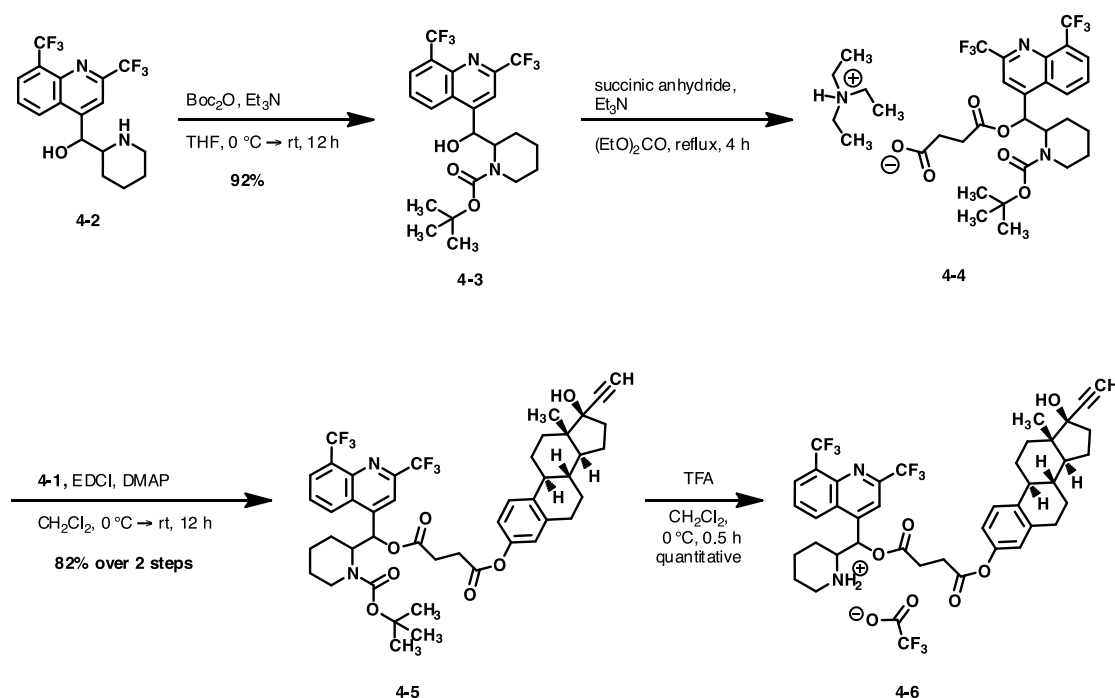


Figure 4.1. Ethynyl estradiol

4.3. Synthesis and hydrolysis studies of EE conjugates

Given the fact that many bipartate and tripartate drug carrier systems have been shown to exhibit ADME traits of their individual parts,⁴ we decided to design

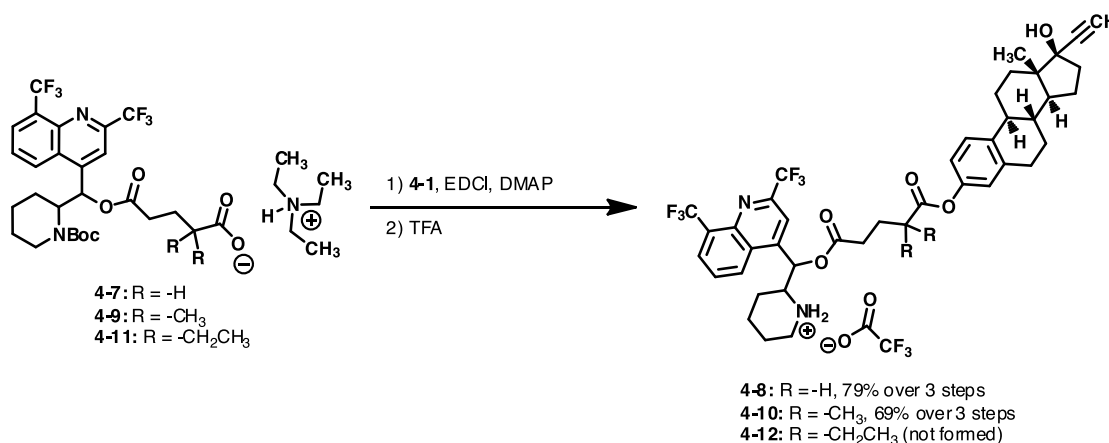
a drug carrier system that would improve the half-life of a given parent drug such as **4-1**. The system involves the connection the drug of interest, **4-1** in this case, to a drug with a long half-life through a linker. Mefloquine, an antimalarial drug, has a half-life of about 20 days, as is therefore a good candidate. Coupling **4-1** to succinate **4-4**⁵ and subsequent deprotection gives the first EE conjugate **4-6** (Scheme 4.1). An *in vitro* hydrolysis study at physiological pH (7.4) showed that **4-6** fully released free EE after 9 days.



Scheme 4.1. Synthetic route to EE conjugate **4-6**

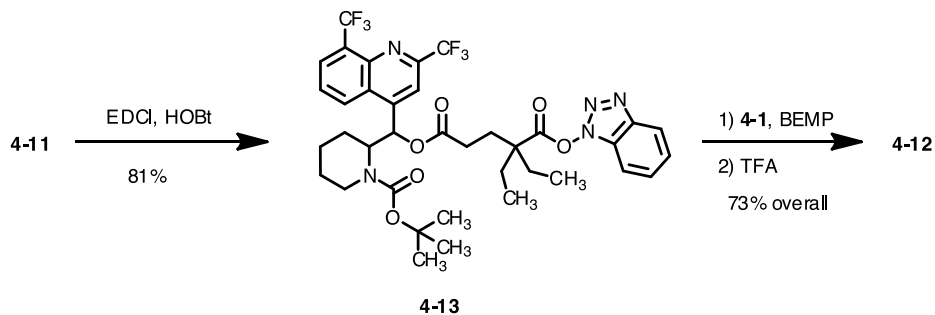
Spurred on by those results, we also designed EE conjugates with a homologated linker, and also explored the effects of increased steric bulk α to the

aromatic ester (Scheme 4.2). Homologation did not appear to affect hydrolysis rate (10 days for **4-8**), but increasing steric bulk near the phenoxycarbonyl group did seem to affect the hydrolysis rate (60 days for **4-10**).



Scheme 4.2. Synthesis of homologated EE conjugates

Unfortunately, the diethylglutarate intermediate **4-11** appeared to be too hindered to add **4-1** to it directly, so it was converted to the activated ester **4-13**, then treated with the phenoxy anion of **4-1** to get **4-11** (Scheme 4.3). Conjugate **4-12** was practically inert to physiological hydrolysis.



Scheme 4.3. Alternate route to hindered conjugate **4-12**

4.4. Biological evaluation of drug conjugates

Esterases are well known to attack ester-based prodrugs,⁶ so we knew that *in vitro* hydrolysis studies would not be enough to validate this mefloquine-linked delivery system. We therefore had conjugates **4-8**, **4-10**, and **4-12** tested in Bama pigs in an attempt to quantify the effect of esterases. The results of this study are shown on Table 4.1. Given the shorter half-life of **4-1** in animals relative to humans,⁷ the results seem positive as a proof of concept. We are now pursuing other EE conjugates with more novel linkers, with the intent to improve on these encouraging *in vivo* results.

| In vivo Pig Data (1) | | | Pharmacokinetic Analysis (2) | | | |
|----------------------|------------|------------|------------------------------|------------|------------|-------------------|
| Days | CRDC A (4) | CRDC B (5) | Days | CRDC C (6) | CRDC D (7) | Immediate Release |
| 1 | 135 | BLQ (8) | 1 | 134 | 36 | 46 |
| 2 | 71 | 38 | 2 | 80 | 32 | 0 |
| 3 | 77 | 50 | 3 | 49 | 29 | 0 |
| 4 | 4 | 3 | 4 | 30 | 26 | 0 |
| 7 | 17 | BLQ | 7 | 11 | 19 | 0 |
| 9 | 5 | 61 | 9 | 4 | 16 | 0 |

1. Serum concentration (pg/ml) of EE in female Bama pigs (one pig per CRDC) following intramuscular administration of 1050 micrograms in CRDC dosage form.
 2. Analysis of EE serum concentrations of two CRDCs versus the immediate release dosage form
 3. No serum EE analysis was performed on days 5,6 and 8.
 4. Rapid release CRDC based on 2,2-dimethylglutamate
 5. Slow release CRDC based on 2,2-diethylglutarate
 6. Rapid release CRDC based on 2,2-dimethylglutamate with first order constant $k=0.54$; half life 3 hours
 7. Slow release CRDC based on 2,2-diethylglutarate with first order constant $k=0.10$; half life 3 hours
 8. BLQ-below limit of quantitation

Table 1. Results from pig study of EE conjugates

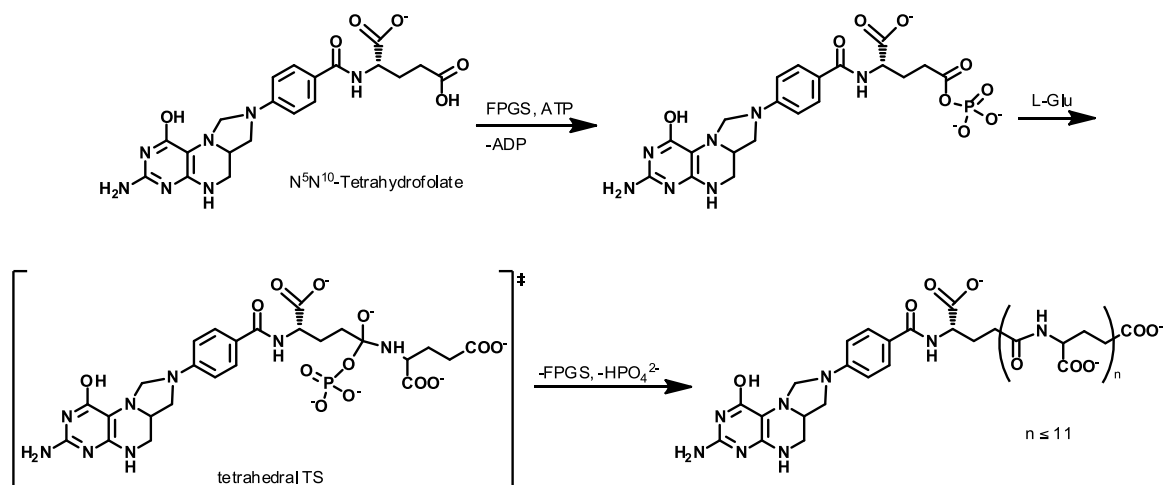
4.5. References

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Chapter 5. Boro-antifolates

5.1. Antifolates in cancer therapy

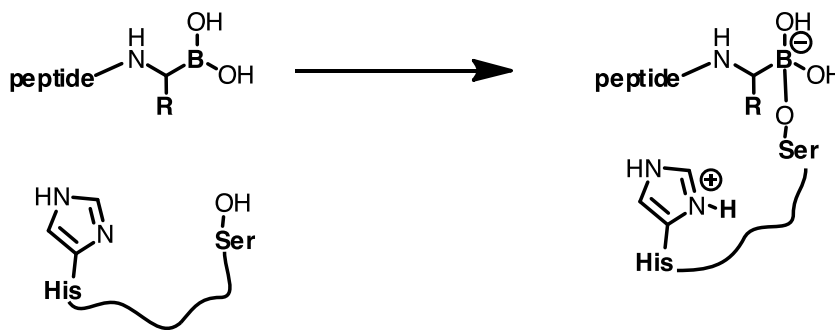
Folate analogs, or antifolates, have been designed and synthesized as potential chemotherapeutic agents for over 50 years, and this remains an important area of research. Antifolates compete with folic acid for folate-dependent enzymes, such as dihydrofolate reductase (DHFR), thymidylate synthase (TS), γ -glutamyl hydrolase (GH), and folylpoly- γ -glutamate synthetase (FPGS).¹ Though antifolates have been in development for more than 50 years, the potential benefits of FPGS inhibition have only been sought after in the past 2 decades. FPGS catalyzes the addition of multiple glutamate residues, in a chain (Scheme 5.1), to folic acid to produce folylpolyglutamates, which are more catalytically efficient than folylmonoglutamates and cannot be actively effluxed or passively diffused from cells.² Because cancerous cells tend to express FPGS at much higher levels than normal cells, FPGS inhibitors are expected to aid in cancer chemotherapy by accelerated cell death due to deprivation of various essential biomolecules.³ Several interesting inhibitors have been reported in the literature.^{4–8}



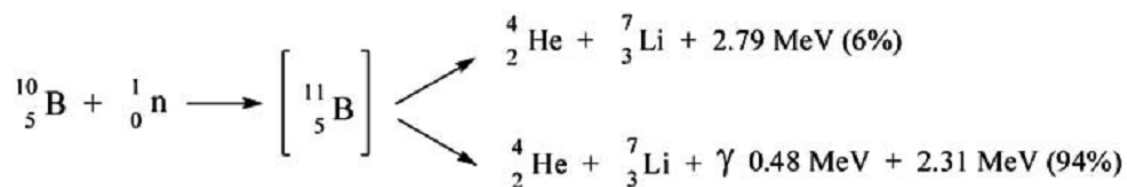
Scheme 5.1. FPGS mechanism

5.2. Organoboron compounds in cancer chemotherapy

The potential benefits of boron-containing compounds for cancer chemotherapy are twofold. Firstly, boronic acids are known to be effective ‘serine traps,’ which may allow a molecule so equipped to act as a reversible inhibitor of an enzyme with an active-site serine residue (Scheme 5.2).^{9,10} Secondly, they may also serve an important role in radiotherapy via a process known as boron neutron capture therapy (BNCT).^{11,12} In this process, ^{10}B captures low-energy neutrons to form ^{11}B , which then undergoes fission to form high-energy α -particles that can destroy cells within a 5-9 micron radius (Scheme 5.3). In collaboration with Dr. Joseph Bertino and coworkers at the Cancer Institute of New Jersey, we set out to make boronic acid analogs of folic acid as BNCT-capable inhibitors of FPGS.



Scheme 5.2. Inhibition mechanism of organoboronates

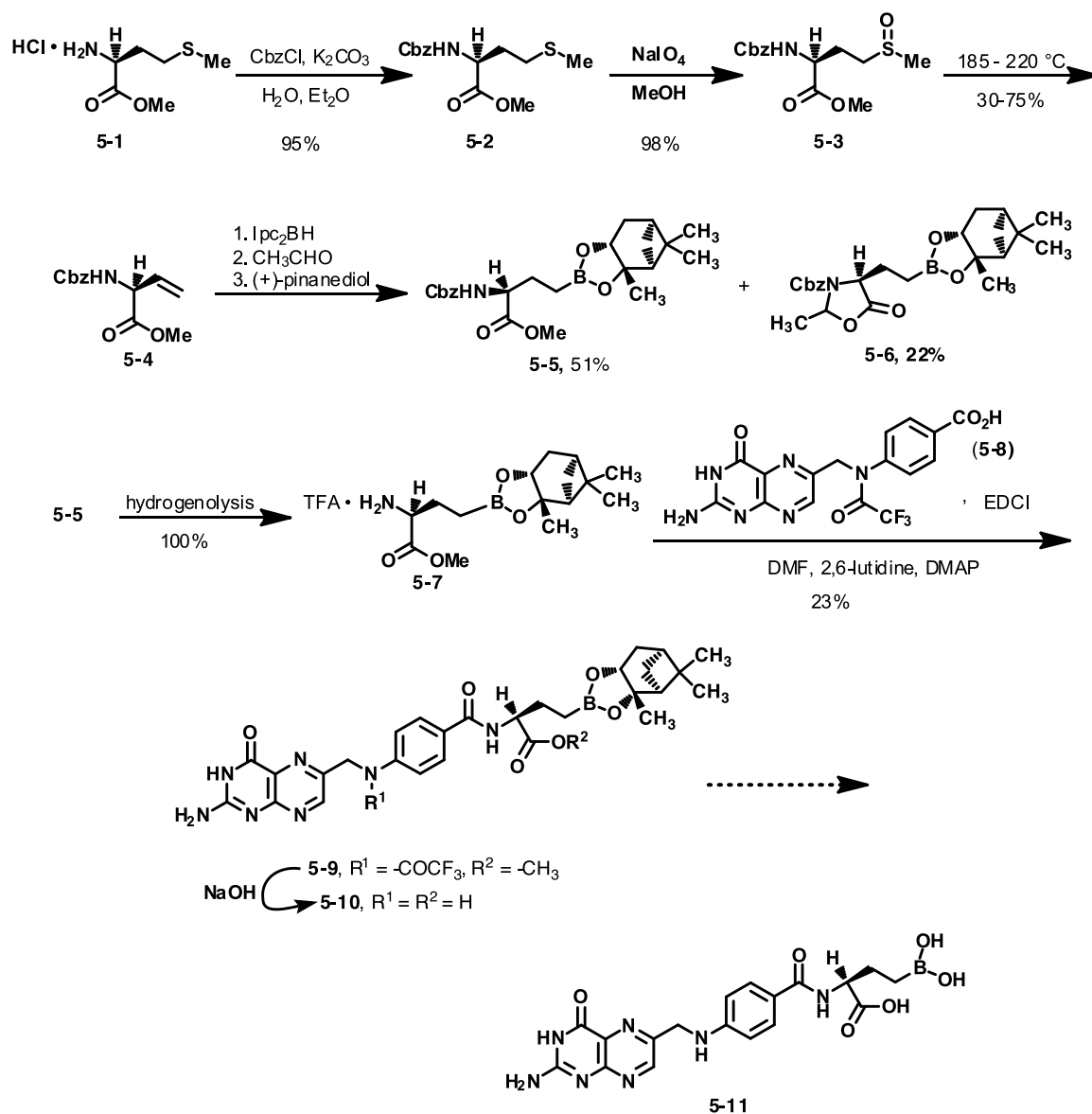


Scheme 5.3. Boron neutron capture therapy

5.3. Synthesis of borofolates by coupling boroglutamates to pteroates

The most straightforward way to produce antifolates is to couple a pterioic acid analogue to a glutamic acid analogue through an amide bond. The synthetic route is shown in Scheme 5.4. Synthesis of a protected vinylglycine via sulfoxide elimination gave modest yields from tedious chromatographic separations.¹³ Hydroboration of protected vinylglycine **5-4** to form pinanediol ester **5-5** was plagued with side reactions, one of which was possibly due to deprotonation of the t-butyl carbamate¹⁴ and subsequent [3+2] addition to acetaldehyde to form

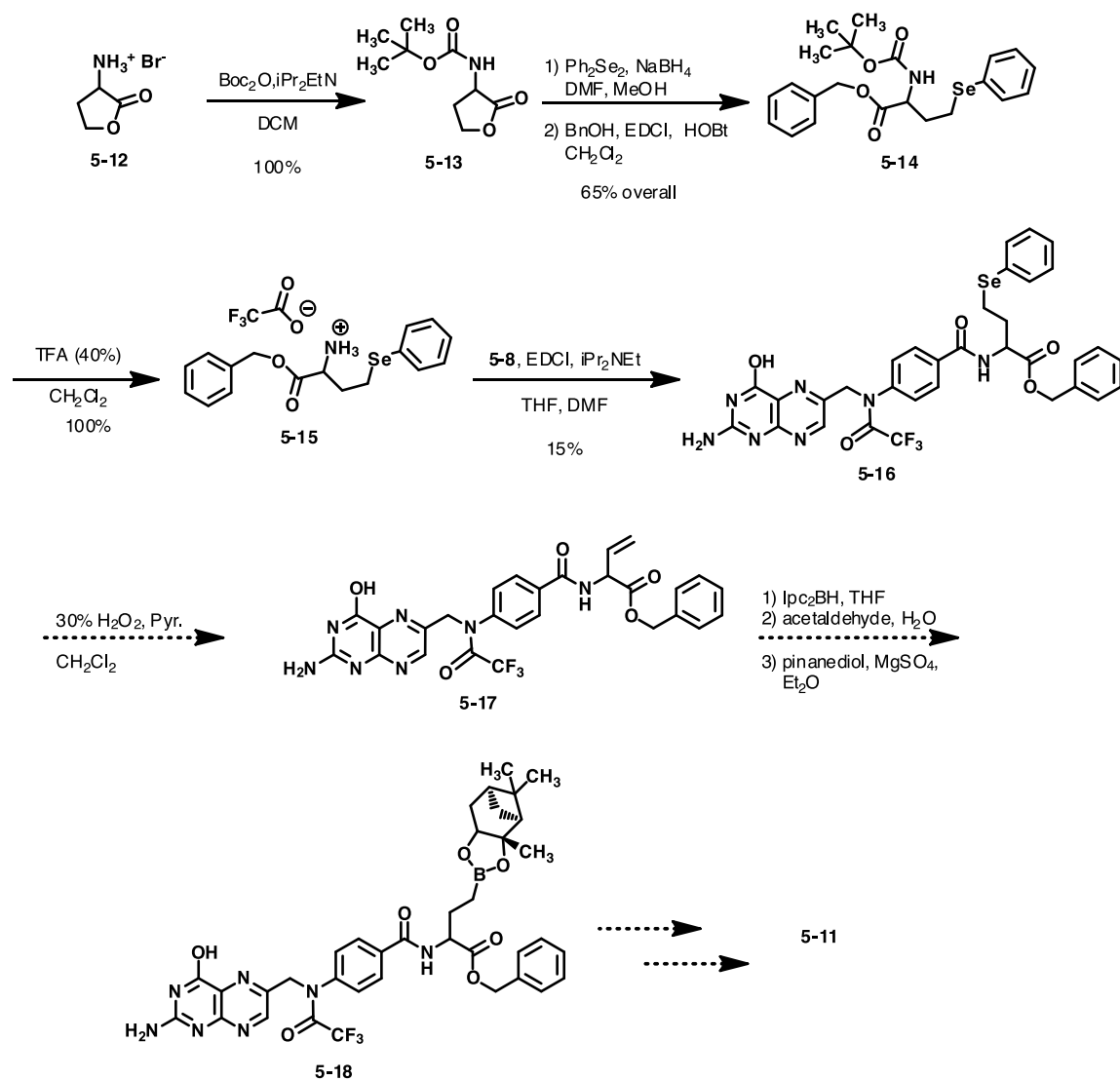
N-protected oxazolidinone **5-6**. The *t*-butyl ester analog of **5-5** is known,¹⁵ though no experimental details were given for its synthesis. Amide formation from a glutamylboronate ester and a protected pteroate such as trifluoroacetyl pteroate **5-8**¹⁶ is already a difficult process,¹⁷ and the Lewis acidity of the boronate ester may have exacerbated the problem. Because of these difficulties, we could not get enough material to produce boronic acid **5-11**, and a new route was therefore devised.



Scheme 5.4. First-generation route to **5-11**

5.4. Synthesis of borofolates by transforming selenofolates

The synthetic route shown in Scheme 5.5 represents a second-generation approach to the desired borofolate, sidestepping most of the problems associated with the previous route. Selenoether **5-15** was synthesized in 4 steps from γ -lactone **5-12**. Unfortunately, the coupling reaction with **5-11** fared no better than in the previous route, giving selenofolate **5-17** in only 15% yield. We are currently pursuing another route that involves the *de novo* construction of the pteroate moiety.



Scheme 5.5. Second-generation route to 5-11

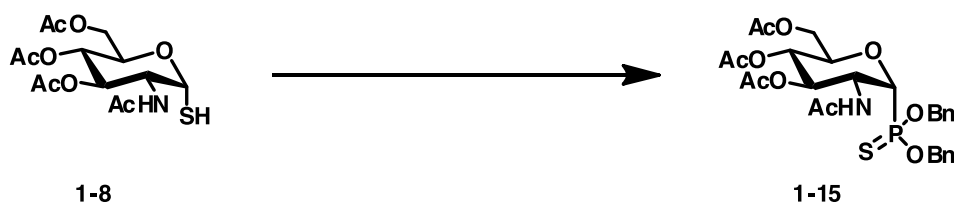
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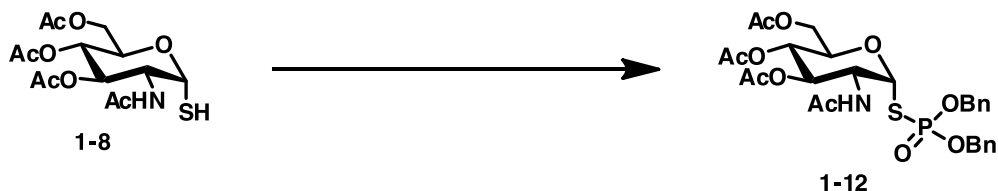
Experimental Section

E1. Experimental procedures for Chapter 1



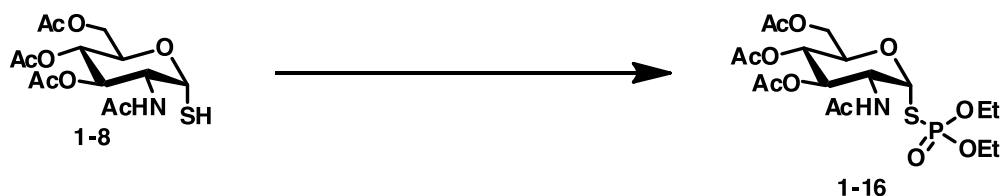
Compound 1-15. Dibenzyl *N,N*-diisopropylphosphoramidite (0.09 mmol, 30.1 mg) was added to a solution of **1-8** (0.05 mmol, 18.6 mg) and tetrazole (0.15 mmol, 10.8 mg) in acetonitrile (0.80 mL) at 0 °C. After 2 h at 23 °C, triethylborane (1 M in hexanes, 0.052 mmol, 5.2 mg) was added, and a slow stream of compressed air was bubbled through the reaction for 15 min. Concentration and then chromatography with 2:3 ethyl acetate/hexanes as the eluant provided 24 mg (79%) of **1-15**: R_f 0.27 (1:1 ethyl acetate/hexanes); ^1H NMR (400 MHz, CDCl_3) (all δ in ppm, then multiplicity, J in Hz, integral or assignments based on COSY analysis) 7.31–7.35 (m, Ph-H's), 5.96 (d, 8.4, -NHAc), 5.82 (dd, 8.4, 10.4, H-3), 5.05 (dd, 5.6, 11.2, -CH₂Ph), 5.03 (app t, 9.6, H-4), 5.03 (dd, 2 -CH₂Ph), 4.93 (dd, 9.2, 11.2, -CH₂Ph), 4.69 (dd, 6.8, 9.2, H-1), 4.55 (dddd, 6.8, 8.4, 10.0, 31.2, H-2), 4.34 (dddd, 2.4, 5.2, 8.4, 9.6, H-5), 4.12 (dd, 5.2, 12.4, H-6), 3.98 (dd, 2.4, 12.4, H-6'), 2.02 (s, 2 -COCH₃). 2.01 (s, -COCH₃), 1.57 (s, -COCH₃); ^{13}C NMR (100

MHz) δ 171.2, 170.6, 170.2, 169.2, 135.5 (d, 6.1), 135.4 (d, 6.1), 128.8, 128.74 (3 C's), 128.68 (2 C's), 128.6 (2 C's), 128.4 (2 C's), 75.1 (d, 120.6), 72.8 (d, 2.3), 70.1, 69.2 (d, 7.6), 67.9, 67.7 (d, 7.6), 61.8, 50.3 (d, 2.3), 22.7, 20.7, 20.64, 20.62; ^{31}P NMR (121 MHz) 88.24; ESI-MS m/z 630 MNa^+ .

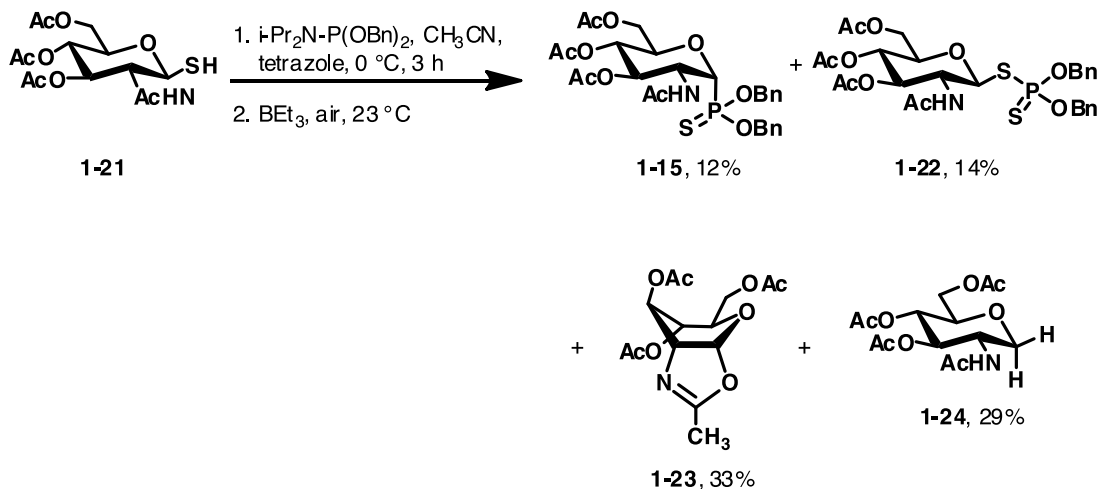


Compound 1-12. A solution of **1-8** (1.42 mmol, 514 mg) in dichloromethane (3.14 mL) was added via cannula to a solution of dibenzyl *N,N*-diisopropylphosphoramidite (5.94 mmol, 2.05 g), 1-methylbenzimidazolium triflate (5.66 mmol, 1.60 g) and powdered, activated 4-Å molecular sieves in 1:1 dichloromethane/acetonitrile (6.29 mL), held at -52°C during addition. After 5 h at -25°C , the reaction was cooled to -50°C and *m*-CPBA (7.08 mmol, 1.22 g) was added. The reaction was stirred for 1 h while warming to 23°C . The mixture was filtered through Celite, diluted with dichloromethane, washed sequentially with 20% aq Na_2SO_3 , 1 N aq HCl, and water, dried over MgSO_4 , and then concentrated. Chromatography with 1:4 ethyl acetate/dichloromethane as the eluant afforded 640 mg (72%) of **1-12** as a sticky solid: R_f 0.36 (1:1 ethyl acetate/dichloromethane); ^1H NMR 7.36–7.34 (m, 10 H), 6.01 (dd, 5.0, 11.6, H-1), 5.73 (d, 8.4, -NHAc), 5.16 (t, 9.6, H-4), 5.11 (m, 4 -CH₂Ph), 5.03 (dd, 10.8, 9.6, H-3), 4.56 (ddd, 10.8, 8.4, 4.8, H-2), 4.16 (dd, 13.6, 3.8, H-6), 4.15 (m, H-5), 3.91 (dd, 13.6, 3.8, H-6), 2.04, 2.03, 1.98, 1.83 (s, 3 H each, -COCH₃); ^{13}C NMR (assignments based on HMQC analysis) 171.6, 170.5, 169.9, 169.1, 135.0, 134.8, 128.9 (2 C's), 128.7 (4 C's), 128.3 (2 C's), 128.2 (2 C's), 85.7 (d, 3.0, C-1), 70.9

(C-3), 70.6 (C-5), 69.7 (d, 6.7, $-\underline{\text{C}}\text{H}_2\text{Ph}$), 69.5 (d, 6.7, $-\underline{\text{C}}\text{H}_2\text{Ph}$), 67.4 (C-4), 61.4 (C-6), 52.6 (d, 6.6, C-2), 23.0, 20.7, 20.6 (2 C's); ^{31}P NMR 24.44; ESI-MS m/z 646 MNa^+ .

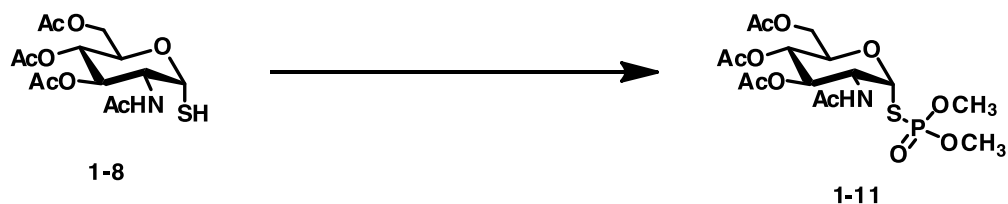


Compound 1-16: Triethylamine (0.55 mmol, 55.6 mg) was added to a solution of **1-8** (0.46 mmol, 166.1 mg) and diethyl chlorophosphate (0.55 mmol, 94.7 mg) in acetonitrile (9.1 mL), held at $-40\text{ }^{\circ}\text{C}$ during addition. After 4 h at $23\text{ }^{\circ}\text{C}$, the reaction was diluted with ethyl acetate, washed with 10% aq NaHCO_3 , dried, concentrated, and then chromatographed with 7:3 ethyl acetate/dichloromethane as the eluant to afford 161 mg (70%) of **1-16** as a white solid, mp $108\text{--}111\text{ }^{\circ}\text{C}$: R_f 0.25 (1:19 methanol/dichloromethane); ^1H NMR 5.89 (dd, 4.8, 12.0, 1H), 5.87 (d, 8.4, 1H), 5.15 (t, 9.6, 1H), 5.01 (dd, 10.8, 9.6, 1H), 4.53 (ddd, 11.1, 8.7, 5.1, 1H), 4.28–4.08 (m, 7H), 2.06 (s, 3H), 2.04 (s, 6H), 1.94 (s, 3H), 1.35 (ddd, 6.6, 3.3, 0.6, 6H); ^{13}C NMR 171.7, 170.6, 170.0, 169.2, 85.7 (d, 3.4), 71.2, 70.8, 67.8, 64.6 (d, 6.3), 64.5 (d, 6.3), 61.9, 52.3 (d, 6.5), 23.5, 21.0 (2 C's), 20.9, 16.5 (d, 2.3), 16.4 (d, 2.3); ^{31}P NMR 23.25; ESI-MS m/z 522 MNa^+ .



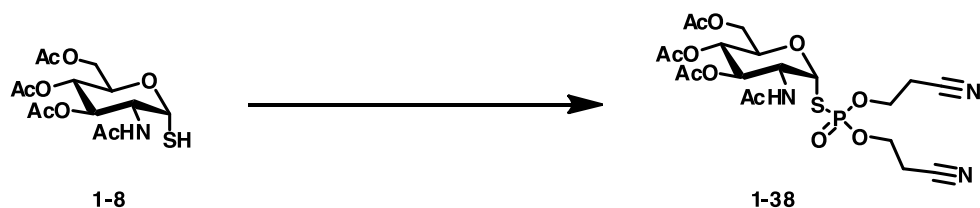
Phosphitylation of 1-21: A solution of **1-21** (0.12 mmol, 42.1 mg) in degassed acetonitrile (0.6 mL) was added to a solution of tetrazole (0.42 mmol, 29.3 mg) and dibenzyl *N,N*-diisopropylphosphoramidite (0.20 mmol, 68.0 mg) in degassed acetonitrile (0.6 mL) at $0\text{ }^\circ\text{C}$. After 3 h at $23\text{ }^\circ\text{C}$, triethylborane (1 M in hexanes, 0.12 mmol, 11.4 mg) was added, and a slow stream of compressed air was bubbled through the reaction for 20 min. The reaction was stirred overnight, and then diluted with ethyl acetate, washed with 5% aq NaHCO_3 , concentrated, and then chromatographed with 2:3 ethyl acetate/hexanes, then ethyl acetate, as the eluant, to give the following products in order of elution. Compound **1-15**, 8.2 mg. Compound **1-22**, 10.4 mg, R_f 0.22 (1:1 ethyl acetate/hexanes); ^1H NMR 7.37–7.32 (m, Ph-H), 5.50 (d, 9.5, -NHAc), 5.16 (dd, 11.5, 10.0, -CH₂Ph), 5.14–5.11 (m, 2 -CH₂Ph), 5.09 (t, 10.0, H-4), 5.09 (dd, 11.5, 10.0, -CH₂Ph), 5.06 (dd, 10.0, 9.5, H-3), 4.97 (dd, 14.0, 10.5, H-1), 4.35 (q, 10.0, H-2), 4.12 (dd, 12.5,

5.0, H-6), 4.04 (dd, 12.5, 2.0, H-6'), 3.69 (ddd, 10.0, 5.0, 2.0, H-5), 2.03 (s, 2 -COCH₃), 1.97 (s, -COCH₃), 1.89 (s, -COCH₃); ¹³C NMR 171.1, 170.6, 170.0, 169.2, 135.4 (d, 9.3), 135.1 (d, 8.8), 128.7, 128.64, 128.61 (2 C's) 128.60 (2 C's), 128.2 (2 C's), 128.1 (2 C's), 87.4 (d, 3.3), 73.81, 73.80, 69.74 (d, 6.5), 69.69 (d, 6.4), 67.8, 61.9, 53.2 (d, 10.6), 23.1, 20.6 (3 C's); ³¹P NMR 94.99; ESI-MS *m/z* 662 MNa⁺. Compound **1-23**, 12.5 mg, *R_f* 0.30 (ethyl acetate). Compound **1-24**, 11.2 mg, *R_f* 0.23 (ethyl acetate).

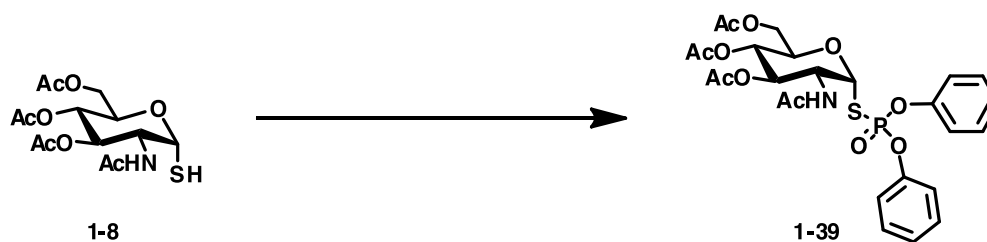


Compound 1-11. A solution containing 69.5 mg (0.191 mmol) of **1-8** in 2.0 mL of acetonitrile was treated at -40 °C with 1.28 mL (0.45 M solution in acetonitrile) of tetrazole and 62.8 mg (0.325 mmol) of dimethyl *N,N*-diisopropylphosphoramidite. After stirring for 3 h at -40 °C, the mixture was treated with 299 mg (1.91 mmol) of *m*-CPBA in 3.8 mL of dichloromethane, then allowed to warm to room temperature over 1 h. The reaction was concentrated, diluted with ethyl acetate, washed with saturated aq. Na₂SO₃ and saturated aq. NaHCO₃, then concentrated and chromatographed through silica gel using 3:1 ethyl acetate/dichloromethane as the eluent to afford 43.5 mg (48%) of **1-11** as a colorless oil: *R_f* 0.16 (7:3 ethyl acetate/dichloromethane); ¹H NMR (300 MHz, CDCl₃) δ 5.96 (dd, *J* = 12.0, 5.4 Hz, 1 H), 5.88 (d, *J* = 8.4 Hz, 1 H), 5.18 (t, *J* = 9.6 Hz, 1 H), 5.03 (dd, *J* = 10.8, 9.3 Hz, 1 H), 4.53 (dddd, *J* = 11.1, 8.4, 5.1, 0.9 Hz, 1 H), 4.27 (dd, *J* = 12.3, 3.9 Hz, 1 H), 4.20 (ddd, *J* = 10.8, 3.9, 1.8 Hz, 1 H), 4.10 (dd, *J* = 12.3, 1.8 Hz, 1 H), 3.85 (d, *J* = 8.1 Hz, 3 H), 3.81 (d, *J* = 7.8 Hz, 3 H), 2.08 (s, 3 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.98 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 171.9, 170.6, 170.2, 169.2, 85.7 (d, *J* = 3.3 Hz), 71.1, 70.9, 67.7, 62.0, 54.7 (d, *J* = 6.0

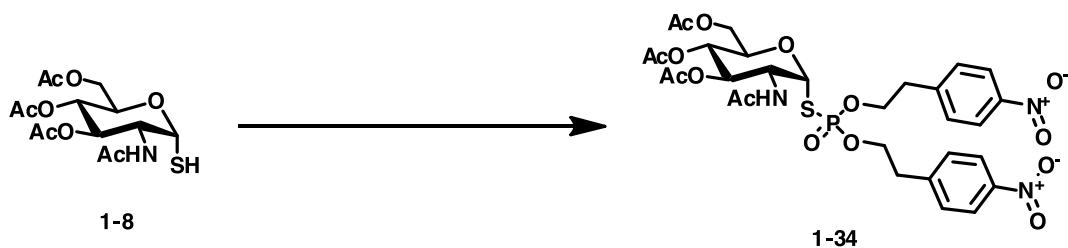
Hz), 54.6 (d, $J = 6.5$ Hz), 53.2 (d, $J = 6.6$ Hz), 23.5, 21.1, 21.0, 20.9; ^{31}P NMR (121 MHz, CDCl_3) δ 26.78; ESI-MS m/z 494 MNa^+ .



Compound 1-38. A solution containing 49.9 mg (0.137 mmol) of **1-8** in 0.45 mL of acetonitrile was stirred on 4 Å molecular sieves for 1 h. The solution was then treated at -40 °C with 0.92 mL of a 0.45 M solution of tetrazole in acetonitrile, followed by 63.2 mg (0.0545 mmol) of bis(2-cyanoethyl)-*N,N*-diisopropyl phosphoramidite. After stirring for 5 h at -40 °C, the reaction was treated with 71.1 mg (0.412 mmol) of *m*-CPBA, and the reaction was warmed to room temperature over 2 h. The reaction was concentrated and chromatographed through silica gel using 10:9:1 diethyl ether/ethyl acetate/methanol to afford 33.7 mg (45%) of **1-38** as a colorless oil: R_f 0.10 (3:2 ethyl acetate/dichloromethane); ^1H NMR (400 MHz, CDCl_3) δ 6.14 (dd, J = 11.6, 5.2 Hz, 1 H), 6.10 (d, J = 7.6 Hz, 1 H), 5.20 (t, J = 9.2 Hz, 1 H), 4.49 (dddd, J = 11.6, 6.8, 5.2, 0.9 Hz, 1 H), 4.26–4.44 (m, 6 H), 4.21 (dd, J = 12.0, 2.4 Hz, 1 H), 2.83 (t, J = 6.4 Hz, 4 H), 2.10 (s, 3 H), 2.07 (s, 3 H), 2.06 (s, 3 H), 2.00 (s, 3 H); ^{31}P NMR (161 MHz, CDCl_3) δ 26.93; ESI-MS m/z 549 MNa^+ .

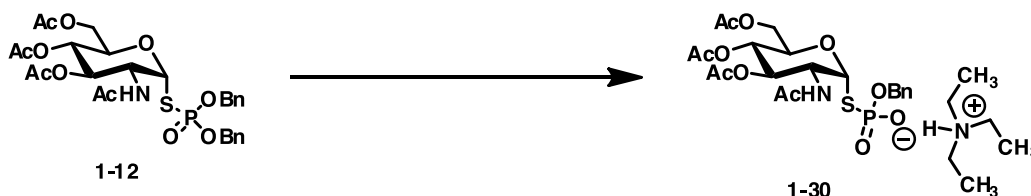


Compound 1-39. A solution containing 64.6 mg (0.240 mmol) of diphenyl chlorophosphate in 1.0 mL of dichloromethane was treated at $-40\text{ }^{\circ}\text{C}$ with a solution containing 83.0 mg (0.229 mmol) of **1-8** and 25.5 mg (0.252 mmol) of triethylamine in 1.0 mL of dichloromethane. The cooling bath was removed after 10 min. and the reaction was allowed to stir for 2 h. The reaction was concentrated and chromatographed using 4:1 ethyl acetate/dichloromethane as the eluent to produce 91.3 mg (67%) of **1-39** as a colorless oil: R_f 0.55 (3:2 ethyl acetate/dichloromethane); ^1H NMR (500 MHz, CDCl_3) δ 7.37 (t, $J = 8.0$ Hz, 4 H), 7.28 (m, 4 H), 7.22 (tdd, $J = 8.0, 3.0, 1.0$ Hz, 2 H), 6.14 (dd, $J = 12.5, 5.0, 1$ H), 5.61 (d, $J = 8.5, 1$ H), 5.15 (t, $J = 10$ Hz, 1 H), 4.96 (app t, $J = 10$ Hz, 1 H), 4.55 (ddd, $J = 11.5, 8.5, 5.0$ Hz, 1 H), 4.12 (dd, $J = 12.5, 3.5$ Hz, 1 H), 3.98 (app dt, $J = 10.0, 2.5$ Hz, 1 H), 3.71 (dd, $J = 12.5, 2.0$ Hz, 1 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.72 (s, 3 H); ^{31}P NMR (202 MHz, CDCl_3) δ 17.78; ESI-MS m/z 618 MNa^+ .

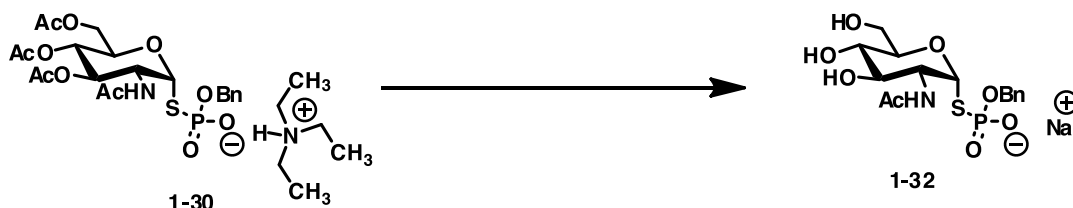


Compound 1-34. Bis(2-(*p*-nitrophenyl)ethyl) chlorophosphate was prepared by stirring 130 mg (0.342 mmol) of bis(2-(*p*-nitrophenyl)ethyl) phosphite and 69.3 mg (0.513 mmol) of sulfuryl chloride together in 4 mL of dichloromethane at 0 °C for 30 min. The crude chlorophosphate was concentrated and dissolved in 1.0 mL of dry THF, then treated at -10 °C with a mixture containing 75.1 mg (0.207 mmol) of **1-8** and 44.2 mg (0.342 mmol) of triethylamine in 1.0 mL of THF. After stirring at room temperature for 1 h, the reaction was concentrated and chromatographed through silica gel using 3:2 ethyl acetate/dichloromethane as the eluent to produce 53.7 mg (35%) of **1-34** as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 8.17 (dd, $J = 8.5, 2.0$ Hz, 4 H), 7.38 (dd, $J = 8.5, 2.0$ Hz, 4 H), 5.95 (dd, $J = 11.5, 5.0$ Hz, 1 H), 5.81 (d, $J = 8.0$ Hz, 1 H), 5.18 (dd, $J = 10.0, 9.5$ Hz, 1 H), 4.98 (dd, $J = 11.0, 9.5$ Hz, 1 H), 4.44 (ddd, $J = 10.0, 8.0, 5.0$ Hz, 1 H), 4.18–4.38 (m, 4 H), 4.19 (dd, $J = 12.5, 3.0$ Hz, 1 H), 4.11 (app dt, $J = 10.0, 3.0$ Hz, 1 H), 4.02 (dd, $J = 12.5, 2.5$ Hz, 1 H), 3.09 (t, $J = 7.0$ Hz, 2 H), 3.08 (t, $J = 7.0$ Hz, 2 H), 2.07 (s, 3 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.90 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.0, 170.4, 169.9, 169.0, 147.2, 144.2, 144.2, 129.8 (2 C), 123.8, 85.4 (d, $J = 3.3$ Hz),

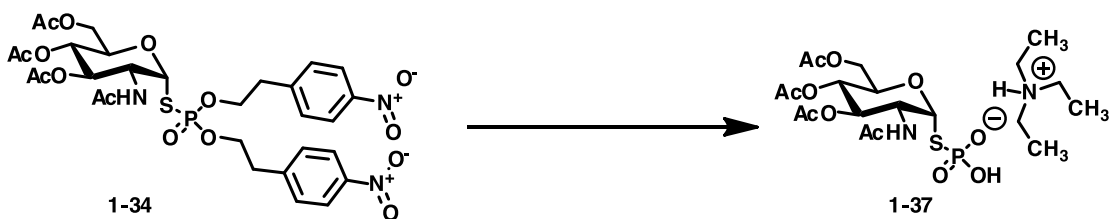
77.4, 77.2, 76.9, 70.7, 70.6, 67.4 (d, $J = 6.5$ Hz), 67.3 (d $J = 6.9$ Hz), 61.2, 53.2 (d, $J = 7.0$ Hz), 36.3 (d, $J = 6.1$ Hz), 36.2 (d, $J = 6.9$ Hz), 23.1, 20.7, 20.6, 20.5; ^{31}P NMR (202 MHz, CDCl_3) δ 24.56; ESI-MS m/z 764 MNa^+ .



Compound 1-30. A solution containing 28.6 mg (0.0459 mmol) of **1-12** in 0.46 mL of dimethylformamide was treated with 4.2 mg (0.064 mmol) of sodium azide. After stirring for 4 h at 70 °C, the reaction was concentrated and chromatographed through silica gel using 44:5:1 dichloromethane/methanol/triethylamine as the eluent to produce 21.5 mg (74%) of **1-30** as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 7.39 (d, $J = 7.0$ Hz, 2 H), 7.32 (t, $J = 7.0$ Hz, 2 H), 7.28 (br s, 1 H), 6.08 (d, $J = 9.5$ Hz, 1 H), 5.82 (dd, $J = 11.0, 5.0$ Hz, 1 H), 5.13–5.16 (m, 2 H), 4.99 (d, $J = 8.0$ Hz, 1 H), 4.98 (d, $J = 7.5$ Hz, 1 H), 4.56 (ddd, $J = 10.5, 9.5, 5.0$ Hz, 1 H), 4.18–4.22 (m, 1 H), 4.14 (dd, $J = 12.5, 4.0$ Hz, 1 H), 3.98 (dd, $J = 12.5, 2.5$ Hz, 1 H), 3.00 (q, $J = 7.5$ Hz, 6 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.86 (s, 3 H), 1.29 (t, $J = 7.5$ Hz, 9 H), ^{13}C NMR (125 MHz, CDCl_3) δ 171.1, 170.6, 170.1, 169.3, 138.0 (d, $J = 8.9$ Hz), 128.3 (d, $J = 6.9$ Hz), 127.7, 127.6, 85.4 (d, $J = 2.8$ Hz), 71.9, 70.0, 68.1, 67.5 (d, $J = 5.6$ Hz), 61.8, 52.3 (d, $J = 4.6$ Hz), 45.6, 23.2, 20.7, 20.62, 20.58, 8.6; ^{31}P NMR (202 MHz, CDCl_3) δ 14.07; ESI-MS m/z 532 M^+ .

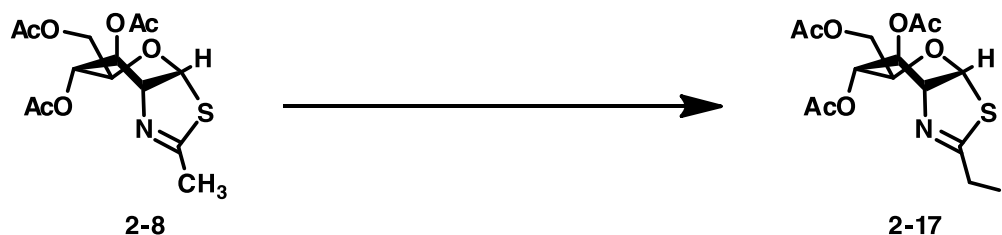


Compound 1-32. A solution containing 27.3 mg (0.0431 mmol) of **1-30** in 0.43 mL of methanol was treated with 0.46 mg (0.0085 mmol) of sodium methoxide in 3 μ L of methanol. The reaction was concentrated and chromatographed through silica gel using 17:2:1 dichloromethane/methanol/conc. ammonium hydroxide as the eluent to give 18.3 mg (99%) of **1-32** as a sticky solid: ^1H NMR (500 MHz, CD_3OD) δ 7.39 (d, $J = 7.0$ Hz, 2 H), 7.32 (t, $J = 7.0$ Hz, 2 H), 7.26 (t, $J = 7.5$ Hz, 1 H), 5.79 (dd, $J = 10.5, 5.0$ Hz, 1 H), 4.93 (d, $J = 6.5$ Hz, 1 H), 4.13 (dd, $J = 10.5, 5.0$ Hz, 1 H), 3.98 (ddd, $J = 10.0, 6.0, 2.5$ Hz, 1 H), 3.78 (dd, $J = 12.0, 2.5$ Hz, 1 H), 3.64 (dd, $J = 12.0, 5.5$ Hz, 1 H), 3.57 (dd, $J = 10.5, 9.0$ Hz, 1 H), 3.34 (dd, $J = 9.0, 1.5$ Hz, 1 H), 1.88 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.7, 139.5 (d, $J = 9.6$ Hz), 129.5, 128.7, 128.5, 86.2 (d, $J = 3.1$ Hz), 75.8, 73.1, 72.7, 68.5 (d, $J = 5.5$ Hz), 62.7, 55.9 (d, $J = 6.0$ Hz), 22.8; ^{31}P NMR (202 MHz, CDCl_3) δ 17.81; ESI-MS m/z 406 M^- .

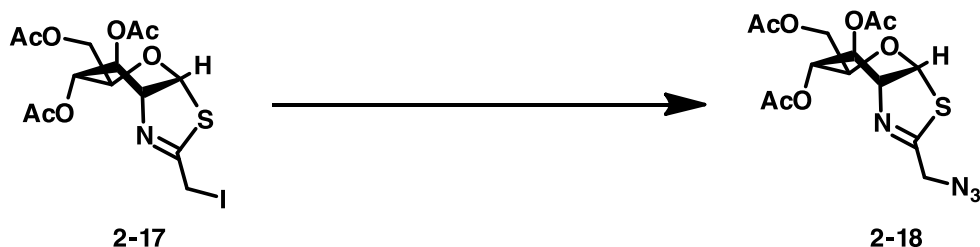


Compound 1-37. A solution containing 14.7 mg (0.0198 mmol) of **1-34** in 0.2 mL of acetonitrile was treated with 12.0 μL (0.0788 mmol) of DBU and 10.0 μL (0.0400 mmol) of *N,O*-bis(trimethylsilyl)acetamide. After stirring for 3 h at room temperature, the solution was treated with an additional 12 μL of DBU and 10 μL of *N,O*-bis(trimethylsilyl)acetamide. After stirring for 4 h at room temperature, the solution was treated with an additional 48 μL of DBU and 40 μL of *N,O*-bis(trimethylsilyl)acetamide. After stirring for 3 more hours, the solution was concentrated and chromatographed through silica gel using 73:25:2 dichloromethane/methanol/triethylamine as the eluent to give 8.0 mg of **1-37** as a thin film: ^1H NMR (500 MHz, CD_3OD) δ 5.76 (dd, $J = 10.0, 5.0$ Hz, 1 H), 5.16 (dd, $J = 11.0, 9.0$ Hz, 1 H), 5.03 (dd, $J = 10.5, 9.0$ Hz, 1 H), 4.48 (dd, $J = 11.0, 4.5$ Hz, 1 H), 4.37 (ddd, $J = 10.0, 3.5, 2.5$ Hz, 1 H), 4.32 (dd, $J = 12.5, 4.0$ Hz, 1 H), 4.10 (dd, $J = 12.5, 2.0$ Hz, 1 H), 3.20 (q, $J = 7.5$ Hz, 6 H), 2.04 (s, 3 H), 2.00 (s, 3 H), 1.97 (s, 3 H), 1.94 (s, 3 H), 1.31 (t, $J = 7.5$ Hz, 9 H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.6, 172.7, 172.1, 171.5, 85.6 (d, $J = 3.8$ Hz), 72.9, 70.7, 70.5, 63.4, 53.8 (d, $J = 6.3$ Hz), 48.1, 22.8, 20.8, 20.8, 20.7, 9.4; ^{31}P NMR (202 MHz, CD_3OD) δ 14.37; ESI-MS m/z 442 M^- .

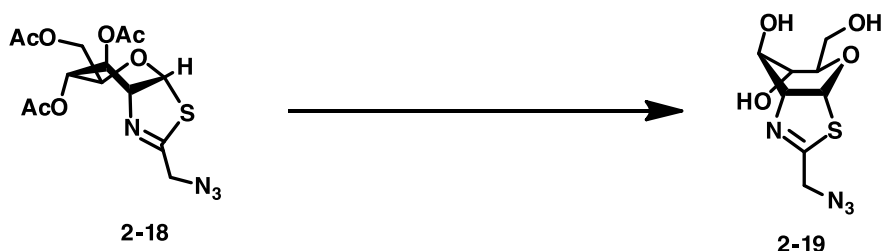
E2. Experimental Procedures for Chapter 2



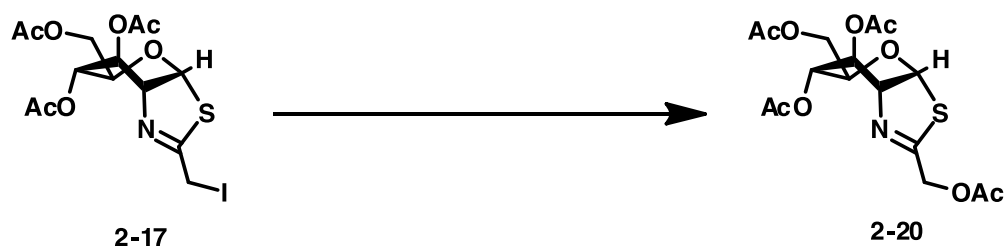
Compound 2-17. A solution containing 207.3 mg (0.60 mmol) of **2-8** in THF (2.4 mL) was cooled in a 0 °C bath, and 142.4 mg (1.8 mmol) of pyridine was added, followed by 108.2 mg (0.72 mmol) of triflic acid and then 304.6 mg (1.2 mmol) of iodine. The reaction was stirred for 15 min at rt, and then was diluted with 5 mL of hexanes and concentrated to ~1 mL. Silica gel column chromatography with 2:3 ethyl acetate/hexanes as the eluent afforded 169.6 mg (60%) of **17** as a brown oil: R_f 0.65 (2:3 ethyl acetate/dichloromethane); ^1H NMR (500 MHz, CDCl_3) δ 6.34 (d, J = 7.0, 1 H), 5.57 (dd, J = 3.5, 1.5, 1 H), 4.95 (dt, J = 9.5, 1.5, 1 H), 4.49 (ddd, J = 7.0, 3.0, 1.0, 1 H), 4.09–4.25 (m, 4 H), 3.62 (ddd, J = 8.5, 5.5, 2.5, 1 H), 2.15 (s, 3 H), 2.11 (s, 3 H), 2.09 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 169.6, 169.3, 168.9, 89.6, 76.6, 70.3, 69.1, 69.0, 63.3, 20.9, 20.87, 20.7, 14.2; ESI-MS m/z 472 MH^+ , 494 MNa^+ .



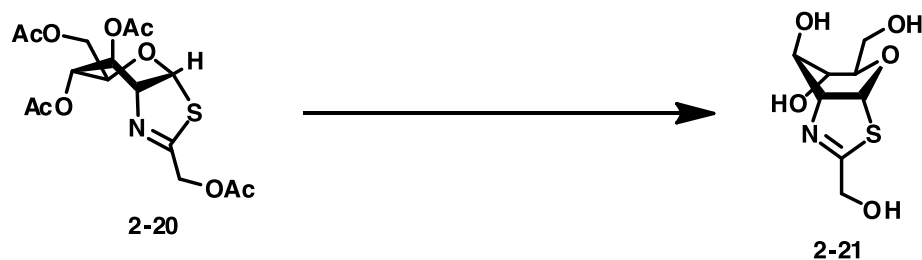
Compound 2-18. A solution containing 68.9 mg (1.1 mmol) of sodium azide in DMF (0.53 mL) was added by cannula to a solution of 50.1 mg (0.11 mmol) of **2-17** in DMF (0.53 mL). After 2 h, the reaction was quenched with 10% aqueous sodium bicarbonate, concentrated, diluted with dichloromethane, washed with 5% aqueous sodium bicarbonate and then dried over sodium sulfate. Silica gel column chromatography with 2:3 ethyl acetate/hexanes as the eluent afforded 38.2 mg (90%) of **2-18** as a light yellow oil: R_f 0.60 (2:3 ethyl acetate/dichloromethane); ^1H NMR (500 MHz, CDCl_3) δ 6.33 (d, $J = 7.5$, 1 H), 5.61 (dd, $J = 3.5$, 2.0, 1 H), 4.97 (dt, $J = 9.0$, 1.5, 1 H), 4.57 (ddd, $J = 7.0$, 3.5, 1.5, 1 H), 4.21 (br t, $J = 2.3$, 2 H), 4.16 (dd, $J = 12.3$, 2.8, 1 H), 4.13 (dd, $J = 12.3$, 5.8, 1 H), 3.55 (ddd, $J = 9.5$, 5.5, 3.5, 1 H), 2.16 (s, 3 H), 2.09 (s, 3 H), 2.087 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 169.6, 169.2, 167.8, 88.5, 76.3, 70.3, 69.1, 68.7, 63.3, 51.8, 20.9, 20.8, 20.7; FT-IR 2962, 2101, 1732, 1622 cm^{-1} ; ESI-MS m/z 387 MH^+ , 409 MNa^+ .



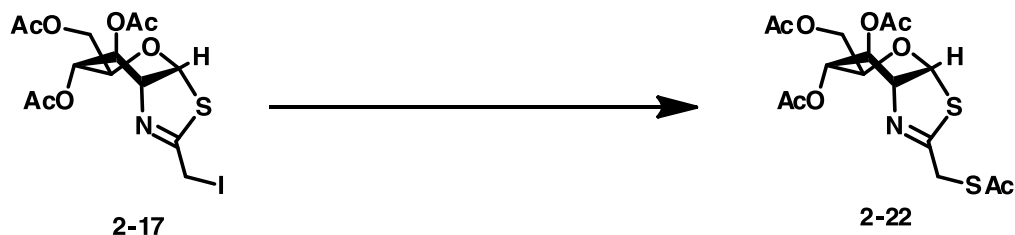
Compound 2-19. A solution containing 1.27 mg (0.02 mmol) of sodium methoxide in methanol (7 μ L) was added to a solution of 45.5 mg (0.12 mmol) of **2-18** in methanol (1.18 mL). After stirring in the absence of light for 30 min, the reaction was quenched with aqueous sodium bicarbonate, filtered through Celite, and concentrated. Silica gel chromatography with 1:9 methanol/dichloromethane as the eluent afforded 28.1 mg (90%) of **2-19**: R_f 0.25 (1:9 methanol/dichloromethane); ^1H NMR (500 MHz, CD_3OD) δ 6.44 (d, $J = 7.0$, 1 H), 4.38–4.42 (m, 1 H), 4.29 (dd, $J = 16.0$, 2.0, 1 H), 4.24 (dd, $J = 15.5$, 2.0, 1 H), 4.15 (dd, $J = 4.0$, 3.5, 1 H), 3.74 (dd, $J = 12.0$, 2.5, 1 H), 3.62 (dd, $J = 12.5$, 6.5, 1 H), 3.58 (ddd, $J = 9.0$, 4.0, 1.0, 1 H), 3.35 (ddd, $J = 8.5$, 6.0, 2.5, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.3, 90.7, 80.6, 76.6, 74.3, 71.4, 63.6, 53.3; FT-IR 2923, 2108, 1661, 1614 cm^{-1} ; ESI-MS m/z 261 MH^+ , 283 MNa^+ .



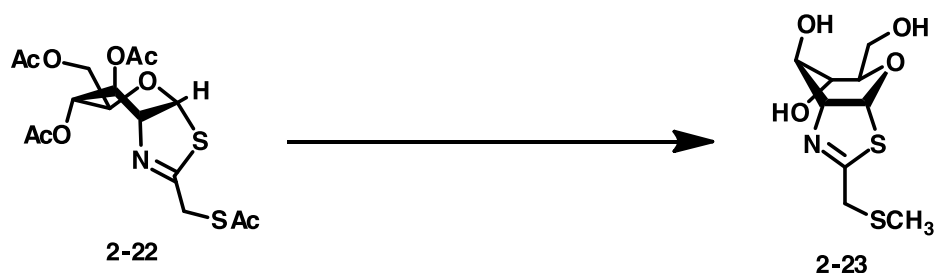
Compound 2-20. Sodium acetate (6.13 mg, 0.08 mmol) was added to a solution of 17.6 mg (0.04 mmol) of **2-17** in DMF (0.37 mL). After stirring for 3 h, the reaction was diluted with diethyl ether, washed with deionized water and dried over sodium sulfate. Silica gel chromatography with 2:3 ethyl acetate/hexanes as the eluent afforded 13.5 mg (84%) of **2-20** as a colorless oil: R_f 0.35 (2:3 ethyl acetate/dichloromethane); ^1H NMR (500 MHz, CDCl_3) δ 6.27 (d, $J = 7.0$, 1 H), 5.59 (dd, $J = 2.5, 1.5$, 1 H), 4.98 (dd, $J = 15.0, 2.0$, 1 H), 4.95 (br d, $J = 9.0$, 1 H), 4.92 (dd, $J = 14.5, 2.0$, 1 H), 4.53 (ddd, $J = 6.0, 2.5, 1.5$, 1 H), 4.14 (dd, $J = 12.0, 2.5$, 1 H), 4.11 (dd, $J = 12.0, 5.0$, 1 H), 3.54 (ddd, $J = 9.5, 5.5, 3.5$, 1 H), 2.17 (s, 3 H), 2.15 (s, 3 H), 2.10 (s, 3 H), 2.09 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.5, 170.0, 169.6, 169.2, 168.7, 88.7, 76.3, 70.4, 69.1, 68.7, 63.3, 31.4, 20.9, 20.8, 20.7, 20.5; ESI-MS m/z 404 MH^+ , 426 MNa^+ .



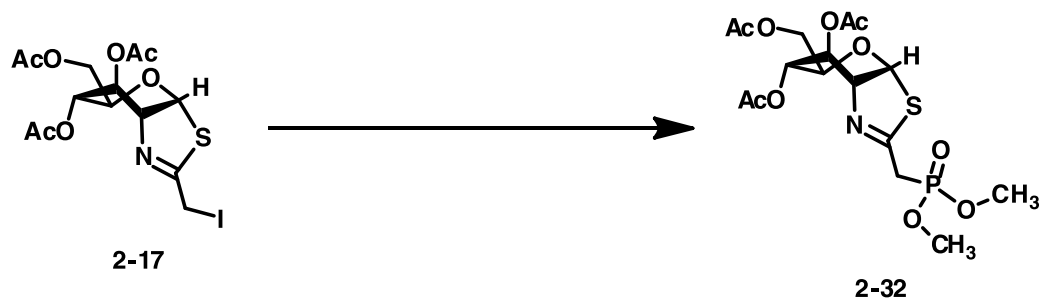
Compound 2-21. A solution of 0.22 mg (4 μ mol) sodium methoxide in methanol (1.1 μ L) was added to a solution of 8.5 mg (0.02 mmol) **2-20** in methanol (0.21 mL). After stirring for 30 min, the reaction was quenched with aqueous sodium bicarbonate, filtered through Celite, and then concentrated, producing 4.7 mg (95%) of **2-21**: R_f 0.25 (1:4 methanol/dichloromethane); ^1H NMR (500 MHz, CD_3OD) δ 6.34 (d, $J = 7.0$, 1 H), 4.42 (dd, $J = 14.5$, 2.0, 1 H), 4.36–4.39 (m, 1 H), 4.36 (dd, $J = 15.0$, 1.5, 1 H), 4.18 (app t, $J = 4.0$, 1 H), 3.73 (dd, $J = 12.0$, 2.0, 1 H), 3.61 (dd, $J = 12.0$, 6.5, 1 H), 3.58 (ddd, $J = 9.0$, 3.5, 0.5, 1 H), 3.33 (ddd, 9.0, 6.5, 3.0, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.2, 89.1, 80.5, 76.4, 74.2, 71.5, 63.7, 63.2; ESI-MS m/z 236 MH^+ , 258 MNa^+ .



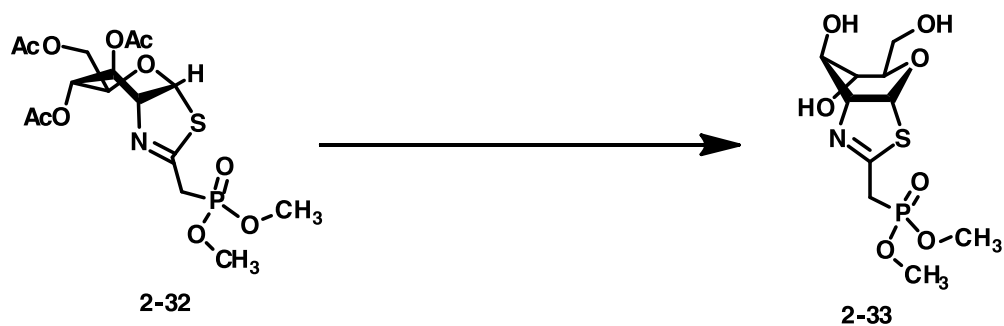
Compound 2-22. A solution containing 42.6 mg (0.09 mmol) of **2-17** in DMF (0.45 mL) was added by cannula to a solution of 205.6 mg (1.8 mmol) potassium thioacetate in DMF (0.45 mL). After stirring for 2 h, the reaction mixture was quenched with 10% aqueous sodium bicarbonate, concentrated, diluted with dichloromethane, washed with 5% aqueous sodium bicarbonate and then dried over sodium sulfate. Silica gel chromatography with 2:3 ethyl acetate/hexanes as the eluent afforded 26.8 mg (71%) of **2-22** as a light yellow oil: R_f 0.45 (2:3 ethyl acetate/dichloromethane); ^1H NMR (500 MHz, CDCl_3) δ 6.25 (d, $J = 7.0$, 1 H), 5.56 (dd, $J = 3.5$, 1.5, 1 H), 4.94 (dt, $J = 9.5$, 1.5, 1 H), 4.51 (ddd, $J = 7.5$, 3.5, 1.5, 1 H), 4.15 (dd, $J = 12.0$, 2.8, 1 H), 4.09 (dd, $J = 12.0$, 5.8, 1 H), 4.01 (dd, $J = 15.5$, 2.0, 1 H), 3.97 (dd, $J = 15.5$, 2.0, 1 H), 3.54 (ddd, $J = 9.5$, 6.0, 3.0, 1 H), 2.41 (s, 3 H), 2.13 (s, 3 H), 2.09 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 193.3, 170.5, 169.5, 169.2, 169.0, 88.7, 76.3, 70.4, 69.1, 68.7, 63.3, 31.4, 30.1, 20.9, 20.8, 20.7; ESI-MS m/z 420 MH^+ , 442 MNa^+ .



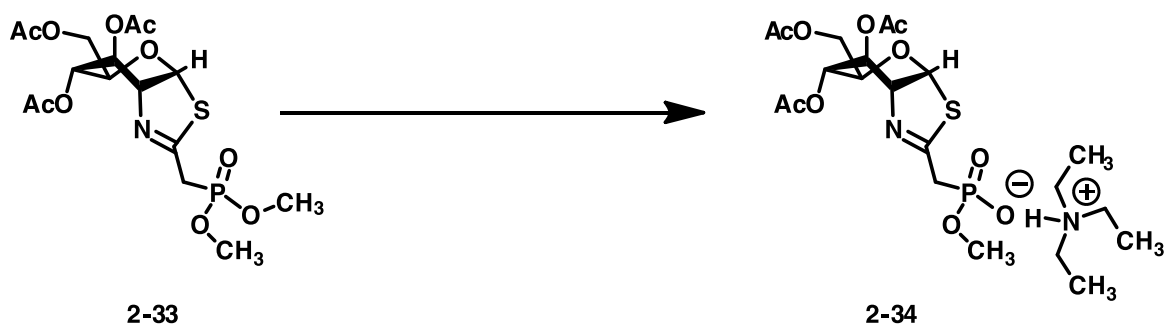
Compound 2-23. A solution containing 2.54 mg (0.05 mmol) of sodium methoxide in methanol (14 μ L) was added to a cooled (-15 $^{\circ}$ C bath) solution of 16.5 (0.04 mmol) **2-22** in methanol (0.39 mL). The resultant mercaptide was trapped *in situ* by adding 11.1 mg (0.08 mmol) of methyl iodide and then stirring at 0 $^{\circ}$ C (bath temperature) for 30 min. The reaction was quenched with sodium bicarbonate and then concentrated. Silica gel chromatography with 1:9 methanol/dichloromethane as the eluent afforded 8.3 mg (80%) of **2-23**: R_f 0.25 (1:9 methanol/dichloromethane); ^1H NMR (500 MHz, CD_3OD) δ 6.38 (d, $J = 7.0$, 1 H), 4.35–4.38 (m, 1 H), 4.11 (app t, $J = 4.5$, 1 H), 3.75 (dd, $J = 12.5$, 3.0, 1 H), 3.63 (dd, $J = 12.0$, 6.0, 1 H), 3.56 (ddd, $J = 9.0$, 4.5, 0.5, 1 H), 3.55 (dd, $J = 15.0$, 1.5, 1 H), 3.49 (dd, 15.0, 1.5, 1 H), 3.41 (ddd, $J = 9.0$, 6.5, 2.5, 1 H), 2.15 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.7, 90.3, 80.5, 76.6, 74.6, 71.4, 63.6, 37.4, 15.9; ESI-MS m/z 266 MH^+ , 288 MNa^+ .



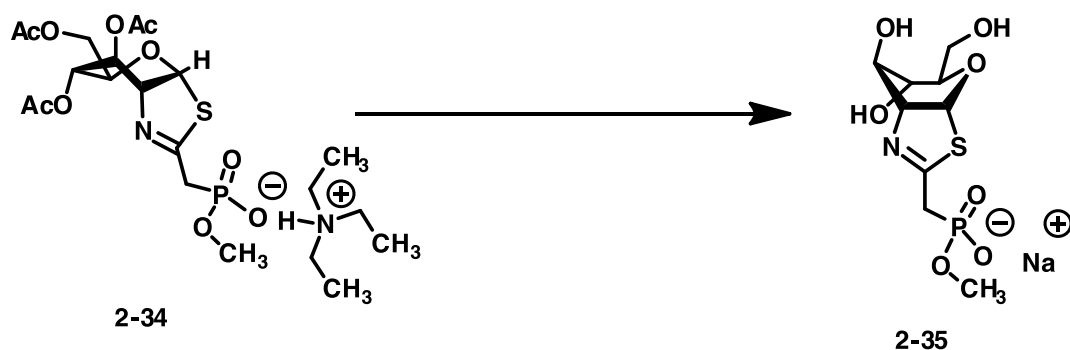
Compound 2-32. A solution containing 164 mg (0.347 mmol) of **2-17** in 3.5 mL of trimethyl phosphite was stirred at 70 °C for 9 h. The reaction was concentrated and chromatographed on silica gel using 9:1 diethyl ether/methanol as the eluent to afford 129 mg (82%) of **2-32** as a colorless oil: R_f 0.40 (4:1 diethyl ether/methanol); ^1H NMR (500 MHz, CDCl_3) δ 6.27 (d, J = 7.0 Hz, 1 H), 5.62 (d, J = 1.5 Hz, 1 H), 4.96 (dt, J = 9.5, 1.5 Hz, 1 H), 4.52 (br s, 1 H), 4.16 (dd, J = 12.5, 3.0 Hz, 1 H), 4.12 (dd, J = 12.5, 5.0 Hz, 1 H), 3.83 (d, J = 1.5 Hz, 3 H), 3.81 (d, J = 1.5 Hz, 3 H), 3.62 (ddd, J = 9.0, 5.0, 3.0 Hz, 1 H), 3.28 (dd, J = 21.0, 15.0 Hz, 1 H), 3.21 (dd, J = 21.0, 15.0 Hz, 1 H), 2.14 (s, 3 H), 2.09 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.5, 169.4, 169.2, 163.2 (d, J = 8.8 Hz), 88.9, 76.4 (d, J = 1.9 Hz), 70.5 (d, J = 1.9 Hz, 69.3, 68.5, 63.2, 53.2 (d, J = 6.5 Hz), 53.1 (d, J = 6.5 Hz), 32.5 (d, J = 11.5 Hz), 20.9, 20.8, 20.7; ^{31}P NMR (202 MHz, CDCl_3) δ 24.70; ESI-MS m/z 454 MH^+ .



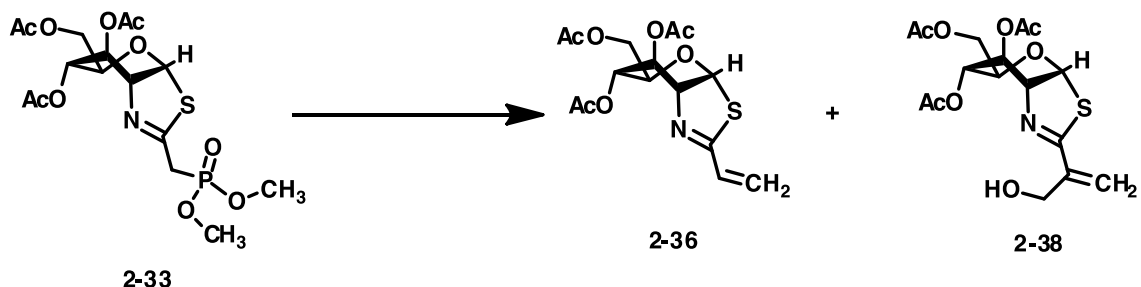
Compound 2-33. A solution containing 2.7 mg (6.0 μ mol) of **2-32** in 0.1 mL of methanol was treated at 0 °C with 0.03 mg of sodium methoxide in 4 μ L of methanol. After 30 min, the reaction was concentrated to give 2.0 mg (100%) of **2-33** as a white, sticky solid: R_f 0.10 (9:1 methanol/dichloromethane); ^1H NMR (500 MHz, CDCl_3) δ 6.42 (d, J = 7.0 Hz, 1 H), 4.39 (dd, J = 11.5, 7.0 Hz, 1 H), 4.20 (t, J = 4.0 Hz, 1 H), 3.82 (d, J = 11.0 Hz, 1 H), 3.81 (d, J = 11.5 Hz, 1 H), 3.74 (dd, J = 12.0, 2.5 Hz, 1 H), 3.61 (dd, J = 12.0, 6.0 Hz, 1 H), 3.54–3.56 (m, 1 H), 3.35–3.39 (m, 1 H), 3.30–3.33 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.8, 90.0, 79.0, 74.9, 72.5, 70.1, 62.2, 52.6; ^{31}P NMR (202 MHz, CDCl_3) δ 30.76; ESI-MS m/z 328 MH^+ .



Compound 2-34. A solution containing 17.0 mg (0.0375 mmol) of **2-33** in 0.40 mL of dimethylformamide was treated with 3.5 mg (0.053 mmol) of sodium azide. After stirring for 3 h at 70 °C, the reaction was concentrated and chromatographed through silica gel using 44:5:1 dichloromethane/methanol/triethylamine as the eluent to afford 18.9 mg (92%) of **2-34** as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 6.16 (d, $J = 7.0$, 1 H), 5.60 (dd, $J = 3.5$, 1.5 Hz, 1 H), 4.96 (d, $J = 9.5$ Hz, 1 H), 4.43 (td, $J = 7.0$, 1.5 Hz, 1 H), 4.08–4.13 (m, 2 H), 3.64–3.67 (m, 1 H), 3.61 (d, $J = 10.5$ Hz, 3 H), 3.10 (d, $J = 20$ Hz, 2 H), 3.04 (q, $J = 7.5$ Hz, 6 H), 2.12 (s, 3 H), 2.07 (s, 3 H), 2.06 (s, 3 H), 1.32 (t, $J = 7.5$ Hz, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 169.6, 169.3, 167.8 (d, $J = 7.9$ Hz), 88.1, 76.1, 71.0 (d, $J = 1.4$ Hz), 69.5, 68.1, 63.2, 52.2 (d, $J = 5.5$ Hz), 45.3, 34.9 (d, $J = 123$ Hz), 21.0, 20.9, 20.7, 8.5; ^{31}P NMR (202 MHz, CDCl_3) δ 14.71; ESI-MS m/z 438 M^+ .



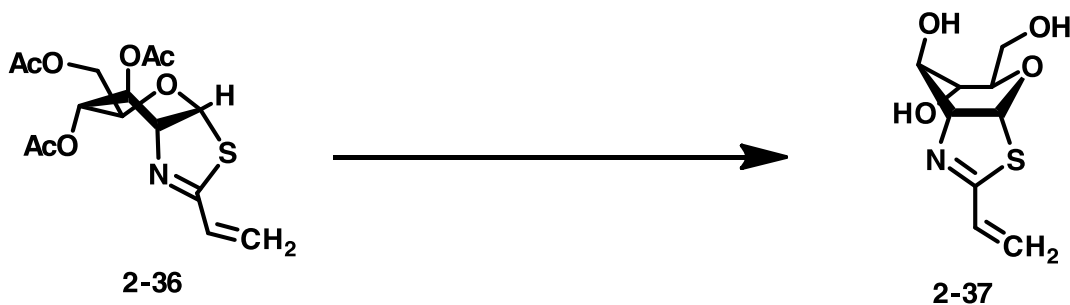
Compound 2-35. A solution containing 9.6 mg (0.018 mmol) of **2-34** in 0.18 mL of methanol was treated at 0 °C with 1.16 mg (0.0216 mmol) of sodium methoxide in 8 μ L of methanol. After 30 min, the reaction was concentrated to give 5.9 mg (98%) of **2-35** as a white, sticky solid: R_f 0.10 (39:10:1 dichloromethane/methanol/triethylamine); ^1H NMR (500 MHz, CD_3OD) δ 6.34 (d, $J = 7.0$ Hz, 1 H), 4.38 (dt, $J = 7.0, 4.0$ Hz, 1 H), 4.24–4.26 (m, 1 H), 3.75 (dd, $J = 12.5, 1.5$ Hz, 1 H), 3.61 (d, $J = 11.0$ Hz, 3 H), 3.58–3.61 (m, 1 H), 3.53–3.55 (m, 2 H), 3.33 (d, $J = 20.0$ Hz, 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.7 (d, $J = 8.3$ Hz), 90.9, 80.1, 75.9, 73.8 (d, $J = 1.9$ Hz), 71.9, 63.9, 52.5 (d, $J = 6.0$ Hz); ^{31}P NMR (202 MHz, CD_3OD) δ 16.28; ESI-MS m/z 312 M^+ .



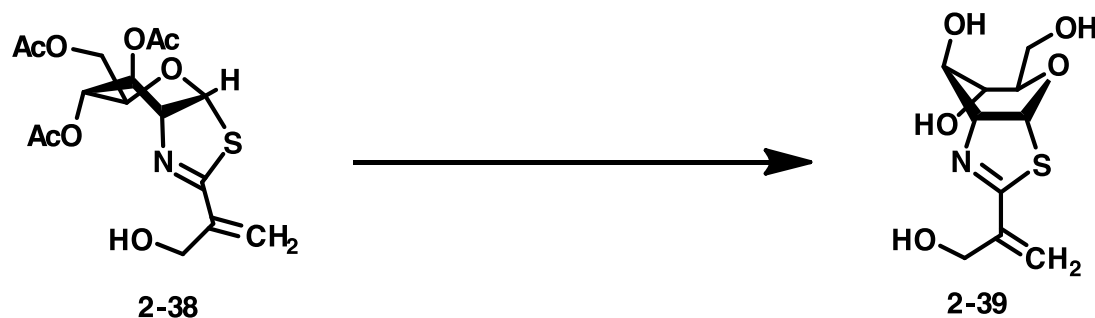
Horner-Wadsworth-Emmons reaction with 2-33. A solution containing 4.7 mg (0.11 mmol) of lithium chloride and 17.1 mg (0.111 mmol) of DBU in acetonitrile was treated with a solution containing 45.9 mg (0.101 mmol) of **2-33** in 0.51 mL of acetonitrile, followed with 3.5 mg (0.12 mmol) of paraformaldehyde. After 2 h, the reaction was concentrated and chromatographed through silica gel using 1:1 ethyl acetate/dichloromethane to give 19.8 mg (55%) of **2-36** and 3.9 mg (10%) of **2-37**, both as colorless oils:

Compound 2-36. R_f 0.85 (23:2 diethyl ether/methanol); ^1H NMR (500 MHz, CDCl_3) δ 6.64 (dd, $J = 17.0, 10.5$ Hz, 1 H), 6.26 (d, $J = 7.0$ Hz, 1 H), 5.89 (dd, $J = 17.5, 2.5$ Hz, 1 H), 5.88 (dd, $J = 10.5, 2.5$, 1 H), 5.62 (dd, $J = 3.0, 1.5$ Hz, 1 H), 4.98 (d, $J = 9.5$ Hz, 1 H), 4.62 (ddd, $J = 7.0, 2.5, 1.0$ Hz, 1 H), 4.08–4.17 (m, 2 H), 3.54 (dt, $J = 9.5, 4.5$ Hz, 1 H), 2.15 (s, 3 H), 2.08 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 169.6, 169.3, 168.5, 131.3, 128.3, 87.0, 76.7, 70.8, 69.3, 68.5, 63.2, 21.0, 20.9, 20.7; ESI-MS m/z 358 MH^+ , 380 MNa^+ .

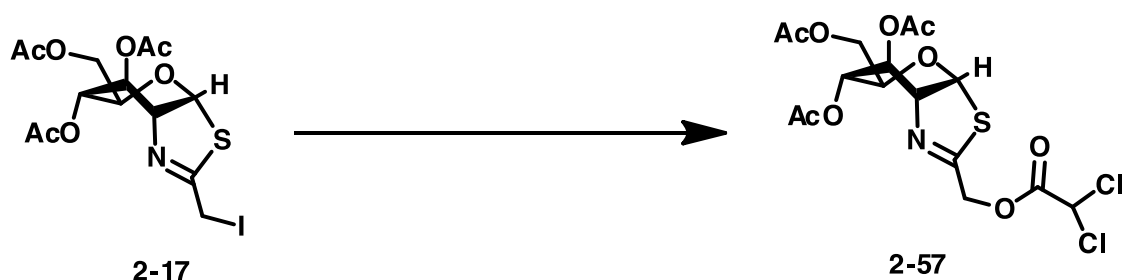
Compound 2-37. R_f 0.80 (23:2 diethyl ether/methanol); ^1H NMR (500 MHz, CDCl_3) δ 6.27 (d, $J = 7.0$ Hz, 1 H), 5.85 (d, $J = 1.0$ Hz, 1 H), 5.74 (d, $J = 0.5$ Hz, 1 H), 5.60 (dd, $J = 3.5, 1.5$ Hz, 1 H), 5.01 (dt, $J = 9.0, 1.5$ Hz, 1 H), 4.67–4.70 (m, 1 H), 4.56 (br d, $J = 12.0$ Hz, 1 H), 4.25 (dd, $J = 12.5, 7.5$ Hz, 1 H), 4.13 (d, $J = 4.5$ Hz, 2 H), 3.53 (dt, $J = 9.0, 4.5$ Hz, 1 H), 3.44 (d, $J = 4.0$ Hz, 1 H), 2.17 (s, 3 H), 2.08 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.5, 169.8, 169.4, 169.3, 141.6, 125.5, 87.1, 76.1, 70.0, 69.0, 68.6, 64.4, 63.4, 21.0, 20.7; ESI-MS m/z 410 MNa^+ .



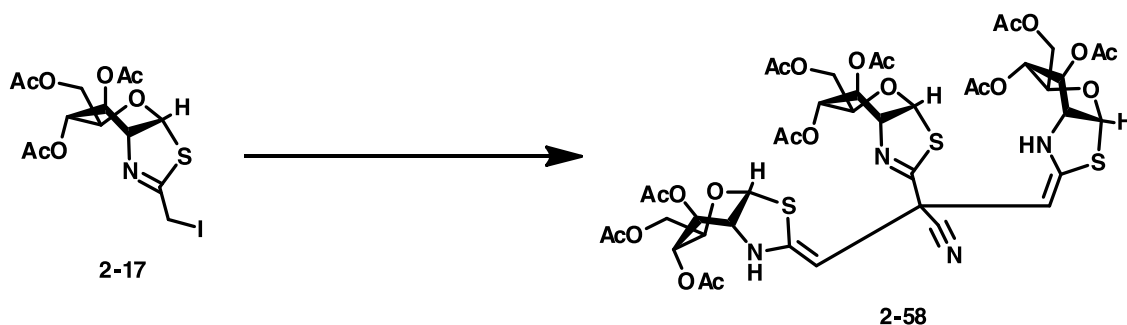
Compound 2-37. A solution containing 9.1 mg (0.025 mmol) of **2-36** in 0.25 mL of methanol was treated at 0 °C with 0.27 mg (5.0 μ mol) of sodium methoxide in 2 μ L of methanol. After 30 min, the reaction was quenched with 1 drop of saturated aqueous sodium bicarbonate, concentrated under reduced pressure, and chromatographed through silica gel using 17:3 dichloromethane/methanol as the eluent to give 5.8 mg (100%) of **2-37** as a white, sticky solid: R_f 0.13 (9:1 methanol/dichloromethane); ^1H NMR (500 MHz, CDCl_3) δ 6.61 (dd, J = 17.5, 11.0 Hz, 1 H), 6.38 (d, J = 6.5 Hz, 1 H), 5.88 (dd, J = 17.0, 6.5 Hz, 1 H), 5.88 (dd, J = 11.0, 6.5 Hz, 1 H), 4.44–4.47 (m, 1 H), 4.15 (app t, J = 4.5 Hz, 1 H), 3.74 (dd, J = 12.0, 2.5 Hz, 1 H), 3.61 (dd, J = 12.0, 6.5 Hz, 1 H), 3.58 (ddd, J = 9.5, 4.0, 1.0 Hz, 1 H), 3.32–3.35 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 133.0, 128.5, 89.4, 80.8, 76.6, 74.6, 71.5, 63.6; ESI-MS m/z 232 MH^+ .



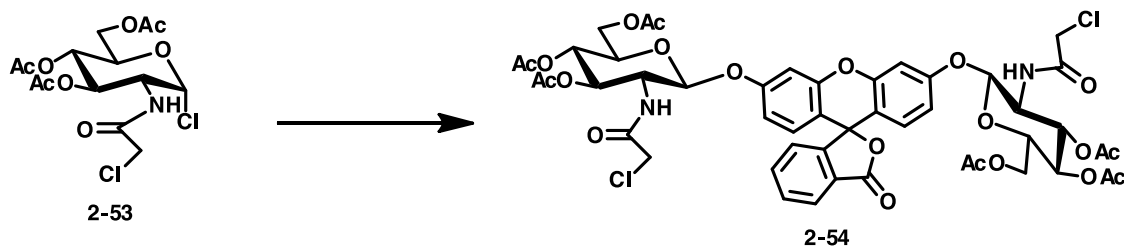
Compound 2-39. A solution containing 2.8 mg (7 μ mol) of **2-38** in 0.07 mL of methanol was treated at 0 °C with 76 μ g (1.4 μ mol) of sodium methoxide in 0.5 μ L of methanol. After 30 min, the reaction was quenched with 1 drop of saturated aqueous sodium bicarbonate and concentrated under reduced pressure to give 1.8 mg (100%) of **2-39** as a white, sticky solid: R_f 0.07 (9:1 methanol/dichloromethane); ^1H NMR (500 MHz, CD_3OD) δ 6.35 (d, J = 6.5 Hz, 1 H), 5.87 (br s, 1 H), 5.75 (br s, 1 H), 4.48–4.50 (m, 1 H), 4.46 (br s, 1 H), 4.31 (dt, J = 14.5, 1.5, 1 H), 4.21 (dd, J = 5.0, 3.5 Hz, 1 H), 3.72 (dd, J = 12.0 2.5 Hz, 1 H), 3.61 (dd, J = 12.0, 6.5 Hz, 1 H), 3.58 (ddd, J = 9.0, 3.5, 1.0 Hz, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.3, 144.8, 123.3, 89.2, 81.7, 76.5, 74.3, 71.6, 63.7, 63.1; ESI-MS m/z 262 MH^+ .



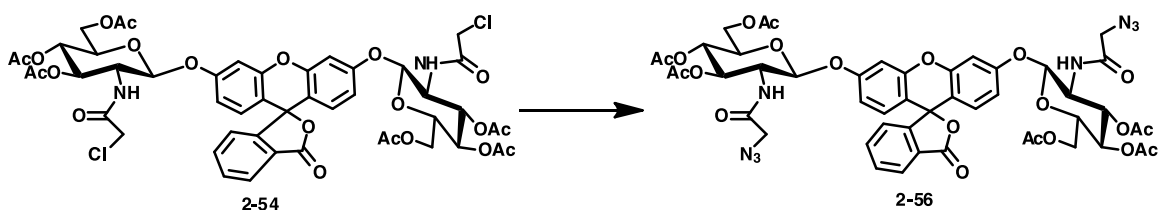
Compound 2-57. A solution containing 34.6 (0.0735 mmol) of **2-17** in 0.75 mL of DMF was treated with 111 mg (0.734 mmol) of sodium dichloroacetate. After 8 h, the reaction was diluted with isopropyl acetate, washed with water and brine, and concentrated. Silica gel chromatography using 3:2 hexanes/ethyl acetate as the eluent produced 19.4 mg (56%) of **2-57** as a colorless oil: R_f 0.19 (7:3 hexanes/ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ 6.32 (d, $J=7.0$ Hz, 1 H), 6.06 (s, 1 H) 5.58 (dd, $J=3.0, 1.5$ Hz, 1 H), 5.14 (dd, $J=14.5, 2.5$, 1 H), 5.09 (dd, $J=14.5, 2.5$ Hz, 1 H), 4.95 (td, $J=9.5, 1.5$ Hz, 1 H), 4.53–4.56 (m, 1 H), 4.12 (dd, $J=12.5, 3.0$ Hz, 1 H), 4.10 (dd, $J=12.5, 5.5$ Hz, 1 H), 3.52 (ddd, $J=9.5, 5.5, 3.0$ Hz, 1 H), 2.15 (s, 3 H), 2.11 (s, 3 H), 2.09 (s 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 169.6, 169.2, 166.5, 163.7, 88.2, 76.2, 70.3, 69.1, 68.8, 64.9. 63.6, 63.3, 20.9, 20.8, 20.7; ESI-MS m/z 472 MH^+ , 494 MNa^+ .



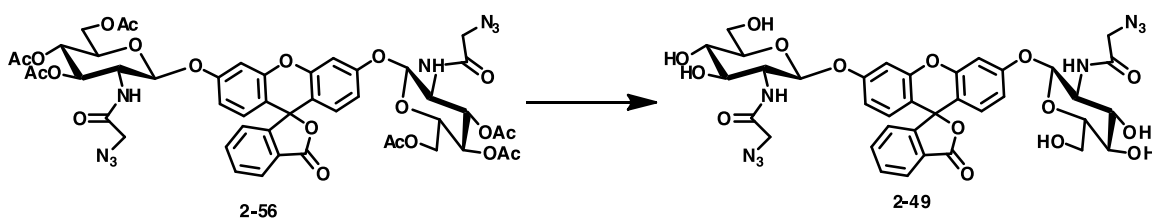
Compound 2-58. A solution containing 34.3 (0.0728 mmol) of **2-17** in 0.75 mL of DMF was treated with 7.1 mg (0.15 mmol) of sodium cyanide. After 0.5 h, the reaction was diluted with diethyl ether, washed with water and brine, and concentrated. Silica gel chromatography using 1:1 hexanes/ethyl acetate as the eluent produced 38.4 mg (50%) of **2-58** as a colorless oil: R_f 0.20 (3:2 hexanes/ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ 6.39 (d, $J = 7.0$ Hz, 1 H), 6.30 (d, $J = 7.0$ Hz, 1 H), 6.27 (d, $J = 7.0$ Hz, 1 H), 5.62 (dd, $J = 3.0, 1.5$ Hz, 1 H), 5.57 (d, $J = 2.5$ Hz, 1 H), 5.56 (d, $J = 2.5$ Hz, 1 H), 4.98 (dt, $J = 9.5, 1.5$, 1 H), 4.96 (dt, $J = 9.5, 1.5$, 1 H), 4.94 (dt, $J = 9.5, 1.5$, 1 H), 4.54 (ddd, $J = 8.0, 3.5, 1.0$ Hz, 1 H), 4.51–4.54 (m, 1 H), 4.30–4.50 (m, 1 H), 4.10–4.18 (m, 7 H), 3.58–3.67 (m, 4 H), 3.49–3.53 (m, 1 H), 3.42 (dd, $J = 16.5, 2.0$ Hz, 1 H), 3.35 (dd, $J = 16.5, 2.0$ Hz, 1 H), 2.16 (s, 3 H), 2.14 (s, 3 H), 2.13 (s, 3 H), 2.11 (s, 3 H), 2.10 (s, 3 H), 2.10 (s, 3 H), 2.08 (s, 3 H), 2.08 (s, 3 H), 2.08 (s, 3 H); ESI-MS m/z 1057 MH^+ , 1079 MNa^+ .



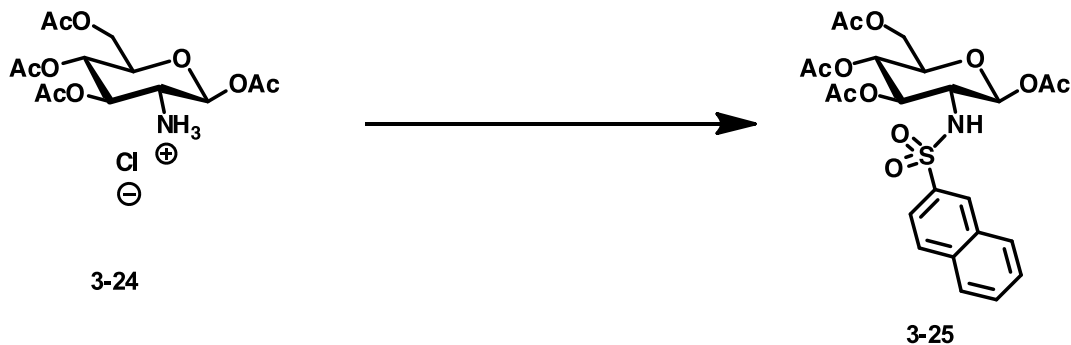
Compound 2-54. A solution containing 41.5 mg (0.104 mmol) of 2-53 and 11.8 mg (0.0355 mmol) of fluorescein was treated at 0 °C with 24.1 mg (0.104 mmol) of silver oxide and 2 μ L (0.02 mmol) of pyridine. After stirring for 24 h at room temperature, the mixture was concentrated and chromatographed through silica gel using 13:7 ethyl acetate/dichloromethane as the eluent to give 27.5 mg (25% yield) of 2-54 as a colorless oil: R_f (); ^1H NMR (500 MHz, CDCl_3) δ 8.02 (d, $J = 7.5$ Hz, 1 H), 7.68 (td, $J = 7.5, 1.0$ Hz, 1 H), 7.63 (td, $J = 7.5, 1.0$ Hz, 1 H), 7.13 (d, $J = 7.5$ Hz, 1 H), 6.89 (d, $J = 2.0$ Hz, 1 H), 6.87 (d, $J = 2.0$ Hz, 1 H), 6.85 (d, $J = 8.5$ Hz, 1 H), 6.83 (d, $J = 8.5$ Hz, 1 H), 6.68–6.73 (m, 4 H), 5.51 (t, $J = 10.5$ Hz, 1 H), 5.49 (t, $J = 10.5$ Hz, 1 H), 5.47 (d, $J = 8.0$ Hz, 1 H), 5.43 (d, $J = 8.0$ Hz, 1 H), 5.15 (d, $J = 9.5$ Hz, 1 H), 5.14 (d, $J = 9.5$ Hz, 1 H), 4.30 (dd, $J = 12.5, 2.5$ Hz, 1 H), 4.27 (dd, $J = 12.5, 2.5$ Hz, 1 H), 4.09–4.22 (m, 4 H), 4.02 (d, $J = 15.0$ Hz, 1 H), 4.01 (d, $J = 15.0$ Hz, 1 H), 3.98 (d, $J = 15.0$ Hz, 1 H), 3.97 (d, $J = 15.0$ Hz, 1 H), 3.93 (ddd, $J = 9.5, 5.5, 2.5$ Hz, 1 H), 3.91 (ddd, $J = 9.5, 5.5, 2.5$ Hz, 1 H), 2.11 (s, 3 H), 2.07 (s, 15 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 170.5, 169.4, 169.3, 166.7, 158.3, 158.2, 152.9, 152.0, 135.3, 130.0, 129.3, 126.3, 125.2, 123.9, 113.8, 113.6, 113.2, 104.7, 104.1, 98.1, 98.0, 82.2, 72.2, 71.2, 71.1, 68.3, 55.0, 42.4, 20.7, 20.6; ESI-MS m/z 1081 MNa^+ .



Compound 2-56. A solution containing 8.5 mg (8.1 μmol) of **2-54** in 0.1 mL of DMF was treated with 1.3 mg (0.019 mmol) of sodium azide. After stirring at 70 $^{\circ}\text{C}$ for 8 h, the reaction was concentrated and chromatographed through silica gel using 3:2 diethyl ether/ethyl acetate as the eluent to give 6.4 mg (74% yield) of **2-54** as a colorless oil: R_f 0.31 (19:1 dichloromethane/methanol); ^1H NMR (500 MHz, CDCl_3) δ 8.002 (d, $J = 7.5$ Hz, 1 H), 7.68 (t, $J = 7.5$ Hz, 1 H), 7.63 (t, $J = 7.5$ Hz, 1 H), 7.13 (d, $J = 7.5$ Hz, 1 H), 6.89 (d, $J = 2.5$ Hz, 1 H), 6.84 (d, $J = 1.5$ Hz, 1 H), 6.71–6.73 (m, 2 H), 6.68 (d, $J = 8.0$ Hz, 1 H), 6.65 (d, $J = 8.5$ Hz, 1 H), 6.67–6.73 (m, 4 H), 5.50 (t, $J = 10.0$ Hz, 1 H), 5.48 (d, $J = 8.0$ Hz, 1 H), 5.45 (t, $J = 10.0$ Hz, 1 H), 5.41 (d, $J = 8.0$ Hz, 1 H), 5.15 (t, $J = 9.5$ Hz, 1 H), 5.14 (t, $J = 9.5$ Hz, 1 H), 4.29 (t, $J = 6.0$ Hz, 1 H), 4.26 (t, $J = 6.0$ Hz, 1 H), 4.07–4.18 (m, 4 H), 3.92–3.96 (m, 4 H), 3.90 (ddd, $J = 9.5, 5.5, 2.5$ Hz, 1 H), 3.85 (ddd, $J = 9.5, 5.5, 2.5$ Hz, 1 H), 2.11 (s, 6 H), 2.07 (s, 3 H), 2.06 (s, 6 H), 2.05 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 170.6, 170.5, 169.4, 169.3, 167.3, 158.3, 158.2, 152.9, 152.0, 135.3, 130.0, 129.3, 129.2, 126.3, 125.2, 123.9, 113.8, 113.7, 113.4, 113.0, 104.6, 103.8, 98.0, 97.9, 72.2, 72.1, 71.5, 71.4, 68.3, 62.0, 54.8, 54.6, 52.6, 52.5, 20.7, 20.6; ESI-MS m/z 1095 MNa^+ .

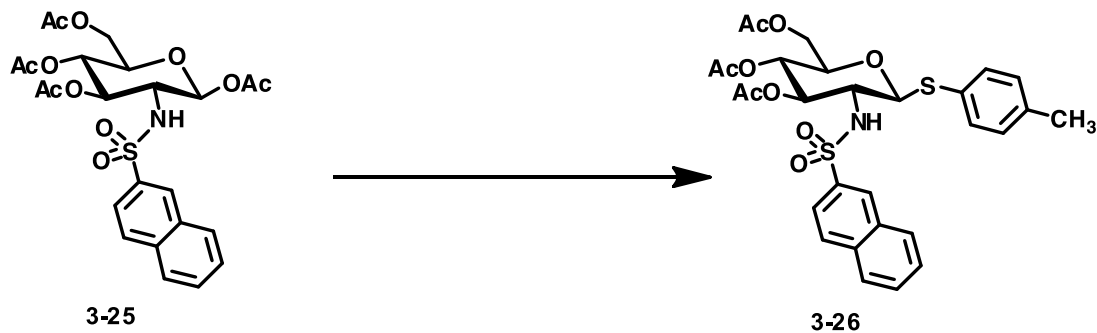


Compound 2-49. A solution containing 6.4 mg (6.0 μ mol) of **2-56** in 0.12 mL of methanol was treated with 2 μ L of a 0.25 M solution of sodium methoxide in methanol. After stirring for 30 min, the mixture was concentrated to produce 4.9 mg (100% yield) of **2-49** as a thin film: R_f (); ^1H NMR (500 MHz, CDCl_3) δ 8.01 (dd, $J = 7.5, 1.0$ Hz), 7.74 (td, $J = 7.5, 1.5$ Hz, 1 H), 7.70 (td, $J = 7.5, 1.0$ Hz, 1 H), 7.14 (d, $J = 7.5$ Hz, 1 H), 6.99 ($J = 7.5, 2.5$ Hz, 2 H), 6.77 (td, $J = 8.5, 2.5$ Hz, 2 H), 6.68 (dd, $J = 9.0, 1.5$ Hz, 2 H), 5.19 (d, $J = 8.5$ Hz, 2 H), 3.98 (dd, $J = 8.5, 3.5$ Hz, 1 H), 3.95 (dd, $J = 8.5, 3.5$ Hz, 1 H), 3.86–3.93 (m, 6 H), 3.74 (t, $J = 6.0$ Hz, 2 H), 3.71 (t, $J = 6.0$ Hz, 2 H), 3.65 (dd, $J = 9.0, 2.5$ Hz, 2 H), 3.63 (dd, $J = 9.0, 2.5$ Hz, 2 H), 3.47–3.51 (m, 2 H), 3.42–3.46 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 170.9, 160.8, 160.7, 136.9*, 131.4, 130.3, 127.8, 125.2, 114.7, 114.6, 114.4, 114.3, 105.4, 105.3, 100.4, 100.3, 84.5, 78.6, 75.6, 71.9, 62.6, 57.4, 53.3; ESI-MS m/z 843 MNa^+ .

E3. Experimental Procedures for Chapter 3

Compound 3-25. A solution containing 664 mg (1.73 mmol) of 1,3,4,6-Tetra-O-acetyl-2-amino-2-deoxy- β -D-glucopyranose hydrochloride in 8.7 mL of dichloromethane was treated at 0 °C with 440 mg (1.94 mmol) of 2-naphthalenesulfonyl chloride and 386 mg (3.82 mmol) of triethylamine. After stirring at room temperature for 2 h, the reaction was chromatographed using 1:1 hexanes/ethyl acetate as the eluent to produce 882 mg (95%) of **3-25** as a colorless oil: R_f 0.32 (1:1 ethyl acetate/hexanes); ^1H NMR (500 MHz, CDCl_3) δ 8.41 (d, 1 H, $J = 1.5$ Hz), 7.95 (d, 1 H, $J = 7.5$ Hz), 7.92 (d, $J = 9.0$ Hz, 1 H), 7.88 (d, 1 H, $J = 8.5$ Hz), 7.79 (dd, 1 H, $J = 8.5, 1.5$ Hz), 7.58–7.64 (m, 2 H), 5.67 (d, $J = 9.5$ Hz, 1 H), 5.66 (d, $J = 8.5$ Hz, 1 H), 5.18 (dd, $J = 10.0, 9.5$ Hz, 1 H), 5.08 (t, $J = 9.5$ Hz, 1 H), 4.25 (dd, $J = 12.5, 4.5$ Hz, 1 H), 4.07 (dd, $J = 12.5, 2.0$ Hz, 1 H), 3.83 (ddd, $J = 10.0, 4.5, 2.0$ Hz, 1 H), 3.78 (dt, $J = 10.5, 9.0$ Hz, 1 H), 2.06 (s, 3 H), 2.00 (s, 3 H), 1.72 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.3, 170.6,

169.4, 169.3, 138.3, 134.7, 132.1, 129.2, 129.2, 128.9, 127.9, 127.7, 127.7, 122.3, 92.4, 72.6, 67.9, 61.5, 57.2, 20.6, 20.5, 20.3, 20.3; ESI-MS m/z 560 MNa^+

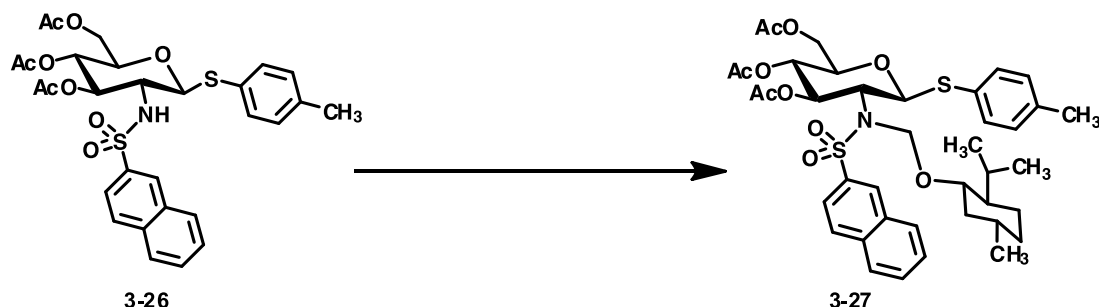


Compound 3-26. A solution containing 473 mg (0.881 mmol) of **3-25** in 4.4 mL of dry dichloromethane was treated at 0 °C with 547 mg (4.41 mmol) of 4-methylbenzenethiol and 676 mg (4.41 mmol) of boron trifluoride diethyl etherate. After stirring for 12 h at room temperature, the reaction was washed with saturated aqueous sodium bicarbonate and concentrated. Silica gel chromatography using 13:7 hexanes/ethyl acetate as the eluent afforded 443 mg (84%) of **3-26 β** and 50 mg (9%) of **3-26 α** , both as colorless oils.

3-26 β : R_f 0.37 (3:2 hexanes/ethyl acetate); 1H (500 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 7.95 (d, J = 8.0 Hz, 1 H), 7.94 (d, J = 8.5 Hz, 1 H), 7.92 (dd, J = 8.5, 1.5 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 7.58–7.65 (m, 2 H), 7.21 (d, J = 8.0 Hz, 2 H), 7.01 (d, J = 8.0 Hz, 2 H), 5.20 (d, J = 9.0 Hz, 1 H), 5.11 (app t, J = 10.0 Hz, 1 H), 5.03 (t, J

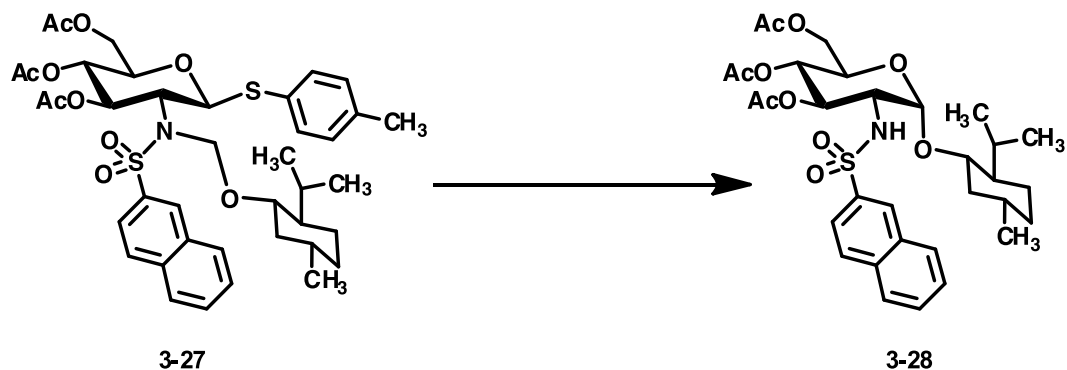
= 9.5 Hz, 1 H), 4.56 (d, J = 10.0 Hz, 1 H), 4.18 (dd, J = 12.5, 5.5 Hz, 1 H), 4.09 (dd, J = 12.5, 2.5 Hz, 1 H), 3.76 (app q, J = 10.0 Hz, 1 H), 3.63 (ddd, J = 10.0, 5.5, 2.5 Hz, 1 H), 2.29 (s, 3 H), 2.05 (s, 3 H), 1.96 (s, 3 H), 1.66 (s, 3 H); ^{13}C (125 MHz, CDCl_3) δ 171.2, 170.5, 169.3, 138.2, 137.9, 134.8, 132.7, 132.0, 129.6, 129.3, 129.2, 128.8, 128.5, 127.8, 127.5, 122.9, 88.2, 75.6, 74.3, 68.5, 62.3, 57.2, 21.1, 20.7, 20.5, 20.4; ESI-MS m/z 624 MNa^+

3-26a: R_f 0.41 (3:2 hexanes/ethyl acetate); ^1H (500 MHz, CDCl_3) δ 8.41 (d, J = 1.5 Hz, 1 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.85 (d, J = 8.5 Hz, 1 H), 7.84 (d, J = 9.0 Hz, 1 H), 7.78 (dd, J = 9.0, 1.5 Hz, 1 H), 7.60–7.67 (m, 2 H), 7.11 (d, J = 8.0 Hz, 2 H), 6.95 (d, J = 8.0 Hz, 2 H), 5.21 (d, J = 9.5 Hz, 1 H)



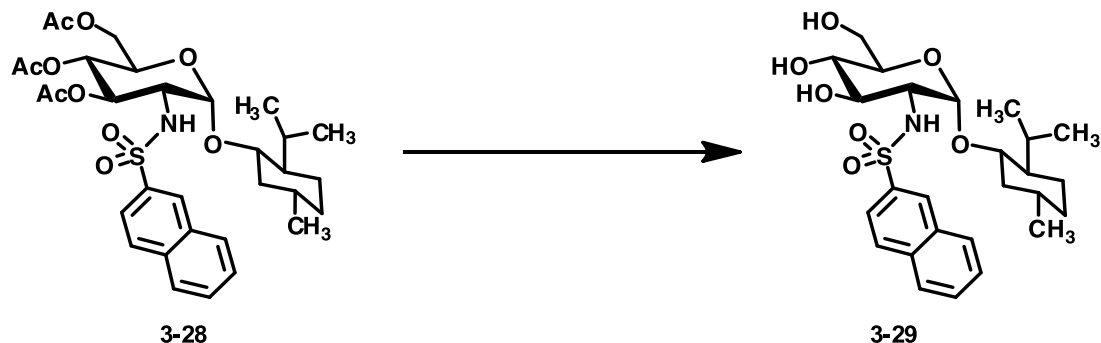
Compound 3-27. A solution containing 110 mg (0.183 mmol) of **3-26** in 3.7 mL of THF was stirred over powdered 4 Å molecular sieves for 1 h. The solution was then treated with 75.3 mg (0.275 mmol) of BEMP, followed with 39.3 mg (0.192 mmol) of chloromethyl menthyl ether. After stirring for 1 h, the reaction was quenched with saturated aqueous ammonium chloride, filtered through Celite, and concentrated under reduced pressure. Silica gel column chromatography using 3:1 hexanes/ethyl acetate afforded 135 mg (96%) of **3-27** as a colorless oil: R_f 0.78 (17:3 dichloromethane/ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ 8.58 (s, 1 H), 8.06 (d, $J = 8.5$ Hz, 1 H), 7.96 (d, $J = 7.5$ Hz, 1 H), 7.94 (d, $J = 9.0$ Hz, 1 H), 7.89 (d, $J = 8.0$ Hz, 1 H), 7.64 (td, $J = 7.5, 1.0$ Hz, 1 H), 7.60 (td, $J = 7.5, 1.0$ Hz, 1 H), 7.32 (d, $J = 7.5$ Hz, 1 H), 7.06 (d, $J = 8.0$ Hz, 1 H), 5.26–5.36 (m, 1 H), 5.07 (t, $J = 9.5$ Hz, 1 H), 4.91 (br s, 1 H), 4.80 (d, $J = 8.0$ Hz, 1 H), 4.68 (d, $J = 10.0$ Hz, 1 H), 4.50 (br s, 1 H), 4.23 (dd, $J = 12.0, 5.5$ Hz, 1 H), 4.15 (dd, $J = 12.0, 2.5$ Hz, 1 H), 3.66 (br s, 1 H), 2.92 (td, $J = 10.5, 9.0$ Hz, 1 H), 2.31 (s, 3 H), 2.08 (s, 3 H), 1.99 (s, 3 H), 1.67 (s, 3 H), 1.65–1.69 (m, 2 H),

1.45–1.53 (m, 2 H), 1.09–1.12 (m, 1 H), 0.76–0.91 (m, 3 H), 0.62–0.70 (m, 9 H), 0.52–0.59 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 170.2, 169.5, 137.7, 137.3, 135.0, 132.1, 132.0, 130.0, 129.7, 129.5, 129.3, 128.9, 128.8, 127.8, 127.4, 123.8, 87.5, 77.6, 75.4, 69.8, 62.5, 47.6, 39.6, 34.1, 31.3, 25.2, 22.6, 22.0, 21.1, 20.8, 20.7, 20.6, 20.4, 15.6; ESI-MS m/z 792 MNa^+ .



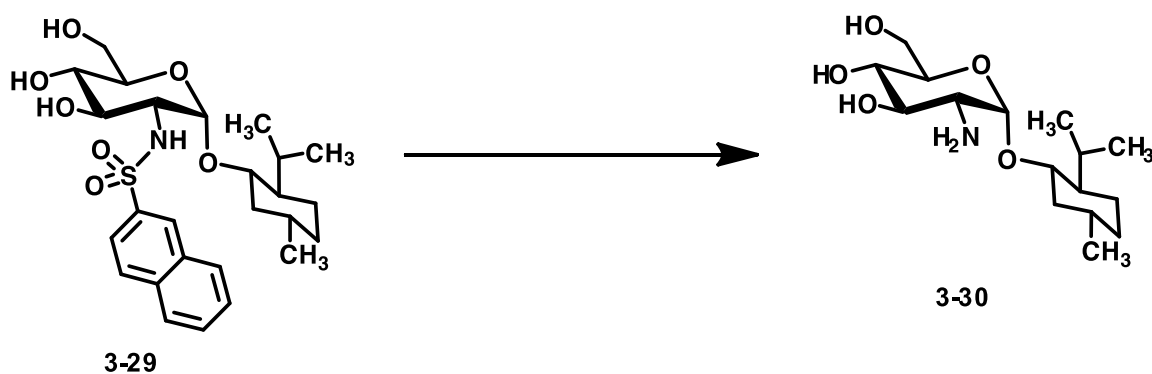
Compound 3-28. A solution containing 127 mg (0.165 mmol) of **3-27** in 3.3 mL of freshly distilled acetonitrile was stirred over powdered 4 Å molecular sieves for 1 h. The solution was then treated with 130 mg (0.661 mmol) of DMTSF. After stirring at 45 °C for 5 h, the reaction was quenched with saturated aqueous sodium bicarbonate, filtered through Celite, and concentrated on rotovap. Silica gel column chromatography using 3:1 hexanes/ethyl acetate afforded 87.8 mg (84%) of **3-28** as a white foam: R_f 0.38 (4:1 hexanes/ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ 8.42 (d, J = 1.5 Hz, 1 H), 7.98 (d, J = 9.0 Hz, 1 H), 7.96 (d, J = 9.0 Hz, 1 H), 7.90 (d, J = 9.0 Hz, 1 H), 7.78 (dd, J = 8.5, 4.0 Hz, 1 H), 7.66 (td, J = 7.0, 1.5 Hz, 1 H), 7.63 (td, J = 7.0, 1.5 Hz, 1 H), 5.14 (dd, J = 10.5, 9.5 Hz, 1 H), 5.00 (d, J = 4.0 Hz, 1 H), 4.94 (dd, J = 10.5, 9.5 Hz, 1 H), 4.89 (d, J = 10.0 Hz, 1 H), 4.20 (dd, J = 12.0, 5.0 Hz, 1 H), 4.08 (ddd, J = 10.5, 5.5, 2.5 Hz, 1 H), 4.02 (dd, J = 12.0, 2.0 Hz, 1 H), 3.59 (td, J = 12.0, 3.5 Hz, 1 H), 3.39 (td, J = 10.5, 4.5 Hz, 1 H), 2.16–2.21 (m, 1 H), 2.08–2.14 (m, 1 H), 2.08 (s, 3 H), 1.96

(s, 3 H), 1.63–1.67 (m, 2 H), 1.42 (s, 3 H), 1.28–1.40 (m, 2 H), 0.95–1.06 (m, 2 H), 0.93 (d, $J = 7.0$ Hz, 3 H), 0.89 (d, $J = 6.0$ Hz, 3 H), 0.79–0.89 (m, 1 H), 0.76 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 170.6, 169.4, 137.6, 134.8, 132.1, 129.4, 129.3, 129.0, 128.2, 127.8, 127.7, 122.2, 99.5, 82.3, 70.5, 68.5, 67.6, 62.2, 56.6, 48.5, 42.6, 34.0, 31.6, 25.6, 22.7, 22.3, 21.1, 20.7, 20.5, 20.2, 15.6; ESI-MS m/z 656 MNa^+ .

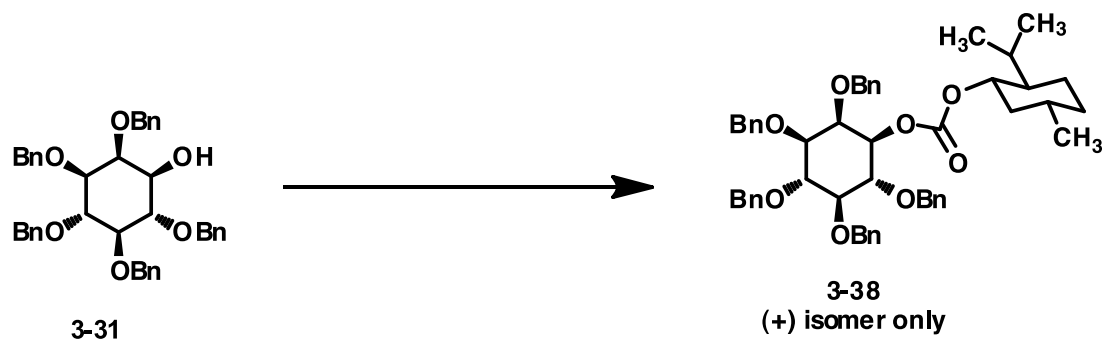


Compound 3-29. A solution containing 56.3 mg (0.0889 mmol) of **3-28** in 1.8 mL of methanol was treated with 43 μ L of a ~ 2.5 M solution of sodium methoxide in methanol. After stirring for 30 minutes, the reaction was quenched with saturated aqueous ammonium chloride, concentrated under reduced pressure, and then chromatographed through silica gel using 19:1 dichloromethane/isopropanol as the eluent to give 44.2 mg (98%) of **3-29** as a white foam: R_f 0.40 (9:1 dichloromethane/methanol); ^1H NMR (500 MHz, CDCl_3) δ 8.47 (d, $J = 1.0$ Hz, 1 H), 8.01 (d, $J = 7.0$ Hz, 1 H), 7.99 (d, $J = 8.0$ Hz, 1 H), 7.94 (d, $J = 8.0$ Hz, 1 H), 7.88 (dd, $J = 9.0, 2.0$ Hz, 1 H), 7.59–7.66 (m, 2 H), 4.96 (d, $J = 4.0$ Hz, 1 H), 3.74 (dd, $J = 11.5, 2.0$ Hz, 1 H), 3.67–3.71 (m, 1 H), 3.66 (dd, $J = 11.5, 5.0$ Hz, 1 H), 3.57 (dd, $J = 10.5, 9.0$ Hz, 1 H), 3.34 (td, $J = 10.5, 5.0$ Hz, 1 H), 3.30–3.32 (m, 1 H), 3.22 (t, $J = 9.5$ Hz, 1 H), 3.16 (dd, $J = 11.0, 4.0$ Hz, 1 H), 2.45–2.51 (m, 1 H), 2.17–2.26 (m, 1 H), 1.60–1.66 (m, 2 H), 1.28–1.37 (m, 1 H), 0.94–1.02 (m, 2 H), 0.88 (d, $J = 7.0$ Hz, 3 H), 0.87 (d, $J = 7.0$ Hz, 3 H), 0.76–0.85

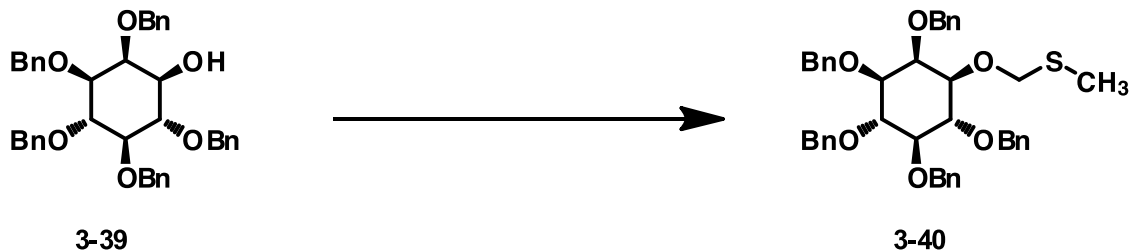
(m, 1 H), 0.72 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.9, 136.3, 133.8, 130.4, 130.3, 129.7, 129.1, 129.0, 128.5, 124.1, 101.7, 82.3, 73.8, 72.5, 72.3, 62.7, 60.0, 50.5, 44.4, 35.6, 33.1, 25.9, 24.0, 22.8, 21.9, 16.4; ESI-MS m/z 530 MNa^+ .



Compound 3-30. A solution containing 15.9 mg (0.0314 mmol) of **3-29** in 0.3 mL of dry methanol was treated with 22.3 mg (0.157 mmol) of dibasic sodium phosphate, followed with 173 mg of a 5% sodium amalgam. After refluxing for 1 h, the reaction was filtered through Celite and concentrated. Silica gel column chromatography using 4:1 dichloromethane/methanol afforded 7.9 mg (79%) of **3-30** as a white foam: R_f 0.10 (17:3 dichloromethane/methanol); ^1H NMR (500 MHz, CDCl_3) δ 4.93 (d, $J = 3.5$ Hz, 1 H), 3.68–3.79 (m, 3 H), 3.45 (dd, $J = 10.5$, 9.0 Hz, 1 H), 3.41 (td, $J = 10.5$, 4.5 Hz, 1 H), 2.59 (dd, $J = 10.0$, 3.5 Hz, 1 H), 2.30–2.36 (m, 1 H), 2.21–2.27 (m, 1 H), 1.64–1.68 (m, 2 H), 1.36–1.44 (m, 1 H), 1.26–1.36 (m, 2 H), 0.98–1.07 (m, 2 H), 0.94 (d, $J = 6.5$ Hz, 3 H), 0.92 (d, $J = 6.5$ Hz, 3 H), 0.85–0.89 (m, 1 H), 0.82 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 101.6, 82.2, 76.0, 74.4, 72.2, 62.8, 58.0, 50.4, 44.4, 35.6, 33.1, 26.7, 24.1, 22.8, 21.8, 16.2; ESI-MS m/z 318 MH^+ .

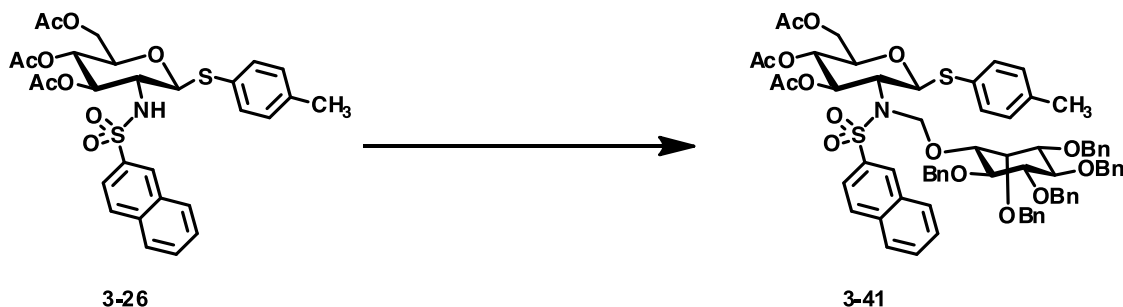


Compound 3-38. A solution containing 273 mg (0.433 mmol) of **3-31** in 3.6 mL of pyridine was treated at 0 °C with 282 mg (1.29 mmol) of (+)-menthyl chloroformate



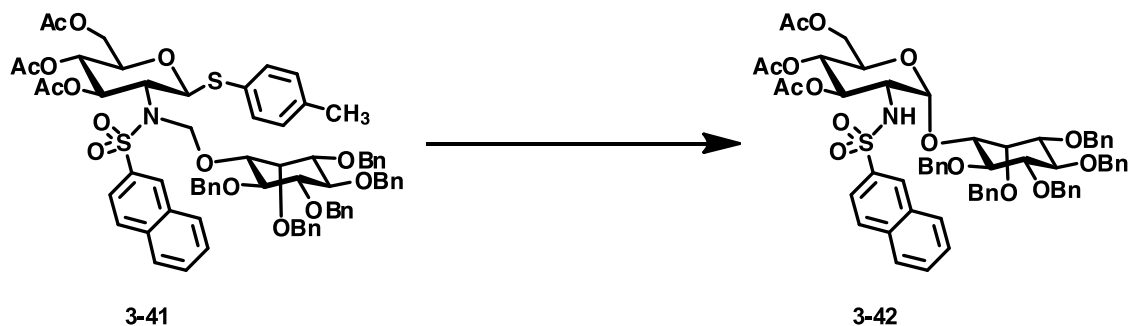
Compound 3-40. A solution containing 524 mg (0.832 mmol) of **3-39** in 2.3 mL of anhydrous DMSO was treated at 0 °C with 6.4 mL of acetic acid, followed with 2.3 mL of acetic anhydride. After stirring for 48 h at room temperature, the reaction was treated with saturated aqueous sodium bicarbonate until gas evolution ceased. The aqueous mixture was extracted several times with dichloromethane. The organic solution was dried with magnesium sulfate, filtered, and then concentrated under reduced pressure. Silica gel column chromatography using 17:3 petroleum ether/diethyl ether afforded 413 (72%) of **3-40** as a colorless oil: R_f 0.65 (4:1 hexanes/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 7.27–7.45 (m, 25 H), 4.95 (d, J = 10.4 Hz, 1 H), 4.92 (d, J = 10.8 Hz, 1 H), 4.91 (d, J = 12.0 Hz, 1 H), 4.89 (d, J = 10.0 Hz, 1 H), 4.87 (s, 2 H), 4.85 (d, J = 12.0 Hz, 1 H), 4.84 (d, J = 11.2 Hz, 1 H), 4.77 (d, J = 12.0 Hz, 1 H), 4.75 (d, J = 12.4 Hz, 1 H), 4.72 (d, J = 11.2 Hz, 1 H), 4.68 (d, J = 11.6 Hz, 1 H), 4.11 (t, J = 9.6 Hz, 1 H), 4.07 (t, J = 9.6 Hz, 1 H), 4.03 (t, J = 2.4 Hz, 1 H), 3.62 (dd, J = 10.0, 2.4 Hz, 1 H), 3.52 (t, J = 9.2 Hz, 1 H), 3.48 (dd, J = 10.0, 2.4 Hz, 1 H), 2.10 (s, 3 H);

^{13}C NMR (100 MHz, CDCl_3) δ 139.1, 139.0, 139.0, 138.9, 138.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 84.0, 81.9, 81.7, 81.3, 77.7, 77.5, 77.2, 76.9, 76.1, 76.1, 76.0, 75.7, 75.5, 74.5, 73.3, 14.1; ESI-MS m/z 713 MNa^+ .



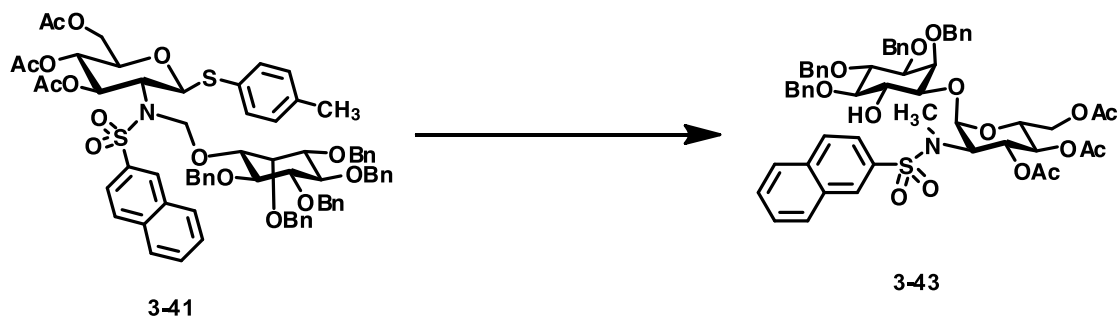
Compound 3-41. A solution containing 62.0 mg (0.0899 mmol) of **3-40** in 1.0 mL of dry dichloromethane was treated at 0 °C with 13.4 mg (0.0993 mmol) of sulfonyl chloride. After stirring for 30 min at 0 °C, the crude chloromethyl ether solution was concentrated and set aside. In a separate flask, a solution containing 64.9 (0.108 mmol) of **3-26** in 1.0 mL of THF was stirred over activated, powdered 4 Å molecular sieves for 30 min, then treated with 54.3 mg (0.198 mmol) of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine. After stirring for 30 min, the reaction was treated with a solution of the crude chloromethyl ether in 1.0 mL of THF. After stirring at rt for 1 h, the reaction was concentrated and chromatographed through silica gel using 7:13 ethyl acetate/hexanes as the eluent to afford 110 mg (98%) of **3-41** as a colorless oil: R_f 0.4 (3:2 hexanes/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, J = 0.8 Hz, 1 H), 7.92 (d, J = 8.4 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 7.80 (d, J = 8.4 Hz, 1 H),

7.72 (d, $J = 8.8$ Hz, 1 H), 7.55–7.63 (m, 2 H), 7.22–7.36 (m, 27 H), 6.94 (d, $J = 7.6$ Hz, 1 H), 5.32 (br d, $J = 11.6$ Hz, 1 H), 5.12 (br s, 1 H), 4.93–5.03 (m, 2 H), 4.90 (d, $J = 10.8$ Hz, 1 H), 4.87 (d, $J = 10.4$ Hz, 1 H), 4.76 (d, $J = 10.8$ Hz, 1 H), 4.65–4.83 (m, 3 H), 4.49 (d, $J = 12.4$ Hz, 2 H), 4.46 (d, $J = 12.4$ Hz, 1 H), 4.43 (d, $J = 11.6$ Hz, 1 H) 4.33–4.37 (m, 1 H), 4.29 (d, $J = 11.6$ Hz, 1 H), 3.90–4.04 (m, 4 H), 3.83 (br s, 1 H), 3.20–3.28 (m, 3 H), 2.81 (br s, 1 H), 2.23 (s, 3 H), 2.07 (s, 3 H), 2.03 (s, 3 H), 1.63 (s, 3 H); ^{13}C (100 MHz, CDCl_3) δ 170.4, 170.3, 169.2, 139.2, 138.7, 138.6, 138.3, 138.2, 137.5, 137.0, 134.8, 131.8, 131.5, 129.7, 129.5, 129.3, 129.1, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 127.2, 127.0, 127.0, 126.9, 123.4, 85.6, 83.8, 81.6, 81.4, 81.0, 77.2, 77.0, 76.6, 76.0, 75.7, 75.5, 74.7, 74.5, 74.0, 72.2, 70.1, 69.0, 61.3, 59.0, 20.9, 20.7, 20.5, 20.2; ESI-MS m/z 1243 MNa^+



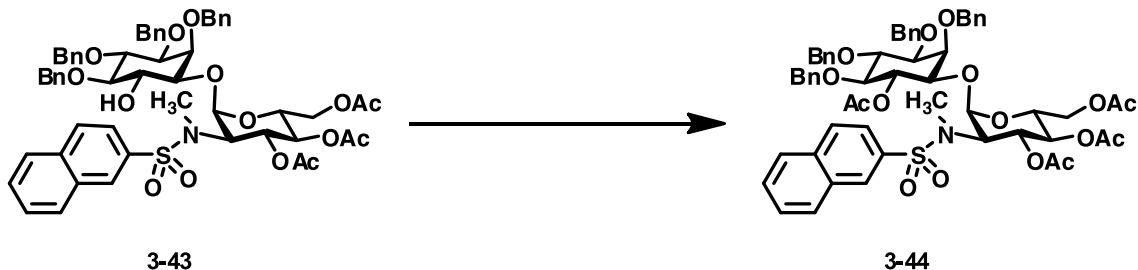
Compound 3-42. A solution containing 23.3 mg (0.0187 mmol) of **3-41** in 0.6 mL of a 2:1 dichloromethane/acetonitrile mixture was stirred over activated, powdered 4 Å molecular sieves for 1 h, then treated at -78 °C with 9 µL of a 0.2 M solution of silver trifluoromethanesulfonate in acetonitrile, followed with 0.13 mL of a 0.45 M solution of phenylsulfenyl chloride in dichloromethane. After stirring for 2 h at -20 °C, the reaction was quenched with 3 drops of saturated aqueous sodium bicarbonate. The reaction was then filtered through Celite, concentrated, and dissolved in ethyl acetate. The organic solution was washed 3x with saturated aqueous sodium bicarbonate, dried with magnesium sulfate, and concentrated. Silica gel chromatography using 13:7 hexanes/ethyl acetate as the eluent afforded 19.3 mg (93%) of **3-42** as a white foam: R_f 0.35 (3:2 hexanes/ethyl acetate); ^1H NMR (500 MHz, CHCl_3) δ 8.23 (d, J = 1.5 Hz, 1 H), 7.91 (dd, J = 7.0, 2.0 Hz, 1 H), 7.84 (dd, J = 9.0, 1.5 Hz, 1 H), 7.80 (d, J = 9.0 Hz, 1 H), 7.59–7.64

(m, 2 H), 7.47 (br d, $J = 7.0$ Hz, 2 H), 7.42 (dd, $J = 8.5, 2.0$ Hz, 1 H), 7.26–7.38 (m, 23 H), 5.89 (d, $J = 10.0$ Hz, 1 H), 5.15 (dd, $J = 10.5, 9.5$ Hz, 1 H), 5.11 (d, $J = 11.0$ Hz, 1 H), 5.07 (d, $J = 12.0$ Hz, 1 H), 4.98 (d, $J = 10.5$ Hz, 1 H), 4.92 (d, $J = 10.5$ Hz, 2 H), 4.90 (t, $J = 10.5$ Hz, 1 H), 4.86 (d, $J = 10.5$ Hz, 1 H), 4.86 (d, $J = 3.5$ Hz, 1 H), 4.81 (d, $J = 10.5$ Hz, 1 H), 4.67 (d, $J = 12.0$ Hz, 1 H), 4.63 (d, $J = 11.5$ Hz, 1 H), 4.56 (d, $J = 12.0$ Hz, 1 H), 4.11 (t, $J = 10.0$ Hz, 1 H), 4.04 (t, $J = 9.5$ Hz, 1 H), 3.98–4.02 (m, 3 H), 3.77 (dd, $J = 13.0, 3.0$ Hz, 1 H), 3.69 (td, $J = 10.5, 3.5$ Hz, 1 H), 3.53 (t, $J = 9.0$ Hz, 1 H), 3.27 (m, 2 H), 1.97 (s, 3 H), 1.93 (s, 3 H), 1.35 (s, 3 H); ^{13}C (125 MHz, CDCl_3) δ 170.4, 170.1, 169.4, 138.6, 138.5, 138.2, 138.1, 138.0, 137.5, 134.6, 132.0, 129.3, 129.1, 128.9, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 126.6, 122.5, 100.1, 83.9, 81.7, 81.6, 81.0, 79.2, 76.6, 75.9, 75.7, 75.4, 74.5, 73.1, 70.1, 68.7, 68.3, 61.6, 56.5, 29.7, 20.6, 20.5, 20.0; ESI-MS m/z 1107 MNa^+



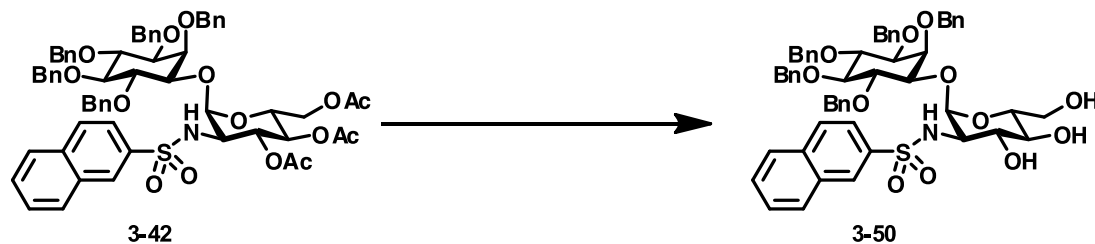
Compound 3-43. A solution containing 67.0 mg (0.0539 mmol) of **3-41** in 1.0 mL of dry acetonitrile was stirred over activated, powdered 3 Å molecular sieves for 1 h, then treated with a solution containing 106 mg (0.539 mmol) of dimethyl(methylthio)sulfonium tetrafluoroborate in 1.0 mL of dry acetonitrile. After stirring for 2 h at 50 °C, the reaction was quenched with 3 drops of saturated aqueous sodium bicarbonate. The reaction was then filtered through Celite, concentrated, and dissolved in ethyl acetate. The organic solution was washed 3x with saturated aqueous sodium bicarbonate, dried with magnesium sulfate, and concentrated. Silica gel chromatography using 13:7 hexanes/ethyl acetate as the eluent afforded 46.1 mg (83%) of **3-43** as a white foam: R_f 0.30 (3:2 hexanes/ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ 8.38 (d, J = 1.0 Hz, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.90 (d, J = 8.0 Hz, 1 H), 7.86 (d, J = 8.0 Hz, 1 H), 7.77 (dd, J = 9.0, 2.0 Hz, 1 H), 7.57–7.64 (m, 2 H), 7.24–7.38 (m, 20 H), 5.50 (d, J = 3.5 Hz, 1 H), 5.40 (dd, J = 11.5, 9.0 Hz, 1 H), 5.03 (dd, J = 10.0, 9.0 Hz, 1 H), 4.97 (d, J = 12.0 Hz, 1 H), 4.94 (d, J = 11.0 Hz, 1 H), 4.91 (d, J = 11.5 Hz, 1 H), 4.83 (d, J =

10.5 Hz, 1 H), 4.78 (d, $J = 11.5$ Hz, 1 H), 4.76 (d, $J = 12.0$ Hz, 1 H), 4.72 (d, $J = 11.0$ Hz, 1 H), 4.69 (d, $J = 11.5$ Hz, 1 H), 4.37 (dd, $J = 12.0, 3.5$ Hz, 1 H), 4.13 (dd, $J = 12.5, 4.0$ Hz, 1 H), 4.09 (td, $J = 9.5, 3.0$ Hz, 1 H), 4.03 (t, $J = 9.5$ Hz, 1 H), 3.90 (dd, $J = 12.0, 2.5$ Hz, 1 H), 3.88–3.90 (m, 1 H), 3.72 (ddd, $J = 10.5, 4.0, 2.5$ Hz, 1 H), 3.48 (dd, $J = 10.0, 2.5$ Hz, 1 H), 3.45 (dd, $J = 10.0, 2.0$, 1 H), 3.28 (t, $J = 9.0$ Hz, 1 H), 2.85 (s, 3 H), 2.47 (br d, $J = 6.0$ Hz, 1 H), 2.07 (s, 3 H), 2.00 (s, 3 H), 1.52 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 170.1, 169.7, 138.8, 138.7, 138.6, 138.3, 136.4, 134.9, 132.3, 129.4, 129.3, 129.1, 129.0, 128.7, 128.7, 128.6, 128.3, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 123.0, 100.8, 83.4, 81.5, 81.2, 77.8, 76.8, 75.8, 75.7, 74.2, 73.6, 73.4, 69.8, 67.6, 67.3, 62.0, 57.7, 30.7, 20.7, 20.6, 20.2; ESI-MS m/z 1054 MNa^+ .



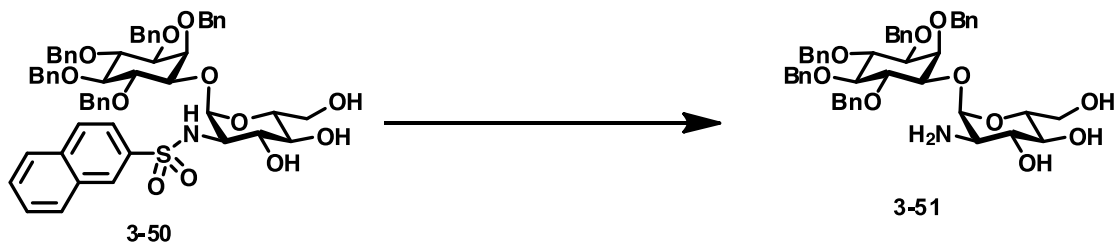
Compound 3-44. A solution containing 46.1 mg (0.0437 mmol) of **3-43** in 0.5 mL of pyridine and 0.4 mL of acetic anhydride was treated with 1 mg (8 μ mol) of DMAP and stirred at room temperature for 24 h. The reaction was concentrated and chromatographed through silica gel using 13:7 hexanes/ethyl acetate as the eluent to give 40.3 mg (86%) of **3-44** as a white foam: R_f 0.30 (3:2 hexanes/ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ 8.35 (d, J = 1.0 Hz, 1 H), 7.98 (dd, J = 7.0, 2.0 Hz, 1 H), 7.94 (d, J = 8.5 Hz, 1 H), 7.87 (dd, J = 7.0, 2.0, 1 H), 7.77 (dd, J = 9.0, 2.0 Hz, 1 H), 7.59–7.65 (m, 2 H), 7.40 (d, J = 7.0, 1 H), 7.22–7.35 (m, 18 H), 5.75 (t, J = 10.0 Hz, 1 H), 5.31 (dd, J = 11.5, 9.0 Hz, 1 H), 5.20 (d, J = 3.5 Hz, 1 H), 5.03 (d, J = 12.0 Hz, 1 H), 4.92 (d, J = 11.0 Hz, 1 H), 4.88 (dd, J = 10.0, 9.0 Hz, 1 H), 4.87 (d, J = 11.5 Hz, 1 H), 4.82 (d, J = 10.5 Hz, 1 H), 4.82 (d, J = 12.0 Hz, 1 H), 4.81 (d, J = 11.5 Hz, 1 H), 4.69 (d, J = 11.5 Hz, 1 H), 4.64 (d, J = 11.0 Hz, 1 H), 4.18 (t, J = 10.0 Hz, 1 H), 4.17 (dd, J = 11.5, 3.5 Hz, 1 H), 4.07 (dd, J = 12.0, 4.0 Hz, 1 H), 3.95 (t, J = 2.0 Hz, 1 H), 3.81 (dd, J = 12.5, 3.0

Hz, 1 H), 3.72 (ddd, $J = 10.5, 4.0, 3.0$ Hz, 1 H), 3.68 (dd, $J = 10.0, 2.0$ Hz, 1 H), 3.48 (dd, $J = 9.5, 2.0$ Hz, 1 H), 3.54 (t, $J = 9.5$ Hz, 1 H), 2.87 (s, 3 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 1.90 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.4, 170.3, 169.4, 169.4, 138.4, 138.2, 138.1, 136.4, 132.2, 129.3, 129.1, 128.9, 128.5, 128.4, 128.4, 128.1, 127.8, 127.6, 127.6, 127.5, 127.5, 123.0, 101.9, 81.8, 81.3, 81.1, 76.8, 76.1, 75.9, 75.4, 74.0, 73.5, 72.9, 70.1, 67.6, 67.4, 62.0, 57.9, 30.8, 21.5, 20.7, 20.5, 19.4; ESI-MS m/z 1096 MNa^+ .



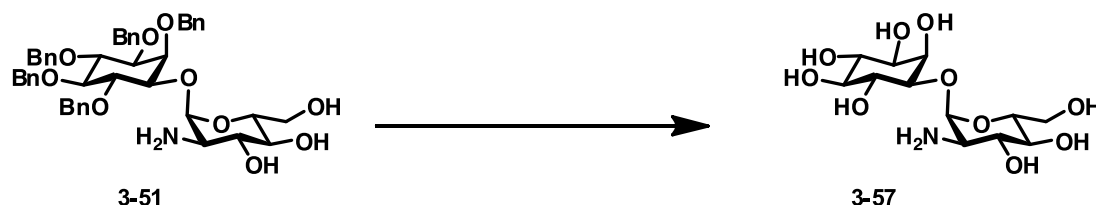
Compound 3-50. A solution containing 31.0 mg (0.0280 mmol) of **3-42** in 0.3 mL of methanol and 0.3 mL of THF was treated at 0 °C with a solution containing 1.81 mg (0.0335 mmol) of sodium methoxide in 14 μ L of methanol. After stirring for 30 min at 0 °C, the reaction was then concentrated and chromatographed on silica gel using 24:1 dichloromethane/isopropanol as the eluent to give 27.0 mg (99%) of **3-50** as a colorless oil: R_f 0.50 (9:1 dichloromethane/methanol); ^1H NMR (500 MHz, CD_3OD) δ 8.42 (d, J = 1.5 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 7.93 (d, J = 9.0 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.82 (dd, J = 8.5, 2.0 Hz, 1 H), 7.56–7.63 (m, 2 H), 7.38 (d, J = 7.0 Hz, 2 H), 7.37 (d, J = 7.5 Hz, 2 H), 7.20–7.32 (m, 21 H), 5.03 (d, J = 11.5 Hz, 1 H), 4.98 (d, J = 3.5 Hz, 1 H), 4.91 (d, J = 11.5 Hz, 1 H), 4.88 (d, J = 11.0 Hz, 1 H), 4.87 (d, J = 11.0 Hz, 1 H), 4.83 (d, J = 11.0 Hz, 1 H), 4.79 (d, J = 11.5 Hz, 1 H), 4.75 (d, J = 11.0 Hz, 1 H), 4.72 (d, J = 11.0 Hz, 1 H), 4.60 (d, J = 11.5 Hz, 1 H), 4.51 (d, J = 11.5 Hz, 1 H), 4.12 (t, J = 2.0 Hz, 1 H), 4.00 (t, J = 10.0 Hz, 1 H), 3.92 (t, J = 9.5 Hz, 1

H), 3.72 (dd, $J = 12.0, 2.0$ Hz, 1 H), 3.68 (ddd, $J = 10.0, 5.5, 2.0$ Hz, 1 H), 3.60 (dd, $J = 12.0, 5.5$ Hz, 1 H), 3.55 (dd, $J = 10.5, 9.0$ Hz, 1 H), 3.40 (dd, $J = 10.5, 3.5$ Hz, 1 H), 3.37 (t, $J = 9.0$ Hz, 1 H), 3.30 (dd, $J = 10.0, 2.0$ Hz, 1 H), 3.26 (dd, $J = 10.0, 9.0$ Hz, 1 H), 3.22 (dd, $J = 10.0, 2.0$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.5, 140.3, 140.3, 140.1, 139.9, 139.9, 136.3, 133.7, 130.6, 130.3, 129.9, 129.6, 129.5, 129.4, 129.4, 129.4, 129.2, 129.2, 129.1, 129.0, 129.0, 128.7, 128.7, 128.7, 128.6, 128.6, 124.2, 101.2, 85.2, 82.8, 82.3, 82.0, 79.8, 78.2, 76.7, 76.6, 75.9, 75.1, 73.7, 73.2, 72.2, 62.8, 60.1; ESI-MS m/z 1004 MNa^+ .

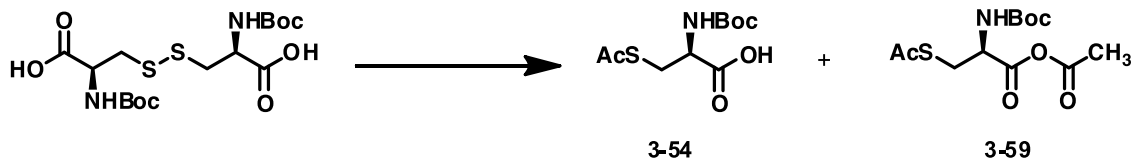


Compound 3-51. A solution containing 20.0 mg (0.0204 mmol) of **3-50** in 1.0 mL of methanol was treated with 14.2 mg (0.100 mmol) of dibasic sodium phosphate. After stirring the solution for 5 min at 0 °C, 110 mg (0.240 mmol) of a 5% sodium amalgam was added, and the reaction was stirred for 15 more minutes at room temperature. The reaction was then filtered through Celite and concentrated. Silica gel chromatography using 9:1 dichloromethane/methanol as the eluent afforded 11.9 mg (75%) of **3-51** as a colorless oil: R_f 0.45 (17:3 dichloromethane/methanol); ^1H NMR (500 MHz, CD_3OD) δ 7.43 (d, $J = 7.0$ Hz, 2 H), 7.37 (d, $J = 8.0$ Hz, 2 H), 7.19–7.34 (m, 21 H), 5.11 (d, $J = 3.5$ Hz, 1 H), 5.00 (d, $J = 11.5$ Hz, 1 H), 4.91 (d, $J = 11.0$ Hz, 2 H), 4.88 (d, $J = 10.0$ Hz, 2 H), 4.84 (d, $J = 11.0$ Hz, 1 H), 4.75–4.77 (m, 3 H), 4.65 (d, $J = 11.5$ Hz, 1 H), 4.37 (d, $J = 2.0$ Hz, 1 H), 4.02 (t, $J = 10.0$ Hz, 1 H), 4.00 (t, $J = 9.5$ Hz, 1 H), 3.79–3.84 (m, 1 H), 3.74 (dd, $J = 10.0, 2.0$ Hz, 1 H), 3.65 (dd, $J = 12.0, 6.0$ Hz, 1 H), 3.61 (dd, $J = 10.0, 2.0$ Hz, 1 H), 3.54 (t, $J = 9.0$ Hz, 1 H), 3.48 (dd, $J = 10.0, 9.0$ Hz, 1 H), 3.24 (t, $J = 9.5$ Hz, 1 H), 2.67 (dd, $J = 10.0, 3.5$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.8,

140.3, 140.2, 140.1, 140.0, 129.5, 129.5, 129.4, 129.4, 129.2, 129.1, 128.9, 128.8, 128.8, 128.7, 128.7, 128.5, 102.5, 85.4, 83.0, 82.6, 82.5, 80.0, 78.7, 76.8, 76.7, 76.4, 76.0, 75.9, 75.3, 73.7, 72.3, 63.1, 57.7; ESI-MS m/z 792 MH^+ .



Compound 3-57. A solution containing 9.1 mg (0.012 mmol) of **3-51** in 1.0 mL of a 5:1 *t*-butanol/water mixture was treated with 40.0 mg of palladium hydroxide (20 wt % on activated carbon) and 13 μ L of 0.1 N aqueous hydrochloric acid. The reaction was purged 3 times with a balloon filled with hydrogen gas, and then stirred under positive hydrogen pressure for 6 h. The reaction was then filtered through Celite and concentrated to produce 1.1 mg (71%) of **3-57** as a colorless oil: R_f (17:3 dichloromethane/methanol); 1H NMR (500 MHz, D_2O) δ 5.47 (d, J = 3.5 Hz, 1 H), 4.25 (t, J = 3.0 Hz, 1 H), 3.99 (dd, J = 10.5, 9.0 Hz, 1 H), 3.93 (dd, J = 12.5, 2.0 Hz, 1H), 3.88–3.91 (m, 1 H), 3.84 (t, J = 10.0 Hz, 1 H), 3.81–3.85 (m, 1 H), 3.75 (dd, J = 10.0, 3.0 Hz, 1 H), 3.67 (t, J = 10.0 Hz, 1 H), 3.59 (dd, J = 10.0, 3.0 Hz, 1 H), 3.55 (t, J = 9.5 Hz, 1 H), 3.42 (dd, J = 10.5, 3.5 Hz, 1 H), 3.35 (t, J = 9.5 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 98.8, 80.5, 75.7, 74.3, 73.5, 73.4, 73.3, 72.5, 71.1, 71.0, 61.8, 55.8; ESI-MS m/z 342 MH^+ .

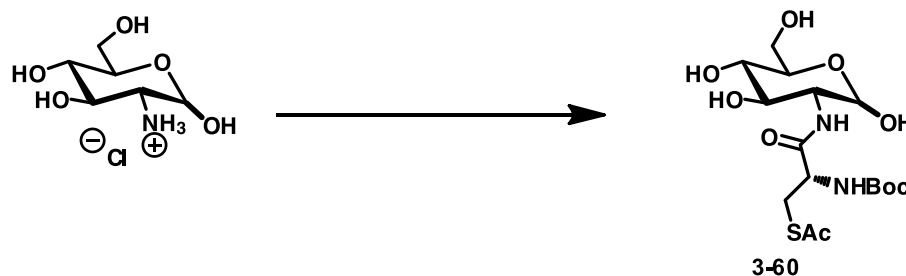


A solution containing 160.0 mg (0.363 mmol) of (Boc-Cys-OH)₂ and 0.25 mL of acetic acid in 3.0 mL of diethyl ether was treated with 637 mg (9.80 mmol) of zinc dust in four portions over a 1-h period. The solution was filtered and concentrated after an additional 2 h of stirring. The oily residue was dissolved with 1.7 mL of acetic anhydride and 0.80 mL of pyridine. After stirring for 4 h, the solution was diluted with 10 mL of saturated aqueous sodium bicarbonate and washed with dichloromethane. The aqueous solution was acidified with 6 N sulfuric acid to pH = 2, then extracted with dichloromethane. The organic layer was concentrated and chromatographed through silica gel using 49:1→4:1 dichloromethane/methanol as the eluent to afford the following products:

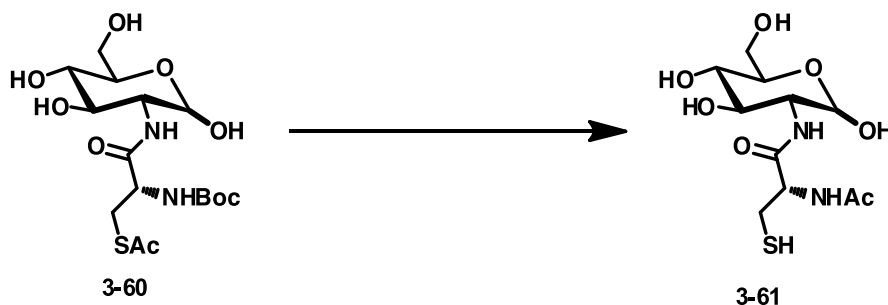
Compound 3-54. 18% yield, *R_f* 0.35 (9:1 dichloromethane/methanol); ¹H NMR (300 MHz, CDCl₃) δ 7.95 (br s, 1 H), 5.31 (d, *J* = 6.9 Hz, 1 H), 4.34–4.60 (m, 1 H), 3.44 (dd, *J* = 14.1, 3.6 Hz, 1 H), 3.31 (dd, *J* = 14.1, 6.6 Hz, 1 H), 2.36 (s, 3 H), 1.45 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 195.5, 174.1, 155.6, 80.7, 54.0, 53.3, 30.8, 30.5, 29.7, 28.2; ESI-MS *m/z* 262 M⁺.

Compound 3-59. 67% yield, R_f 0.52 (9:1 dichloromethane/methanol); ^1H NMR (500 MHz, CDCl_3) δ 5.40 (br s, 1 H), 4.40–4.51 (m, 1 H), 3.60 (dd, $J = 14.0$, 5.0 Hz, 1 H), 3.42 (dd, $J = 14.0$, 9.5 Hz, 1 H), 2.51 (s, 3 H), 2.32 (s, 3 H), 1.52 (s, 9 H); ^{13}C NMR (75 MHz, CDCl_3) δ 194.8, 172.8, 151.7, 84.8, 30.4, 30.3, 28.8, 27.9, 27.8, 26.3; ESI-MS m/z 328 MNa^+ .

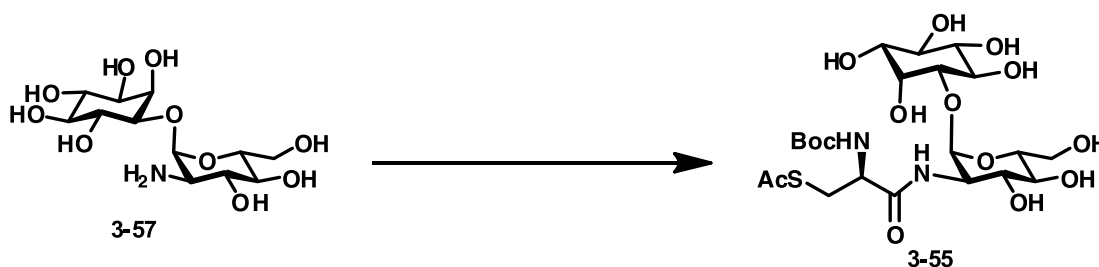
Alternate procedure for 3-54. A solution containing 283 mg (0.642 mmol) of $(\text{Boc-Cys-OH})_2$ in 4.5 mL of acetic acid was treated with 417 mg (6.42 mmol) of zinc dust in four portions over a 1 h period. The solution was filtered and concentrated after an additional 2 h of stirring. The oily residue was dissolved with 1.4 mL of acetic anhydride and 2.0 mL of a 1.0 N solution of cold aqueous potassium hydrogen carbonate. After stirring for 0.5 h at 2 °C, the solution was diluted with water and washed with dichloromethane. The aqueous solution was acidified with 6 N sulfuric acid to pH = 2, then extracted with dichloromethane. The organic layer was concentrated and chromatographed through silica gel using 9:1 dichloromethane/methanol as the eluent to afford **3-54** in 75% yield.



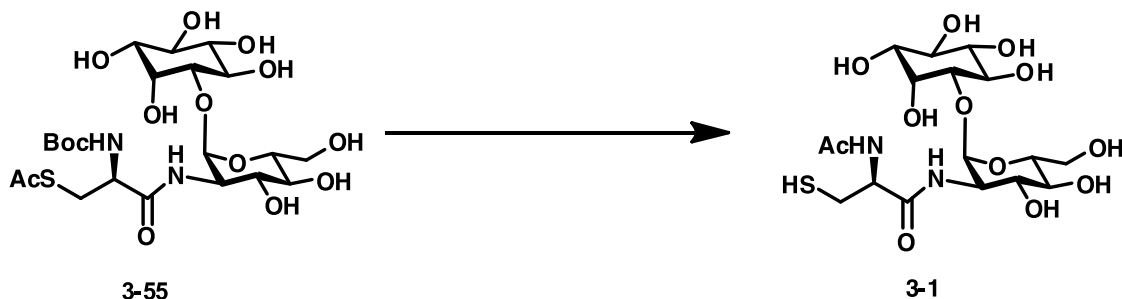
Compound 3-60. A solution containing 7.0 mg (0.033 mmol) of *D*-glucosamine hydrochloride and 13.0 mg (0.0494 mmol) of **3-54** in 0.3 mL of DMF was treated at 0 °C with 18.6 mg (0.0494 mmol) of HATU and 14.3 μ L (0.0820 mmol) of diisopropylethylamine. After stirring at room temperature for 12 h, the reaction was concentrated and chromatographed using 17:3 dichloromethane/methanol as the eluent to produce 10.1 mg (72%) of **3-60** as a colorless oil: R_f 0.10 (9:1 dichloromethane/methanol); ^1H NMR (400 MHz, CD_3OD) δ 5.10 (d, J = 3.5 Hz, 1 H), 4.28 (dd, J = 8.4, 4.8 Hz, 1 H), 3.80–3.88 (m, 2 H), 3.80 (dd, J = 12.0, 2.0 Hz, 1 H), 3.70 (dd, J = 12.0, 6.0 Hz, 1 H), 3.65–3.70 (m, 1 H), 3.35–3.43 (m, 2 H), 3.09 (dd, J = 14.0, 9.2 Hz, 1 H), 2.34 (s, 3 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, CD_3OD) δ ; ESI-MS m/z 447 MNa^+ .



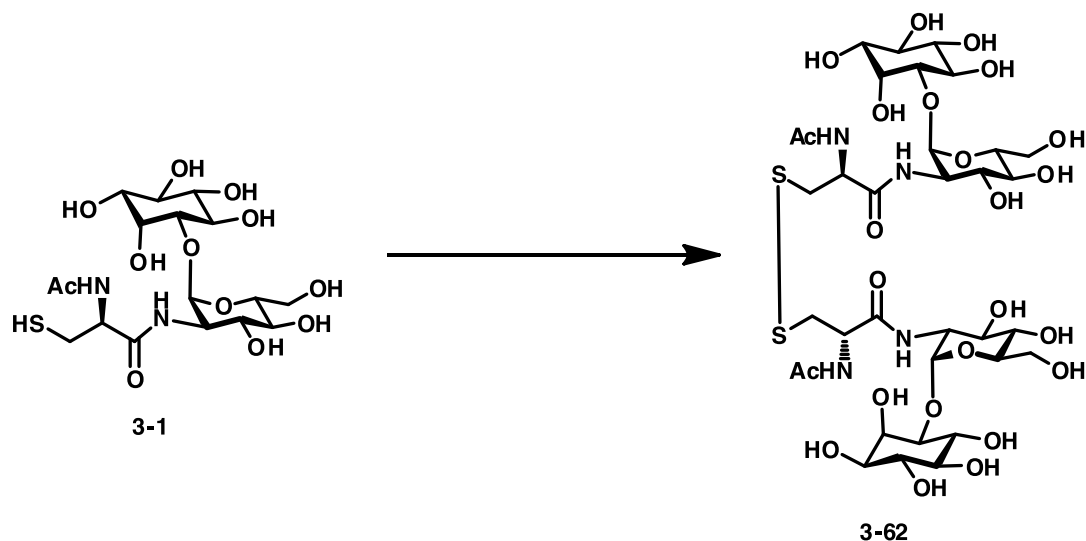
Compound 3-61. A solution containing 8.2 mg (0.019 mmol) of **3-60** in 1.0 mL of cold trifluoroacetic acid was stirred for 15 minutes, and then concentrated under reduced pressure. The colorless residue was then treated with 0.6 mL of pyridine. After 30 minutes of stirring, the mixture was concentrated and chromatographed through silica gel using 4:1 dichloromethane/methanol as the eluent to give 6.2 mg (100%, 5:2 α/β) of **3-61** as a white, sticky solid: R_f 0.5 (3:2 dichloromethane/methanol); ^1H NMR (500 MHz, CD_3OD) δ 5.10 (d, $J = 3.5$ Hz), 4.66 (d, $J = 8.0$ Hz), 4.51–4.55 (m, 1 H), 3.85–3.88 (m, 1 H), 3.78–3.84 (m, 2 H), 3.68–3.73 (m, 2 H) 3.59 (dd, $J = 10.5, 8.0$ Hz, 1 H), 3.48 (dd, $J = 10.5, 8.0$ Hz, 1 H), 2.90 (dd, $J = 14.0, 5.5$ Hz, 1 H), 2.79 (dd, $J = 14.0, 7.5$ Hz, 1 H), 2.03 (s, 3 H), 2.02 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.6, 172.8, 96.8, 92.7, 78.2, 76.0, 73.3, 72.9, 72.7, 72.4, 63.0, 62.9, 59.2, 57.4, 57.3, 56.1, 27.5, 27.3, 22.7, 22.6; ESI-MS m/z 347 MNa^+ .



Compound 3-55. A solution containing 4.0 mg (0.012 mmol) of **3-57** and 6.0 mg (0.023 mmol) of **3-54** in 0.5 mL of DMF was treated at 0 °C with 8.7 mg (0.023 mmol) of HATU and 6.1 μ L (0.035 mmol) of diisopropylethylamine. After stirring at room temperature for 12 h, the reaction was concentrated and chromatographed using 79:20:1 dichloromethane/methanol/acetic acid as the eluent to produce 5.2 mg (77%) of **3-55** as a colorless oil: R_f 0.41 (3:2 dichloromethane/methanol); ^1H NMR (500 MHz, D_2O) δ 5.20 (d, J = 3.5 Hz, 1 H), 4.39 (dd, J = 8.0, 4.5 Hz, 1 H), 4.25 (app s, 1 H), 4.01 (dd, J = 10.5, 3.5 Hz, 1 H), 3.90–3.94 (m, 2 H), 3.81–3.89 (m, 3 H), 3.67 (t, J = 10.0 Hz, 1 H), 3.62–3.65 (m, 1 H), 3.57 (dd, J = 10.0, 2.5 Hz, 1 H), 3.53 (t, J = 10.0 Hz, 1 H), 3.47 (dd, J = 14.0, 5.0 Hz, 1 H), 3.33 (t, J = 10.0 Hz, 1 H), 3.18 (dd, J = 14.0, 9.0 Hz, 1 H), 2.45 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, D_2O) δ 200.0, 172.5, 157.4, 99.1, 81.9, 79.0, 74.2, 72.5, 72.0, 71.7, 71.0, 70.7, 70.0, 60.5, 54.1, 54.0, 30.7, 29.8, 27.5; ESI-MS m/z 609 MNa^+ .



Compound 3-1. A solution containing 4.0 mg (6.8 μmol) of **3-55** in 0.3 mL of cold trifluoroacetic acid was stirred for 15 minutes, and then concentrated under reduced pressure. The colorless residue was then treated with 0.25 mL of pyridine. After 30 minutes of stirring, the mixture was concentrated and azeotroped several times with water and toluene to give 3.3 mg (100%) of **3-1** as a white, sticky solid: R_f 0.19 (3:2 dichloromethane/methanol); ^1H NMR (500 MHz, D_2O) δ 5.18 (d, $J = 3.5$ Hz, 1 H), 4.58 (t, $J = 6.5, 5.5$ Hz, 1 H), 4.24 (t, $J = 2.5$ Hz, 1 H), 4.03 (dd, $J = 10.5, 4.0$ Hz, 1 H), 3.89–3.93 (m, 2 H), 3.85 (dd, $J = 10.0, 9.5$ Hz, 1 H), 3.83 (t, $J = 10.0$ Hz, 1 H), 3.81–3.84 (m, 1 H), 3.67 (t, $J = 10.0$ Hz, 1 H), 3.63 (dd, $J = 10.0, 2.5$ Hz, 1 H), 3.57 (dd, $J = 10.0, 2.5$ Hz, 1 H), 3.52 (t, $J = 9.5$ Hz, 1 H), 3.33 (t, $J = 9.5$ Hz, 1 H), 3.00 (dd, $J = 14.0, 5.5$ Hz, 1 H), 2.95 (dd, $J = 14.0, 6.5$ Hz, 1 H), 2.12 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.4, 172.0, 99.2, 79.0, 74.2, 72.5, 72.1, 72.0, 71.7, 71.0, 70.8, 70.0, 60.5, 55.7, 53.8, 25.6, 21.7; ESI-MS m/z 509 MNa^+ ; FT ESI-MS m/z 487.1593 MH^+ , calculated mass for $\text{C}_{17}\text{H}_{31}\text{O}_{12}\text{N}_2\text{S}$ 487.1592.

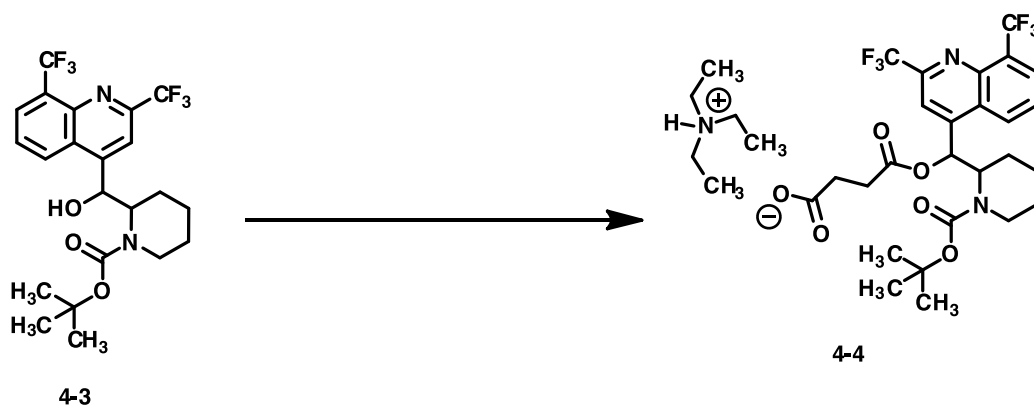


Compound 3-62. A solution containing 3.0 mg (6.2 μmol) of **3-1** in 0.4 mL of methanol was treated with 15 μL of a 0.2 M solution of iodine in methanol. After stirring for 15 min, the reaction was concentrated to give 3.0 mg (100%) of **3-62** as a white solid: ^1H NMR (500 MHz, D_2O) δ 5.19 (d, $J = 3.5$ Hz, 2 H), 4.78–4.83 (m, 1 H), 4.24 (t, $J = 3.0$ Hz, 1 H), 4.02 (dd, $J = 10.5, 3.5$ Hz, 1 H), 3.93 (dd, $J = 12.5, 2.0$ Hz, 1 H), 3.89–3.92 (m, 1 H), 3.87 (dd, $J = 11.0, 9.0$ Hz, 1 H), 3.83 (t, $J = 9.5$ Hz, 1 H), 3.82 (dd, $J = 12.5, 4.5$ Hz, 1 H), 3.68 (t, $J = 9.5$ Hz, 1 H), 3.64 (dd, $J = 10.0, 3.0$ Hz, 1 H), 3.58 (dd, $J = 10.0, 3.0$ Hz, 1 H), 3.53 (t, $J = 9.5$ Hz, 1 H), 3.34 (t, $J = 9.5$ Hz, 1 H), 3.30 (dd, $J = 14.0, 5.0$ Hz, 1 H), 3.02 (dd, $J = 14.0, 9.0$ Hz, 1 H), 2.12 (s, 3 H); ^{13}C NMR (125 MHz, D_2O) δ 174.4, 172.3, 99.0, 78.9, 74.2, 72.5, 72.1, 72.0, 71.7, 71.0, 70.6, 70.0, 60.5, 54.0, 52.7, 39.0, 21.8; ESI-MS m/z 993 MNa^+ ; FT ESI-MS m/z M^+ , calculated mass for $\text{C}_{34}\text{H}_{58}\text{O}_{24}\text{N}_4\text{S}_2$ 970.2883.

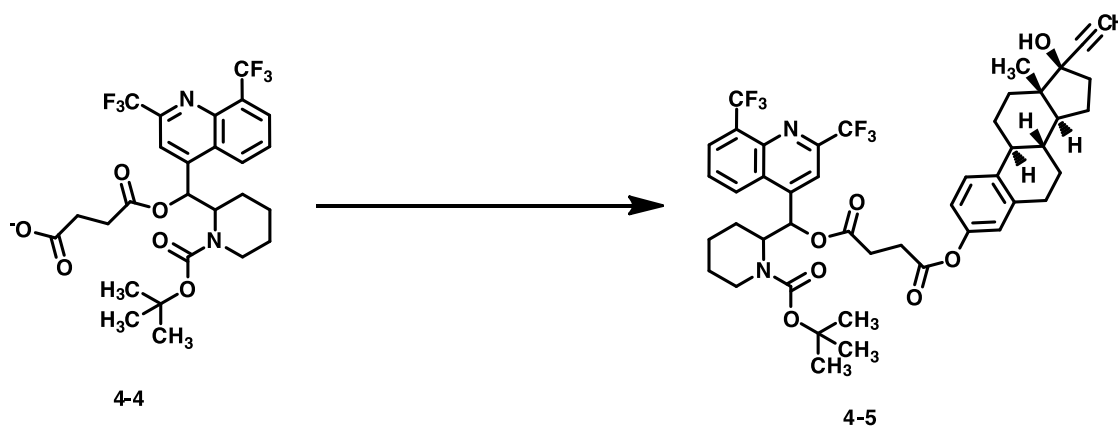
E4. Experimental Procedures for Chapter 4



Compound 4-3. Mefloquine **4-2** (249.5 mg, 0.665 mmol) was dissolved in 3.33 mL of distilled THF, and the solution was cooled in a 0 °C ice bath. Di-*tert*-butyl dicarbonate (217.8 mg, 0.998 mmol) and triethylamine (168.0 mg, 1.66 mmol) was added to the cooled solution. After stirring at rt for 12 h, the mixture was washed with water and brine, dried on magnesium sulfate, then concentrated under reduced pressure. Silica gel column chromatography using 1:4 ethyl acetate/hexanes as the eluent afforded 292 mg of **4-4** in 92% yield: ¹H NMR (500 MHz, CDCl₃) δ 8.65 (d, *J* = 8.5 Hz, 1 H), 8.17 (d, *J* = 7.0 Hz, 1 H), 8.04 (s, 1 H), 7.76 (t, *J* = 8.0 Hz, 1 H), 5.83 (t, *J* = 4.0 Hz, 1 H), 4.29 (q, *J* = 5.5 Hz, 1H), 3.82 (br d, *J* = 13.0 Hz, 1 H), 3.24 (ddd, *J* = 4.0, 10.5, 14.5 Hz, 1H), 3.15 (br s, 1 H), 1.73–1.95 (m, 2H), 1.34–1.66 (m, 4 H), 1.32 (s, 9 H); ESI-MS *m/z* 501 MNa⁺.

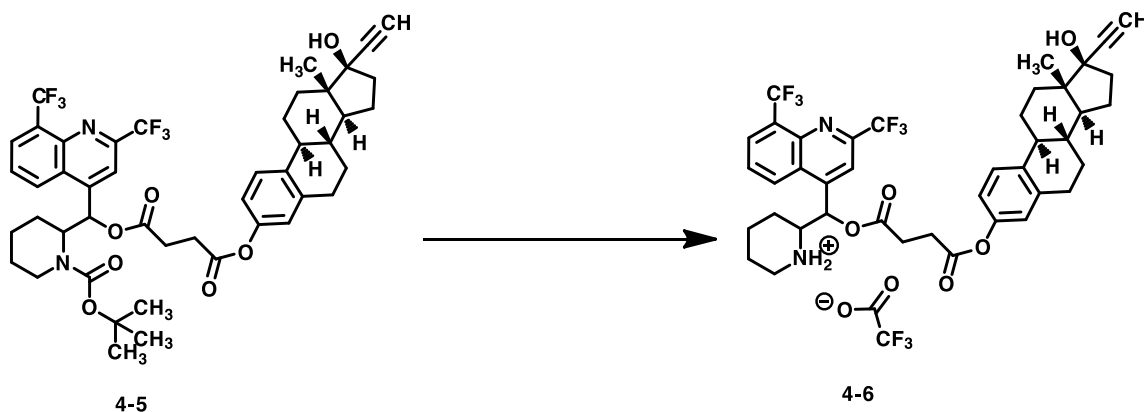


Compound 4-4. Triethylamine (253 mg, 2.50 mmol) was added to a solution containing 478 mg (1.00 mmol) of **4-3** and 200 mg (2.00 mmol) of succinic anhydride in 8.4 mL chloroform. After refluxing for 18 h, the solution was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried on magnesium sulfate, filtered, and concentrated under reduced pressure to give 612 mg of **4** as light-brown oil, which was carried to the next step without further purification: ^1H NMR (500 MHz, CDCl_3) δ 12.46 (br s, 1 H), 8.71 (br s, 1 H), 8.13 (d, $J = 7.0$ Hz, 1 H), 7.85 (s, 1 H), 7.76 (t, $J = 8.0$ Hz, 1 H), 6.68 (br s, 1 H), 4.74 (br s, 1 H), 3.95 (br s, 1 H), 2.93 (dt, $J = 13.0, 3.0$, 1 H), 2.87 (q, $J = 7.5$, 6 H), 2.66 (t, $J = 7.0$ Hz, 2 H), 2.51 (t, $J = 7.0$, 2 H), 1.97 (br s, 1 H), 1.34–1.80 (m, 5 H), 1.09 (t, $J = 7.5$ Hz, 9 H), 1.04 (br s, 9 H); ESI-MS m/z 601 MNa^+ , 577 M^- .



Compound 4-5. A solution of crude succinate **4-4** (612 mg) in 9.0 mL dichloromethane was cooled in a 0 °C ice bath. Ethynyl estradiol (270 mg, 0.911 mmol) was added to the cooled solution, followed by 172 mg (0.911 mmol) of *N*-(3-diethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride and 22.0 mg (0.180 mmol) of DMAP. After 12 h of stirring at rt, the reaction was washed with water and brine, concentrated, and chromatographed on silica gel using 3:7 ethyl acetate/hexanes as eluent, affording 701 mg of **4-5** as a colorless oil (82% yield over 2 steps): ^1H NMR (500 MHz, CDCl_3) δ 8.71 (br s, 1 H), 8.17 (d, $J = 7.5$ Hz, 1 H), 7.86 (s, 1 H), 7.79 (t, $J = 8.0$ Hz, 1 H), 7.24 (d, $J = 8.5$ Hz, 1 H), 6.80 (br d, $J = 3.0$ Hz, 1 H), 6.73 (dt, $J = 8.5, 3.0$ Hz, 1 H), 6.68 (d, $J = 2.0$ Hz, 1 H), 4.79 (br s, 1 H), 3.97 (br s, 1 H), 2.74–2.98 (m, 7 H), 2.61 (s, 1 H), 2.20–2.40 (m, 3 H),

1.62–2.06 (m, 10 H), 1.30–1.58 (m, 7 H), 1.09 (br s, 9 H), 0.88 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.1, 171.6, 148.1, 148.0 (q, $J = 35.6$ Hz), 144.0, 143.4, 138.3, 138.2 (d, $J = 1.4$ Hz), 127.4, 127.2, 126.3, 123.2 (q, $J = 273$ Hz), 121.0 (d, $J = 274$ Hz), 121.0, 118.1, 115.0, 87.1, 80.1, 79.8, 74.3, 49.4, 47.0, 43.6, 39.0, 38.8, 32.6, 29.7, 29.4, 29.1, 27.8, 26.9, 26.2, 26.2, 24.5, 22.7, 21.9, 21.8, 21.6, 12.6; ESI-MS m/z 879 MNa^+ .

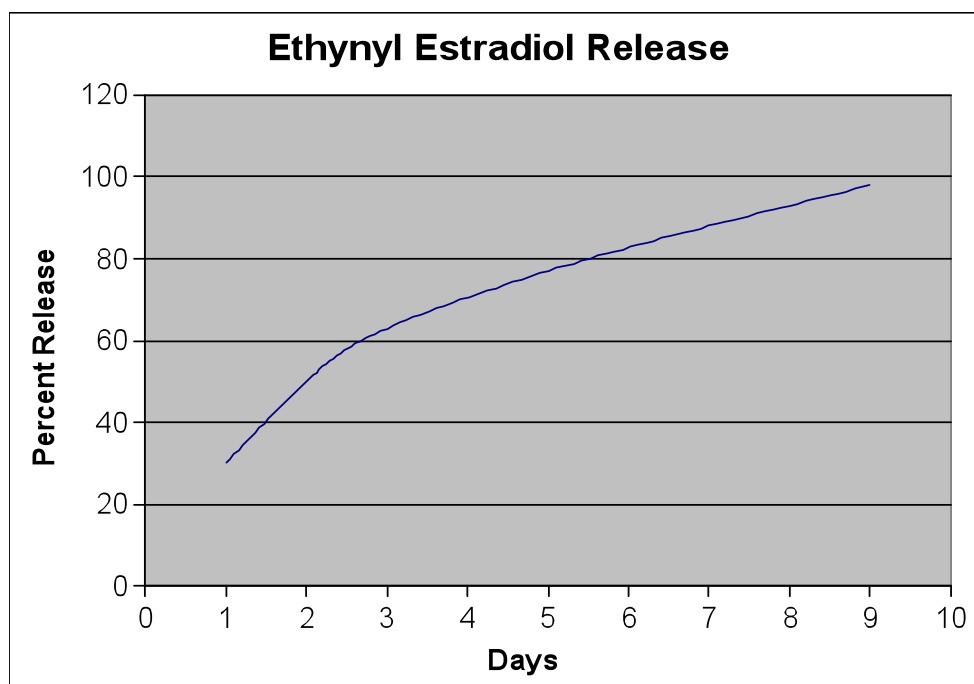


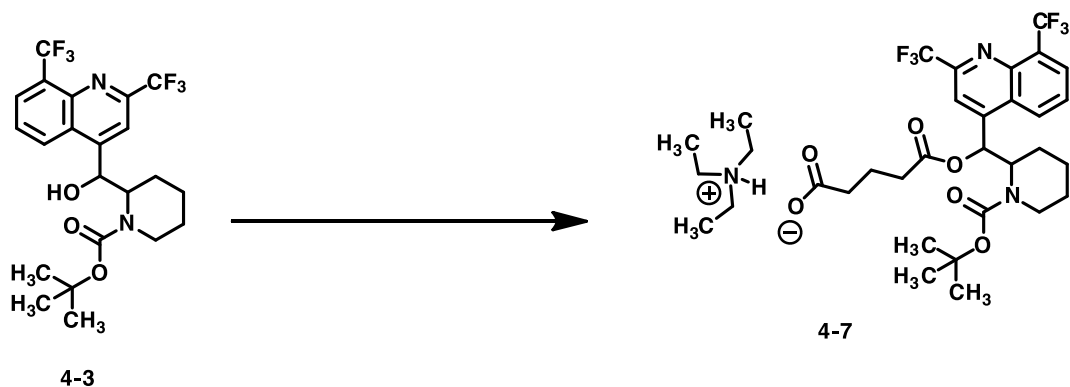
Compound 4-6. Ester **4-5** (302 mg, 0.352 mmol) was dissolved in 3.5 mL dichloromethane, and the solution was cooled in a 0 °C ice bath. Trifluoroacetic acid (2.34 mL) was added to the cooled solution. After 0.5 h of stirring at 0 °C, the reaction was concentrated, then concentrated twice more from toluene to produce 304 mg of crude **4-6** as a hygroscopic white solid: ^1H NMR (500 MHz, CDCl_3) δ 10.23 (br s, 1 H), 9.77 (br s, 1 H), 8.87 (d, $J = 8.5$ Hz, 1 H), 8.26 (d, $J = 7.0$ Hz, 1 H), 7.91 (t, $J = 8.0$ Hz, 1 H), 7.87 (s, 1 H), 7.28 (br s, 1 H), 7.18 (t, $J = 9.0$ Hz, 1 H), 6.73 (ddd, $J = 2.5, 4.5, 7.5$ Hz, 1 H), 6.66 (br s, 1 H), 3.72 (d, $J = 12$ Hz, 1 H), 3.38 (br s, 1 H), 3.14 (dt, $J = 6.0, 17.5$ Hz, 1 H), 3.01 (dt, $J = 7.0, 18$ Hz, 1 H), 2.70 – 2.92 (m, 5 H), 2.59 (s, 1 H), 2.14 – 2.28 (m, 3 H), 1.62 – 2.08 (m, 10 H), 1.12–1.58 (m, 7 H), 0.83 (d, $J = 3.5$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.1, 171.6, 161.5 (q, $J = 39.3$ Hz), 148.1, 148.0 (q, $J = 35.6$ Hz), 144.0, 143.4, 138.3, 138.2 (d, $J = 1.4$ Hz), 129.8 (q, $J = 30.6$ Hz), 129.7, 129.6, 128.7, 127.1, 126.3, 125.7,

123.2 (q, $J = 273$ Hz), 121.0 (d, $J = 274$ Hz), 121.0 (d, $J = 5.1$ Hz), 118.1 (d, $J = 3.3$ Hz), 115.0, 87.1, 80.1, 74.3, 70.1, 59.3, 49.4, 47.0, 45.8, 43.6, 39.0, 38.8, 32.6, 32.6, 29.7, 29.4, 29.1, 26.9, 26.2, 26.2, 22.7, 21.9, 21.8, 21.6, 12.6; FT-IR 3465, 3305, 2938, 2871, 2250, 1755, 1674; ESI-MS m/z 757 MH^+ .

Hydrolysis study on **4-6**

Estradiol conjugate **4-6** (33.5 mg, 0.039 mmol) was dissolved in 58 mL of a 9:4 ethanol/0.05 M aqueous phosphate buffer (pH 7.4) mixture, and the solution was shaken in a 37 °C incubator for 9 days. Six 8 mL aliquots were collected at 1-, 2-, 3-, 5-, 7-, and 9-day intervals. Estradiol release was quantified by adding 33 μ L of a 0.09 M solution of butylated hydroxytoluene (BHT) in deuteriochloroform as an internal standard, then comparing integrals of ^1H NMR signals corresponding to the steroid and the internal standard.

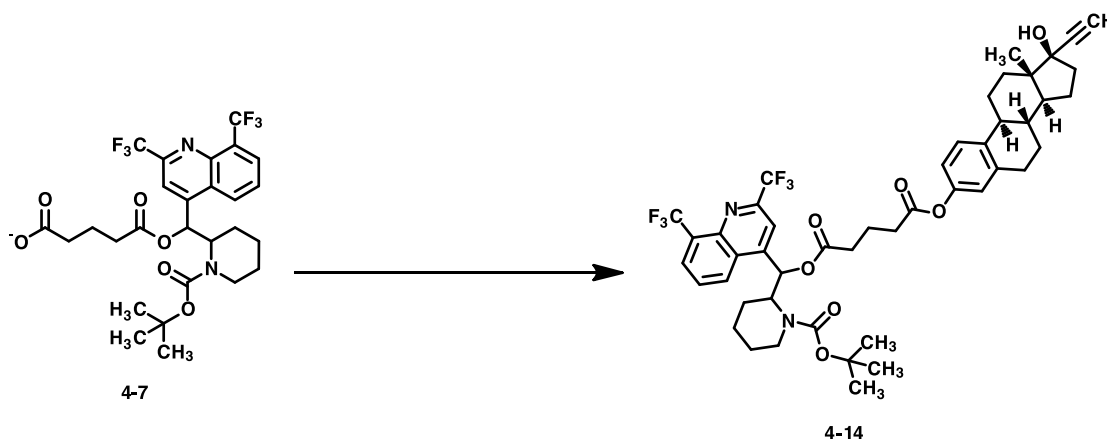




Compound 4-7. A solution containing 67.9 mg (0.142 mmol) of **4-3** in 1.2 mL of chloroform was treated with 50 μ L (0.335 mmol) of triethylamine and 34.1 mg (0.284 mmol) of glutaric anhydride. After refluxing for 18 h, the solution was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried on magnesium sulfate, filtered, and concentrated under reduced pressure to give 100 mg of **4-7** as light-brown oil, which was carried to the next step without further purification: ^1H NMR (500 MHz, CDCl_3) δ 10.59 (br s, 1 H), 8.69 (br s, 1 H), 8.16 (d, $J = 7.0$ Hz, 1 H), 7.83 (s, 1 H), 7.78 (t, $J = 8.0$ Hz, 1 H), 6.72 (br s, 1 H), 4.75 (br s, 1 H), 3.97 (br s, 1 H), 3.03 (q, $J = 7.5$ Hz, 6 H), 2.92 (t, $J = 12$ Hz, 1 H), 2.43–2.54 (m, 2 H), 2.26 (t, $J = 7.5$ Hz, 2 H), 1.87–1.93 (m, 3 H), 1.64–1.73 (m, 3 H), 1.43–1.55 (m, 3 H), 1.24 (t, $J = 7.5$ Hz, 9 H), 1.07 (br s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 177.3, 172.0, 154.2, 144.9, 143.9, 128.9, 128.3, 127.4, 127.2, 123.8 (d, $J = 273$ Hz),

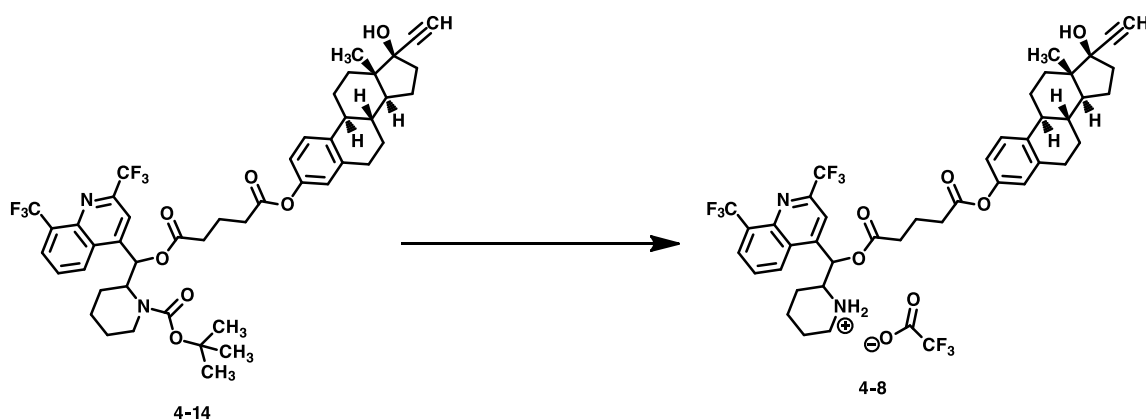
121.4 (q, $J = 274$ Hz), 116.1, 80.0, 45.0, 34.4, 33.6, 27.7, 24.5, 20.5, 19.1, 8.3;

ESI-MS m/z 591 M^+ .



Compound 4-14. A solution of crude glutarate **4-7** (100 mg) in 1.4 mL dichloromethane was cooled in a 0 °C ice bath. Ethynyl estradiol (40.5 mg, 0.134 mmol) was added to the cooled solution, followed by 26.3 mg (0.137 mmol) of *N*-(3-diethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride and 3.3 mg (0.027 mmol) of DMAP. After 12 h of stirring at rt, the reaction was washed with water and brine, concentrated, and chromatographed on silica gel using 3:7 ethyl acetate/hexanes as eluent, affording 96.3 mg of **4-14** as a colorless oil (79% yield over 2 steps): ¹H NMR (500 MHz, CDCl₃) δ 8.71 (s, 1 H), 8.17 (d, *J* = 7.5 Hz, 1 H), 7.85 (s, 1 H), 7.80 (t, *J* = 7.5 Hz, 1 H), 7.28 (d, *J* = 8.5 Hz, 1 H), 6.80 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.78 (br s, 1 H), 6.75 (d, *J* = 2.5 Hz, 1 H), 4.78 (s, 1 H), 4.00 (br s, 1 H), 2.94 (td, *J* = 13.0, 2.0 Hz, 1 H), 2.83–2.87 (m, 2 H), 2.60 (s, 1 H), 2.54–2.66 (m, 4 H), 2.36 (dd, *J* = 9.5, 5.5 Hz, 1 H), 2.33 (dd, *J* = 9.5, 5.5 Hz, 1 H), 2.25 (td, *J* = 11.0, 4.0 Hz, 1 H), 1.82–2.10 (m, 6 H), 1.65–1.81 (m, 6 H), 1.36–1.57 (m, 7 H),

1.11 (br s, 9 H), 0.88 (s, 3 H) ; ^{13}C NMR (125 MHz, CDCl_3) δ 171.6, 171.4, 148.2, 144.0, 138.3, 138.0, 129.0, 128.2, 127.5, 127.2, 126.4, 123.8 (q, $J = 273$ Hz), 121.3, 121.2 (q, $J = 274$ Hz), 118.4, 116.1, 87.4, 80.1, 79.8, 74.1, 49.5, 47.0, 43.7, 39.0, 33.1, 33.0, 32.7, 31.6, 29.5, 27.7, 27.0, 26.2, 25.2, 24.5, 22.8, 22.6, 19.9, 19.2, 14.1, 12.6; ESI-MS m/z 893 MNa^+ .

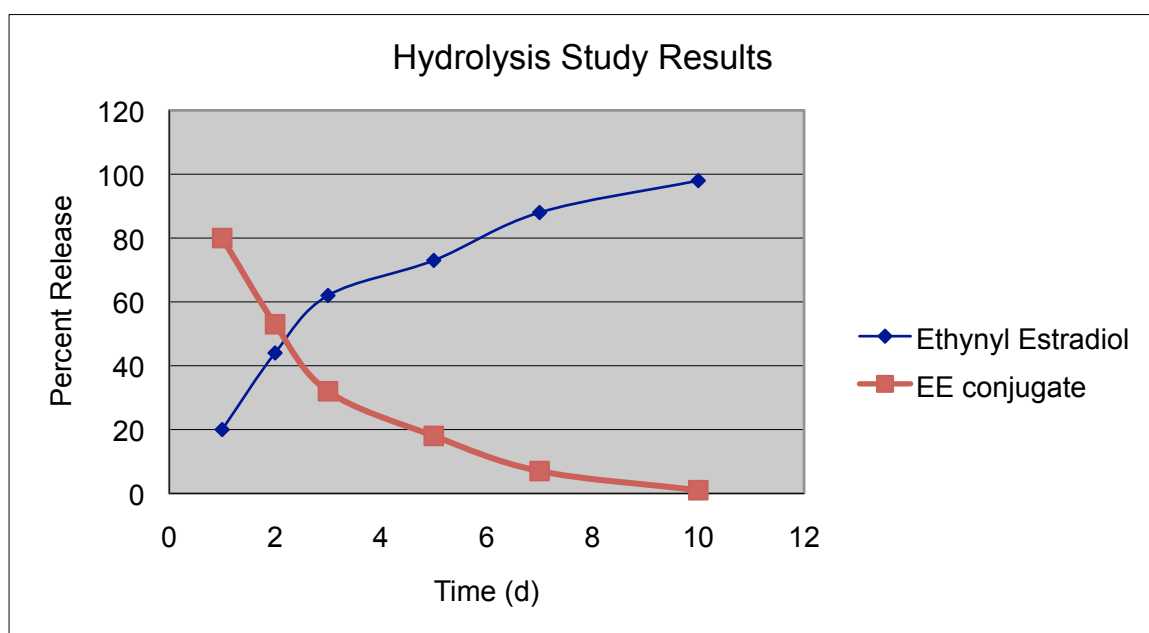


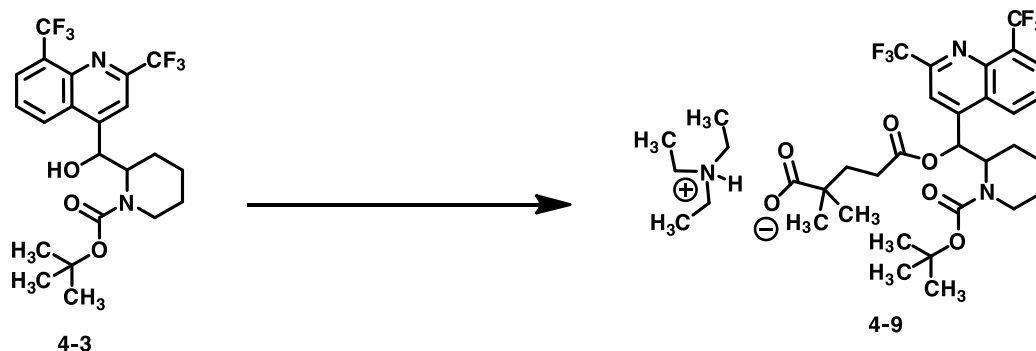
Compound 4-8. Ester **4-14** (47.6 mg, 0.055 mmol) was dissolved in 0.6 mL of dichloromethane, and the solution was cooled in a 0 °C ice bath. Trifluoroacetic acid (0.374 mL) was added to the cooled solution. After 0.5 h of stirring at 0 °C, the reaction was concentrated, then concentrated twice more from toluene to produce 49 mg of crude **4-8** as a hygroscopic white solid: ^1H NMR (500 MHz, CDCl_3) δ 10.0 (br s, 1 H), 8.65 (d, $J = 8.0$ Hz, 1 H), 8.23 (d, $J = 7.0$ Hz, 1 H), 8.09 (br s, 1 H), 7.86 (t, $J = 8.0$ Hz, 1 H), 7.84 (s, 1 H), 7.27 (d, $J = 9.0$ Hz, 1 H), 7.17 (s, 1 H), 6.83 (d, $J = 8.0$ Hz, 1 H), 6.77 (s, 1 H), 6.64 (br s, 3 H), 3.52 (br s, 1 H), 3.35 (br s, 1 H), 2.96 (br s, 1 H), 2.81–2.85 (m, 2 H), 2.64–2.79 (m, 4 H), 2.61 (s, 1 H), 2.36 (dd, $J = 9.0, 5.0$ Hz, 1 H), 2.33 (dd, $J = 9.0, 5.0$ Hz, 1 H), 2.22 (br t, $J = 11$ Hz, 1 H), 2.14 (br s, 2 H), 2.03 (td, $J = 12.5, 3.0$ Hz, 1 H), 1.78–1.95 (m, 5 H), 1.67–1.76 (m, 3 H), 1.30–1.54 (m, 6 H), 0.87 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3)

δ 173.3, 172.3, 161.2 (q, $J = 39.4$ Hz), 148.0, 147.8 (q, $J = 35.6$ Hz), 143.9, 143.7, 138.5, 138.5, 138.3, 129.8, 129.7, 128.8, 127.1, 126.6, 125.7, 123.8 (q, $J = 273$ Hz), 121.3, 121.2 (q, $J = 274$ Hz), 118.4, 114.9, 87.1, 80.0, 74.3, 69.7, 59.4, 49.4, 47.0, 45.7, 43.7, 39.1, 39.0, 38.8, 33.2, 33.1, 32.6, 29.4, 27.5, 26.9, 26.2, 22.7, 21.8, 21.6, 19.6, 12.6; ESI-MS m/z 771 MH^+ .

Hydrolysis Study on **4-8**

Estradiol conjugate **4-8** (14.5 mg, 0.016 mmol) was dissolved in 28 mL of a 9:4 ethanol/0.05 M aqueous phosphate buffer (pH 7.4) mixture, and the solution was shaken in a 37 °C incubator for 10 days. Six 4 mL aliquots were collected at 1-, 2-, 3-, 5-, 7-, and 10-day intervals. Estradiol release was quantified by adding 23 μ L of a 0.103 M solution of butylated hydroxytoluene (BHT) in deuteriochloroform as an internal standard, then comparing integrals of ^1H NMR signals corresponding to the steroid and the internal standard.

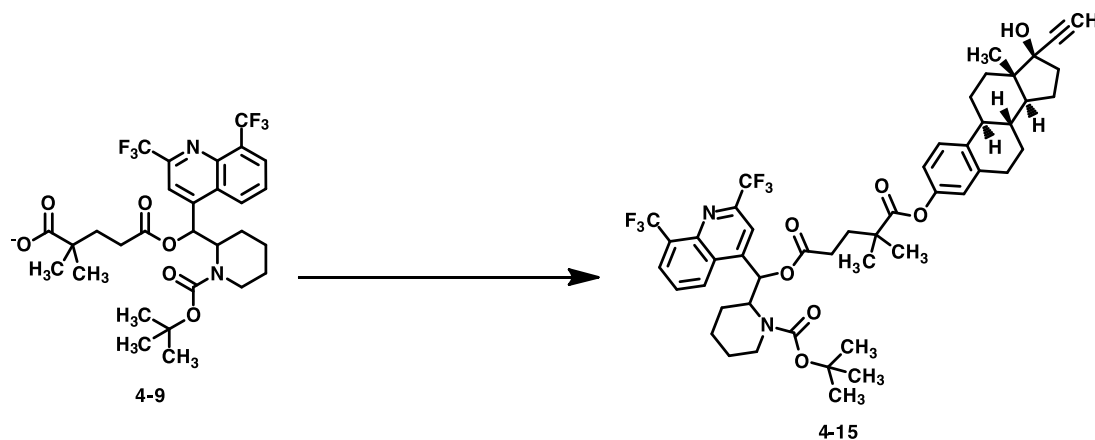




Compound 4-9. Triethylamine (61.6 mg, 0.609 mmol) was added to a solution containing 116 mg (0.244 mmol) of **4-3** and 69.2 mg (0.487 mmol) of 2,2-dimethylglutaric anhydride in 2.0 mL of diethyl carbonate. After refluxing for 4 h, the solution was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried on magnesium sulfate, filtered, and concentrated under reduced pressure to give 166 mg of **4-9** as light-brown oil, which was carried to the next step without further purification:

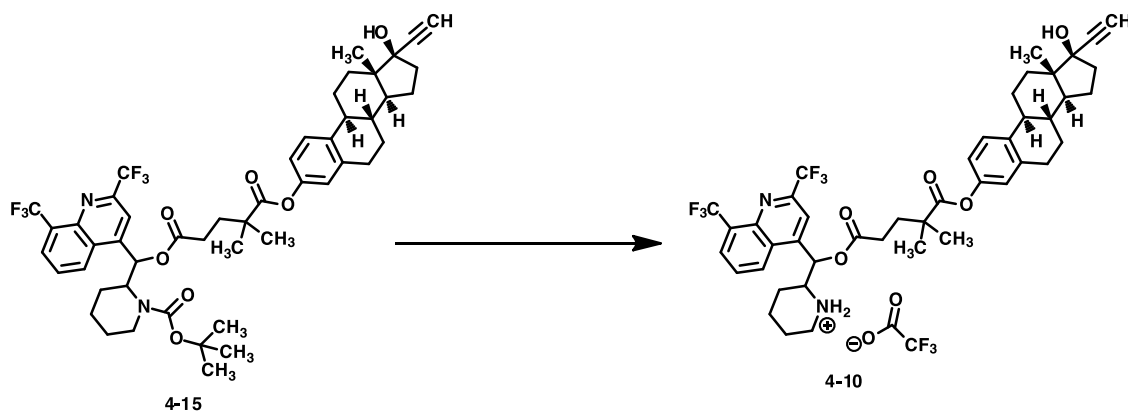
^1H NMR (500 MHz, CDCl_3) δ 11.14 (br s, 1 H), 8.70 (br s, 1 H), 8.18 (d, $J = 7.0$ Hz, 1 H), 7.85 (s, 1 H), 7.79 (t, $J = 8.0$ Hz, 1 H), 6.75 (d, $J = 7.0$ Hz, 1 H), 4.79 (s, 1 H), 3.99 (br s, 1 H), 2.93 (t, $J = 12.0$ Hz, 1 H), 2.46 (dd, $J = 10.0, 1.5$ Hz, 1 H), 2.45 (dd, $J = 10.0, 1.5$ Hz, 1 H), 1.83–1.96 (m, 3 H), 1.66–1.76 (m, 3 H), 1.44–1.64 (m, 2 H), 1.19 (s, 3 H), 1.18 (s, 3 H), 1.09 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 183.1, 172.1, 147.8 (q, $J = 35.6$ Hz), 144.0, 129.0, 128.9, 127.4, 127.3, 123.8 (q, J

= 273 Hz), 121.3, 121.2 (q, $J = 274$ Hz), 116.2, 80.2, 70.5, 41.5, 34.5, 30.2, 27.8, 24.8, 24.7, 24.5, 19.1; ESI-MS m/z 619 M^+ .



Compound 4-15. A solution of crude 2,2-dimethylglutarate **4-9** (166 mg) in 2.3 mL dichloromethane was cooled in a 0 °C ice bath. Ethynyl estradiol (71.6 mg, 0.242 mmol) was added to the cooled solution, followed by 46.4 mg (0.242 mmol) of *N*-(3-diethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride and 5.6 mg (0.05 mmol) of DMAP. After 12 h of stirring at rt, the reaction was washed with water and brine, concentrated, and chromatographed on silica gel using 3:7 ethyl acetate/hexanes as the eluent, affording 151 mg of **4-15** as a colorless oil (69% yield over 2 steps): ^1H NMR (500 MHz, CDCl_3) δ 8.67 (br s, 1 H), 8.17 (d, J = 7.5 Hz, 1 H), 7.84 (s, 1 H), 7.80 (t, J = 8.0 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 6.77 (dd, J = 8.0, 1.5 Hz, 1 H), 6.72 (d, J = 2.0 Hz, 1 H), 6.66 (br s, 1 H), 4.82 (s, 1 H), 4.01 (br s, 1 H), 2.99 (t, J = 12.5 Hz, 1 H), 2.84–2.86 (m, 2 H), 2.61 (s, 1 H), 2.32–2.42 (m, 3 H), 2.26 (td, J = 11.0, 4.0 Hz, 1 H), 2.01–2.09 (m, 3 H), 1.87–1.95 (m, 3 H), 1.69–1.84 (m, 6 H), 1.36–1.63 (m, 8 H), 1.30 (s, 3 H), 1.27 (s, 3 H), 1.06 (br s, 9 H), 0.89 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.0, 171.6, 148.2, 144.0, 138.2,

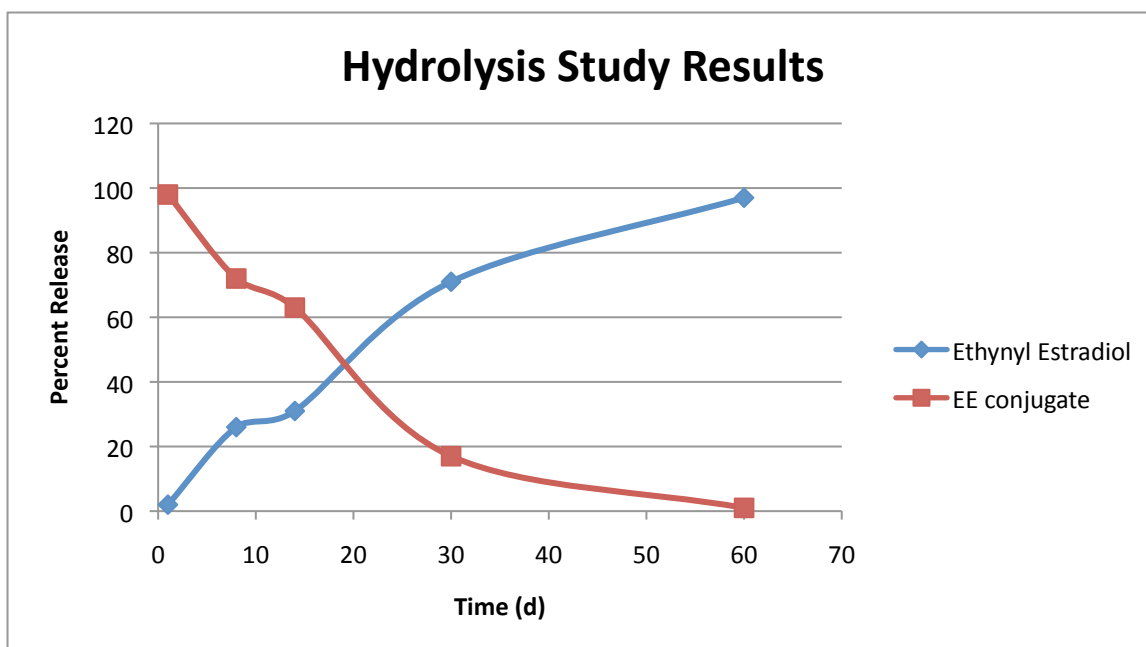
137.9, 129.1, 127.4, 127.2, 126.4, 123.8 (q, $J = 273$ Hz), 121.3, 121.2 (q, $J = 274$ Hz), 118.4, 87.4, 80.1, 79.8, 74.1, 49.5, 47.1, 43.7, 42.0, 39.0, 34.8, 32.7, 30.1, 29.5, 27.7, 24.9, 19.0, 12.7; ESI-MS m/z 921 MNa^+ .

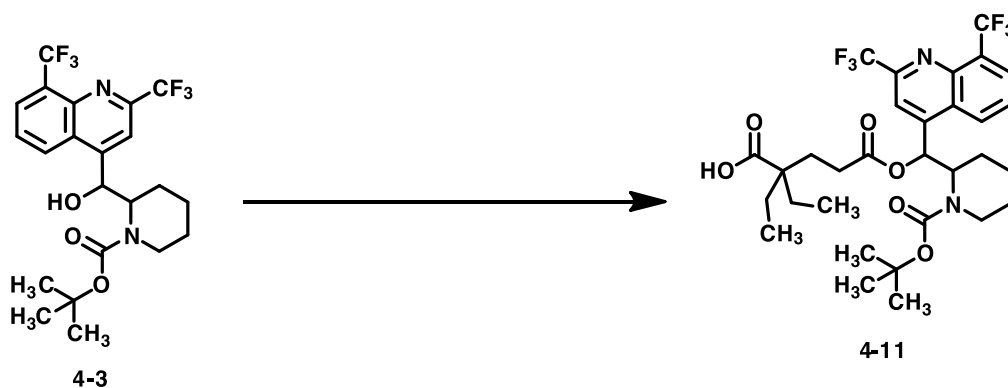


Compound 4-10. Ester **4-15** (13.6 mg, 0.015 mmol) was dissolved in 0.08 mL dichloromethane, and the solution was cooled in a 0 °C ice bath. Trifluoroacetic acid (0.05 mL) was added to the cooled solution. After 0.5 h of stirring at 0 °C, the reaction was concentrated, then concentrated twice more from toluene to produce 13.6 mg of crude **4-10** as a hygroscopic white solid: ^1H NMR (125 MHz, CDCl_3) δ ESI-MS m/z 799 MH^+ .

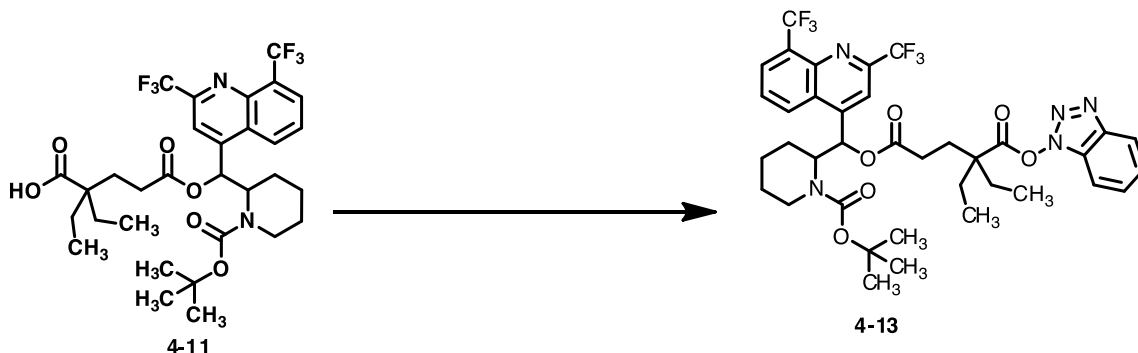
Hydrolysis Study on **4-10**

Estradiol conjugate **4-10** (13.7 mg, 0.015 mmol) was dissolved in 30 mL of a 9:4 ethanol/0.05 M aqueous phosphate buffer (pH 7.4) mixture, and the solution was shaken in a 37 °C incubator for 60 days. Five 6 mL aliquots were collected at 1-, 8-, 14-, 30-, and 60-day intervals. Estradiol release was quantified by adding 23 μ L of a 0.10 M solution of butylated hydroxytoluene (BHT) in deuteriochloroform as an internal standard, then comparing integrals of ^1H NMR signals corresponding to the steroid and the internal standard.



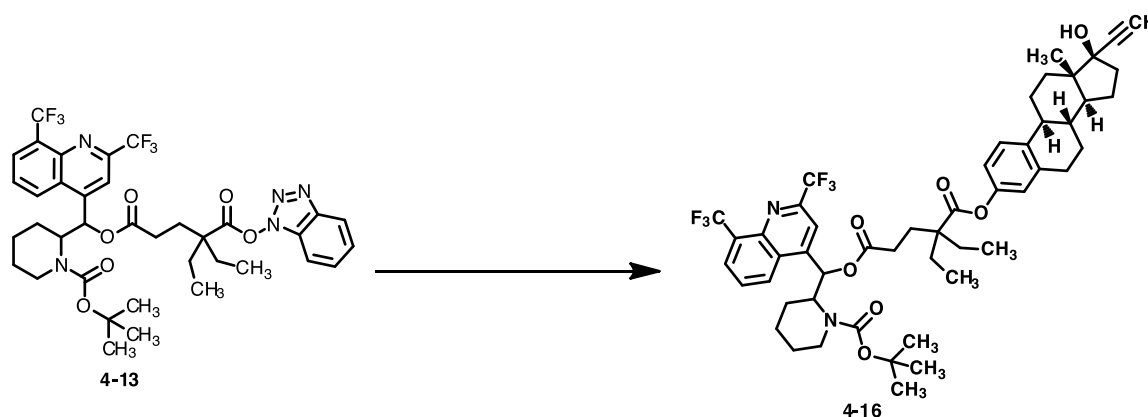


Compound 4-11. Triethylamine (107 mg, 1.06 mmol) was added to a solution containing 168 mg (0.244 mmol) of **4-3** and 150 mg (0.881 mmol) of 2,2-diethylglutaric anhydride in 3.0 mL of diethyl carbonate. After refluxing for 8 h, the solution was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The organic layer was dried on magnesium sulfate, filtered, and concentrated under reduced pressure. The crude oil was loaded onto a silica gel column and eluted with a 7:3 hexanes/ethyl acetate solution to give 166 mg (73% yield) of **4-11** as a light-yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 8.70 (br s, 1 H), 1.18 (d, $J = 7.0$ Hz, 1 H), 7.84 (s, 1 H), 7.79 (t, $J = 8.0$ Hz, 1 H), 6.75 (br d, $J = 7.0$ Hz, 1 H), 4.77 (br s, 1 H), 3.90 (br s, 1 H), 2.93 (t, $J = 12.5$ Hz, 1 H), 2.38 (t, $J = 7.0$ Hz, 1 H), 4.77 (br s, 1 H), 3.90 (br s, 1 H), 2.93 (t, $J = 12.5$ Hz, 1 H), 2.38 (t, $J = 7.0$ Hz, 1 H), 2.36 (t, $J = 7.5$ Hz, 1 H), 2.23–2.27 (m, 2 H), 1.49–1.74 (m, 7 H), 1.61 (q, $J = 7.5$ Hz, 4 H), 1.10 (br s, 9 H), 0.84 (t, $J = 7.5$ Hz, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 182.2, 172.2, 154.3, 144.0, 129.0, 128.3, 127.4, 127.2, 121.2 (q, $J = 292$ Hz) 120.9 (q, $J = 277$ Hz), 116.1, 80.2, 60.5, 48.8, 48.7, 29.5, 29.3, 28.3, 28.1, 27.8, 26.7, 26.5, 26.5, 24.5, 19.2, 14.2, 8.2, 8.2, 8.1; ESI-MS m/z 647 M^- .

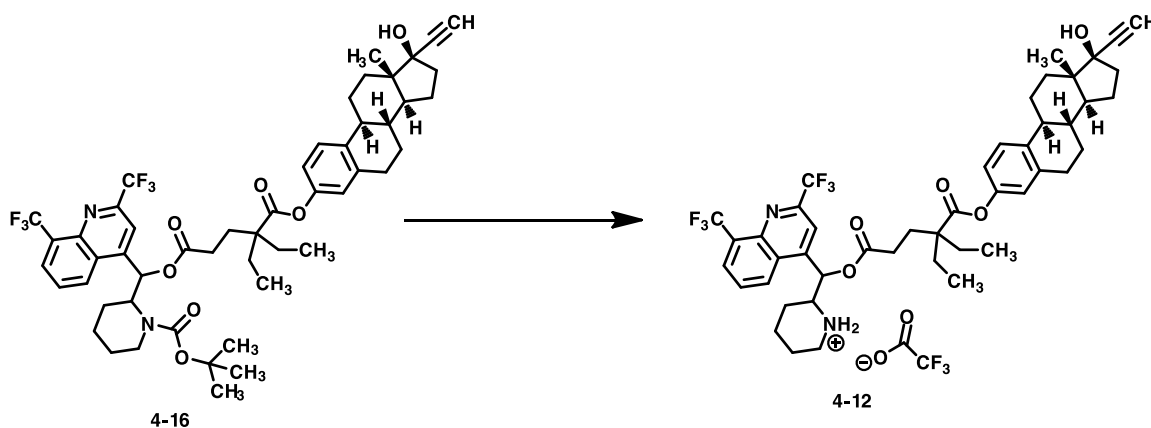


Compound 4-13. A solution containing 24.6 mg (0.038 mmol) of **4-11** in 0.4 mL of THF was cooled to 0 °C with an ice bath. HOBt (20.5 mg, 0.152 mmol) and EDCI (8.73 mg, 0.046 mmol) were added sequentially to the THF solution. The ice bath was removed after 5 min, and the solution was allowed to stir for 16 h. The reaction was concentrated, dissolved in 10 mL of ethyl acetate, and washed with 5% aq. citric acid (2x5 mL), sat. sodium bicarbonate (2x5 mL), and brine (5 mL). After drying over magnesium sulfate, the crude mixture was chromatographed on silica gel using 3:1 hexanes/ethyl acetate as the eluent to give 23 mg (81% yield) of **4-13** as a hygroscopic solid: ^1H NMR (400 MHz, CDCl_3) δ 8.71 (br s, 1 H), 8.17 (d, J = 6.8 Hz, 1 H), 8.08 (d, J = 8.4 Hz, 1 H), 7.84 (s, 1 H), 7.79 (t, J = 8.0 Hz, 1 H), 7.52 (?), 7.43 (?), 7.34 (d, J = 8.4 Hz, 1 H), 6.74 (br d, J = 7.6 Hz, 1 H), 4.79 (br s, 1 H), 3.98 (br s, 1 H), 2.92 (td, J = 9.6, 2.4 Hz, 1 H), 2.48–2.63 (m, 2 H), 2.10–2.22 (m, 2 H), 1.90 (q, J = 7.6 Hz, 2 H), 1.88 (q, J = 7.2 Hz, 2 H), 1.41–1.73 (m, 6 H), 1.08 (br s, 9 H), 1.04 (t, J = 7.6 Hz, 3 H), 1.01 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 171.6, 144.0, 143.6, 129.0,

128.8, 128.6, 128.3, 127.5, 127.2, 124.8, 121.7 (q, J = 288 Hz) 121.1 (q, J = 275 Hz), 120.7, 116.2, 107.9, 80.2, 49.6, 29.3, 28.4, 27.8, 26.8, 26.5, 24.5, 19.2, 8.3, 8.2; ESI-MS m/z 766 MH⁺.



Compound 4-16. A solution containing 17.4 mg (0.023) of **4-13** in 0.45 mL of tetrahydrofuran was cooled in a 0 °C ice bath. BEMP (6.31 mg, 0.023 mmol) was added to the cooled solution, followed by 6.95 mg (0.023 mL) of ethynyl estradiol. After 12 h of stirring at room temperature, the reaction was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate, and concentrated under reduced pressure. The crude **4-16** was used in the next step without further purification; ESI-MS *m/z*



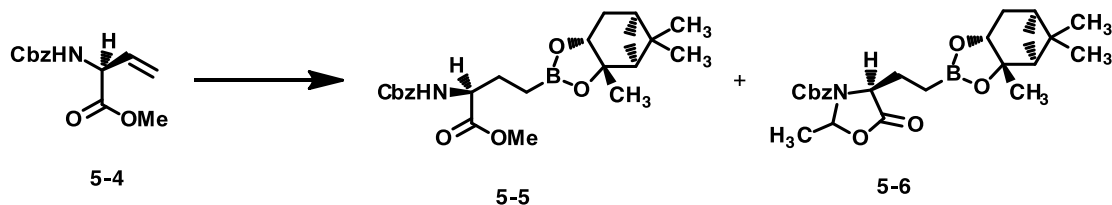
Compound 4-12. Crude ester **4-16** (13.6 mg, 0.015 mmol) was dissolved in 0.08 mL dichloromethane, and the solution was cooled in a 0 °C ice bath. Trifluoroacetic acid (0.05 mL) was added to the cooled solution. After 0.5 h of stirring at 0 °C, the reaction was concentrated and chromatographed using 95:4:1 dichloromethane/isopropanol/TFA as the eluent to produce 13.6 mg of **4-12** as a hygroscopic solid: ¹H NMR (500 MHz, CD₃OD) δ 8.53 (t, J = 8.0 Hz, 1 H), 8.29 (br d, J = 5.5 Hz, 1 H), 7.91–7.94 (m, 1 H), 7.90 (d, J = 3.0 Hz, 1 H), 7.17 (dd, J = 8.5, 4.5 Hz, 1 H), 6.93 (s, 1 H), 6.68 (dd, J = 8.0, 20.0 Hz, 1 H), 6.62 (s, 1 H), 3.67 (d, J = 10.5 Hz, 1 H), 3.38 (d, J = 12 Hz, 1 H), 3.08 (t, J = 12 Hz, 1 H), 2.79 (s, 1 H), 2.75–2.78 (m, 2 H), 2.64–2.71 (m, 2 H), 2.23–2.33 (m, 2 H), 2.11–2.16 (m, 1 H), 2.07 (br s, 2 H), 1.91–2.00 (m, 2 H), 1.73–1.86 (m, 6 H), 1.77 (q, J = 7.0 Hz, 4 H), 1.62–1.71 (m, 3 H), 1.27–1.41 (m, 8 H), 0.92 (t, J = 7.0 Hz, 6 H), 0.85 (s, 3 H); ¹³C NMR (125 MHz, CD₃OD) δ 176.9, 173.5, 149.5, 145.4, 139.3, 139.2, 139.1, 139.0, 130.9, 129.7, 128.3, 127.3, 122.2 (q, J = 288 Hz), 119.3 (q, J = 279 Hz),

116.3, 88.5, 80.2, 74.6, 71.2, 71.1, 59.8, 50.5, 50.2, 48.0, 46.7, 44.9, 40.3, 39.7, 33.7, 30.6, 30.3, 30.0, 28.1, 27.8, 27.3, 23.6, 22.8, 22.6, 13.3, 8.7; ESI-MS m/z 827 MH^+ .

Hydrolysis study on **4-12**

Estradiol conjugate **4-12** (2.2 mg, 2.4 μmol) was dissolved in 4.8 mL of a 9:4 ethanol/0.05 M aqueous phosphate buffer (pH 7.4) mixture, and the solution was shaken in a 37 °C incubator for 30 days. Estradiol release was quantified by adding 10 μL of a 0.10 M solution of butylated hydroxytoluene (BHT) in deuteriochloroform as an internal standard, then comparing integrals of ^1H NMR signals corresponding to the steroid and the internal standard. The spectrum showed ~6% EE release after 30 days.

E5. Experimental Procedures for Chapter 5

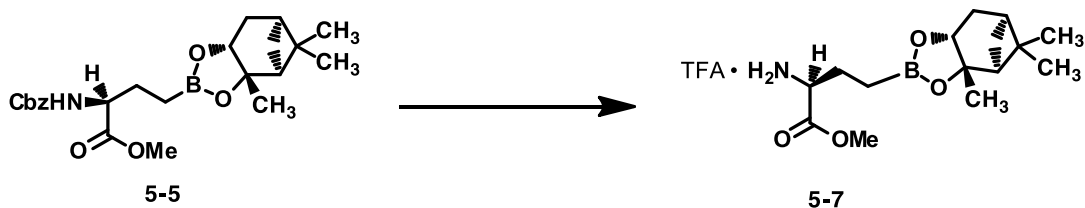


Hydroboration of 5-4. A solution containing 2.22 g (7.74 mmol) of diisopinocampheylborane (ref: Petter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: New York, 1988; p. 427) in 2.6 mL of THF was treated dropwise at 0 °C with 1.02 g (3.87 mmol) of **5-4** in 6.5 mL of THF. After 24 h of stirring at room temperature, the mixture was treated at 0 °C with 4.34 mL (77.4 mmol) of acetaldehyde. After 10 h of stirring at room temperature, the mixture was treated with 5 mL of water and concentrated. The residue was then dissolved with 26 mL of diethyl ether and treated with 659 mg (3.87 mmol) of (+)-pinanediol and a small amount of magnesium sulfate. After stirring for 4 h, the reaction was concentrated and chromatographed through silica gel using 4:1 hexanes/diethyl ether as the eluent to produce 847 mg (51%) of **5-5** and 375 mg (22%) of **5-6**, both as colorless oils.

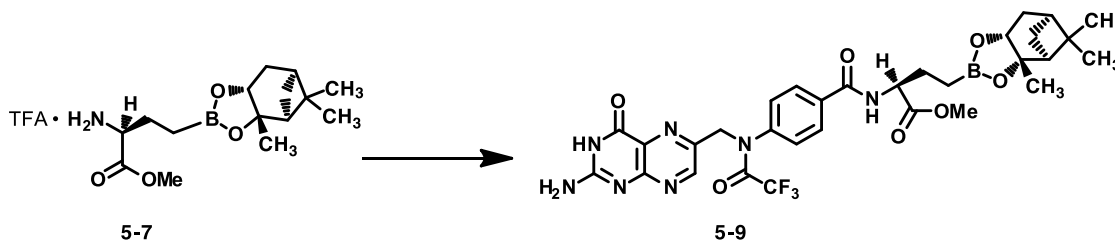
Compound 5-5. R_f 0.50 (4:1 hexanes/ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ 7.31–7.38 (m, 5 H), 5.53 (d, J = 5.5 Hz, 1 H), 5.11 (d, J = 12.5 Hz, 1 H), 5.07 (d, J = 12.5 Hz, 1 H), 4.33 (td, J = 8.0, 5.5 Hz, 1 H), 4.20 (d, J = 8.5 Hz, 1 H),

3.72 (s, 3 H). 2.36–2.30 (m, 1 H), 2.16 (dt, $J = 11.0, 5.5$ Hz, 1 H), 2.00 (t, $J = 5.5$ Hz, 1 H), 1.95–1.99 (m, 1 H), 1.77–1.84 (m, 3 H), 1.35 (s, 3 H), 1.25 (s, 3 H), 1.06 (d, $J = 11.0$ Hz, 1 H), 0.81 (s, 3 H), 0.80–0.89 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.2, 156.2, 136.5, 128.6, 128.3, 86.0, 78.0, 67.1, 55.7, 52.4, 51.4, 39.6, 38.3, 35.5, 28.7, 27.2, 26.6, 24.1; ESI-MS m/z 452 MNa^+ , 881 (2xM) Na^+ .

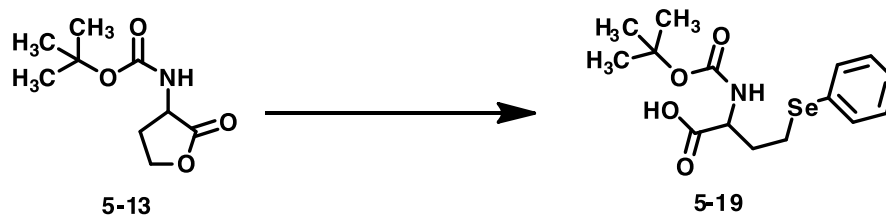
Compound 5-6. R_f 0.65 (4:1 hexanes/ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ 7.33–7.37 (m, 5 H), 5.72 (app d, $J = 5.0$ Hz, 1 H), 5.21 (d, $J = 12.0$ Hz, 1 H), 5.12 (d, $J = 12.0$ Hz, 1 H), 4.31 (br s, 1 H), 4.22 (dd, $J = 8.5, 1.5$ Hz, 1 H), 2.32 (dt, $J = 9.0, 2.5$ Hz, 1 H), 2.29 (dt, $J = 9.0, 2.5$ Hz, 1 H), 2.19 (dtd, $J = 11.0, 6.0, 2.0$ Hz, 1 H), 2.02–2.06 (m, 1 H), 2.01 (t, $J = 5.5$ Hz, 1 H), 1.88–1.91 (m, 1 H), 1.81 (br d, $J = 14.5$ Hz, 1 H), 1.60–1.68 (m, 1 H), 1.37 (s, 3 H), 1.28 (s, 3 H), 0.87–1.21 (m, 5 H), 0.83 (s, 3 H); ESI-MS m/z 464 MNa^+ .



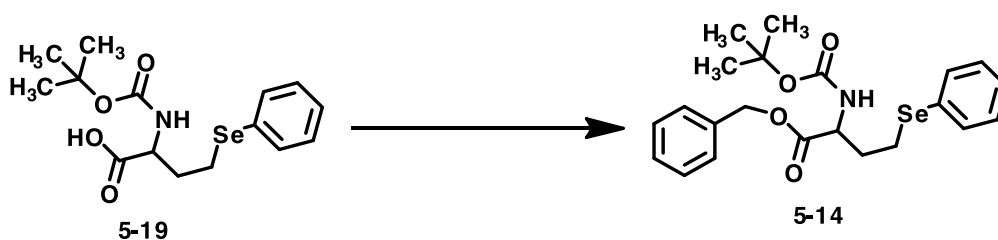
Compound 5-7. A solution containing 68.4 mg (0.159 mmol) of **5-5** in 1.6 mL of methanol was treated with 20 mg of 20% palladium hydroxide on charcoal and 14 μ L (0.20 mmol) of trifluoroacetic acid. The mixture was then purged 3 times with hydrogen gas and then stirred under positive hydrogen atmosphere for 2 h. The mixture was then filtered through Celite and concentrated to give 65 mg (100%) of **5-7** as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 8.42 (br s, 1 H), 4.47 (dd, $J = 8.5, 1.5$ Hz, 1 H), 4.09 (t, $J = 5.5$ Hz, 1 H), 3.78 (s, 3 H), 2.31 (ddt, $J = 14.5, 8.5, 2.0$ Hz, 1 H), 2.21 (dtd, $J = 11.0, 6.0, 2.0$ Hz, 1 H), 2.09 (d, $J = 7.0$ Hz, 1 H), 2.06 (d, $J = 7.0$ Hz, 1 H), 2.02 (t, $J = 6.0$ Hz, 1 H), 1.88–1.91 (m, 1 H), 1.81 (dt, $J = 14.5, 2.0$ Hz, 1 H), 1.37 (s, 3 H), 1.27 (s, 3 H), 1.04 (d, $J = 11$ Hz, 1 H), 0.95 (td, $J = 8.5, 2.0$ Hz, 2 H), 0.82 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.2, 86.6, 78.3, 54.5, 53.3, 51.3, 39.6, 38.3, 35.4, 28.6, 27.2, 26.5, 25.1, 24.1; ESI-MS m/z 296 MH^+ .



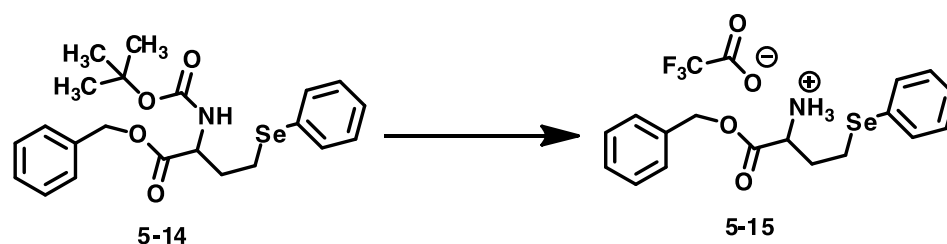
Compound 5-9. A solution containing 26 mg (0.052 mmol) of **5-8** and 21 mg (0.052 mmol) of **5-7** in 0.5 mL of 1:1 DMF/dichloromethane was treated at 0 °C with 7 μ L (0.057 mmol) of 2,6-lutidine, 11 mg (0.057 mmol) of EDCI, and 1.3 mg (10 μ mol) of DMAP. After stirring at room temperature for 24 h, the mixture was concentrated and chromatographed through silica gel using 23:2 dichloromethane/methanol as the eluent to give 8.2 mg (23%) of **5-9** as a light-yellow powder: R_f 0.38 (9:1 dichloromethane/methanol); ^1H NMR (500 MHz, CD_3OD) δ 8.68 (s, 1 H), 7.88 (d, J = 8.5 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 5.18 (s, 1 H), 4.58 (dd, J = 9.0, 5.0 Hz, 1 H), 4.28 (dd, J = 9.0, 2.0 Hz, 1 H), 3.73 (s, 3 H), 2.34 (ddt, J = 14.5, 8.5, 2.0 Hz, 1 H), 2.21 (dtd, J = 11.0, 6.0, 2.0 Hz, 1 H), 2.02–2.08 (m, 2 H), 1.99 (t, J = 5.5 Hz, 1 H), 1.85–1.95 (m, 2 H), 1.79 (ddd, J = 14.5, 2.0, 1.5 Hz, 1 H), 1.34 (s, 3 H), 1.28 (s, 3 H), 1.11 (d, J = 11.0 Hz, 1 H), 0.89–0.93 (m, 2 H), 0.85 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.4, 169.5, 130.4, 129.9, 129.7, 87.2, 79.2, 56.3, 52.8, 41.0, 39.4, 36.5, 29.2, 27.6, 27.4, 27.0, 24.4; ESI-MS m/z 708 MNa^+ .



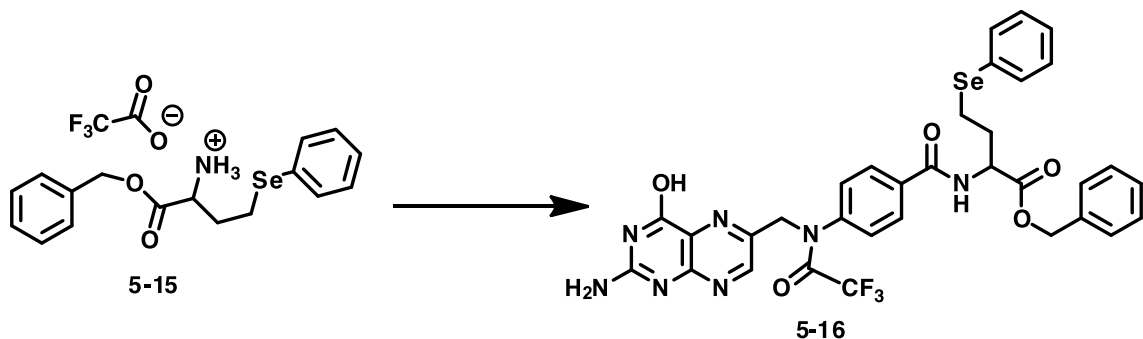
Compound 5-19. A solution containing 61.5 mg (0.197 mmol) of diphenyl diselenide and 17.4 mg (0.459 mmol) of sodium borohydride in 1.0 mL of DMF was treated at 85 °C with 66.0 mg (0.328 mmol) of **5-13**. After 3 h of stirring at 100 °C, the mixture was cooled to room temperature, treated with methanol, and concentrated to give crude **5-19** to be used in the next step without further purification: ESI-MS m/z 358 M^- .



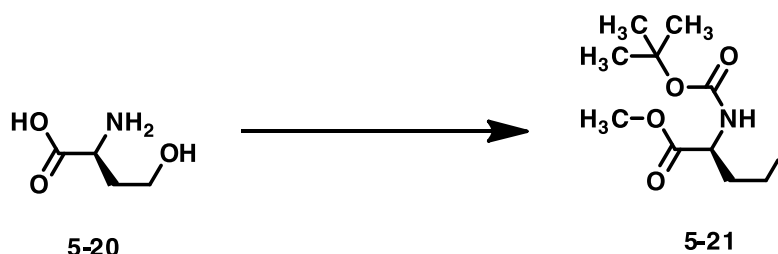
Compound 5-14. A solution containing 80.8 mg of crude **5-19**, 49 μL (0.473 mmol) of benzyl alcohol, and 5.5 mg (0.045 mmol) of DMAP in 2.3 mL of dichloromethane was treated at 0 $^{\circ}\text{C}$ with 45.2 mg (0.236 mmol) of EDCI. After stirring at room temperature for 16 h, the mixture was washed with water and brine, then concentrated and chromatographed through silica gel using 9:1 hexanes/ethyl acetate as the eluent to give 96 mg (65% over 2 steps) of **5-14** as a colorless oil: R_f (); ^1H NMR (500 MHz, CDCl_3) δ 7.43–7.48 (m, 2 H), 7.29–7.37 (m, 6 H), 7.21–7.26 (m, 2 H), 5.19 (d, $J = 12.0$ Hz, 1 H), 5.13 (d, $J = 12.0$ Hz, 1 H), 4.43–4.52 (m, 1 H), 2.81–2.90 (m, 2 H), 2.14–2.28 (m, 1 H), 1.95–2.07 (m, 1 H), 1.44 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.9, 155.2, 135.2, 132.9, 128.5, 128.4, 128.2, 127.1, 80.0, 67.1, 53.6, 33.3, 28.2, 23.0; ESI-MS m/z 472 MNa^+ .



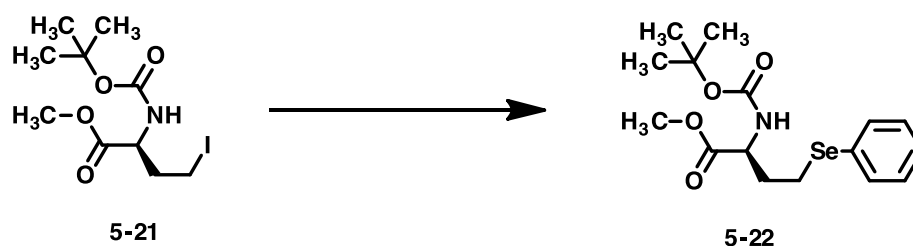
Compound 5-15. A solution containing 59.5 mg (0.133 mmol) of **5-14** in 0.7 mL of dichloromethane was treated with 0.47 mL of trifluoroacetic acid. After stirring at room temperature for 0.5 h, the mixture was concentrated to give 62 mg (100%) of **5-15** as a light-yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 8.41 (s, 1 H), 7.41 (d, J = 7.5 Hz, 2 H), 7.31–7.33 (m, 3 H), 7.144–7.24 (m, 5 H), 5.15 (d, J = 12.0 Hz, 1 H), 5.09 (d, J = 12.0 Hz, 1 H), 4.22 (br s, 1 H), 2.87–2.98 (m, 2 H), 2.26 (d, J = 25.5 Hz, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.2, 134.2, 133.3, 129.1, 128.8, 128.7, 128.5, 128.4, 127.4, 68.5, 52.8, 30.7, 22.1; ESI-MS m/z 351 MH^+ .



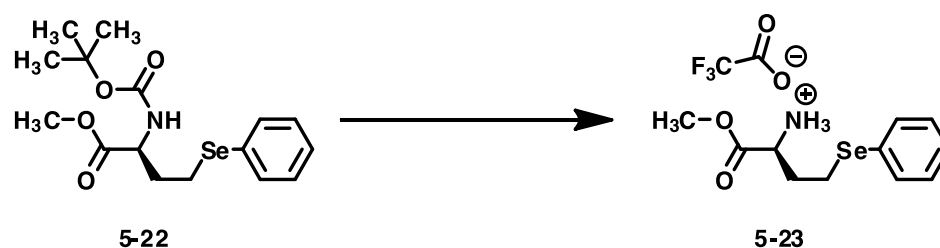
Compound 5-16. A solution containing 36 mg (0.087 mmol) of **5-8**, 40 mg (0.087 mmol) of **5-15**, and 35 μL (0.20 mmol) of diisopropylethylamine in 0.8 mL of 4:1 THF/DMF was treated at 0 $^{\circ}\text{C}$ with 17 mg (0.091 mmol) of EDCI, and 0.21 mg (2 μmol) of DMAP. After stirring at room temperature for 24 h, the mixture was concentrated and chromatographed through silica gel using 6:1:1:1 ethyl acetate/acetonitrile/methanol/water as the eluent to give 8.4 mg (15%) of **5-9** as a yellow powder: R_f 0.22 (6:1:1:1 ethyl acetate/acetonitrile/methanol/water); ^1H NMR (500 MHz, 1:1 DMSO- d_6 /CD $_3$ OD) δ 8.70 (s, 1 H), 7.97 (d, J = 8.5 Hz, 2 H), 7.68 (d, J = 8.5 Hz, 2 H), 7.55–7.57 (m, 2 H), 7.40 (app s, 5 H), 7.32–7.34 (m, 3 H), 5.26 (d, J = 12.5 Hz, 1 H), 5.24 (s, 2 H), 5.21 (d, J = 12.5 Hz, 1 H), 4.82 (dd, J = 8.5, 5.5 Hz, 1 H), 3.05–3.18 (m, 2 H), 2.26–2.32 (m, 2 H); ESI-MS m/z 762 MNa^+ .



Compound 5-21. A solution containing 496 mg (4.17 mmol) of **5-20** in 5.0 mL of acetonitrile was treated with 5.0 mL of 0.84 N aqueous sodium hydroxide and 1.05 mL (4.58 mmol) of Boc anhydride. After stirring for 8 h, the mixture was concentrated and triturated several times with diethyl ether. The residue was then dissolved in DMF and treated with 290 μ L (4.58 mmol) of methyl iodide. After 2 h of stirring, the solution was concentrated and dissolved in a minimal amount of dichloromethane, then transferred via cannula to a cooled solution containing 1.93 g (7.34 mmol) of triphenylphosphine and 1.96 g (7.71 mmol) of iodine in 18 mL of dichloromethane. The mixture was subsequently treated with 500 mg (7.34 mmol) of imidazole and stirred for 16 h. Afterwards, the mixture was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, and concentrated under reduced pressure. Silica gel chromatography using 17:3 hexanes/ethyl acetate as the eluent produced 643 mg (45% over 3 steps) of **5-21** as a colorless oil: R_f 0.45 (3:1 hexanes/ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ 5.19 (d, J = 8.0 Hz, 1 H), 4.29 (d, J = 6.0 Hz, 1 H), 3.70 (s, 3 H), 3.13 (t, J = 8.0 Hz, 1 H), 2.31–2.39 (m, 1 H), 2.10–2.18 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.9, 155.2, 80.0, 54.1, 52.4, 36.8, 28.2; ESI-MS m/z 366 MNa^+ .

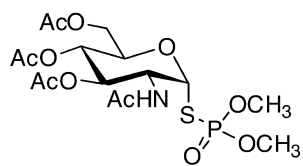
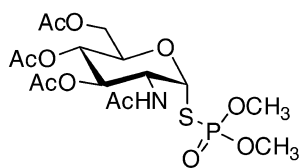
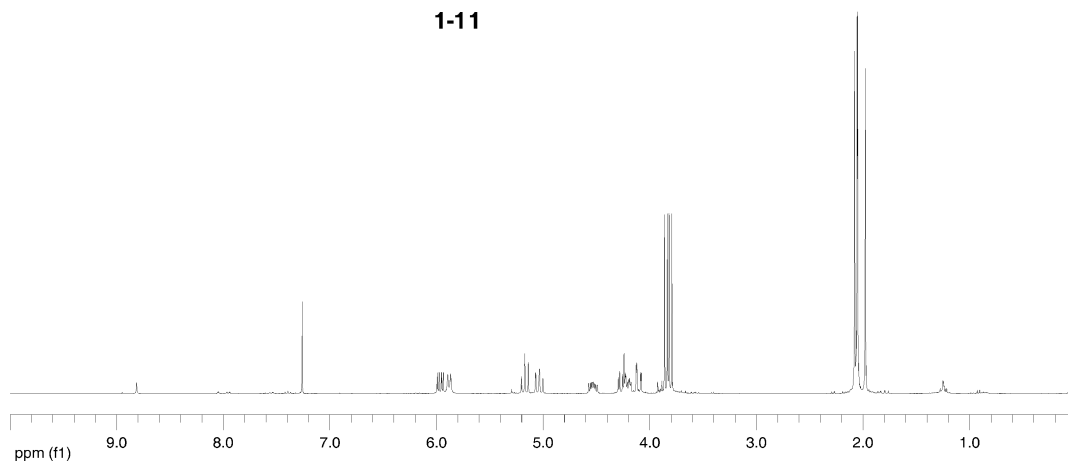
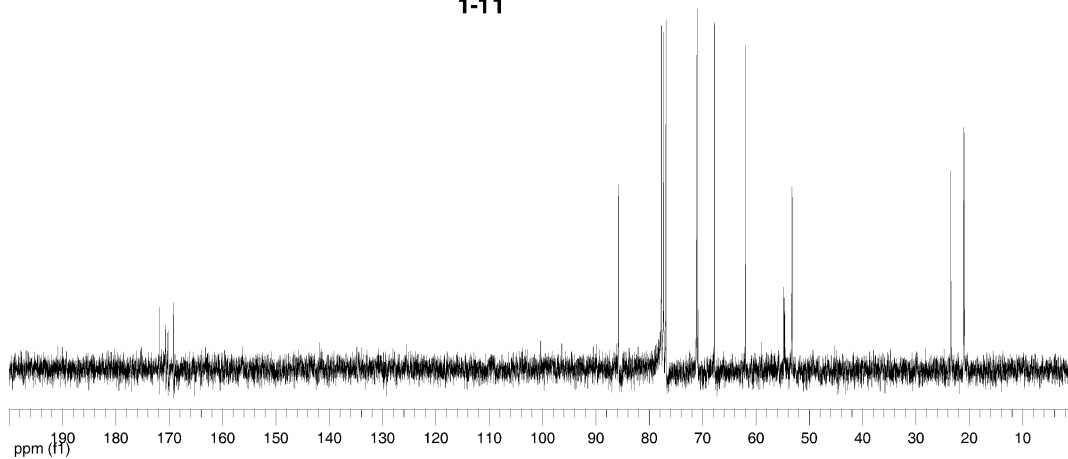


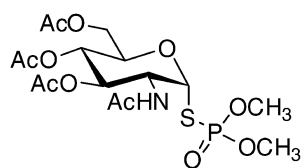
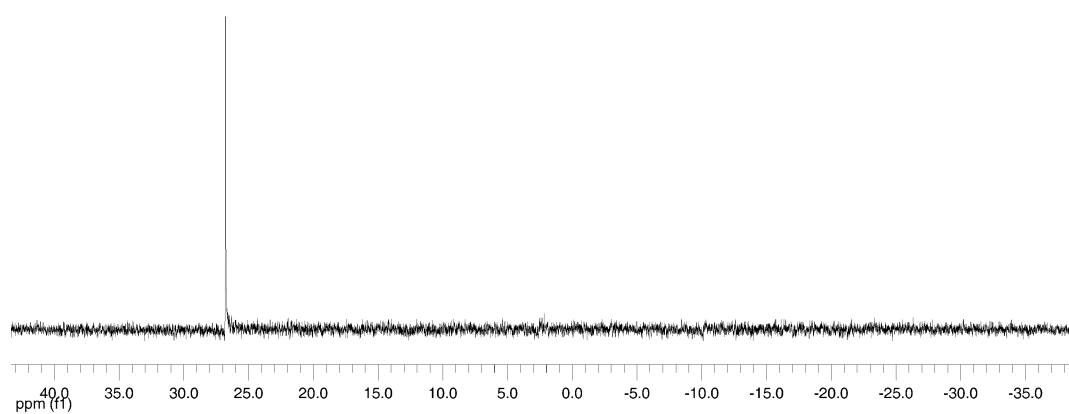
Compound 5-22. A solution containing 106 mg (0.310 mmol) of **5-21** in 0.7 mL of THF was sequentially treated with 53.2 mg (0.171 mmol) of diphenyl diselenide, 2.1 mL of methanol, and 13.2 mg (0.347 mmol) of sodium borohydride. After stirring for 1 h, the mixture was concentrated and chromatographed through silica gel using 17:3 hexanes/ethyl acetate as the eluent to give 109 mg (94%) of **5-22** as a light-yellow oil: R_f 0.41 (3:1 hexanes/ethyl acetate); ^1H NMR (500 MHz, CDCl_3) δ 7.46–7.49 (m, 2 H), 7.23–7.27 (m, 3 H), 5.09 (d, J = 6.5 Hz, 1 H), 4.09 (d, J = 4.5 Hz, 1 H), 3.71 (s, 3 H), 2.89 (d, J = 9.0 Hz, 1 H), 2.89 (t, J = 8.0 Hz, 1 H), 2.16–2.23 (m, 1 H), 1.95–2.03 (m, 1 H), 1.43 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.5, 155.2, 132.8, 129.6, 129.1, 127.1, 80.0, 53.5, 52.3, 33.4, 28.2, 23.0; ^{77}Se NMR (95 MHz, CDCl_3) δ 302.1; ESI-MS m/z 373 MNa^+ .

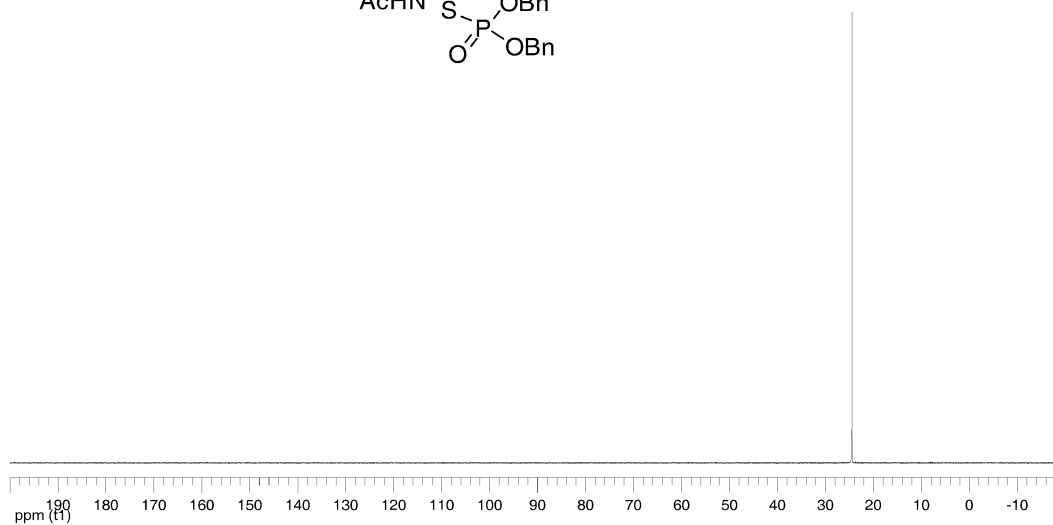
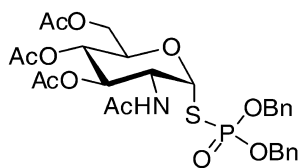
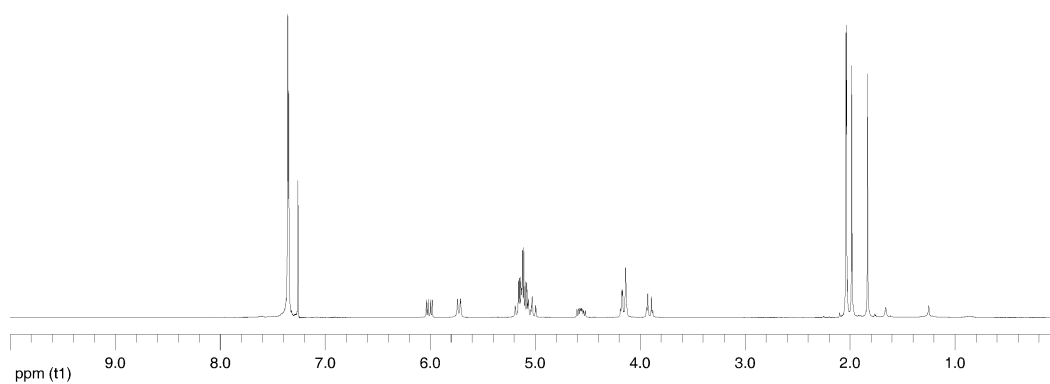
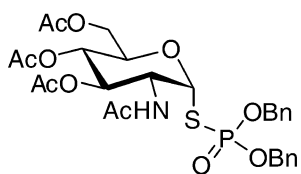


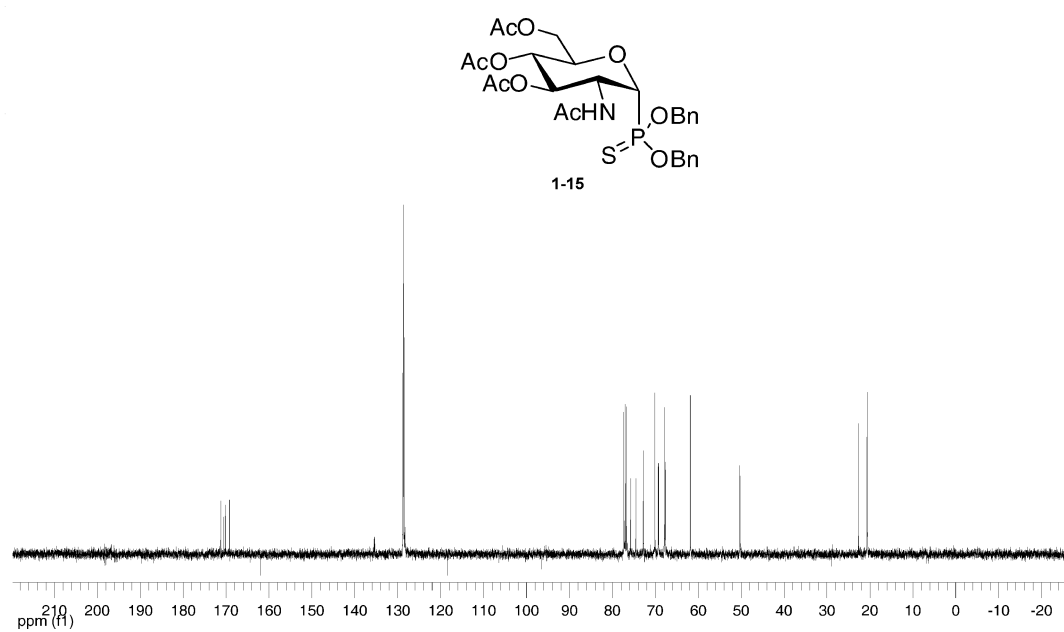
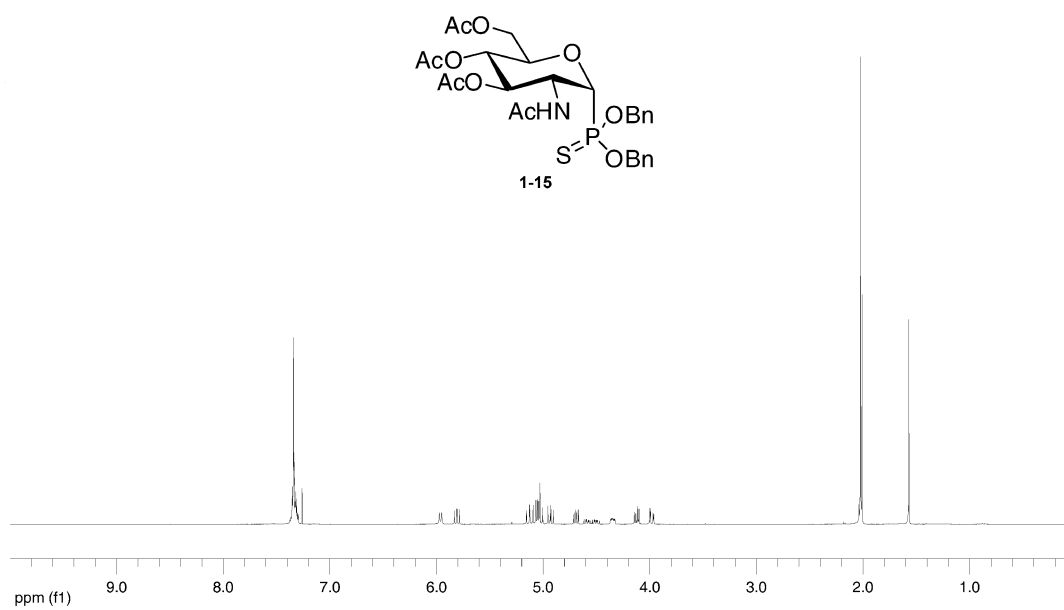
Compound 5-23. A solution containing 95.4 mg (0.256 mmol) of **5-22** in 1.0 mL of dichloromethane was treated with 0.67 mL of trifluoroacetic acid. After stirring at room temperature for 0.5 h, the mixture was concentrated to give 99 mg (100%) of **5-23** as a light-yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 8.22 (br s, 1 H), 7.47–7.49 (m, 2 H), 7.24–7.28 (m, 3 H), 4.25 (t, J = 6.5 Hz, 1 H), 3.74 (s, 3 H), 2.97 (t, J = 7.5 Hz, 2 H), 2.21–2.33 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.0, 133.6, 129.5, 128.5, 127.9, 53.8, 53.3, 30.7, 22.4; ^{77}Se NMR (95 MHz, CDCl_3) δ 296.9; ESI-MS m/z 275 MH^+ .

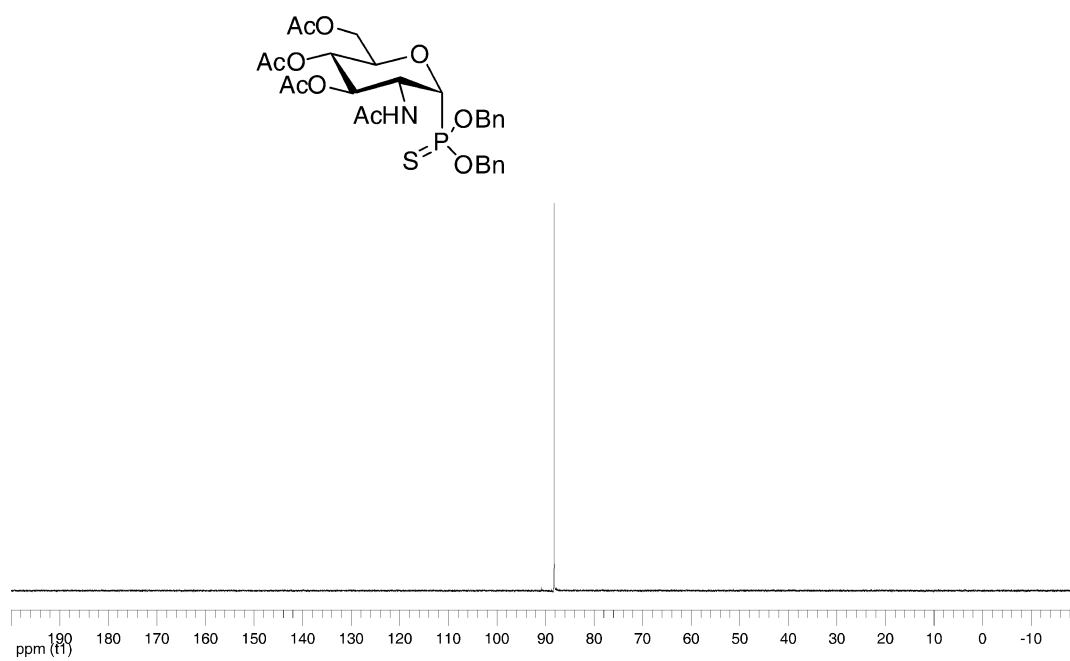
Appendix

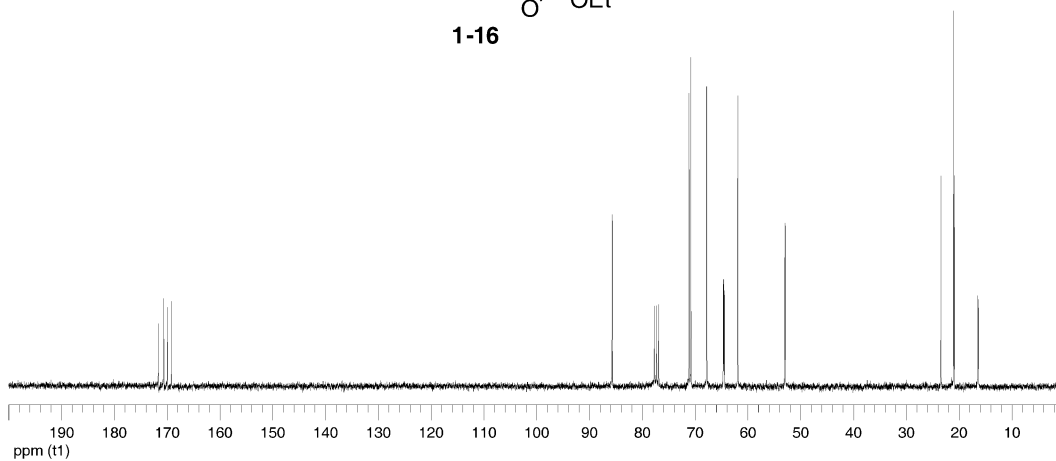
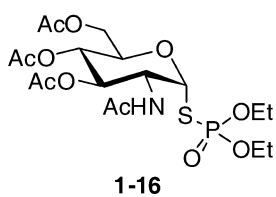
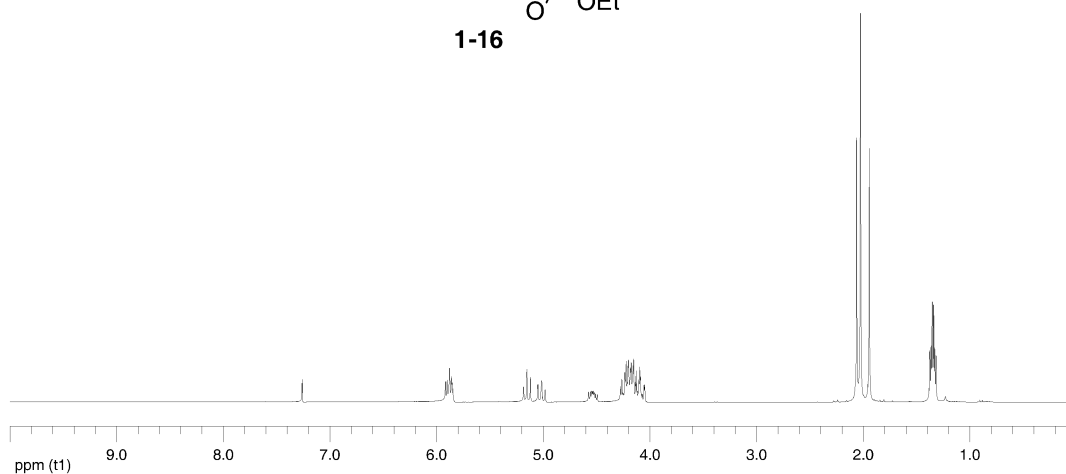
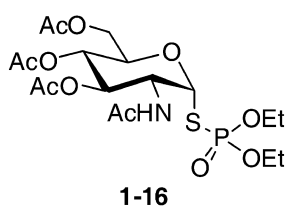
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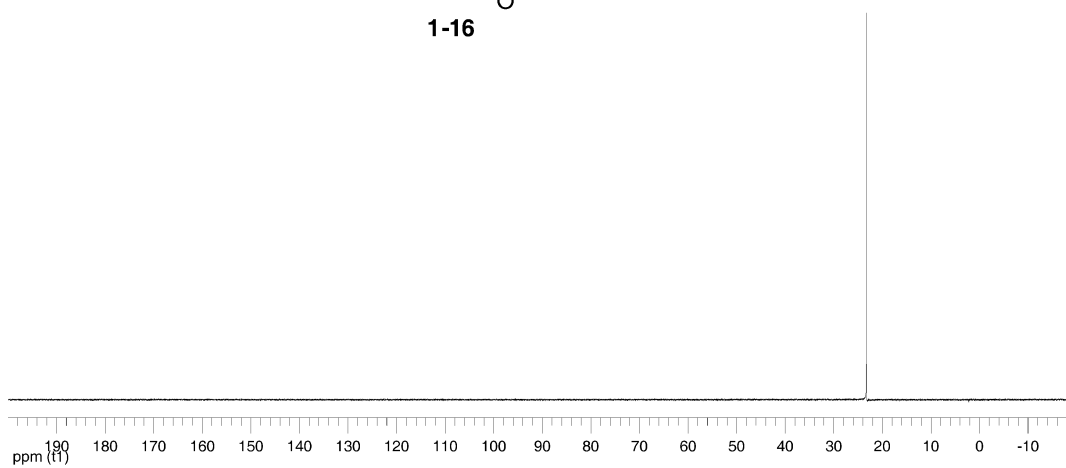
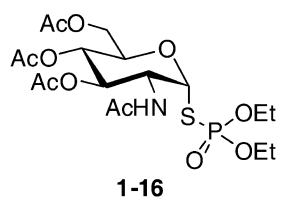
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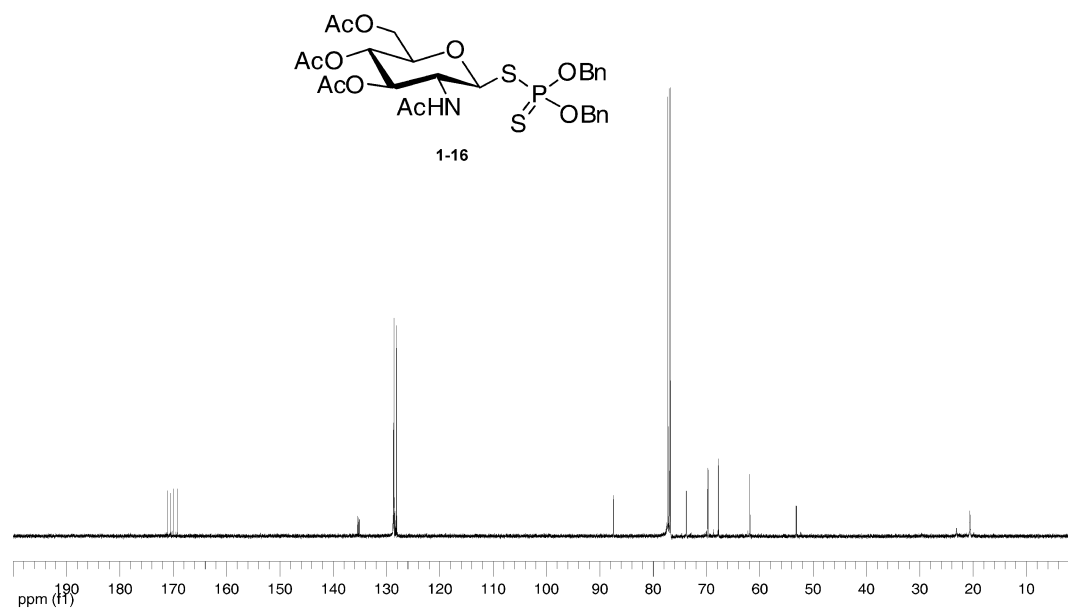
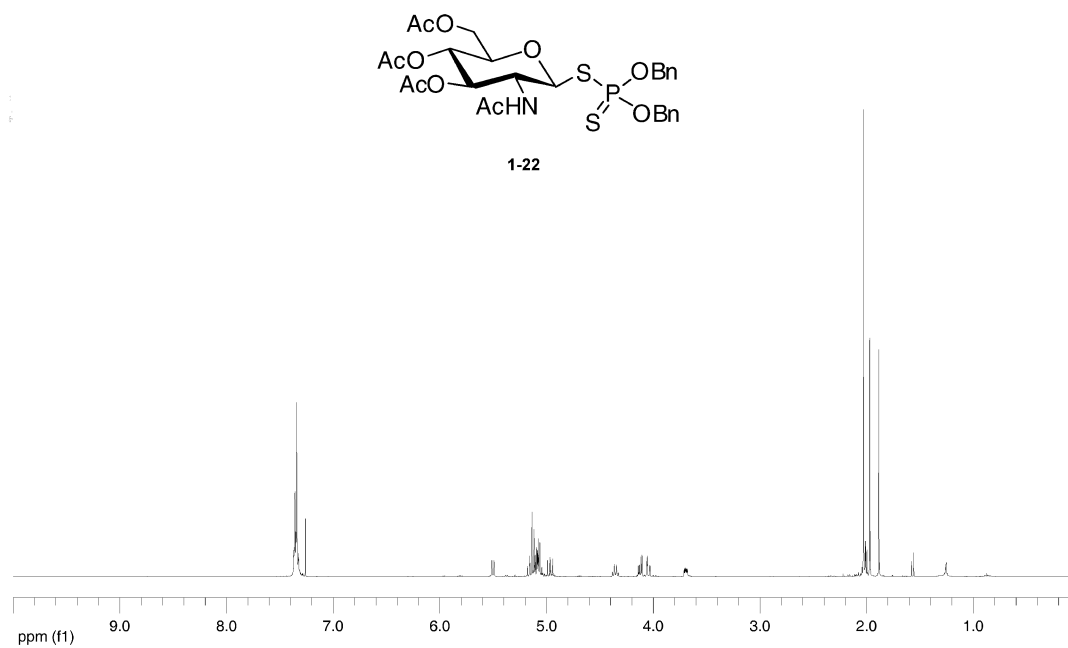


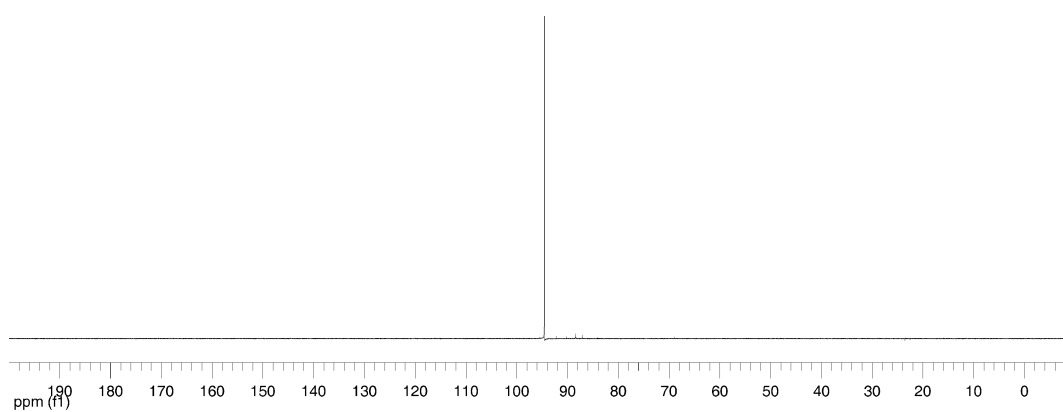
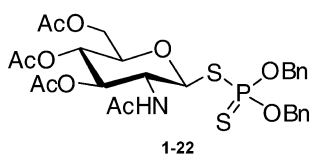


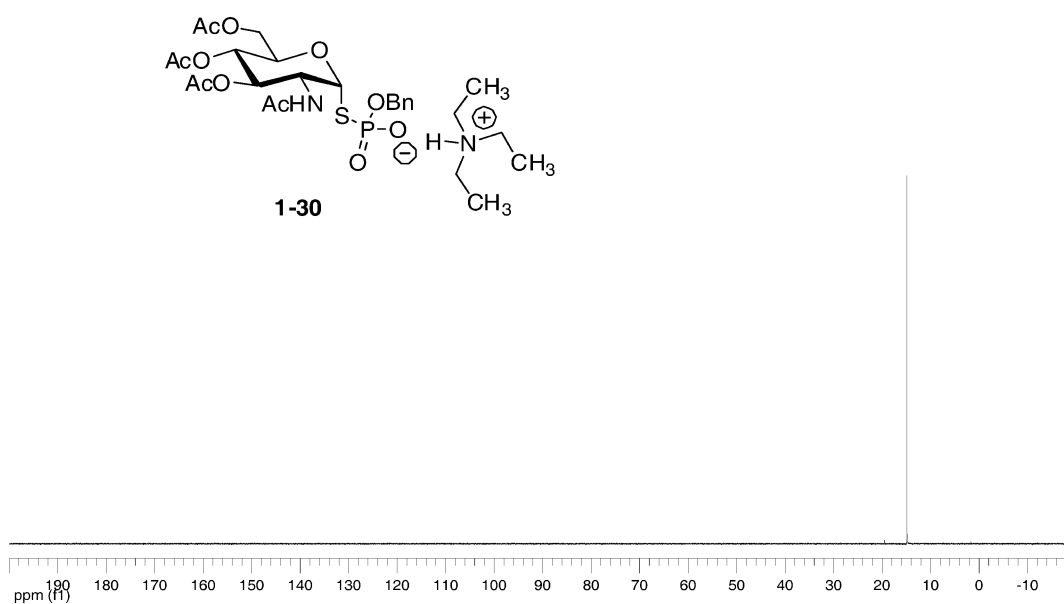
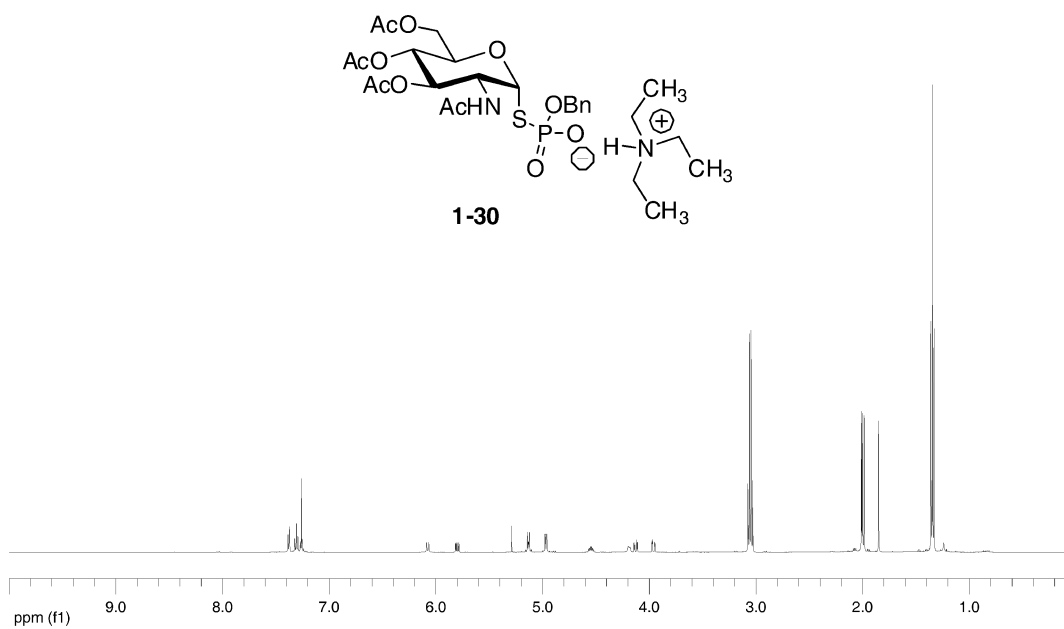


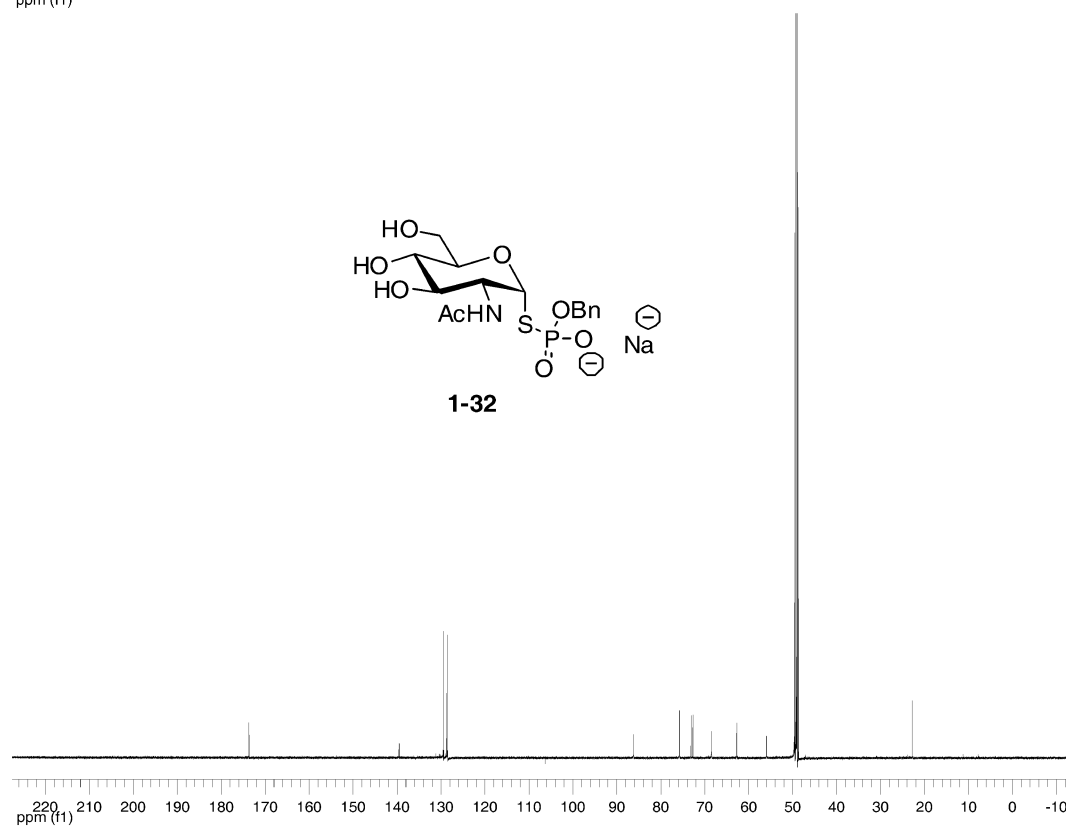
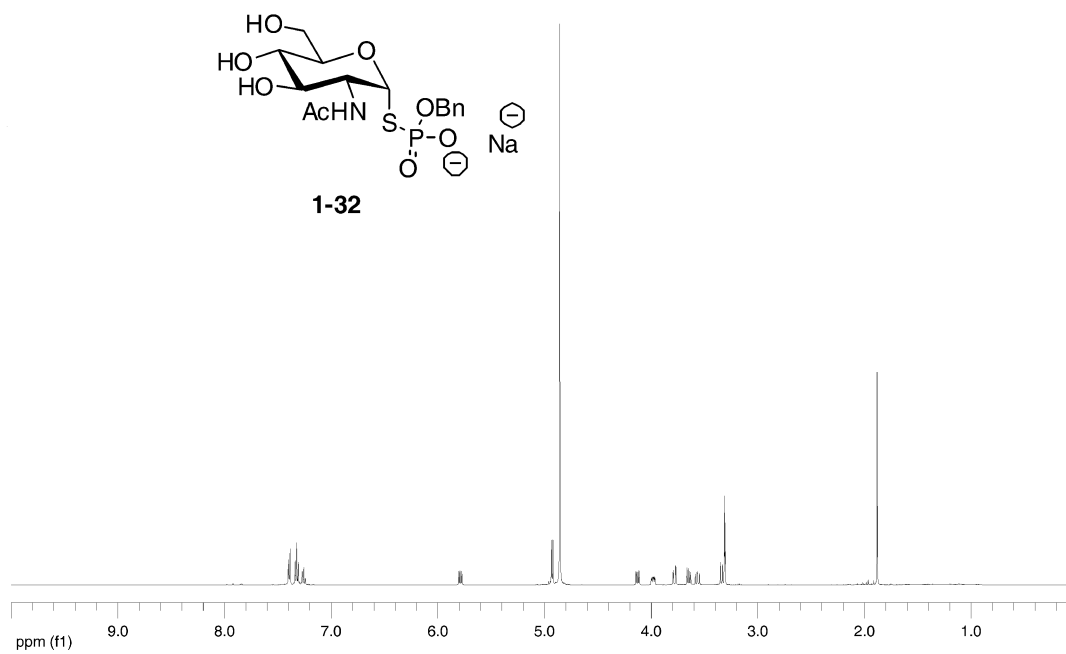


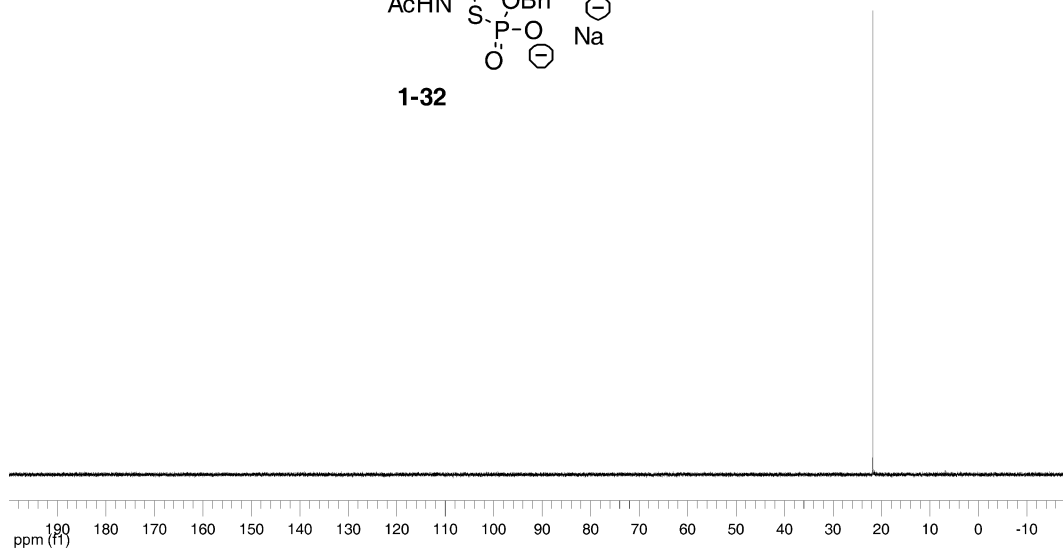
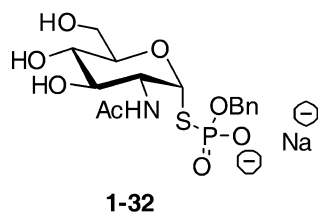


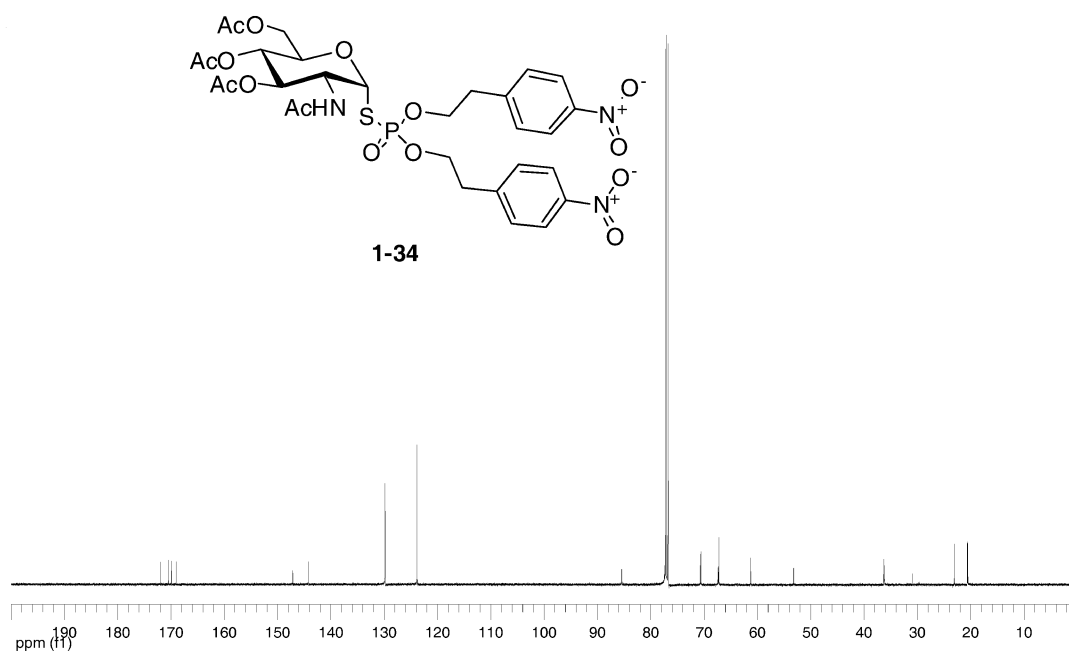
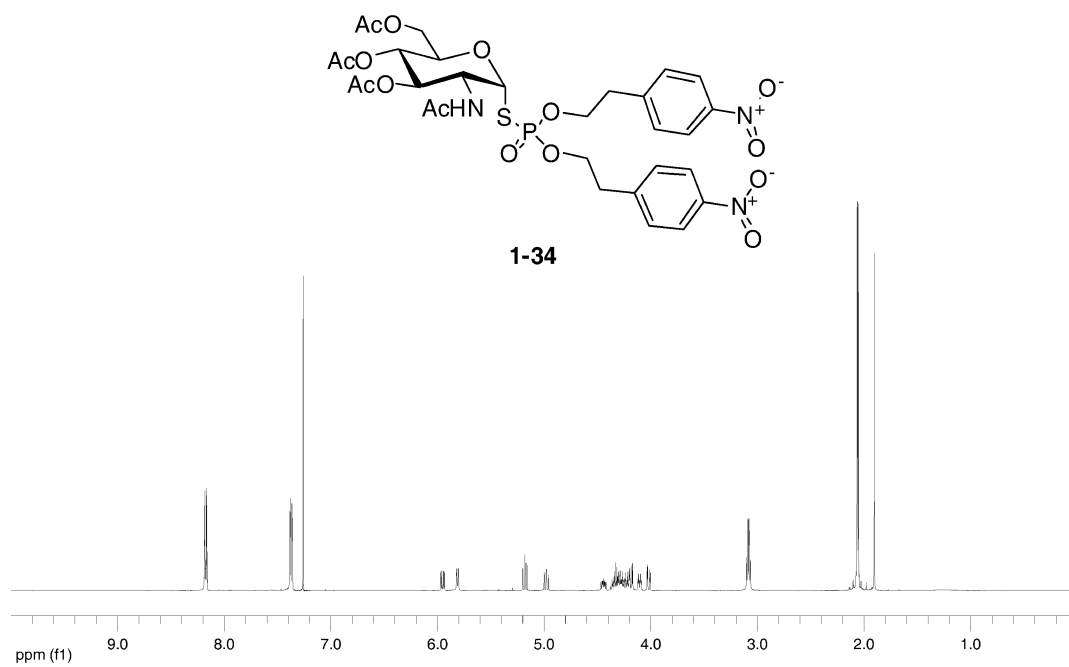


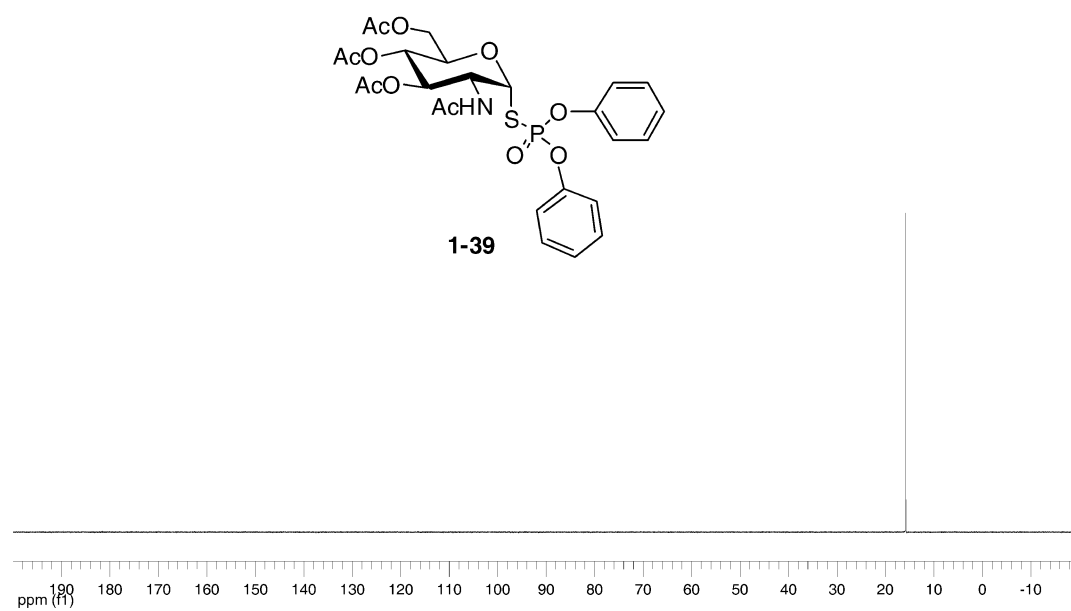
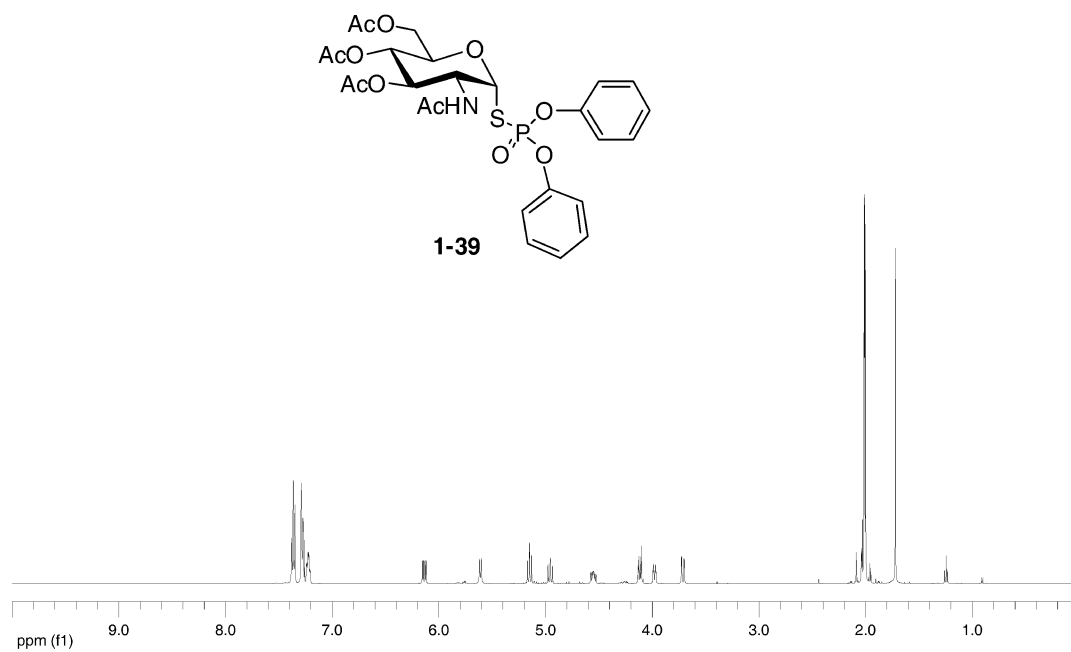


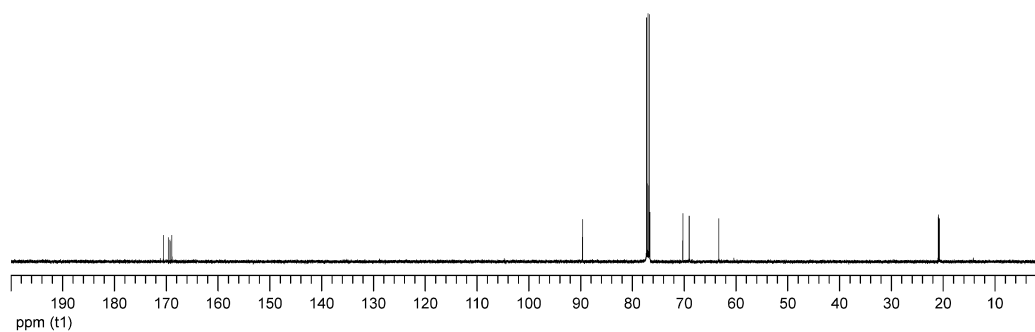
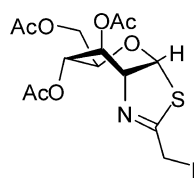
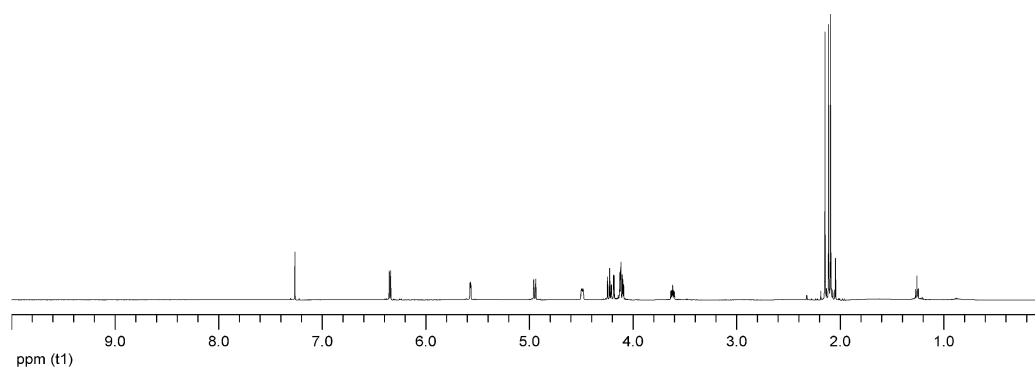
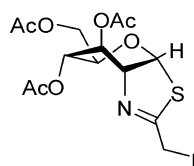


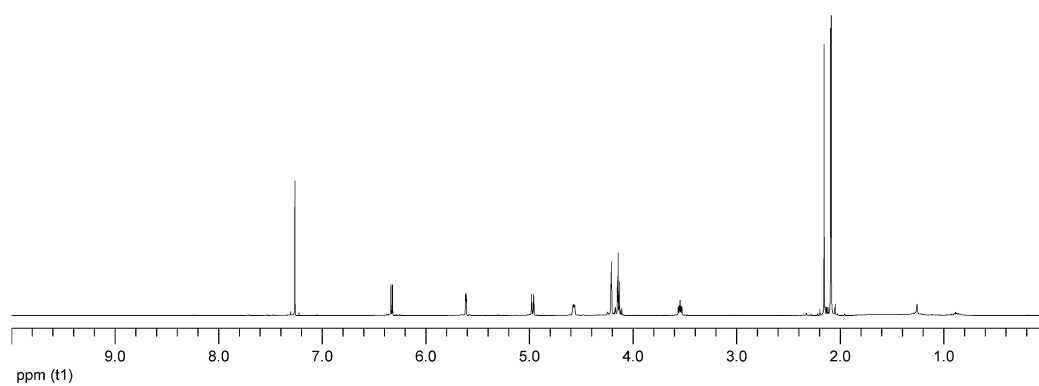
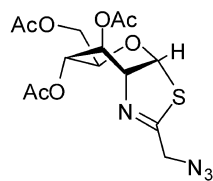


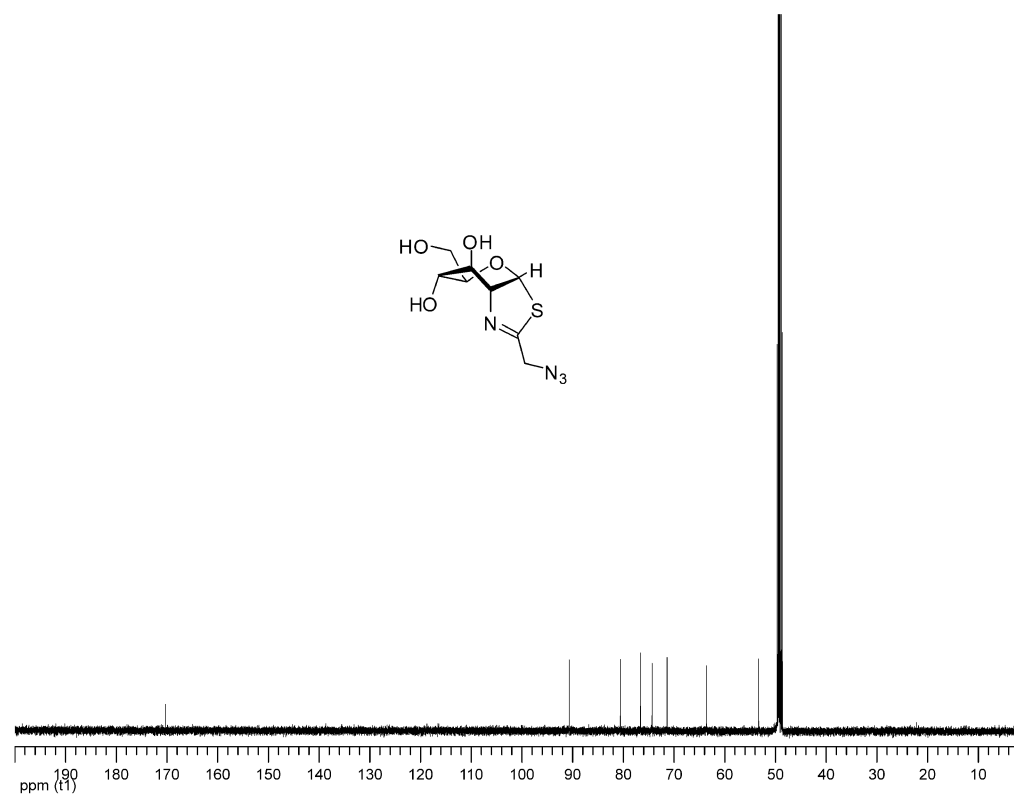
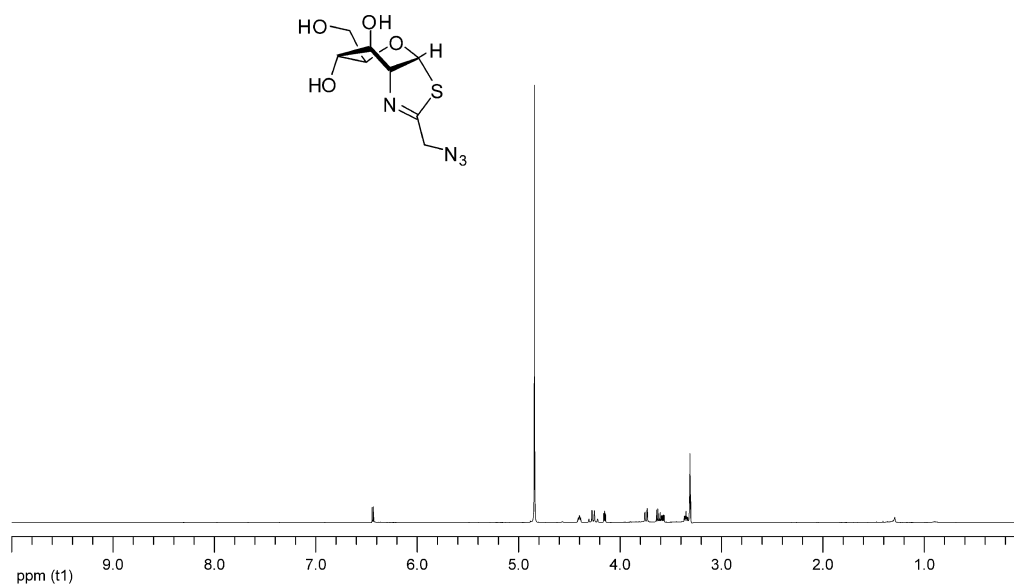


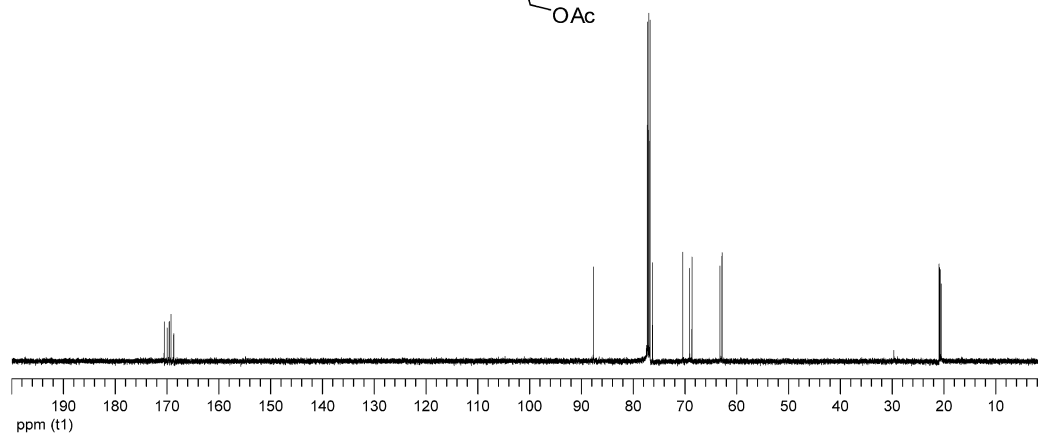
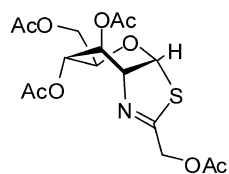
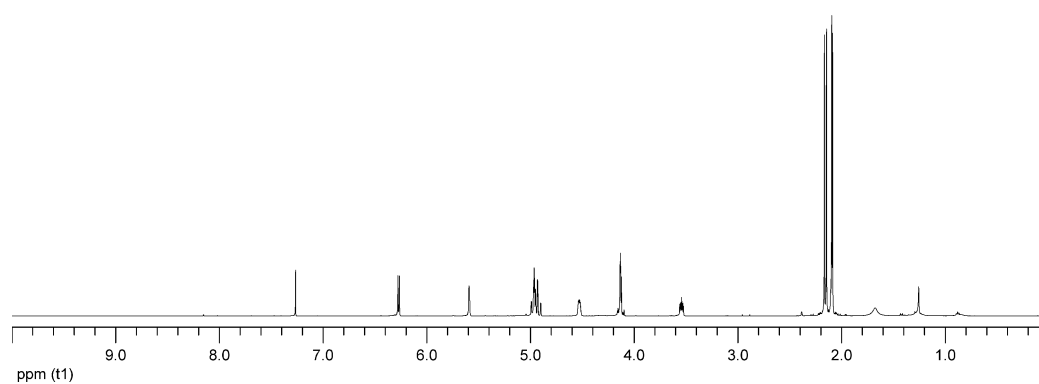
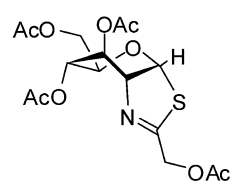


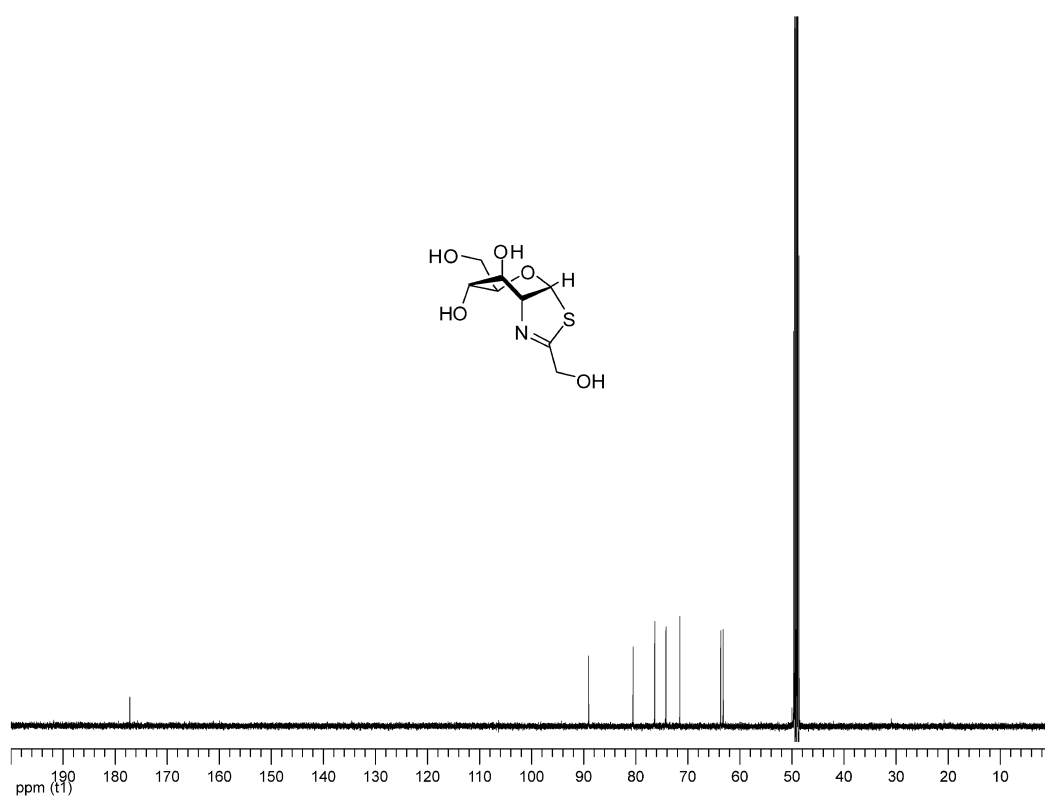
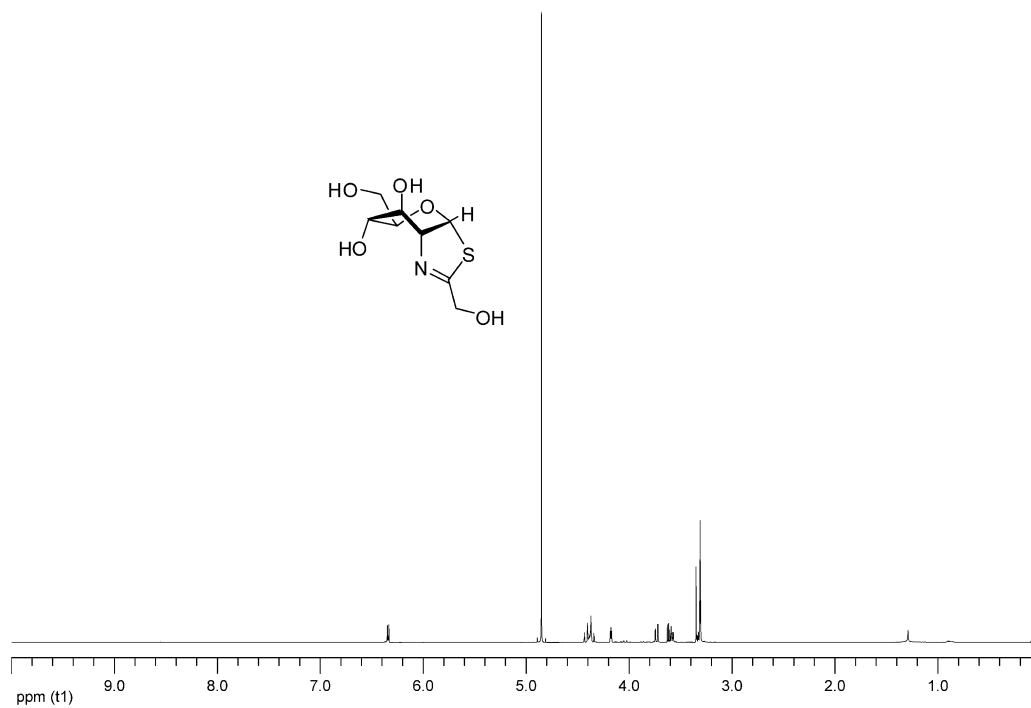


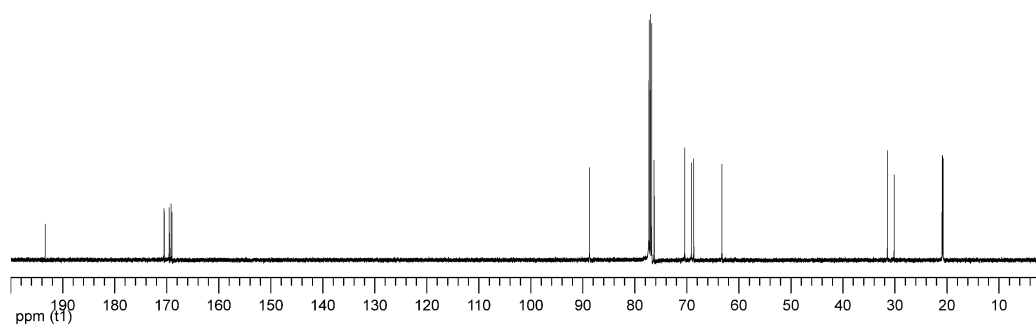
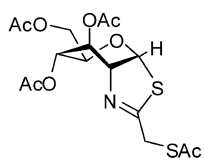
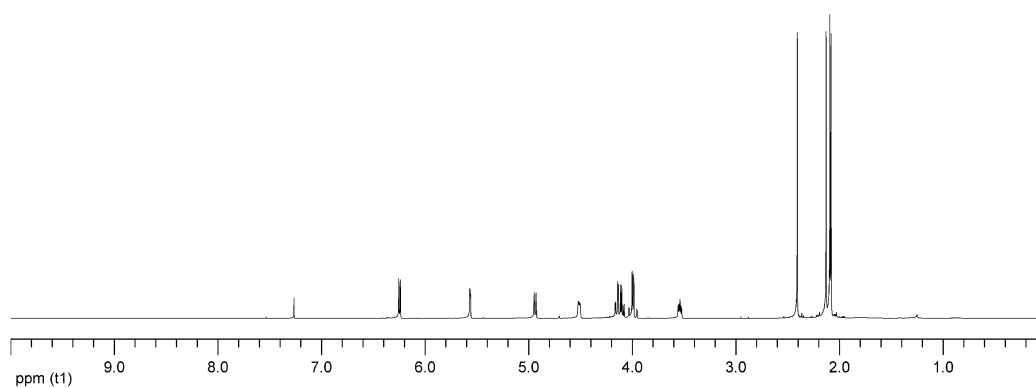
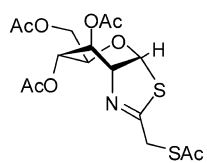


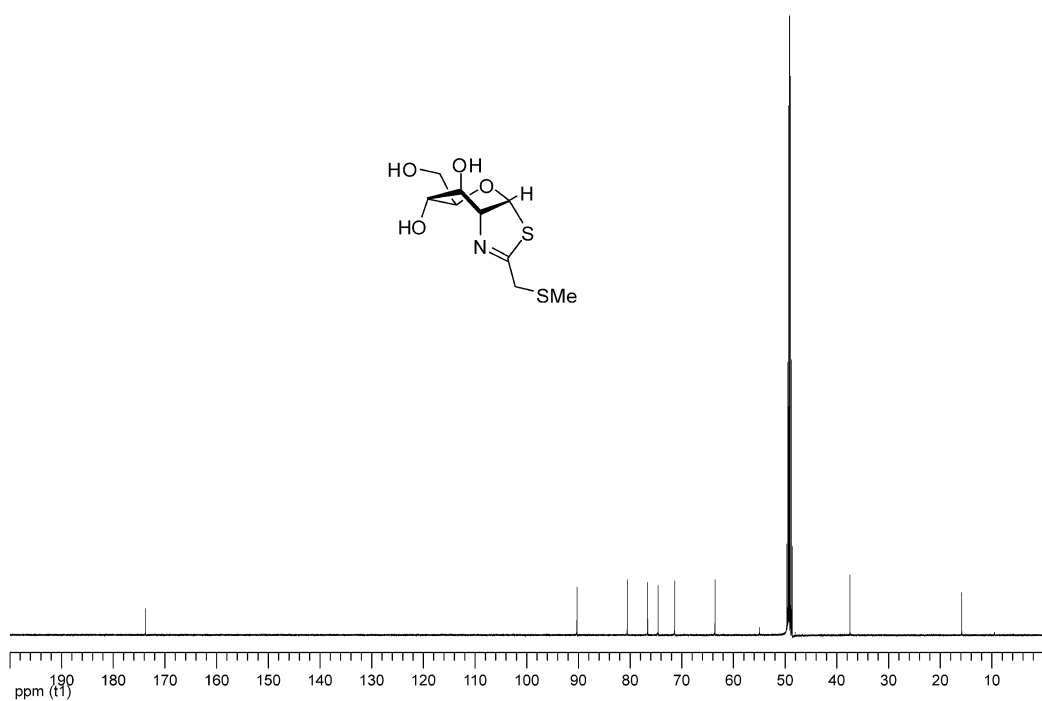
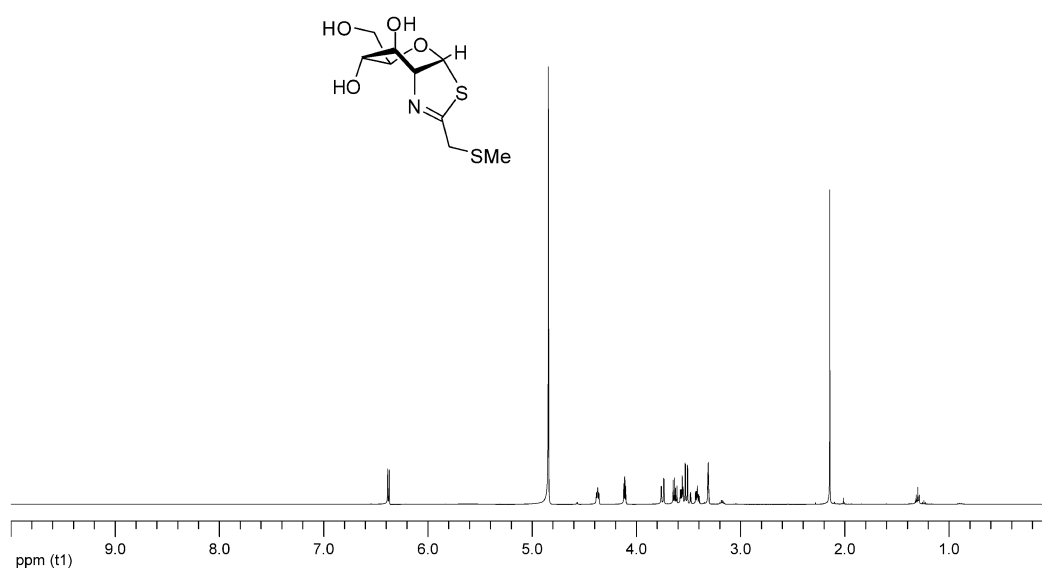


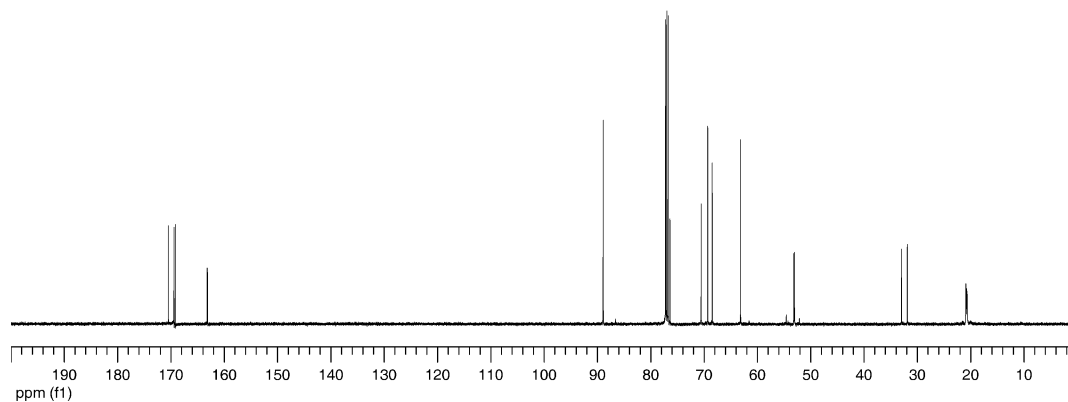
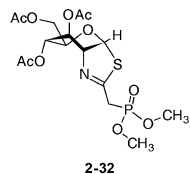
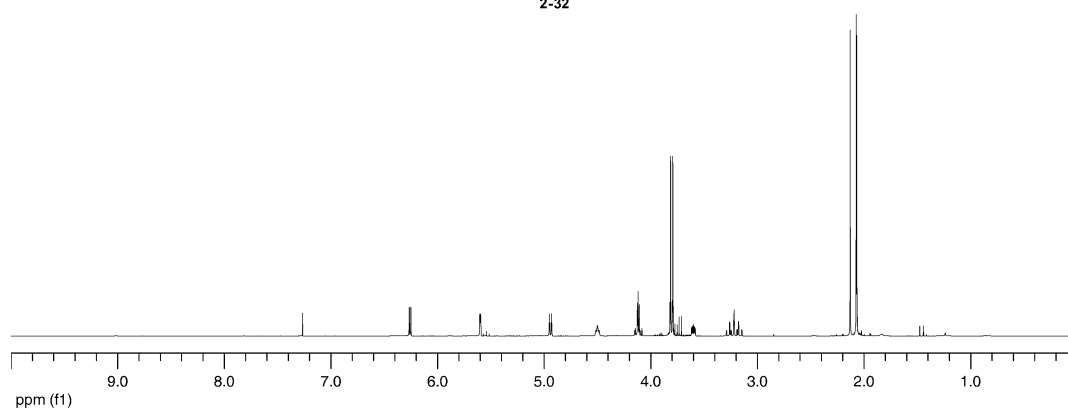
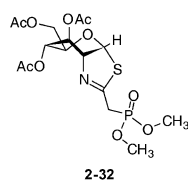


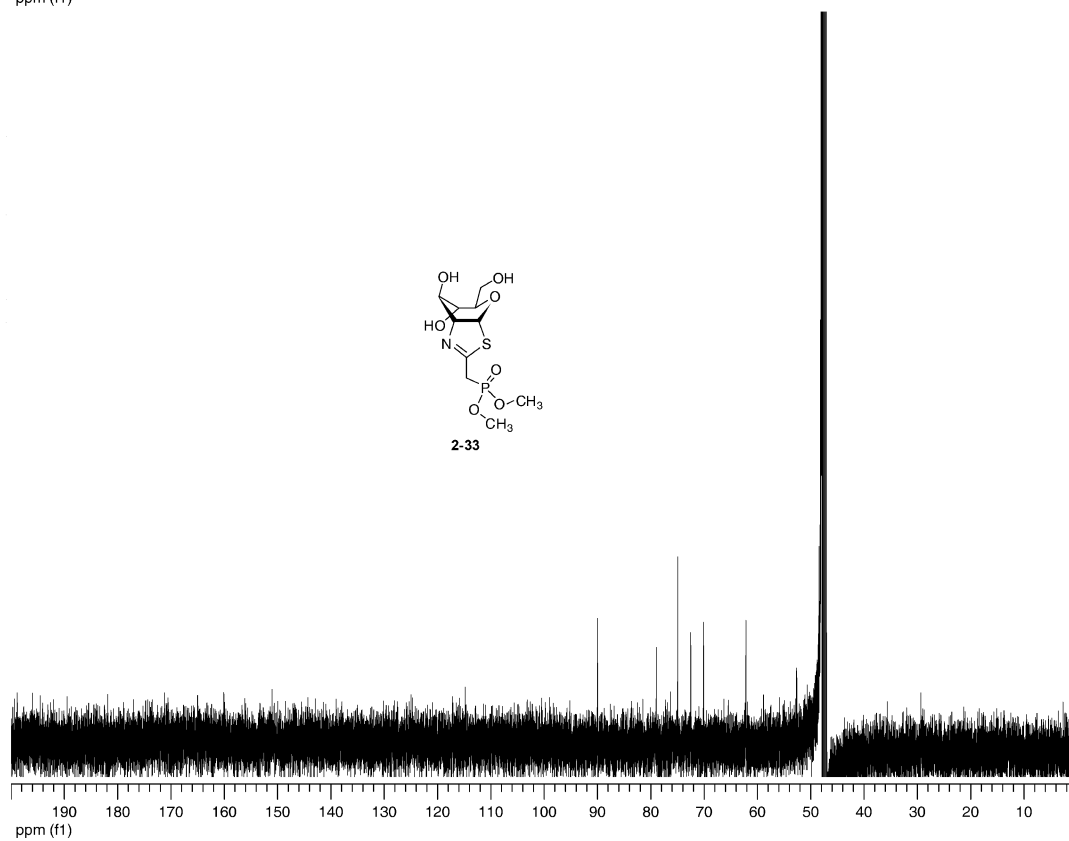
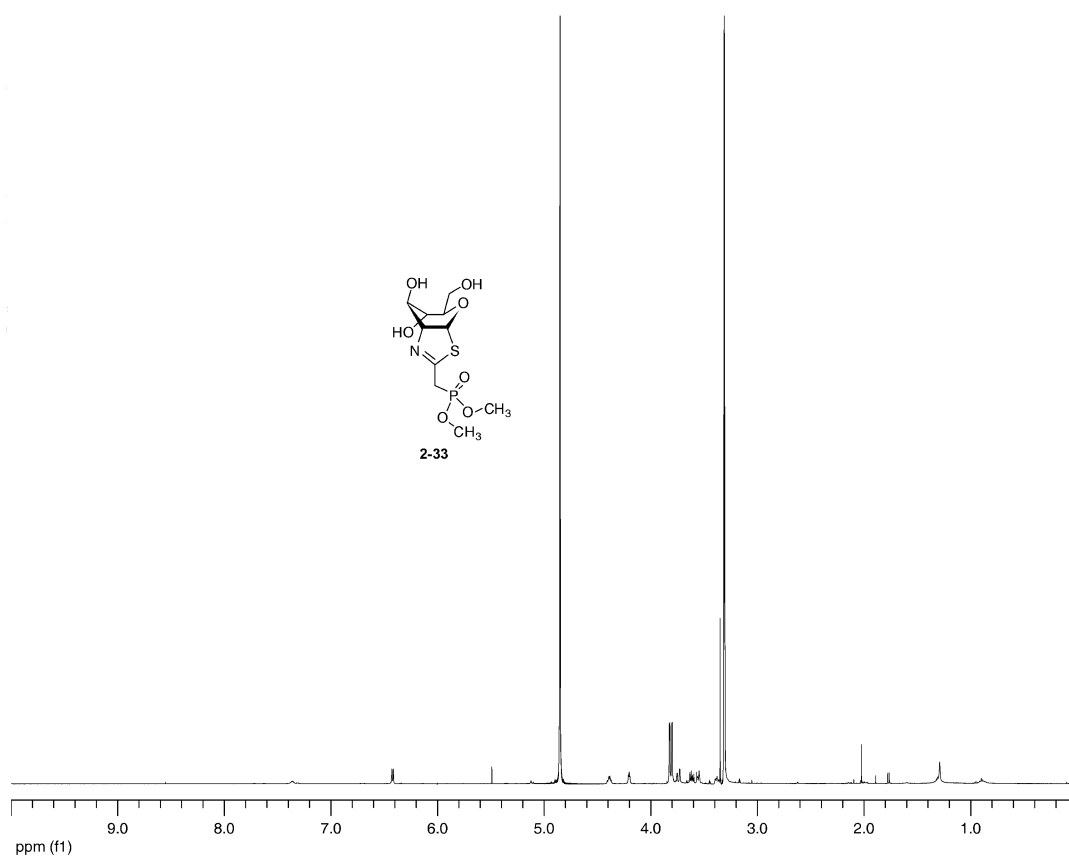


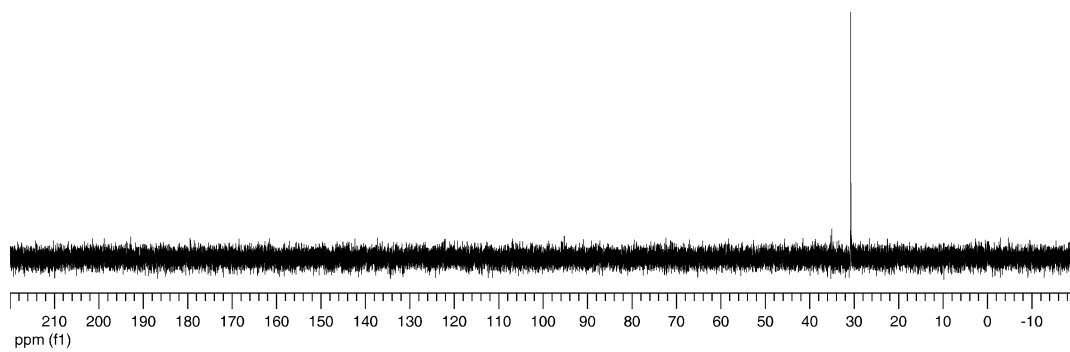
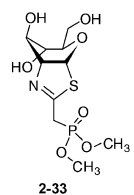


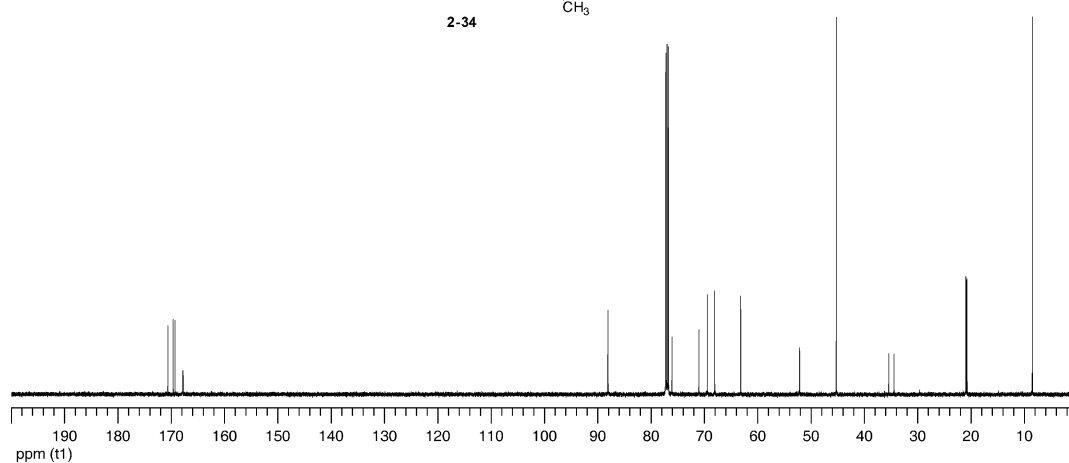
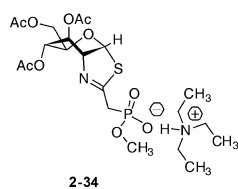
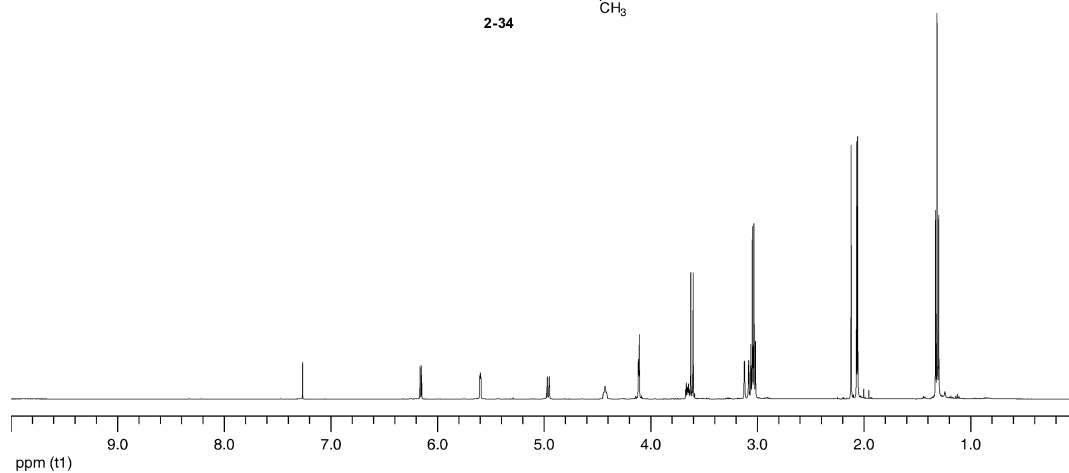
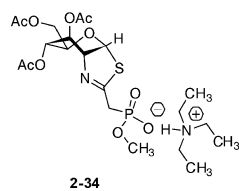


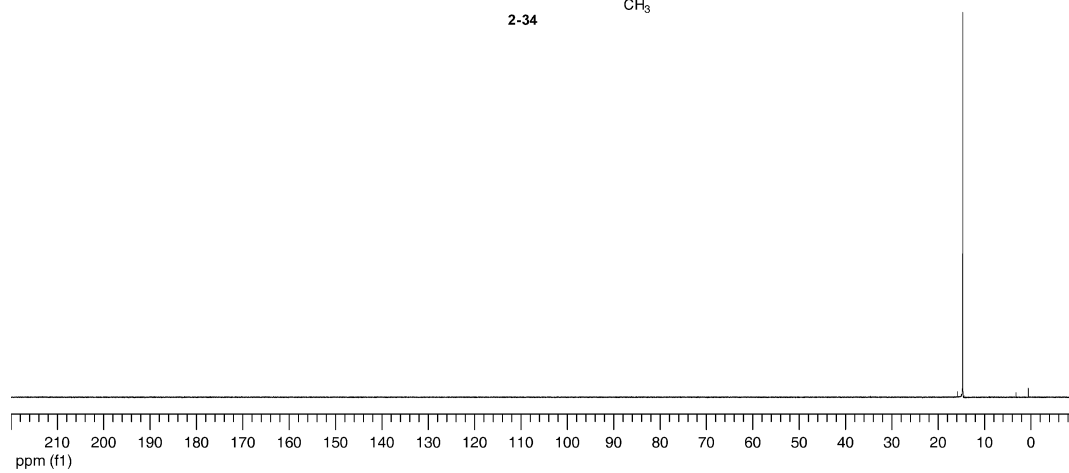
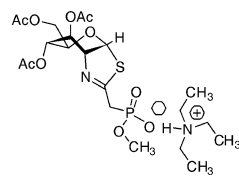


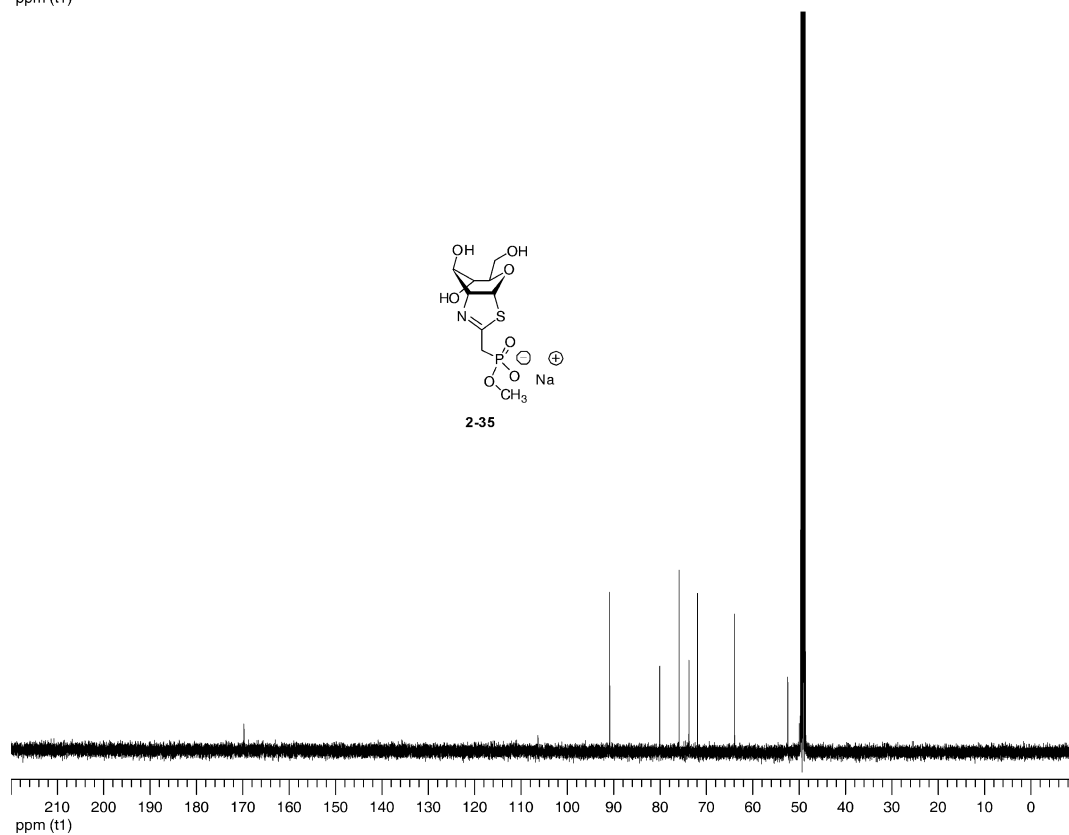
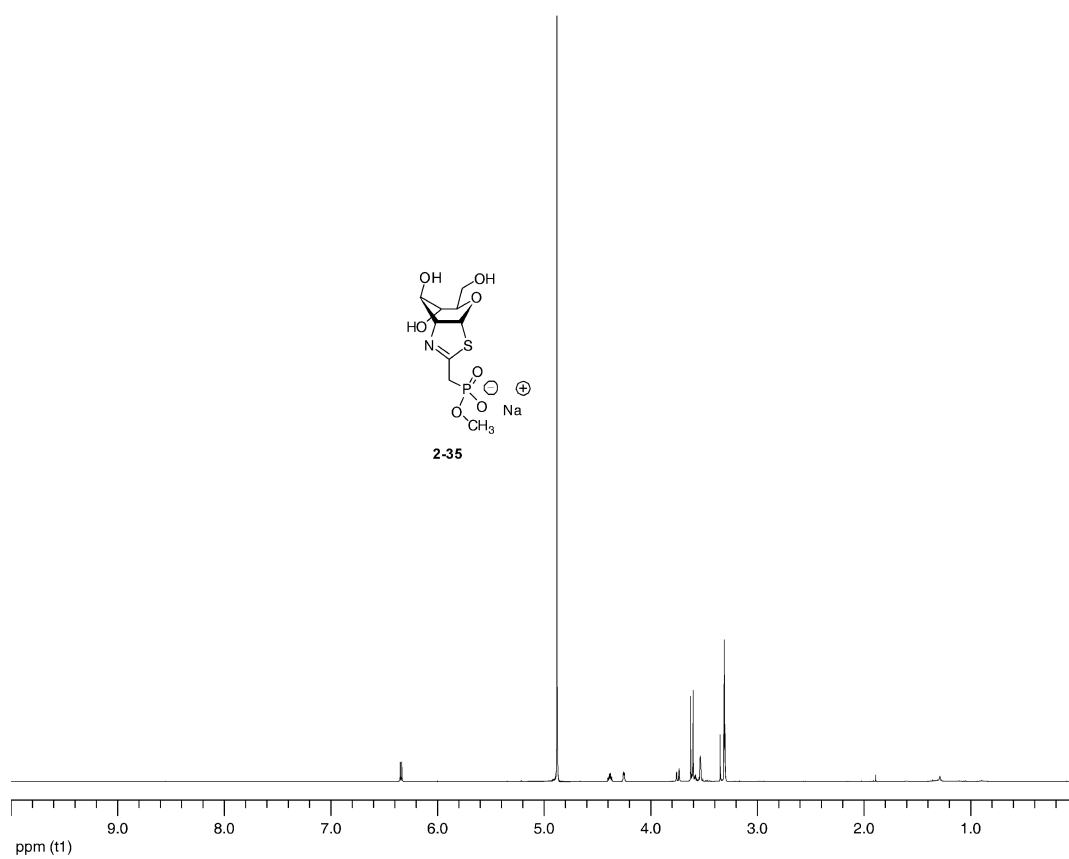


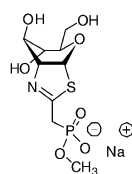




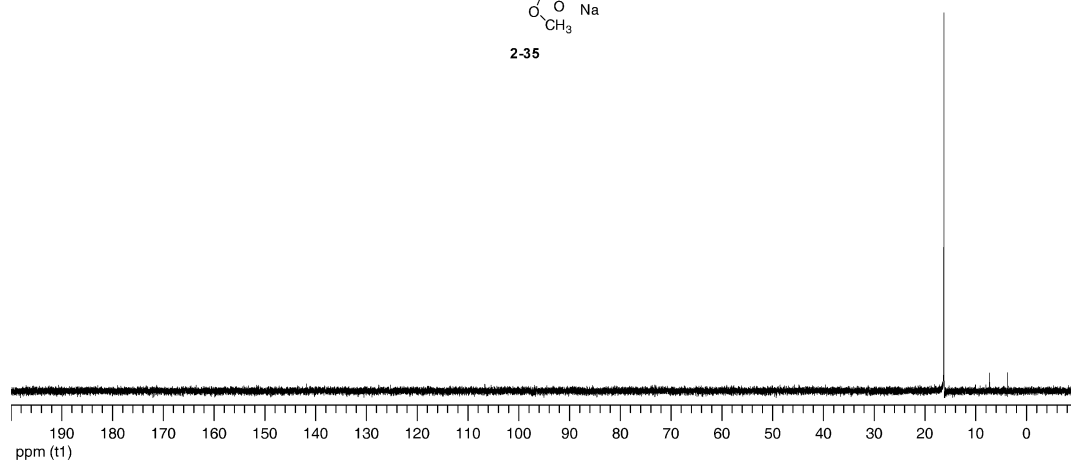


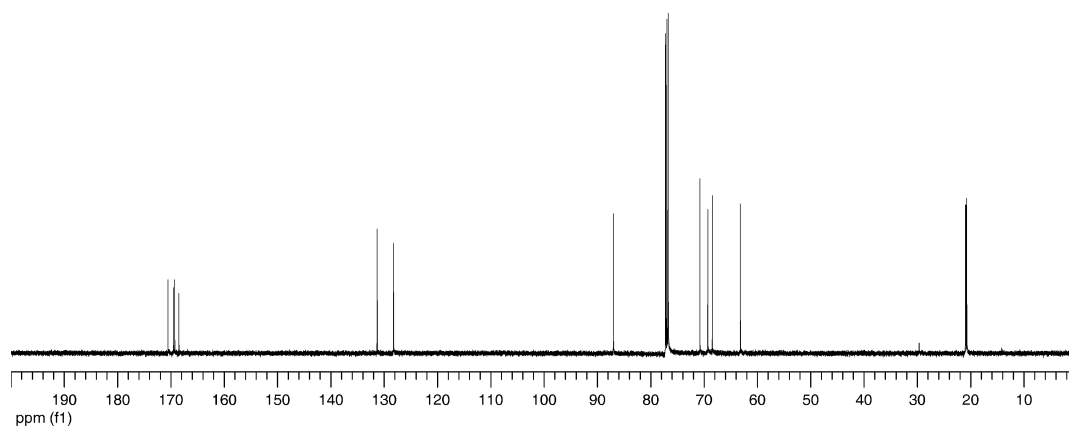
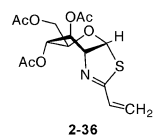
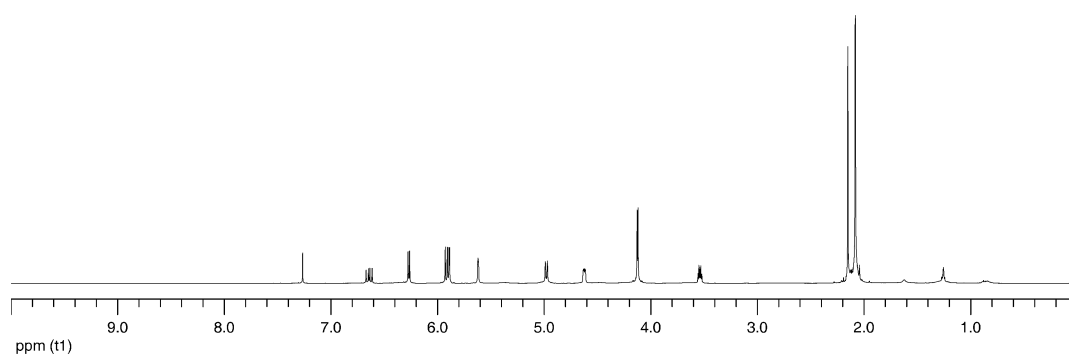
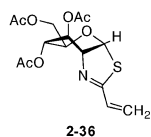


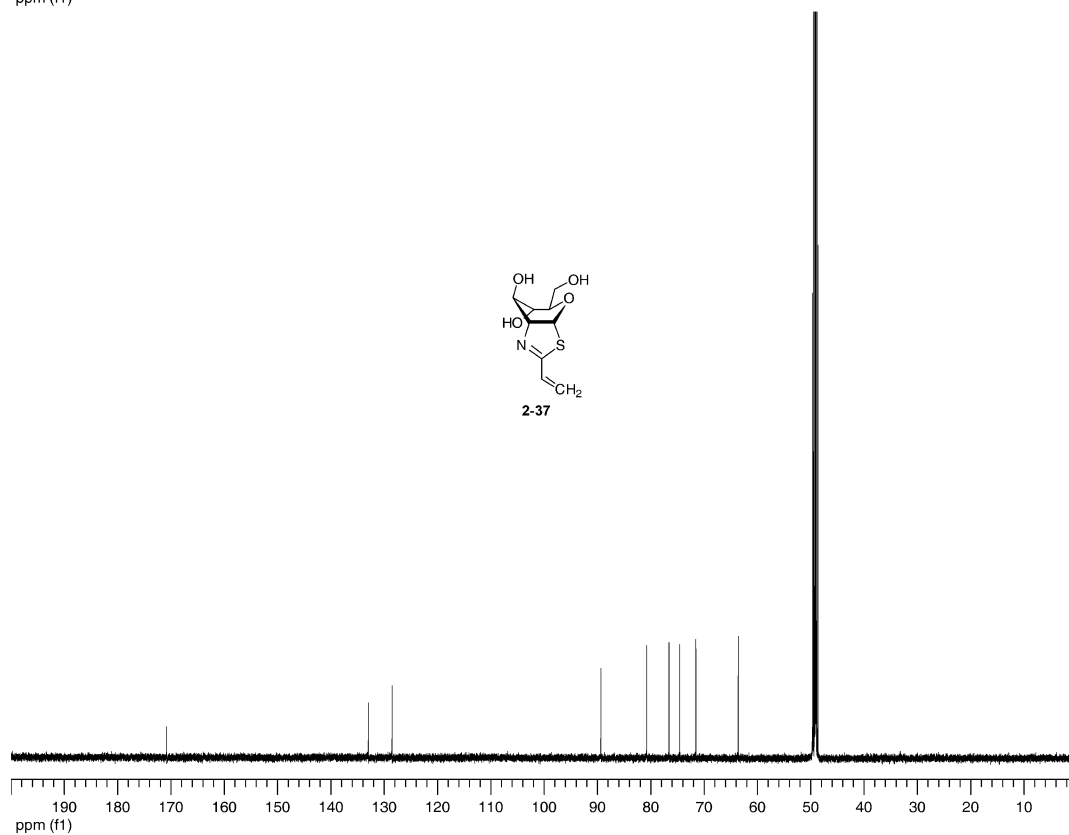
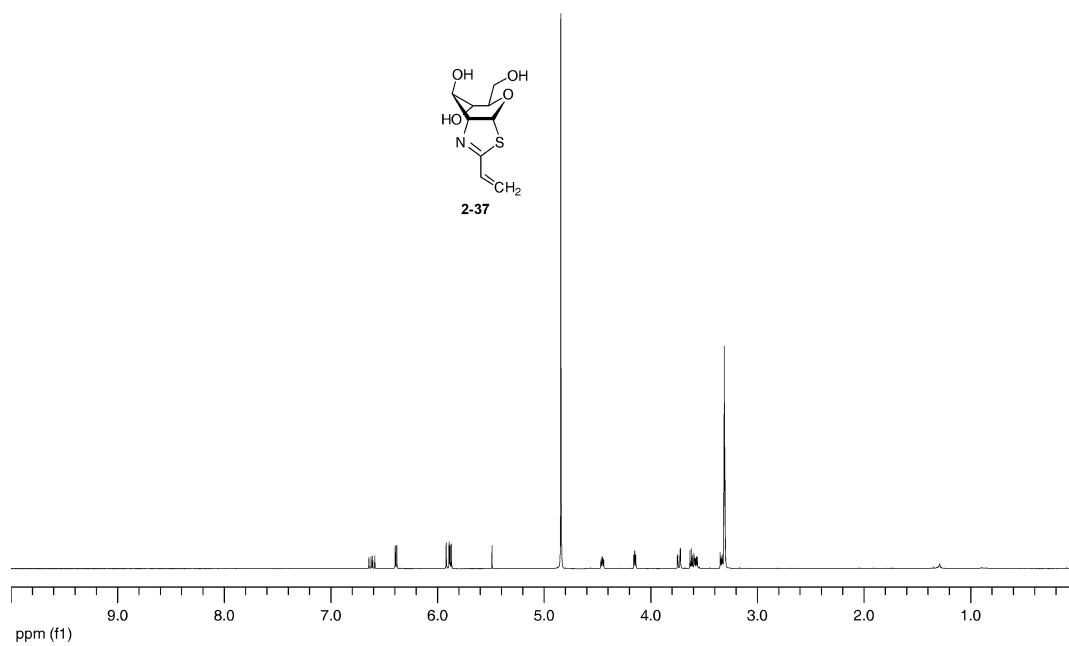


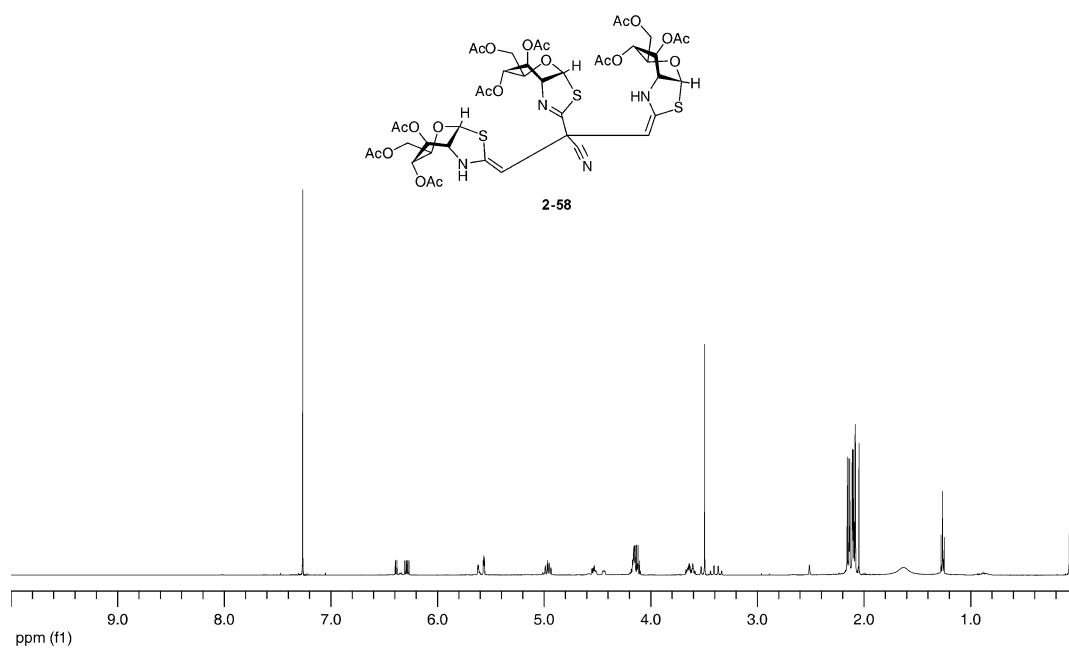


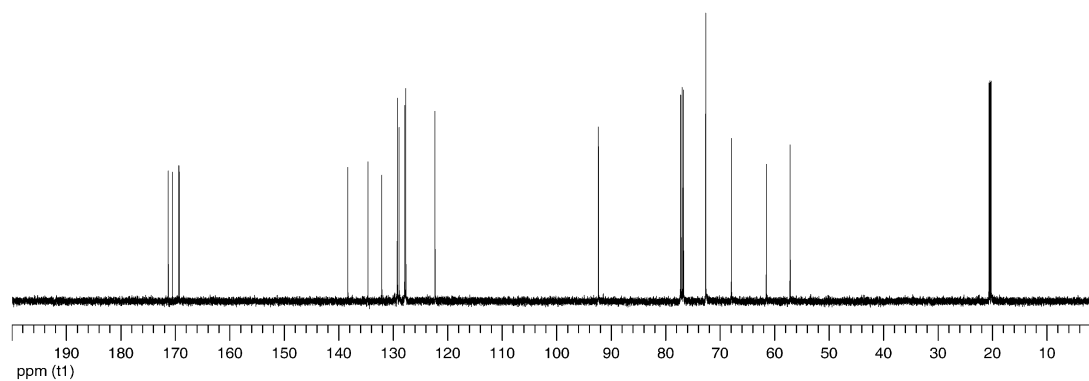
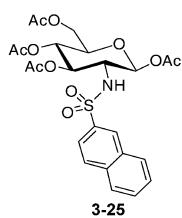
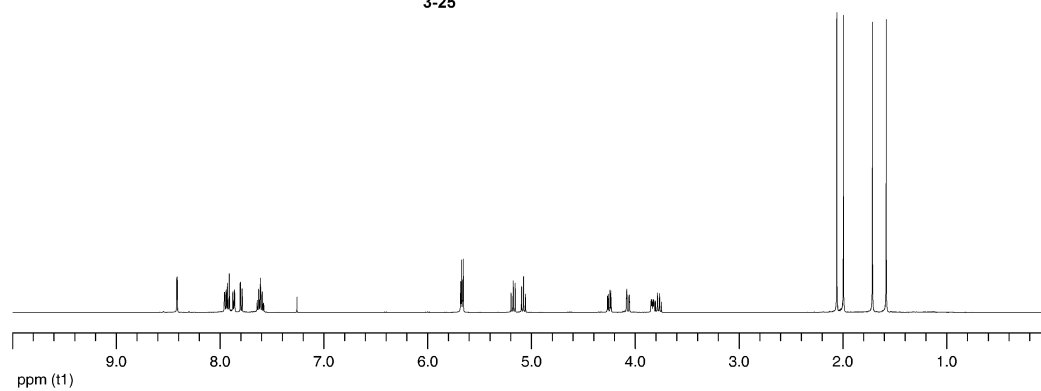
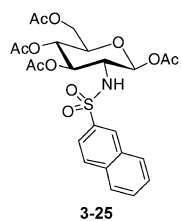
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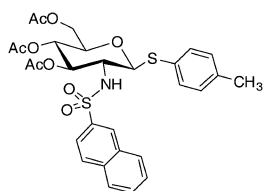
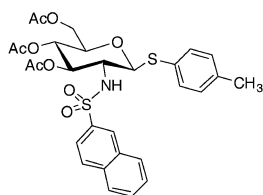
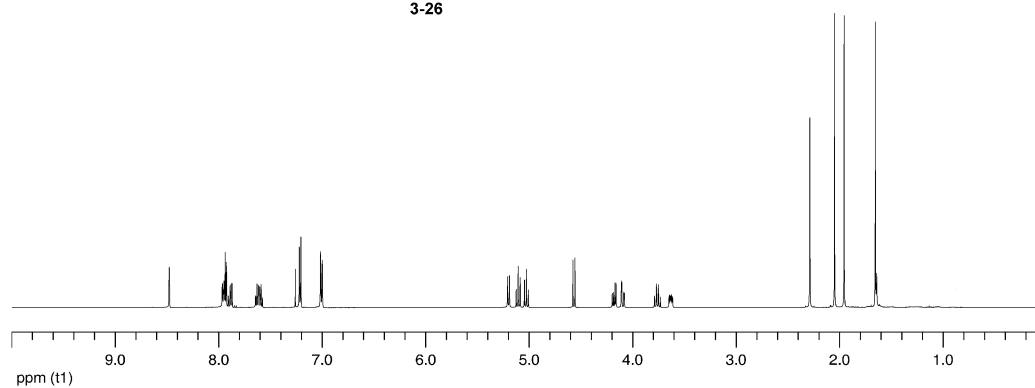
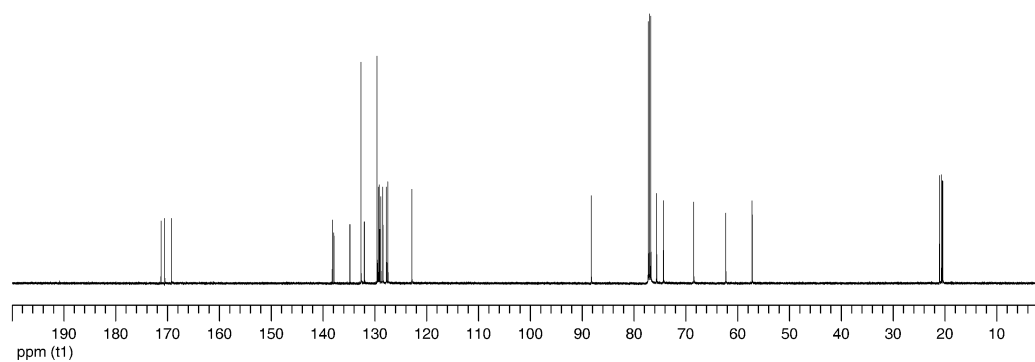


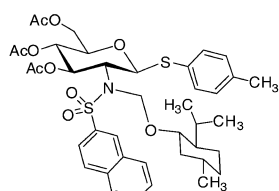




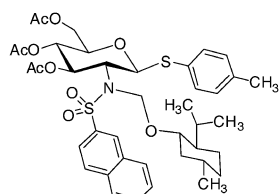
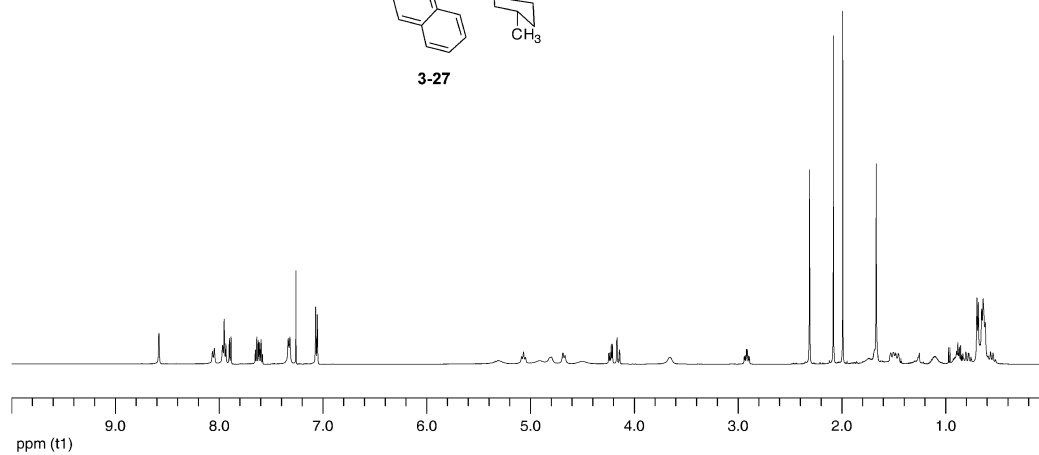




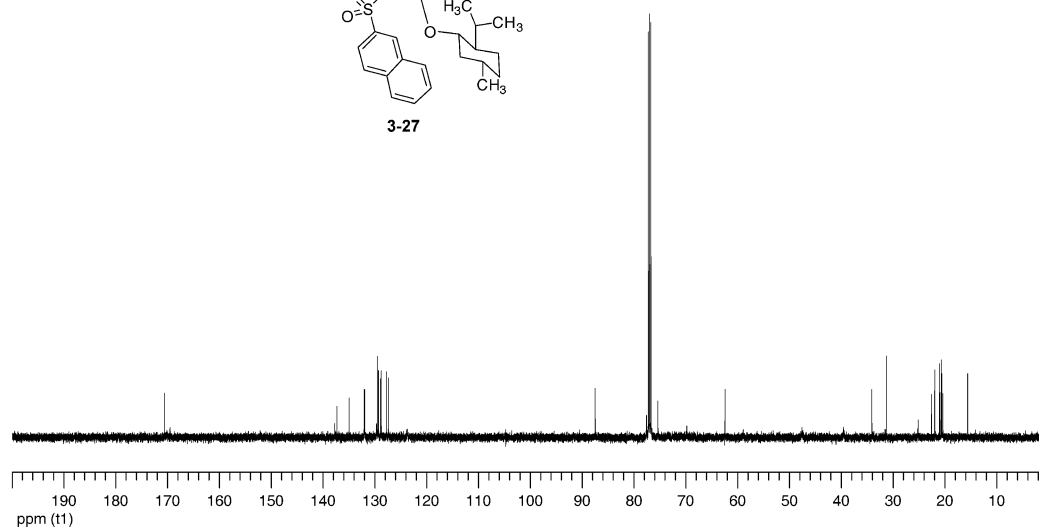
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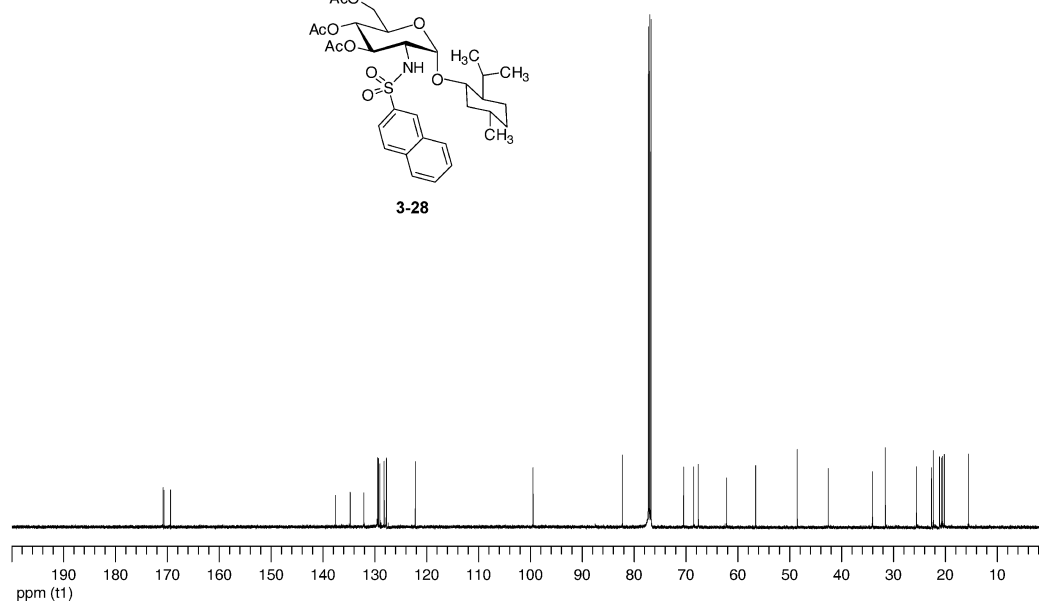
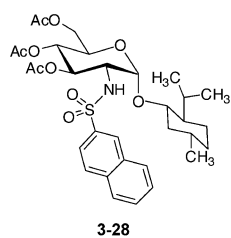
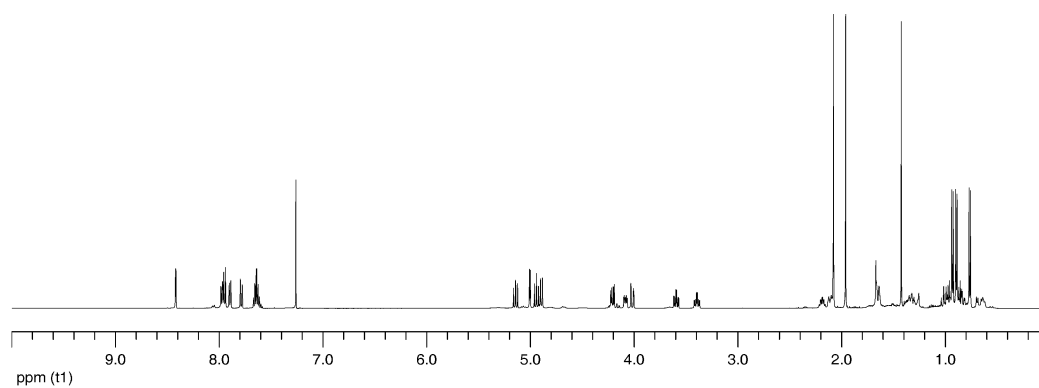
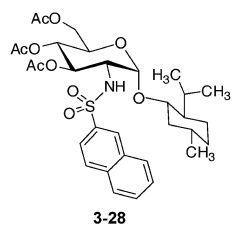


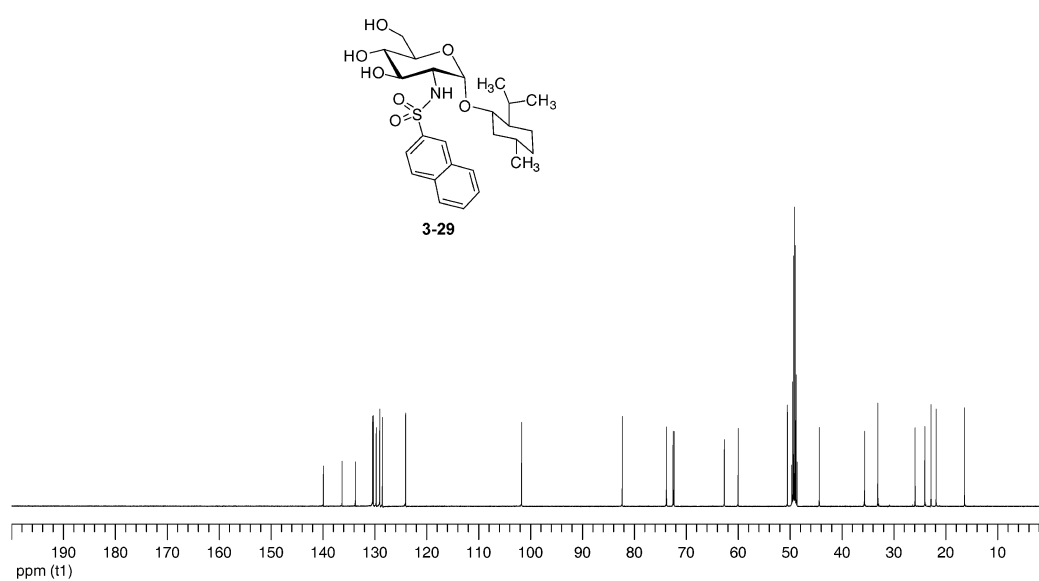
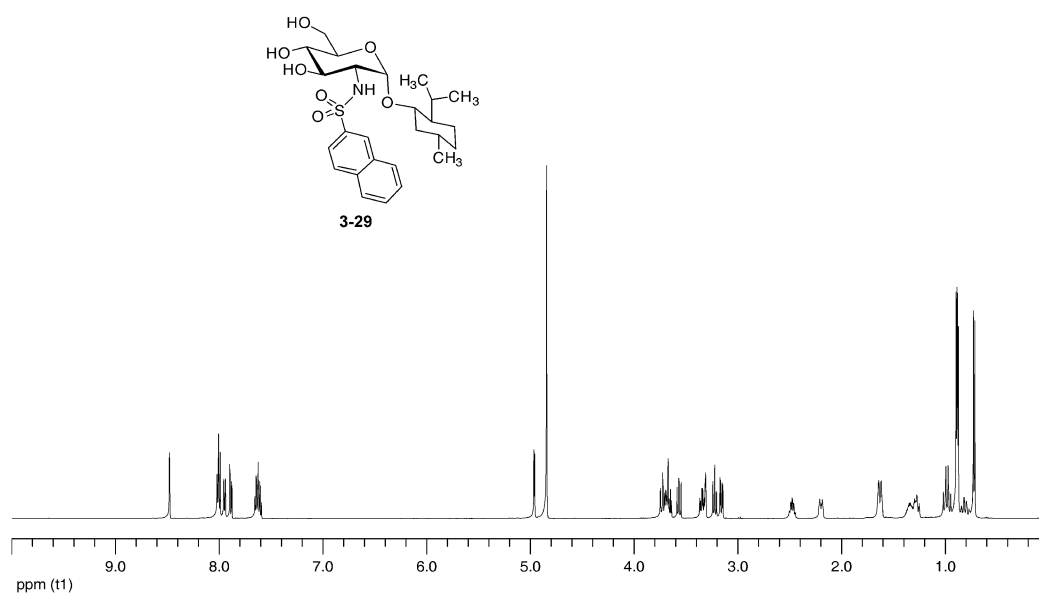
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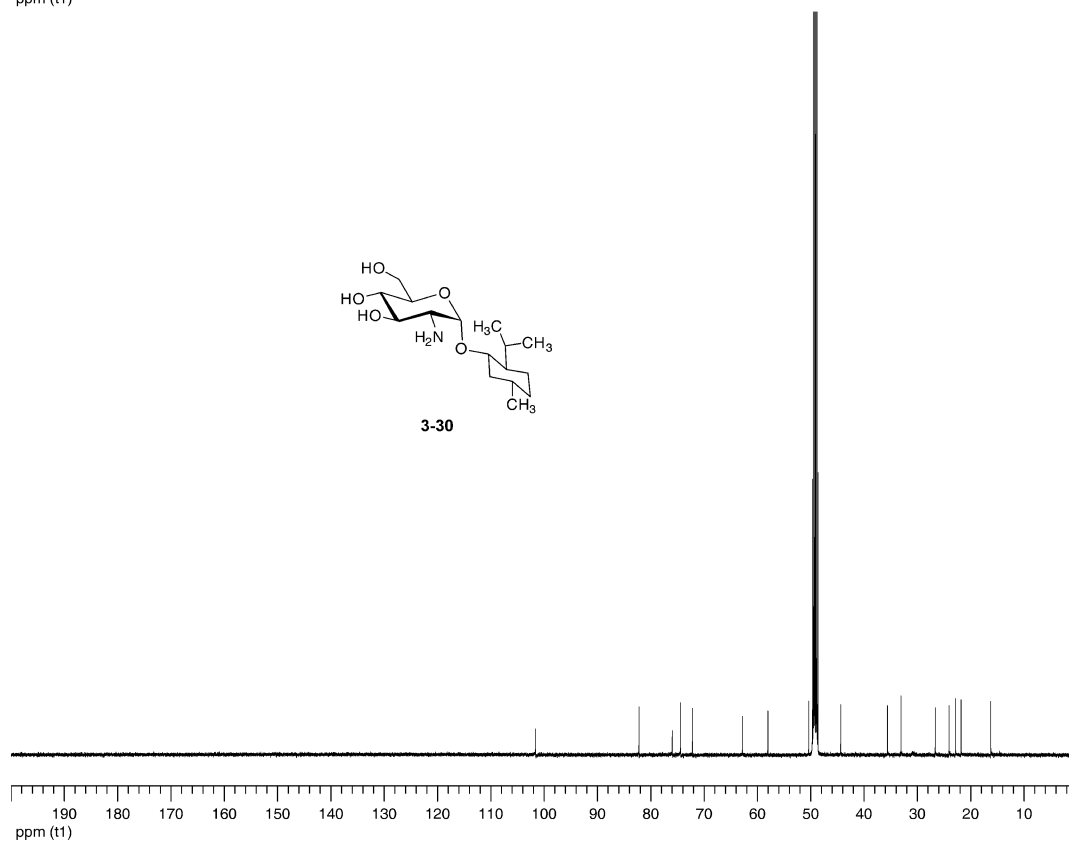
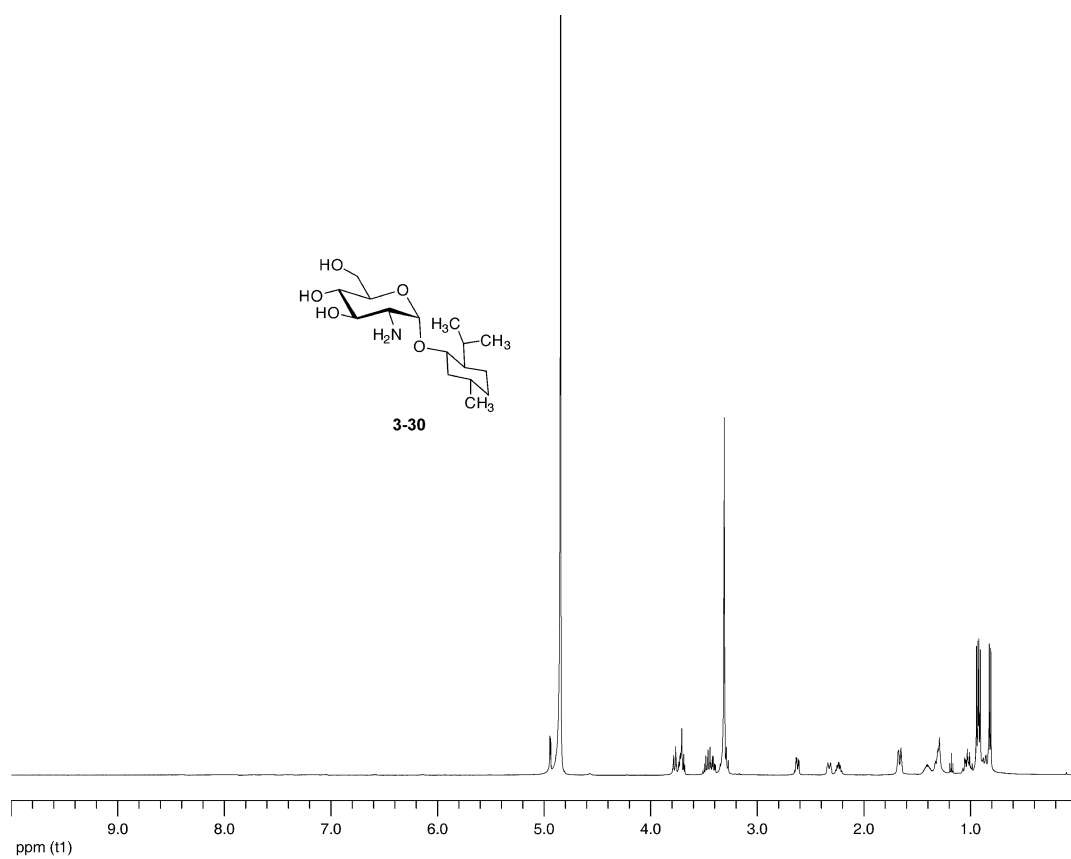


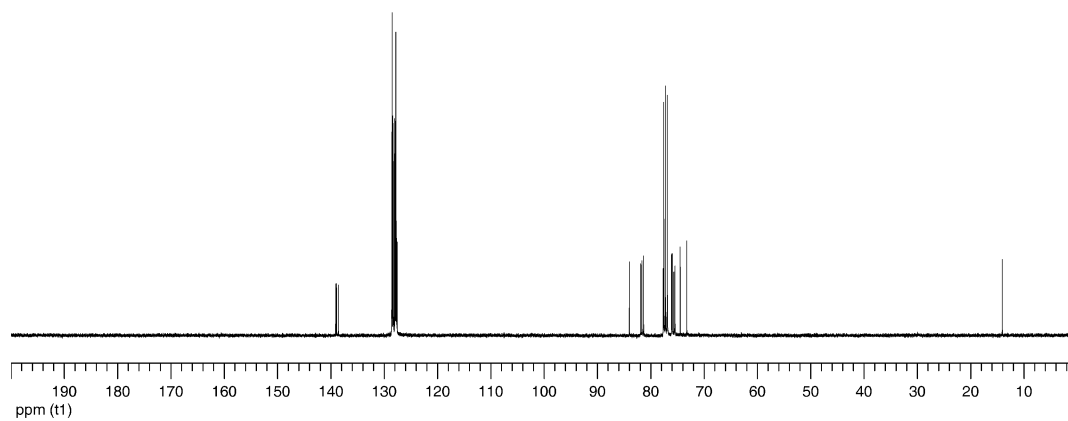
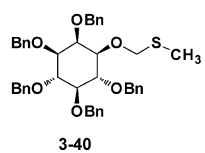
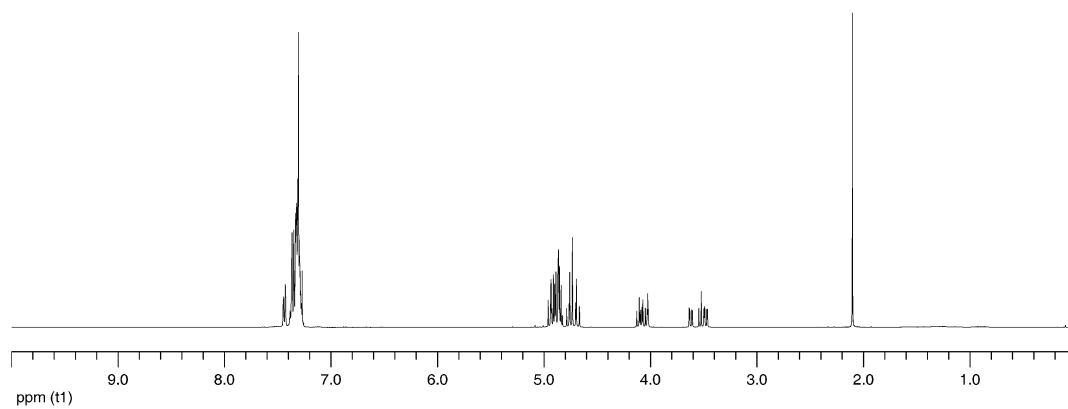
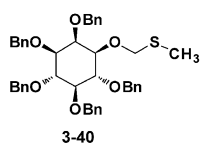
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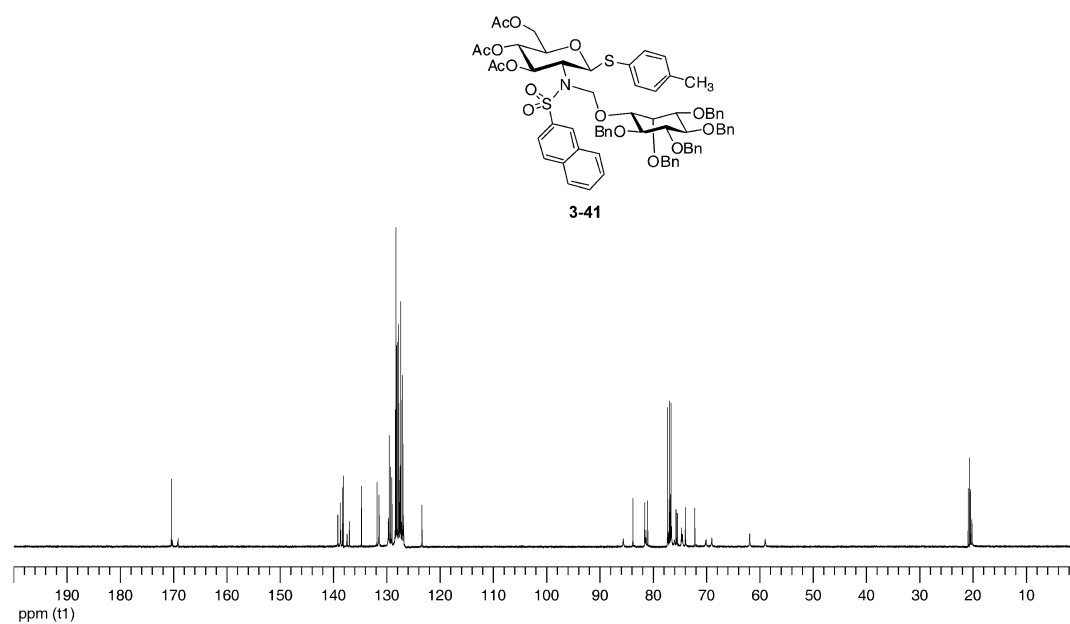
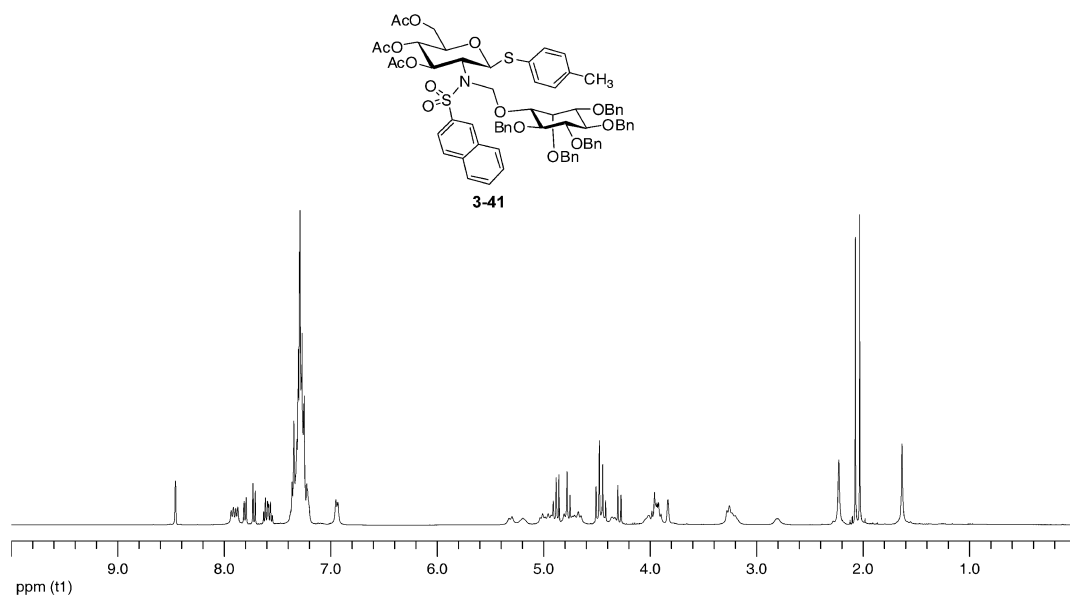


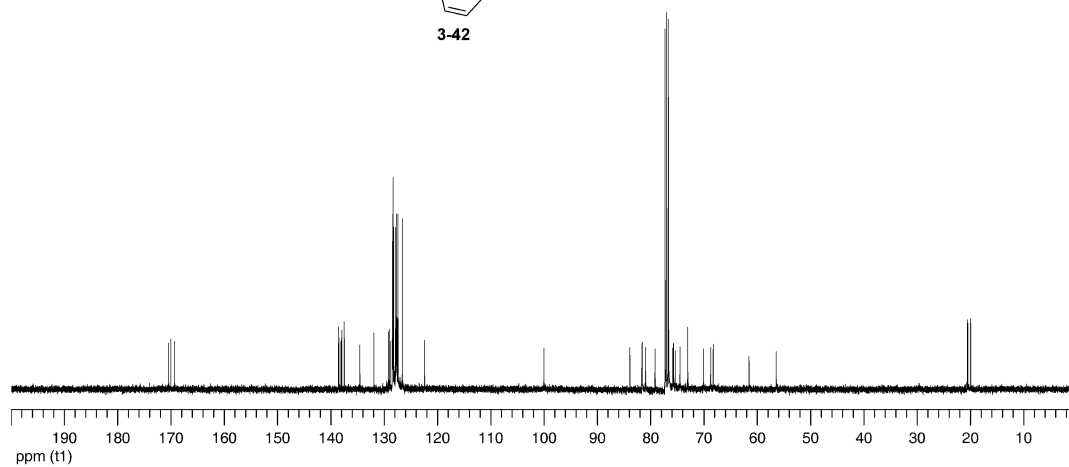
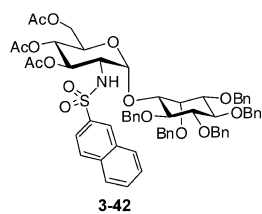
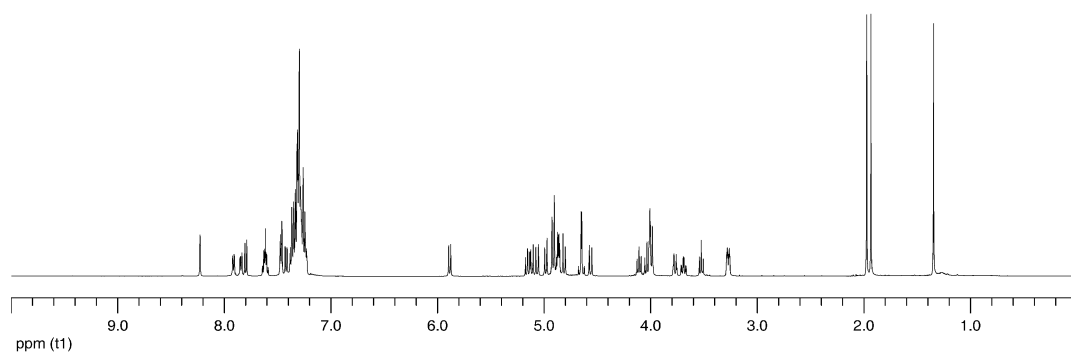
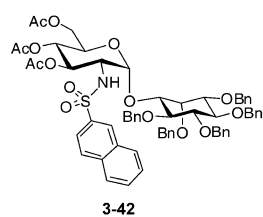


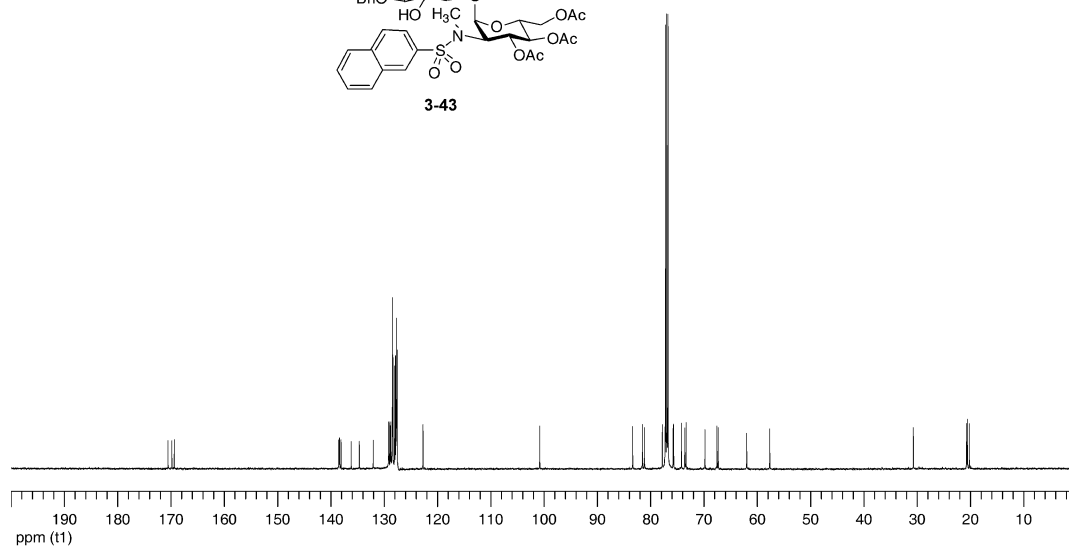
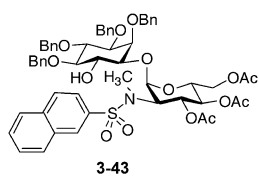
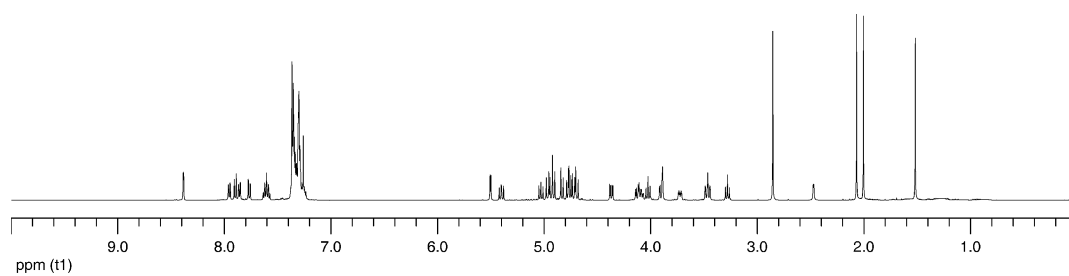
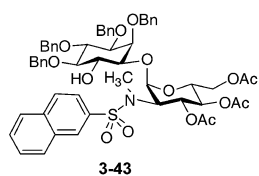


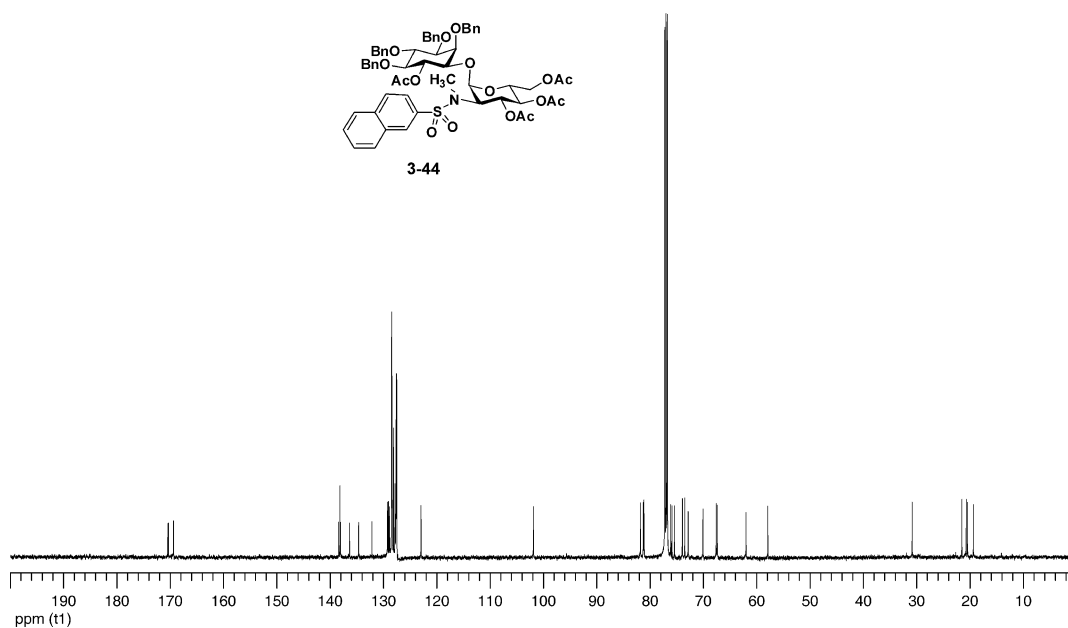
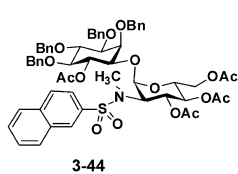
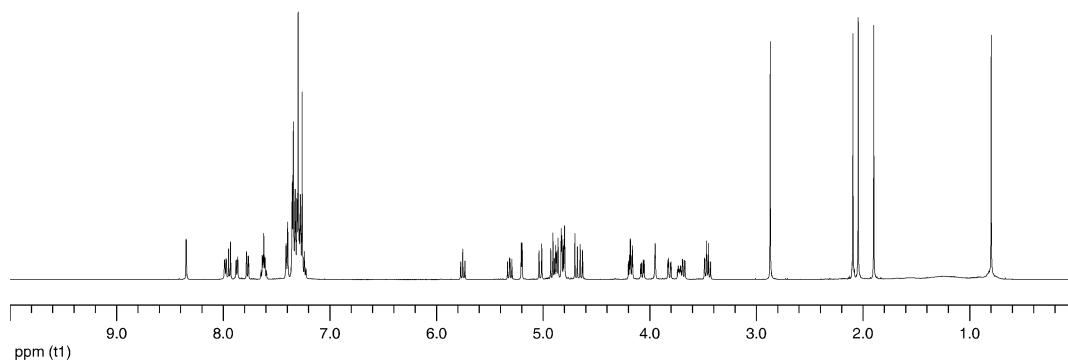
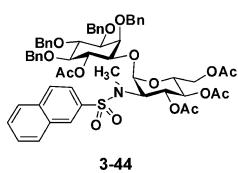


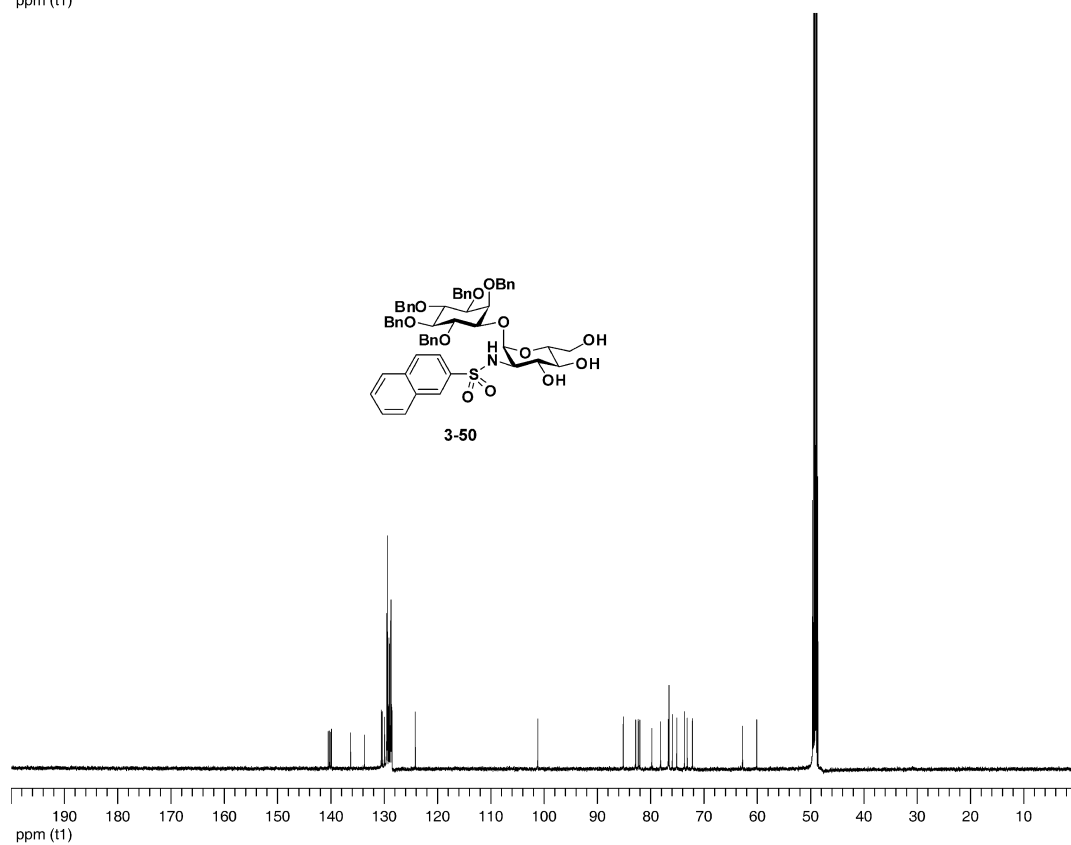
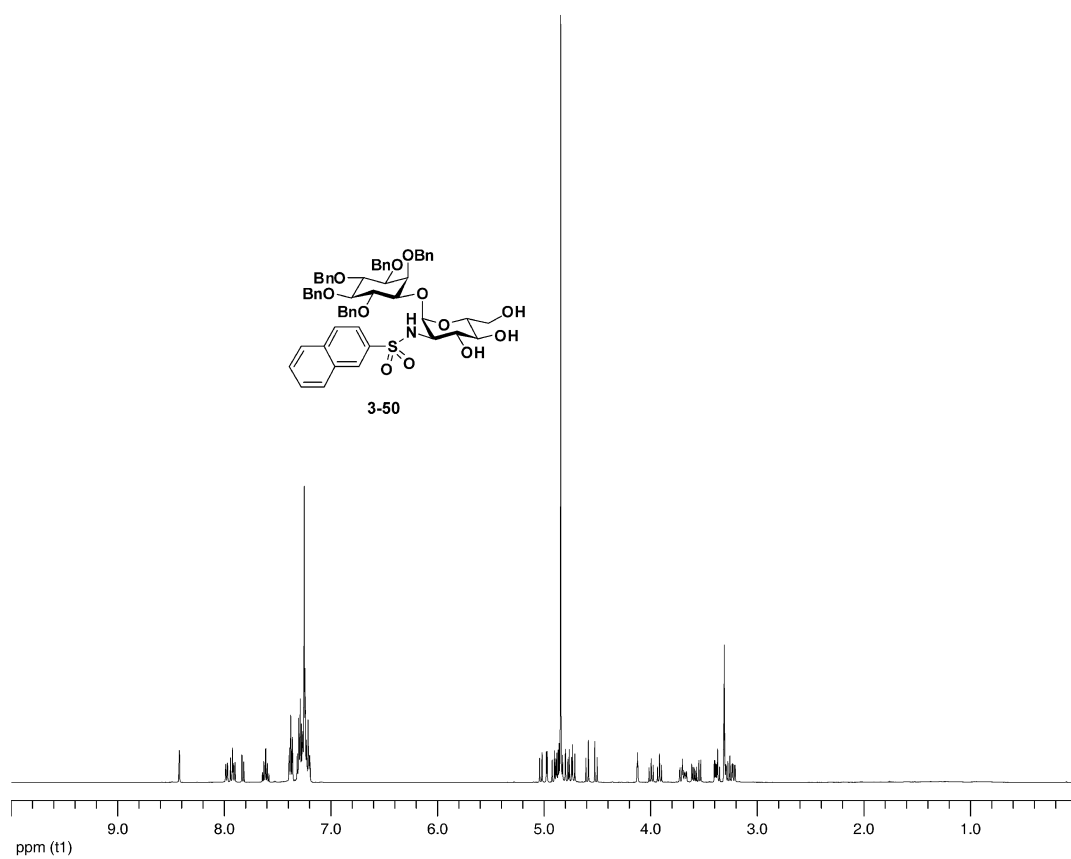


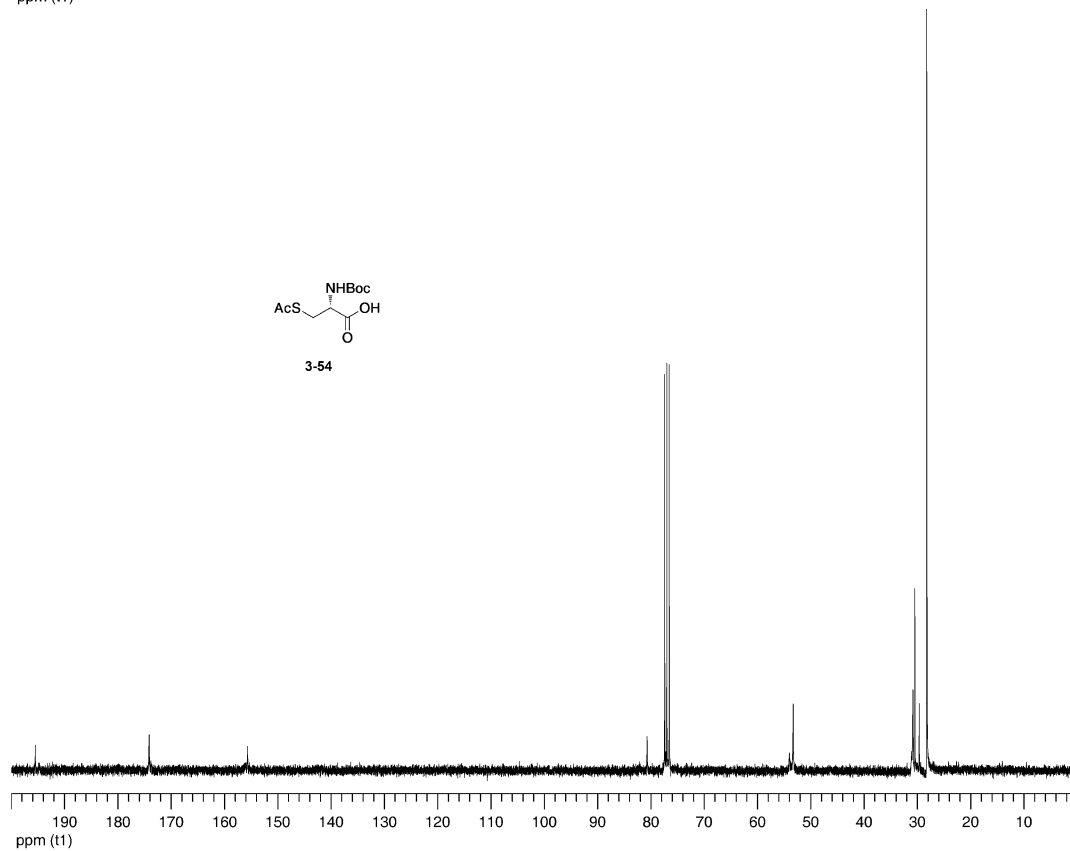
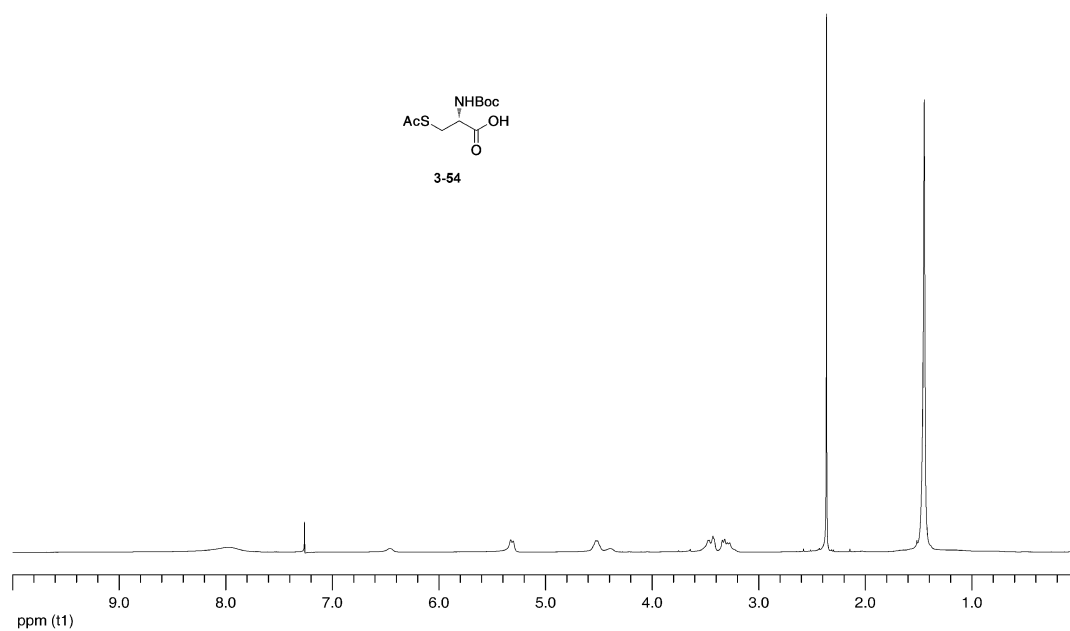


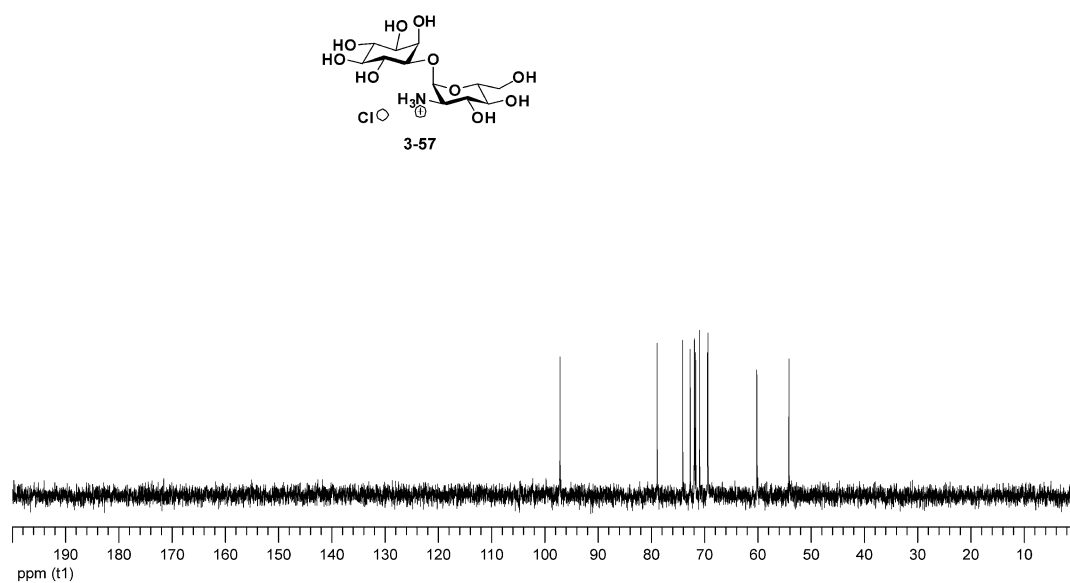
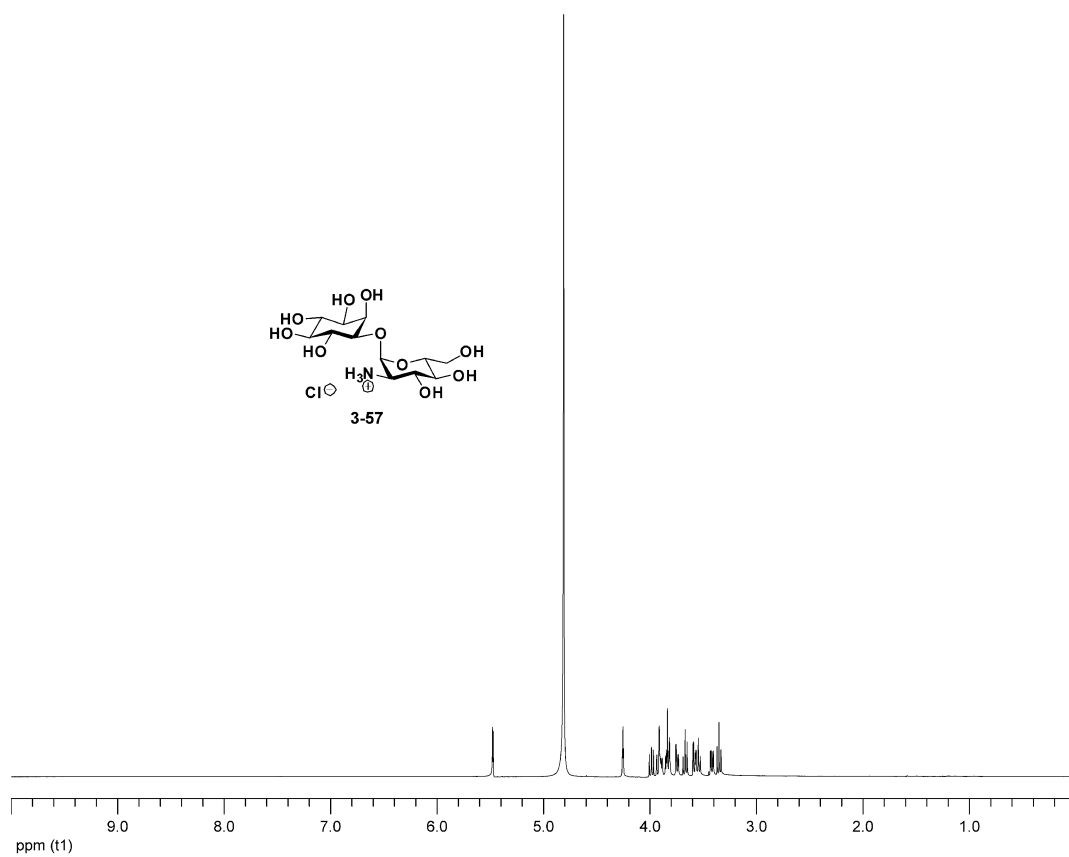


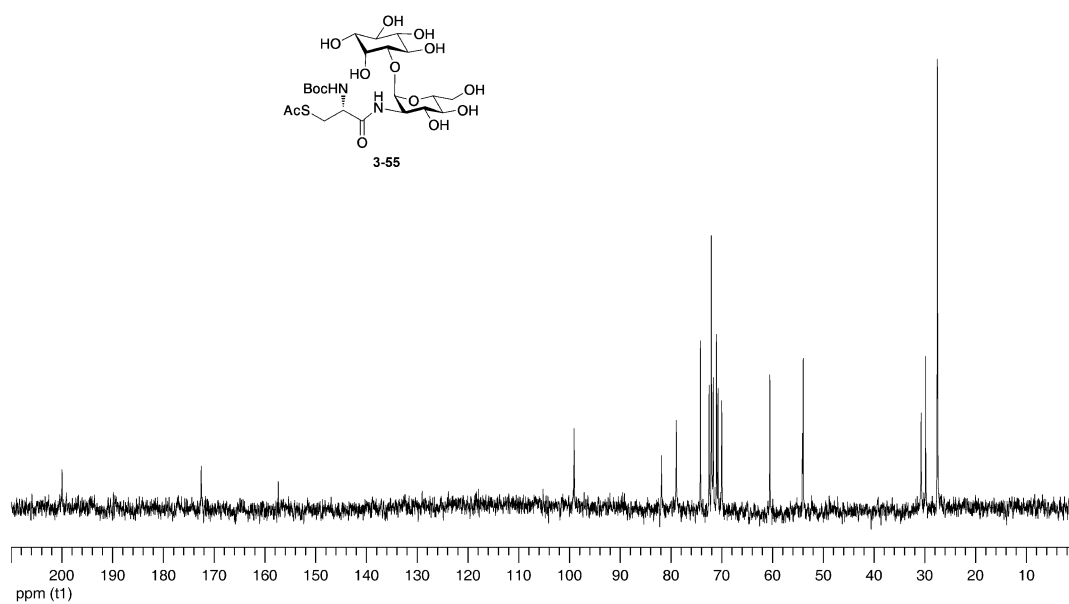
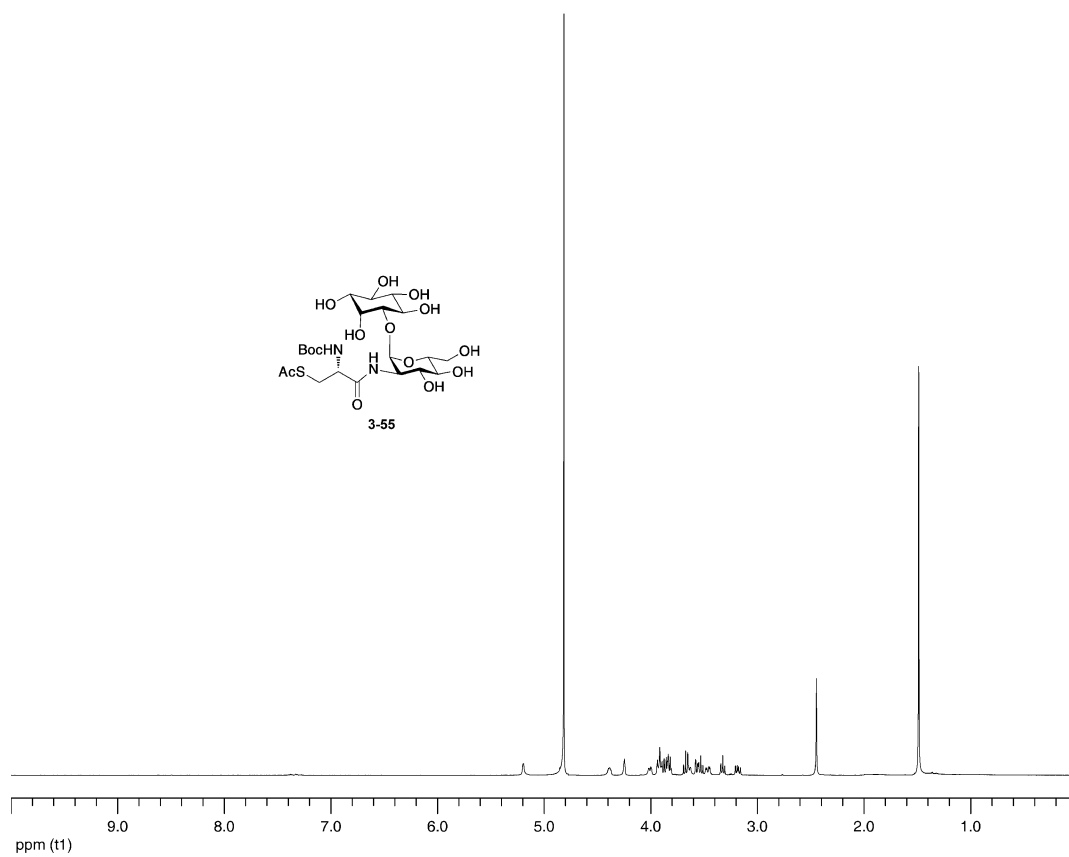


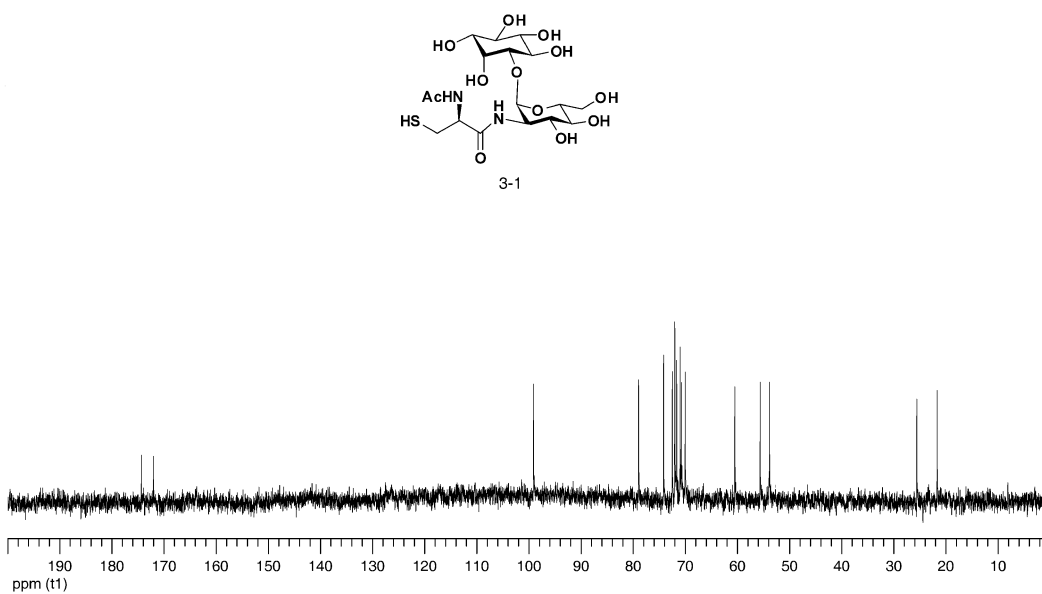
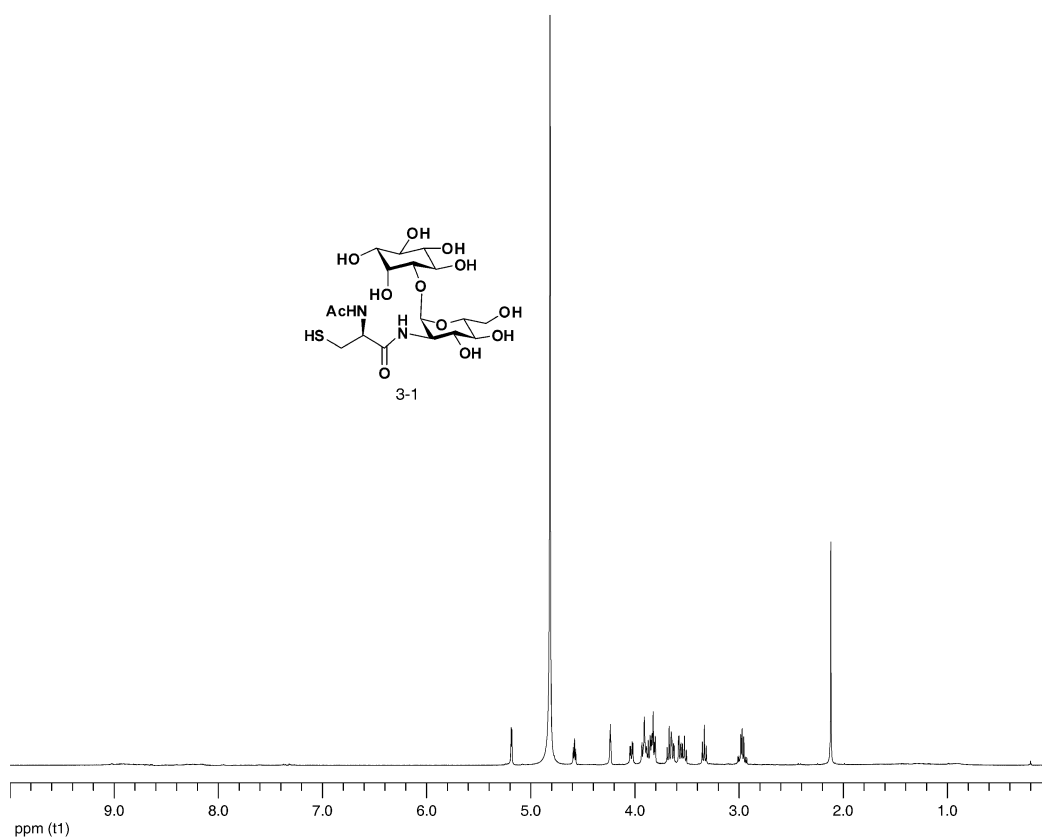


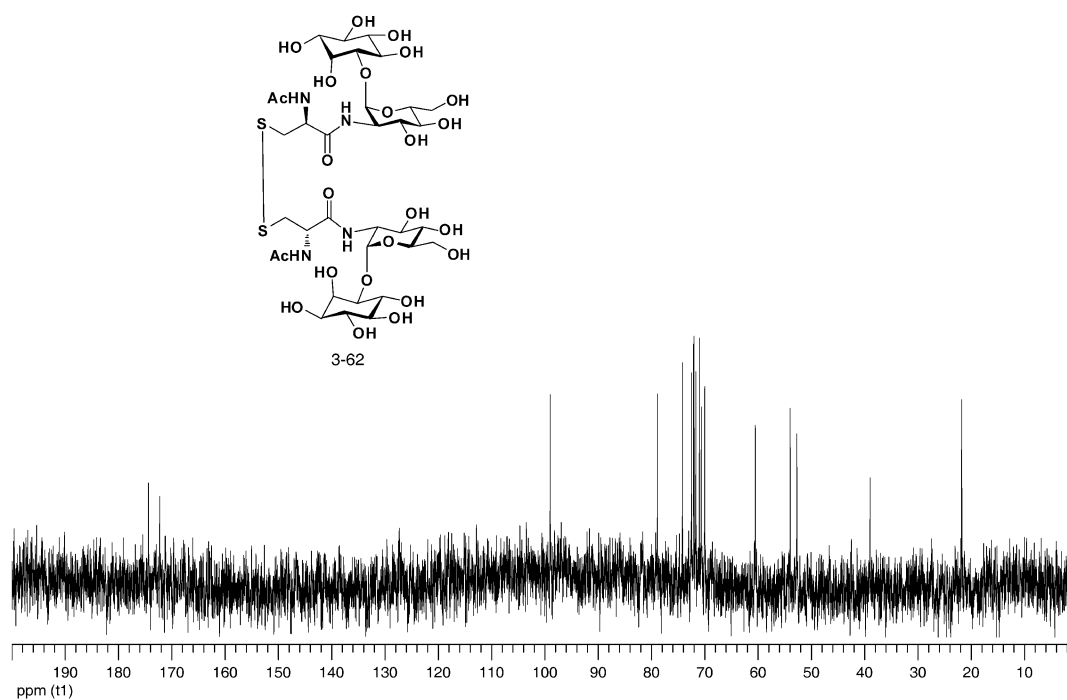
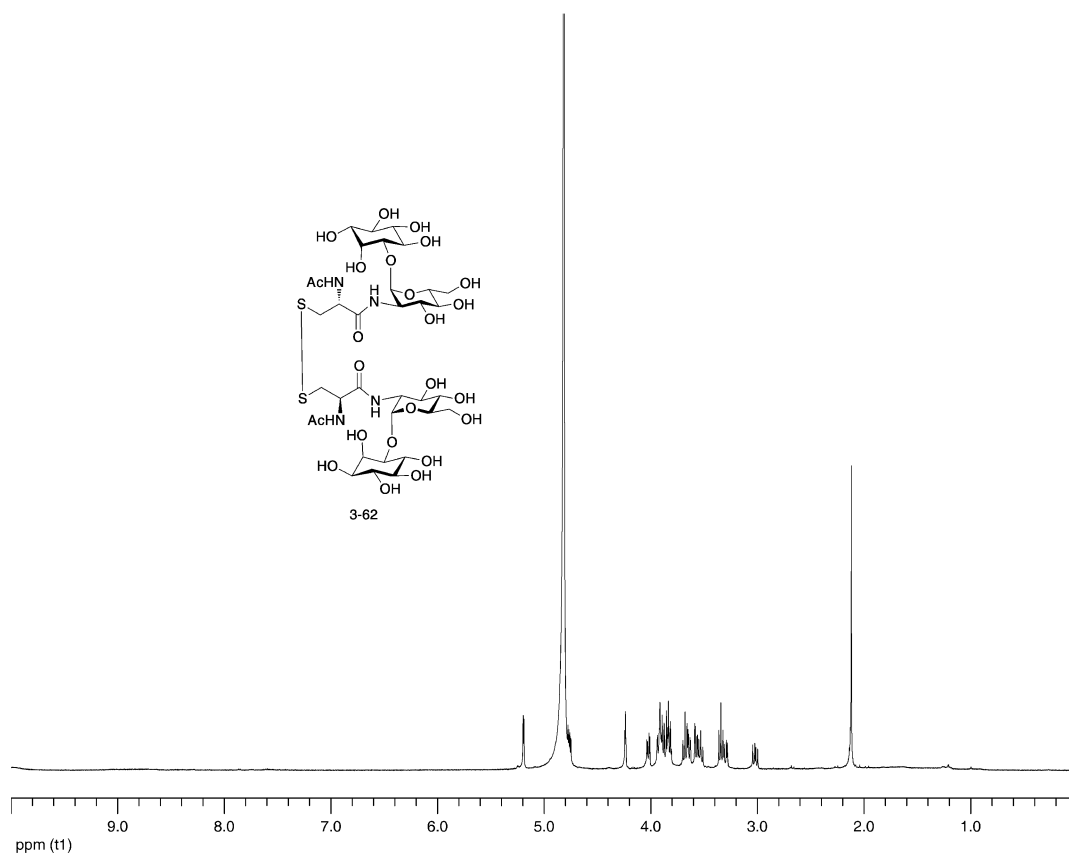


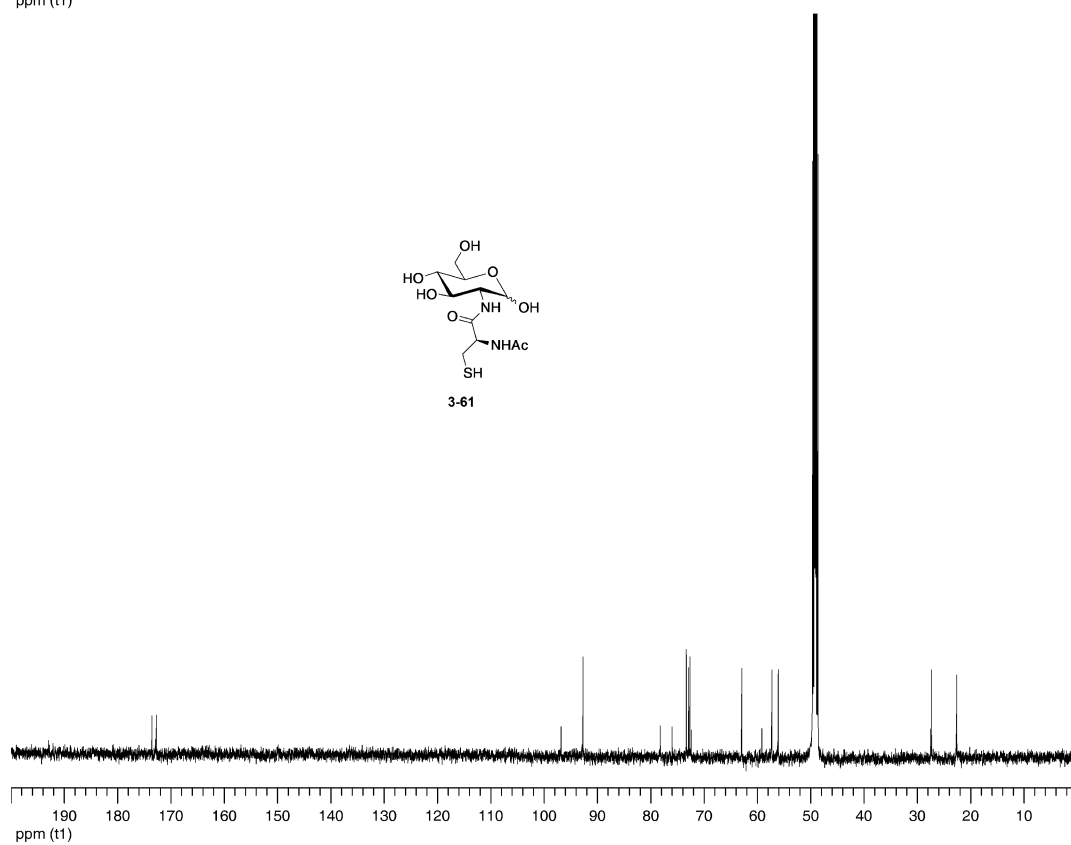
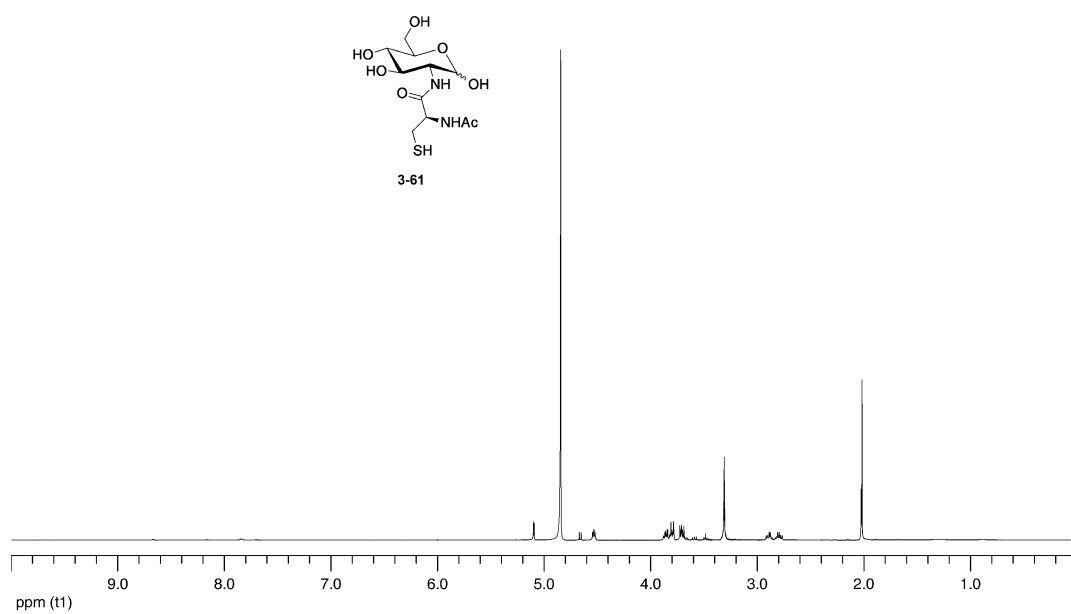


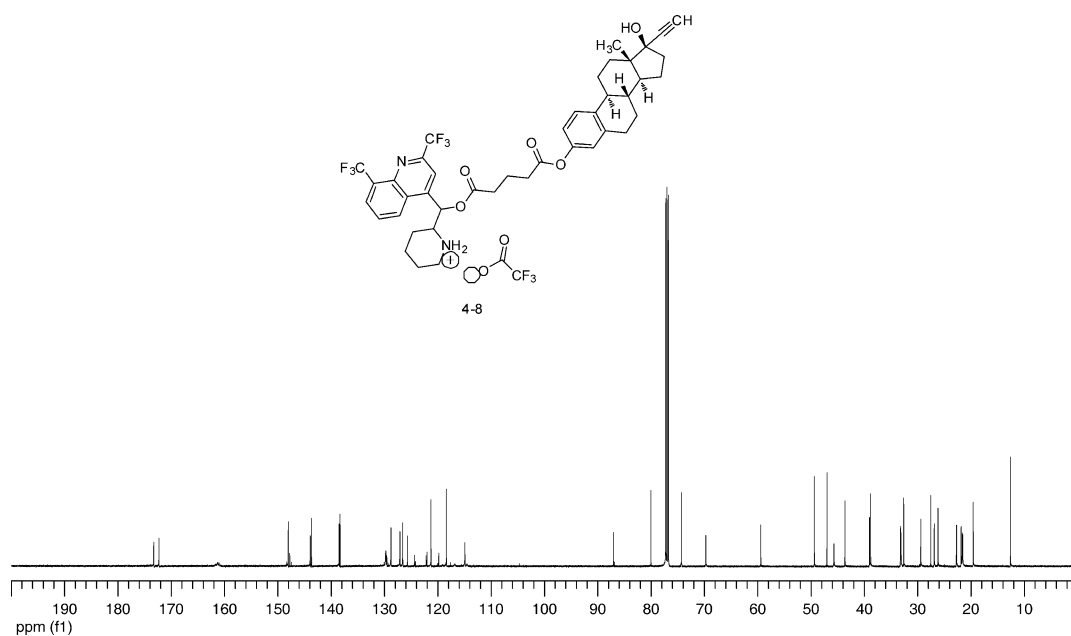
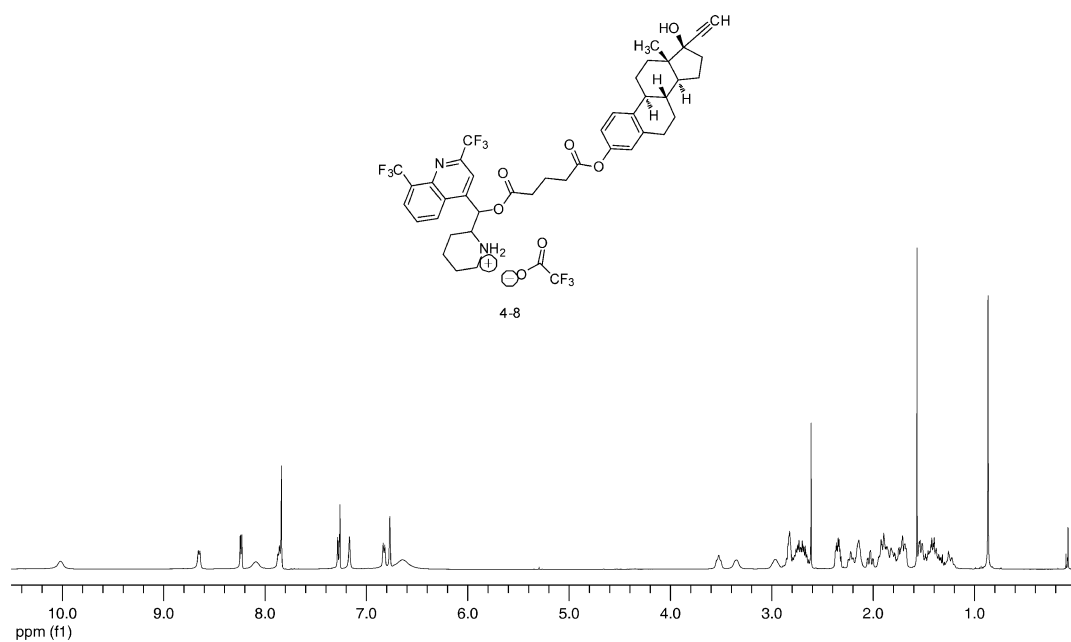


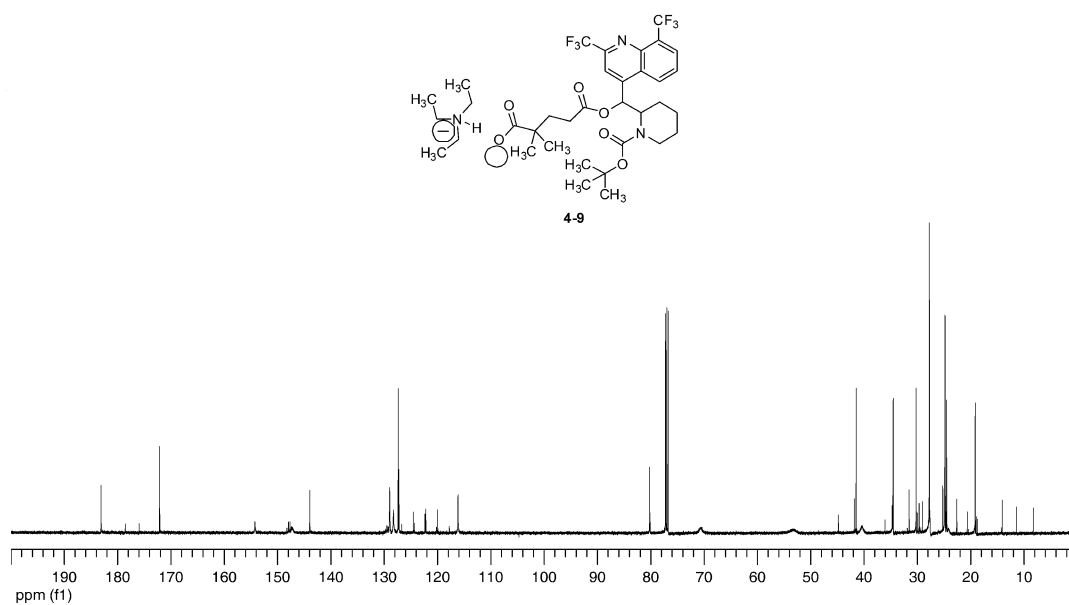
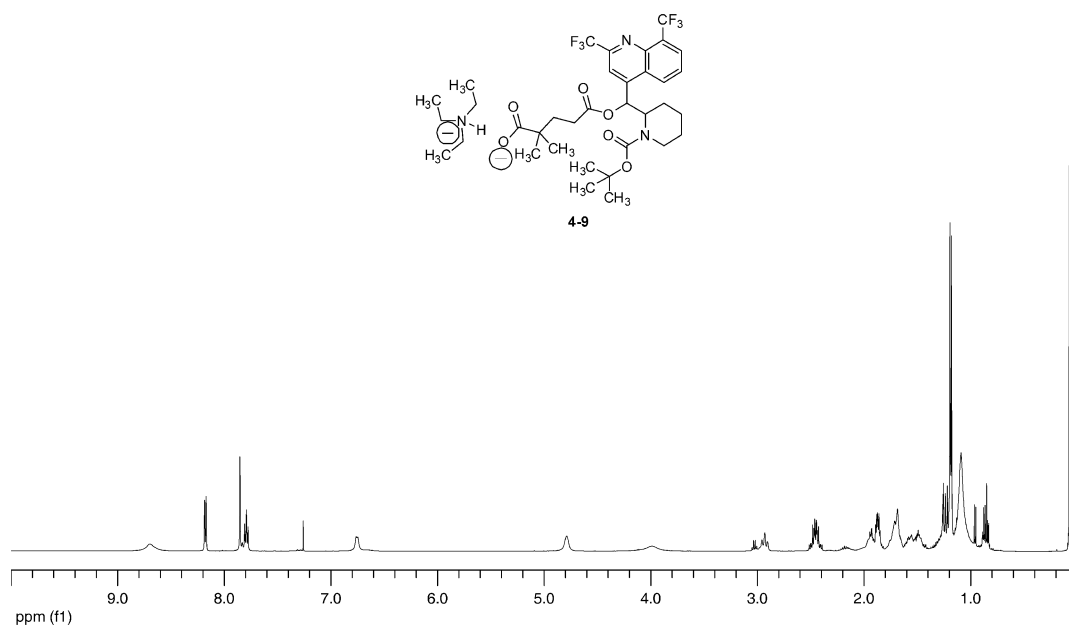


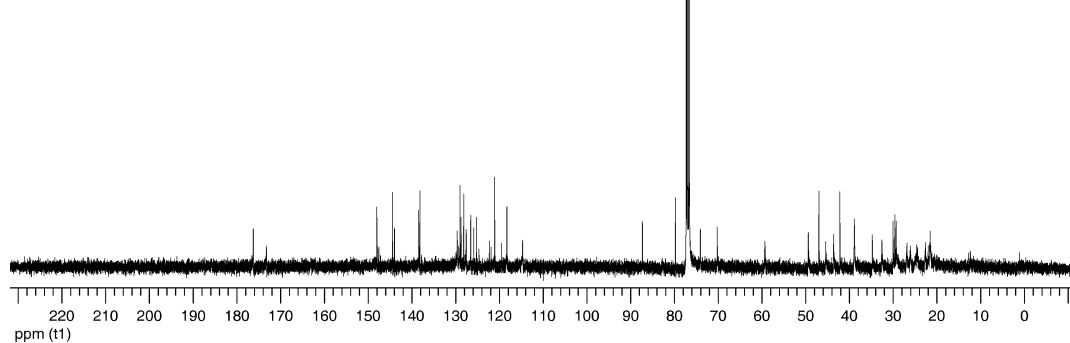
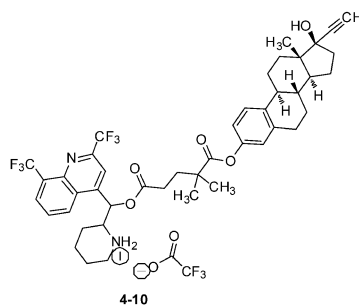
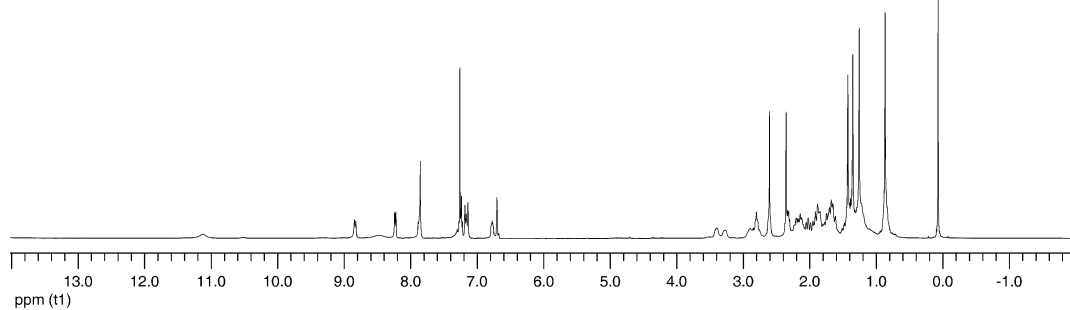
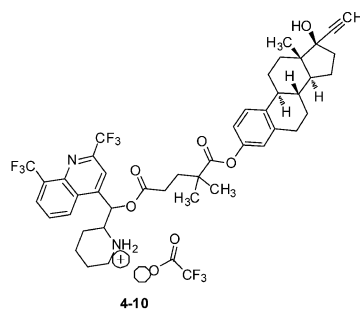


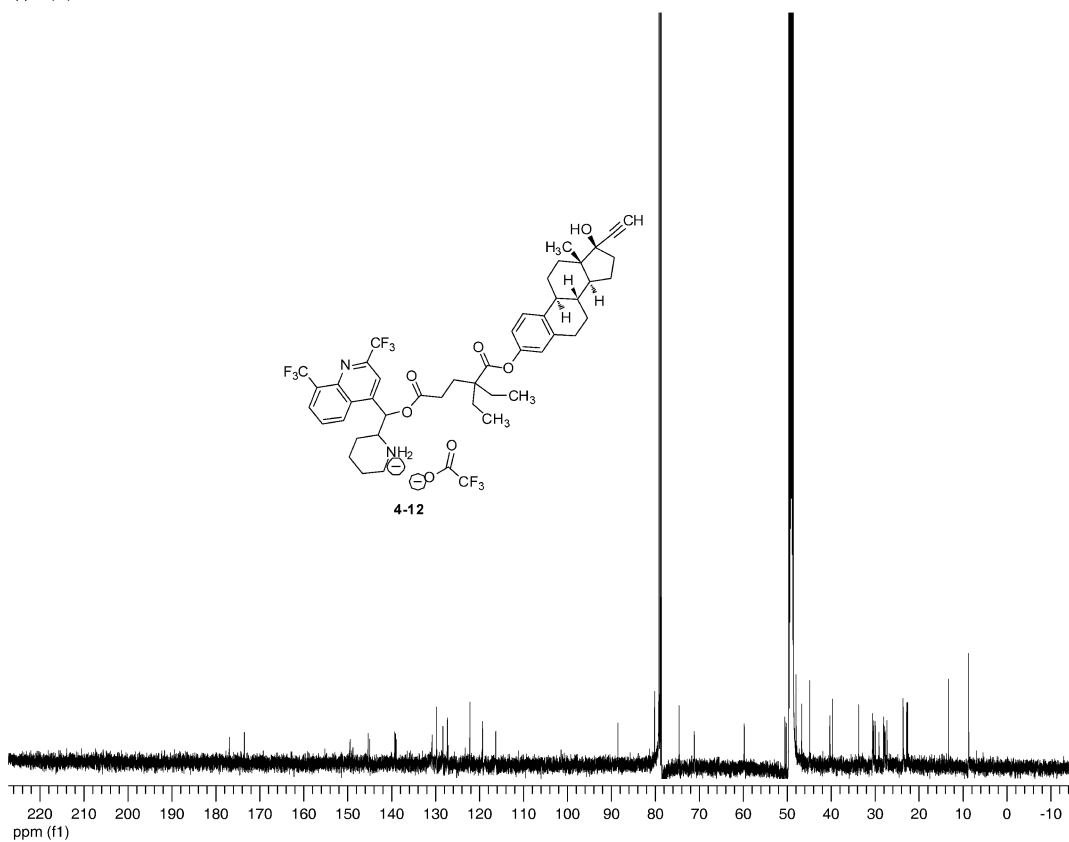
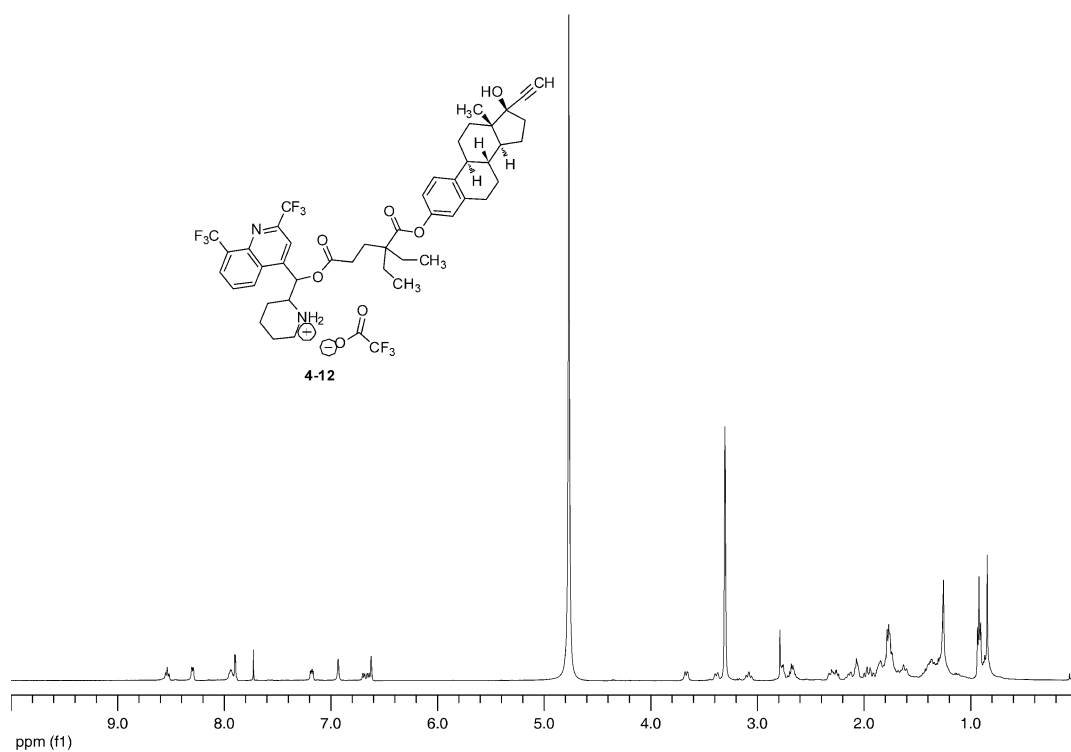


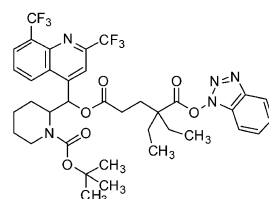




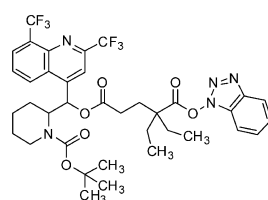
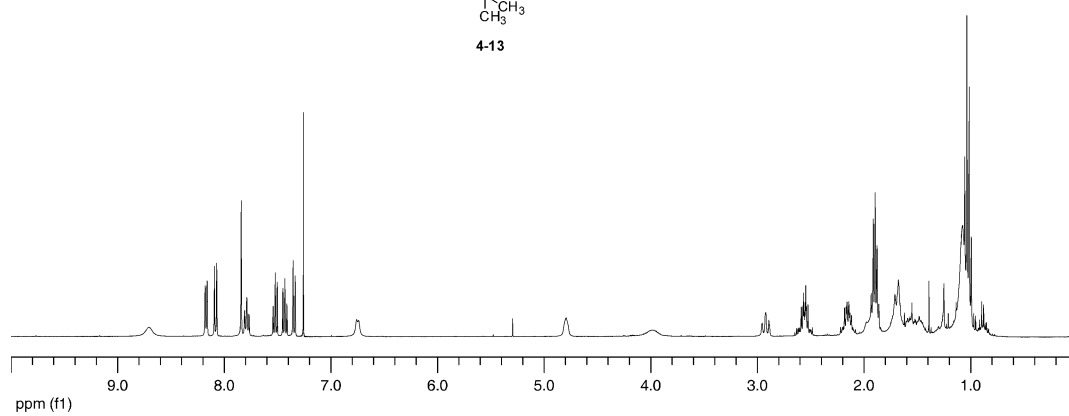




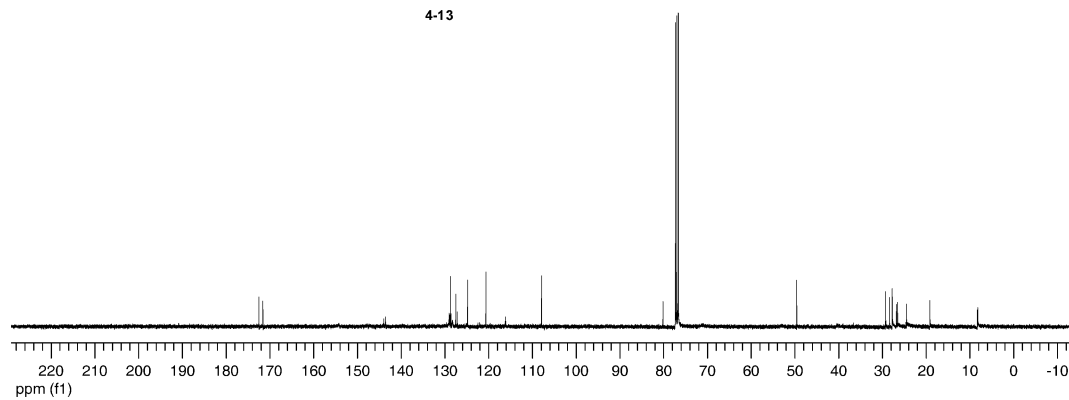


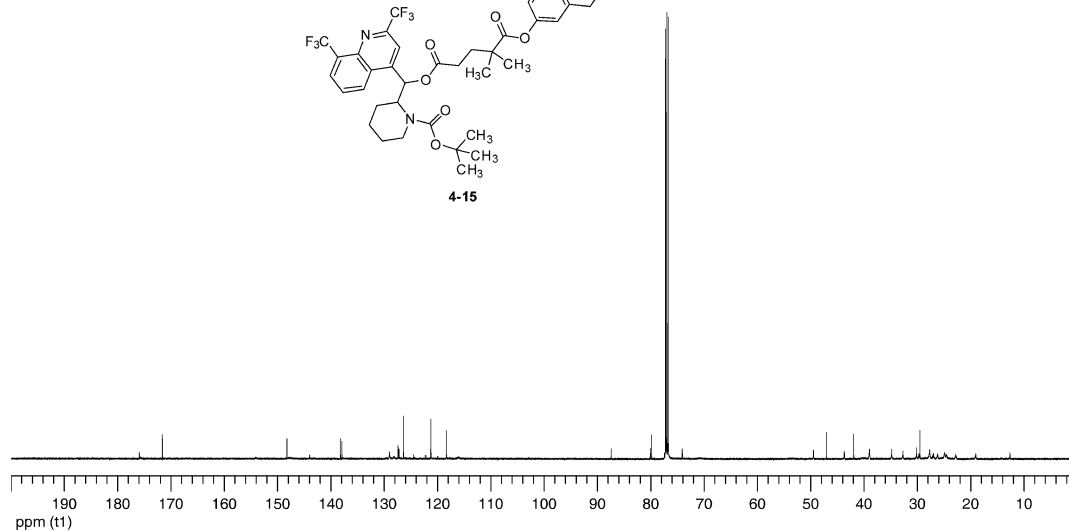
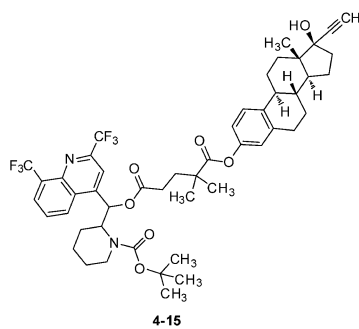
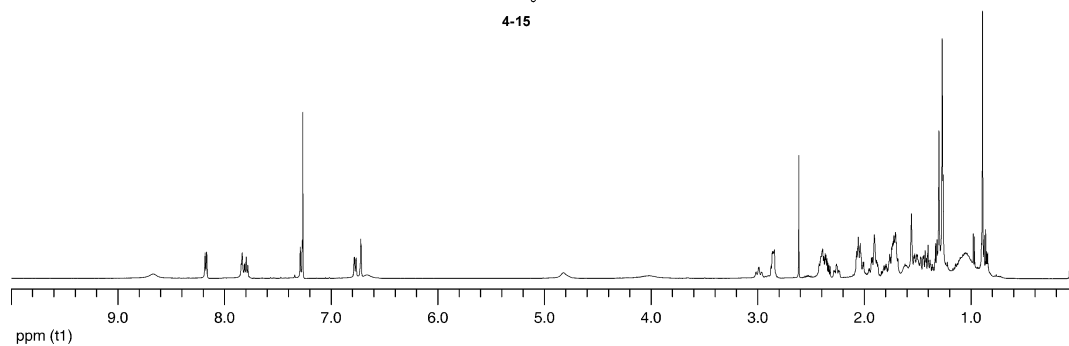
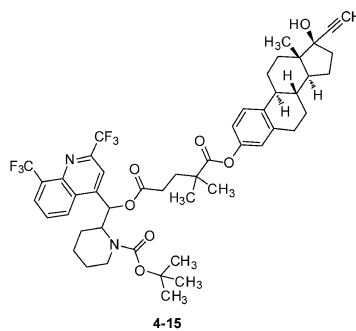


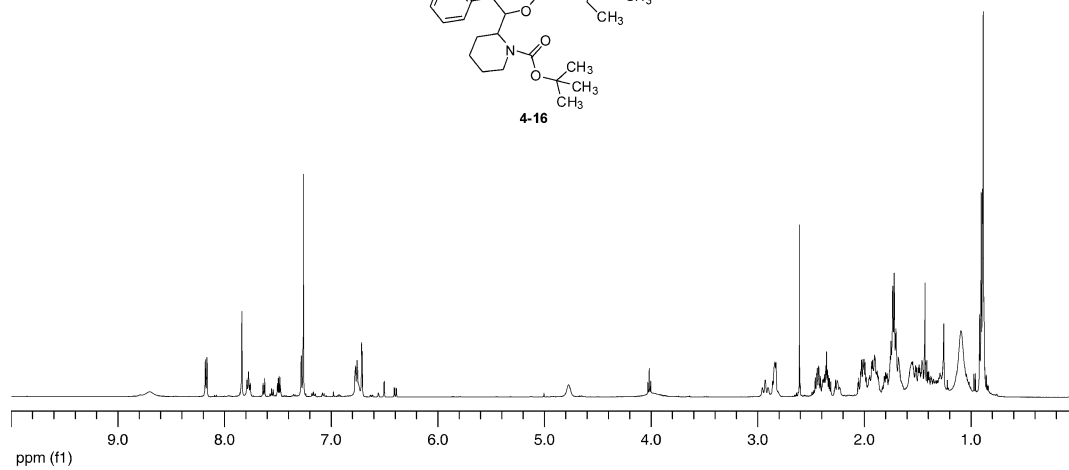
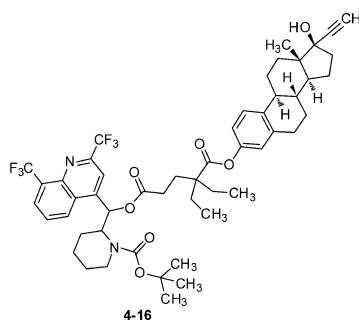
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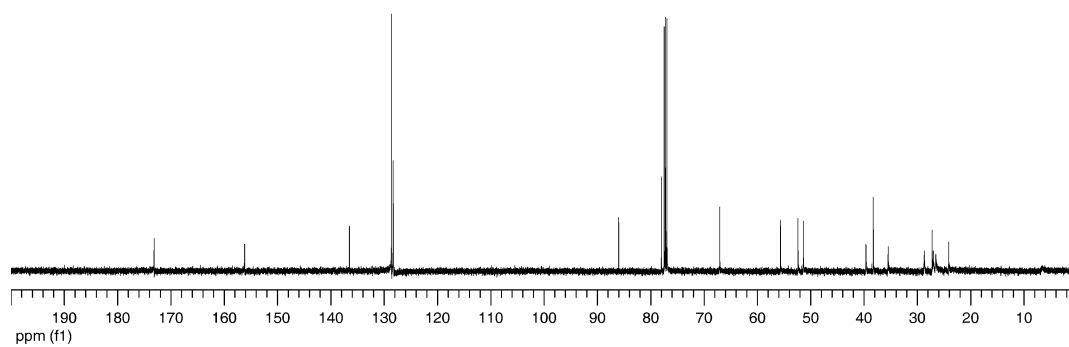
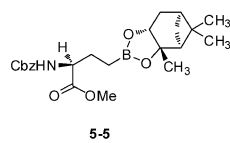
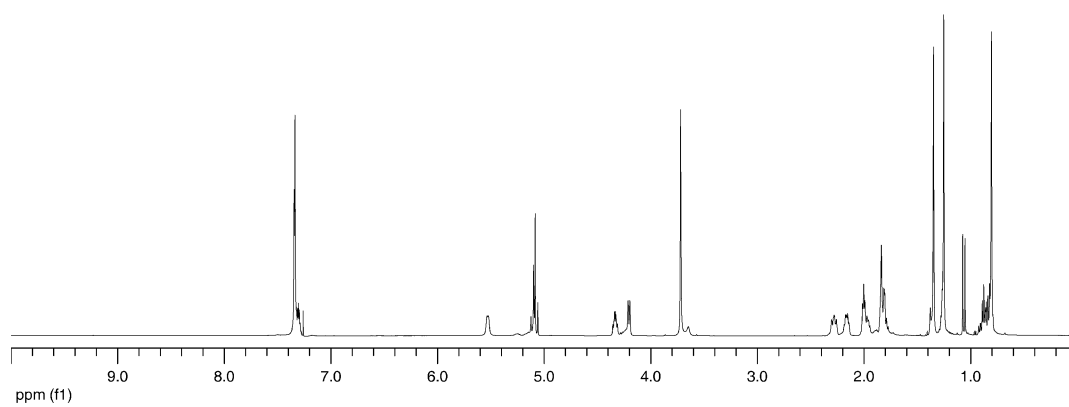
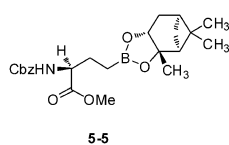


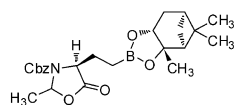
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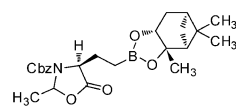
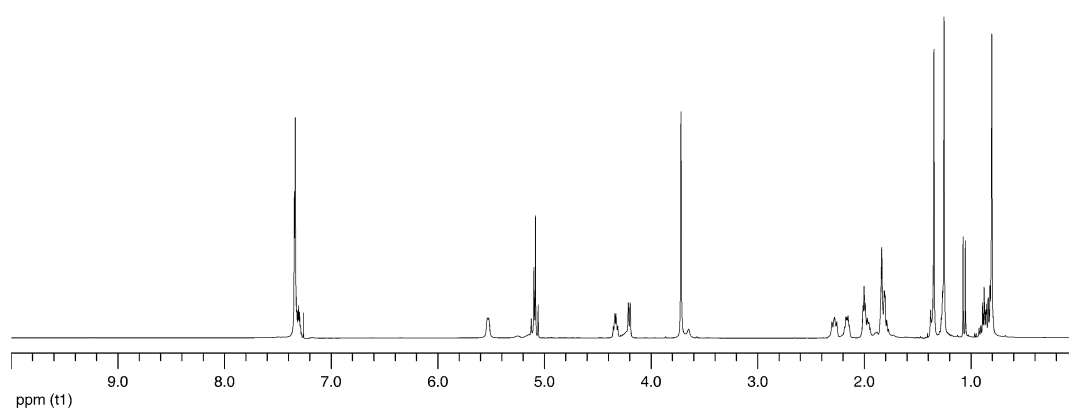




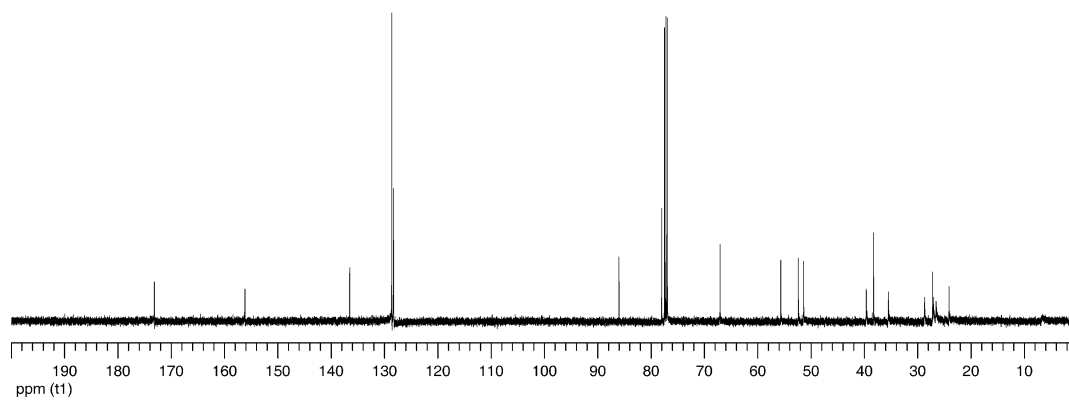


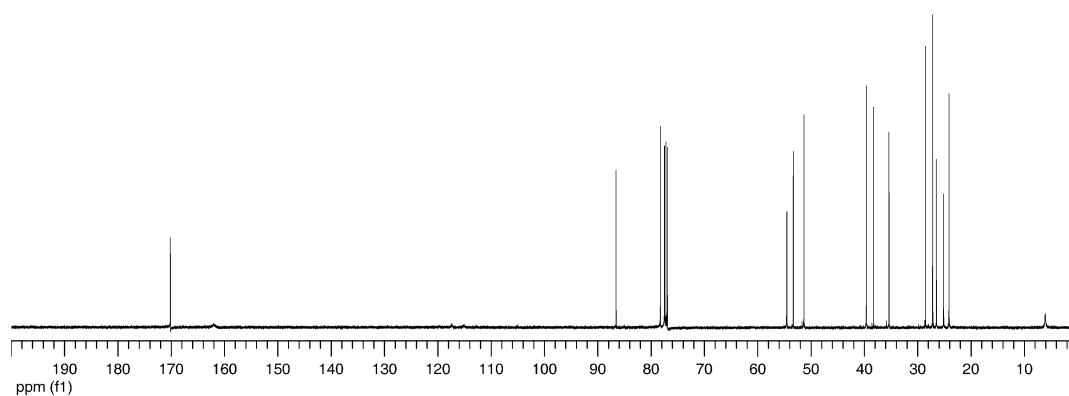
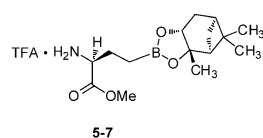
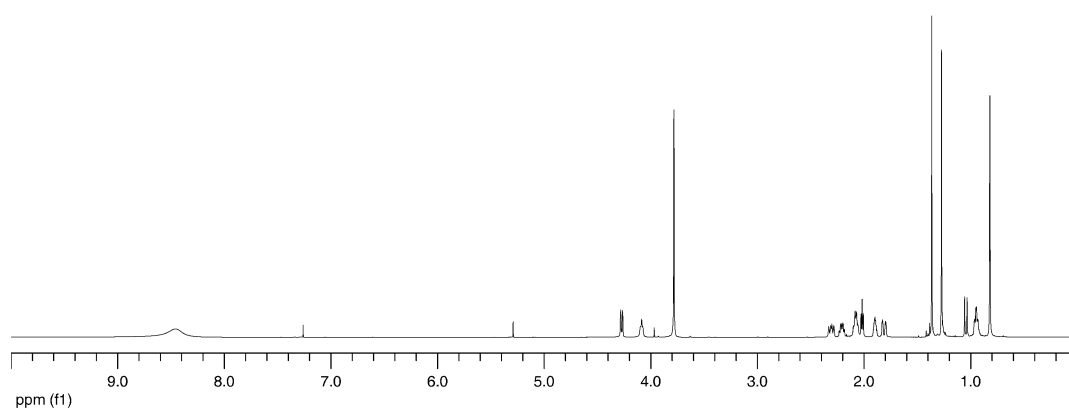
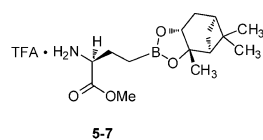


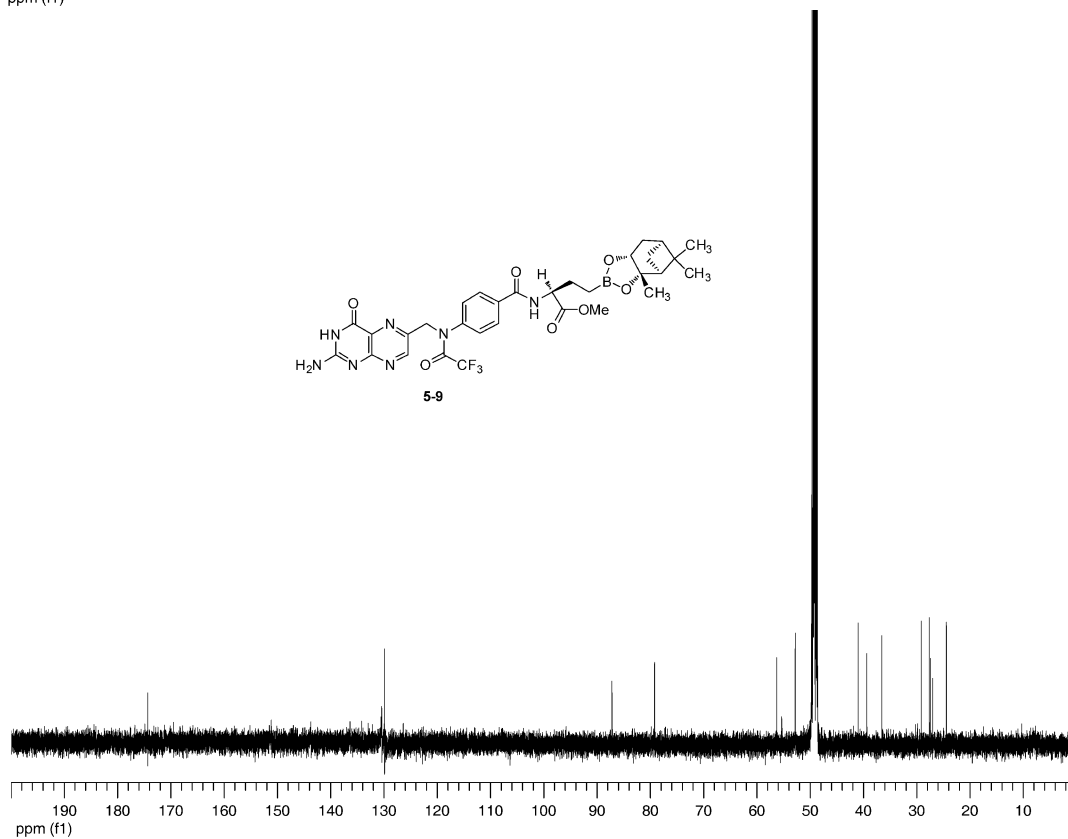
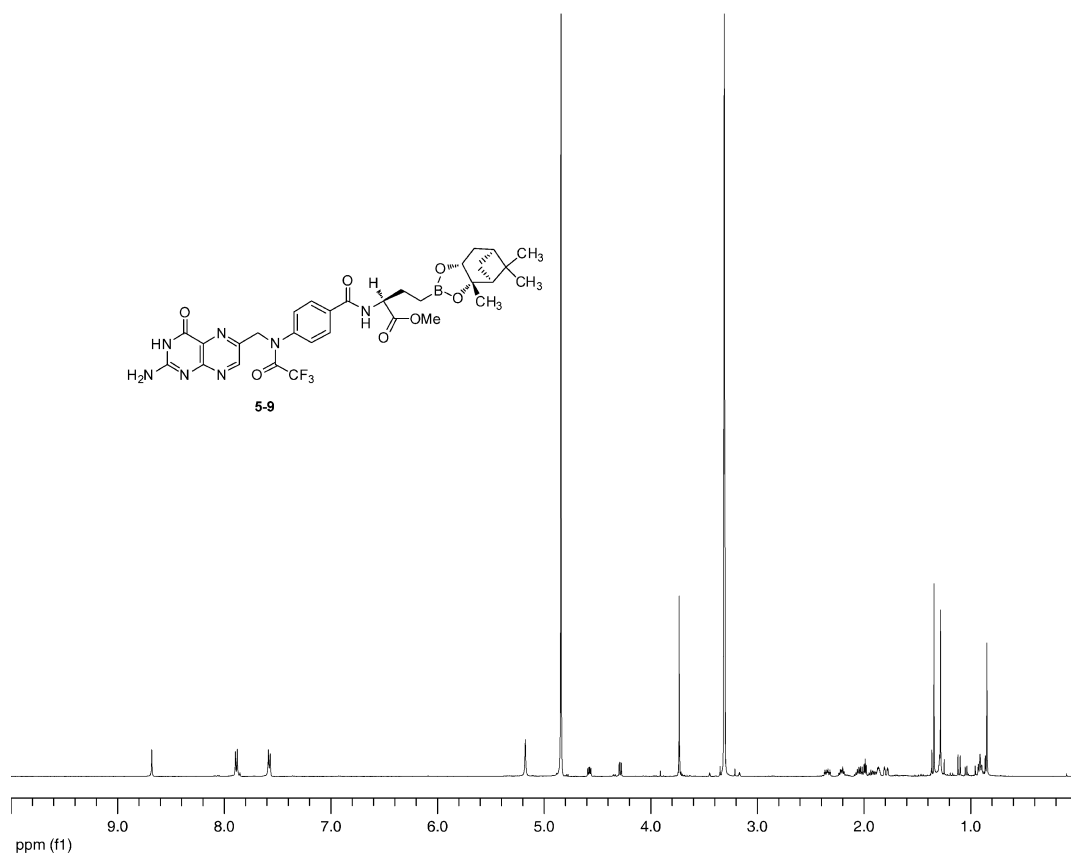
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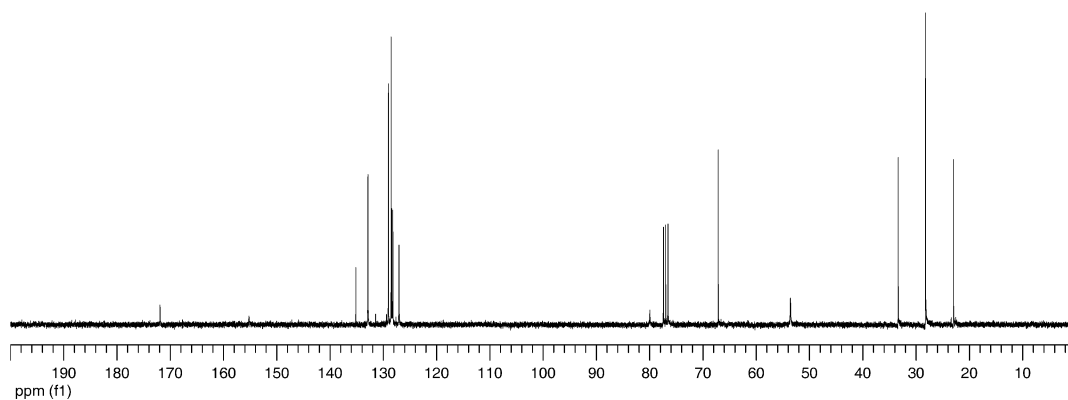
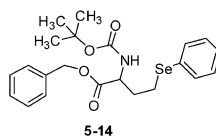
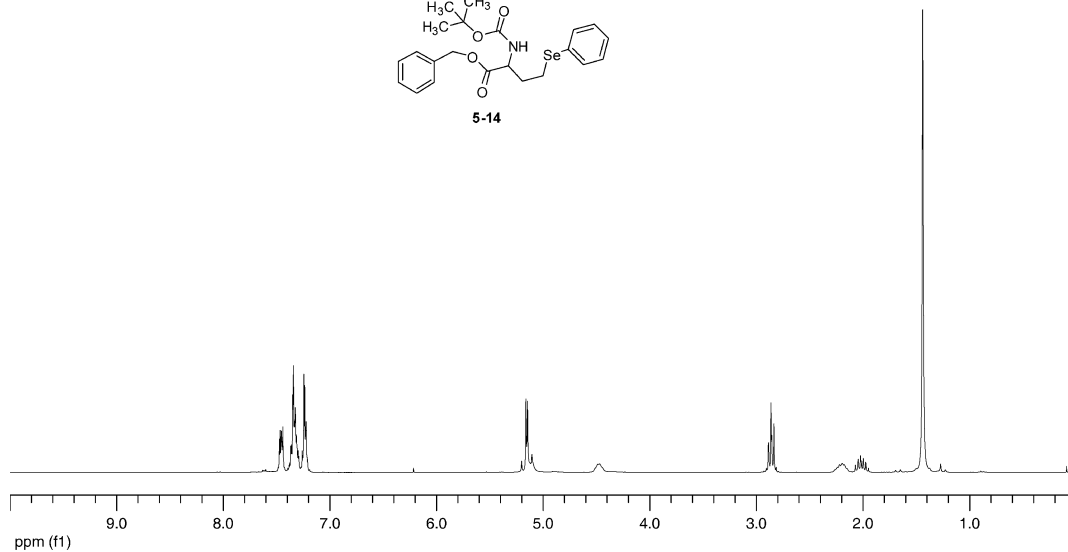
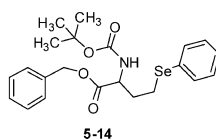


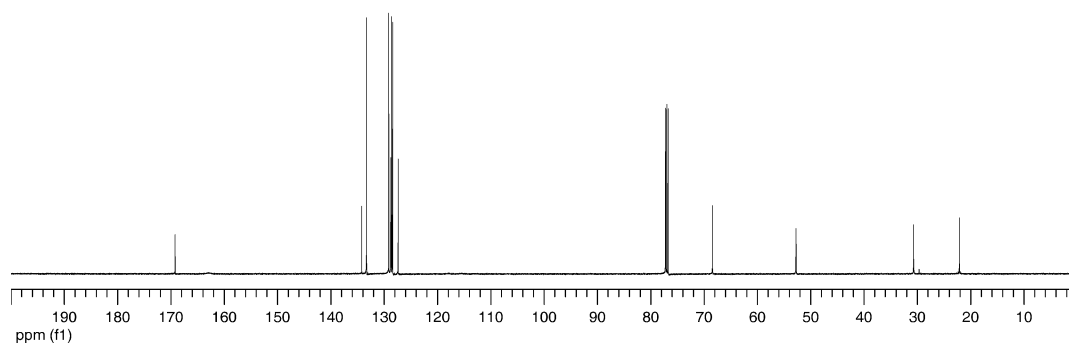
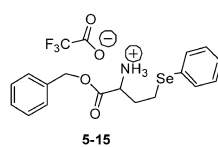
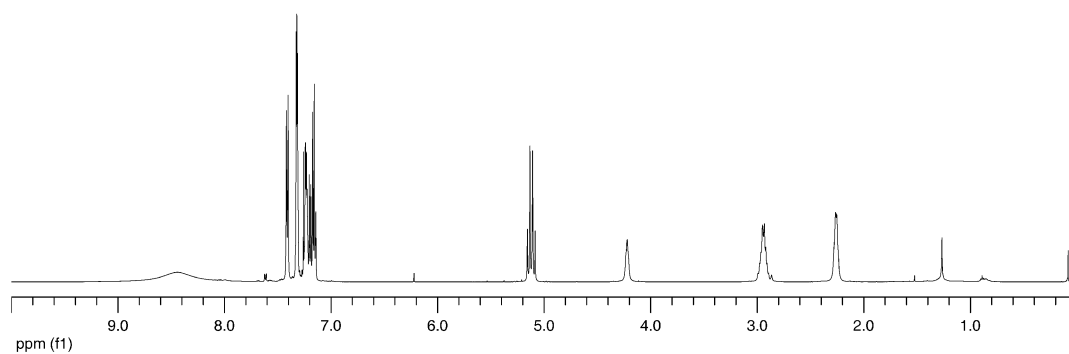
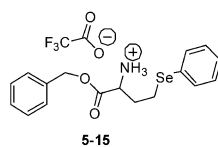
5-6











Curriculum Vitae

Kehinde Ajayi

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| | |
|----------|------------------------------------------------------------------------------------|
| May 2004 | B.A., Philosophy University of Connecticut, Storrs, CT |
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Publications:

Knapp, S.; **Ajayi, K.** "The Anomeric Pudovik Rearrangement." *Tetrahedron Lett.*, **2007**, 48, 1945-1949.

Knapp, S.; Abdo, M.; **Ajayi, K.**; Huhn, R.; Emge, T. J.; Kim, E-J.; Hanover, J. A. "Tautomeric Modification of GlcNAc-Thiazoline." *Org. Lett.* **2007**, 9, 2321-2324.

Ajayi, K.; Thakur, V.; Lapo, R.; Knapp, S.; "Intramolecular α -Glucosaminidation: Synthesis of Mycothiol." *Org. Lett.*, submitted.