

Synthesis of Novel Types of Polyester Glycodendrimers and the Development and Applications of an Efficient Alternative to Multistep Regioselective Esterification in Diols and Polyols

by

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DALHOUSIE UNIVERSITY
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To my father who always advised me to make education my top priority no matter what else maybe going on in my life and to Manuela Gania Twibanire, who I love very much.

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ABSTRACT

Polyester dendrimers are attractive for biological applications because they are biodegradable and non-toxic. The preparation of a variety of core molecules that are compatible with deprotection using hydrogenolysis is presented. Previous syntheses of polyester dendrimers have mainly focused on the use of dibranched building blocks or dendrons. Chemistry was developed for the synthesis of novel tribranched dendrons and lower generation dendrimers have been prepared. It was found that formation of successive generations using tribranched dendrons was not possible, presumably because of steric hindrance, but dendrimers containing alternating generations of dibranched and tribranched dendrons could be formed.

In the search for a mild esterification method which would allow convergent synthesis of dendrimers, it was demonstrated that coupling agents namely, TBTU, TATU, and COMU are efficient promoters of ester bond formation between carboxylic acids and all types of alcohols in the presence of organic bases. It was shown that regioselective esterification of diols and polyols is possible based on whether the alcohols are primary, secondary, or tertiary, with choice of base and coupling agent. The base sensitivity of the TBTU-promoted esterification was used in the preparation of a library of the Lyme disease antigens termed *Borrelia burgdorferi* glycolipid 1 that contain esters of different fatty acids connected to O-6 of cholesteryl β -D-galactopyranoside. In addition, the direct synthesis of maradolipids from the dauer form of the nematode *Caenorhabditis elegans*, and other trehalose 6-monoesters and 6,6'-diesters was demonstrated.

Finally, novel types of polyester glycodendrimers have been synthesized using click chemistry to attach α -D-mannopyranosyl glycosides bearing alkyne groups at the termini of their aglycones to polyester dendrimers with terminal azide groups, and these will be evaluated as anti adhesion drugs against urinary tract infections.

LIST OF ABBREVIATIONS AND SYMBOLS USED

| | |
|----------|--|
| Ac | acetyl |
| ADH | alcohol dehydrogenase |
| ADH-LB | alcohol dehydrogenase from <i>Lactobacillus brevis</i> |
| ADH-T | alcohol dehydrogenase from <i>Thermoanaerobacter sp.</i> |
| ax | axial |
| bis-HMPA | 2,2-bis(hydroxymethyl)propanoic acid |
| Bn | benzyl |
| br | broad |
| Bz | benzoyl |
| °C | degree Celcius |
| CAN | ceric ammonium nitrate |
| COMU | 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminoxy) dimethylaminomorpholinomethylene)] methanaminium hexafluorophosphate |
| d | doublet |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | <i>N,N</i> -dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DIBAL-H | diisobutylaluminium hydride |
| DIEA | diisopropylethylamine |
| DMAP | 4-(<i>N,N</i> -dimethylamino)pyridine |

| | |
|----------------|--|
| DMF | <i>N,N</i> -dimethylformamide |
| DOX | doxorubicin |
| DPTS | 4-(dimethylamino)pyridinium <i>p</i> -toluenesulfonate |
| DTPA | diethylenetriaminepentaacetic acid |
| EDC | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| ESI | electrospray ionization |
| Et | ethyl |
| eq | equatorial |
| equiv | equivalent(s) |
| EtOAc | ethyl acetate |
| FLCPs | ferroelectric liquid crystalline polymers |
| <i>J</i> | coupling constant |
| LCPs | linear crystalline polymers |
| LD | Lyme disease |
| M | unit of concentration: moles per litre |
| Me | methyl |
| MeOH | methanol |
| MRI | magnetic resonance imaging |
| MS | mass spectrum |
| MTBD | 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene |
| M _w | molecular weight |
| <i>m/z</i> | mass to charge ratio |
| NaAsc | sodium ascorbate |

| | |
|----------------|--|
| NADH | nicotinamide adenine dinucleotide (reduced form) |
| NMR | nuclear magnetic resonance |
| NSERC | Natural Science and Engineering Research Council of Canada |
| PAMAM | polyamidoamine |
| PBS | phosphate buffered saline |
| PEG | polyethylene glycol |
| PVA | polyvinyl alcohol |
| Py | pyridine |
| quat | quaternary |
| R _F | retention factor for relative migration of a compound on a TLC plate |
| rt | room temperature |
| t | triplet |
| TATU | 2-(1 <i>H</i> -7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate |
| TBTU | 2-(1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate |
| TEMPO | (2,2,6,6-tetramethylpiperidin-1-yl)oxyl |
| TLC | thin layer chromatography |
| TMS | tetramethylsilane |
| TOF | time of flight |
| TsOH | <i>p</i> -toluenesulfonic acid |
| TTF | tetrathiafulvalene |
| UPEC | uropathogenic <i>Escherichia coli</i> |
| UTIs | urinary tract infections |

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Chapter 1. Introduction

Dendrimers are complex macromolecules with well-defined chemical structures. These molecules have attracted the interest of chemists owing to their potential applications in many areas.¹⁻⁵ Dendrimers are nearly perfect monodisperse macromolecules with regular and highly branched three-dimensional architectures, extending outwards from a central core bearing more than one identical reactive center using branched monomers. These architectures are in contrast to those of traditional polymers, which are linear macromolecules with limited branching. The rapidly expanding area of hyperbranched polymers lies between dendrimers and linear polymers.⁶⁻¹² The spectrum of the fields of potential applications of dendrimers is very diverse, ranging from the engineering sector to the medical sector. Activity in the dendrimer field has continued to accelerate since its inception in the 1980s.¹³⁻²¹ For instance, there were 132 citations to the terms “dendrimer or dendrimers” in 1995, 677 citations in 2000, 1196 citations in 2005, 16372 citations in 2008, 28429 in 2011, and 37189 in 2012. Although many types of structures have been synthesized, the enormous structural diversity of both organic and inorganic chemistry guarantees that there are a huge number of potential novel types of dendrimers yet to be synthesized. Consequently, properties and new potential applications are still essentially unexplored.

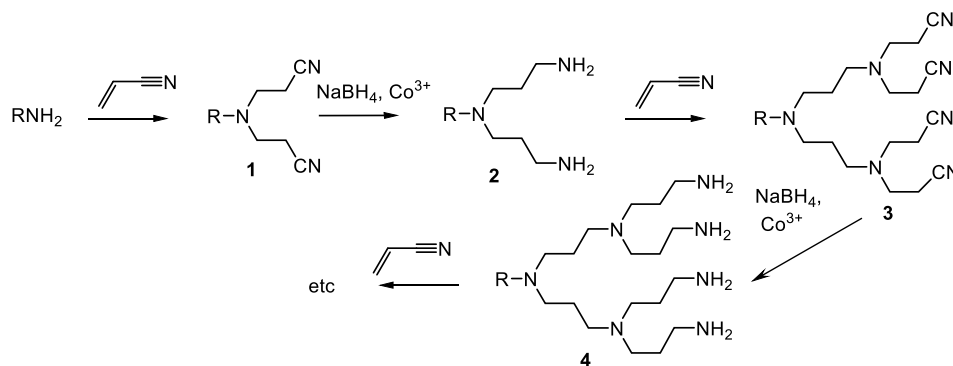
The synthesis of new types of dendrimers with new properties and new potential applications was targeted here. By using known methods, the focus was on the synthesis of polyester dendrimers because they are non-toxic and they offer the possibility of releasing entrapped or covalently attached biologically active molecules *in vivo*.²²

This thesis contains an introduction to dendrimers that discusses a wide range of key issues including their origin, chemistry and structure, functionalization and properties, synthetic

methods, and applications. Following this is a summary of other polyester dendrimers that have appeared in the literature. The next five chapters discuss results, which include the design and synthesis of core molecules and dendrons, esterification using uronium-based coupling agents, the preparation of Lyme disease antigens, the direct synthesis of maradolipids, and the preparation of early generation dendritic polyols. Also discussed herein is the synthesis of novel polyester glycodendrimers as potential inhibitors of urinary tract infections.

1.1. Origin of Dendrimers

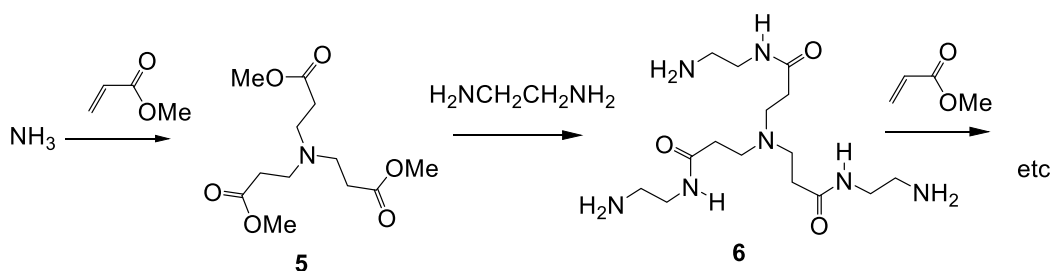
Dendrimers are the most recently recognized members of the polymer family, with the first dendrimer report published in 1978.²³ In this report, Vögtle and coworkers described highly branched molecules prepared by exhaustively performing Michael-type reactions of acrylonitrile with an amine followed by the reduction of nitrile groups to primary amines. When this first generation polyamine was treated with acrylonitrile followed by reduction in the same way, a second-generation dendrimer was produced. Further repetition produced higher generation highly branched amines with defined structures as shown in Scheme 1.²³



Scheme 1 Vögtle's early synthesis of dendritic species

In 1981, Denkewalter (then at Allied Corporation) and coworkers described dendritic polylysine.²⁴ A few years later in 1985, Tomalia reported the synthesis and characterization of a

new dendritic family.²⁵ In this synthesis, ammonia was reacted with methyl acrylate, followed by amidation of the resulting esters with excess ethylenediamine, which produced the next layer of reactive amine groups. Scheme 2 illustrates the synthesis of Tomalia's dendrimers, now commercialized as poly(amido amine) (PAMAM) dendrimers.²⁵ Shortly after, in the same year, Newkome reported initial results about the synthesis of tribranched dendritic amides.²⁶ Further developments occurred in the late 1980s but the review by Tomalia²⁷ sparked an explosion of research that has continued to the present,²⁸⁻³² including the first syntheses of polyester dendrimers.^{33,34}



Scheme 2 Tomalia's synthesis of the class of dendrimers known as PAMAM

1.2. Chemistry, Structure, and Synthetic Methods

Dendrimers are regularly branched macromolecules composed of multiple perfectly branched monomers that elongate radially from a central core, similar to the branches of some trees. A dendrimer can be divided into three different regions: the core, the interior (or branches) and the periphery.³⁵⁻³⁷ Figure 1 depicts the features of a dendritic architecture.^{36,37} The number of branching points encountered upon moving outward from the core to its periphery defines its generation. These macromolecules are prepared in a stepwise fashion^{25,30,38,39} and therefore, the products are theoretically monodisperse in size. A monodisperse product is extremely desirable not only for synthetic reproducibility, but also for reducing experimental and therapeutic

variability.^{22,40,41} A dendrimer may be based on practically any type of chemistry, the nature of which can determine its solubility, degradability and biological activity. Dendrimers are associated with various interesting properties, but perhaps the most exploited of them all is their multivalency. Unlike in linear polymers, as dendrimer molecular weight and generation increase, the terminal units become more closely packed. This feature has been exploited by many researchers as a way of achieving concentrated payloads of drugs or spectroscopic labels for therapeutic and imaging applications.⁴²⁻⁴⁴ The resulting interaction between a dendritic array of ligands and a cell or other target bearing multiple receptors leads to a greatly increased binding affinity between the dendrimer and the cell compared with the binding of the monovalent ligand to the cell.^{45,46}

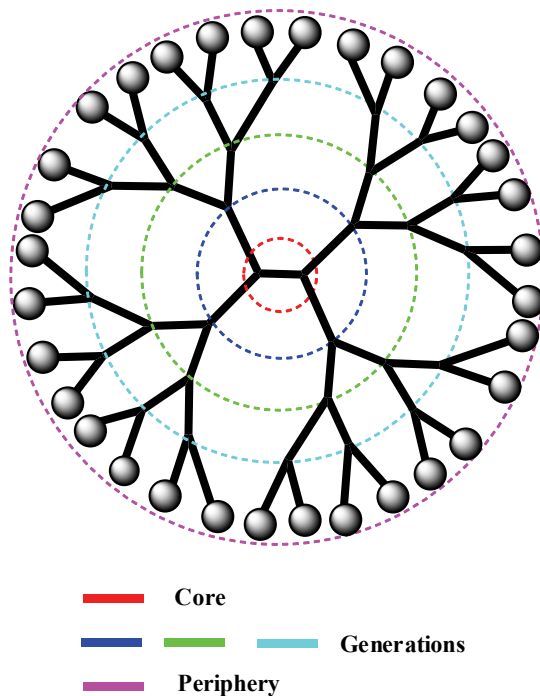
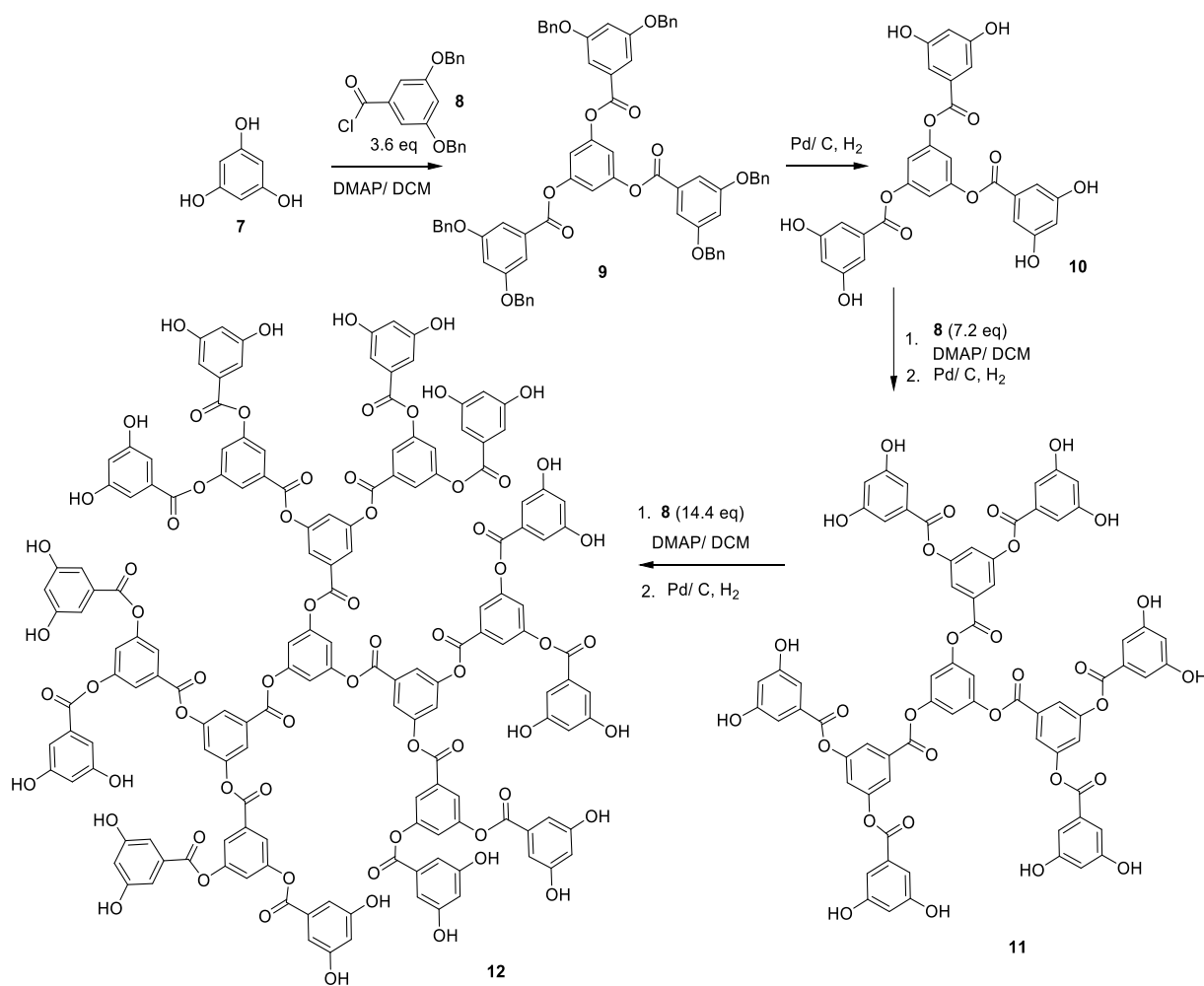


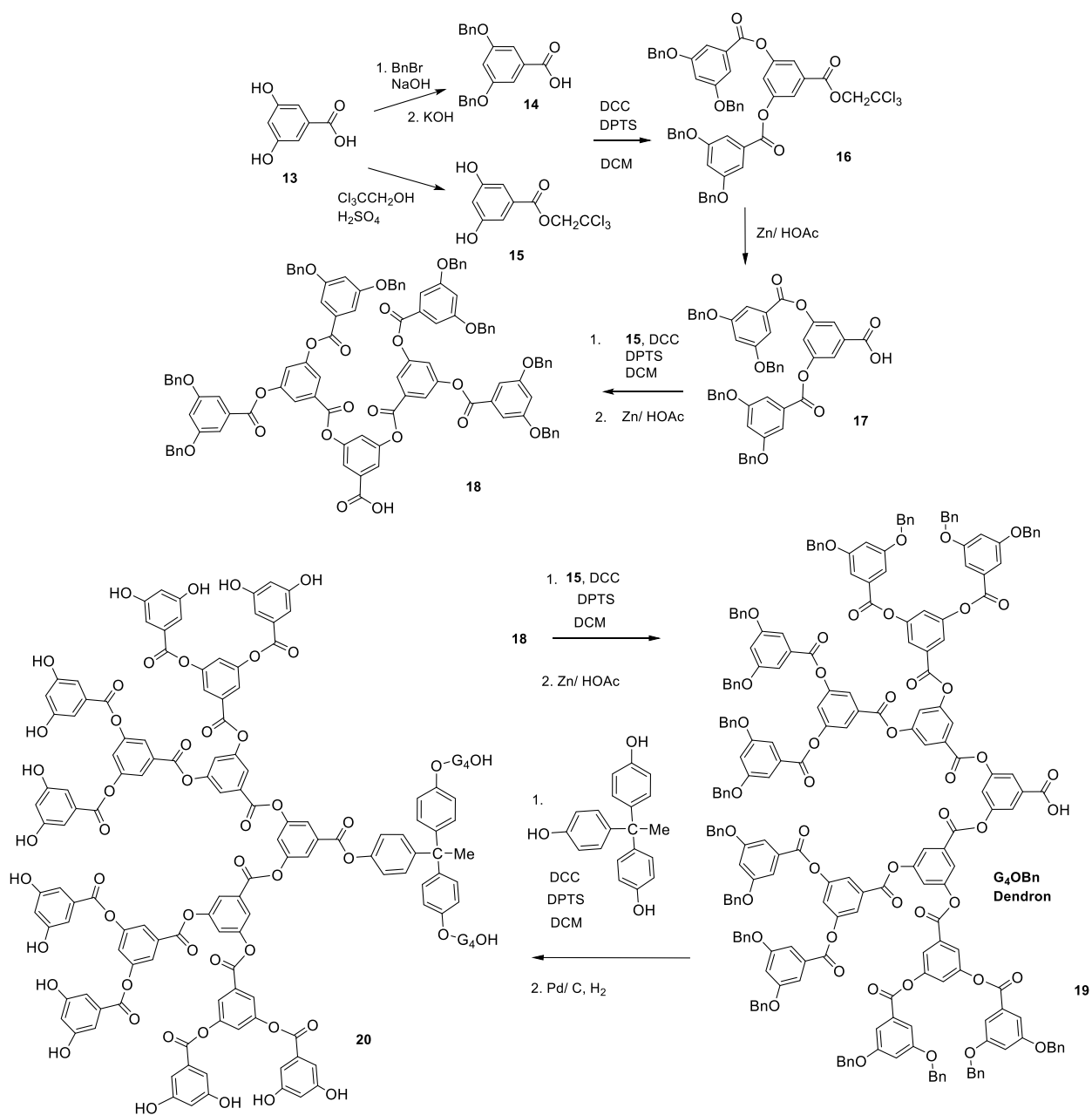
Figure 1 A depiction of the features of dendritic architecture

Two strategies have been formulated for dendrimer synthesis. The divergent approach is more obvious and was used by most of the early workers in the area.^{23,25,26} In this method,

dendrimers grow outwards from a multifunctional core molecule. The core molecule reacts with monomeric molecules containing one reactive and various dormant groups giving the first generation dendrimer. Then the new periphery of the molecule is activated for reactions with more monomers. The process is repeated several times and a dendrimer is built generation after generation. See Scheme 3 for the first example of polyester dendrimer synthesis using this approach.⁴⁷



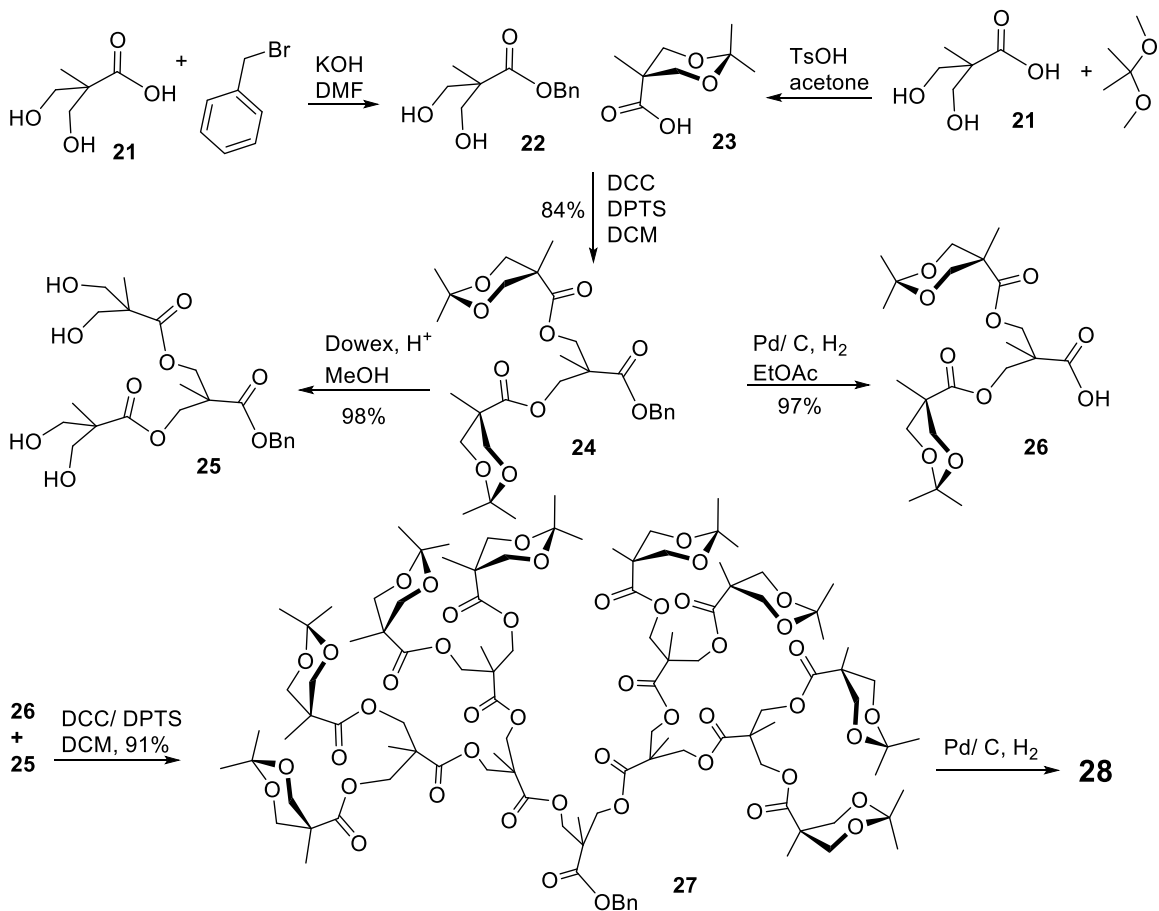
Scheme 3 The first example of the divergent growth approach to polyester dendrimers



Scheme 4 The first convergent synthesis of a deprotected polyester dendrimer

The second, convergent route was developed by Hawker and Fréchet³⁹ as a response to the weaknesses of the divergent approach. In this approach, the units that will be attached to the core, the dendrons, are constructed first. When the growing dendrons have reached the desired size, they are attached to the multifunctional core molecule. This method has several advantages.

It is relatively easy to purify the final product and the occurrence of defects in the final structure is minimised. The convergent route provides better structural control since intermediates are purified better at successive stages of the synthesis. However, this method may not allow the formation of high generations because steric problems may occur in the reactions of the dendrons with the core molecule. Scheme 4 illustrates this approach.³⁴



Scheme 5 Double exponential dendron growth

Reduction in the number of both synthetic and purification steps in convergent dendrimer synthesis can be achieved if a convergent approach is taken to dendron synthesis rather than the strictly divergent synthesis of the dendron illustrated in Scheme 4. This approach, termed double exponential growth,^{15,48,49} is illustrated for polyester dendrimers in Scheme 5.⁵⁰ In this

methodology, monomers of both convergent and divergent growth are prepared using a single starting material. When the two resulting monomers are reacted, an orthogonally protected trimer that is usually ready to repeat the growth is obtained.

1.3. Functionalization and Properties of Dendrimers

Polymer chemistry and technology have traditionally focused on linear polymers, which are widely in use.⁵¹⁻⁵⁵ Linear macromolecules only occasionally contain some smaller or longer branches. In the recent past it has been found that the properties of highly branched macromolecules can be very different from conventional polymers.²² The structure of these materials has also a great impact on their applications.

Following their synthesis, dendrimers are typically functionalized in accordance to the features the researcher wants them to display and the application they are intended for. The functionalization methods most commonly used are filling the dendrimer cavities, modification of the dendrimer core, and modification of the dendrimer surface.^{56,57} A literature review revealed that modification of the dendrimer's surface is the method mostly used, after which dendrimers may display a range of properties such as polyvalency, flexible charge, solubility properties, and flexible binding properties.^{25,56-60}

Because of their molecular architecture, dendrimers show some significantly different physical and chemical properties when compared to traditional linear polymers. In solution, linear chains exist as flexible coils; in contrast, dendrimers form tightly packed balls.⁶¹ The presence of many chain-ends is responsible for high solubility and miscibility and for high reactivity.⁶² Because of their globular shape and the presence of internal cavities, dendrimers have some interesting properties; one of the most important ones is the possibility to encapsulate guest molecules in the macromolecule's interior. Meijer and co-workers⁶³ trapped small

molecules like *p*-nitrobenzoic acid inside the ‘dendritic box’ of a poly(propylene imine) dendrimer with 64 branches on the periphery and guest molecules were stably encapsulated inside the dendritic box. Hydrolysing the outer shell could liberate the guest molecules.

1.4. Applications of Dendrimers

1.4.1. Introductory Remarks

There are now many families of dendrimers, each with interesting properties, since the surface, interior and core can be tailored to different sorts of applications. Many potential applications of dendrimers are based on their unparalleled molecular uniformity, multifunctional surface and presence of internal cavities.^{25,64,65} These specific properties make dendrimers suitable for a variety of high technology uses including biomedical and industrial applications. Properties like polyvalency, defined architecture, size and shape control, loading capacity, and biocompatibility could be exploited singularly or in combination, making it possible to use dendrimers in a large variety of fields.

1.4.2. Dendrimers for Biological Applications

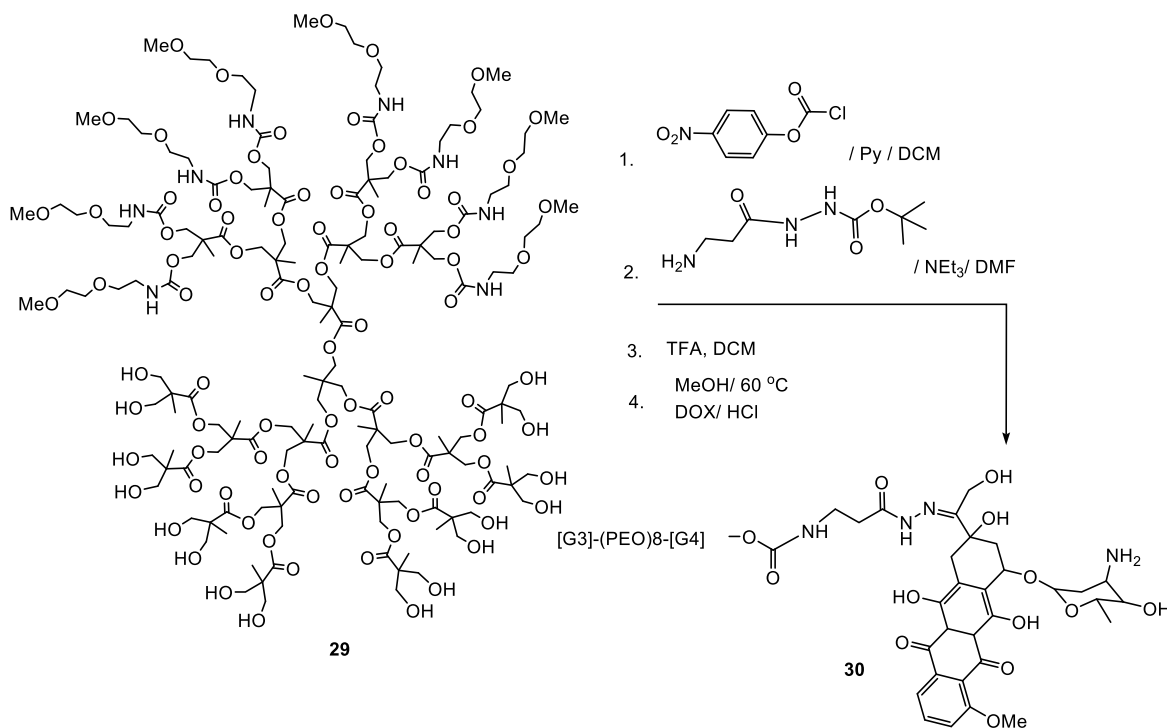
The early use of dendrimers in biology and medicine has been reviewed.^{17,21,41} However, new applications and new dendrimer architectures have appeared in the past few years.

1.4.2.1. Drug Delivery

By attaching a drug to a suitable carrier it is possible to enhance its aqueous solubility, increase its circulation half-life, target the drug to certain tissues, improve drug transit across biological barriers, and slow drug metabolism. Optimization of these features to maximize drug bioavailability to diseased tissues while minimizing drug exposure to healthy tissues, results in improved therapeutic efficacy.

A variety of carriers, including small molecule substrates for cellular receptors and transporters, proteins, and soluble polymers, have been used for this purpose.⁶⁶ Numerous reports on the *in vitro* efficacy of purely dendrimer-based drug carriers have been published,^{35,60,67,68} but only a few *in vivo* therapeutic studies exist. One of the earliest examples of anti-tumor drug delivery with dendrimers was achieved by complexing cisplatin (20–25% by weight) to the surface groups of a G-4 carboxylate-terminated PAMAM dendrimer.⁶⁹ A PAMAM dendrimer with a sodium carboxylate surface was conjugated to cisplatin giving a dendrimer-platinate which was highly water soluble and released platinum slowly *in vitro*. The dendrimer-Pt was also less toxic than cisplatin and thus had potential for further investigation as a novel antitumor approach.

Polyester dendrimers also look very promising as drug delivery systems. A classic example is that of Lee, Gillies, Fréchet, and coworkers.²² The antitumor effect of doxorubicin (DOX) conjugated to a polyester dendrimer was evaluated in mice bearing cancerous tumors. An asymmetric biodegradable polyester dendrimer containing doxorubicin was prepared as shown in Scheme 6.²² The design of the dendrimer carrier optimized blood circulation time through size and molecular architecture, drug loading through multiple attachment sites, solubility through PEGylation, and drug release through the use of pH-sensitive hydrazone linkages. In culture, dendrimer–DOX was greater than 10 times less toxic than free DOX after exposure for 72 h. Upon *in vivo* administration to mice with tumors, dendrimer–DOX was eliminated from the serum with a half-life of 16 hours, and its tumor uptake was ninefold higher than *in vivo* administered free DOX at 48 h.



Scheme 6 Functionalization of bow-tie dendrimers for therapeutic studies

1.4.2.2. Dendrimers with Drug-like Properties

Whereas the majority of dendrimers have been used as carriers for drugs and nucleic acids, some dendrimers act as drugs themselves. Supattapone and coworkers⁷⁰ discovered that branched polyamines, including PAMAM dendrimers and hyperbranched polymers, stimulate the removal of prion proteins present in infected cells. The branched architecture appears essential to this application because linear polyamines and small molecule amines were ineffective.

Multivalent display of ligands on the surface of a dendrimer has also proven to be a viable method of inhibiting multivalent binding between cells, viruses, bacteria, and proteins.^{45,46,71} For example, a G-4 poly(lysine) dendrimer bearing sulfate groups at its periphery is being utilized as an anti-viral topical ointment.^{72,73} By binding in a multivalent fashion to viral

envelope proteins, the dendrimer is able to block adsorption and subsequent entrance of the virus into cells. Although similar results have been achieved previously with linear polyanions, dendrimer polysulfates should be easier to move from the laboratory to the clinic because of their monodispersity, which translates into a consistent product with less therapeutic variability.

1.4.2.3. Imaging

Magnetic resonance imaging (MRI) is a diagnostic method which produces anatomical images of organs and blood vessels. Addition of contrast agents improves the sensitivity and specificity of the method. The gadolinium salt of diethylenetriaminepentaacetic acid (DTPA) is used clinically, but it diffuses into the extravascular area due to its low molecular mass.⁷⁴ Dendrimers are now being utilized as contrast agents for magnetic resonance.^{75,76} Due to their properties dendrimers are highly suited for use as image contrast agents. Several groups have designed and prepared dendritic species for this purpose.^{77,78} Independent findings by these research groups were that dendrimers are stronger contrast agents than conventional ones.

1.4.3. Concluding Remarks

Dendrimers have shown to be associated with various novel applications and are particularly very promising as drug carriers. However, an understanding of the pharmacokinetics of dendrimers is essential for their applications in medicine because the bioavailability, toxicity and ultimately the efficiency of dendrimer-based drugs or imaging agents will depend on their pharmacokinetic profiles.⁷⁹

1.5. Polyester Dendrimers

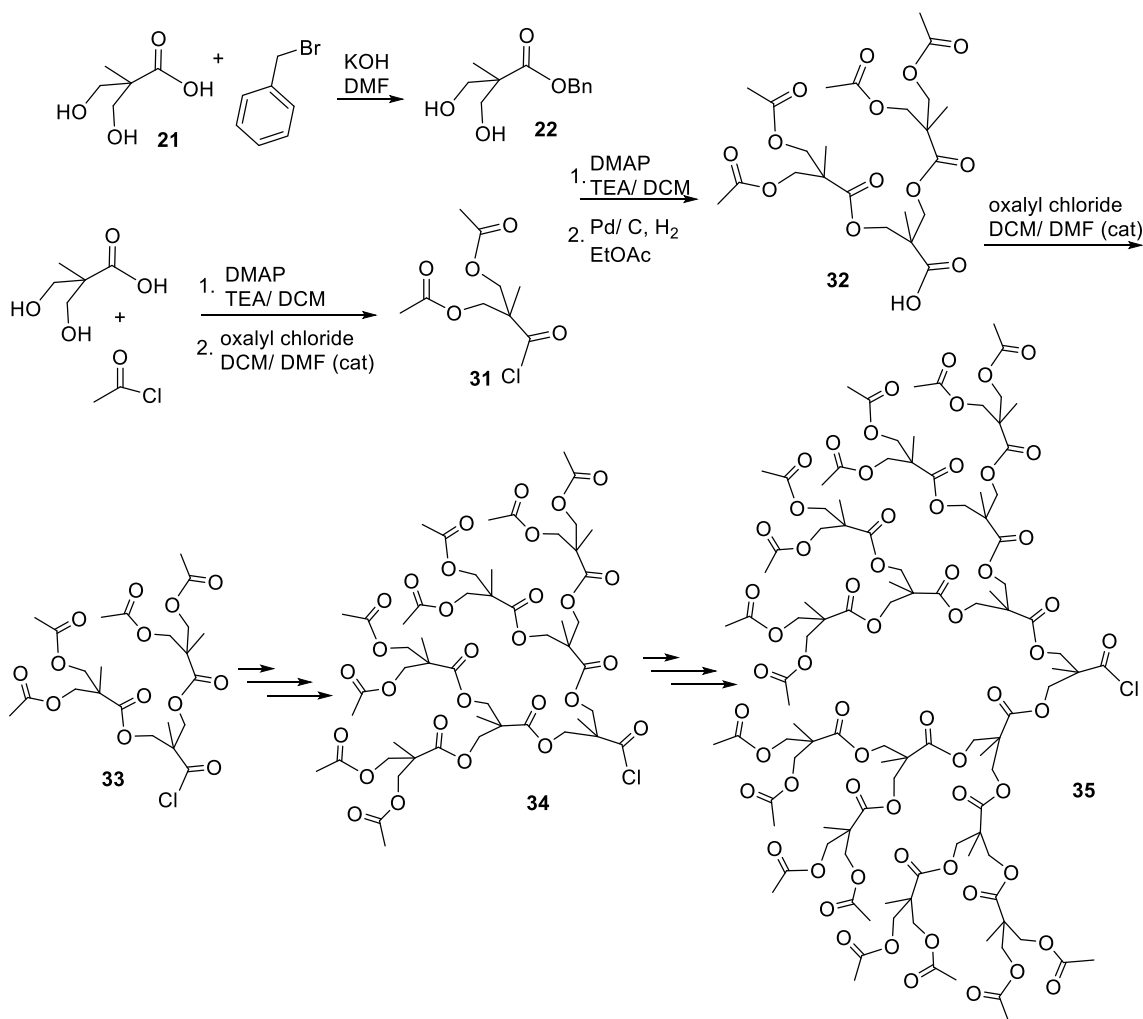
1.5.1. Introductory Remarks

Polyester dendrimers are of considerable interest for biological applications because they are biodegradable and biocompatible.³⁵ A major incentive for the use of polyester dendrimers as frameworks for biological applications is that whenever they have been tested, they have been found to have low toxicity,^{44,80,81} unlike many other dendrimers.⁸² The first report for macromolecules of this type was published in 1991. In this report, Hawker and Fréchet described a one-step synthesis of a hyperbranched polyester possessing a dendritic structure achieved by thermal self-condensation of 3,5-bis(trimethylsiloxy)benzoyl chloride.⁸ Interest in polyester dendrimers have increased considerably since the late 1990s, and today many types of polyester dendrimers have been prepared.

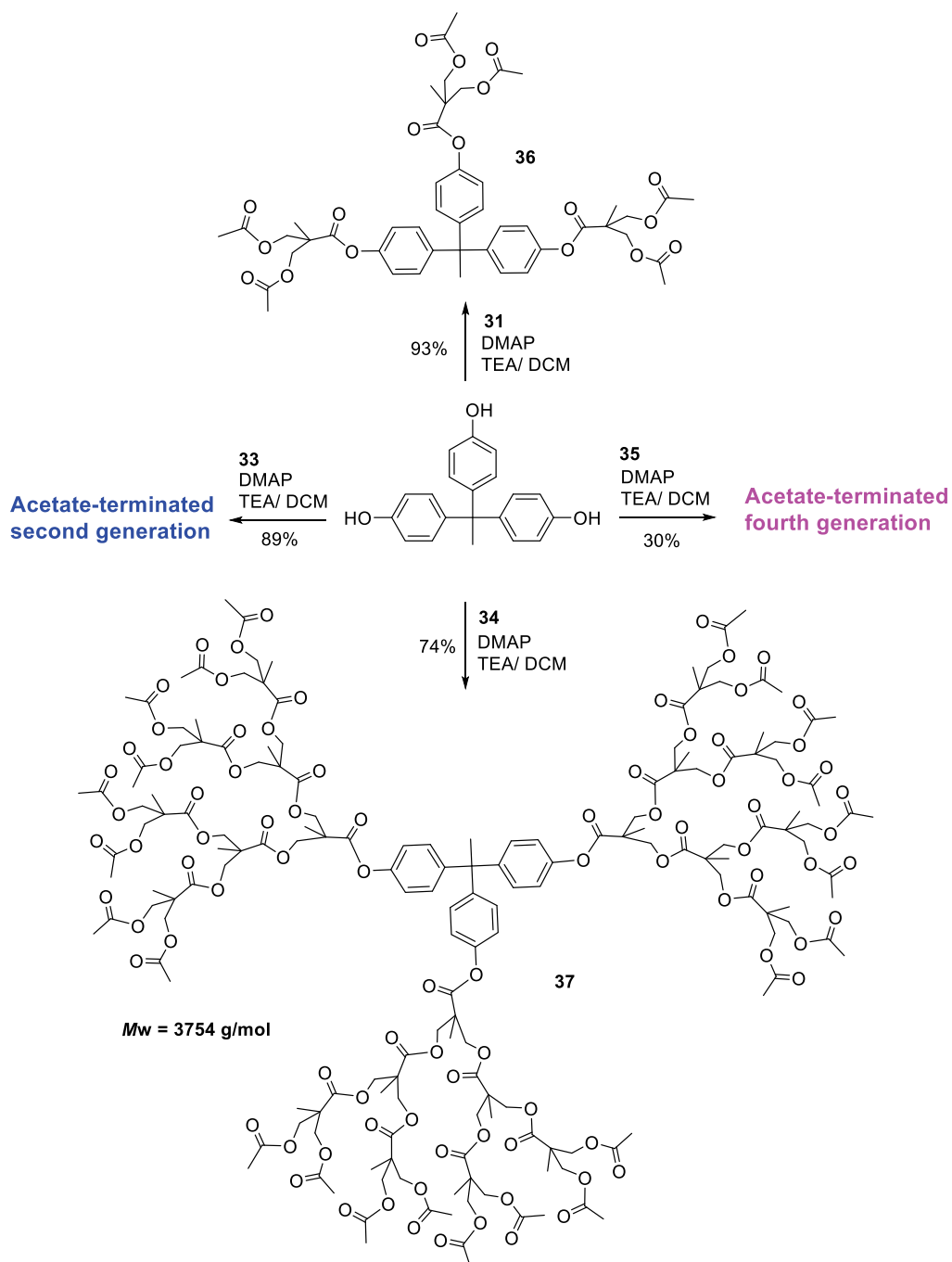
1.5.2. Summary of Other Polyester Dendrimers

Since the pioneering work of Vögtle,²³ Tomalia,^{25,83} and Newkome,²⁶ regarding the synthesis of well-defined three-dimensional macromolecules, interest in dendrimers has continued to increase. Early reports about the synthesis of polyester dendrimers include the work of Ihre, Hult, and Söderlind.²⁸ First to fourth generation dendrons were synthesized from **21** by protecting the carboxylic acid as a benzyl ester group and the hydroxyls as acetate esters (Scheme 7).²⁸ Esterifications were performed by conversion of the acid into the corresponding acid chloride with oxalyl chloride followed by reaction of the acid chloride with the hydroxyl groups in the presence of triethylamine (TEA) and 4-(dimethylamino)pyridine (DMAP). Deprotection using hydrogenolysis allowed repetition. Acetate-terminated polyester dendrimers with 1,1,1-tris(*p*-hydroxyphenyl)ethane as a core were synthesized from generation one to four

(M_w : 906, 1,856, 3,754, and 7,549 g/mol) by adding the above dendrons in a convergent growth approach.²⁸ The simplicity of the ^1H NMR and ^{13}C NMR spectra and elemental analyses suggest that pure and monodisperse dendrimers were obtained. However, attempts to selectively remove the acetate groups in order to obtain the corresponding hydroxyl terminated dendrimers for further chemical surface modification were not successful due to the lack of selectivity in the hydrolysis of the acetate and other ester groups. In addition, lower yields were obtained in the final coupling step of the fourth generation dendrons to the core molecule when compared to the coupling steps used to prepare lower generation dendrimers.



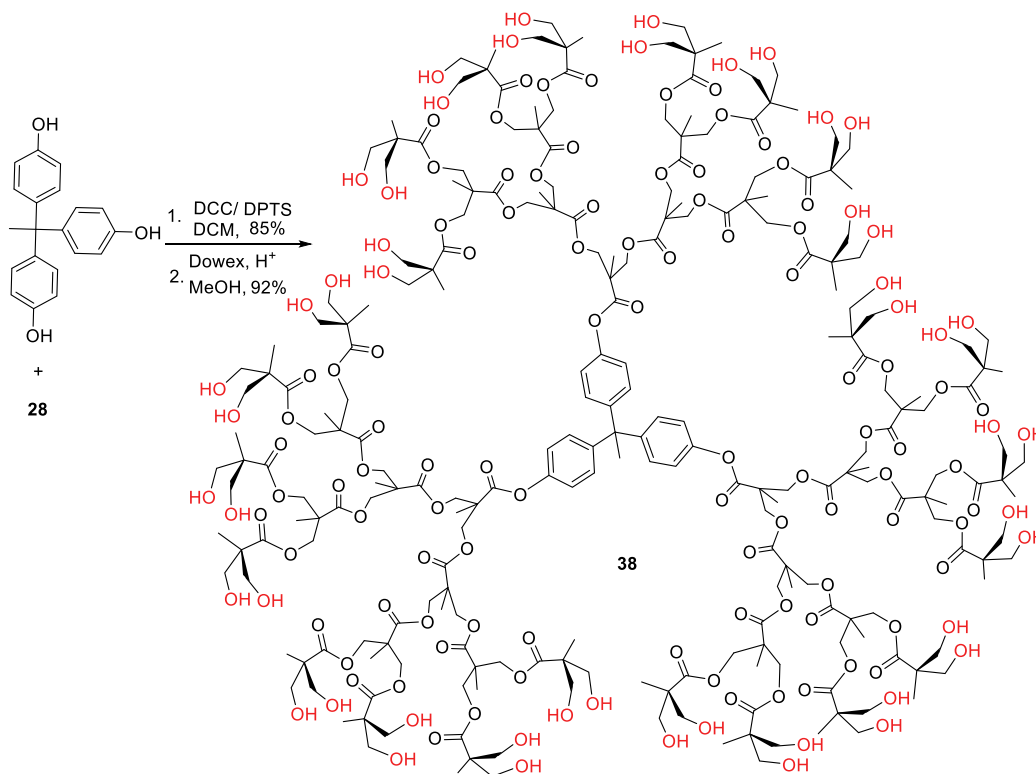
Scheme 7 Synthetic route to 1st, 2nd, 3rd, and 4th generation dendrons



Scheme 8 Synthetic route to 1st, 2nd, 3rd, and 4th generation acetate-terminated dendrimers

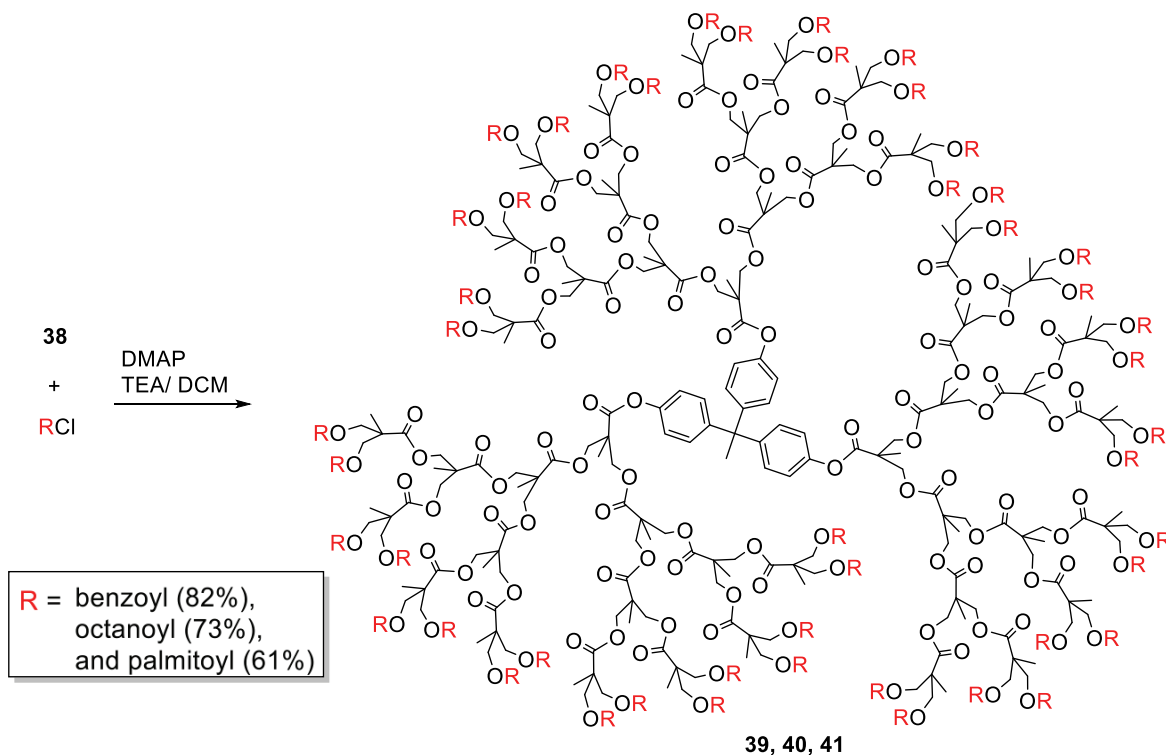
Two years later, Ihre and Hult in collaboration with Fréchet and Gitsov⁵⁰ published their new work as a response to weaknesses of the strict convergent approach described above. Here, a double-stage convergent growth approach, which allowed the synthesis of the fourth generation

hydroxyl-terminated polyester dendrimer to be synthesized in nine steps involving only three purification steps by column chromatography, was employed. The reduced number of steps in the new synthetic route also afforded a significantly improved yield of the product when compared to a strict convergent growth approach. In addition, the modified synthetic route allowed the selection of different protective groups, allowing the selective and high yield deprotection of the fourth generation protected polyester dendrimer. Hydroxyl groups of bis-HMPA were protected to afford acetonide groups by reacting bis-HMPA with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid (TsOH) in acetone. Scheme 5 illustrates the preparation of a fourth generation dendron using the double-stage convergent growth approach. Reacting this dendron with 1,1,1-tris(hydroxyphenyl)ethane as in Scheme 9 gave a fourth generation polyester dendrimer in good yield.



Scheme 9 Synthesis and deprotection of the acetonide-protected 4th generation dendrimer

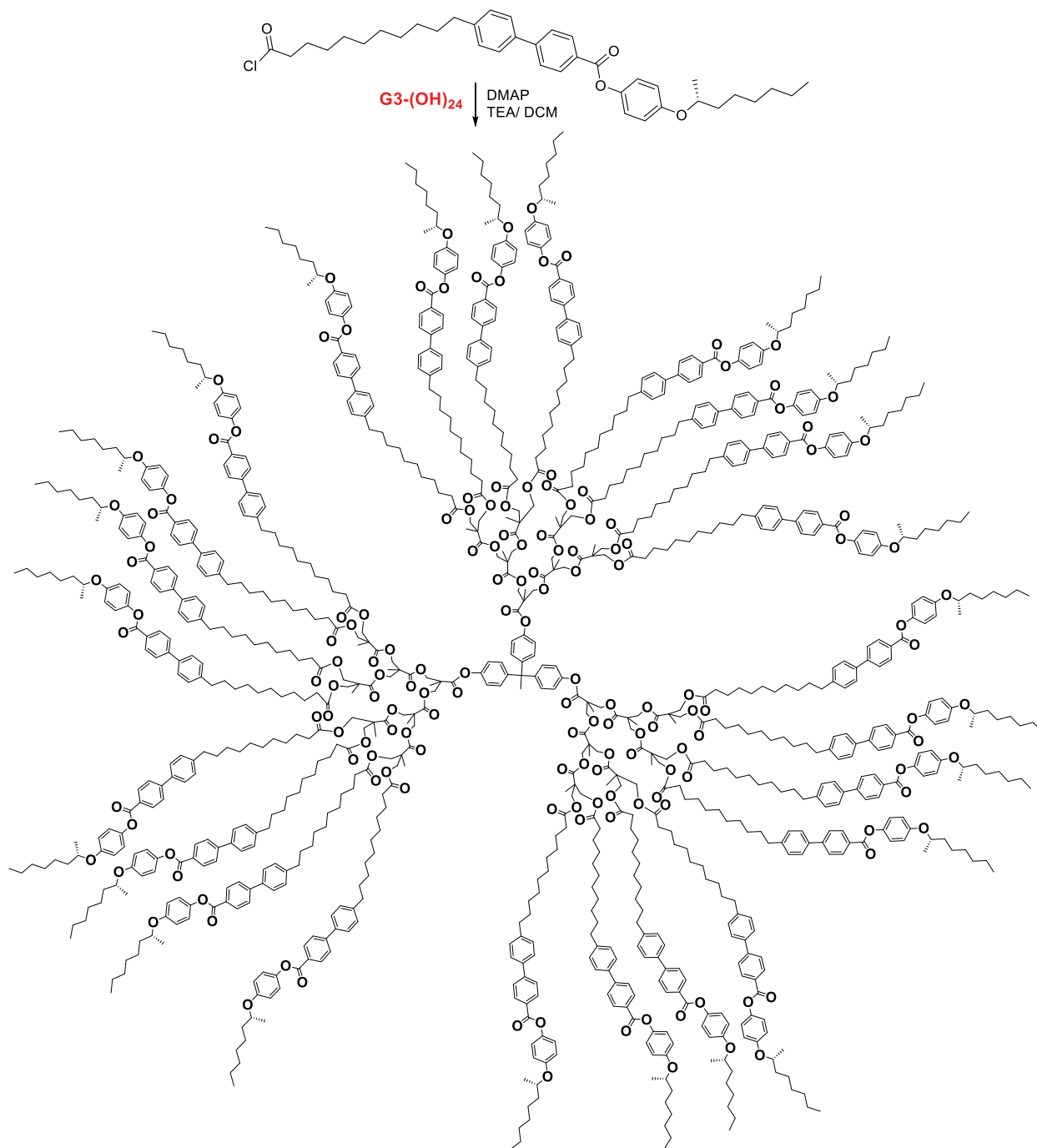
The periphery of the hydroxyl-terminated polyester dendrimer was then functionalized using reactions of its hydroxyl groups with various acid chlorides (benzoyl, octanoyl, and palmitoyl chloride) in the presence of TEA and DMAP to give high yields of monodisperse dendrimers, according to ^1H NMR spectra, ^{13}C NMR spectra, size exclusion chromatography, and elemental analyses of the products (Scheme 10).⁵⁰



Scheme 10 Surface functionalization of the 4th generation polyester dendrimer

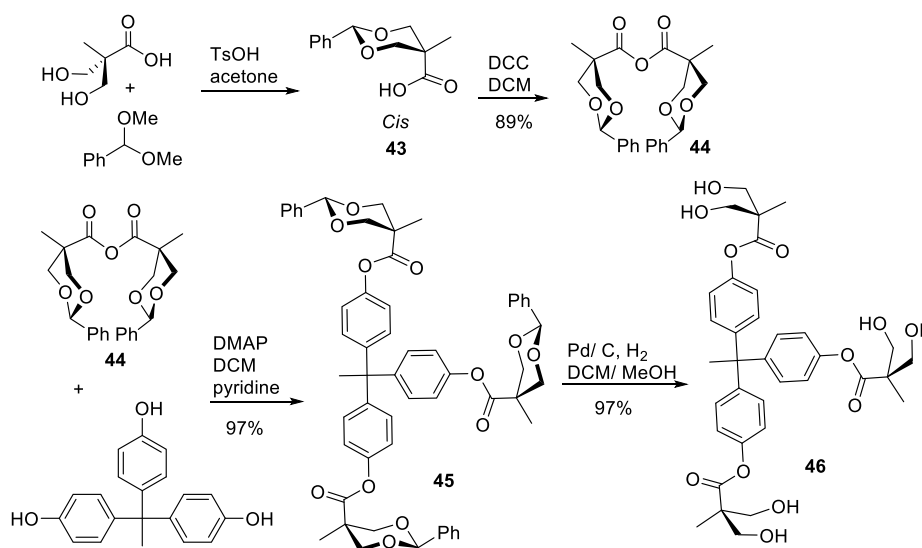
When conventional mesogenic groups in linear crystalline polymers (LCPs) are replaced by chiral mesogens, ferroelectric liquid crystalline polymers (FLCPs) are obtained.⁸⁴⁻⁸⁶ FLCPs are regarded as important species for optical switching and electrooptical applications.^{87,88} Because of chain entanglements however, their viscosity is often high which leads to slow switching thereby narrowing the field of their potential practical applications. Knowing that using dendritic structures may result in monodisperse FLCPs and therefore low viscosity and less chain

entanglements, Busson, Ihre, and Hult synthesized the first ferroelectric dendritic liquid crystalline polymer. In this work,⁸⁹ a third generation aliphatic polyester dendrimer, bearing 24 hydroxyl groups on its surface, was functionalized using a ferroelectric mesogen.



Scheme 11 Synthesis of the first ferroelectric dendritic liquid crystalline polymer

The mesogenic group, 4''-((*R*)-1-methylheptyloxy)phenyl 4-(4'-(10-(hydroxycarbonyl)decyloxy)-phenyl)benzoate, responsible for realization of the liquid crystalline state, was coupled to the dendritic matrix via acid chloride reaction as shown in Scheme 11.⁸⁹ The purity and hence the monodispersity of the final compound was established using ¹H NMR spectroscopy and size exclusion chromatography (SEC) measurements. For instance, the SEC trace of the final product consisted of a single peak after purification.



Scheme 12 Preparation of 1st generation using benzylidene-protected bis-HMPA

While exploring various routes to dendrimers, Annby, Malmberg, Pettersson, and Rehnberg demonstrated that the benzylidene-protected bis-HMPA was a versatile reagent for the formation of esters.⁹⁰ Here, polyester dendrimers were prepared up to the fourth generation using even sterically congested cores like pentaerythritol in good yields. Since then, a number of research groups have continued to synthesize and utilize the benzylidene-protected bis-HMPA as a convenient building block.⁹¹⁻⁹⁵ Using 1,1,1-tris(hydroxyphenyl)ethane as the core molecule, the benzylidene-protected anhydride of bis-HMPA as the dendron, and a catalytic amount of DMAP, a novel divergent approach was developed for the synthesis of dendritic aliphatic polyester

structures.⁹⁴ As mentioned in section 1.2, structural uniformity is usually difficult to maintain in the divergent approach, because the number of reactions that must be completed at each step of growth increases exponentially, thus requiring large excesses of reagents. However, this divergent approach, unlike all others, required only a small excess of reagent to achieve quantitative growth, and it required no means of purification other than a simple solvent extraction or precipitation to obtain monodisperse dendritic structures up to the sixth generation. The preparation of the activated building block **44** is shown in Scheme 12. Compound **44** was then coupled to the core using only 1.25 equivalents per hydroxyl group to give a trivalent benzylidene-protected first generation **45**. Catalytic hydrogenolysis selectively removed the benzylidene protecting groups of **45** and other higher generation dendrimers without affecting the ester bonds of the dendritic backbone. Figures 2 and 3 illustrate protected and hydroxyl-terminated fourth generations of this type.⁹⁴

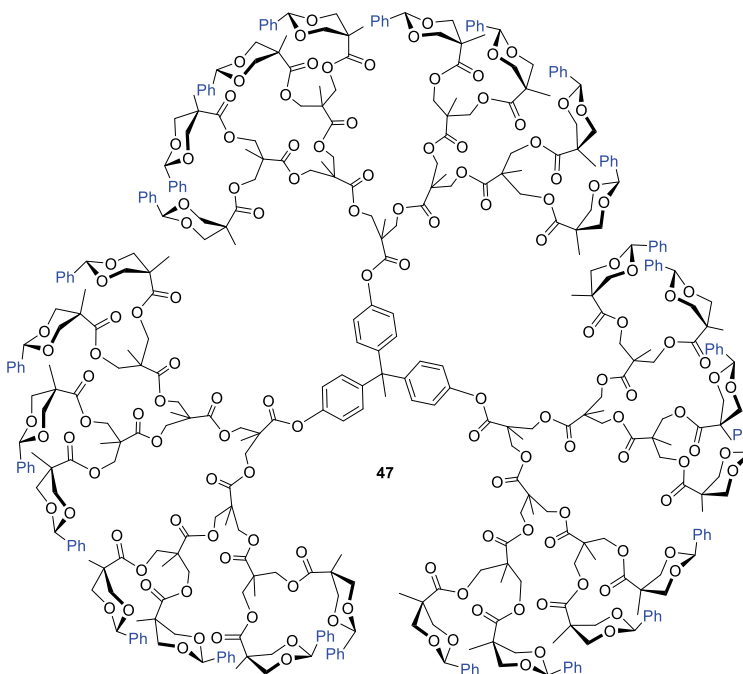


Figure 2 Benzylidene-protected 4th generation polyester dendrimer

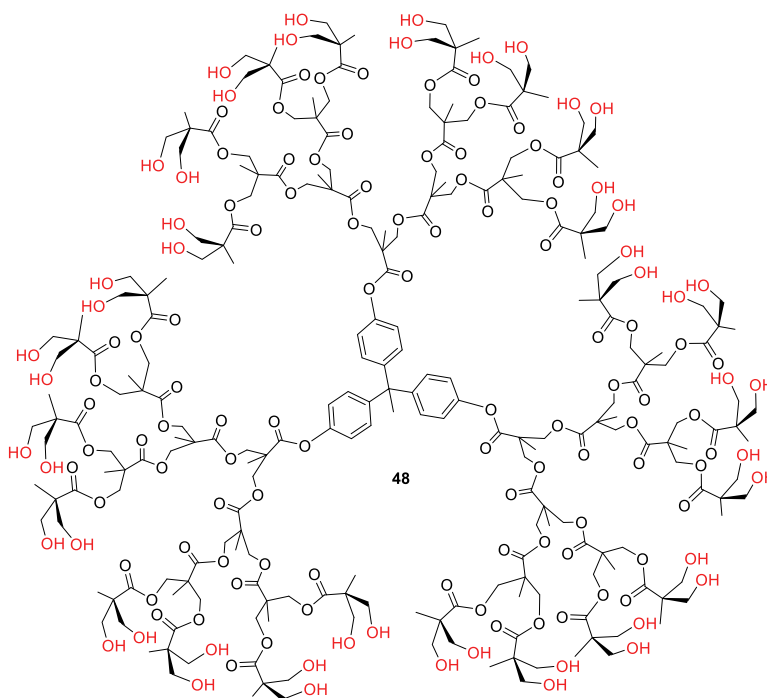
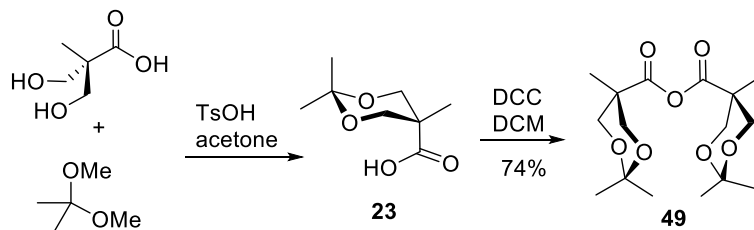


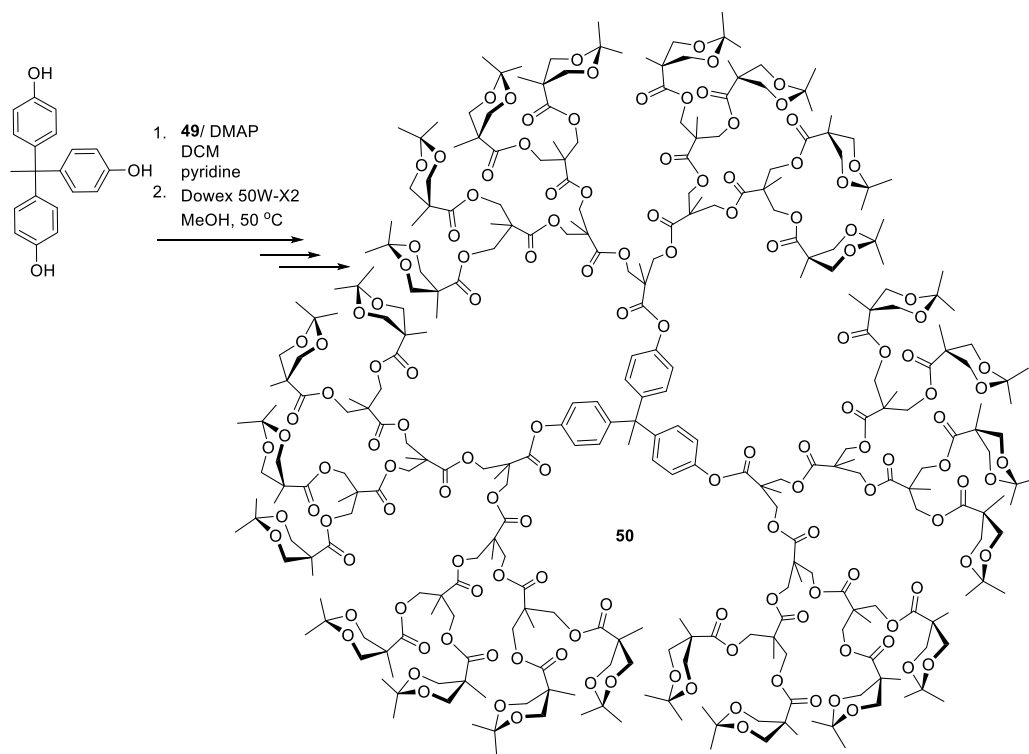
Figure 3 Hydroxyl-terminated 4th generation polyester dendrimer

In efforts to establish a large dendritic library comprising of dendritic compounds based on bis-HMPA, Malkoch, Malmström, and Hult became inspired by the efficiency of the above anhydride chemistry. However, the synthesis of dumbbell-shaped dendrimers often requires the use of orthogonally protected dendrons. The benzylidene-protected anhydride does not allow selective deprotection in the presence of other groups susceptible toward hydrogenolysis, such as a benzyl ester which is commonly employed in the synthesis of bis-HMPA dendrons. To complement the benzylidene-protected anhydride esterification strategy reported by Fréchet and coworkers in the synthesis of aliphatic polyester dendrons and dendrimers,⁹⁴ the acetonide-protected bis-HMPA anhydride⁹⁶ was introduced to combine the anhydride chemistry with the possibility of using the benzyl ester-protected focal point.⁹⁶ About the same time, a paper by Fréchet and coworkers appeared describing the use of the acetonide-protected bis-HMPA anhydride but no synthetic details were reported.⁹⁷



Scheme 13 Acetonide-protected building block

Three different fourth generation dendrons based on a 2,2,2-tris(chloroethyl) ester, a benzyl ester, and a decanoyl benzyl ether as focal points were divergently synthesized in high yields. In order to demonstrate the versatility of the anhydride chemistry, a fourth generation polyester dendrimer **50** was also divergently constructed as in Scheme 14.⁹⁶

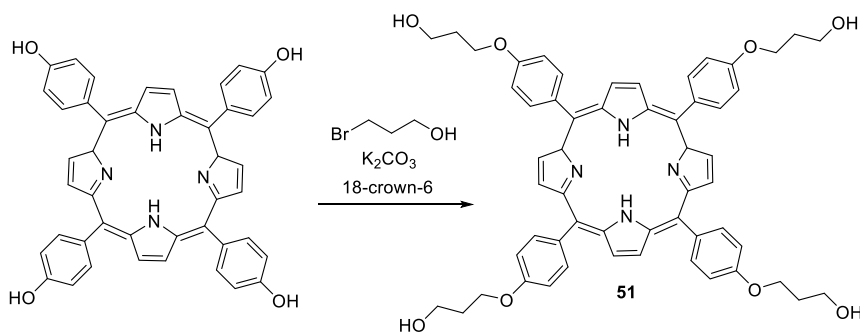


Scheme 14 Divergently-grown acetonide-protected 4th generation dendrimer

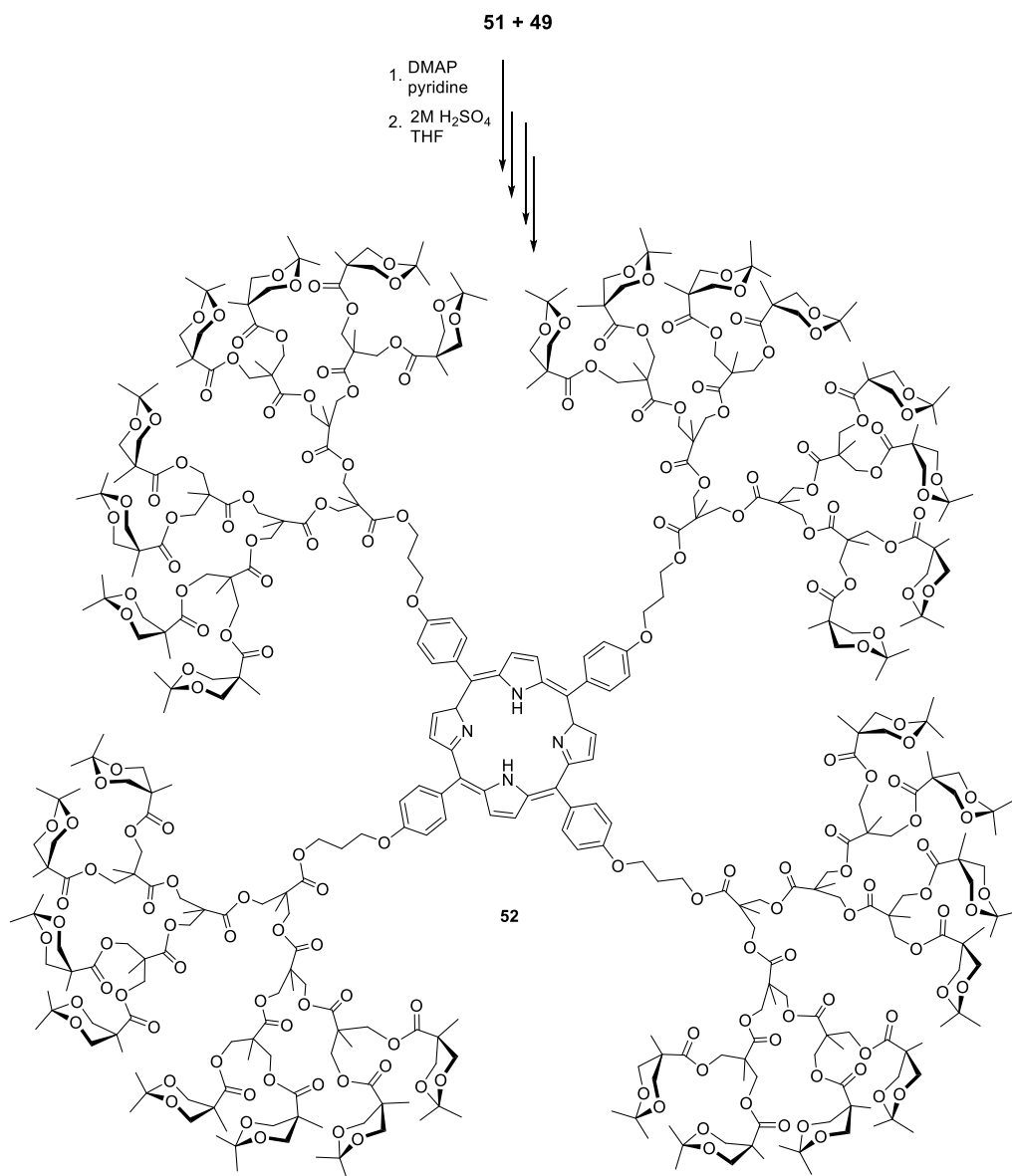
Two years later, Malmström, Hult and coworkers reported the synthesis and characterization of dendron-coated porphyrins up to the fifth generation.⁹⁸ Here, both free-base

and zinc-cored tetraphenylporphyrin (TPPH₂ and TPPZn) were used, from which the dendrons were divergently grown using the acetonide-protected bis-HMPA anhydride **49**. Porphyrins were selected as core molecules because of their potential applications in many areas.⁹⁹⁻¹⁰³ Reports dealing with porphyrin-decorated dendrimers had previously appeared.¹⁰⁴⁻¹¹³

After investigating three different synthetic strategies for this study, it was concluded that a spacer was required to be attached to the porphyrin to increase the hydrolytic stability and allow synthesis of higher generations. Normally acidic DOWEX resin is used for the deprotection of the acetonide groups, but here the porphyrin core attached irreversibly to the resin. A number of various dilute acids were explored for this deprotection, but the results from these acidic deprotections showed that the porphyrin phenolic ester linkage also hydrolyzes, hence the need for a spacer. The spacer was added through the reaction of the the porphyrin with 3-bromopropanol to afford **51**. The dendrimers were then grown by subsequent addition of an acetonide-protected building block followed by deprotection with 2M H₂SO₄ in tetrahydrofuran. The preparation of a fourth generation free base porphyrin-cored polyester dendrimer of this type is shown in Scheme 16.⁹⁸



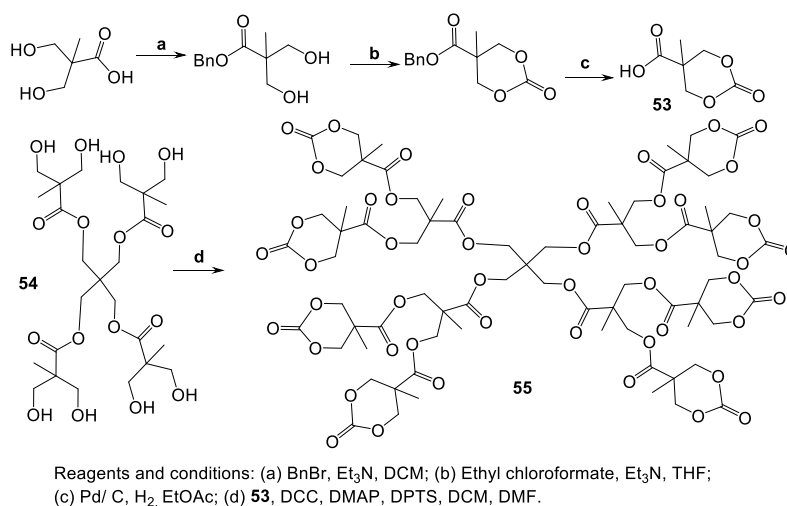
Scheme 15 Spacer addition to the porphyrin core



Scheme 16 Divergent construction of the 4th generation free base porphyrin-cored dendrimer

The synthesis of bis-HMPA acid-based polyester dendrimers continued to accelerate around this time as various researchers continued to publish reports of new dendritic architectures with new potential applications. For example, novel carborane-containing dendritic species based on bis-HMPA were reported by both Adronov¹¹⁴ and Zharov¹¹⁵ and one year later, Fréchet and coworkers¹¹⁶ presented polyester dendrimers bearing two types of peripheral groups

prepared by employing a cyclic carbonate as a symmetrical substrate that can yield a bifunctional product. The reaction of a cyclic carbonate and an amine has been used previously¹¹⁷ and has even shown to be efficient and selective enough to be run in water with quantitative yields.¹¹⁸ In the reaction, the amine opens the ring, forming a carbamate linkage with liberation of an alcohol that may then be used for a subsequent functionalization step. Two different moieties may be added in immediate succession without any deprotection steps or functional group conversions.



Scheme 17 Synthesis of a 2nd generation dendrimer with a cyclic carbonate periphery

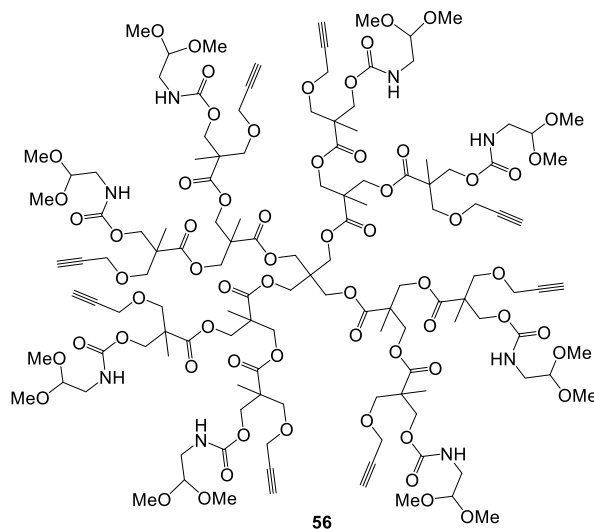


Figure 4 Second-generation dendrimer with a bifunctionalized periphery

To provide a model platform for testing the reaction, dendrimer **54** with eight hydroxyl groups was prepared from pentaerythritol. DCC coupling of **53** and **54** furnished carbonate-bearing dendrimer **55** (Scheme 17). Finally, reacting **55** with $(\text{MeO})_2\text{CHCH}_2\text{NH}_2$ and then propargyl bromide afforded dendrimer **56** (Figure 4). This is an example of how dendrimers can be precisely designed and functionalized to impart certain desired properties.¹¹⁶

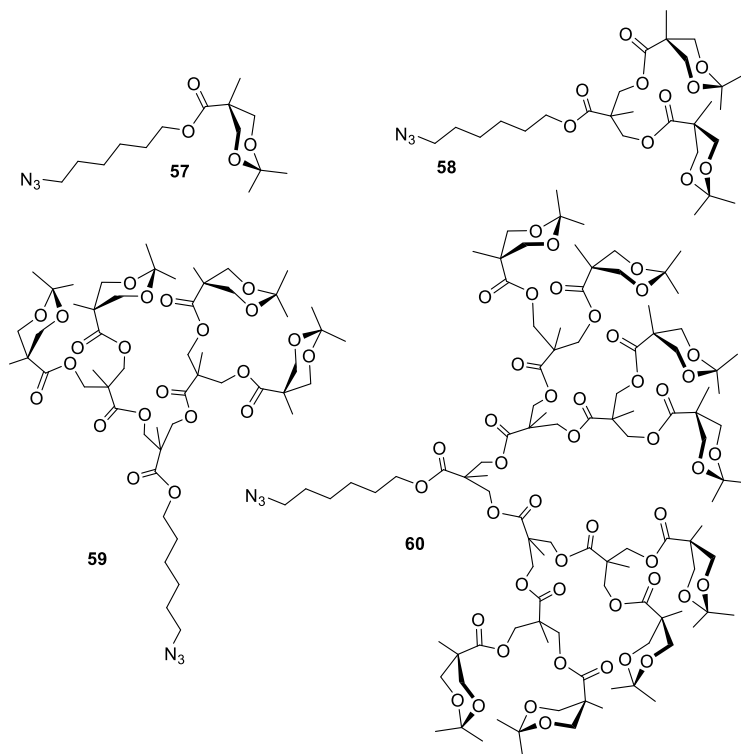
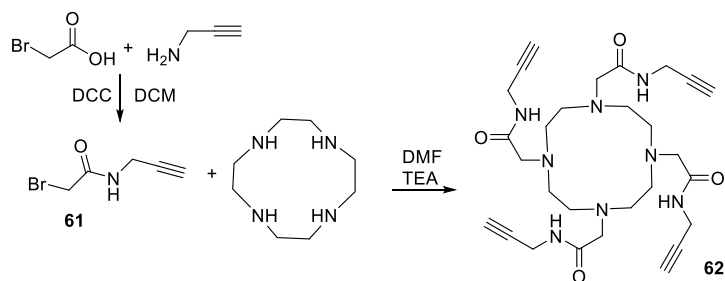


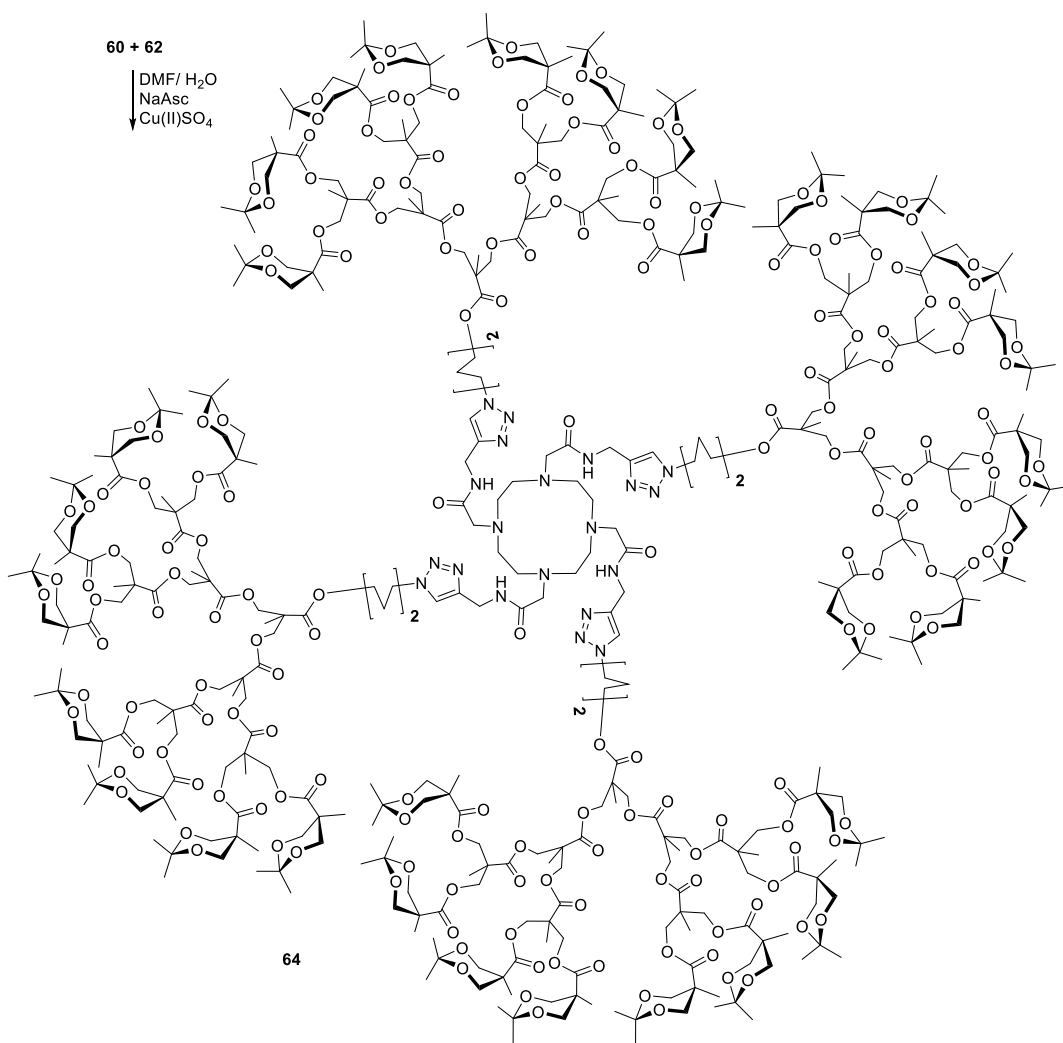
Figure 5 Azide-functionalized polyester dendrons

The work of Malkoch and Hult presenting novel architectures of bis-HMPA-based polyester dendrimers has also received attention.¹¹⁹ Polyester dendrimers up to the fourth generation were successfully synthesized using a click reaction. Here, acetonide-protected dendrons wedges were divergently grown and after being functionalized at the focal point using 6-azidohexanol, they were subsequently attached to a tetravalent alkyne functional cyclen core to give new dendrimer architectures. Figure 5 illustrates four generations of azide-functionalized

dendrons. The preparation of tetravalent alkyne functional cyclen core is shown in Scheme 18.¹¹⁹ Architectures of first to fourth generation polyester dendrimers of this type were obtained



Scheme 18 Synthesis of tetravalent cyclen core



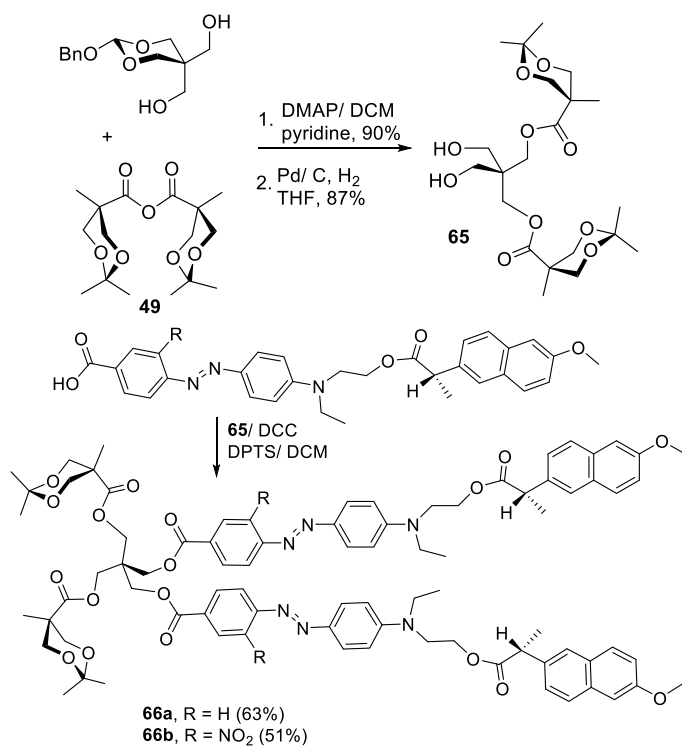
Scheme 19 Synthesis of 4th generation dendrimer using a click reaction

when the cyclen core **62** was reacted with **57**, **58**, **59**, and **60** respectively. Scheme 19 illustrates the preparation of a fourth generation of this type of dendrimers.¹¹⁹

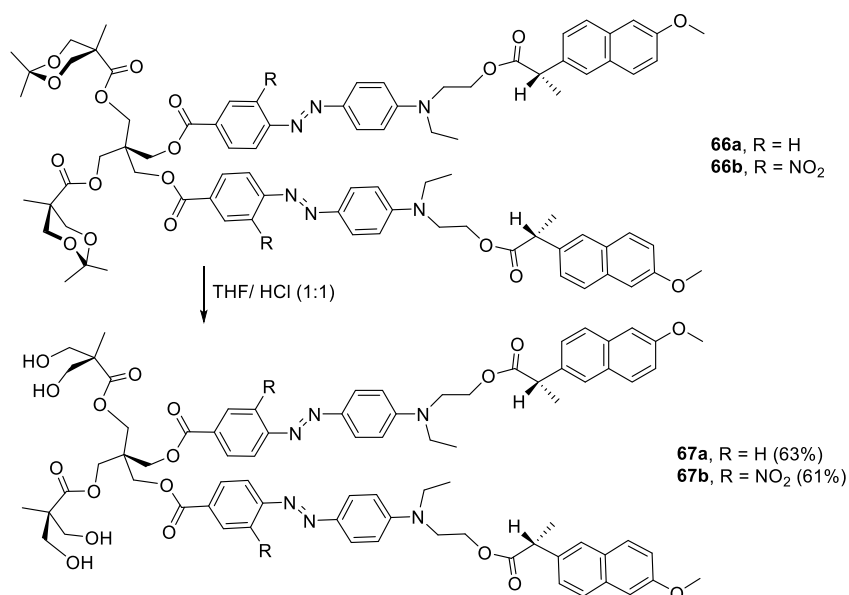
The synthesis and exploration of dendrimers containing functionalities associated with well-known interesting applications have continued to be of particular interest for many researchers. For example, since the publication of the first azobenzene dendrimers,¹²⁰ various reports of azobenzene-containing dendrimers¹²¹⁻¹²⁴ have continued to appear mostly because azobenzenes, which are synthetic dyes, are associated with several applications due to their interesting properties.¹²⁵⁻¹²⁹ With this in mind, Rissanen's group has shown interest in the synthesis of Janus-type dendrimers having possible non-linear optical properties arising from the non-centrosymmetric structure of the chiral azobenzene conjugates. One report describes the synthesis of bisfunctionalized Janus-type polyester dendrimers, which consist of a polar hydroxyl functionalized end, and a photoactive end constructed from donor-acceptor azobenzenes and chiral naproxen units.¹³⁰ Using pentaerythritol core and anhydride of bis-HMPA, the aliphatic polyester skeleton was constructed. Incorporated azobenzene moieties, previously reported by the same research group¹³¹ were chosen as electron donor-acceptor chromophores, since they possess non-linear optical properties.¹³² Shown in Schemes 20 and 21 are the syntheses of first and second generations for this type of unsymmetrical dendrimers.¹³⁰

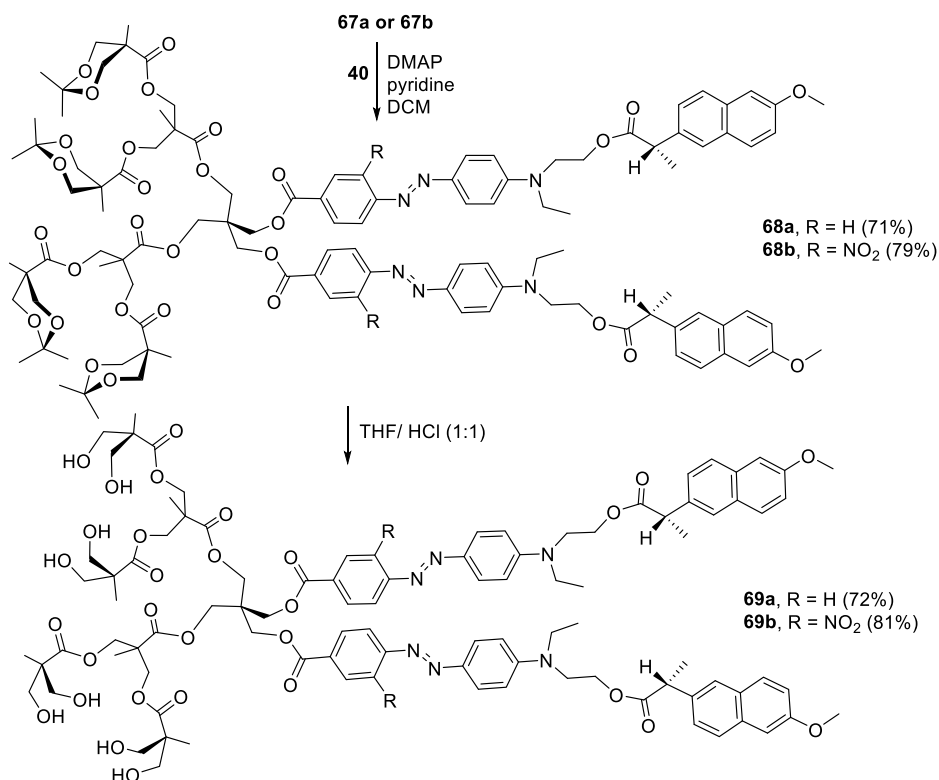
Heise and coworkers reported the synthesis of encoded dendrimers with defined chiral composition via 'click' reaction of enantiopure building blocks.¹³³ Heise had previously reported the synthesis of copolymers from the enantiomerically pure monomers of (*R*) and (*S*)-*p*-vinylphenylethanol,¹³⁴ but copolymers have a disadvantage in that there is uncertainty about the distribution of chiral units along the polymer skeleton. A viable approach was then to use

dendrimers of defined architectures in which orthogonal functionalization encodes a defined optical rotation into the dendrimer by the use of enantiomerically pure building blocks.



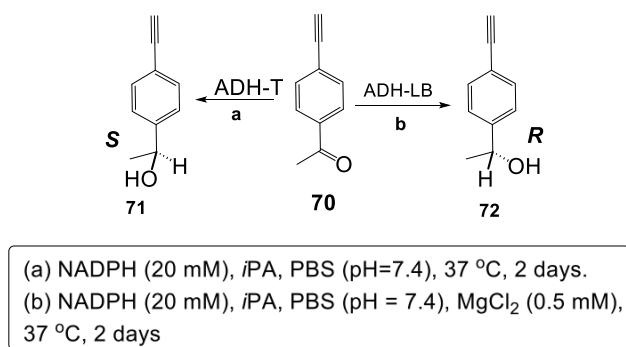
Scheme 20 Synthesis of acetonide-protected 1st generation



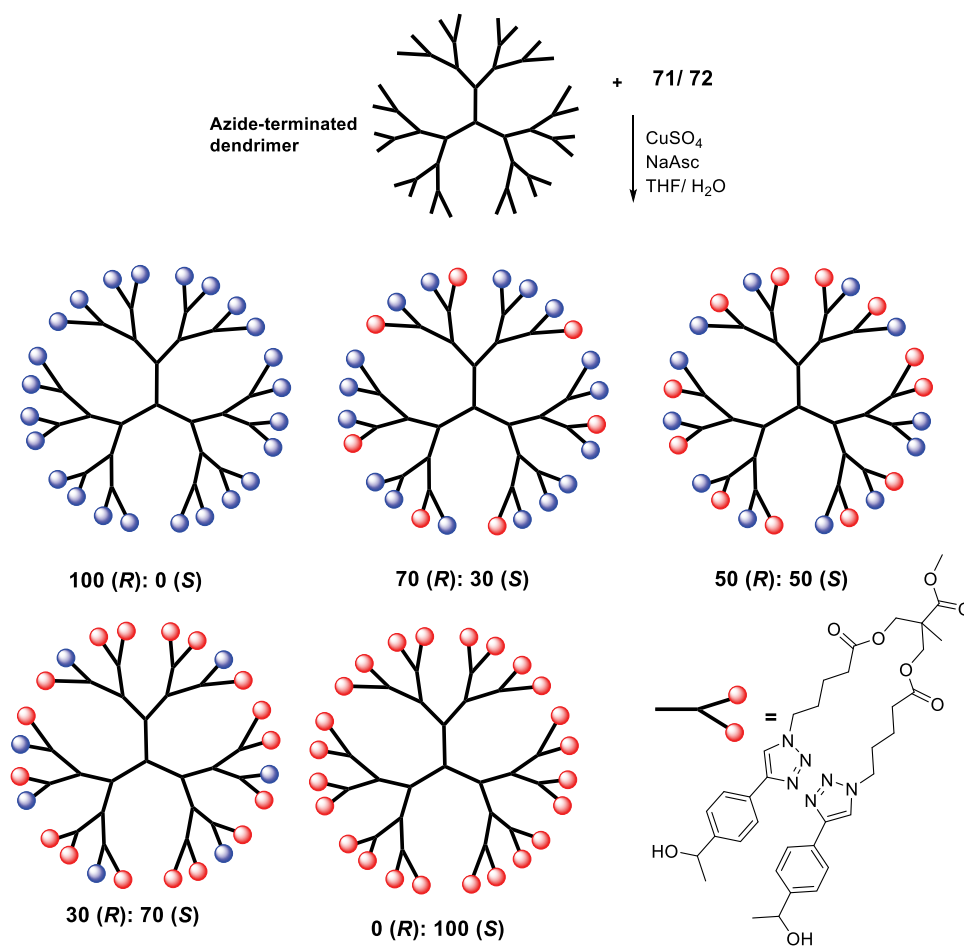


Scheme 21 Synthesis of 2nd generation unsymmetrical polyester dendrimers

Here, an azide-terminated dendrimer¹³³ based on bis-HMPA was divergently constructed as previously described¹³⁵ and functionalized using the 1,3-dipolar cycloaddition reaction and different ratios of the matching alkyne functional enantiopure building blocks (Scheme 23).¹³³ Scheme 22 shows the selective alcohol dehydrogenase (ADH) reduction of 1-(4-ethynylphenyl)ethanone to give the desired chiral building blocks.¹³³ When measurements of the optical rotation were taken, it was found that the specific optical rotation of the dendrimers increased linearly with increasing percentage of (*R*) end-groups in the dendrimer, indicating that both (*R*) and (*S*) building blocks had been incorporated into the dendrimer in agreement with the enantiomeric feed ratio.



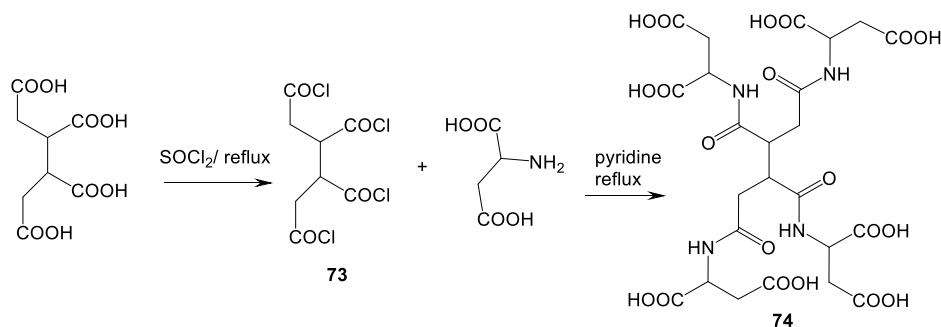
Scheme 22 Enzymatic preparation of enantiopure building blocks



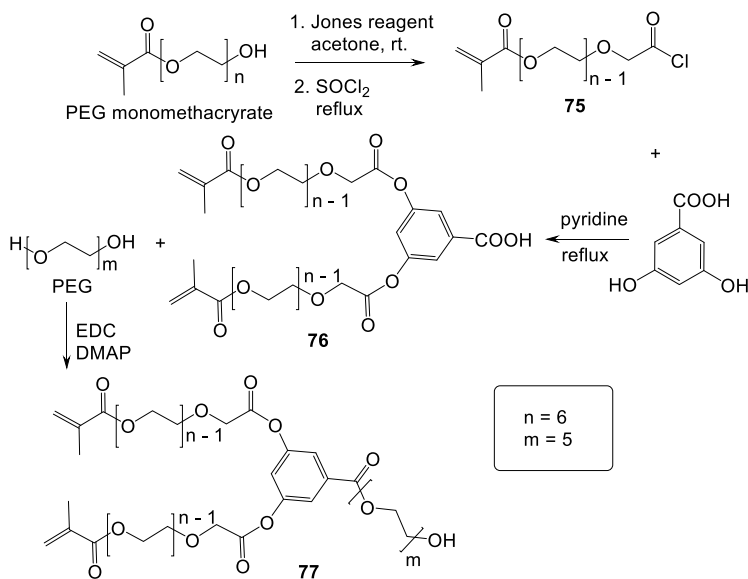
Scheme 23 Modification of azide-terminated dendrimers with different ratios of enantiomers

The discovery and development of new and potent drugs is a time-consuming and costly process. It may take up to 15 years to develop mostly because of lengthy clinical trials.¹³⁶ A

more economical and viable strategy is to devise effective delivery systems for drugs that have failed to provide optimum therapeutic benefit. It is postulated that controlled release of a drug at a specific target can significantly improve the effectiveness of a drug and thereby increase the therapeutic benefit.¹³⁷



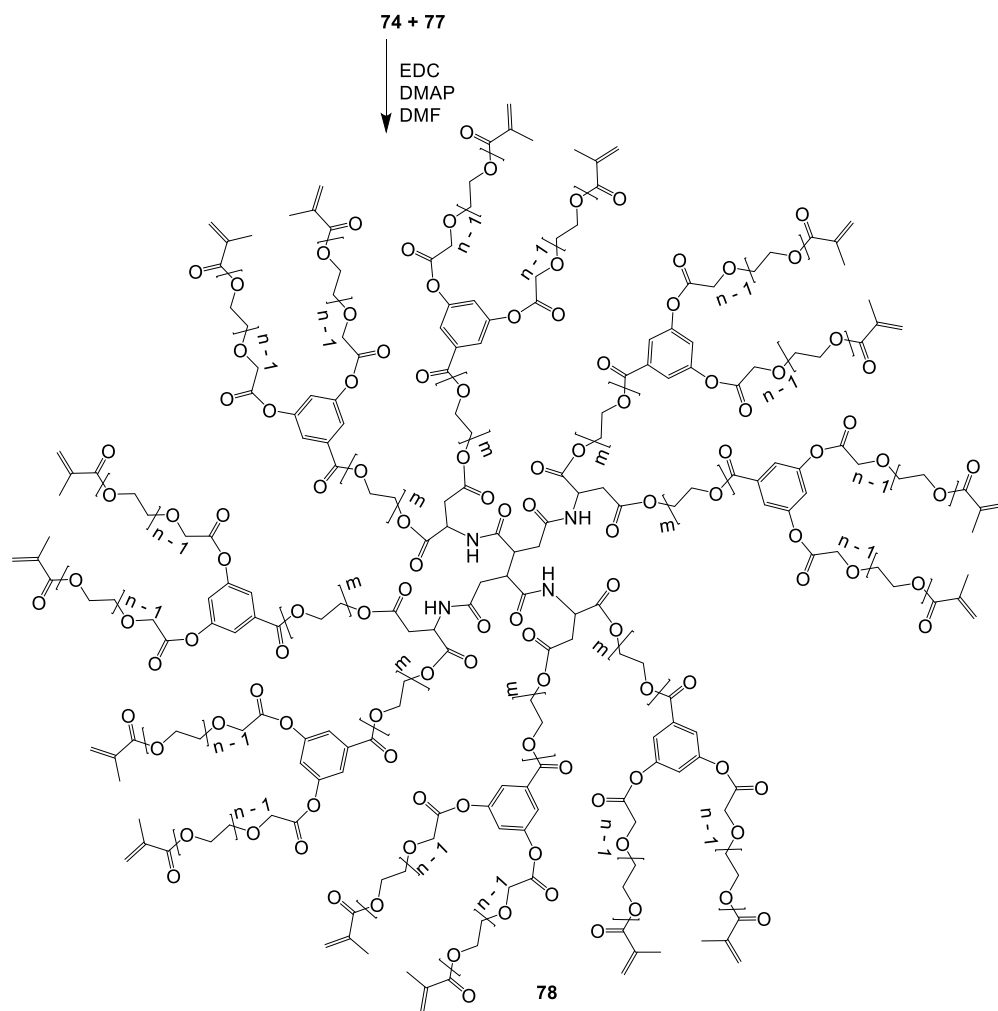
Scheme 24 Synthesis of core molecule **74**



Scheme 25 Synthesis of dendron **77**

Hildgen and coworkers⁵ at the Université de Montréal synthesized novel polyester-co-polyether dendrimers consisting of a hydrophilic core. The core was synthesized using biocompatible moieties, butanetetracarboxylic acid and aspartic acid, and the dendrons from

PEG (poly(ethylene glycol)), dihydroxybenzoic acid or gallic acid, and PEG monomethacrylate. The dendrimers were then obtained by coupling the dendrons to the core. Syntheses of core molecule **74**, dendron **77**, and a second generation **78** are shown in Schemes 24, 25, and 26.⁵



Scheme 26 A novel second generation dendrimer **78**

This type of dendrimer demonstrated good ability to encapsulate the guest molecule, with loadings of 15.80 and 6.47% w/w for rhodamine and β -carotene, respectively. The release of the encapsulated compounds was found to be slow and sustained, suggesting that these dendrimers can serve as potential drug delivery systems.

1.5.3. Concluding Remarks

There has been a substantial interest in the area of dendrimers because of their interesting properties and wide potential applications and activity in this area has intensified over the last few years. However, there is still a wide range of dendrimer families with new properties and new potential applications that have not yet been synthesized. The following chapters discuss obtained results. Chapter 2 of this thesis discusses new dendrons and core molecules that have been prepared. This discussion will lead to esterification using uronium-based coupling agents, the direct synthesis of maradolipids, and the synthesis of Lyme disease glycolipid antigens.

Chapter 2. Design and Synthesis of Core Molecules and Dendrons

2.1. Core Molecules

2.1.1. Introductory Remarks

Stable and non-sterically congested core molecules are essential for the successful preparation of higher generation dendrimers. From the early days of dendrimers to the present day, dendrimer synthesis has largely focused on the use of easily accessible cores from commercial sources. Examples of these include pentaerythritol, 1,1,1-tris(hydroxyphenyl)ethane, and 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, just to name a few. It is therefore interesting to synthesize cores that have never been used before in the preparation of dendrimers and to see the impact these would have on the architectures, properties, and applications of the resulting dendrimers.

2.1.2. Design and Synthesis

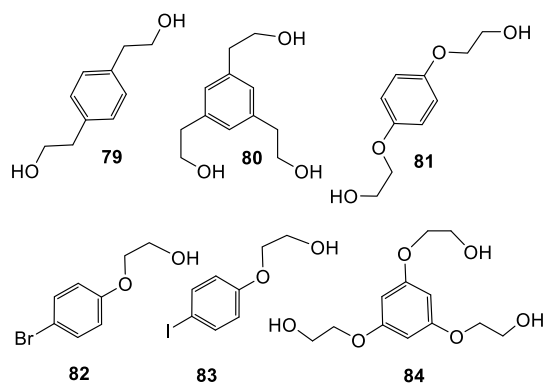
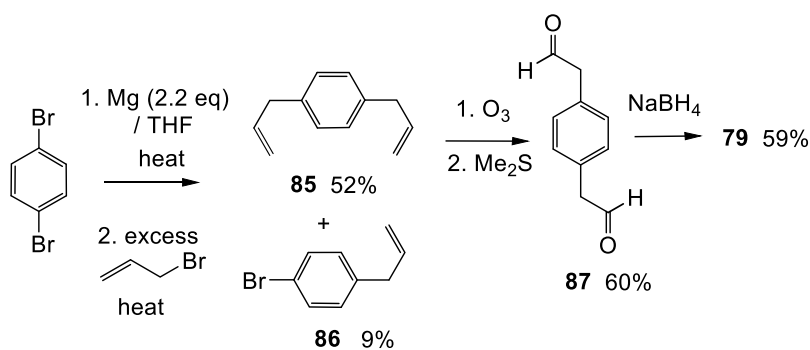


Figure 6 Selected cores

We wanted aromatic cores with non-benzylic and non-phenolic hydroxyl groups for ester stability that would not be cleaved under mild acidic (for selective removal of isopropylidene acetals) or hydrogenolysis conditions (for reductive removal of benzylidene acetals and benzyl

ethers). Molecules in Figure 6 were selected as synthetic targets. None of these compounds has been used previously for the preparation of dendrimers. These compounds all have terminal $\text{CH}_2\text{CH}_2\text{OH}$ groups and so one synthetic route that could be used for all was employed: reduction of the products of reductive ozonolysis of allyl groups. This approach had not been used previously to prepare any of these compounds and it proved to be convenient and high yielding. 1,4-Benzenediethanol **79** has been prepared previously by Clark and O'Reilly using the reaction of the Grignard reagent obtained from 1,4-dibromobenzene with ethylene oxide.¹³⁸ However, the yield reported was 52% and ethylene oxide, a toxic gas, is both expensive and inconvenient to handle on a laboratory scale. Our initial approach via the diallyl derivative **85** is shown in Scheme 27. Steiger and coworkers reported the synthesis of **85** in 32% yield via coupling of the bis Grignard reagent of 1,4-dibromobenzene with allyl bromide.¹³⁹ In our hands, **85** was always accompanied by the monoadduct **86**, even after chromatography. Figure 7 shows a 500 MHz ^1H NMR spectrum of chromatographically purified **85**, which contains about 15% of the mono-allylated product **86** as part of the mixture. Performing the reaction in two separate steps did not improve the yield. Reaction of the mono Grignard reagent with allyl bromide gives **86**¹⁴⁰ in 63% yield in our hands and the yield in the second step was similar (59%).



Scheme 27 Initial synthesis of 1,4-benzenediethanol

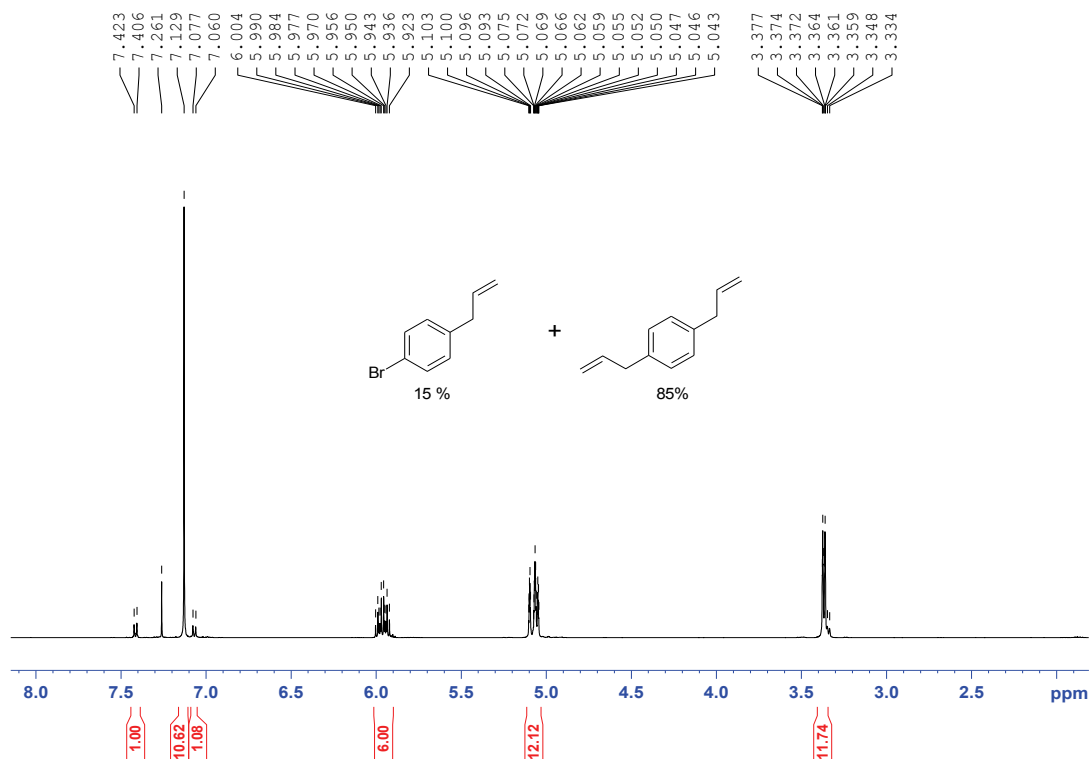
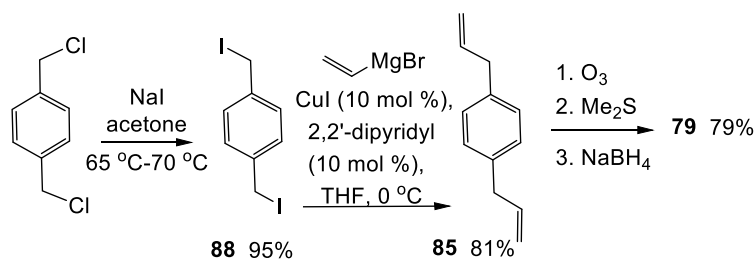


Figure 7 500.13 MHz ^1H NMR spectrum of a 5:1 mixture of **85** and **86** in chloroform-*d*



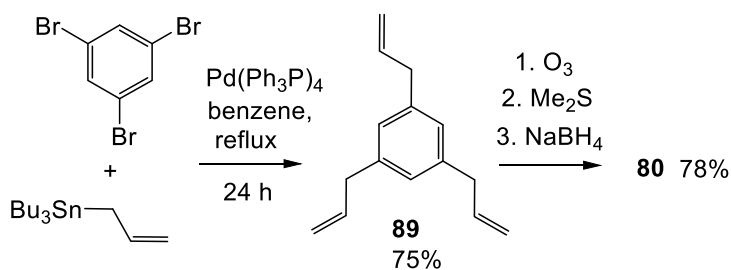
Scheme 28 Improved synthesis of 1,4-benzenediethanol

An alternative route to 1,4-diallylbenzene **85** proved to be cost effective and high yielding. The copper-catalysed coupling of vinyl magnesium bromide with the known diiodide **88**¹⁴¹ gave a good yield of the diallyl derivative in one hour. Compound **85** has also been made in excellent yield by performing Stille coupling of the bistriflate of hydroquinone with tributylallylstannane in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ (20 mol%) and LiCl .¹⁴² Conversion to **79** via ozonolysis followed by the same-pot reduction proceeded in good yield (Scheme 28).

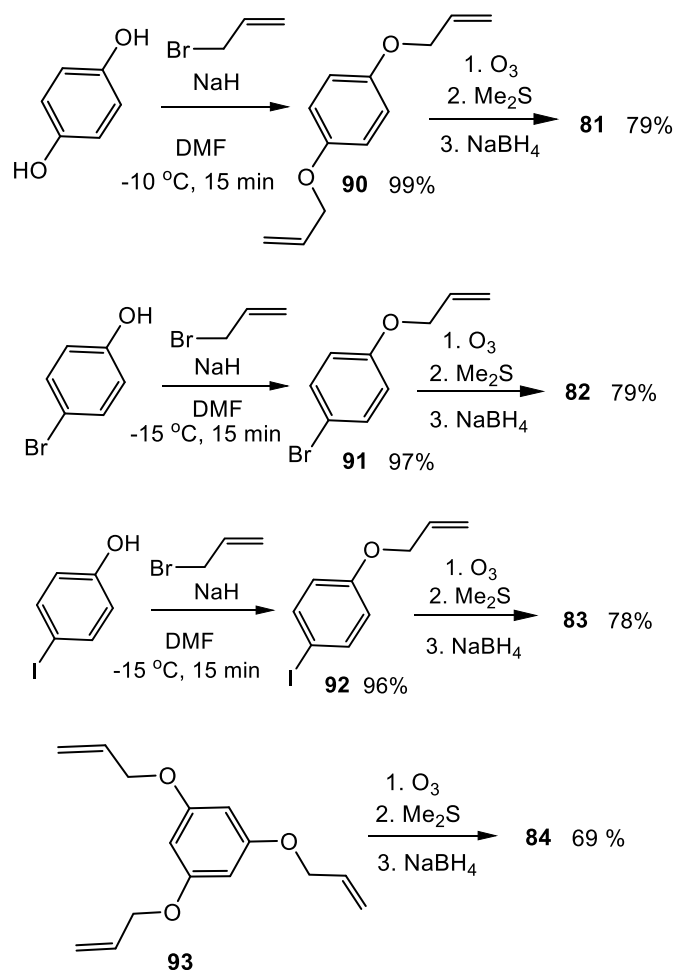
Two groups had reported the synthesis of 1,3,5-benzenetriethanol **80** by quite different methods. Cochrane *et al.*¹⁴³ prepared it by reduction of triethyl 1,3,5-benzenetriacetate.¹⁴⁴ The precursor 1,3,5-benzenetriacetic acid was made from 1,3,5-triacetylbenzene using the Kindler modification of the Willgerodt reaction¹⁴⁴ and 1,3,5-triacetylbenzene can be prepared by an acid-catalyzed trimerization of formyl acetone,¹⁴⁵ overall a four-step process. Bradshaw and Krakowiak used the same method but chose to reduce the precursor triacid in 45% yield.¹⁴⁶ An alternative one-pot synthesis of compound **80** gave a non-separated mixture of tris-(2-hydroxyethyl)benzenes using a cobalt-catalyzed trimerization of 3-butyn-1-ol but the starting material is expensive and the separation is impractical.¹⁴⁷

A reaction scheme analogous to Scheme 28 could not be followed because the required precursor, 1,3,5-tris(chloromethyl)benzene, is not commercially available. An attempt was made to prepare 1,3,5-triallylbenzene **89** from 1,3,5-tribromobenzene via the Grignard method but it gave inseparable mixtures of partially allylated derivatives along with the desired product.

Allylation of aromatic halides with allyltributyltin¹⁴⁸ in the presence of tetrakis(triphenylphosphine)palladium(0) has been known for more than 30 years.¹⁴⁹ The triplicate version of this reaction worked well with 1,3,5-tribromobenzene on scales of < 10 g as shown in Scheme 29. The product **89** was converted to the desired triol **80** as described above in the synthesis of **79**.



Scheme 29 The synthesis of 1,3,5-triallylbenzene and 1,3,5-benzenetriethanol



Scheme 30 The synthesis of 2-hydroxyethoxy derivatives

2-Hydroxyethoxy derivatives of aromatic compounds, such as **81** - **84**, have been made in a variety of ways. Compounds **81** and **84** were originally prepared by reaction of the sodium salts of the phenols with 2-chloroethanol¹⁵⁰ and 2-bromoethanol has also been used.¹⁵¹ The patent literature contains numerous reports of the formation of **81** by reaction of the dianion with ethylene oxide. Compound **83** has been made by iodination of 2-hydroxyethoxybenzene.¹⁵²⁻¹⁵⁴ Surprisingly, compound **84** has commonly been made from phloroglucinol by reaction with ethylene carbonate in DMF at 150 °C in the presence of tetrabutylammonium bromide.¹⁵⁵ Although this reaction is a one-step reaction, it suffers from low yields. Values of between 20

and 37% have been reported.^{146,156-158} An alternative two-step approach involving displacement of methyl bromoacetate by phenoxide,¹⁵⁹ followed by reduction has also been used for **84**.¹⁶⁰

The reduction of the products of reductive ozonolysis of allyl ethers yielded the remaining core molecules, compounds **81**,¹⁶¹ **82**,^{150,162} **83**,¹⁶³ and **84**,¹⁴⁶ in excellent yields (see Scheme 30). The required allyl ethers were obtained in 10 to 15 min at -10 to -15 °C by reaction of the phenoxide anions with allyl bromide in DMF.

2.1.3. Concluding Remarks

One-pot reductive ozonolysis of allyl derivatives followed by reduction with sodium borohydride is an efficient general procedure for the production of terminal CH₂CH₂OH groups. The allyl groups can be either C-allyl or O-allyl groups. The latter are readily accessible and a variety of strategies have been employed for the introduction of one to three C-allyl groups onto aromatic rings.

2.2. Dendrons

2.2.1. Introductory Remarks

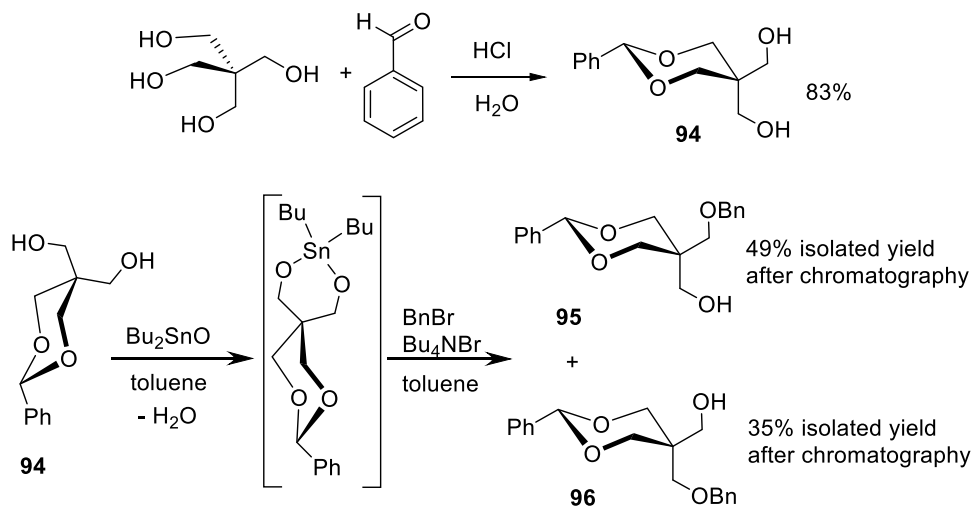
The synthesis of polyester dendrimers has largely relied on the use of bis-HMPA acid dendron. Since the 1990s, this aliphatic building block has continued to be the dendron of choice. Bis-HMPA is commercially available. It has allowed easy preparation of higher generation polyester dendrimers because it is not sterically hindered, and most importantly, the resulting polyester dendrimers are non-toxic and biodegradable, which makes them attractive for biological and drug delivery applications. The following section describes our approaches to the preparation of new dendrons.

2.2.2. Design and Synthesis

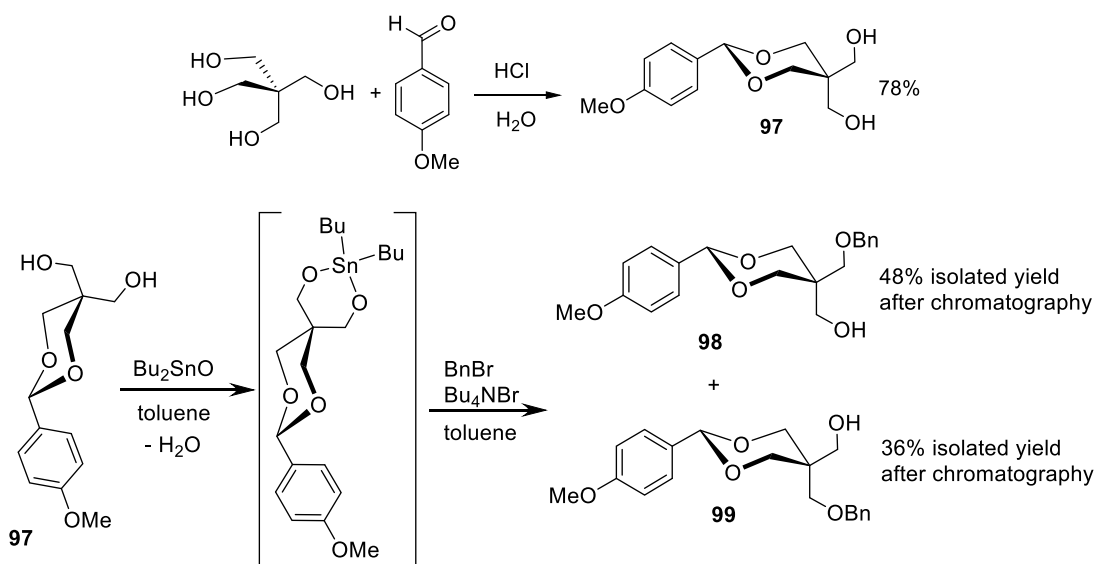
The preparation of polyester dendrimers with new properties and new potential applications depends largely on the ability of researchers to synthesize new dendrimers with increasing structural diversity. The use of new building blocks that have never been used previously is one way of achieving this goal. We decided to design and prepare dendrons derived from pentaerythritol that have three branching points. Dendrons with three branching points can potentially allow the synthesis of polyester dendrimers that are more highly branched than any polyester dendrimer in the literature today. Such dendrimers should have the advantage that they are likely to be less easily hydrolyzed *in vivo* than previously synthesized polyester dendrimers, but share the advantages of synthesis under mild conditions of other polyester dendrimers and potential biological release of bioactive molecules either trapped or conjugated. We desired a flexible high-yielding route to trivalent dendrons. Issidorides and Gulen¹⁶⁴ described an efficient procedure for the synthesis of 5,5-bis(hydroxymethyl)-2-phenyl-1,3-dioxane, also known as mono-*O*-benzylidenepentaerythritol **94**. As shown in Scheme 31, slow addition of benzaldehyde to a solution of pentaerythritol in water, in the presence of an acid catalyst yields the acetal in good yield. We prepared compound **94** on a large scale.

Dibutyltin acetals have shown to be useful for selective chemical manipulations of diols and polyols.¹⁶⁵⁻¹⁶⁷ They are formed readily from diols^{168,169} and have served as convenient intermediates for the formation of monobenzyl ethers from diols or polyols by reacting with benzyl bromide in benzene or toluene in the presence of tetrabutylammonium bromide.^{168,170} Following the procedure developed earlier in this laboratory,¹⁷¹ **94** was refluxed with one equivalent of dibutyltin oxide in toluene followed by the subsequent benzylation *in situ*, to give

isomers **95** and **96** as thick colorless syrups. When *p*-methoxybenzaldehyde is employed as in Scheme 32, the resulting isomers **98** and **99** are colorless crystalline solids.

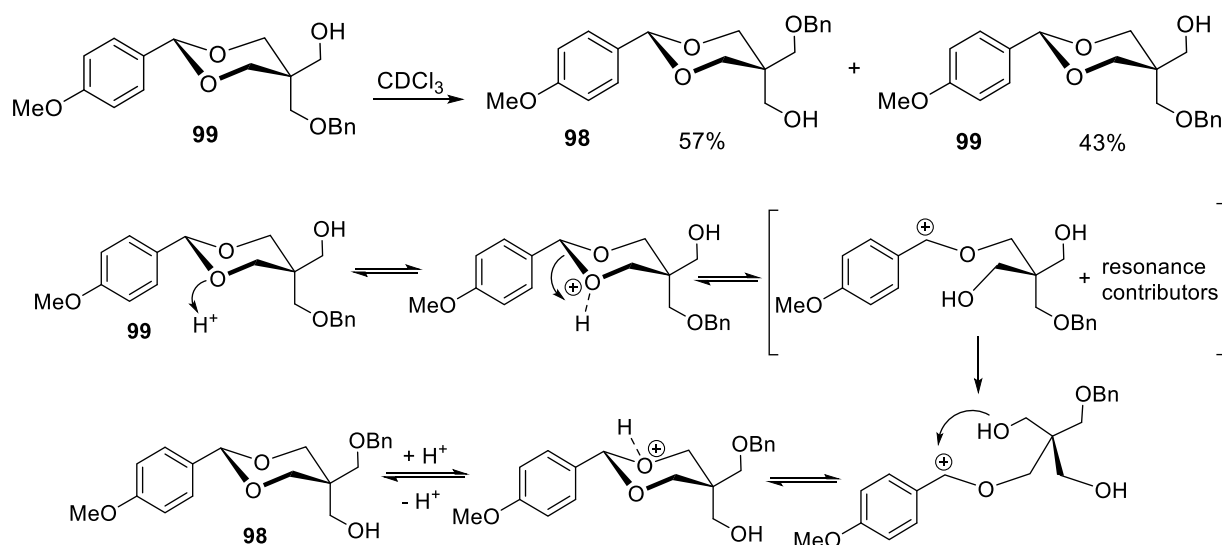


Scheme 31 Mono-*O*-benzylation



Scheme 32 Mono-*O*-benzylation

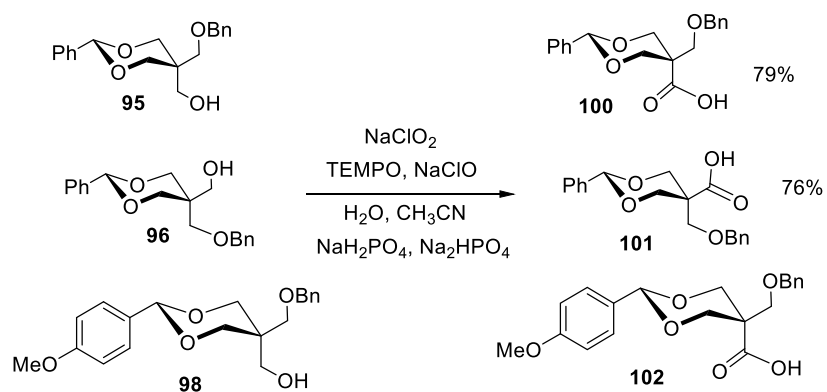
These isomers were characterized using ^1H NMR and ^{13}C NMR spectroscopy and their structures were assigned. While clean NMR spectra for **95**, **96**, and **98** could be obtained in chloroform-*d*, a pure sample of **99** equilibrated when it was dissolved in chloroform-*d* to give a 3:2 mixture of **98** and **99** respectively. This ratio was consistent each time NMR experiments were performed on **99** regardless of the length of time the sample was left in the chloroform-*d* solution (right away, two hours, or 36 hours after dissolving the sample in chloroform-*d*). It is known that chloroform-*d* decomposes slightly on standing to release dichlorocarbene and HCl. When acetone-*d*₆ was used for NMR experiments on **99**, no equilibration was observed. Scheme 33 shows the observed equilibrium in chloroform-*d*.



Scheme 33 Acid-catalyzed equilibrium of **98/99**

Oxidation is a fundamental transformation in organic synthesis and numerous methods have been reported for the desired transformation.¹⁷²⁻¹⁷⁵ When the starting alcohols have labile functional groups that can cleave under acidic conditions as it is the case here for **95**, **96**, **98**, and **99**, fewer methods exist for the transformation to carboxylic acids. After trying a few other methods, we found that Zhao's method, the so-called "Merck oxidation",¹⁷⁶ worked efficiently

either on the individual isomers **95**/**96** or the mixture of isomers. The reaction between each of the primary alcohols and a stoichiometric amount of sodium chlorite in the presence of catalytic TEMPO and bleach at 38 °C for 12 h in a buffered solution, gave the corresponding acid in good yield as shown in Scheme 34. When isomer **98** was subjected to the same conditions, a low yield of the corresponding acid was obtained. Consequently, this reaction was investigated in more detail by varying temperature and reaction times. Results are summarized in Table 1. Oxidation of compound **99** always gave a mixture of the two corresponding isomeric acids.

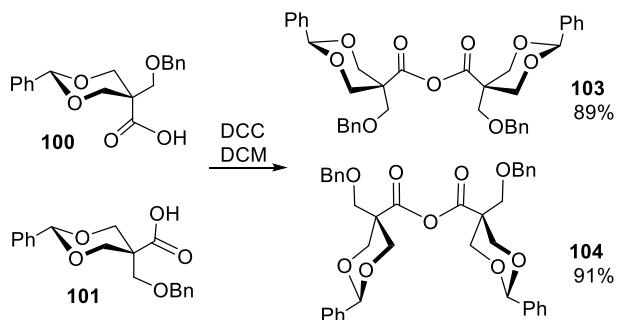


Scheme 34 Merck oxidation

Table 1 Merck oxidation results on compound **98**

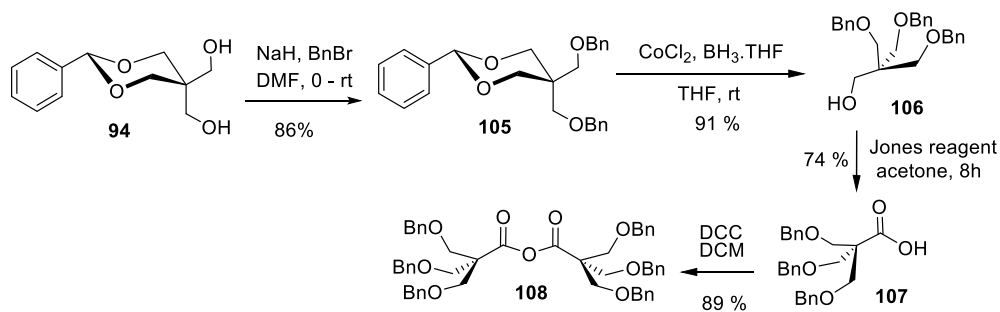
| Temp. (°C) | rxn time (h) | % yield | Observation |
|------------|--------------|---------|--------------------------------------|
| 0 - RT | 12 | 0 | Most of the alcohol recovered |
| RT | 12 | 15 | |
| RT | 20 | 17 | |
| 30 | 12 | 22 | Some alcohol recovered |
| 30 | 16 | 21 | |
| 35 | 6 - 8 | 25 | No alcohol was recovered |
| 35 | 11 - 12 | 40 | |
| 35 | 16 | 20 | |
| 35 | 18 | 16 | |
| 45 | 4 | 15 | No alcohol was recovered |
| 45 | 8 | 0 | |

The activated anhydride dendrons were synthesized from the respective carboxylic acids using DCC as in Scheme 35. Anhydrides **103** and **104** are crystalline products, and they remained stable over a period of several months at room temperature.



Scheme 35 Dendron activation

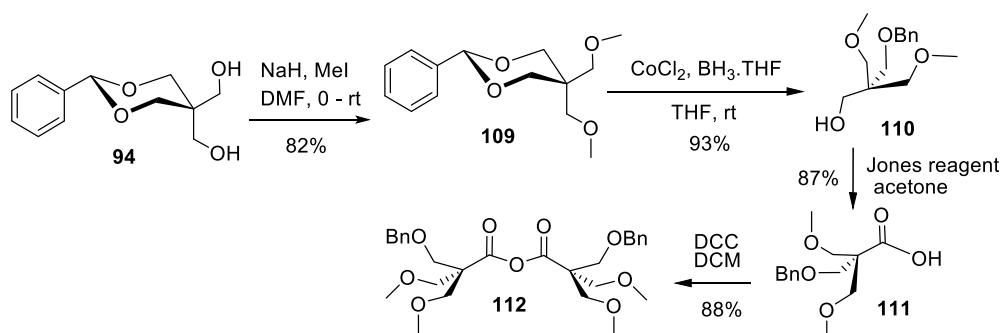
In other reactions, a symmetrical dendron **107** that is an AB₃ dendron, was prepared by selective reduction of known¹⁷⁷ di-*O*-benzyl-*O*-benzylidene-pentaerythritol **105** to tri-*O*-benzyl-pentaerythritol **106** as shown in Scheme 36. This approach avoids the use of excess benzyl bromide required for the direct synthesis of **106** from pentaerythritol.^{178,179} Jones oxidation of **106** gave carboxylic acid **107**, that was converted to crystalline anhydride **108** using DCC.



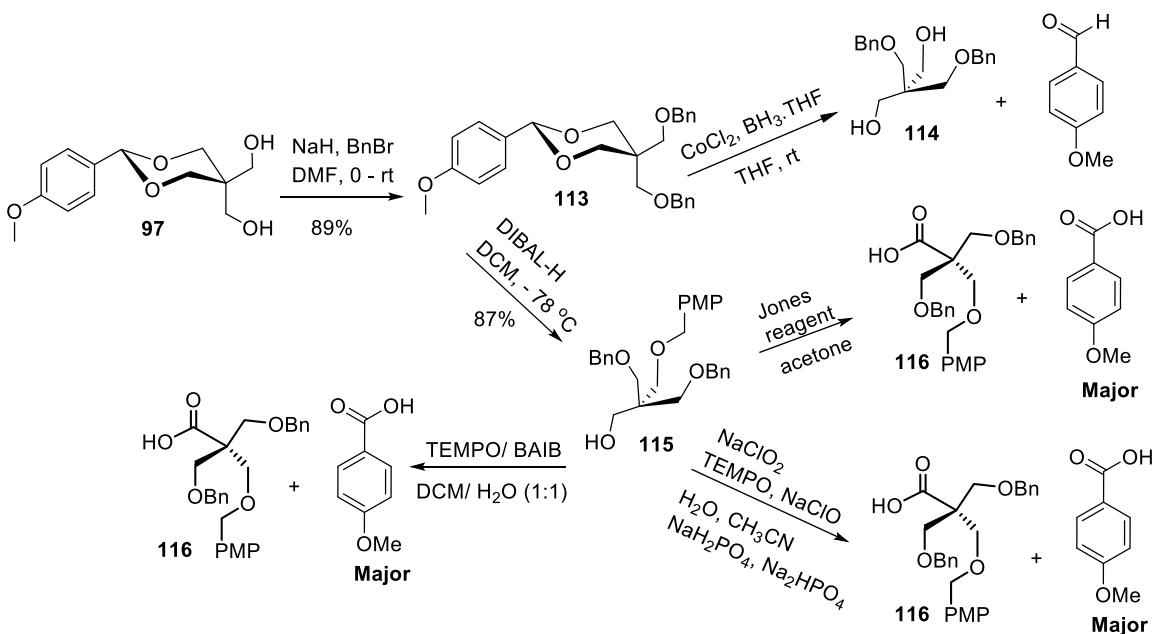
Scheme 36 Preparation of anhydride **108**

When benzyl bromide was replaced by methyl iodide in step one of Scheme 36, a new dendron **111** was produced in good yield. Using hydrogenolysis, dendrons such as **111** can be

activated at a single position for the next round of reaction. This could be important for alleviating steric hindrance at higher generations and for dendrimer surface functionalization.



Scheme 37 Preparation of anhydride **112**

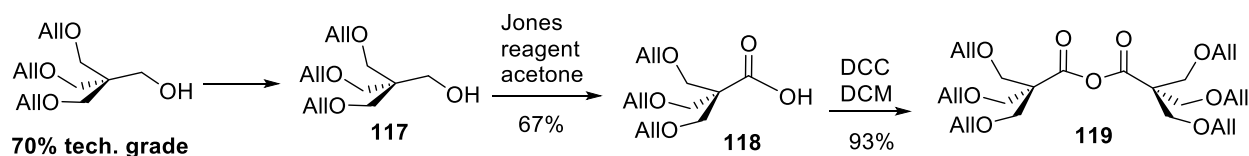


Scheme 38 Potential preparation of orthogonally protected **116**

Orthogonal protection plays an essential part in organic synthesis manipulations. By choosing the right protecting groups, it is possible to remove one set of protecting groups in any order, using reagents and conditions that do not affect other sets of protecting groups present in the molecule. Dendrons such as **116** that have both benzyl and *p*-methoxybenzyl groups would

be of considerable utility as the *p*-methoxybenzyl group can be selectively removed in high yield using DDQ or CAN.^{180,181} This would allow subsequent manipulation of the resulting single hydroxyl group without affecting the rest of the molecule. Attempts to prepare **116** are illustrated in Scheme 38. When selective cleavage of *p*-methoxybenzylidene acetal was tried on compound **113** using cobalt (II) chloride and borane-tetrahydrofuran complex, equimolar amounts of dibenzylpentaerythritol and *p*-methoxybenzaldehyde were obtained in 30 minutes. Successful cleavage of the acetal to the corresponding alcohol **115** was achieved in 87% yield when DIBAL-H was used at - 78 °C (for 6 h) or in 92% yield at - 10 °C (for 3 h) in dichloromethane. Unfortunately, all attempts to oxidize the alcohol to the corresponding acid dendron **116** gave *p*-methoxybenzoic acid as the major product as shown in Scheme 38.

Technical tri-*O*-allylpenterythritol, the commercially available tri-*O*-allylpenterythritol, is stated to have 70% purity, and contains small amounts of both monoallylpenterythritol and diallylpenterythritol, which are easily removed using column chromatography. Jones oxidation of the purified triallyl derivative gave acid dendron **118**, which was transformed into the corresponding acid anhydride with DCC (Scheme 39).



Scheme 39 Preparation of allyl-protected anhydride **119**

2.2.3. Configuration of Synthetic 5-Methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (**43**)

A number of research groups have synthesized and utilized compound **43**,^{90,92,93,95,182} apparently as a single isomer, but its configuration had not been established as far as we are

aware. Two stereoisomers of compound **43** are possible as shown in Figure 8. ^1H NMR and ^{13}C NMR spectra of this compound showed that a single isomer had also been isolated here (Scheme 40), not the mixture of *cis*- and *trans*- isomers expected based on the free energy difference for the isomers of 5-carboxymethyl-2-isopropyl-5-methyl-1,3-dioxane.¹⁸³

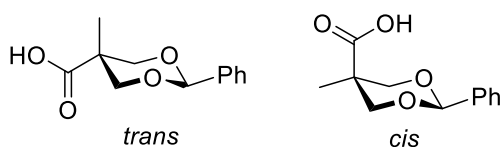
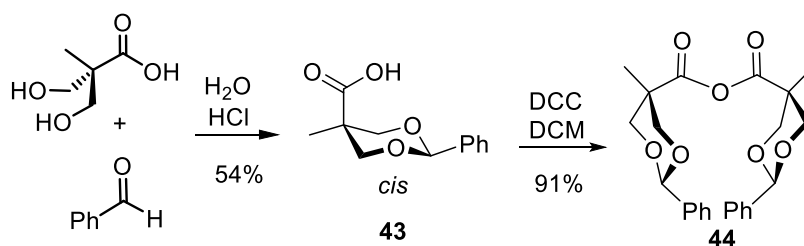


Figure 8 *Cis* and *trans* isomers of 5-methyl-2-phenyl-1,3-dioxane-5-carboxylic acid, **43**

Piasecki and coworkers¹⁸⁴⁻¹⁸⁶ synthesized a series of 1,3-dioxanes bearing various long chain alkyl substituents at C-2 and a methyl group and a carboxyl group at C-5. The protons of the methyl group at C-5 in these compounds resonated as singlets at 1.02 ppm. Eliel and Enanoza had noted that an axially-oriented $-\text{CH}_3$ group at C-5 (chemical shifts $\sim 1.5 - 1.6$ ppm in 5-methyl-2-substituted-1,3-dioxanes) is deshielded by 0.5 - 0.6 ppm with respect to an equatorially-oriented CH_3 group (chemical shifts ~ 1 ppm).¹⁸³ In addition, in isomers with the CH_3 group and the C-2 group *cis*, the chemical shift difference between the two protons at C-4,6 is negligible or small,¹⁸³ whereas in the *trans*-isomer it is large, about 1 ppm for those prepared by Piasecki.¹⁸⁶ For **43**, the methyl group resonated at 1.11 ppm when the sample was run in chloroform-*d* or at 1.05 ppm when the sample was run in acetone-*d*₆. The chemical shift difference between the two protons on C-4,6 was 0.91 ppm in chloroform-*d* and 0.83 ppm in acetone-*d*₆. Based on these grounds, compound **43** is the *cis*-isomer (Figure 8).

Kaloustian *et al.* attributed the axial preference at C-5 of 1,3-dioxanes for positively charged groups such as trimethylammonium groups on the electrostatic attraction of the resultant C-O dipole and the C-N⁺ dipole in this geometric arrangement and suggested that the small

conformational effect of a carbonyl group at C-5 had a contribution from the same effect.¹⁸⁷ However, a similar favoring of the axial orientation for 5-fluoro derivatives must arise from the gauche effect,¹⁸⁸ where bonding interactions favor gauche arrangements and dipole-dipole repulsion disfavors them. Piasecki found that formation of the acetal in non-polar solvents such as hexane gave mixtures whereas formation in polar solvents such as acetonitrile gave only the *cis*-isomer,¹⁸⁵ consistent with the measured effects of solvent polarity on conformational equilibria and with decrease of through space dipole-dipole repulsion in polar solvents.¹⁸⁷ Compound **43** was prepared here in a polar solvent, water, and only the *cis*-isomer was observed. This acid was converted into the anhydride **44** as earlier^{90,182} using DCC for dendrimer formation (Scheme 40).



Scheme 40 Preparation of anhydride **44**

2.2.4. Concluding Remarks

Pentaerythritol is an easily accessible versatile starting material. The manipulation of its hydroxyl groups using various chemical transformations and various protection/ deprotection strategies allowed the preparation of new types of tribranched dendrons such as **100**, **101**, **102**, **107**, **111**, and **118**. The successful synthesis of these dendrons leaves the desire to investigating how versatile they are in the preparation of polyester dendrimers. This will be discussed in Chapter 6, in which an efficient esterification method between carboxylic acids and alcohols (discussed in Chapter 3 and applied in Chapters 4 and 5) will also be applied in some examples.

2.3. Experimental Section

2.3.1. General

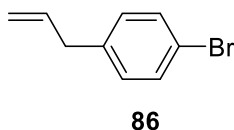
^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-500 NMR spectrometer operating at 500.13 and 125.7 MHz respectively using the solvent resonances as secondary chemical shift references. The signals of carbon and hydrogen nuclei of new compounds were assigned from the analysis of their one dimensional (^1H , ^{13}C , and DEPT-135) and two dimensional (COSY, HSQC, and HMBC) NMR spectral data. The ^1H and ^{13}C NMR spectra may be found in Appendix B. High-resolution mass spectra were recorded using electrospray ionization with Bruker Microtof time of flight mass analyser. Melting points were determined on a Fisher-John's melting point apparatus and are uncorrected.

Acetone was refluxed over K_2CO_3 and distilled over molecular sieves. Dichloromethane was refluxed over calcium hydride and distilled onto molecular sieves. Benzene was refluxed over CaCl_2 and distilled over molecular sieves. Methanol was refluxed over calcium oxide and distilled over molecular sieves. Tetrahydrofuran was refluxed over LiAlH_4 and distilled over molecular sieves. Unless otherwise noted, non-aqueous reactions were carried out under a nitrogen atmosphere. Jones reagent (0.56 M) was prepared by dissolving sodium dichromate dihydrate ($\text{Na}_2\text{Cr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$, 300 g, 1.01 mol) in 1.5 L of water followed by slowly adding conc. sulfuric acid (300 mL) to the cooled solution (0 °C). Compounds were visualized/ located by spraying the TLC plate with a solution of 2 % ceric ammonium sulfate in 0.5 M H_2SO_4 followed by heating on a hot plate until color developed. Solid compounds were purified on silica gel using flash column chromatography and specified eluents, or by crystallization. Liquids and oils were purified using flash column chromatography. The sodium phosphate buffer stock solution

was made by dissolving sodium phosphate monobasic (803 mg, 6.7 mmol) and sodium phosphate dibasic (950 mg, 6.7 mmol) in water (20 mL).

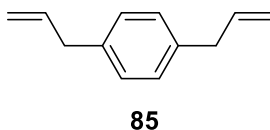
2.3.2. Synthesis of Core Molecules

2.3.2.1. 1-Allyl-4-bromobenzene (86).



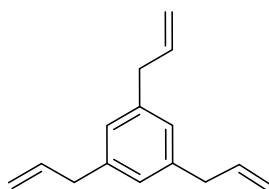
A stirred mixture of magnesium turnings (3.62 g, 0.149 mol) and dry THF (150 mL) in a two-neck round-bottomed flask was flushed with N₂ for 10 min then heated to 40 °C when two drops of 1,2-dibromoethane were added. A 10 % of a solution of 1,4-dibromobenzene (29.3 g, 0.124 mol) in THF (50 mL) was added and when the magnesium had started to react, the rest of this solution was added slowly over 0.5 h. Stirring was continued until the magnesium turnings were completely consumed. The flask was cooled to 0 °C and a solution of allyl bromide (16.5 g, 0.136 mol) in dry THF (30 mL) was added slowly over 0.5 h. The mixture was heated under reflux for 12 h, and then allowed to cool to rt. Water (60 mL) was carefully added and the mixture was extracted using diethyl ether (40 mL x 3). The combined extracts were dried (MgSO₄), filtered, and concentrated. Purification using column chromatography (hexanes/EtOAc; 2: 1, R_F 0.44) afforded a colorless syrup (15.4 g, 63 % yield). ¹H NMR and ¹³C NMR data were more or less similar to lit.¹⁸⁹

2.3.2.2. 1,4-Diallylbenzene (85).



An oven-dried two-neck round-bottomed flask charged with diiodide **88** (48.0 g, 0.134 mol), CuI (2.55 g, 0.013 mol), and 2,2'-dipyridyl (2.10 g, 0.013 mol) was evacuated and flushed with N₂. Anhydrous THF (700 mL) was added and the stirred reaction mixture was cooled to 0 °C. A 1 M solution of vinyl magnesium bromide in THF (540 mL, 0.536 mol) was added quickly via cannula, and the reaction mixture was allowed to warm to rt. After 1 h, saturated NH₄Cl (200 mL) and 28% NH₃ (150 mL) were added and the mixture was stirred for 1 h at rt. The product was extracted using hexanes (100 mL × 3) and the combined extracts were washed with brine (60 mL × 2), dried (MgSO₄), filtered, and concentrated. Purification using column chromatography (hexanes, R_F 0.37) gave a colorless oily syrup (17.2 g, 81% yield); ¹H and ¹³C NMR data were similar to lit.^{139,142}

2.3.2.3. 1,3,5-Triallylbenzene (**89**).

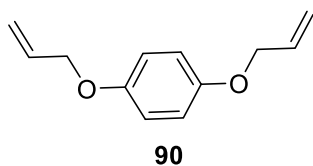


89

A tube was charged with allyltributylstannane¹⁴⁸ (3.10 mL, 0.010 mol), 1,3,5-tribromobenzene (1.00 g, 0.003 mol), tetrakis(triphenylphosphine)palladium(0) (0.280 g, 0.242 mmol), dry benzene (5 mL), and a stirring bar. The tube was evacuated and back-filled with N₂ three times. The reaction mixture was stirred in the sealed tube at a bath temperature of 120 °C for 24 h and then allowed to cool to rt. After carefully releasing the pressure, the reaction mixture was diluted with diethyl ether (15 mL) and stirred for 15 min with saturated aqueous KF (10 mL). The organic layer was separated and stirred with 10% NH₄OH (10 mL) for 20 min. The organic layer was separated, washed with brine (10 mL), dried (MgSO₄), and concentrated to

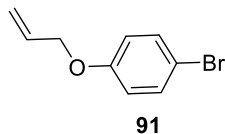
give crude triallylbenzene that was distilled (bp 125 °C/ 1.5 torr) to give the pure product as a colorless syrup (0.47 g, 75% yield): ^1H NMR (500.13 MHz, CDCl_3) δ 3.35 (d, $J = 6.5$ Hz, 6H, $3\text{CH}_2 \text{sp}^3$), 5.05 – 5.11 (m, 6H, $3\text{CH}_2\text{CH}=\text{CH}_2$), 5.92 – 6.01 (m, 3H, $3\text{CH}_2\text{CH}=\text{CH}_2$), 6.87 (s, 3H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 140.3 (PhC), 137.6 ($3\text{CH}_2\text{CH}=\text{CH}_2$), 126.6 (PhC), 115.7 ($3\text{CH}_2\text{CH}=\text{CH}_2$), 40.2 ($3\text{CH}_2 \text{sp}^3$). HR-EI MS m/z calcd for $\text{C}_{15}\text{H}_{18}$ 198.1409, found 198.1419.

2.3.2.4. General method for forming allyl ethers: 1,4-diallyloxybenzene (90).



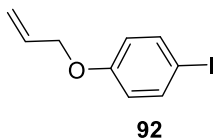
Allyl bromide (220 g, 1.82 mol) and anhydrous DMF (200 mL) were cooled to -10 °C and sodium hydride (60% oil dispersion, 17.6 g, 0.440 mol) was added. The resulting mixture was stirred for 10 min, and a solution of hydroquinone (20.0 g, 0.182 mol) in DMF (200 mL) was added dropwise over 30 min. The reaction mixture was stirred for 15 min after which TLC confirmed the disappearance of hydroquinone. The flask was allowed to warm to 0 °C and water (150 mL) was carefully added. The product was extracted using diethyl ether (150 mL) and the aqueous layer was extracted with ether (2×60 mL). The organic layers were combined, dried (MgSO_4), filtered, and concentrated under vacuum. The crude product was obtained as a pale yellow oily liquid and crystallized out of hexanes at -10 °C to give colorless crystals (34.2 g, 99% yield): mp 38 - 40 °C; lit.¹⁹⁰ mp 31.9 – 32.4 °C; ^{13}C NMR (125.7 MHz, CDCl_3) δ 153.1 (PhC), 133.8 (CH sp^2), 117.6 ($\text{CH}_2 \text{sp}^2$), 115.8 (PhC), 69.6 ($\text{CH}_2 \text{sp}^3$); ^1H NMR more or less similar to lit.¹⁹¹

2.3.2.5. 1-Allyloxy-4-bromobenzene (91).



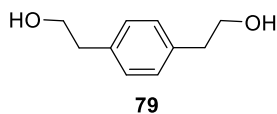
Prepared from allyl bromide (70.0 g, 0.580 mol) in anhydrous DMF (200 mL), sodium hydride (60% oil dispersion, 5.60 g, 0.140 mol), and a solution of 4-bromophenol (20.0 g, 0.116 mol) in DMF (100 mL) as for **90**. The product was obtained as a colorless oily liquid after purification using column chromatography (24 g, 97% yield): (EtOAc/hexanes; 1:2, R_F 0.52); ^1H NMR and ^{13}C NMR spectra similar to lit.¹⁹²

2.3.2.6. 1-Allyloxy-4-iodobenzene (92).



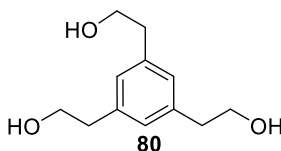
The general method for allylation with allyl bromide (68.7 g, 0.568 mol) in DMF (200 mL), sodium hydride (60% oil dispersion, 5.45 g, 0.136 mol), and a solution of 4-iodophenol (25.0 g, 0.114 mol) in DMF (100 mL) gave after purification using column chromatography (hexanes, R_F 0.43), the title compound as a yellow oil (28.3 g, 96 % yield): ^1H NMR (500.13 MHz, CDCl_3) δ 4.49 (dt, $J = 5.0, 1.5$ Hz, 2H, OCH_2), 5.33 (dq, $J = 10.5$ Hz, 1.5 Hz, 1H, H_{cis}), 5.44 (dq, $J = 17.5$ Hz, 1.5 Hz, 1H, H_{trans}), 6.05 (ddt, $J = 17.5$ Hz, 10.5 Hz, 5 Hz, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$), 6.69 - 6.72 (m, 2H, PhH), 7.55 - 7.58 (m, 2H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 158.3, 138.1 (PhC), 132.8 (vinyl CH) 117.8 (vinyl CH_2), 117.1 (PhCH), 83.0 (PhCI), 68.6 ($\text{CH}_2 \text{sp}^3$); HR EIMS m/z calculated for $\text{C}_9\text{H}_9\text{IO}$ 259.9698, found 259.9690. Note that the ^1H NMR data are more or less similar to those of Taskinen,¹⁹³ but neither the ^1H NMR nor ^{13}C NMR data match those in the characterization of **92** provided by Qu *et al.*¹⁹⁴

2.3.2.7. General method for one pot reductive ozonolysis and reduction: 1,4-benzenediethanol (79).



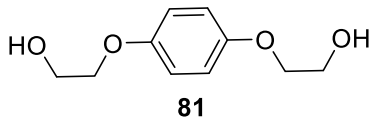
Ozone was bubbled through a solution of **85** (4.65 g, 29.4 mmol) maintained at $-78\text{ }^{\circ}\text{C}$ in a 1:1 mixture of methanol (100 mL) and dichloromethane (100 mL) until TLC confirmed the disappearance of the olefin. N_2 was then bubbled through the reaction mixture for 15 min. Excess dimethyl sulfide was added at $-78\text{ }^{\circ}\text{C}$, and the reaction mixture was allowed to warm to rt with stirring. The reaction mixture was concentrated under vacuum, and the resulting syrup was dissolved in absolute ethanol (100 mL). The reaction flask was cooled to $0\text{ }^{\circ}\text{C}$ and excess NaBH_4 was added in portions with stirring. Stirring was continued at rt for 20 h and water (20 mL) was added. The reaction mixture was acidified to $\text{pH} \sim 6$ (20% HCl) and filtered. Concentration of the filtrate under vacuum gave a thick oily residue, which was then dissolved in EtOAc (65 mL) and water (15 mL). The organic layer was collected, dried (MgSO_4), and concentrated. The product was obtained as a colorless solid and was purified using column chromatography (EtOAc, R_F 0.52) to give colorless crystals (3.86 g, 79% yield): mp $84 - 86\text{ }^{\circ}\text{C}$; lit.¹³⁸ mp $85\text{ }^{\circ}\text{C}$.

2.3.2.8. 1,3,5-Benzenetriethanol (80).



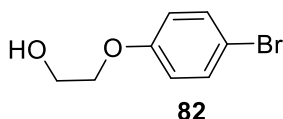
Compound **80** was prepared from **89** (4.26 g, 0.022 mol) by the general method and purified using column chromatography to give colorless crystals (3.52 g, 78% yield): mp $74 - 76\text{ }^{\circ}\text{C}$; lit.¹⁴³ mp $75\text{ }^{\circ}\text{C}$. ^1H and ^{13}C NMR data were similar to lit.¹⁴⁷

2.3.2.9. 1,4-Bis-(2-hydroxyethoxy)benzene (**81**).



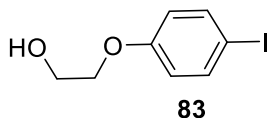
Prepared from **90** (4.68 g, 0.025 mol) as for **79** and purified using column chromatography (EtOAc; R_F 0.51) to give the product as a colorless crystalline powder (3.87 g, 79% yield): mp 102 - 104 °C; lit.¹⁶¹ mp 103 - 104 °C.

2.3.2.10. 2-(4-Bromophenoxy)ethanol (**82**).



The general method with **91** (12.5 g, 0.058 mol) gave the product as a thick residue that was purified using column chromatography (EtOAc, R_F 0.31). The product solidified on cooling (fridge) to give colorless crystals (10 g, 79% yield): mp 54 - 56 °C; lit.¹⁵⁰ mp 55 °C.

2.3.2.11. 2-(4-Iodophenoxy)ethanol (**83**).



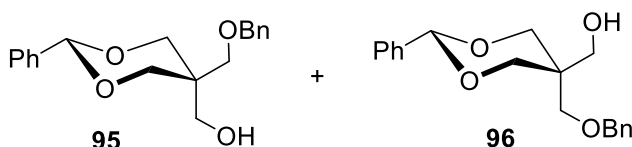
The general method with **92** (5.00 g, 0.019 mol) gave the product as a colorless solid that was purified using column chromatography (EtOAc, R_F 0.31) to give a colorless crystalline solid (3.96 g, 78% yield): mp 75 - 76 °C; lit.¹⁵⁴ mp 73.5 - 74.5 °C.

2.3.3. Synthesis of Dendrons

2.3.3.1. General procedure for mono-*O*-benzylation of diols

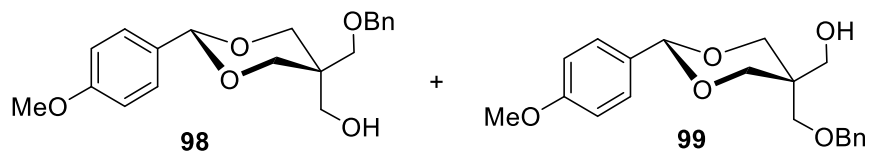
trans-5-Benzyloxymethyl-*cis*-5-hydroxymethyl-2-phenyl-1,3-dioxane and

cis-5-benzyloxymethyl-*trans*-5-hydroxymethyl-2-phenyl-1,3-dioxane (**95**, **96**)



Mono-*O*-benzylidene pentaerythritol **94**¹⁶⁴ (5.00 g, 0.022 mol) and dibutyltin oxide (5.55 g, 0.022 mol) were dissolved in dry toluene (300 mL) in a 500 mL round bottom flask. The flask was fitted with a Dean-Stark apparatus, and the mixture was heated at reflux (115 °C) for 12 h. The mixture was then allowed to cool to rt, and benzyl bromide (3.81 g, 0.223 mol) and tetrabutylammonium bromide (1.00 g, 3.10 mmol) were added. Heating at reflux temperature (115 °C) was continued for another 12 h. The reaction mixture was allowed to cool to rt and then concentrated under vacuum. The concentrated residue was dissolved in CH₂Cl₂ (150 mL) and this organic layer was washed repeatedly with water until the aqueous layer became clear. The organic layer was dried (MgSO₄), filtered, and concentrated to give a crude mixture of **95** and **96** as a pale yellow syrup. Purification was achieved using column chromatography (EtOAc/hexanes, 1:2). First to elute was compound **95** as a thick colorless syrup (3.40 g, 49 %); (EtOAc/hexanes, 1:2, R_F 0.51); ¹H and ¹³C NMR spectra similar to lit.¹⁷¹ The second component **96** was also a thick colorless syrup (2.41, 35 %); (EtOAc/hexanes, 1:2, R_F 0.41); ¹H and ¹³C NMR more or less similar to lit.¹⁷¹

2.3.3.2. *trans*-5-Benzyloxymethyl-*cis*-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane and *cis*-5-benzyloxymethyl-*trans*-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (98, 99)

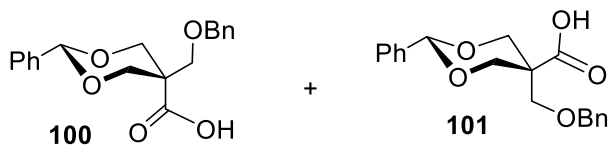


The general procedure using 5,5-bis(hydroxymethyl)-2-(4-methoxyphenyl)-1,3-dioxane (**97**)^{195,196} (6.00 g, 0.024 mol) gave a mixture of **98** and **99** as a colorless solid. Purification was achieved using column chromatography (EtOAc/ hexanes, 1:2). First to elute was compound **98** as a colorless crystalline solid (3.90 g, 48 %); (EtOAc/ hexanes, 1:2, R_F 0.38): mp 90 – 91 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 2.55 (s, br, 1H), 3.52 (s, 2H), 3.75 (d, J = 11.5 Hz, 2H), 3.81 (s, 3H), 3.97 (s, 2H) 4.18 (d, J = 11.5 Hz, 2H), 4.62 (s, 2H), 5.38 (s, 1H), 6.88 – 6.91 (m, 2H), 7.30 – 7.39 (m, 7H); ¹³C NMR (125.7 MHz, CDCl₃) δ 160.2, 138.0, 130.8, 128.7, 128.0, 127.8, 127.5, 113.8, 102.1, 73.9, 72.2, 70.5, 66.1, 55.4, 38.7. HR ESI MS: m/z calcd for C₂₀H₂₄NaO₅ 367.1516, found 367.1524. The second component **99** was also a colorless crystalline solid (2.93 g, 36 %); (EtOAc/hexanes, 1:2, R_F 0.33); mp 101 – 102 °C; ¹H NMR (500.13 MHz, acetone-*d*₆) δ 3.49 (d, J = 5.5 Hz, 2H), 3.73 (t, J = 5.5 Hz, 1H), 3.79 (s, 3H), 3.85 (s, 2H), 3.87 (d, J = 12 Hz, 2H), 4.07 (d, J = 12 Hz, 2H), 4.60 (s, 2H), 5.39 (s, 1H), 6.88 – 6.91 (m, 2H), 7.27 – 7.40 (m, 7H); ¹³C NMR (125.7 MHz, acetone-*d*₆) δ 160.8, 139.9, 132.5, 129.0, 128.4, 128.1, 114.0, 102.2, 73.8, 70.5, 70.0, 63.1, 55.5, 39.9. HR ESI MS: m/z calcd for C₂₀H₂₄NaO₅ 367.1516, found 367.1518.

2.3.3.3. General procedure for Merck oxidation of alcohols

trans-5-Benzyloxymethyl-*cis*-2-phenyl-1,3-dioxane-5-carboxylic acid and

cis-5-benzyloxymethyl-*trans*-2-phenyl-1,3-dioxane-5-carboxylic acid (**100**, **101**)

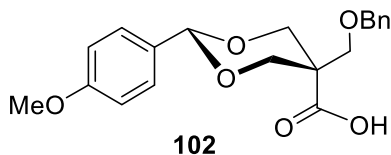


Benzyl alcohol (**95**) (8.56 g, 27.2 mmol), 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) (0.300 g, 1.91 mmol), and sodium phosphate buffer (pH 6.7) (105 mL) were dissolved in acetonitrile (140 mL). The resulting mixture was stirred and heated to 38 °C for 5 min. About 20 % of a solution of 80% sodium chlorite (6.22 g, 54.5 mmol) in water (28 mL) was added to the mixture through a pressure-equalizing funnel. Via another pressure-equalizing funnel, 20 % of a solution of household bleach (6% sodium hypochlorite) (0.64 mL) in water (13 mL) was also added. The remaining bleach and sodium chlorite solutions were added simultaneously over a period of 0.5 h. Stirring at 38 °C was continued for another 10 to 12 h. The reaction mixture was allowed to cool to rt, water was added (140 mL), and the pH was adjusted to 8 using a 0.5 M NaOH solution. The reaction flask was cooled with a water-ice bath, and an ice-cold solution of sodium sulfite (8.30 g, 66.0 mmol) in water (136 mL) was added. The resulting mixture was stirred for 45 min, diluted with CH₂Cl₂ (150 mL), and stirring was continued for a further 20 min. The organic layer was separated, discarded, and more CH₂Cl₂ (150 mL) was added. After stirring for 10 min, this organic layer was also separated and discarded. The aqueous layer was acidified (pH = 5- 6) using 20 % HCl and CH₂Cl₂ (150 mL) was added. The organic layer was collected, and the aqueous layer extracted with CH₂Cl₂ (2 x 100 mL). The organic layers were combined, dried (MgSO₄), filtered, and concentrated to give a

crude colorless solid. The product was purified using crystallization (EtOAc/hexanes) to afford **100** as colorless crystals (7.06 g, 79 %): mp 113 - 114 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 3.46 (s, 2H), 3.92 (d, *J* = 11.5 Hz, 2H), 4.49 (s, 2H), 4.67 (d, *J* = 11.5 Hz, 2H), 5.46 (s, 1H), 7.24 - 7.47 (m, 10H); ¹³C NMR (125.7 MHz, CDCl₃) δ 176.8, 137.6, 137.4, 129.3, 128.7, 128.5, 128.1, 127.8, 126.3, 102.1, 73.8, 70.32, 70.28, 47.2. HR ESI MS: *m/z* calcd for C₁₉H₁₉O₅ 327.1238, found 327.1233.

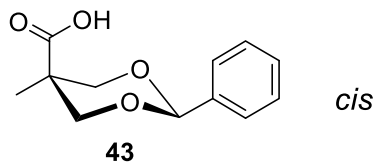
In a similar fashion, 7.25 g of **96** was oxidized and afforded **101** also as colorless crystals (5.76 g, 76 %): mp 134 – 135 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 4.10 (s, 2H), 4.15 (d, *J* = 12 Hz, 2H), 4.38 (d, *J* = 12 Hz, 2H), 4.65 (s, 2H), 5.45 (s, 1H), 7.29 - 7.43 (m, 10H); ¹³C NMR (125.7 MHz, CDCl₃) δ 175.3, 137.7, 137.6, 129.4, 128.6, 128.5, 128.0, 127.8, 126.2, 102.0, 73.9, 69.3, 68.7, 46.0. HR ESI MS: *m/z* calcd for C₁₉H₁₉O₅ 327.1238, found 327.1238.

2.3.3.4. *trans*-5-Benzyloxymethyl-*cis*-2-(4-methoxyphenyl)-1,3-dioxane-5-carboxylic acid (**102**)



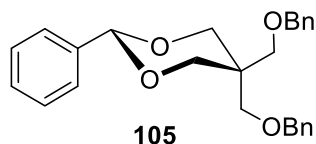
The general procedure using **98** (1.38 g, 4.01 mmol) at 35 °C for 11 h (see table 2.1) gave a colorless solid which was crystallized (EtOAc/ hexanes) to afford **102** as colorless crystals (0.57 g, 40 %): mp 125 – 126 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 3.47 (s, 2H), 3.78 (s, 3H), 3.91 (d, *J* = 12 Hz, 2H), 4.50 (s, 2H), 4.66 (d, *J* = 12 Hz, 2H), 5.43 (s, 1H), 6.85 - 6.88 (m, 2H), 7.27 – 7.41 (m, 7H); ¹³C NMR (125.7 MHz, CDCl₃) δ 177.6, 160.2, 137.4, 130.2, 128.7, 128.1, 127.73, 127.66, 113.8, 102.0, 73.7, 70.3, 70.2, 55.4, 47.3. HR ESI MS: *m/z* calcd for C₂₀H₂₁O₆ 357.1333, found 327.1336.

2.3.3.5. *cis*-5-Methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (43)



2,2-Bis(hydroxymethyl)propanoic acid (30.0 g, 0.224 mol) was dissolved in water (300 mL). Under vigorous stirring, conc. HCl (3 mL) was added, and benzaldehyde (23.7 g, 0.224 mol) was added dropwise over a period of 2 h at 38 °C. When the addition was complete, stirring was continued for 12 h at 40 °C. The reaction mixture was allowed to cool to rt, and the precipitated solid product was collected using suction filtration and was washed with water (2 x 50 mL), then crystallized (EtOAc) to give colorless needles (27 g, 54% yield): mp 149 - 151 °C; lit. mp 185 - 187 °C,⁹³ 197 - 198 °C;⁹² ¹H NMR (500.13 MHz, CDCl₃) δ 1.11 (s, 3H, CH₃), 3.71 (d, *J* = 11.5 Hz, 2H, H-4_{ax}, H-6_{ax}), 4.62 (d, *J* = 11.5 Hz, 2H, H-4_{eq}, H-6_{eq}), 5.49 (s, 1H, H-2), 7.32 - 7.37 (m, 3H, PhH), 7.44 - 7.48 (m, 2H, PhH), 10.6 (br, 1H, COOH); ¹H NMR (500.13 MHz, acetone-*d*₆) δ 1.05 (s, 3H, CH₃), 3.74 (d, *J* = 11.5 Hz, 2H, H-4_{ax}, H-6_{ax}), 4.57 (d, *J* = 11.5 Hz, 2H, H-4_{eq}, H-6_{eq}), 5.53 (s, 1H, H-2), 7.31 - 7.44 (m, 5H, PhH); ¹³C NMR (125.7 MHz, acetone-*d*₆): δ 175.7 (C=O), 139.8, 129.4, 128.7, 127.1 (PhC), 102.1 (C-2), 74.0 (C-4, C-6), 42.6 (C-5), 18.2 (CH₃). HR ESI MS: *m/z* calcd for C₁₂H₁₃O₄ 221.0819, found 221.0834.

2.3.3.6. 5,5-Bis(benzyloxymethyl)-2-phenyl-1,3-dioxane (105)

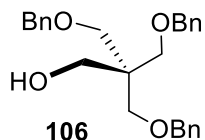


Mono-*O*-benzylidene pentaerythritol (**94**)¹⁶⁴ (0.740 g, 3.30 mmol) and benzyl bromide (1.35 g, 7.89 mmol) were dissolved in dry DMF (15 mL) at 0 °C. NaH (60%) (0.318 g, 7.95

mmol) was then added in portions, and the reaction mixture was allowed to warm to rt with stirring for 12 h. Water (3 mL) and CH₂Cl₂ (20 mL) were added and the resulting mixture was stirred for 10 min. The organic layer was collected, washed with water (3 x 7 mL), dried (MgSO₄), filtered, and concentrated to give a crude colorless solid. Purification using column chromatography (hexanes/EtOAc; 5:1, R_F 0.45) gave **105** as a colorless crystalline solid (1.15 g, 86 % yield): mp 79 °C; lit.¹⁷⁷ mp 72 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 3.46 (s, 2H, CH₂eq), 3.99 (s, 2H, CH₂ax), 4.03 (d, *J* = 11.5 Hz, 2H, H-4_{ax}, H-6_{ax}), 4.31 (d, *J* = 11.5 Hz, 2H, H-4_{eq}, H-6_{eq}), 4.58 (s, 2H, OCH₂Ph_{eq}), 4.70 (s, 2H, OCH₂Ph_{ax}), 5.54 (s, 1H, H-2), 7.38 – 7.50 (m, 13H, PhH), 7.57 – 7.59 (m, 2H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 138.7, 138.4, 138.3, 129.0, 128.4, 128.33, 128.30, 127.7, 127.52, 127.46, 126.2 (PhC), 101.8 (C-2), 73.4 (OCH₂Ph_{ax}), 73.3 (OCH₂Ph_{eq}), 70.3 (CH₂ax), 70.2 (C-4, C-6), 68.9 (CH₂eq), 39.0 (C-5). HR ESI MS: *m/z* calcd for C₂₆H₂₈NaO₄ 427.1880, found 427.1852.

2.3.3.7. General procedure for reductive opening of benzylidene acetals

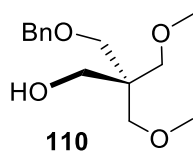
3-(Benzyloxy)-2,2-bis(benzyloxymethyl)propan-1-ol (**106**)



To a solution of benzylidene acetal (**105**) (2.00 g, 4.94 mmol) in anhydrous THF (10 mL) was added a 1 M solution of BH₃*THF complex (9.88 mL, 9.88 mmol) under nitrogen. Anhydrous CoCl₂ (1.28 g, 9.88 mmol) was added in one portion and the reaction mixture was stirred at rt for 20 min when TLC confirmed the disappearance of the starting material. The reaction mixture was diluted using EtOAc (40 mL) and undissolved CoCl₂ was filtered off. The blue solution was cooled to 0 °C and aqueous NaBH₄ solution was added dropwise with stirring

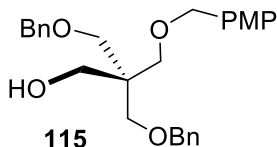
until the blue color disappeared and there was formation of a black precipitate. The precipitate was filtered off and the organic layer was separated, washed with NaHCO₃ (1 M, 10 mL), water (10 mL) and dried (MgSO₄). Concentration followed by column chromatography (hexanes/EtOAc; 3:1, R_F 0.39) gave the product as a colorless syrup (1.83 g, 91% yield): ¹H and ¹³C NMR spectra similar to lit.¹⁷⁸

2.3.3.8. 3-(Benzyloxy)-2,2-bis(methoxymethyl)propan-1-ol (**110**)



Using the general procedure with benzylidene acetal (**109**)¹⁷⁷ (16.4 g, 65.1 mmol), **110** was obtained as colorless syrup (15.4 g, 93% yield) after purification using column chromatography (hexanes/EtOAc; 2:1, R_F 0.33). ¹H and ¹³C NMR spectra similar to lit.¹⁹⁷

2.3.3.9. 3-(Benzyloxy)-2-(benzyloxymethyl)-2-((4-methoxybenzyloxy)methyl)propan-1-ol (**115**)

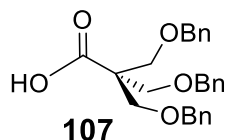


Acetal **113** (8.61 g, 19.8 mmol) was dissolved in dichloromethane (15 mL) and the reaction flask was cooled to -78 °C. Diisobutylaluminum hydride (DIBAL-H) (40 mL, 39.6 mmol) (1 M in CH₂Cl₂) was added dropwise to the cooled solution with stirring. The reaction mixture was stirred for 6 h at -78 °C or for 3 h at -10 °C when TLC confirmed the disappearance of the starting material. The mixture was diluted using dichloromethane (15 mL)

and quenched using methanol at 0 °C. To the reaction mixture was then added 10 % KOH (10 mL) and the mixture was stirred for 10 min at rt. The organic layer was collected, dried (MgSO₄), filtered, and concentrated. Purification using column chromatography (hexanes/ EtOAc; 3:1, R_F = 0.23) gave the product as a colorless syrup (8.04 g, 93% yield): ¹H NMR (500.13 MHz, CDCl₃) δ 3.13 (t, *J* = 6.0 Hz, 1H, OH), 3.69 (s, 2H, OCH₂C_{quat}), 3.70 (s, 4H, C_{quat}CH₂OBn), 3.84 (s, 3H, OCH₃), 3.92 (d, *J* = 6.0 Hz, 2H, CH₂OH), 4.53 (s, 2H, OCH₂PMP), 4.59 (s, 4H, 2OCH₂Ph), 6.96 – 6.99 (m, 2H, PhH), 7.32 – 7.34 (m, 2H, PhH), 7.36 – 7.45 (m, 10H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 159.0, 138.3, 130.3, 129.0, 128.2, 127.4, 127.3, 113.6 (PhC), 73.30 (2OCH₂Ph), 73.0 (OCH₂PMP), 70.6 (C_{quat}CH₂OBn), 70.3 (C_{quat}CH₂OCH₂PMP), 65.6 (CH₂OH), 55.0 (OCH₃), 45.0 (C_{quat}). HR ESI MS: *m/z* calculated for calcd for C₂₇H₃₂NaO₅ 459.2142, found 459.2152.

2.3.3.10. General oxidation procedure using Jones reagent

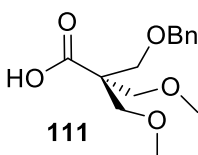
3-(Benzyloxy)-2,2-bis(benzyloxymethyl)propanoic acid (**107**)



Alcohol **106** (1.13 g, 2.80 mmol) was dissolved in acetone (12 mL) and the Jones reagent (0.56 M, 7.5 mL, 4.20 mmol) was added dropwise at 0 °C with stirring over a 1 h period. The ice-water bath was removed and stirring was continued for 8 h at rt. Acetone was removed under vacuum and water (12 mL) was added. The aqueous layer was extracted using diethyl ether (12 mL x 3). The combined organic layers were washed with water (9 mL x 3), dried (MgSO₄), and concentrated. Purification using column chromatography (hexanes/ EtOAc; 3:1, R_F 0.27) gave the acid as a colorless solid (0.87 g, 74 % yield). Purification was also achieved using

crystallization (hexanes/ EtOAc) in 61 % yield: mp 94 - 95 °C; ^1H NMR (500.13 MHz, acetone- d_6) δ 3.77 (s, 6H, $3\text{C}_{\text{quat}}\text{CH}_2\text{O}$), 4.53 (s, 6H, $3\text{OCH}_2\text{Ph}$), 7.25 - 7.34 (m, 15H, PhH), 10.89 (br, 1H, OH); ^{13}C NMR (125.7 MHz, acetone- d_6) δ 173.9 (C=O), 139.5, 129.0, 128.14, 128.10 (PhC), 73.7 ($3\text{CH}_2\text{Ph}$), 68.8 ($3\text{C}_{\text{quat}}\text{CH}_2\text{O}$), 53.8 (C_{quat}). HR ESI MS: m/z calcd for $\text{C}_{26}\text{H}_{27}\text{O}_5$ (M-H) 419.1864, found 419.1850.

2.3.3.11. 3-(Benzyloxy)-2,2-bis(methoxymethyl)propanoic acid (**111**)

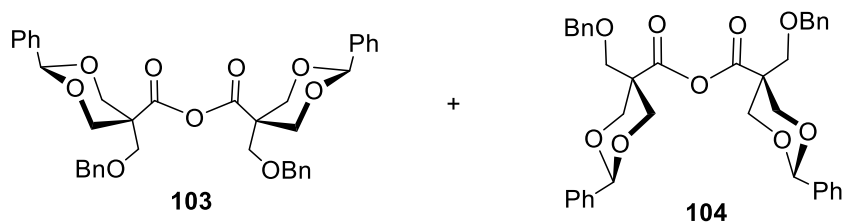


According to the general procedure, alcohol **110** (1.53 g, 6.02 mmol) and the Jones reagent (0.56 M, 16 mL, 9.00 mmol) in acetone (15 mL) were reacted for 8 h. After work up as above, a pure product was obtained as a colorless syrup (1.40 g, 87 % yield). ^1H NMR (500.13 MHz, CDCl_3) δ 3.36 (s, 6H), 3.63 (s, 4H), 3.70 (s, 2H), 4.56 (s, 2H), 7.27 - 7.37 (m, 5H), 11.80 (br, 1H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 178.3, 138.2, 128.3, 127.6, 127.5, 73.3, 70.4, 67.8, 59.4, 53.4. HR ESI MS: m/z calcd for $\text{C}_{14}\text{H}_{19}\text{O}_5$ (M-H) 267.1238, found 267.1236.

2.3.3.12. General procedure for anhydride formation

A carboxylic acid (9.14 mmol) and DCC (1.04 g, 5.02 mmol) were dissolved in dry CH_2Cl_2 (25 mL), and the mixture was stirred at rt until TLC confirmed the disappearance of the acid (6 – 10 h). The precipitated urea by-product was filtered off, and the organic layer was concentrated to give the crude product, which was purified as indicated below for individual anhydrides.

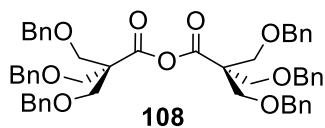
2.3.3.13. *trans*-5-Benzyloxymethyl-*cis*-2-phenyl-1,3-dioxane-5-carboxylic anhydride and *cis*-5-benzyloxymethyl-*trans*-2-phenyl-1,3-dioxane-5-carboxylic anhydride (103 and 104)



According to the general procedure, carboxylic acid **100** (3.00 g, 9.14 mmol) and DCC in dry CH_2Cl_2 were stirred at rt for 6 h to give crude **103** as a colorless solid. Crystallization (EtOAc/ hexanes) afforded colorless crystals (2.60 g, 89% yield): mp 121 – 122 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 3.45 (s, 4H), 3.86 (d, $J = 11.5\text{Hz}$, 4H), 4.40 (s, 4H), 4.72 (d, $J = 11.5\text{ Hz}$, 4H), 5.46 (s, 2H), 7.23 - 7.47 (m, 20H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 167.0, 137.8, 137.3, 129.2, 128.6, 128.3, 128.0, 127.8, 126.5, 102.2, 73.7, 70.1, 70.0, 49.3. HR ESI MS: m/z calcd for $\text{C}_{38}\text{H}_{38}\text{NaO}_9$ 661.2408, found 661.2418.

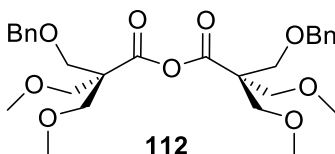
In a similar manner, carboxylic acid **101** (4.36 g, 13.3 mmol) and DCC (1.51 g, 7.29 mmol) afforded anhydride **104** as colorless crystals (3.86 g, 91% yield): mp 129 - 131 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 4.08 (s, 4H), 4.14 (d, $J = 11.5\text{ Hz}$, 4H), 4.37 (d, $J = 11.5\text{ Hz}$, 4H), 4.64 (s, 4H), 5.44 (s, 2H), 7.27 - 7.42 (m, 20H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 166.6, 137.4, 136.9, 128.8, 128.2, 128.0, 127.6, 127.4, 126.1, 101.8, 73.3, 69.7, 69.6, 48.9. HR ESI MS: m/z calcd for $\text{C}_{38}\text{H}_{38}\text{NaO}_9$ 661.2408, found 661.2403.

2.3.3.14. 3-(Benzyloxy)-2,2-bis(benzyloxymethyl)propanoic anhydride (108)



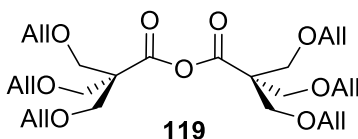
According to the general procedure, carboxylic acid **107** (3.84 g, 9.14 mmol) and DCC in dry CH₂Cl₂ were stirred at rt for 8 h and gave the crude product as a colorless solid. Purification using column chromatography (hexanes/ EtOAc; 3:1; R_F 0.45) gave a colorless crystalline solid (3.34 g, 89% yield). Purification was also achieved using crystallization (MeOH, - 10 °C) to give colorless crystals: mp 69 - 70 °C; ¹H NMR (500.13 MHz, acetone-*d*₆) δ 3.70 (s, 12H, 6C_{quat}CH₂O), 4.46 (s, 12H, 6OCH₂Ph), 7.24 - 7.32 (m, 30H, PhH); ¹³C NMR (125.7 MHz, acetone-*d*₆) δ 167.4 (C=O), 139.2, 129.1, 128.4, 128.3 (PhC), 73.9 (CH₂Ph), 68.1 (C_{quat}CH₂O), 55.8 (C_{quat}). HR ESI MS: *m/z* calcd for C₅₂H₅₄NaO₉ 845.3660, found 845.3651.

2.3.3.15. 3-(Benzyloxy)-2,2-bis(methoxymethyl)propanoic anhydride (**112**)



According to the general procedure, carboxylic acid **111** (2.45 g, 9.14 mmol) and DCC in dry CH₂Cl₂ were stirred at rt for 7 h and gave the crude product as a pale yellow oil. The oil was then purified using column chromatography (hexanes/ EtOAc; 3:1; R_F 0.30) to give a colorless oil (2.23 g, 94 % yield): ¹H NMR (500.13 MHz, CDCl₃) δ 3.34 (s, 12H), 3.62 (s, 8H), 3.69 (s, 4H), 4.54 (s, 4H), 7.29 - 7.37 (m, 10H); ¹³C NMR (125.7 MHz, CDCl₃) δ 166.9 (C=O), 138.1, 128.2, 127.5, 127.4 (PhC), 73.3 (CH₂Ph), 69.7 (C_{quat}CH₂OBn), 67.4 (C_{quat}CH₂OMe), 59.2 (C_{quat}), 54.9 (OMe). HR ESI MS: *m/z* calcd for C₂₈H₃₈NaO₉ 541.2419, found 541.2414.

2.3.3.16 3-(Allyloxy)-2,2-bis(allyloxymethyl)propanoic anhydride (**119**)



According to the general procedure, carboxylic acid **118**¹⁹⁸ (2.47 g, 9.14 mmol) and DCC in dry CH₂Cl₂ were stirred at rt for 9 h and gave the crude product as a thick oil. The oil was then purified using column chromatography (hexanes/ EtOAc; 3:1; R_F 0.58) to give a colorless oil (2.22 g, 93 % yield). ¹H NMR (500.13 MHz, CDCl₃) δ 3.63 (s, 12H), 3.96 (dt, *J* = 5.5 Hz, 1.5 Hz, 12H), 5.12 (dtd, *J* = 10.5, 3.0, 1.5 Hz, 6H), 5.23 (dtd, *J* = 17.3, 3.0, 1.5 Hz, 6H), 5.79 - 5.87 (m, 6H); ¹³C NMR (125.7 MHz, CDCl₃) δ 167.0 (C=O), 134.6 (CH_{sp2}), 116.7 (CH_{2sp2}), 72.4 (OCH₂), 67.4 (C_{quat}CH₂O), 55.0 (C_{quat}). HR ESI MS: *m/z* calcd for C₂₈H₄₂NaO₉ 545.2721, found 545.2747.

Chapter 3. Efficient and Controllably Selective Preparation of Esters

3.1. Introductory Remarks

A very large number of methods are available for the formation of esters from carboxylic acids and alcohols.¹⁹⁹⁻²⁰² When both the carboxylic acid and the alcohol are large and acid or base-sensitive, fewer options are available but these are still numerous. The methods used most commonly include dehydration using DCC and DMAP^{203,204} or 4-(1-pyrrolidinyl)-pyridine,²⁰⁵ reaction with 2-halopyridinium salts^{206,207} or sterically hindered aromatic acid anhydrides²⁰⁸⁻²¹⁰ or chlorides.²¹¹ Some newer reagents include dimethyl-sulfamoyl chloride,²¹² triphenylphosphine dihalides,²¹³ 1-tosylimidazole,²¹⁴ and *O*-alkylisoureas.²¹⁵

3.2. The Use of Uronium-based Coupling Agents

We wanted conditions for ester formation that could be used for the efficient convergent synthesis of polyester dendrimers under very mild conditions.⁹¹ The ester groups present in both the divergently assembled polyalcoholic core and the carboxylic acid-terminated dendron, ruled out transesterification conditions and either strong Brønsted or Lewis acids or bases. Agents for formation of amides from amino acids under mild conditions meet these requirements.²¹⁶⁻²²⁰ Many of these reagents are commercially available compounds that are stable in air at room temperature. They are very effective at promoting amide formation at room temperature but only scattered reports²²¹⁻²²⁴ have appeared about their application to ester formation and those concerned formation of phenolic esters²²¹ and primary aliphatic esters²²¹⁻²²⁴ using TBTU and HBTU. An alternative approach only employed with primary alcohols is to use the uronium salt precursor, 1-hydroxybenzotriazole, with DCC and DMAP.²²⁵⁻²²⁷

Uronium-based coupling agents, namely, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (**120**),²¹⁷ 2-(1*H*-7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU) (**121**),²²⁰ and 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylaminomorpholinomethylene)]methanaminium hexafluorophosphate (COMU) (**122**)²¹⁸ depicted in Figure 9 and commercially available were used in this study. The acids and alcohols used are shown in Figure 10.

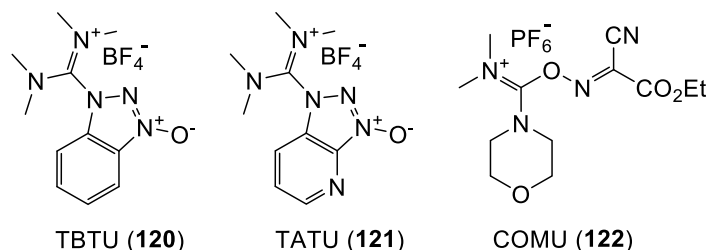


Figure 9 Coupling agents investigated

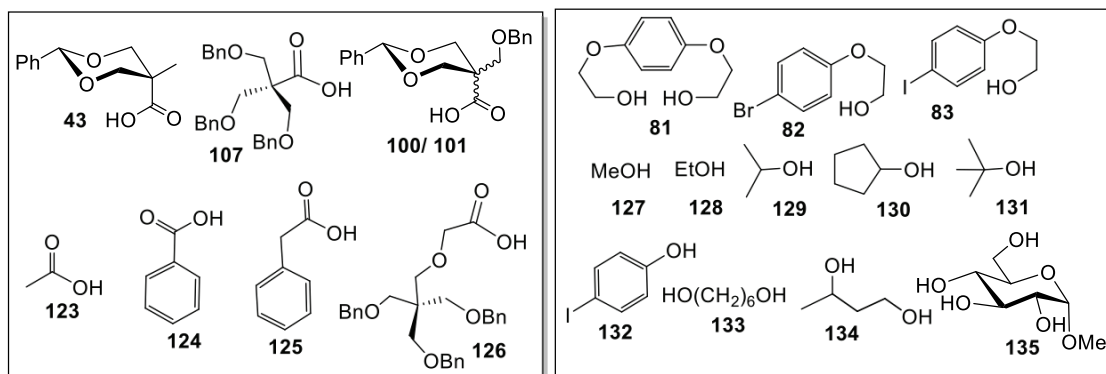


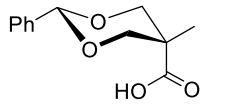
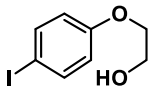
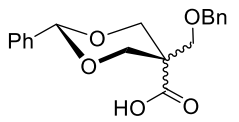
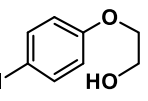
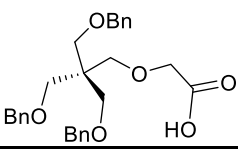

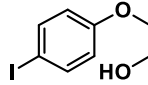
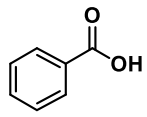
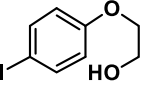
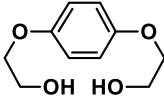
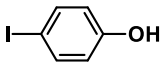

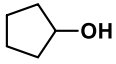
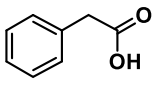
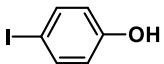
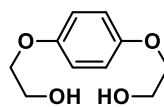
Figure 10 Structures of alcohols and carboxylic acids used

3.3. Esterification Using COMU

Reactions were initially performed using COMU and equivalent amounts of acid and alcohol at room temperature with two equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the non-nucleophilic base. Table 2 shows the results obtained under these conditions, with the yields given being of isolated products. In DMF, ester formation with small or phenolic alcohols

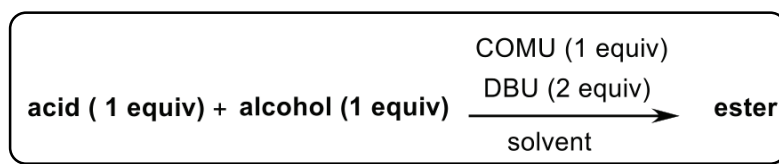
occurred rapidly and in good yields. Secondary alcohols showed slow reactivity and tertiary alcohols did not react even after 36 hours.

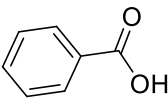
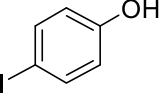
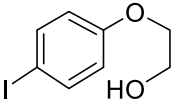
Table 2 Esterification results using COMU (equimolar conditions)

| entry | acid | alcohol | reaction time (h) | % yield | |
|-------|---|---|---|---------|----|
| 1 |  |  | 12 | 73 | |
| 2 |  |  | 14 | 62 | |
| 3 |  | MeOH | 2 | 81 | |
| 4 |  |  | 2 | 86 | |
| 5 |  | EtOH | 2.5 | 89 | |
| 6 | |  | 4.5 | 74 | |
| 7 | |  | 5 | 69 | |
| 8 | |  | 3 | 78 | |
| 9 | |  | 16 | 71 | |
| 10 | |  | 16 | 68 | |
| 11 | | <i>tert</i> -butanol | 36 | no rxn | |
| 12 | |  |  | 3 | 81 |
| 13 | | |  | 4 | 67 |
| 14 | | | 1,6-hexanediol | 4 | 83 |

The reactions worked equally well in acetonitrile but were much slower in tetrahydrofuran because of poor solubility of the coupling agent in the solvent. Table 3 shows the results obtained using benzoic acid.

Table 3 Solvent flexibility with COMU



| entry | acid | alcohol | solvent | reaction time (h) | % yield |
|-------|---|--|--------------------|-------------------|---------|
| 1 |  |  | CH ₃ CN | 3 | 80 |
| 2 | | | DMF | 3 | 78 |
| 3 | | | THF | 24 | 69 |
| 4 | |  | CH ₃ CN | 4.5 | 71 |
| 5 | | | DMF | 4.5 | 74 |

To test whether the base has an effect on the rate of the reaction with COMU, a set of parallel reactions was performed using both DBU and *N,N*-diisopropylethyl amine (DIEA) as non-nucleophilic bases. The results in Table 4 show that the two bases performed in a similar manner with this coupling agent.

As seen in Table 2, reactions of secondary alcohols were observed to be slow with moderate yields when equimolar amounts of the acid, alcohol, and coupling agent were used. To find optimum conditions for these, reactions were carried out using different equivalents of benzoic acid/ 2° alcohol and the coupling agent in DMF or in acetonitrile. When excess amounts of the acid or alcohol and the coupling agent were used, reactions reached completion faster and

yields up to 81% were obtained. For example, using 1.2 equiv of acid and 1.5 equiv of coupling agent increased the yield of esterification of benzoic acid with cyclopentanol from 68% in 16 h to 81% in 10 h. (Table 5).

Table 4 Base flexibility with COMU

$$\text{acid (1 equiv) + alcohol (1 equiv)} \xrightarrow[\text{DMF}]{\text{COMU (1 equiv) Base (2 equiv)}} \text{ester}$$

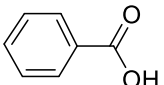
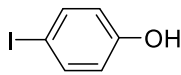
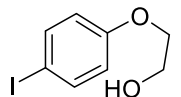
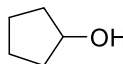

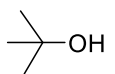
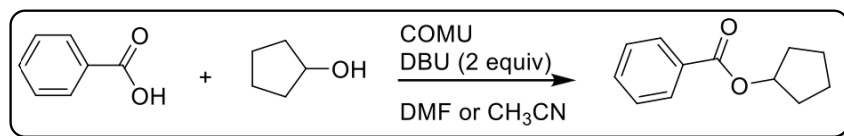
| entry | acid | alcohol | base 2 equiv | reaction time (h) | % yield |
|-------|--|---|--------------|-------------------|---------|
| 1 |  |  | DBU | 3 | 78 |
| 2 | | | DIEA | 3 | 79 |
| 3 | |  | DBU | 4.5 | 74 |
| 4 | | | DIEA | 6 | 69 |
| 5 | |  | DBU | 16 | 68 |
| 6 | | | DIEA | 18 | 61 |
| 7 | |  | DBU | 16 | 71 |
| 8 | | | DIEA | 18 | 65 |
| 9 | |  | DBU | 36 | no rxn |
| 10 | | | DIEA | 36 | no rxn |

Table 5 Optimization for secondary alcohols with COMU

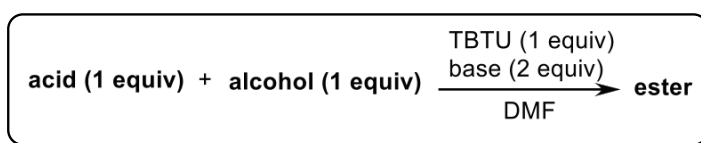


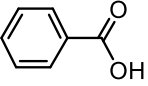
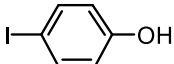
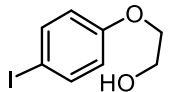
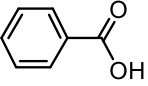
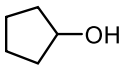

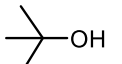
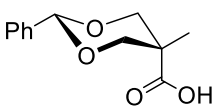
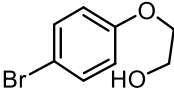
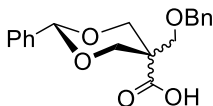
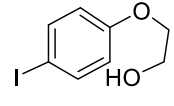
| entry | acid (equiv) | alcohol (equiv) | COMU (equiv) | reaction time (h) | % yield |
|-------|--------------|-----------------|--------------|-------------------|---------|
| 1 | 1 | 1 | 1 | 16 | 68 |
| 2 | 1 | 1 | 1.5 | 16 | 79 |
| 3 | 1.2 | 1 | 1.5 | 10 | 81 |
| 4 | 1 | co-solvent | 1.5 | 7 | 80 |

3.4. Esterification Using TBTU

The next coupling agent that was closely examined is TBTU. Initial investigation was to see whether esterification using this coupling agent was base-sensitive, using equimolar amounts of the acid, the alcohol, and the coupling agent in DMF. Surprisingly, secondary alcohols did not react when the weaker base DIEA was used (Table 6).

Table 6 Base flexibility with TBTU



| entry | acid | alcohol | base (2 equiv) | reaction time (h) | % yield | |
|-------|---|---|---|-------------------|---------|--------|
| 1 |  |  | DBU | 0.25 | 85 | |
| 2 | | | DIEA | 0.25 | 86 | |
| 3 | |  | DBU | 0.50 | 81 | |
| 4 | | | DIEA | 0.50 | 78 | |
| 5 | |  |  | DBU | 4 | 59 |
| 6 | | | | DIEA | 12 | no rxn |
| 7 | | |  | DBU | 4 | 63 |
| 8 | | | | DIEA | 12 | no rxn |
| 9 | | |  | DBU | 36 | no rxn |
| 10 | | | | DIEA | 36 | no rxn |
| 11 |  |  | DBU | 1 | 72 | |
| 12 |  |  | DBU | 3 | 60 | |

Even though TBTU required about 30 minutes of activation time between the acid and the coupling agent before the alcohol could be added, reactions reached completion much faster than

in the case of COMU. Here also, tertiary alcohols did not react. These observations are summarized in Table 6.

As in the case of COMU, the reactions worked equally well in acetonitrile but were much slower in tetrahydrofuran because of poor solubility of the coupling agent in the solvent. Table 7 illustrates the results obtained for esterification between benzoic acid and 2-propanol. Esterification using secondary alcohols resulted in lower yields compared to yields obtained when primary or phenolic alcohols were used (Tables 6 and 7). It was found that using excess amounts of the acid or the alcohol and the coupling agent resulted in substantial improvement of the yields. Table 8 illustrates the optimum conditions.

Table 7 Solvent flexibility with TBTU

$$\text{acid (1 equiv)} + \text{alcohol (1 equiv)} \xrightarrow[\text{solvent}]{\text{TBTU (1 equiv), DBU (2 equiv)}} \text{ester}$$

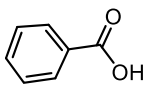


| entry | acid | alcohol | solvent | reaction time (h) | % yield |
|-------|---|---|--------------------|-------------------|---------|
| 1 |  |  | CH ₃ CN | 4 | 65 |
| 2 | | | DMF | 4 | 63 |
| 3 | | | THF | 4 | traces |

Table 8 Optimization for secondary alcohols with TBTU

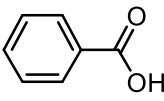
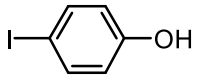
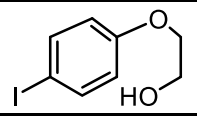
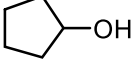
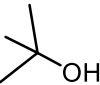


| entry | acid (equiv) | alcohol (equiv) | TBTU (equiv) | reaction time (h) | % yield |
|-------|--------------|-----------------|--------------|-------------------|---------|
| 1 | 1 | 1 | 1 | 4 | 63 |
| 2 | 1 | 1 | 1.5 | 4 | 72 |
| 3 | 1.2 | 1 | 1.5 | 4 | 93 |
| 4 | 1 | co-solvent | 1.5 | 2-3 | 96 |

3.5. Esterification Using TATU

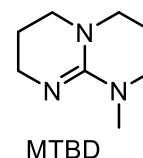
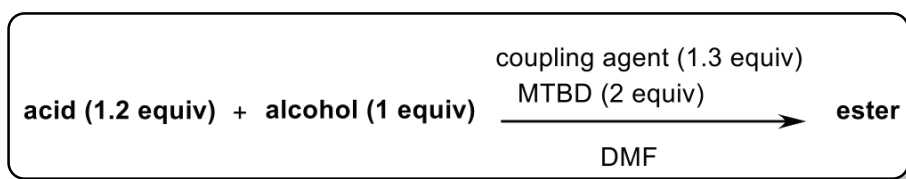
This coupling agent is relatively expensive, which is a disadvantage especially for large-scale applications. Here, only one single reaction between every different type of alcohol (phenolic, 1°, 2°, 3°) and benzoic acid was carried out using conditions that had been found to be optimum for TBTU. As summarized in Table 9, it can be concluded that TATU and TBTU give comparable results concerning short reaction times and yields. In addition, esterification using TATU also required about 30 minutes to activate the carboxylic acid and when esterification between cyclopentanol and benzoic acid was tried using the weaker base DIEA, no reaction was observed. Esterification using *tert*-butanol, a tertiary alcohol, was unsuccessful, just as in the cases of both TBTU and COMU.

Table 9 Esterification results using TATU

| entry | acid | alcohol | reaction time (h) | % yield |
|-------|---|---|-------------------|---------|
| 1 |  |  | 0.25 | 96 |
| 2 | |  | 0.5 | 94 |
| 3 | |  | 3 - 4 | 89 |
| 4 | |  | 36 | no rxn |

TBTU and TATU had been observed to be base-sensitive for esterification of secondary alcohols, requiring the strength of the base to be at least similar to that of DBU for the reaction to proceed. For this reason, it was interesting to find out what kind of observations if any, would be made when a stronger base such as 7-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene (MTBD) was used. To study this point, all three coupling agents were examined. Interestingly, only COMU gave successful results for esterification between *tert*-butanol and benzoic acid. There was no reaction in case of both TBTU and TATU. Additionally, MTBD did not improve the reaction with secondary alcohols. These observations are illustrated in Table 10.

Table 10 Esterification results with MTBD

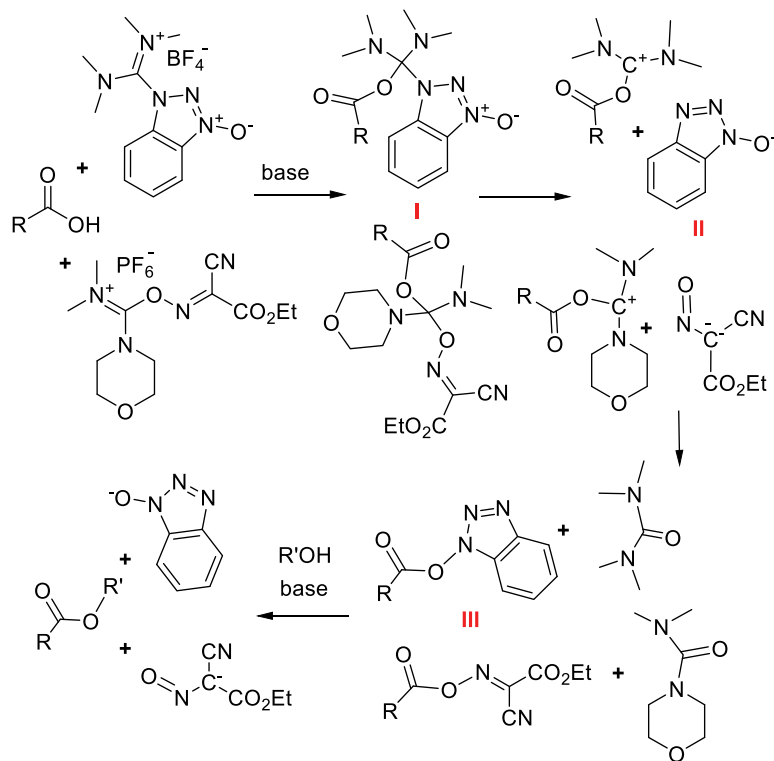


| entry | acid | alcohol | coupling agent | reaction time (h) | % yield |
|-------|------|---------|----------------|-------------------|---------|
| 1 | | | TBTU | 16 | no rxn |
| 2 | | | TATU | 16 | no rxn |
| 3 | | | COMU | 16 | 79 |
| 4 | | | TBTU | 4 -5 | 91 |

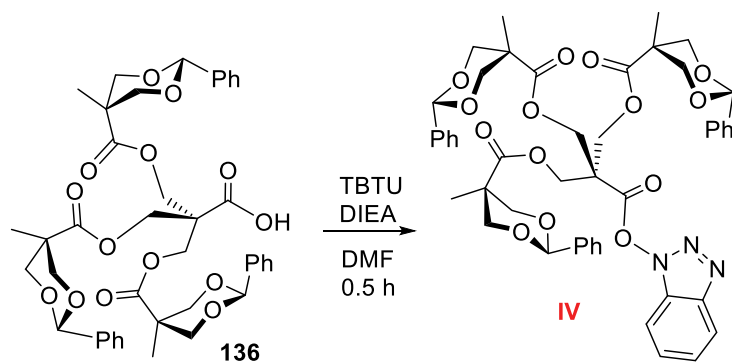
3.6. Mechanistic Considerations

Mechanisms have been proposed for the reactions involving COMU and amines²²⁸ and for TBTU and alcohols (Scheme 41).²²¹ These mechanisms have the following steps: addition of the carboxylate salt to the uronium reagent, decomposition of the resulting tetrahedral intermediate **I**, addition of the released anion **II** to the carbonyl center followed by loss of a urea

derivative, and alcohol addition to the activated carbonyl group **III**. The base sensitivity of the reaction with secondary alcohols performed with the benzotriazole-derived coupling agents (TBTU and TATU) indicates that the last step is rate determining in this case. To investigate the validity of this observation, the activation of a hindered carboxylic acid-terminated second generation dendron was attempted using TBTU in the presence of the weaker base DIEA (Scheme 42). After 30 minutes, the desired reactive intermediate complex **IV** whose ^{13}C NMR spectrum is shown in Figure 11 was isolated. Therefore, the fact that secondary alcohols do not react when DIEA is used means that without a doubt, the alcohol addition to the activated complex, which is the last step, is rate determining. It appears that the base must partially deprotonate the alcohol before the nucleophile attacks the activated complex.



Scheme 41 Proposed reaction mechanisms: top level on each line, TBTU mechanism; bottom level, COMU mechanism



Scheme 42 Reactive intermediate IV forms quickly even in the presence of DIEA

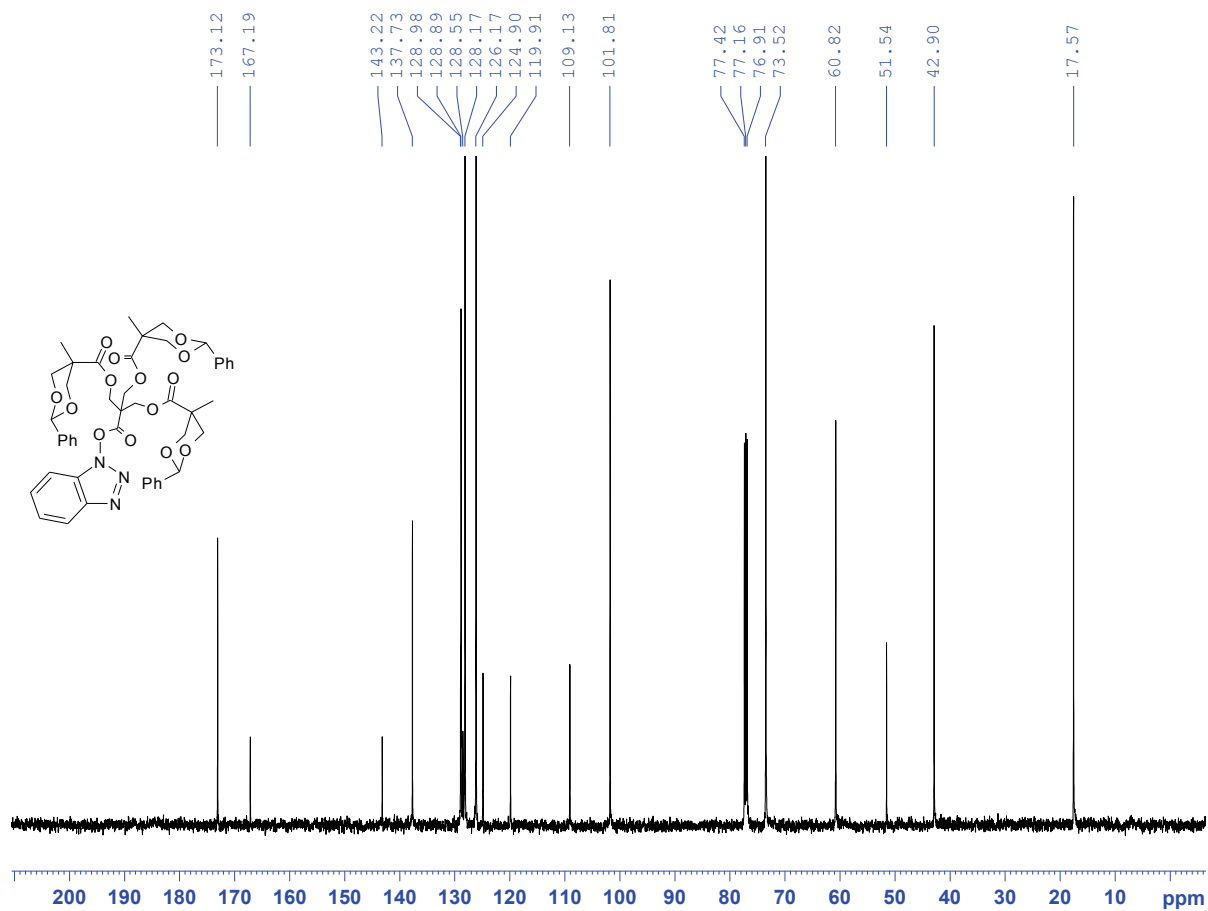
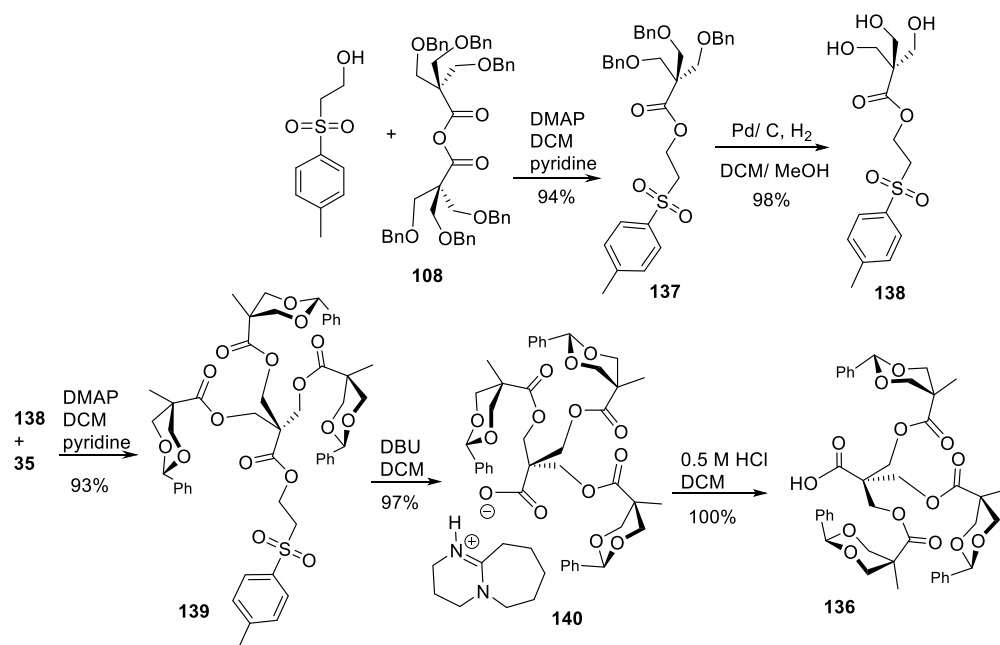


Figure 11 125.7 MHz ^{13}C NMR spectrum of the reactive intermediate IV in CDCl_3

For the slower base-insensitive COMU reactions, an earlier step must be rate determining for primary and secondary alcohols, either the decomposition of the initial tetrahedral

intermediate or the readdition of the stable anion. However, with the tertiary alcohol, *tert*-butanol, ester formation only occurs with the strong organic base MTBD using COMU. Clearly, the rate-determining step for COMU has switched to being the last step for this hindered alcohol. The relative acidities in DMSO and acetonitrile of alcohols and the conjugate acids of the organic bases employed²²⁹⁻²³² indicate that the alcohol will only be slightly ionized under the reaction conditions. The difference in pKa between isopropanol and *tert*-butanol²³¹ is similar to that between DBU and MTBD.^{229,230} It appears that the tetrahedral intermediate for alcohol addition is lower in energy relative to starting materials for COMU than for the benzotriazole-derived coupling agents, either for electronic or steric reasons.

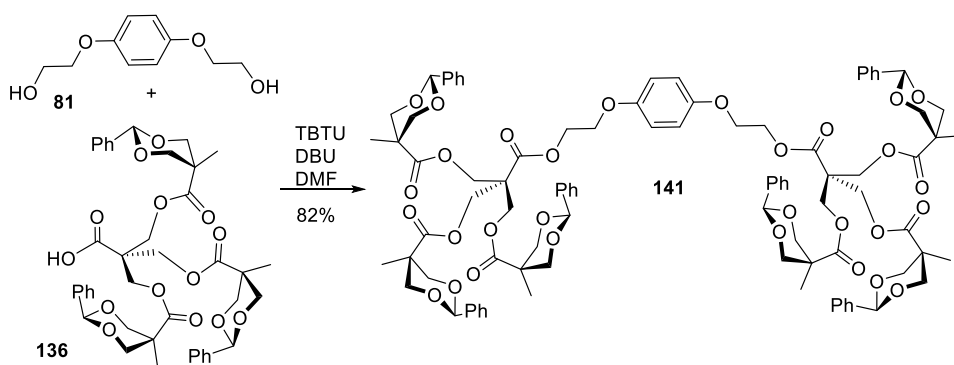
3.7. Convergent Synthesis



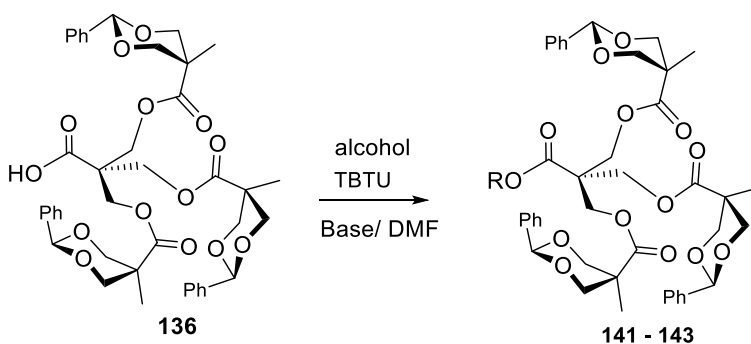
Scheme 43 Divergent growth of second generation acid dendron

Having established that these conditions were effective for ester formation, we tested whether they could be used for the convergent synthesis of polyester dendrimers. The

preparation of diol **81** was discussed in Chapter 2.⁹¹ The addition of tribranched dendrons to compound **81** to form ester linkages when the carboxylic acid of the dendron is preactivated as the anhydride will be discussed in Chapter 6. As shown in Scheme 44, peptide-coupling agents can also be used for this purpose, forming the two ester linkages between **81** and **136** in good yield under mild conditions. The divergent synthesis of dendron **136** proceeding through two dendron growth steps is described in Scheme 43 while the formation of other esters from this acid dendron with simple alcohols is summarized in Scheme 45 and Table 11.


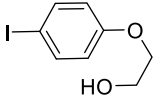
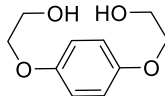


Scheme 44 TBTU-promoted convergent synthesis of a 2nd generation dendrimer



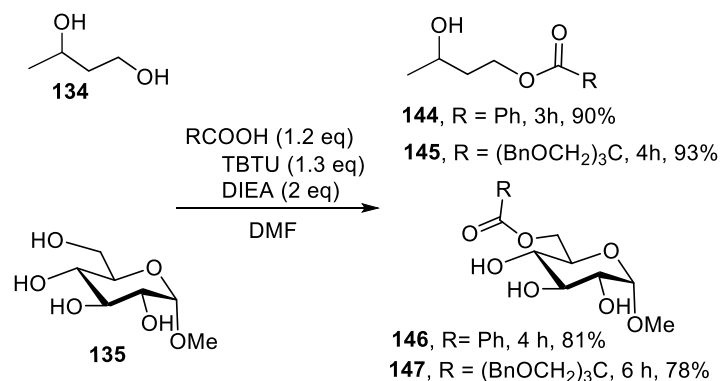
Scheme 45 TBTU-promoted ester formation

Table 11 TBTU-promoted esterification (Scheme 45) using second-generation acid dendron **136**

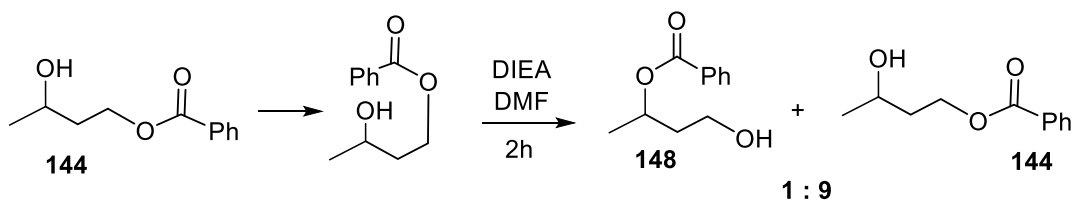
| alcohol | base (2 equiv) | reaction time (h) | % yield | ester |
|---|-------------------|----------------------|----------|------------|
|  | DBU DIEA | 1 1 | 92 90 | 142 |
|  | DBU DIEA | 1.5 1.5 | 91 88 | 143 |
|  | DBU | 3 | 82 | 141 |

3.8. Regioselective Esterification of Diols and Polyols

An evaluation of whether the base sensitivity of reaction outcome to alcohol structure could be used to obtain regioselectivity was tested with a diol (**134**) and a polyol (**135**) using TBTU and DIEA with an aryl (**124**) and an aliphatic acid (**107**). The reactions were highly selective for the primary hydroxyls; in only one reaction was a small amount of the secondary product obtained, that is for 1,3-butanediol (**134**) (see Scheme 46), where benzylation gave 5% of the secondary product in addition to the major primary product (90%). Most other selective esterification methods²³³⁻²³⁶ are less selective in benzylation of **134** than this method. When a pure sample of **144** was mixed with DIEA and stirred at room temperature for 2 h in DMF, the resulting mixture contained compound **144** and 10% of the secondary product. This observation clearly shows that the secondary product forms because of migration of benzoic acid from the primary position to the secondary position (Scheme 47). The migration product was not observed when the hindered acid **107** was employed possibly for steric reasons.



Scheme 46 Selective esterifications. Note that **144** was accompanied by 5% of the ester of the secondary alcohol



Scheme 47 Formation of secondary product is via migration

3.9. Concluding Remarks

Peptide coupling reagents, COMU, TBTU, and TATU can be used to prepare esters in excellent yields from all types of alcohols at room temperature under mild conditions using organic bases and short reaction times. Esterification of secondary alcohols promoted by TBTU and TATU require a base, such as DBU, that is stronger than tertiary amines. Only COMU is effective for the preparation of esters from tertiary alcohols, and then only when the still stronger base, MTBD is used. The base sensitivity of the TBTU and TATU promoted reactions can be used for the regioselective esterification of primary hydroxyls in diols and polyols. This protecting group-free esterification method is an important discovery, which has a significant advantage over the protection/ deprotection methods, especially in carbohydrate chemistry. The following two chapters illustrate some applications for this.

3.10. Experimental Section

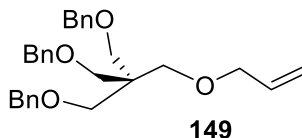
3.10.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 NMR spectrometer operating at 500.13 and 125.7 MHz respectively using the solvent resonances as secondary standards. The carbon and hydrogen atoms of new compounds were assigned following the analysis of their one dimensional (^1H , ^{13}C , and DEPT-135) and two dimensional (COSY, HSQC, and HMBC) NMR spectral data. The ^1H and ^{13}C NMR spectra of all compounds may be found in Appendix A. High-resolution mass spectra were recorded on a Bruker Micro-TOF mass spectrometer using electrospray ionization. Melting points were determined on a Fisher-John's melting point apparatus and are uncorrected.

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), and *N,N*-diisopropylethylamine (DIEA), tetrahydrofuran, acetonitrile, and dichloromethane were refluxed over calcium hydride and distilled onto molecular sieves. Methanol, ethanol, *tert*-butanol, cyclopentanol, and 2-propanol were dried over calcium oxide and distilled over molecular sieves. Pyridine was dried over potassium hydroxide and was stored over molecular sieves. All reactions were carried out under a nitrogen atmosphere. Compounds were visualized/ located by spraying the TLC plate with a solution of 2 % ceric ammonium sulfate in 0.5 M H_2SO_4 followed by heating on a hot plate until color developed. Jones reagent (0.56 M) was prepared by dissolving sodium dichromate dihydrate ($\text{Na}_2\text{Cr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$, 300 g, 1.01 mol) in 1.5 L of water followed by slowly adding conc. sulfuric acid (300 mL) to the cooled solution (0 °C).

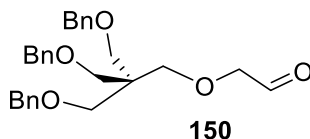
3.10.2. Synthesis

3.10.2.1. 3-Allyloxy-2,2'-bis(benzyloxymethyl)propan-1-ol (149).



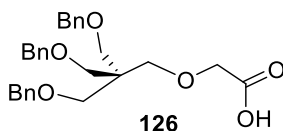
Allyl bromide (10.5 mL, 121 mmol) and 3-(benzyloxy)-2,2'-bis(benzyloxymethyl)propan-1-ol^{91,178} (16.4 g, 40.3 mmol) were dissolved in anhydrous DMF (150 mL) and the mixture was cooled to 0 °C. Sodium hydride (60 % oil dispersion, 1.94 g, 48.5 mmol) was then added in portions with stirring at 0 °C. The mixture was allowed to warm to rt with stirring for 12 h. The mixture was diluted using Et₂O (100 mL), cooled to 0 °C, and ice-water (50 mL) was added slowly with stirring. The organic layer was separated and the aqueous layer was extracted using Et₂O (60 mL x 2). Organic layers were combined, washed with brine (50 mL x 2), and water (50 mL x 2), then dried (MgSO₄), filtered, and concentrated. Purification using column chromatography (hexanes/ EtOAc; 5:1; R_F 0.60) gave the product as a colorless syrup (16.8 g, 93 %): ¹H NMR (500.13 MHz, CDCl₃) δ 3.57 (s, 2H, OCH₂C_{quat}), 3.60 (s, 6H, C_{quat}(CH₂O)₃), 3.98 (dt, *J* = 5.5, 1.5 Hz, 2H, CH₂ (sp³, allyl)), 4.53 (s, 6H, 3CH₂Ph), 5.16 (ddt, *J* = 10.5, 2, 1.5 Hz, 1H, *cis*, allyl), 5.27 (ddt, *J* = 17, 2, 1.5 Hz, 1H, *trans*, allyl), 5.90 (m, 1H, CH (sp², allyl)), 7.27 - 7.36 (m, 15H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 139.1 (PhC), 135.3 (CH sp², allyl), 128.3, 127.4 (PhC), 116.3 (CH₂, sp², allyl), 73.4 (3CH₂Ph), 72.4 (CH₂, sp³, allyl), 69.6 C_{quat}(CH₂O)₃, 69.5 (OCH₂C_{quat}), 45.7 (C_{quat}). HR ESI MS: *m/z* calcd for C₂₉H₃₄NaO₄ (M+Na) 469.2354, found 469.2352.

3.10.2.2. (3-Benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetaldehyde (**150**)



Ozone was bubbled through a solution of olefin **149** (2.56 g, 5.73 mmol) maintained at – 78 °C in a 1:1 mixture of methanol (8 mL) and dichloromethane (8 mL) until TLC confirmed the disappearance of the starting material. N₂ was then bubbled through the mixture for 15 min. Excess dimethyl sulfide was added at - 78 °C and the mixture was allowed to warm to rt with stirring. The reaction mixture was concentrated under vacuum and the resulting yellow syrup was purified using column chromatography (hexanes/ EtOAc; 3:1; R_F 0.35) to give the product as a colorless syrup: yield 2.03 g (79 %); ¹H NMR (500.13 MHz, CDCl₃) δ 3.74 (s, 6H, 3C_{quat}CH₂O), 3.77 (s, 2H, C_{quat}CH₂O), 4.05 (d, *J* = 1 Hz, 2H, CH₂C=O), 4.64 (s, 6H, 3CH₂Ph), 7.38 – 7.47 (m, 15H, PhH), 9.73 (t, *J* = 1 Hz, 1H, O=CH); ¹³C NMR (125.7 MHz, CDCl₃) δ 201.6 (C=O), 138.7, 128.2, 127.4, 127.4 (PhC), 76.7(CC=O), 73.3 (3CH₂Ph), 71.0 (C_{quat}CH₂O), 69.0 (3C_{quat}CH₂O), 45.7 (C_{quat}). HR ESI MS: *m/z* calcd for C₂₈H₃₂NaO₅ (M+Na) 471.2142, found 471.2137.

3.10.2.3. (3-Benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetic acid (**126**)



Aldehyde **150** (1.70 g, 3.79 mmol) was dissolved in acetone (8 mL) in a round-bottomed flask maintained at 0 °C. The Jones reagent (16.3 mL, 10.9 mmol) was then added drop wise during a period of 30 min. When the addition was complete, the ice-water bath was removed and stirring was continued for another 40 min when TLC confirmed the disappearance of the

aldehyde. Water (20 mL) and ether (25 mL) were added and the resulting mixture was stirred for 10 min. The organic layer was collected, washed with water (9 mL x 3), dried (MgSO₄), filtered, and concentrated. The resulting syrup was purified using column chromatography (hexanes/EtOAc; 2:1; R_F 0.2) to give **126** as a colorless syrup: yield 1.43 g (81 %): ¹H NMR (500.13 MHz, CDCl₃) δ 3.67 (s, 6H, 3C_{quat}CH₂O), 3.69 (s, 2H, C_{quat}CH₂O), 4.11 (s, 2H, CH₂C=O), 4.56 (s, 6H, 3CH₂Ph), 7.34 – 7.42 (m, 15H, PhH), 10.88 (br, 1H, OH); ¹³C NMR (125.7 MHz, CDCl₃) δ 173.0 (C=O), 138.0, 128.4, 127.7 (PhC), 73.5 (3CH₂Ph), 72.2 (C_{quat}CH₂O), 69.5 (3C_{quat}CH₂O), 68.5 (OCH₂C=O), 45.1 (C_{quat}). HR ESI MS: *m/z* calcd for C₂₈H₃₁O₆ (M-H) 463.2126, found 463.2109.

3.10.2.4. General esterification procedure using COMU

In an oven-dried round-bottomed flask equipped with a magnetic stir bar, an acid (0.724 mmol), COMU (0.310 g, 0.724 mmol), and the base specified in the Table or the procedure below, for instance 1,8-diazabicyclo[5.4.0]undec-7-ene (0.22 mL, 1.45 mmol), were dissolved in anhydrous DMF (3 mL) and the resulting orange-red solution was stirred at rt for 10 min under a nitrogen atmosphere. An alcohol (0.724 mmol of hydroxyl groups) in DMF (1 mL) was then injected into the reaction mixture via syringe and vigorous stirring at rt was continued until there was a noticeable color change or until TLC confirmed the completion of the reaction (1 - 16 h). The reaction mixture was diluted with CH₂Cl₂ (15 mL) and the resulting mixture was washed with 5% HCl (2 x 3 mL), 1M NaHCO₃ (3 x 3 mL) and water (2 x 3 mL). The organic layer was collected, dried (MgSO₄), filtered and concentrated to give a crude ester product. Solid crude products were purified using precipitation out of cold methanol or cold hexanes/ EtOAc, or

column chromatography to give colorless solids. Liquids or oils crude products were purified using column chromatography to give colorless products.

3.10.2.5. General esterification procedure using TBTU or TATU

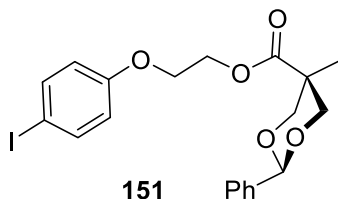
In an oven-dried round-bottomed flask equipped with a magnetic stir bar, an acid (1.25 mmol), TBTU (0.40 g, 1.25 mmol), and the base specified in the Table or the procedure below, for instance 1,8-diazabicyclo[5.4.0]undec-7-ene (0.38 mL, 2.49 mmol) were dissolved in anhydrous DMF (3 mL) and the resulting mixture was stirred at rt for 30 min. under a nitrogen atmosphere. An alcohol (1.25 mmol of hydroxyl groups) in DMF (1 mL) was then injected into the reaction mixture via syringe and stirring was continued at rt until TLC confirmed the completion of the reaction (0.25 – 5 h). The reaction mixture was diluted with CH₂Cl₂ (15 mL) and the resulting mixture was washed with 5% HCl (2 x 3 mL), 1 M NaHCO₃ (3 x 3 mL) and water (2 x 3 mL). The organic layer was collected, dried (MgSO₄), filtered and concentrated to give a crude ester product, which was purified as described above for the COMU procedure.

3.10.2.6. General procedure for dendron growth

In an oven-dried round-bottomed flask equipped with a magnetic stir bar under a nitrogen atmosphere, the benzylidene or benzyl protected anhydride, the hydroxyl-terminated dendron or 2(*p*-toluenesulfonyl)ethanol, and *N,N*-dimethyl-4-aminopyridine (DMAP) were dissolved in a 3:1 mixture of CH₂Cl₂/ pyridine (v/v). The reaction mixture was stirred at rt for 10 - 12 h and diluted with water (3 mL) in pyridine (3 mL). Stirring was continued overnight to quench the excess anhydride. The mixture was diluted using CH₂Cl₂ (150 mL) and washed with NaHCO₃ (1 M, 30 mL x 3), 10% aq. Na₂CO₃ (30 mL x 3), brine (30 mL x 2), and water (30 mL), then dried (MgSO₄), filtered, and concentrated. The crude product was then purified using column

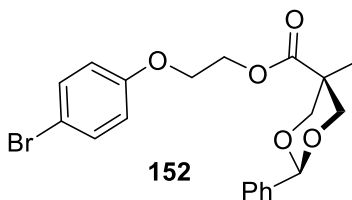
chromatography to give the desired product (> 93% yield). The NaHCO₃ layers were combined, acidified (pH = 5- 6), and the precipitated carboxylic acid by-product was recovered.

3.10.2.7. 2-(4-Iodophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (151)



Synthesized using the COMU procedure (base in Table 3.1): a colorless solid; R_f 0.35 (hexanes/ EtOAc; 3:1); mp 128 – 130 °C; ^1H NMR (500.13 MHz, CDCl₃) δ 1.04 (s, 3H, CH₃), 3.65 (d, J = 11.5 Hz, 2H, H-4_{ax}, H-6_{ax}), 4.17 (t, J = 5 Hz, 2H, IPhOCH₂), 4.54 (t, J = 5 Hz, 2H, CH₂O), 4.66 (d, J = 11.5 Hz, 2H, H-4_{eq}, H-6_{eq}), 5.45 (s, 1H, H-2), 6.66 – 6.68 (m, 2H, PhH), 7.28 – 7.54 (m, 7H, PhH); ^{13}C NMR (125.7 MHz, CDCl₃) δ 174.1, (C=O), 158.6, 138.4, 137.9, 129.1, 128.3, 126.3, 117.3 (PhC), 101.9 (C-2), 83.4 (PhC), 73.6 (C-4, C-6), 66.2 (IPhOC), 63.3 (CH₂OC=O), 42.7 (C_{quat}), 18.0 (CH₃). HR ESI MS m/z calcd for C₂₀H₂₁INaO₅ 491.0326, found 491.0322.

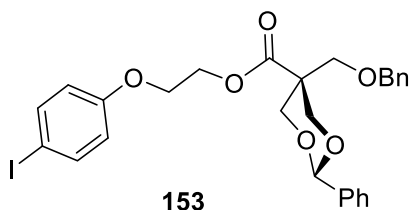
3.10.2.8. 2-(4-Bromophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (152).



Synthesized using the TBTU procedure (base in Table 3.5): a colorless solid; R_f 0.41 (hexanes/ EtOAc; 3:1); mp 121 – 122 °C; ^1H NMR (500.13 MHz, CDCl₃) δ 1.04 (s, 3H, CH₃), 3.65 (d, J = 11.5 Hz, 2H, H-4_{ax}, H-6_{ax}), 4.18 (t, J = 5 Hz, 2H, BrPhOCH₂), 4.55 (t, J = 5 Hz, 2H,

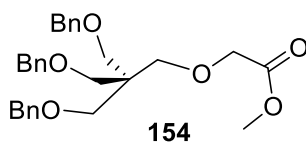
CH_2O), 4.67 (d, $J = 11.5$ Hz, 2H, H-4_{eq}, H-6_{eq}), 5.45 (s, 1H, H-2), 6.76 – 6.79 (m, 2H, PhH), 7.28 – 7.42 (m, 7H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 174.1, (C=O), 157.8, 137.9, 132.4, 129.1, 128.3, 126.3, 116.7, 113.5 (PhC), 101.9 (C-2), 73.6 (C-4, C-6), 66.4 (BrPhOC), 63.3 ($\text{CH}_2\text{OC}=\text{O}$), 42.6 (C_{quat}), 17.9 (CH_3). HR ESI MS m/z calcd for $\text{C}_{20}\text{H}_{21}\text{BrNaO}_5$ 443.0465, found 443.0455.

3.10.2.9. 2-(4-Iodophenoxy)ethyl 5-benzyloxymethyl-2-phenyl-1,3-dioxane-5-carboxylate (153)



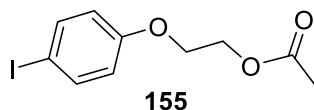
Synthesized using the COMU procedure (base in Table 3.1): a colorless solid; R_f 0.39 (hexanes/ EtOAc; 3:1); mp 67 – 69 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 4.09 – 4.11 (m, 6H (2H-5', H-4_{ax}, H-6_{ax}, 2H-IPhOCH₂), 4.41 (d, $J = 11.5$ Hz, 2H, H-4_{eq}, H-6_{eq}), 4.48 (t, $J = 4.5$ Hz, 2H, CH_2O), 4.57 (s, 2H, CH_2Ph), 5.44 (s, 1H, H-2), 6.65 (d, $J = 9$ Hz, PhH), 7.29 – 7.46 (m, 10H, PhH), 7.56 (d, $J = 9$ Hz, 2H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 171.2 (C=O), 158.4, 138.4, 138.1, 137.7, 129.2, 128.4, 127.6, 127.5, 126.2, 117.1 (PhC), 101.9 (C-2), 83.5 (PhC), 73.4 (CH_2Ph), 69.8 ($\text{CH}_{2\text{ax}}$), 68.8 (C-4, C-6), 65.8 (IPhOC), 63.0 ($\text{CH}_2\text{OC}=\text{O}$), 46.1 (C_{quat}). HR ESI MS m/z calcd for $\text{C}_{27}\text{H}_{27}\text{INaO}_6$ 597.0741, found 507.0749.

3.10.2.10. Methyl 2-(3-(benzyloxy)-2,2-bis(benzyloxymethyl)propoxy)acetate (154).



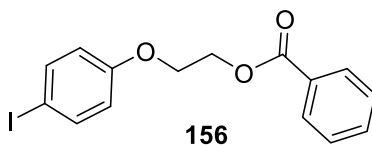
Synthesized using the COMU procedure (base in Table 3.1): a colorless syrup; R_f 0.58 (hexanes/ EtOAc; 3:1); ^1H NMR (500.13 MHz, CDCl_3) δ 3.72 (s, 6 H, $\text{C}_{\text{quat}}3\text{CH}_2\text{O}$), 3.78 (s, 2H, $\text{C}_{\text{quat}}\text{CH}_2\text{O}$), 3.78 (s, 3H, OCH_3), 4.16 (s, 2H, $\text{OCH}_2\text{C}=\text{O}$), 4.61 (s, 6H, $3\text{CH}_2\text{Ph}$), 7.34 – 7.43 (m, 15H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 171.0 (C=O), 138.8, 128.2, 127.3 (PhC), 73.3 ($3\text{CH}_2\text{Ph}$), 71.2 ($\text{C}_{\text{quat}}\text{CH}_2\text{O}$), 69.3 ($3\text{C}_{\text{quat}}\text{CH}_2\text{O}$), 69.0 ($\text{OCH}_2\text{C}=\text{O}$), 51.6 (OCH_3), 45.7 (C_{quat}). HR ESI MS: m/z calcd for $\text{C}_{29}\text{H}_{34}\text{NaO}_6$ 501.2248, found 501.2238.

3.10.2.11. 2-(4-Iodophenoxy)ethyl acetate (155)



Synthesized using the COMU procedure (base in Table 3.1): a pale yellow solid; R_f 0.39 (hexanes/ EtOAc; 4:1); mp 50 – 51 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 2.08 (s, 3H, CH_3), 4.10 (t, $J = 5$ Hz, 2H, IPhOCH_2), 4.38 (t, $J = 5$ Hz, 2H, $\text{CH}_2\text{OC}=\text{O}$), 6.65 – 6.68 (m, 2H, PhH), 7.52 – 7.55 (m, 2H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 170.9 (C=O), 158.3, 138.3, 117.0, 83.4 (PhC), 66.0 (IPhOC), 62.6 ($\text{CH}_2\text{OC}=\text{O}$), 20.9 (CH_3). HR ESI MS m/z calcd for $\text{C}_{10}\text{H}_{11}\text{INaO}_3$ 328.9645, found 328.9635.

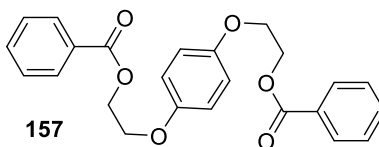
3.10.2.12. 2-(4-Iodophenoxy)ethyl benzoate (156)



Synthesized using both the COMU and TBTU procedures (bases in Tables 3.1, 3.3, and 3.5): a cotton-like colorless solid; R_f 0.40 (hexanes/ EtOAc; 3:1); mp 84 – 85 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 4.28 (t, $J = 4.5$ Hz, 2H, IPhOCH_2), 4.66 (t, $J = 4.5$ Hz, 2H, $\text{CH}_2\text{OC}=\text{O}$),

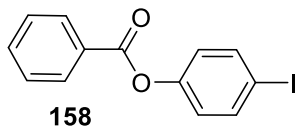
6.71 – 6.74 (m, 2H, PhH), 7.43 – 7.46 (m, 2H, PhH), 7.55 – 7.58 (m, 3H, PhH), 8.04 – 8.05 (m, 2H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 166.6 (C=O), 158.6, 138.4, 133.3, 129.89, 129.85, 128.5, 117.2, 83.5 (PhC), 66.3 (IPhOC), 63.3 ($\text{CH}_2\text{OC}=\text{O}$). HR ESI MS m/z calcd for $\text{C}_{15}\text{H}_{13}\text{INaO}_3$ 390.9802, found 390.9809.

3.10.2.13. 1,4-Bis(2-benzoyloxyethoxy)benzene (157)



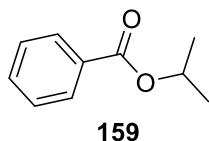
Synthesized using the COMU procedure (base in Table 3.1): a colorless crystalline solid; R_f 0.41 (hexanes/ EtOAc; 2:1); mp 130 - 131 $^\circ\text{C}$; ^1H NMR (500.13 MHz, CDCl_3) δ 4.27 (t, $J = 5$ Hz, 4H, PhOCH_2), 4.65 (t, $J = 5$ Hz, 4H, $\text{CH}_2\text{OC}=\text{O}$), 6.90 (s, 4H, PhH), 7.42 – 7.45 (m, 4H, PhH), 7.54 – 7.58 (m, 2H, PhH), 8.05 – 8.07 (m, 4H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 166.6 (C=O), 153.2, 133.2, 130.0, 129.8, 128.5, 116.0 (PhC), 66.9 (PhOC), 63.6 ($\text{CH}_2\text{OC}=\text{O}$). HR ESI MS m/z calcd for $\text{C}_{24}\text{H}_{22}\text{NaO}_6$ 429.1309, found 429.1318.

3.10.2.14. 4-Iodophenyl benzoate (158)



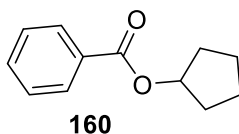
Synthesized using both the COMU and TBTU procedures (bases in Table 3.1, 3.3, and 3.5): a colorless crystalline solid; R_f 0.50 (hexanes/ EtOAc; 6:1); mp 123 – 124 $^\circ\text{C}$; lit.²³⁷ mp 115 -117 $^\circ\text{C}$; lit.²³⁸ mp 118.5 -119.5 $^\circ\text{C}$; ^{13}C NMR (125.7 MHz, CDCl_3) δ 164.8 (C=O), 150.9, 138.6, 133.9, 130.3, 129.2, 128.7, 124.0, 90.0 (PhC). ^1H NMR spectrum similar to lit.²³⁷ HR ESI MS m/z calcd for $\text{C}_{13}\text{H}_9\text{INaO}_2$ 346.9539, found 346.9544.

3.10.2.15. Isopropyl benzoate (159)



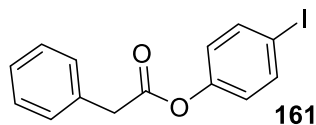
Synthesized using both the COMU and TBTU procedures; a colorless syrup: R_f 0.68 (hexanes/ EtOAc; 6:1); ^1H NMR and ^{13}C NMR data were similar to lit.²³⁹

3.10.2.16. Cyclopentyl benzoate (160)



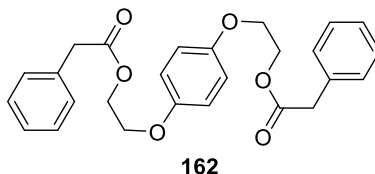
Synthesized using both the COMU and TBTU procedures; a colorless syrup: R_f 0.57 (hexanes/ EtOAc; 10:1); ^{13}C NMR (125.7 MHz, CDCl_3) δ 166.3, 132.7, 130.9, 129.5, 128.3 (PhC), 77.7 (OCH), 32.8 (OCH(CH₂)₂), 23.8 (2CH₂); ^1H NMR data were similar to lit.²⁴⁰

3.10.2.17. 4-Iodophenyl 2-phenylacetate (161)



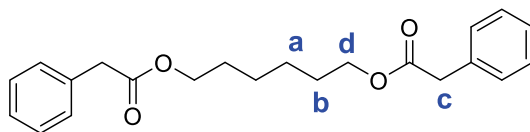
Synthesized using the COMU procedure, a colorless crystalline solid: R_f 0.53 (hexanes/ EtOAc; 4:1); mp 60 – 61 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 3.86 (s, 2H, CH₂), 6.84 – 6.86 (m, 2H, PhH), 7.31 – 7.41 (m, 5H, PhH), 7.66 – 7.69 (m, 2H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 169.7 (C=O), 150.7 138.5, 133.3, 129.4, 128.9, 127.6, 123.8, 90.0 (PhC), 41,5 (CH₂). HR ESI MS m/z calcd for C₁₄H₁₁INaO₂ 360.9696, found 360.9685.

3.10.2.18. 1,4-Bis(2-(2-phenylacetyloxy)ethoxy)benzene (162)



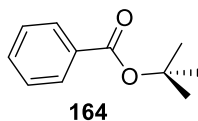
Synthesized using both the COMU procedure; a cotton-like colorless solid: R_f 0.38 (hexanes/ EtOAc; 3:1); mp 82 – 84 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 3.68 (s, 4H, CH_2Ph), 4.13 (t, $J = 5$ Hz, 4H, PhOCH_2), 4.44 (t, $J = 5$ Hz, 4H, $\text{CH}_2\text{OC}=\text{O}$), 6.83 (s, 4H, PhH), 7.26 – 7.34 (m, 10H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 171.7 (C=O), 153.2, 133.9, 129.4, 128.7, 127.3, 115.9 (PhC), 66.8 (PhOC), 63.4 ($\text{CH}_2\text{OC}=\text{O}$), 41.3 (CH_2Ph). HR ESI MS m/z calcd for $\text{C}_{26}\text{H}_{26}\text{NaO}_6$ 457.1622, found 457.1620.

3.10.2.19. 1,4-Bis(2-phenylacetyloxy)butane (163)



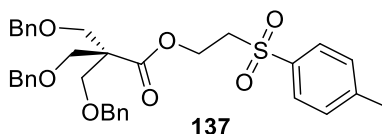
Synthesized using both the COMU procedure; a colorless syrup: R_f 0.42 (hexanes/ EtOAc; 4:1); ^1H NMR (500.13 MHz, CDCl_3) δ 1.32 (m, 4H, H_a), 1.62 (quin, $J = 7$ Hz, 4H, H_b), 3.63 (s, 4H, H_c), 4.10 (t, $J = 7$ Hz, 4H, H_d), 7.27 – 7.37 (m, 10H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 171.5 (C=O), 134.2, 129.2, 128.5, 127.0 (PhC), 64.5 (C_D), 41.4 (C_C), 28.4 (C_B), 25.4 (C_A). HR ESI MS m/z calcd for $\text{C}_{22}\text{H}_{26}\text{NaO}_4$ 377.1723, found 377.1724.

3.10.2.20. *Tert*-butyl benzoate (164)



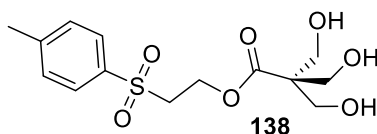
Synthesized using the COMU procedure: a colorless syrup; R_f 0.68 (hexanes/ EtOAc; 9:1); ^1H NMR and ^{13}C NMR spectral data were similar to lit.²⁴¹

3.10.2.21. 2-Tosylethyl 3-(benzyloxy)-2,2-bis(benzyloxymethyl)propanoate (**137**)



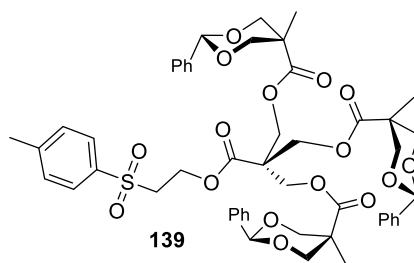
2(*p*-Toluenesulfonyl)ethanol (4.00 g, 20.0 mmol), dry pyridine (30 mL), CH_2Cl_2 (90 mL), DMAP (0.489 g, 4.00 mmol), and the anhydride **108** (20.6 g, 25.0 mmol) were stirred at rt for 12 h under nitrogen, and diluted with water (~ 3 mL) in pyridine (3 mL). Stirring was continued overnight to quench the excess anhydride. The mixture was diluted with CH_2Cl_2 (150 mL) and the organic layer was washed with NaHCO_3 (1 M, 30 mL \times 3), 10% aq. Na_2CO_3 (30 mL \times 3), brine (30 mL \times 2), and water (30 mL), then dried (MgSO_4), filtered, and concentrated. The crude product was then purified using column chromatography to give **137** as a thick colorless syrup (11.3 g, 94% yield): R_f 0.44 (hexanes/ EtOAc; 2:1); ^1H NMR (500.13 MHz, acetone- d_6) δ 2.41 (s, 3H, Ar CH_3), 3.45 (t, $J = 6$ Hz, 2H, SCH_2 -), 3.60 (s, 6H, $\text{C}_{\text{quat}}(\text{CH}_2)_3$), 4.40 (t, $J = 6$ Hz, 2H, $-\text{CH}_2\text{OC}=\text{O}$), 4.49 (s, 6H, CH_2Ph), 7.26 – 7.35 (m, 15H, PhH), 7.37 (d, 2H, $J = 8$ Hz, PhH), 7.75 (d, 2H, $J = 8$ Hz, PhH); ^{13}C NMR (125.7 MHz, acetone- d_6) δ 172.1 (C=O), 145.4, 139.3, 137.7, 130.7, 128.9, 128.8, 128.14, 128.12 (PhC), 73.6 (CH_2Ph), 68.1 ($\text{C}_{\text{quat}}\text{CH}_2$), 58.3 ($-\text{CH}_2\text{OC}=\text{O}$), 55.5 (SCH_2 -), 54.1 (C_{quat}), 21.5 (CH_3Ar). HR ESI MS m/z calcd for $\text{C}_{35}\text{H}_{38}\text{NaO}_7\text{S}$ 625.2230, found 625.2214.

3.10.2.22. 2-Tosylethyl 3-hydroxy-2,2-bis(hydroxymethyl)propanoate (138)



Compound **137** (8.00 g, 13.3 mmol) was dissolved in a 1:2 mixture of CH_2Cl_2 / MeOH (v/v) in an oven-dried round-bottomed flask equipped with a magnetic stir bar and a catalytic amount of Pd/C was added. The flask was evacuated and back-filled with hydrogen three times. After stirring the mixture overnight under H_2 atmosphere, the catalyst was removed via filtration using celite and this celite was washed with MeOH. The filtrate was concentrated to dryness to afford the product as a colorless solid (4.32 g, 98% yield): mp 103 – 104 °C; ^1H NMR (500.13 MHz, acetone- d_6) δ 2.46 (s, 3H, ArCH₃), 3.60 (t, J = 6 Hz, 2H, SCH₂-), 3.70 (s, 6H, C_{quat}(CH₂)₃), 4.40 (t, J = 6 Hz, 2H, -CH₂OC=O), 7.50 (d, 2H, J = 8 Hz, PhH), 7.85 (d, 2H, J = 8 Hz, PhH); ^{13}C NMR (125.7 MHz, acetone- d_6) δ 173.6 (C=O), 145.9, 137.5, 130.9, 129.0 (PhC), 61.7 (C_{quat}CH₂), 58.2 (-CH₂OC=O), 56.7 (C_{quat}), 55.5 (SCH₂), 21.5 (CH₃Ar). HR ESI MS m/z calcd for C₁₄H₂₀NaO₇S 355.0822, found 355.0829.

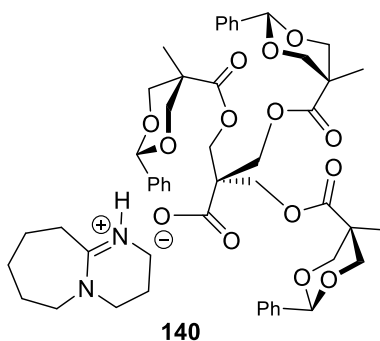
3.10.2.23. 2-(Toluenesulfonyl)ethyl-protected second generation dendron (139)



First generation dendron **138** (2.05 g, 6.17 mmol), dry pyridine (20 mL), CH_2Cl_2 (60 mL), DMAP (0.452 g, 3.70 mmol), and anhydride **35** (9.86 g, 23.12 mmol) were stirred at rt for 10 h

under nitrogen. After work up and purification as described above for **137**, the product was obtained as a colorless crystalline solid (5.42 g, 93% yield): R_f 0.41 (hexanes/ EtOAc; 1:1); mp 127 - 128 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 0.89 (s, 9H, 3 CH_3), 2.33 (s, 3H, CH_3Ar), 2.93 (t, $J = 5.5$ Hz, 2H, SCH_2^-), 3.58 (d, $J = 11$ Hz, 6H, 3H-4 $_{\text{ax}}$, 3H-6 $_{\text{ax}}$), 4.14 (t, $J = 5.5$ Hz, 2H, - $\text{CH}_2\text{OC}=\text{O}$), 4.22 (s, 6H, $\text{C}_{\text{quat}}(\text{CH}_2)_3$), 4.54 (d, $J = 11$ Hz, 6H, 3H-4 $_{\text{eq}}$, 3H-6 $_{\text{eq}}$), 7.23 – 7.64 (m, 19H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 173.0 (3 $\text{C}=\text{O}$), 169.3 ($\text{C}=\text{O}$), 145.0, 137.9, 136.4, 130.1, 129.0, 128.3, 128.1, 126.2 (PhC), 101.7 (C-2), 73.6 (C-4, C-6), 61.3 ($\text{C}_{\text{quat}}(\text{CH}_2)_3$), 58.7 (- $\text{CH}_2\text{OC}=\text{O}$), 54.5 (SCH_2^-), 51.0 (C_{quat}), 42.7 (C-5), 21.6 (CH_3Ar), 17.7 (3 CH_3). HR ESI MS m/z calcd for $\text{C}_{50}\text{H}_{56}\text{NaO}_{16}\text{S}$ 967.3181, found 967.3219.

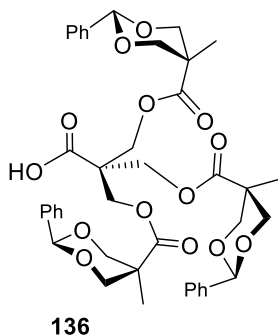
3.10.2.24. 1,8-Diazabicyclo[5.4.0]undec-7-ene-8-ium salt of second generation dendron (**140**)



Compound **139** (4.27g, 4.52 mmol) was dissolved in dry CH_2Cl_2 (85 mL) in an oven-dried round-bottom flask equipped with a magnetic stir bar. The system was closed and flushed with nitrogen for 5 min. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (2.40 mL, 15.8 mmol) was added via syringe, the mixture was stirred at rt for 9 h and then concentrated to give a thick syrup. Crystallization from hexanes/ CH_2Cl_2 gave the title compound as colorless crystals (4.0 g, 97% yield): mp 175 – 177 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 0.88 (s, 9H, 3 CH_3), 1.47 – 1.66 (m, 8H, 4(CH_2), DBU), 2.65 (t, $J = 5$ Hz, 2H, DBU), 3.07 (t, $J = 5.5$ Hz, 2H, DBU), 3.12 – 3.13

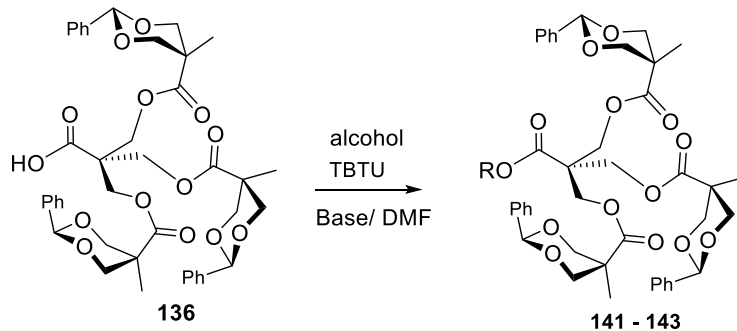
(m, 2H, DBU), 3.21 (t, $J = 5.5$ Hz, 2H), 3.52 (d, $J = 11$ Hz, 6H, 3H-4_{ax}, 3H-6_{ax}), 4.49 (s, 6H, C_{quat}(CH₂)₃), 4.60 (d, $J = 11$ Hz, 6H, 3H-4_{eq}, 3H-6_{eq}), 5.36 (s, 3H, H-2), 7.25 – 7.41 (m, 15H, PhH), 13.04 (br, 1H, N-H-O); ¹³C NMR (125.7 MHz, CDCl₃) δ 174.1 (C=O), 173.4 (3C=O), 165.9 (C, sp², DBU), 138.2, 128.7, 128.1, 126.5 (PhC), 101.8 (C-2), 73.6 (C-4, C-6), 64.1 (C_{quat}(CH₂)₃), 53.9, 50.8 (2CH₂), DBU), 48.4 (C_{quat}), 42.4 (C-5), 37.9, 31.9, 29.0, 27.0, 24.1, 19.5 (6CH₂), DBU), 18.0 (3CH₃).


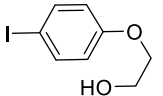
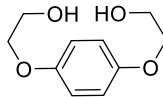
3.10.2.25. Protected second generation acid dendron (136)



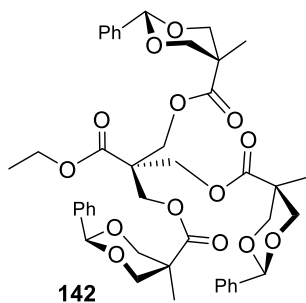
Salt **140** (2.15 g, 2.35 mmol) was dissolved in CH₂Cl₂ (60 mL) in a separatory funnel and this organic layer was washed with a 0.5 M HCl solution (15 mL x 3). The organic layer was collected, dried (MgSO₄), filtered, and concentrated to give acid **136** as a colorless crystalline solid in quantitative yield: mp 197 – 199 °C; ¹H NMR (500.13 MHz, DMSO-d₆) δ 0.86 (s, 9H, 3CH₃), 3.69 (d, $J = 11$ Hz, 6H, 3H-4_{ax}, 3H-6_{ax}), 4.37 (s, 6H, C_{quat}(CH₂)₃), 4.38 (d, $J = 11$ Hz, 6H, 3H-4_{eq}, 3H-6_{eq}), 5.48 (s, 3H, H-2), 7.29 – 7.34 (m, 15H, PhH), 13.43 (br, 1H, COOH); ¹³C NMR (125.7 MHz, DMSO-d₆) δ 173.0 (3C=O), 171.5 (C=O), 138.1, 128.7, 128.0, 126.2 (PhC), 100.6 (C-2), 72.3 (C-4, C-6), 61.5 (C_{quat}(CH₂)₃), 50.0 (C_{quat}), 42.4 (C-5), 17.2 (3CH₃).). HR ESI MS m/z calcd for C₄₁H₄₅O₁₄ 761.2815, found 761.2776.

3.10.2.26. Formation of esters from protected second generation acid dendron (136)



| alcohol | base (2 equiv) | reaction time (h) | % yield | ester |
|--|-------------------|----------------------|---------|------------|
|  | DBU | 1 | 92 | 142 |
| | DIEA | 1 | 90 | |
|  | DBU | 1.5 | 91 | 143 |
| | DIEA | 1.5 | 88 | |
|  | DBU | 3 | 82 | 141 |

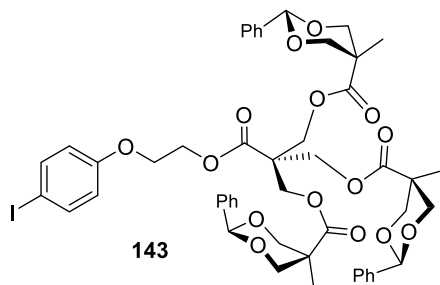
3.10.2.27. Ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (142) (table above)



Synthesized using the TBTU procedure; a colorless solid: R_f 0.55 (hexanes/ EtOAc; 1:1); mp 159 – 160 °C; $^1\text{H NMR}$ (500.13 MHz, CDCl_3) δ 0.91 (s, 9H, 3 CH_3), 1.02 (t, $J = 7$ Hz, 3H, CH_3), 3.58 (d, $J = 11.5$ Hz, 6H, 3H-4 $_{\text{ax}}$, 3H-6 $_{\text{ax}}$), 3.98 (q, $J = 7$ Hz, 2H, $\text{CH}_2\text{OC}=\text{O}$), 4.48 (s, 6H,

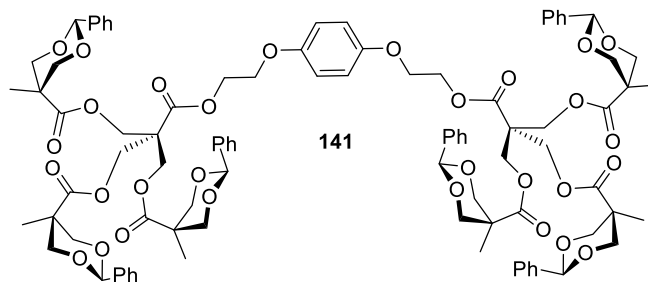
$C_{\text{quat}}(\text{CH}_2)_3$, 4.56 (d, $J = 11.5$ Hz, 6H, 3H-4_{eq}, 3H-6_{eq}), 5.41 (s, 3H, H-2), 7.28 – 7.43 (m, 15H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 173.0 (3C=O), 169.9 (C=O), 137.8, 128.8, 128.1, 126.2 (PhC), 101.7 (C-2), 73.5 (C-4, C-6), 61.78 ($\text{CH}_2\text{OC}=\text{O}$), 61.77 ($C_{\text{quat}}(\text{CH}_2)_3$), 50.9 (C_{quat}), 42.6 (C-5), 17.6 (3 CH_3), 13.9 (CH_3). HR ESI MS m/z calcd for $\text{C}_{43}\text{H}_{50}\text{NaO}_{14}$ 813.3093, found 813.3150.

3.10.2.28. 2-(4-Iodophenoxy)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (143)



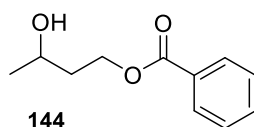
Synthesized using both the COMU and TBTU procedures; a colorless solid: R_f 0.55 (hexanes/ EtOAc; 1:1); mp 155 – 157 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 0.89 (s, 9H, 3 CH_3), 3.56 (d, $J = 11.5$ Hz, 6H, 3H-4_{ax}, 3H-6_{ax}), 3.68 (t, $J = 4.5$ Hz, 2H, ArOCH_2), 4.13 (t, $J = 4.5$ Hz, 2H, $\text{CH}_2\text{OC}=\text{O}$), 4.47 (s, 6H, $C_{\text{quat}}(\text{CH}_2)_3$), 4.55 (d, $J = 11.5$ Hz, 6H, 3H-4_{eq}, 3H-6_{eq}), 5.40 (s, 3H, H-2), 6.48 (d, $J = 8.5$ Hz, 2H, PhH), 7.28 - 7.46 (m, 15H, PhH), 7.47 (d, $J = 7$ Hz, 2H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 173.0 (3C=O), 170.0 (C=O), 158.3, 138.2, 137.9, 128.9, 128.2, 126.2, 117.1 (PhC), 101.7 (C-2), 73.5 (C-4, C-6), 65.4 (ArOCH_2), 63.8 ($\text{CH}_2\text{OC}=\text{O}$), 61.7 ($C_{\text{quat}}(\text{CH}_2)_3$), 51.2 (C_{quat}), 42.7 (C-5), 17.7 (3 CH_3). HR ESI MS m/z calcd for $\text{C}_{49}\text{H}_{53}\text{INaO}_{15}$ 1031.2321, found 1031.2413.

3.10.2.29. Benzylidene-protected hydroquinone-cored second generation dendrimer (141)



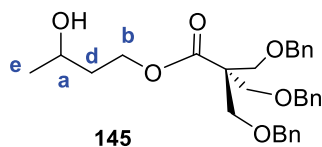
Synthesized using the TBTU procedure; a colorless crystalline solid: R_f 0.14 (hexanes/EtOAc; 1:1); mp 183 – 185 °C; ^1H NMR (500.13 MHz, acetone- d_6 / DMSO- d_6) δ 3.70 (d, J = 11.5 Hz, 12H, 6H-4_{ax}, 6H-6_{ax}), 3.93 (t, J = 4.5 Hz, 4H, 2PhOCH₂), 4.27 (t, J = 4.5 Hz, 4H, 2CH₂OC=O), 4.44 (d, J = 11.5 Hz, 12H, 6H-4_{eq}, 6H-6_{eq}), 4.47 (s, 12H, 2C_{quat}(CH₂)₃), 5.50 (s, 6H, H-2), 6.73 (s, 4H, PhH), 7.30 – 7.38 (m, 30H, PhH); ^{13}C NMR (125.7 MHz, acetone- d_6 / DMSO- d_6) δ 173.4 (6C=O), 170.5 (2C=O), 153.2, 138.9, 129.1, 128.4, 126.7, 116.0 (PhC), 101.5 (6C-2), 73.2 (6C-4, 6C-6), 66.4 (2PhOC), 64.4 (2CH₂OC=O), 62.0 (2C_{quat}(CH₂)₃), 51.4 (2C_{quat}), 42.9 (6C-5), 17.5 (6CH₃). HR EI MS: m/z calcd for C₉₂H₁₀₂Na₂O₃₀ 866.3120, found 866. 3048.

3.10.2.30. 3-Hydroxybut-1-yl benzoate (144)



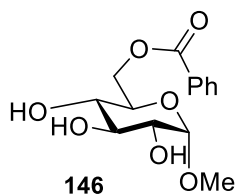
Synthesized using the TBTU procedure with diisopropylethylamine (DIEA) as base, a colorless syrup, a 95/5 mixture of the primary and secondary benzoates: R_f 0.32 (hexanes/EtOAc; 2:1); ^1H and ^{13}C NMR spectra similar to lit.²³³

3.10.2.31. 3-Hydroxybutyl 3-benzyloxy-2,2'-bis(benzyloxymethyl)propanoate (145)



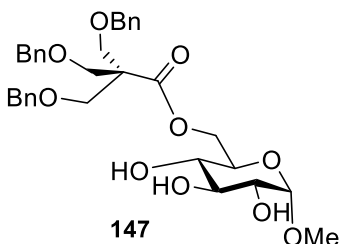
Synthesized using the TBTU procedure with diisopropylethylamine (DIEA) as base, 1,3-butanediol (**134**) and 3-benzyloxy-2,2'-bis(benzyloxymethyl)propanoic acid (**107**): a colorless syrup; R_f 0.36 (hexanes/ EtOAc; 2:1); ^1H NMR (500.13 MHz, DMSO- d_6 / methanol- d_4) δ 1.91 (d, $J = 6.5$ Hz, 3H, CH₃), 2.32 – 2.37 (m, 2H, CHCH₂CH₂), 4.35 – 4.42 (m, 2H, CH₂OC=O), 4.42 (s, 6H, C_{quat}(CH₂)₃), 4.59 – 4.65 (m, 1H, CH), 5.23 (s, 6H, CH₂Ph), 8.00 – 8.09 (m, 15H, PhH); ^{13}C NMR (125.7 MHz, DMSO- d_6 / methanol- d_4) δ 174.8 (C=O), 139.2, 128.9, 128.1, 128.0 (PhC), 73.5 (CH₂Ph), 68.6 (C_{quat}CH₂), 65.1 (C_a), 59.5 (C_b), 53.6 (C_{quat}), 42.2 (C_d), 23.8 (C_e). HR ESI MS m/z calcd for C₃₀H₃₆NaO₆ 515.2411, found 515.2402.

3.10.2.32. Methyl 6-*O*-benzoyl- α -D-glucopyranoside (146)



Synthesized using the TBTU procedure with diisopropylethylamine (DIEA) as base: a thick colorless oil; ^1H NMR data similar to lit.²⁴² ^{13}C NMR (125.7 MHz, DMSO- d_6 / methanol- d_4) δ 168.9 (C=O), 134.1, 131.9, 130.6, 129.7 (PhC), 101.0 (C-1), 74.8 (C-3), 73.6 (C-5), 73.3 (C-2), 71.6 (C-4), 62.4 (C-6), 55.5 (OCH₃).

3.10.2.33. Methyl 6-*O*-(3-benzyloxy-2,2'-bis(benzyloxymethyl)propanoyloxy)- α -D-glucopyranoside (147)



Synthesized using the TBTU procedure with diisopropylethylamine (DIEA) as base: a viscous colorless oil; ^1H NMR (500.13 MHz, DMSO- d_6 / methanol- d_4) δ 3.28 (t, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4), 3.35 (s, 3H, OCH₃), 3.38 (dd, $J_{1,2} = 3.7$ Hz, $J_{2,3} = 9.6$ Hz, H-2), 3.48 – 3.51 (m, 1H, H-5), 3.61 (t, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-3), 3.63 (s, 6H, C_{quat}(CH₂)₃), 3.65 (dd, $J_{5,6a} = 5.5$ Hz, $J_{6a,6b} = 12.1$ Hz, H-6a), 3.78 (dd, $J_{5,6b} = 1.5$ Hz, $J_{6a,6b} = 11.5$ Hz, H-6b), 4.41 (s, 6H, CH₂Ph), 4.65 (d, $J_{1,2} = 3.5$ Hz, H-1); ^{13}C NMR (125.7 MHz, DMSO- d_6 / methanol- d_4) δ 175.3 (C=O), 139.5, 129.1, 128.3 (PhC), 100.1 (C-1), 74.7 (C-3), 73.8 (CH₂Ph), 73.3 (C-5), 73.1 (C-2), 71.4 (C-4), 68.9 (C_{quat}(CH₂)₃), 62.3 (C-6), 55.3 (OCH₃), 53.9 (C_{quat}). HR ESI MS m/z calcd for C₃₃H₄₀NaO₁₀ 619.2518, found 619.2519.

Chapter 4: Synthesis of Lyme Disease Glycolipid Antigens

4.1. Introductory Remarks

Lyme disease (LD) is a rapidly expanding multi-system illness that is the most common tick-borne disease in the northern hemisphere.²⁴³⁻²⁴⁶ It is caused by species of the spirochete *Borrelia burgdorferi sensu lato*; at least three species cause the disease in Europe, *Borrelia afzelii*, *Borrelia garinii*, and *Borrelia burgdorferi sensu stricto* but only the latter is important in North America.²⁴⁶⁻²⁴⁸ The bacteria are transmitted to humans by bites of ticks of species of the genus *Ixodes*.²⁴⁸ These ticks have a three-host life cycle where the larvae feed on small rodents and birds that act as reservoirs for the bacteria.²⁴⁸⁻²⁵⁰ The larvae leave the initial host then molt into nymphs that feed on a second host, primarily small rodents but also humans, then leave the second host and molt into adults that feed on large mammals, primarily deer but including dogs and occasionally humans.^{248,250} The bacteria reside in the mid-gut of the ticks and only migrate to the salivary glands after changes in surface protein expression (OspA to OspC) occur induced by a mammalian blood meal. These changes require at least 17 h of feeding.²⁴³

4.2. Antigens Against Lyme Disease

A vaccine against Lyme disease based on the outer surface protein OspA was introduced in 1998 but withdrawn in 2002 for several reasons among which was the recognition that the change in surface protein expression made it an unusual transmission-blocking vaccine.²⁵¹ Other possible antigens include two glycolipids first isolated from *Borrelia burgdorferi* in 2001²⁵² and shown to be cholesteryl 6-*O*-acyl- β -D-galactopyranoside (BbGL1) and 1,2-di-*O*-acyl-3-*O*- α -D-galactopyranosyl-*sn*-glycerol (BbGL2) (see Figure 12),^{253,254} abundant in the outer membranes of the LD-causing *Borrelia burgdorferi* species.²⁵⁵ The acyl groups in both BbGL1 and BbGL2 are

a mixture of palmitoyl and oleoyl groups and it was recently shown that at least one of the acyl groups in BbGL2 must contain a cis-alkene for antigenicity to be maintained.²⁵⁶

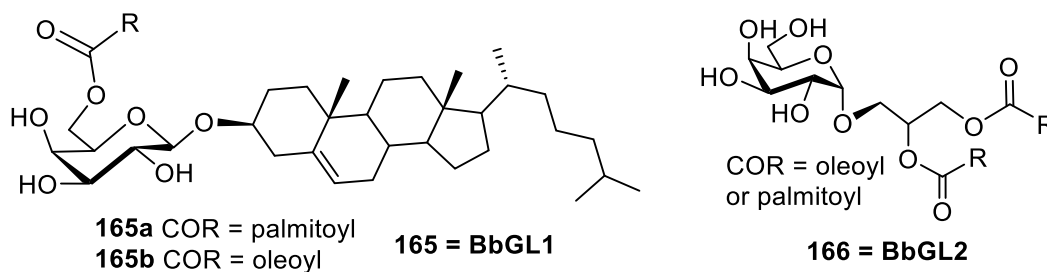
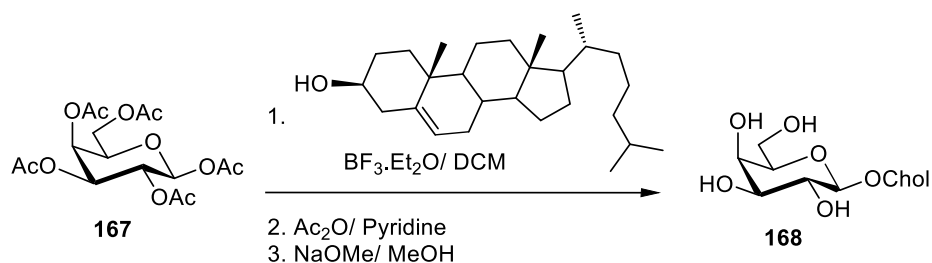


Figure 12 *Borrelia burdorferi* glycolipid antigens

In this chapter, the synthesis of a library of BbGL1 derivatives is discussed. This short and efficient synthesis makes use of the primary-selective synthesis of esters described in Chapter 3 for the acylation step. BbGL1 and its derivatives have been synthesized five times since its structure was determined in 2003.^{253,254} Pozsgay *et al.* outlined a twelve-step synthesis from D-galactose using pivaloyl groups to achieve β -selective glycosylation via neighbouring group participation and protecting group chemistry to introduce the ester group at O-6 in 11% overall yield.²⁵⁷ This group also reported the synthesis of a derivative allowing conjugation to protein using a similar pathway.²⁵⁸ Wu *et al.* prepared the palmitoyl version of BbGL1 in low yield (38%) on a small scale enzymically but did not indicate how they prepared the cholesterol glycoside.²⁵⁹ Kulkarni and Gervay-Hague reported a short synthesis but the yield in the glycosylation step was moderate (56% β/α 9/1) and that in the esterification step was worse (43%).²⁶⁰ In addition, Stübs *et al.* were unable to repeat the carbodiimide-promoted selective esterification reaction, despite extensive studies.²⁶¹ This latter group synthesized the cholesteryl glycoside in four steps from D-galactose then added a number of different acyl groups

enzymically using acyl transfer from acetone oxime esters catalysed by a lipase in low yields (5 to 31%).²⁶¹

Two key steps are required for the synthesis of BbGL1 analogues from D-galactose: a β -selective glycosylation and regioselective esterification. We opted to perform the glycosylation using the single step Lewis acid catalysed reaction of cholesterol with easily accessible β -D-galactose pentaacetate (**167**) even though the yield is expected to be lower than two or three step processes involving more active glycosyl leaving groups. Lewis acid catalysis of glycosylation of pentaacetates has been known for some time using acids such as tin tetrachloride²⁶²⁻²⁶⁵ and zinc chloride,^{266,267} but we choose to investigate boron trifluoride etherate to avoid the use of toxic or solid hydroscopic metal catalysts. This activator has been used before but only with primary alcohols for preparative purposes as far as we are aware.^{268,269} Ellervik *et al.* demonstrated that these reactions proceed rapidly with glycosyl acetates under equimolar conditions to give the desired product accompanied by slower anomerization and equilibration.²⁷⁰



Scheme 48 Synthesis of cholesteryl β -D-galactopyranoside (**168**)

The effects of changing conditions were investigated as outlined in Table 12. Increasing the relative amount of cholesterol increased the yield. Increasing the amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ increased the rate but decreased the β/α ratio. Adding acetonitrile slowed the reaction rate but

improved the β/α ratio, although we could not find conditions that eliminated the need for separation of the anomers by column chromatography. The best conditions were in DCM with 1.5 equiv of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, which gave an acceptable 73% yield (β/α 6:1).

Cholesterol had an R_F that was similar to that of the product. We found it convenient to separate excess cholesterol by acetylation followed by silica gel chromatography, which also allowed separation of the minor amount of the α -glycoside. De-*O*-acetylation gave cholesteryl β -D-galactopyranoside (**168**) (Scheme 48).

Table 12 Effect of variation of conditions on glycosylation

| GalPa conc (M) | cholesterol (equiv) | solvent | BF_3 (equiv) | time (h) | yield (%) | β/α |
|----------------|---------------------|------------------|-----------------------|----------|-----------|----------------|
| 0.087 | 3.0 | DCM | 0.5 | 48 | 61 | 5/1 |
| 0.032 | 3.0 | DCM | 1.5 | 72 | 58 | 6/1 |
| 0.032 | 10 | DCM | 1.5 | 72 | 73 | 6/1 |
| 0.032 | 10 | DCM | 3.0 | 48 | 62 | 5/1 |
| 0.032 | 10 | DCM | 4.5 | 48 | 59 | 3/1 |
| 0.01 | 3 | DCM/ MeCN 6:1 | 1.5 | 96 | 51 | 12/1 |
| 0.01 | 10 | DCM/ MeCN 6:1 | 1.5 | 96 | 66 | 11/1 |

The critical step is the regioselective addition of fatty acid esters at O-6 of compound **168**. We found that the TBTU-promoted esterification procedure described in Chapter 3 worked well with a variety of fatty acids as shown in Table 13 with yields in the 78 to 84% range. Three changes were made to the conditions previously used for the regioselective acylation of primary hydroxyls in the presence of secondary hydroxyls. The poor solubility of **168** in DMF required a change of solvent and the reaction was found to proceed well in pyridine. The much longer chain lengths in the fatty acids used here required longer reaction times and 36 h was found to give

reasonable yields. Reactions performed in pyridine without the addition of the more basic tertiary amine, DIEA, gave approximately the same yields as those with DIEA added. This latter observation provides more information about the cause of the selectivity of this TBTU-promoted esterification of primary hydroxyls. The pKa of the conjugate acid of pyridine in water is 5.25.²²⁹ The smallest pKa of the non-anomeric secondary hydroxyls of glucose derivatives is about 12.3.^{271,272} That of the primary hydroxyl is about 1.5 to 2 pKa units larger,^{272,273} approximately 14, and those of galactose are similar.²⁷³ Possible pathways for the last step in the esterification reaction promoted by TBTU are shown in Scheme 49. The amount of alkoxide present with DIEA as the base would be approximately 0.001 [alcohol] because the pKa of DIEA is about 11.²²⁹ If alkoxide were the nucleophile (lower pathway in Scheme 49), the reaction rate would slow drastically on removal of DIEA because it is approximately 6 pKa units more basic than pyridine. The absence of marked effects on rates indicates that the base serves only to remove protons after a rate-determining addition of the primary alcohols (upper pathway in Scheme 49).

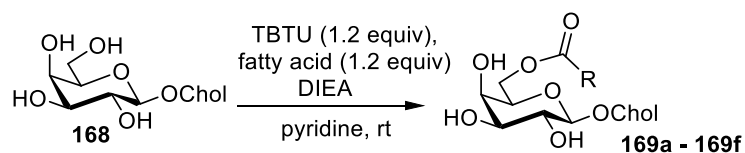
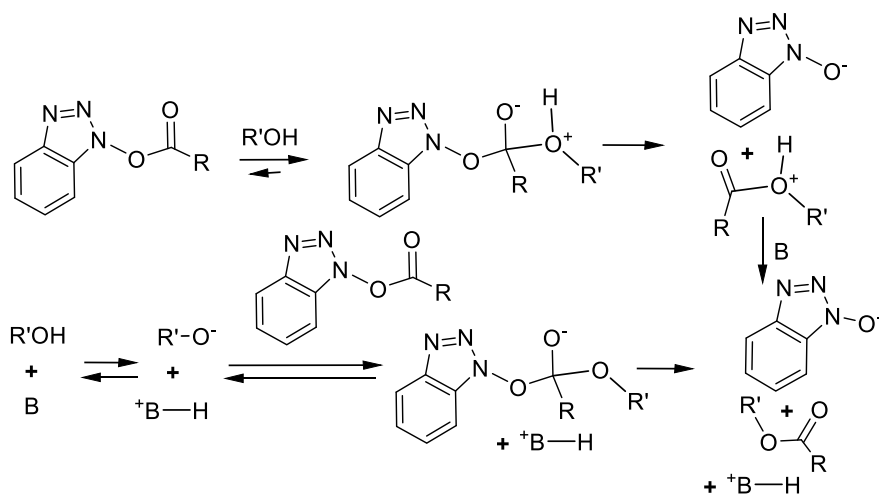


Table 13 Regioselective esterification results

| fatty acid | DIEA (equiv) | time (h) | yield (%) |
|------------|--------------|----------|-----------|
| palmitic | 2 | 12 | 49 |
| palmitic | 2 | 24 | 67 |
| palmitic | 2 | 36 | 82 |
| stearic | 2 | 36 | 84 |
| stearic | 0 | 36 | 80 |
| myristic | 2 | 36 | 79 |
| lauric | 2 | 36 | 78 |
| oleic | 2 | 36 | 83 |
| erucic | 2 | 36 | 81 |
| erucic | 0 | 36 | 77 |

Secondary alcohols do not form esters under TBTU-promoted conditions unless the stronger base DBU is present (Chapter 3).^{274,275} Since a stronger base would have little effect on the rate of the upper pathway of Scheme 49, the pathway followed when the base is changed to DBU must involve alkoxide ions. Apparently, primary alcohols are sufficiently less hindered and more nucleophilic to permit their direct addition to the carbonyl group of the benzotriazole-activated ester whereas secondary alcohols need to be activated as alkoxides before they can add.



Scheme 49 Possible pathways for the last step of TBTU-promoted esterification. B = base

4.3. Concluding Remarks

Regioselective esterification of primary hydroxyls promoted by the peptide coupling agent TBTU is an efficient method for the O-6 acylation on carbohydrates. This method was used in the development of short and efficient syntheses of a library of one of the two glycolipid antigens against Lyme disease, BbGL1. The reduction in synthetic steps means less cost for the final product and in addition, the elimination of protection/ deprotection steps leads to minimized chemical wastes, which is important as we move towards a greener chemistry and a greener

world. Overall yields for the three steps from β -D-galactopyranose pentaacetate ranged from 48 to 52% for the different fatty acids.

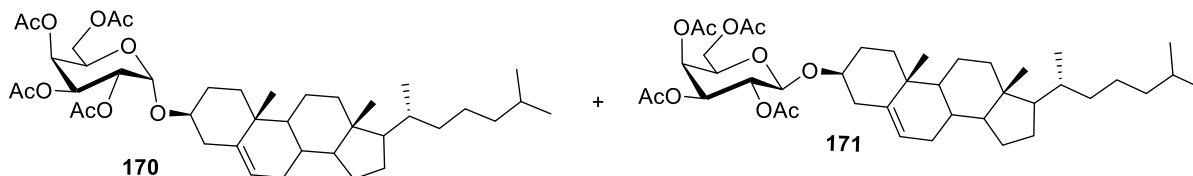
4.4. Experimental Section

4.4.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-500 MHz NMR spectrometer operating at 500.13 and 125.7 MHz respectively using the solvent resonances as secondary chemical shift references. The carbon and hydrogen atoms of new compounds were assigned following the analysis of their one dimensional (^1H , ^{13}C , and DEPT-135) and two dimensional (COSY, HSQC, and HMBC) NMR spectral data. The ^1H and ^{13}C NMR spectra of all compounds may be found in Appendix A. Coupling constant (J) values are reported in Hertz. High-resolution mass spectra were recorded using electrospray ionization with a time of flight mass analyser. Melting points are uncorrected. Acetonitrile, dichloromethane, and *N,N*-diisopropylethylamine (DIEA) were refluxed over calcium hydride and distilled onto molecular sieves. Methanol was dried over calcium oxide and distilled over molecular sieves. Unless otherwise noted, non-aqueous reactions were carried out under a nitrogen atmosphere. Pyridine was dried over potassium hydroxide and was stored over molecular sieves. Compounds were visualized/ located by spraying the TLC plate with a solution of 2 % ceric ammonium sulfate in 0.5 M H_2SO_4 followed by heating on a hot plate until color developed.

4.4.2. Synthesis

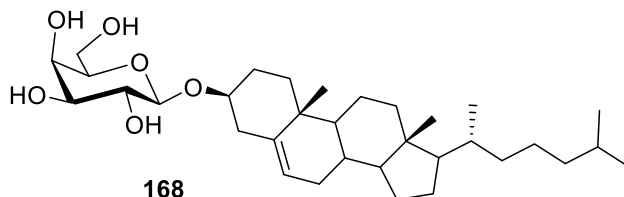
4.4.2.1. Cholesteryl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside (**170**) and cholesteryl 2,3,4,6-tetra-O-acetyl- β -D-galactopyranoside (**171**)



β -D-Galactose pentacetate (**167**)²⁷⁶ (2.00 g, 5.12 mmol) and cholesterol (19.8 g, 51.2 mmol) were dissolved in anhydrous dichloromethane (160 mL), and the mixture was stirred for 30 min with 4 Å molecular sieves at rt under a nitrogen atmosphere. The solution was slowly treated with boron trifluoride diethyl etherate at rt. After the addition was complete, stirring at rt was continued for a further 72 h when TLC confirmed the disappearance of the sugar. The solution was washed with NaHCO₃ (1 M, 30 mL × 3) and water (30 mL × 2), then dried (MgSO₄), filtered, and concentrated. The resulting dry solid was dissolved in anhydrous dichloromethane (100 mL) and dry pyridine (100 mL). Excess acetic anhydride was slowly added and the mixture was stirred under nitrogen for 6 h at rt. The mixture was diluted with dichloromethane (60 mL), poured in ice and stirred for 4 h. The organic layer was separated and washed with NaHCO₃ (1 M, 30 mL × 3), 10% aq. Na₂CO₃ (30 mL × 3), brine (30 mL × 2), water (30 mL), dried (MgSO₄), filtered, and concentrated. The crude solid was then purified using column chromatography (EtOAc/ hexanes, 1: 3). First to elute was the α anomer (**170**) as a colorless crystalline solid (0.29 g, 8%); (EtOAc/ hexanes, 1: 3, R_F 0.32); mp 192 – 194 °C; lit.²⁷⁷ 193 – 195 °C; ¹H and ¹³C NMR spectra similar to lit.²⁶⁰ The second component was the β anomer (**171**) also as a colorless crystalline solid: yield 2.39 g (65%); R_F 0.24 (EtOAc/hexanes,

1: 3); mp 164 - 166 °C; lit.²⁷⁸ 152 - 154 °C; lit.²⁷⁷ 157 - 159 °C; ¹H and ¹³C NMR data similar to lit.^{260,279}

4.4.2.2. Cholesteryl β-D-galactopyranoside (168)

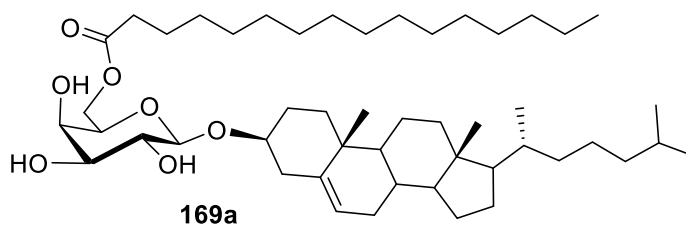


Compound **168** was prepared following a literature procedure²⁸⁰ and was obtained as a colorless solid: mp 271 – 271 °C; lit.²⁷⁸ 265 – 267 °C; ¹H and ¹³C NMR data similar to lit.^{260,279}

4.4.2.3. General regioselective esterification procedure using TBTU

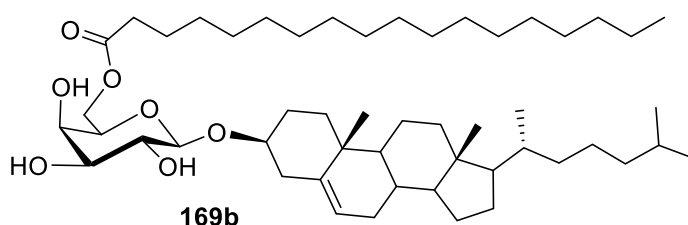
In an oven-dried round-bottomed flask equipped with a magnetic stir bar, an acid (0.722 mmol), TBTU (0.230 g, 0.722 mmol), and diisopropyl ethylamine (DIEA) (0.210 mL) were dissolved in anhydrous pyridine (10 mL) and the resulting mixture was stirred at rt for 30 min. under a nitrogen atmosphere. Cholesteryl β-D-galactopyranoside (**168**) (0.330 g, 0.601 mmol) in pyridine (3 mL) was then injected into the reaction mixture via syringe and stirring was continued at rt for 36 h. Pyridine was removed under vacuum and the resulting solid was purified using column chromatography (hexane/ EtOAc) to give colorless solids.

4.4.2.3.1. Cholesteryl 6-O-palmitoyl-β-D-galactopyranoside (169a)



A colorless solid: R_f 0.15 (hexanes/EtOAc; 1: 2); ^1H NMR (500.13 MHz, CDCl_3) δ 5.35 - 5.36 (m, 1H, H-6 Chol), 4.27 - 4.37 (m, 3H, H-1, H-6a, H-6b), 3.88 (br, 1H, H-4), 3.61 - 3.68 (m, 3H, H-2, H-3, H-5), 3.55 (m, 1H, H-3 Chol), 2.85 (br, 1H, HO-2), 2.68 (br, 1H, HO-3), 2.58 (br, 1H, HO-4), 0.85 - 2.37 (m, 71H, aliphatic FA and Chol), 0.67 (s, 3H, H-18 Chol); ^{13}C NMR data similar to lit.²⁶⁰ HR ESI MS m/z calcd for $\text{C}_{49}\text{H}_{86}\text{NaO}_7$ 809.6266, found 809.6235.

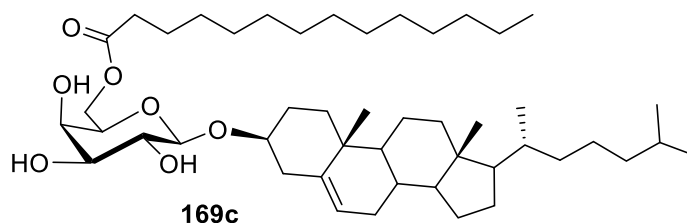
4.4.2.3.2. Cholesteryl 6-*O*-stearoyl- β -D-galactopyranoside (169b)



A colorless solid: R_f 0.29 (hexanes/EtOAc; 1: 3); ^1H NMR (500.13 MHz, CDCl_3) δ 5.32 (br, 1H, H-6 Chol), 4.73 (br, 1H, HO-2), 4.33 - 4.37 (m, 1H, H-6a), 4.32 (br, 1H, HO-3), 4.30 (d, $J = 7.5$ Hz, 1H, H-1), 4.19 - 4.23 (m, 1H, H-6b), 4.04 (br, 1H, HO-4), 3.89 (br, 1H, H-4), 3.59 - 3.68 (m, 3H, H-2, H-3, H-5), 3.51 (m, 1H, H-3 Chol), 2.24 - 2.36 (m, 4H, H-2 FA, H-4a, H-4b Chol), 1.80 - 2.02 (m, 5H, Chol), 0.79 - 1.59 (m, 67H, aliphatic FA and Chol), 0.67 (3H, H-18 Chol); ^{13}C NMR (125.7 MHz, CDCl_3) δ 173.7 (C=O), 140.5 (C-5 Chol), 122.1 (C-6 Chol), 101.9 (C-1), 79.9 (C-3 Chol), 73.6 (C-5), 72.6 (C-3), 71.1 (C-2), 69.0 (C-4), 63.3 (C-6), 56.9 (C-14 Chol), 56.4 (C-17 Chol), 50.3 (C-9 Chol), 42.5 (C-13 Chol), 39.9 (C-4 Chol), 39.7 (C-24 Chol), 39.0 (C-12 Chol), 37.5 (C-10 Chol), 36.8 (C-1 Chol), 36.3 (C-22 Chol), 36.0 (C-20 Chol), 34.4 (C-2 FA), 32.1 (C-7 Chol), 32.0 (C-8 Chol), 30.0 (C-2 Chol), 29.97, 29.9, 29.84, 29.78, 29.7, 29.6, 29.5 (C-4 - C-15 FA), 28.4 (C-25 Chol), 28.1 (C-15 Chol), 25.1 (C-16 Chol), 24.4 (C-3 FA), 24.1 (C-23 Chol), 23.0 (C-27 Chol), 22.8 (C-26 Chol), 22.7 (C-17 FA), 21.2 (C-11 Chol),

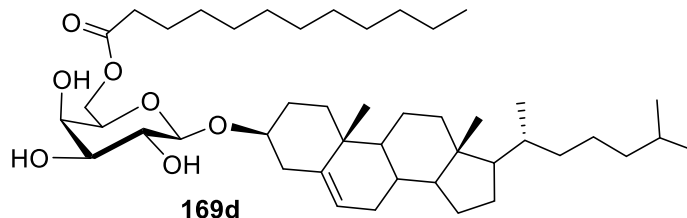
19.5 (C-21 Chol), 18.9 (C-19 Chol), 14.3 (C-18 FA), 12.0 (C-18 Chol). HR ESI MS m/z calcd for $C_{51}H_{90}NaO_7$ 837.6579, found 837. 6598.

4.4.2.3.3. Cholesteryl 6-*O*-myristoyl- β -D-galactopyranoside (169c)



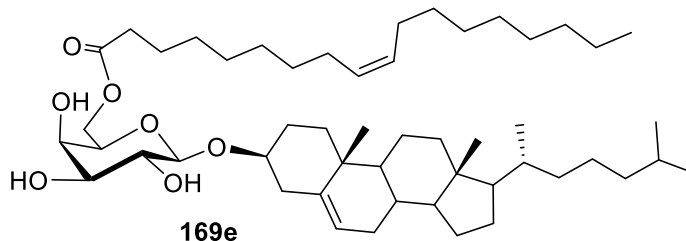
A colorless solid: R_f 0.28 (hexanes/EtOAc; 1: 3); 1H NMR (500.13 MHz, pyridine- d_5) δ 7.07 (br, 1H, HO-2), 6.89 (br, 1H, HO-3), 6.62 (br, 1H, HO-4), 5.34 -5.35 (m, 1H, H-6 Chol), 4.95 (dd, $J_{5,6a} = 7.5$ Hz, $J_{6a,6b} = 11$ Hz, H-6a), 4.87 (d, $J_{1,2} = 8$ Hz, 1H, H-1), 4.70 (dd, $J_{5,6b} = 4.5$ Hz, $J_{6a,6b} = 11$ Hz, 1H, H-6b), 4.39 (t, $J = 9$ Hz, 1H, H-5), 4.35 (d, $J = 2.5$ Hz, 1H, H-4), 4.11 - 4.16 (m, 2H, H-2, H-3), 3.90 (tt, $J = 4.5$ Hz, 11.5 Hz, 1H, H-3 Chol), 2.42 (m, 1H, H-4a Chol), 2.38 (t, $J = 7.5$ Hz, 2H, H-2 FA), 1.71 - 2.03 (m, 6H, Chol), 0.90 - 1.60 (m, 48H, aliphatic FA and Chol), 0.77 - 0.89 (m, 9H, aliphatic FA and Chol), 0.66 (s, 3H, H-18 Chol); ^{13}C NMR (125.7 MHz, pyridine- d_5) δ 173.5 (C=O), 141.0 (C-5 Chol), 121.9 (C-6 Chol), 103.3 (C-1), 78.6 (C-3 Chol), 75.1 (C-5), 73.6 (C-3), 72.3 (C-2), 70.1 (C-4), 64.7 (C-6), 56.9 (C-14 Chol), 56.4 (C-17 Chol), 50.4 (C-9 Chol), 42.5 (C-13 Chol), 40.0 (C-4 Chol), 39.7 (C-24 Chol), 39.4 (C-12 Chol), 37.6 (C-10 Chol), 36.96 (C-1 Chol), 36.5 (C-22 Chol), 36.1 (C-20 Chol), 34.5 (C-2 FA), 32.21, 32.16, 32.1 (3C, C-7, C-8 Chol, C-12 FA), 30.4, 30.1, 30.04, 30.01, 29.99, 29.9, 29.68, 29.66, 29.5 (9C, C-2 Chol, C-4 - C-22 FA), 28.5 (C-25 Chol), 28.2 (C-15 Chol), 25.4 (C-16 Chol), 24.5 (C-3 FA), 24.2 (C-23 Chol), 23.0 (2C, C-26, C-27 Chol), 22.7 (C-13 FA), 21.3 (C-11 Chol), 19.4 (C-21 Chol), 18.9 (C-19 Chol), 14.3 (C-12 FA), 12.0 (C-18 Chol). HR ESI MS m/z calcd for $C_{47}H_{82}NaO_7$ 781.5953, found 781.5929.

4.4.2.3.4. Cholesteryl 6-*O*-lauroyl- β -D-galactopyranoside (169d)



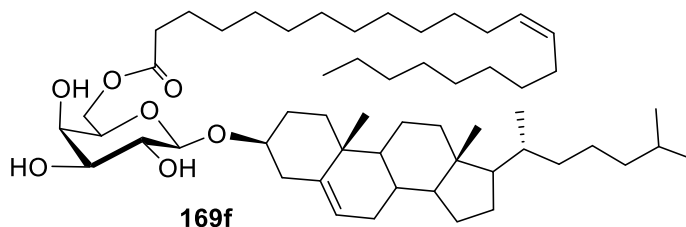
A colorless solid: R_f 0.16 (hexanes/EtOAc; 1: 3); ^1H NMR (500.13 MHz, pyridine- d_5) δ 5.32 - 5.33 (m, 1H, H-6 Chol), 4.91(dd, $J_{5,6a} = 7.5$ Hz, $J_{6a,6b} = 11$ Hz, H-6a), 4.85 (d, $J_{1,2} = 7.5$ Hz, 1H, H-1), 4.64 (dd, $J_{5,6b} = 4.5$ Hz, $J_{6a,6b} = 11.5$ Hz, 1H, H-6b), 4.36 (m, 1H, H-5), 4.35 (br, 1H, H-4), 4.16 (dd, $J_{3,4} = 3$ Hz, $J_{2,3} = 9.5$ Hz, 1H, H-3), 4.10 (dd, $J = 4.5$ Hz, 7 Hz, 1H, H-2), 3.87 (tt, $J = 4.5$ Hz, 11.5 Hz, 1H, H-3 Chol), 2.39 (br, 1H, H-4a Chol), 2.36 (t, $J = 7.5$ Hz, 2H, H-2 FA), 2.14 (d, $J = 12$ Hz, 1H, H-4b Chol), 1.37 - 2.00 (m, 16H, aliphatic FA and Chol), 0.84 - 1.26 (m, 43H, aliphatic FA and Chol), 0.65 (s, 3H, H-18 Chol); ^{13}C NMR (125.7 MHz, pyridine- d_5) δ 173.4 (C=O), 140.9 (C-5 Chol), 121.8 (C-6 Chol), 103.1 (C-1), 78.6 (C-3 Chol), 74.7 (C-5), 73.5 (C-3), 72.2 (C-2), 70.0 (C-4), 64.5 (C-6), 56.8 (C-14 Chol), 56.4 (C-17 Chol), 50.4 (C-9 Chol), 42.5 (C-13 Chol), 40.0 (C-4 Chol), 39.7 (C-24 Chol), 39.2 (C-12 Chol), 37.6 (C-10 Chol), 36.9 (C-1 Chol), 36.4 (C-22 Chol), 36.0 (C-20 Chol), 34.4 (C-2 FA), 32.1, 32.0 (3C, C-7, C-8 Chol, C-10 FA), 30.2, (C-2 Chol), 29.9, 29.8, 29.6, 29.4 (C-4 - C-9 FA), 28.5 (C-25 Chol), 28.2 (C-15 Chol), 25.3 (C-16 Chol), 24.5 (C-3 FA), 24.1 (C-23 Chol), 22.9 (2C, C-26, C-27 Chol), 22.6 (C-11 FA), 21.3 (C-11 Chol), 19.4 (C-21 Chol), 18.9 (C-19 Chol), 14.3 (C-12 FA), 11.9 (C-18 Chol). HR ESI MS m/z calcd for $\text{C}_{45}\text{H}_{78}\text{NaO}_7$ 753.5640, found 753.5626.

4.4.2.3.5. Cholesteryl 6-*O*-oleoyl- β -D-galactopyranoside (169e)



A colorless solid; R_f 0.38 (hexanes/EtOAc; 1: 3); ^1H NMR (500.13 MHz, pyridine- d_5) δ 6.75 (br, 1H, HO-2), 6.30 (br, 1H, HO-3), 5.48 (m, 2H, FA H-9, H-10), 5.37 (m, 1H, H-6 Chol), 4.92 (dd, $J_{5,6a} = 7.5$ Hz, $J_{6a,6b} = 11$ Hz, H-6a), 4.87 (d, $J_{1,2} = 8$ Hz, 1H, H-1), 4.72 (dd, $J_{5,6b} = 4.5$ Hz, $J_{6a,6b} = 11$ Hz, 1H, H-6b), 4.62 (br, 1H, HO-4), 4.37 (t, $J = 9$ Hz, 1H, H-5), 4.35 (d, $J_{3,4} = 3$ Hz, 1H, H-4), 4.11 – 4.15 (m, 2H, H-2, H-3), 3.91 (tt, $J = 6.5$ Hz, 11 Hz, 1H, H-3 Chol), 2.38 – 2.41 (m, 3H), 0.86 – 2.12 (m, 68H, aliphatic FA and Chol), 0.69 (s, 3H, H-18 Chol); ^{13}C NMR data similar to lit.²⁷⁹ HR ESI MS m/z calcd for $\text{C}_{51}\text{H}_{88}\text{NaO}_7$ 835.6422, found 835.6403.

4.4.2.3.6. Cholesteryl 6-*O*-erucoyl- β -D-galactopyranoside (169f)



A colorless solid; R_f 0.29 (hexanes/EtOAc; 1: 2); ^1H NMR (500.13 MHz, CDCl_3) δ 5.31 – 5.37 (m, 3H, H-6 Chol, H-13, H-14 FA), 3.25 – 4.55 (br, 3H, HO-2, HO-3, HO-4), 4.26 – 4.35 (m, 3H, H-1, H-6a, H-6b), 3.88 (s, 1H, H-4), 3.50 – 3.68 (m, 4H, H-2, H-3, H-5 Gal, H-3 Chol), 2.26 – 2.34 (m, 4H, H-2 FA, H-4a, H-4b Chol), 1.88 – 2.08 (m, 7H, Chol), 0.85 - 1.70 (m, 66H, aliphatic FA and Chol), 0.67 (s, 3H, H-18 Chol); ^{13}C NMR (125.7 MHz, CDCl_3) δ 173.8 (C=O), 140.5 (C-5 Chol), 130.1 (C-13 FA), 130.0 (C-14 FA), 122.2 (C-6 Chol), 101.8 (C-1), 79.8 (C-3

Chol), 73.6 (C-5), 72.5 (C-3), 71.4 (C-2), 68.9 (C-4), 63.0 (C-6), 56.9 (C-14 Chol), 56.4 (C-17 Chol), 50.3 (C-9 Chol), 42.5 (C-13 Chol), 39.9 (C-4 Chol), 39.7 (C-24 Chol), 39.0 (C-12 Chol), 37.5 (C-10 Chol), 36.8 (C-1 Chol), 36.3 (C-22 Chol), 36.0 (C-20 Chol), 34.4 (C-2 FA), 32.1 (C-12 FA), 32.0 (C-15 FA), 29.97, 29.9, 29.82, 29.79, 29.7, 29.6, 29.5 (10C, C-2 Chol, C-6 – C-11 FA, C-16 – C-18 FA), 28.2 (C-25 Chol), 27.38 (C-15 Chol), 27.37 (C-16 Chol), 25.1 (C-3 FA), 24.0 (C-23 Chol), 23.0, 22.8 (2C, C-26, C-27 Chol), 22.7 (C-21 FA), 21.2 (C-11 Chol), 19.5 (C-21 Chol), 18.9 (C-19 Chol), 14.3 (C-22 FA), 12.0 (C-18 Chol). HR ESI MS m/z calcd for $C_{55}H_{96}NaO_7$ 891.7048, found 891.7074.

Chapter 5: Direct Synthesis of Maradolipids and Other Trehalose 6-monoesters and 6,6'-diesters

5.1. Introductory Remarks

Primary monoesters and diesters of trehalose (Figure 13) have been of interest since the recognition²⁸¹ that they are important components of the outer membranes of mycobacteria in which the carboxylic acids are mycolic acids, complex long-chain β -hydroxy acids.²⁸²⁻²⁸⁴ They are also of interest for many diverse biological activities.^{283,285,286} Recently, they have been identified as components of the outer membrane of dauer (enduring) larva of the well-known nematode, *Caenorhabditis elegans*.²⁸⁷ This form of larva appears when the nematode is exposed to extremely dry conditions and the altered membrane allows the nematode to survive extreme desiccation.²⁸⁸ The mixture of fatty acids present in the outer membrane, the "maradolipids",²⁸⁷ is extremely complex, with about 38% of the fatty acids being monomethyl branched fatty acids and about 16% containing cyclopropyl groups. The most abundant component is a nonsymmetric 6,6'-trehalose diester, 6-*O*-(13-methylmyristoyl)-6'-*O*-oleoyltrehalose (**176b**).²⁸⁷ The only monomethyl branched fatty acids that have been identified in *C. elegans* are branched next to the terminal carbon, that is, they are iso fatty acids.^{287,289-291} Nevertheless, ante monomethyl branched fatty acids, that is, fatty acids branched on the carbon second from the terminal carbon, are common in nature.²⁹⁰

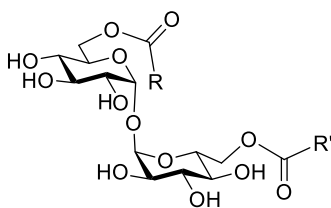


Figure 13 Trehalose 6,6'-diesters

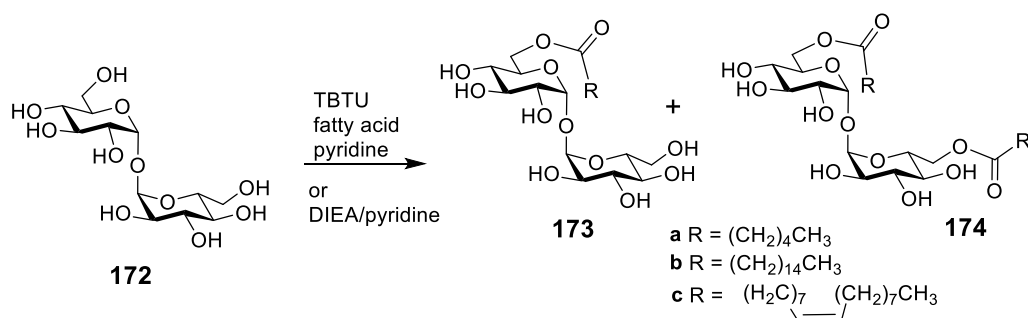
5.2. Trehalose Primary Esters

There has been extensive effort directed at the synthesis of trehalose primary esters.^{283,292,293} Most authors have chosen to use protecting group strategies. One approach has been to use temporary protection of the primary hydroxyls with trityl or *tert*-butyldimethylsilyl or *tert*-butyldiphenylsilyl groups before benzylation, removal of the primary protecting groups and acylation.²⁹⁴⁻³⁰⁰ The discovery³⁰¹ that primary trimethylsilyl groups can be selectively removed by mild aqueous base has led to the extensive use of the 2,2',3,3',4,4'-hexa-*O*-trimethylsilyl derivative for acylation studies.³⁰¹⁻³¹¹ An alternative strategy has been to selectively convert the primary hydroxyls into leaving groups, either sulfonates³¹² or halides,³⁰¹ before introducing acyl groups via S_N2 substitution with carboxylate salts.^{294,295,302} Trehalose has also been monoesterified at O-6 enzymically using a variety of vinyl fatty acid esters in dimethyl formamide by a protease from *Bacillus subtilis* in good yields.³¹³ Very recently, the major trehalose diester (**176b**) has been synthesized chemoenzymatically using vinyl esters as acyl donors, and using the commercially available Alcalase from *Bacillus licheniformis* to do the initial monoacylation in 18 days with vinyl oleate, then performing the second acylation under Mitsunobu conditions.³¹⁴ Protecting-group-free strategies are inherently attractive but few have been disclosed to this point. Transesterification gave quite low yields.^{285,315} Tributylstannylation gave moderate yields only when the conditions using the toxic tributylstannyl ethers were carefully optimized.³¹⁶ Mitsunobu reactions are more attractive but again the yields are in the 50 to 60% range and the best solvent is toxic hexamethylphosphoramide.^{317,318} The following section discusses the protecting-group-free synthesis of 6-monoesters and 6,6'-diesters of trehalose using the primary-selective acylation procedure which was discussed in Chapter 3.²⁷⁵

5.3. Synthesis of Trehalose 6-monoesters and 6,6'-diesters

The conditions developed for the regioselective acylation of primary alcohols in the presence of secondary alcohols involved reaction of the diol or polyol with the carboxylic acid in *N,N*-dimethylformamide (DMF) with at least 2 equiv of diisopropylethylamine (DIEA) and 1.2 equiv of TBTU (Chapter 3). Trehalose is relatively insoluble in DMF but it was found that pyridine was a good solvent for this reaction as it was for the selective acylation of galactosides in Chapter 4.³¹⁹ Reaction of trehalose (**172**) with a slight excess of the fatty acid at room temperature gave good yields (65-69%) of the 6-*O*-monoacylated products as pictured in Scheme 50 and shown in entries 1, 5 and 9 of Table 14. Under these conditions, small amounts of the 6,6'-di-*O*-acylated products were also obtained, consistent with the first substitution having little effect on the reactivity of the second primary hydroxyl group. The long chains of the fatty acids caused these reactions to be considerably slower than the corresponding reactions with simple acids, such as benzoic acid, and longer reaction times were required to achieve complete reaction of the fatty acids. As noted in the reactions with galactose derivatives (Chapter 4)³¹⁹ the added base was unnecessary if the solvent is pyridine (compare entries 1, 5, and 9 in Table 14), consistent with the role of the base in the reactions of primary alcohols being to accept protons released from the initial reaction of the acid with the uronium salt (TBTU) and from the addition of the alcohol to the active ester. Use of two or more equivalents of fatty acids gives reasonable yields of the 6,6-di-*O*-acyl products (see entries 2, 3, 7, and 10 in Table 14). Neither increasing the relative amount of fatty acid beyond 2.1 equiv nor raising the reaction temperature improved the yields of the disubstituted products. Instead, additional products were obtained of which the 2,6,6'-triester (Figure 14) was the most prominent, isolated in 20% yield from the reaction of trehalose with 3.5 equiv of hexanoic acid for 48 h and in 40% yield from the reaction with 5

equiv of oleic acid for 168 h. No products of esterification on secondary oxygen atoms have previously been observed in reactions of this type with monosaccharides. Perhaps the hydroxyl group at O-2 of trehalose is more acidic than hydroxyls of monosaccharides because the anomeric oxygen is more electron withdrawing in a non-reducing disaccharide.



Scheme 50 Synthesis of trehalose 6-monoesters and 6,6'-diesters

Table 14 Conditions and outcomes for the reactions of trehalose (**172**) with fatty acids

| entry | fatty acid (equiv) | TBTU (equiv) | DIEA (equiv) | time (h) | temp | product, yield (%) | |
|-------|--------------------|--------------|--------------|----------|-------|--------------------|-------------------------------|
| | | | | | | 6-mono | 6,6'-di |
| 1 | hexanoic (1.1) | 1.1 | 2.1 | 36 | rt | 173a , 69 | 174a , 14 |
| 2 | hexanoic (2.1) | 2.1 | 2.1 | 36 | rt | 173a , 20 | 174a , 63 |
| 3 | hexanoic (2.1) | 2.1 | 0 | 36 | rt | 173a , 19 | 174a , 63 |
| 4 | hexanoic (3.5) | 3.5 | 3.5 | 48 | rt | 173a , 10 | 174a , 48 ^a |
| 5 | palmitic (1.1) | 1.1 | 0 | 72 | rt | 173b , 67 | 174b , 14 |
| 6 | palmitic (1.1) | 1.1 | 2.1 | 48 | 40 °C | 173b , 37 | 174b , 32 |
| 7 | palmitic (2.1) | 2.1 | 0 | 72 | rt | 173b , 16 | 174b , 66 |
| 8 | palmitic (2.2) | 2.2 | 0 | 168 | rt | 173b , 18 | 174b , 69 |
| 9 | oleic (1.1) | 1.1 | 0 | 60 | rt | 173c , 65 | 174c , 15 |

| | | | | | | | |
|----|-------------|-----|---|-----|----|------------------|-------------------------------|
| 10 | oleic (2.1) | 2.1 | 0 | 72 | rt | 173c , 18 | 174c , 66 |
| 11 | oleic (2.2) | 2.2 | 0 | 192 | rt | 173c , 22 | 174c , 70 |
| 12 | oleic (3.5) | 3.5 | 0 | 60 | rt | 173c , 19 | 174c , 66 |
| 13 | oleic (5.0) | 5.0 | 0 | 168 | rt | 173c , 0 | 174c , 48 ^a |

^a Plus the 2,6,6'-triester in the yield given in the experimental section.

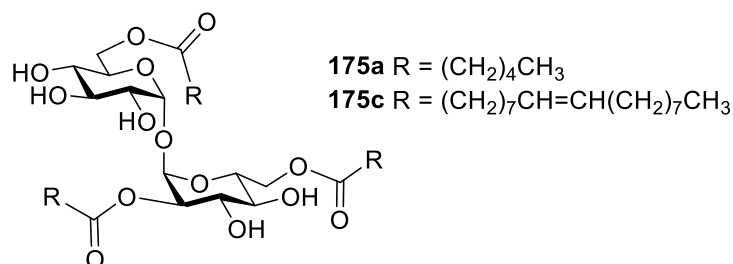
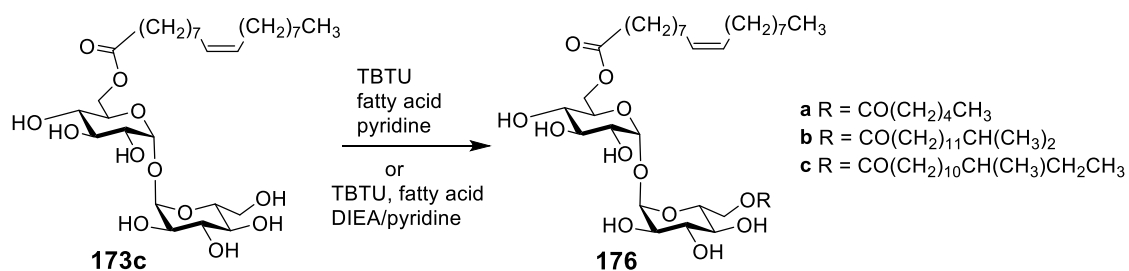


Figure 14 Structure of triester products (**175**)

The most abundant component in the maradolipid mixture is 6-*O*-(13-methylmyristoyl)-6'-*O*-oleoyltrehalose (**176b**).²⁸⁷ It was found that unsymmetrical derivatives of this type could be synthesized in good yields by reacting the monooleoyl derivative **173c** with 1.1 equiv of the fatty acid for extended reaction times at room temperature (see Scheme 51 and entries 4 and 6 of Table 15). Branched fatty acids such as 13-methylmyristic acid are available commercially from specialized companies at great expense for the amounts necessary for synthetic purposes but here this acid was synthesized using the method of Foglia and Vail.³²⁰ Compound **176b** (maradolipid) had been synthesized twice previously in five-step routes using TMS ethers as temporary protecting groups.^{309,310}



Scheme 51 Synthesis of nonsymmetric trehalose 6,6'-diesters

The ante derivative 6-*O*-(12-methyltetradecanoyl)-6'-*O*-oleoyltrehalose (**176c**) was prepared in the same way (see Scheme 51) from **173c** and 12-methylmyristic acid. This fatty acid was prepared in racemic form using a Wittig reaction of the Wittig reagent derived from 11-bromoundecanoic acid with 2-butanone followed by hydrogenation as previously described.³²¹ Compound **176c** had never been synthesized previously and provides a sample for examining whether such compounds are part of the complex maradolipid mixture.

Table 15 Conditions and outcomes for the reactions of 6-*O*-oleoyltrehalose with fatty acids

| Entry | fatty acid (equiv) | TBTU (equiv) | time (h) | temp | yield (%) |
|-------|------------------------------|--------------|----------|------|-----------------|
| 1 | hexanoic (1.1) | 1.1 | 72 | rt | 59 ^a |
| 2 | 13-methyltetradecanoic (1.1) | 1.1 | 72 | rt | 62 ^b |
| 3 | 13-methyltetradecanoic (1.1) | 1.1 | 120 | rt | 72 ^c |
| 4 | 13-methyltetradecanoic (1.1) | 1.1 | 170 | rt | 81 |
| 5 | 12-methyltetradecanoic (1.1) | 1.1 | 72 | rt | 54 ^d |
| 6 | 12-methyltetradecanoic (1.1) | 1.1 | 170 | rt | 79 |

^aPlus 26% of **173c** also isolated. ^bPlus 22% of **173c**. ^cPlus 10% of **173c**. ^dPlus 27% of **173c**.

5.4. Conformational Analysis

It was also of interest to determine whether the diverse biological activities of these compounds is influenced by alteration of the populations of the rotameric conformations adopted by the hydroxymethyl groups of trehalose caused by the interactions of the hydrophobic fatty acid alkyl groups. Trehalose itself adopts a conformation with both anomeric linkages adopting normal exo-anomeric conformations both in the solid state³²²⁻³²⁴ and in solution.³²⁵⁻³²⁷ Hydroxymethyl rotameric populations have been discussed extensively³²⁸⁻³³¹ and have been determined carefully for glucose derivatives by making use of all H,H and C,H coupling constants of isotopically enriched derivatives.³³²⁻³³⁴ 4,6-Unsubstituted derivatives slightly prefer the *gt* conformer over the *gg* conformer with the *tg* conformer having a population of about 10% or slightly less.³³¹⁻³³⁴ Barnett and Naidoo suggest that the preference for the *gt* conformer is due to direct and water-mediated hydrogen bonds between the O6 hydroxyl hydrogen and O5.³³⁰ In the solid state, trehalose and its dihydrate are present in conformations where the two hydroxymethyl groups each adopt one of the two rotamers populated in solution, the *gg* and *gt* rotamers, giving rise to ¹³C CP/ MAS spectra with one signal for each of the 12 carbon atoms. H5-H6 vicinal coupling constants were determined for the three monoesters (**173**), the three symmetrical diesters (**174**), and the two 2,6,6'-triesters (**175**) making the reasonable (all $\Delta\nu/J > 6$) assumption that the coupling patterns were first order. The values obtained are reported in Table 16. The hydroxymethyl groups can adopt three energy minima conformers, termed the *gg*, *gt*, and *tg* rotamers, according to whether O5 and C4, respectively, are *gauche* or *trans* to O6. The coupling constants for the C6 protons were used to calculate rotameric populations using the values of the coupling constants for each rotamer calculated by Stennutz *et al.*³³² Fractional

rotameric populations ρ_{gg} , ρ_{gt} , ρ_{tg} , were obtained by solving the following three linear equations:

$$J_{5,6R} = \rho_{gg} (0.8) + \rho_{gt} (9.9) + \rho_{tg} (4.5). \quad J_{5,6S} = \rho_{gg} (1.3) + \rho_{gt} (1.5) + \rho_{tg} (10.8). \quad \rho_{gg} + \rho_{gt} + \rho_{tg} = 1.$$

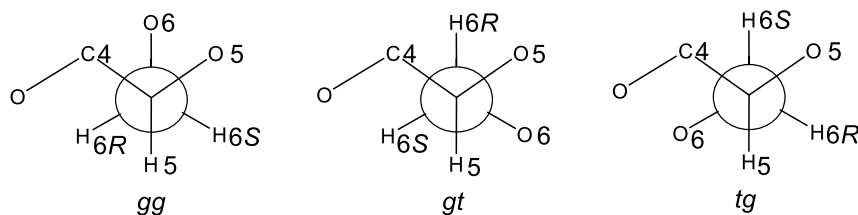


Figure 15 Newman projection from C5 to C6 illustrating the three rotamers and atom labeling

Table 16 Three-bond coupling constants observed for C6 protons (CD₃OD, 22 °C)

| Compound | $^3J_{5,6R}$ (Hz) | $^3J_{5,6S}$ (Hz) | $^3J_{5',6R}$ (Hz) | $^3J_{5',6S}$ (Hz) |
|-------------|-------------------|-------------------|--------------------|--------------------|
| 173a | 4.98 | 2.01 | 5.31 | 1.87 |
| 173b | 5.08 | 2.00 | 5.53 | 2.04 |
| 173c | 5.05 | 2.06 | 5.48 | 2.16 |
| 174a | 5.20 | 2.11 | 5.20 | 2.11 |
| 174b | 5.29 | 2.05 | 5.29 | 2.05 |
| 174c | 5.28 | 2.11 | 5.28 | 2.11 |
| 175a | 4.96 | 2.09 | 7.43 | 2.07 |
| 175c | 4.87 | 2.07 | 7.90 | 1.89 |

The percentage populations for each rotamer are listed in Table 17. The percentage populations for the monoesters and diesters are similar to those obtained for glucose previously^{331,332} although the relative amounts of the *gg* rotamer appears to have increased slightly at the expense of the *gt* conformer. This is consistent with loss of the stabilizing effect for the *gt* isomer rotamer of direct and hydroxylic solvent mediated hydrogen bonds between the

O6 hydroxyl hydrogen and O5.³³⁰ Therefore, aggregation of the long lipophilic groups on O6 does not appear to influence the rotameric populations for the hydroxymethyl groups of these two classes of compounds significantly.

Table 17 Percentage population of rotamers (CD₃OD, 22 °C)

| Compound | % <i>gt</i> for C5C6 bond | % <i>gg</i> for C5C6 bond | % <i>tg</i> for C5C6 bond | % <i>gt</i> for C5'C6' bond | % <i>gg</i> for C5'C6' bond | % <i>tg</i> for C5'C6' bond |
|-------------|---------------------------------|------------------------------|------------------------------|--------------------------------|--------------------------------|--------------------------------|
| 173a | 43 | 50 | 6.6 | 48 | 47 | 5.0 |
| 173b | 45 | 49 | 6.4 | 41 | 52 | 6.9 |
| 173c | 44 | 49 | 7.1 | 48 | 44 | 8.4 |
| 174a | 45 | 47 | 7.6 | 45 | 47 | 7.6 |
| 174b | 47 | 47 | 6.9 | 47 | 47 | 6.9 |
| 174c | 46 | 46 | 7.6 | 46 | 46 | 7.6 |
| 175a | 43 | 50 | 7.4 | 70 | 23 | 6.6 |
| 175c | 42 | 51 | 7.4 | 76 | 19 | 4.6 |

In contrast, for the 2,6,6'-triesters, the two sets of H5,H6 coupling constants were different; the set for the disubstituted glucose unit was similar to those observed for the mono and diesters but for the monosubstituted glucose residue, the $J_{5,6R}$ value was between 2.2 and 2.7 Hz bigger than those observed for all other residues. For this residue, the *gt* conformer was calculated to be more favored, to the extent of 70 and 76% of the rotamers for **175a** and **175c**, respectively, mostly at the expense of the *gg* conformer. This change is probably caused by

intramolecular van der Waals interactions between the long chains of the 6'-ester and the 2-ester, favoring the rotamer where the C6' ester is turned toward the disubstituted glucose residue, as illustrated in Figure 16.

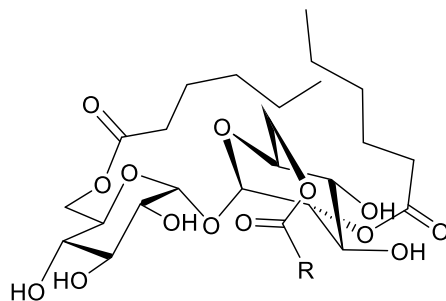


Figure 16 A conformation illustrating how adopting the *gt* conformation for C5-C6 bond in the monosubstituted glucose ring allows van der Waals between the long chains of the 6'-ester and the 2-ester

5.5. Concluding Remarks

The regioselective esterification of primary hydroxyls promoted by TBTU is an excellent way for the direct synthesis of trehalose 6-monoesters, and other trehalose 6,6'-diesters. One equiv of fatty acid provides 6-*O*-monoesters in one step in good yields (~70%) accompanied by small amounts of the diprimary ester; two equiv provides symmetrical 6,6'-diesters in fair yields. In comparison, enzymatic esterification using commercially available protease from *Bacillus subtilis* gave the monopalmitate **173b** in 84% yield and the monooleoate **173c** in 55% yield after 12 days. Other protecting-group-free chemical transformations give monoesters in lower yields, of which, the Mitsunobu reaction is most efficient (47 - 61%). The monoesters can be again be monoesterified in the same way to provide non-symmetric 6,6'-*O*-diesters in two steps from trehalose in very good yields. This method allows expeditious synthesis of any desired structure. Compounds synthesized include the most abundant component of the very complex

maradolipid mixture, 6-*O*-(13-methyltetradecanoyl)-6'-*O*-oleoyltrehalose, and a component potentially present in this mixture, 6-*O*-(12-methyltetradecanoyl)-6'-*O*-oleoyltrehalose, a derivative of an ante fatty acid. The C5-C6 rotameric populations of 6-*O*-monoesters, symmetrical 6,6'-diesters, and 2,6,6'-triesters of fatty acids were calculated from the values of the H5-H6*R* and H5-H6*S* coupling constants and found to be similar to those found for glucose. The rotameric population of the monosubstituted glucose residue was altered considerably in the 2,6,6'-triesters to favor the *gt* rotamer, presumably because of attraction between the 2- and 6'-fatty acid chains.

5.6. Experimental Section

5.6.1. General

¹H and ¹³C NMR spectra were recorded on a Bruker Avance-500 MHz NMR spectrometer operating at 500.13 and 125.7 MHz respectively using the solvent resonances as secondary chemical shift references. The carbon and hydrogen atoms were assigned following analysis of their one dimensional (¹H, ¹³C) and two dimensional (COSY, HSQC, HMBC, and TOCSY) NMR spectral data. Coupling constant (*J*) values are reported in Hertz. High-resolution mass spectra were recorded using electrospray ionization with a time of flight mass analyzer. Melting points are uncorrected. *N,N*-Diisopropylethylamine (DIEA) was refluxed over calcium hydride and distilled onto molecular sieves. All non-aqueous reactions were performed under a nitrogen atmosphere. Pyridine was refluxed over potassium hydroxide and distilled onto molecular sieves. Compounds were visualized/ located by spraying the TLC plate with a solution of 5 % H₂SO₄ in ethanol followed by heating on a hot plate until color developed.

5.6.2. Synthesis

5.6.2.1. General esterification procedure using TBTU

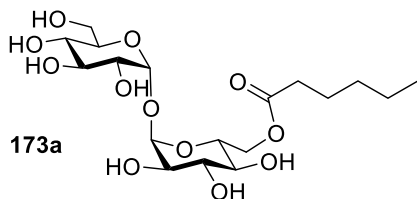
A. Use of trehalose (172)

In an oven-dried round-bottomed flask equipped with a magnetic stir bar, a fatty acid (number of equiv given in Table 5.1) and TBTU (number of equiv given in Table 5.1) were dissolved in anhydrous pyridine (5 mL) and the resulting mixture was stirred at rt for 30 min under a nitrogen atmosphere. A solution of trehalose (amount used listed with the individual products) in dry pyridine (3 mL) was then injected into the reaction mixture via syringe and stirring was continued at rt for a time given in Table 5.1. Pyridine was removed under vacuum and the resulting residue was purified using silica gel column chromatography with elution using a solvent gradient of 5 - 25% methanol in EtOAc - DCM (1:1).

B. Use of 6-*O*-oleoyl- α,α -trehalose (173c)

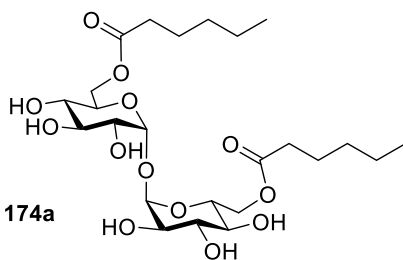
In an oven-dried round-bottomed flask equipped with a magnetic stir bar, a fatty acid (1.1 equiv) and TBTU (1.1 equiv) were dissolved in anhydrous pyridine (5 mL), and the resulting mixture was stirred at rt for 30 min under a nitrogen atmosphere. 6-*O*-Oleoyl- α,α -trehalose (173c) (amount used given with individual products) in dry pyridine (3 mL) was then injected into the reaction mixture via syringe and stirring was continued at rt for the time given in Table 5.2. Pyridine was removed under vacuum and the resulting residue was dissolved in EtOAc-THF (3:1, 20 mL). After washing the mixture using saturated aq. NaHCO₃ (2 x 3 mL), the organic layer was collected, dried (MgSO₄), filtered and concentrated to give a crude product, which was purified using silica gel column chromatography with elution using a gradient of 5 - 25% methanol in EtOAc - DCM (1:1).

5.6.2.1.1. 6-*O*-Hexanoyl- α,α -trehalose (173a)



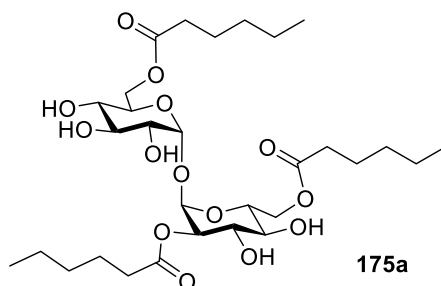
The title compound was synthesized using procedure A above with trehalose (1) (200 mg, 0.58 mmol) and hexanoic acid under conditions listed in Table 5.1, entry 1 and was obtained as a colorless solid (178 mg, 69% yield): R_F 0.20 [25% MeOH in EtOAc-DCM(1:1), v/v], mp 136 – 138 °C, lit³⁰⁰ mp 135-137 °C; ^1H NMR (500.13 MHz, CD_3OD) δ 0.91 (t, 3H, $J = 7.0$ Hz, Me), 1.28 - 1.36 (m, 4H, 2 x CH_2), 1.61 (m, 2H, CH_2CH_3), 2.33 (t, 2H, $J = 7.5$ Hz, CH_2CO), 3.34 - 3.38 (m, 2H, H-4, H-4'), 3.49 (dd, 2H, $J = 3.9, 7.9$ Hz, H-2, H-2'), 3.67 (dd, 1H, $J = 5.2, 11.7$ Hz, H-6'R), 3.79 - 3.83 (m, 4H, H-3, H-3', H-6', H-5'), 4.02 (ddd, 1H, $J_{4,5} = 10.1$ Hz, $J_{5,6R} = 5.2$ Hz, $J_{5,6S} = 2.1$ Hz, H-5), 4.20 (dd, 1H, $J = 5.2, 11.9$ Hz, H-6R), 4.38 (dd, 1H, $J = 2, 11.9$ Hz, H-6S), 5.08 (d, 1H, $J = 3.8$ Hz, H-1'), 5.10 (d, 1H, $J = 3.7$ Hz, H-1); ^{13}C NMR (125.7 MHz, CD_3OD) δ 175.6 (C=O), 95.3, 95.2 (C-1, C-1'), 74.8, 74.6, 74.0, 73.33 (C-2, C-2', C-3, C-3'), 73.3, 72.0, 71.6 (C-4, C-4', C-5, C-5'), 64.5, 62.7 (C-6, C-6'), 35.1, 32.6 (COCH_2 , COCH_2CH_2), 32.5, 26.0 (hexanoyl CH_2), 23.6 (CH_2CH_3), 14.4 (Me). HR ESI MS m/z calcd for $\text{C}_{18}\text{H}_{32}\text{NaO}_{12}$ 463.1786, found 463.1764. In addition, compound **174a** (44 mg, 14% yield) was obtained.

5.6.2.1.2. 6,6'-*Di-O*-hexanoyl- α,α -trehalose (174a)



The title compound was synthesized using procedure A above with trehalose (200 mg, 0.58 mmol) and hexanoic acid under conditions listed in Table 5.1, entry 2 and was obtained as a colorless solid (198 mg, 63% yield): R_F 0.40 [20% MeOH in EtOAc-DCM(1:1), v/v], mp = 157 - 160 °C, lit³⁰⁰ mp 157.7 - 159.0 °C; ¹H NMR (500.13 MHz, CD₃OD) δ 0.91 (t, J = 6 Hz, 6H, 2 x Me), 1.30 - 1.37 (m, 8H, 4 x CH₂), 1.62 (m, 4H, CH₂CH₃), 2.34 (t, 4H, J = 7 Hz, CH₂CO), 3.33 (dd, 2H, J = 9, 10 Hz, H-4, H-4'), 3.47 (dd, 2H, J = 3.7, 9.7 Hz, H-2, H-2'), 3.77 (dd, 2H, J = 9.1, 9.6 Hz, H-3, H-3'), 4.01 (ddd, 2H, $J_{4,5}$ = 10.0 Hz, $J_{5,6R}$ = 5.2 Hz, $J_{5,6S}$ = 2.1 Hz, H-5, H-5'), 4.19 (dd, 2H, J = 5.2, 11.9 Hz, H-6R), 4.35 (dd, 2H, J = 2.1, 11.9 Hz, H-6S), 5.03 (d, 2H, J = 3.7 Hz, H-1', H-1); ¹³C NMR (125.7 MHz, CD₃OD) δ 175.5 (C=O), 95.3 (C-1, C-1'), 74.5, 73.1 (C-2, C-2'), C-3, C-3'), 71.9, 71.5 (C-4, C-4', C-5, C-5'), 64.4 (C-6, C-6'), 35.0, 32.4 (COCH₂, COCH₂CH₂), 25.8 (hexanoyl CH₂), 23.4 (CH₂CH₃), 14.3 (Me). HR ESI MS m/z calcd for C₂₄H₄₂NaO₁₃ 561.2518, found 561.2517. In addition, compound **173a** (49 mg, 20% yield) was obtained.

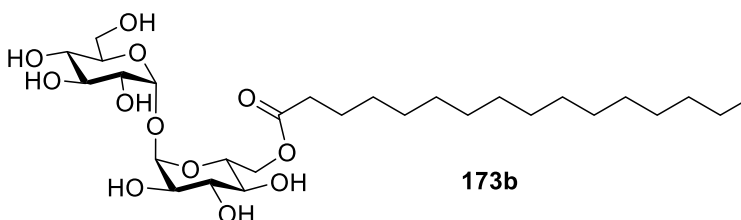
5.6.2.1.3. 2,6,6'-Tri-*O*-hexanoyl- α,α -trehalose (**175a**)



Following procedure A above using trehalose (325 mg, 0.95 mmol) with hexanoic acid (386 mg, 3.32 mmol, 3.5 equiv) as in Table 5.1 entry 4, the reaction gave compounds **173a** and **174a** as listed in Table 5.1 plus the title compound as a colorless syrup (119 mg, 20% yield): R_F 0.60 [5% MeOH in EtOAc-DCM (1:1), v/v]; ¹H NMR (500.13 MHz, CD₃OD) δ 0.91 (t, 9H, J =

6.0 Hz, 3 x Me), 1.30 - 1.39 (m, 12H, 6 x CH₂), 1.59-1.63 (m, 6H, CH₂CH₃), 1.95-2.45 (m, 6H, CH₂CO), 3.27 (dd, 1H, *J* = 9.0, 10 Hz, H-4'), 3.43 (dd, 1H, *J* = 9.1, 10 Hz, H-4), 3.47 (dd, 1H, *J* = 3.8, 9.8 Hz, H-2'), 3.69 (t, 1H, *J* = 9.0 Hz, H-3'), 3.77 (ddd, 1H, *J*_{4',5'} = 9.6 Hz, *J*_{5',6'R} = 7.2 Hz, *J*_{5',6'S} = 2.0 Hz, H-5'), 3.99 (t, 1H, *J* = 9.1 Hz, H-3), 4.04 (ddd, 1H, *J*_{4,5} = 7.0 Hz, *J*_{5,6R} = 4.9 Hz, *J*_{5,6S} = 2.0 Hz, H-5), 4.16 (dd, 1H, *J* = 7.0, 11.9 Hz, H-6'R), 4.23 (dd, 1H, *J* = 5, 12 Hz, H-6R), 4.29 (dd, 1H, *J* = 2 Hz, 11.8 Hz, H-6'S), 4.39 (dd, 1H, *J* = 2, Hz, 12 Hz, H-6S), 4.70 (dd, 1H, *J* = 3.6, 10 Hz, H-2), 5.02 (d, 1H, *J* = 3.7 Hz, H-1'), 5.18 (d, 1H, *J* = 3.6 Hz, H-1); ¹³C NMR (125.7 MHz, CD₃OD) δ 175.52, 175.44, 174.8 (C=O), 95.3, 92.6 (C-1, C-1'), 74.8, 74.2, 73.0, 72.94 (C-2, C-2', C-3, C-3'), 72.09, 72.04, 71.9, 71.6 (C-4, C-4', C-5, C-5'), 64.9, 64.2 (C-6, C-6'), 39.0, 35.1, 35.0, 34.96, 32.55, 32.52 (COCH₂, COCH₂CH₂), 25.9, 25.8, 25.76, 25.73, 25.66 (hexanoyl CH₂), 23.5 (CH₂CH₃), 14.5 (Me). HR ESI MS *m/z* calcd for C₃₀H₅₂NaO₁₄ 659.3249, found 659.3240.

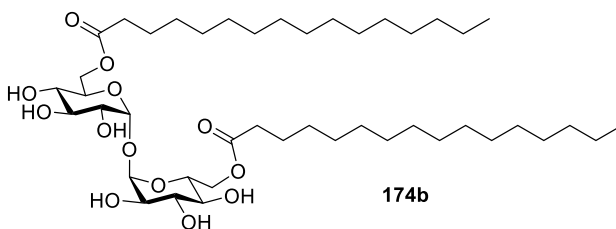
5.6.2.1.4. 6-*O*-Palmitoyl- α,α -trehalose (173b)



The title compound was synthesized using procedure A above with trehalose (300 mg, 0.87 mmol) and palmitic acid under conditions listed in Table 5.1, entry 5 and was obtained as a colorless solid (341 mg, 67% yield): *R*_F 0.33 [20% MeOH in EtOAc-DCM (1:1)], mp 156 - 159 °C, lit³³⁵ mp 114 - 116 °C; ¹H NMR (500.13 MHz, CD₃OD) δ 0.90 (t, 3H, *J* = 6.0 Hz, Me), 1.29 - 1.37 (m, 24H, 12 x CH₂), 1.62 (m, 2H, CH₂CH₃), 2.34 (t, 2H, *J* = 7.2 Hz, CH₂CO), 3.30 - 3.33 (m, 2H, H-4, H-4'), 3.46, 3.47 (2 overlapping dd, 2H, *J*_{1,2} = 4.0 Hz, *J*_{2,3} = 9 Hz, H-2, H-2'), 3.67

(dd, 1H, $J = 5.7, 12.1$ Hz, H-6'R), 3.76 - 3.83 (m, 4H, H-3, H-3', H-6', H-5'), 4.01 (ddd, 1H, $J_{4,5} = 10.1$ Hz, $J_{5,6R} = 5.1$ Hz, $J_{5,6S} = 2.0$ Hz, H-5), 4.19 (dd, 1H, $J = 5.1, 11.9$ Hz, H-6R), 4.35 (dd, 1H, $J = 2, 11.9$ Hz, H-6S), 5.07 (d, 1H, $J = 3.7$ Hz, H-1'), 5.10 (d, 1H, $J = 3.7$ Hz, H-1); ^{13}C NMR (125.7 MHz, CD_3OD) δ 175.6 (C=O), 95.4, 95.3 (C-1, C-1'), 74.8, 74.6, 74.1, 73.2 (C-2, C-2', C-3, C-3'), 73.4, 72.1, 71.6 (C-4, C-4', C-5, C-5'), 64.5, 62.8 (C-6, C-6'), 35.2 (COCH_2 , COCH_2CH_2), 33.2, 30.9, 30.8, 30.6, 30.6, 30.4, 26.0 (palmitoyl CH_2), 23.9 (CH_2CH_3), 14.6 (Me). HR ESI MS m/z calcd for $\text{C}_{28}\text{H}_{52}\text{NaO}_{12}$ 603.3351, found 603.3335. In addition, compound **174b** (71 mg, 14% yield) was obtained.

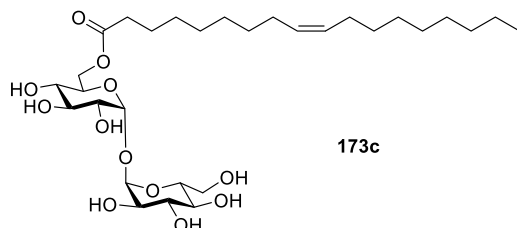
5.6.2.1.5. 6,6'-Di-*O*-palmitoyl- α,α -trehalose (**174b**)



The title compound was synthesized using procedure A above with trehalose (300 mg, 0.87 mmol) and palmitic acid under conditions listed in Table 5.1, entry 7 and was obtained as a gummy solid (480 mg, 66% yield): R_f 0.62 [20% MeOH in EtOAc-DCM (1:1), v/v]; ^1H NMR (500.13 MHz, CD_3OD) δ 0.90 (t, 6H, $J = 6.0$ Hz, 2 x Me), 1.26 - 1.39 (m, 48H, 24 x CH_2), 1.61 (m, 4H, CH_2CH_3), 2.34 (t, 4H, $J = 7.2$ Hz, CH_2CO), 3.30 - 3.34 (m, 2H, H-4, H-4'), 3.47 (dd, 2H, $J = 3.7, 9.7$ Hz, H-2, H-2'), 3.77 (t, 2H, $J = 9.3$ Hz, H-3, H-3'), 4.02 (ddd, 2H, $J_{4,5} = 10.0$ Hz, $J_{5,6R} = 5.3$ Hz, $J_{5,6S} = 2.1$ Hz, H-5, H-5'), 4.19 (dd, 2H, $J = 5.3, 11.9$ Hz, H-6R, H-6'R), 4.35 (dd, 2H, $J = 2.1, 11.9$ Hz, H-6S, H-6'S), 5.04 (d, 2H, $J = 3.7$ Hz, H-1, H-1'); ^{13}C NMR (125.7 MHz, CD_3OD) δ 175.5 (C=O), 95.4 (C-1, C-1'), 74.7, 73.3 (C-2, C-2', C-3, C-3'), 72.1, 71.7 (C-4, C-4', C-5, C-5'), 64.6 (C-6, C-6'), 35.2, 33.2 (COCH_2 , COCH_2CH_2), 30.96, 30.93, 30.8, 30.6, 30.6,

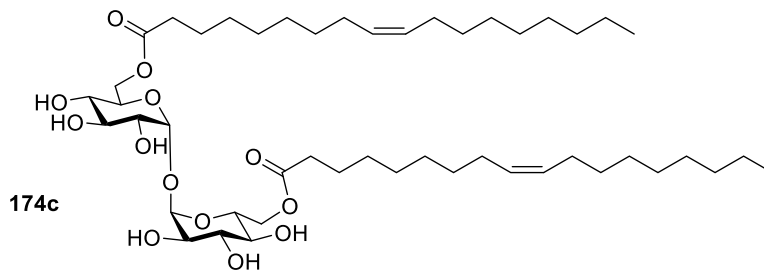
30.4, 26.2 (palmitoyl CH₂), 23.9 (CH₂CH₃), 14.6 (Me). HR ESI MS *m/z* calcd for C₄₄H₈₂NaO₁₃ 841.5648, found 841.5648. In addition, compound **173b** (82.0 mg, 16% yield) was obtained.

5.6.2.1.6. 6-*O*-Oleoyl- α,α -trehalose (**173c**)



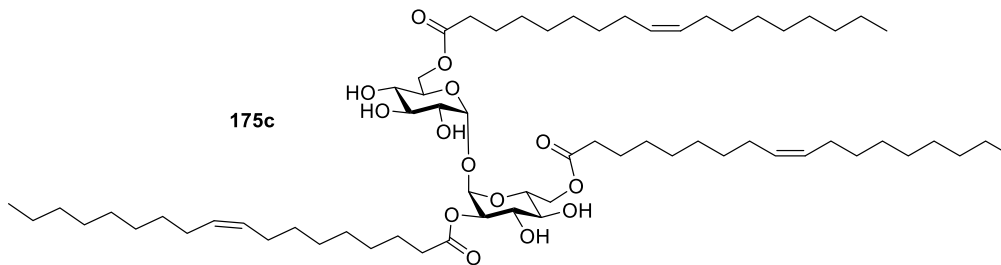
The title compound was synthesized using procedure A above with trehalose (300 mg, 0.87 mmol) and oleic acid under conditions listed in Table 5.1, entry 9 and was obtained as a colorless solid (346 mg, 65% yield): *R_F* 0.37 [20 % MeOH in EtOAc-DCM (1:1), v/v], mp become transparent at 120 - 130 °C, melted at 166 - 168 °C (lit³¹³ mp 165 - 167 °C); ¹H NMR (500.13 MHz, CD₃OD) δ 0.90 (t, 3H, *J* = 6.5 Hz, Me), 1.25 - 1.40 (m, 20H, 10 x CH₂), 1.45 - 1.61 (m, 2H, CH₂CH₃), 2.02 - 2.04 (m, 4H, 2 x CH₂CHCH), 2.34 (t, 2H, *J* = 7.0 Hz, CH₂CO), 3.30 - 3.32 (m, 2H, H-4, H-4'), 3.46, 3.47 (2 overlapping dd, 2H, *J*_{1,2} = 3.9 Hz, *J*_{2,3} = 8.8 Hz, *J*_{1',2'} = 4.0 Hz, *J*_{2',3'} = 9.2 Hz, H-2, H-2'), 3.67 (dd, 1H, *J* = 5.5, 12.1 Hz, H-6'R), 3.76 - 3.85 (m, 4H, H-3, H-3', H-6S', H-5'), 4.02 (ddd, 1H, *J*_{4,5} = 10.1 Hz, *J*_{5,6} = 5.1 Hz, *J*_{5,6} = 2.1 Hz, H-5), 4.20 (dd, 1H, *J* = 5.1, 11.9 Hz, H-6R), 4.36 (dd, 1H, *J* = 2.1, 11.9 Hz, H-6S), 5.07 (d, 1H, *J* = 3.7 Hz, H-1'), 5.09 (d, 1H, *J* = 3.7 Hz, H-1), 5.35 (t, 2H, *J* = 4.8 Hz, CH=CH); ¹³C NMR (125.7 MHz, CD₃OD) δ 175.4 (C=O), 130.9, 130.8 (CH=CH), 95.2, 95.1 (C-1, C-1'), 74.6, 74.4, 73.9, 73.19, 73.16, 71.91, 71.86, 71.4 (C-2, C-2', C-3, C-3', C-4, C-4', C-5, C-5'), 64.4, 62.6 (C-6, C-6'), 35.0, 33.1 (COCH₂, COCH₂CH₂), 30.8, 30.6, 30.5, 30.3, 30.2, 28.1, 26.0 (oleoyl CH₂), 23.7 (CH₂CH₃), 14.5 (Me). HR ESI MS *m/z* calcd for C₃₀H₅₄NaO₁₂ 629.3507, found 629.3527. In addition, compound **174c** (115 mg, 15% yield) was obtained.

5.6.2.1.7. 6,6'-Di-*O*-oleoyl- α,α -trehalose (**174c**)



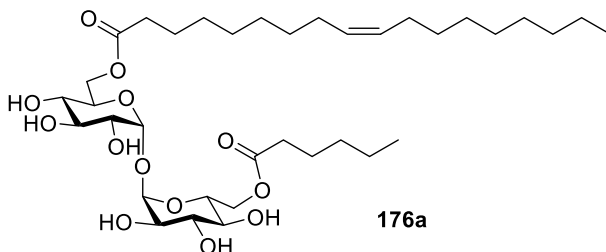
The title compound was synthesized using procedure A above with trehalose (150 mg, 0.43 mmol) and oleic acid under conditions listed in Table 5.1, entry 10 and was obtained as a gummy solid (260 mg, 66% yield): R_F 0.63 [20% MeOH in EtOAc-DCM (1:1), v/v]; ^1H NMR (500.13 MHz, CD_3OD) δ 0.94 (t, 6H, $J = 6.5$ Hz, 2 x Me), 1.32 - 1.45 (m, 40H, 20 x CH_2), 1.64 - 1.67 (m, 4H, CH_2CH_3), 2.05 - 2.07 (m, 8H, CH_2CHCH), 2.38 (t, 4H, $J = 7.0$ Hz, CH_2CO), 3.33 (dd, 2H, $J_{3,4} = 8.9$ Hz, $J_{4,5} = 10.1$ Hz, H-4, H-4'), 3.50 (dd, 2H, $J_{1,2} = 3.8$ Hz, $J_{2,3} = 9.7$ Hz, H-2, H-2'), 3.81 (dd, 2H, $J_{3,4} = 9.1$ Hz, $J_{2,3} = 9.5$ Hz, 2H, H-3, H-3'), 4.05 (ddd, 2H, $J_{4,5} = 10.1$ Hz, $J_{5,6} = 5.1$ Hz, $J_{5,6'} = 2.1$ Hz, H-5, H-5'), 4.23 (dd, 2H, $J = 5.1$ Hz, 11.9 Hz, H-6R, H-6'R), 4.39 (dd, 2H, $J = 2.1, 11.9$ Hz, H-6S, H-6'S), 5.09 (d, 2H, $J = 3.8$ Hz, H-1',H-1), 5.35 (t, 4H, $J = 4.8$ Hz, 4H, CH=CH); ^{13}C NMR (125.7 MHz, CD_3OD) δ 175.5 (C=O), 131.1, 131.0 (CH=CH), 95.3 (C-1, C-1'), 74.7, 73.3, 72.1, 71.6 (C-2, C-2', C-3, C-3', C-4, C-4', C-5, C-5'), 64.6 (C-6, C-6'), 35.2, 33.2 (COCH_2 , COCH_2CH_2), 31.0, 31.0, 30.8, 30.6, 30.5, 30.4, 28.3, 26.2 (oleoyl CH_2), 23.9 (CH_2CH_3), 14.6 (Me). HR ESI MS m/z calcd for $\text{C}_{48}\text{H}_{86}\text{NaO}_{13}$ 893.5961, found 893.5950. In addition, compound **173c** (48 mg, 18% yield) was obtained.

5.6.2.1.8. 2,6,6'-Tri-O-oleoyl- α,α -trehalose (175c)



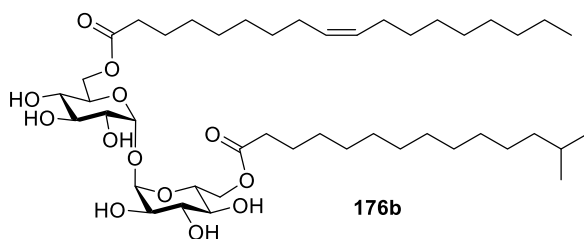
The title compound was synthesized from trehalose (150 mg, 0.43 mmol) and oleic acid (610 mg, 2.16 mmol, 5 equiv) using procedure A under the conditions listed in Table 5.1 entry 13. Compounds **173c** and **174c** were obtained as listed in Table 5.1, entry 13 plus the title compound as a thick colorless syrup (198 mg, 40% yield): R_F 0.43 [1% MeOH in EtOAc-DCM (1:1), v/v]; 1H NMR (500.13 MHz, CD_3OD) δ 0.90 (t, 9H, $J = 6.5$ Hz, 3 x Me), 1.19 - 1.35 (m, 60H, 30 x CH_2), 1.57-1.66 (m, 6H, CH_2CH_3), 1.99 - 2.07 (m, 12H, CH_2CHCH), 2.32-2.46 (m, 6H, CH_2CO), 3.24 (dd, 1H, $J = 9.0, 10$ Hz, H-4'), 3.44 (overlapped dd, 1H, H-4), 3.47 (dd, 1H, $J = 3.8, 10$ Hz, H-2'), 3.68 (t, 1H, $J = 9.2$ Hz, H-3'), 3.78 (ddd, 1H, $J_{4',5'} = 10.0$ Hz, $J_{5',6'R} = 7.7$ Hz, $J_{5',6'S} = 2.0$ Hz, H-5'), 3.99 (t, 1H, $J = 9.6$ Hz, H-3), 4.07 (ddd, 1H, $J_{4,5} = 7.0$ Hz, $J_{5,6'R} = 4.5$ Hz, $J_{5,6'S} = 2.2$ Hz, H-5), 4.15 (dd, 1H, $J = 7.8, 11.7$ Hz, H-6'R), 4.24 (dd, 1H, $J = 5.0, 12.0$ Hz, H-6R), 4.29 (dd, 1H, $J = 1.9, 12.0$ Hz, H-6'S), 4.39 (dd, 1H, $J = 2.2, 12.0$ Hz, H-6S), 4.70 (dd, 1H, $J = 3.7, 10$ Hz, H-2), 5.01 (d, 1H, $J = 3.7$ Hz, H-1'), 5.18 (d, 1H, $J = 3.6$ Hz, H-1), 5.33-5.36 (m, 6H, $CH=CH$); ^{13}C NMR (125.7 MHz, CD_3OD) δ 175.52, 175.38, 174.8 (C=O), 131.06, 131.02 ($CH=CH$), 95.3, 92.7 (C-1, C-1'), 74.9, 74.2, 73.0, 72.28 (C-2, C-2', C-3, C-3'), 72.06, 72.00, 71.9, 71.6 (C-4, C-4', C-5, C-5'), 65.0, 64.2 (C-6, C-6'), 35.3, 35.1, 35.0 ($COCH_2$, $COCH_2CH_2$), 33.2, 31.0, 30.8, 30.7, 30.6, 30.55, 30.47, 30.40. 28.3, 26.3, 26.2, 26.0 (oleoyl CH_2), 24.0 (CH_2CH_3), 14.7 (Me). HR ESI MS m/z calcd for $C_{66}H_{118}NaO_{14}$ 1157.8414, found 1157.8451.

5.6.2.1.9. 6-*O*-Hexanoyl-6'-*O*-oleoyl- α,α -trehalose (176a)



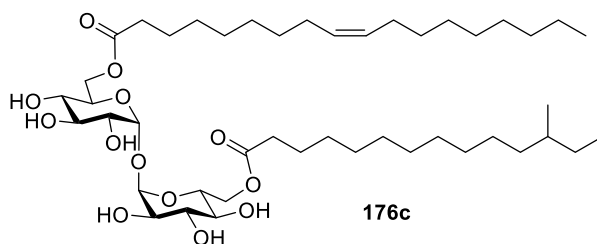
The title compound was synthesized using procedure B above with 6-*O*-oleoyl- α,α -trehalose (**173c**) (100 mg, 0.17 mmol) and hexanoic acid (21 mg, 0.18 mmol) and was obtained as a gummy solid (69 mg, 59% yield): R_F 0.46 [20% MeOH in EtOAc-DCM (1:1), v/v]; ^1H NMR (500.13 MHz, CD_3OD) δ 0.89 - 0.93 (m, 6H, 2 x Me), 1.25 - 1.41 (m, 24H, 12 x CH_2), 1.61 - 1.64 (m, 4H, CH_2CH_3), 2.01 - 2.04 (m, 4H, CH_2CHCH), 2.34 (t, 4H, $J = 7.3$ Hz, CH_2CO), 3.32 - 3.35 (m, 2H, H-4, H-4'), 3.46 (dd, 2H, $J = 3.8, 9.7$ Hz, H-2, H2'), 3.77 (t, 2H, $J = 9.3$ Hz, H-3, H-3'), 3.99 - 4.03 (m, 2H, H-5, H-5'), 4.21 (dd, 2H, $J = 5.4, 11.8$ Hz, H-6R, H-6'R), 4.35 (dd, 2H, $J = 2.0, 11.9$ Hz, H-6S, H-6'S), 5.04 (d, 2H, $J = 3.8$ Hz, H-1',H-1), 5.35 (t, 2H, $J = 4.8$ Hz, CH=CH); ^{13}C NMR (125.7 MHz, CD_3OD) δ 175.62, 175.61 (C=O), 131.12, 130.97 (CH=CH), 95.4 (C-1, C-1'), 74.7, 73.3 (C-2, C-2', C-3, C-3'), 72.1, 71.6 (C-4, C-4', C-5, C-5'), 64.6 (C-6, C-6'), 35.2, 33.2 (COCH_2 , COCH_2CH_2), 32.6, 30.99, 30.95, 30.8, 30.6, 30.5, 30.4, 30.3, 28.3, 26.2, 25.9 (CH_2), 23.9, 23.5 (CH_2CH_3), 14.6, 14.4 (Me). HR ESI MS m/z calcd for $\text{C}_{36}\text{H}_{64}\text{NaO}_{13}$ 727.4239, found 727.4216.

5.6.2.1.10. 6-*O*-(13-Methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (maradolipid) (176b)



The title compound was synthesized using procedure B above and the conditions in Table 5.2, entry 4 with 6-*O*-oleoyl- α,α -trehalose (**173c**) (150 mg, 0.24 mmol) and 13-methyltetradecanoic acid (66 mg, 0.27 mmol), prepared using a literature method.³²⁰ A gummy solid (168 mg, 81% yield): R_F 0.51 [20% MeOH in EtOAc-DCM (1:1), v/v]; ^1H NMR (500.13 MHz, CD_3OD) δ 0.88 - 0.92 (m, 9H, 3 x Me), 1.06 - 1.12 (m, 2H, CH_2), 1.25 - 1.35 (m, 36H, 18 x CH_2), 1.53 (sept, 1H, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.60 - 1.64 (m, 4H, CH_2CH_3), 2.01 - 2.05 (m, 4H, CH_2CHCH), 2.34 (t, 4H, $J = 7.4$ Hz, CH_2CO), 3.31 - 3.35 (m, 2H, H-4, H-4'), 3.43 (dd, 2H, $J = 3.7$ Hz, 9.8 Hz, H-2, H-2'), 3.78 (t, 2H, $J = 9.5$ Hz, H-3, H-3'), 3.99 - 4.03 (m, 2H, H-5, H-5'), 4.20 (dd, 2H, $J = 5.3, 11.8$ Hz, H-6R, H-6'R), 4.35 (dd, 2H, $J = 1.7, 11.8$ Hz, H-6S, H-6'S), 5.05 (d, 2H, $J = 3.7$ Hz, H-1, H-1'), 5.35 (t, 2H, $J = 4.8$ Hz, $\text{CH}=\text{CH}$); ^{13}C NMR (125.7 MHz, CD_3OD) δ 175.44, 175.41 (C=O), 130.9, 130.8 ($\text{CH}=\text{CH}$), 95.1 (C-1, C-1'), 74.5, 73.1 (C-2, C-2', C-3, C-3'), 71.9, 71.5 (C-4, C-4', C-5, C-5'), 64.4 (C-6, C-6'), 40.3 (CH), 35.1, 33.1 (COCH_2 , COCH_2CH_2), 31.1, 30.9, 30.8, 30.8, 30.6, 30.5, 30.4, 30.3, 30.2, 29.2, 28.6, 28.2, 26.1 (CH_2), 23.8, 23.1 (CH_2CH_3), 14.9 (Me). HR ESI MS m/z calcd for $\text{C}_{45}\text{H}_{82}\text{NaO}_{13}$ 853.5648, found 853.5626.

5.6.2.1.11. 6-*O*-(12-Methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (**176c**)



The title compound was synthesized using procedure B above under the conditions in Table 2, entry 6 with 6-*O*-oleoyl- α,α -trehalose (**173c**) (100 mg, 0.17 mmol) and 12-

methyltetradecanoic acid (44 mg, 0.18 mmol) and was obtained as a gummy solid (108 mg, 79%): R_F 0.51 [20% MeOH in EtOAc-DCM (1:1), v/v]; 1H NMR (500.13 MHz, DMSO- d_6) δ 0.80 - 0.90 (m, 9H, 3 x Me), 1.05 - 1.12 (m, 2H, CH₂), 1.16 - 1.18 (m, 2H, CH₂), 1.20 - 1.35 (m, 37H, CHCH₂CH₃, 19 x CH₂), 1.48 - 1.51 (m, 2H, CH₂CH₃), 1.95 - 1.99 (m, 2H, CH₂CHCH), 2.26 (t, 4H, $J = 7.0$ Hz, CH₂CO), 3.10 - 3.14 (m, 2H, H-4, H-4'), 3.22 - 3.26 (m, 2H, H-2, H-2'), 3.52 - 3.57 (m, 2H, H-3, H-3'), 3.86 - 3.90 (m, 2H, H-5, H-5'), 4.02 (dd, 2H, $J = 5.7, 11.7$ Hz, H-6R, H-6'R), 4.22 (m, 2H, H-6S, H-6'S), 4.70 (d, 2H, $J = 5.5$ Hz, OH), 4.82 (d, 2H, $J = 3.6$ Hz, H-1, H-1'), 4.97 (d, 2H, $J = 5.5$ Hz, OH), 5.07 (d, 2H, $J = 5.5$ Hz, OH), 5.30 (t, 2H, $J = 5$ Hz, CH=CH); ^{13}C NMR (125.7 MHz, DMSO- d_6) δ 172.70, 172.68, (C=O), 129.6 (CH=CH), 93.3 (C-1, C-1'), 72.7, 71.4, 71.3, 70.1, 70.0, 69.7 (C-2, C-2', C-3, C-3', C-4, C-4', C-5, C-5'), 63.1 (C-6, C-6'), 36.0, 33.8, 33.6, 31.3 (COCH₂, COCH₂CH₂), 29.4, 29.0, 28.9, 28.86, 28.74, 28.70, 28.6, 28.50, 28.46, 26.6, 26.5 (CH, CH₂), 24.3, 22.1 (CH₂CH₃), 13.9, 11.2 (Me). HR ESI MS m/z calcd for C₄₅H₈₂NaO₁₃ 853.5648, found 853.5620.

Chapter 6: Synthesis of Polyester Dendrimers

6.1. Introductory Remarks

Polyester dendrimers have been shown to be efficient drug carriers.^{2,3} Drug molecules can be attached to the surface of the dendrimers,⁴ or the encapsulation method, where the drug is housed inside the cavities, can be used. In both methods, the polyester dendrimer may increase solubility, cellular uptake, and cellular retention of the drug to enhance the efficacy of the drug. Slow release of drugs inside the cell is achieved because of the instability of ester bonds under acidic conditions. The activity of the dendrimer-DOX and its reduced toxicity relative to free DOX,²² is convincing evidence of the polyester dendrimer's ability to improve the pharmacokinetic profiles of attached drugs. Although much work needs to be performed to demonstrate that polyester dendrimers are general drug delivery systems, the possibility that a single polyester dendrimer carrier can be used to impart multiple classes of drugs, imaging agents or combinations of agents with the same improved solubilities, biodistribution, and pharmacokinetic profiles warrants further synthesis and investigation of these molecules.

The number of dendritic families that are synthetically accessible is only limited by the imagination of the synthetic chemist. The following sections discuss attempts to prepare new dendritic polyol species. This work was guided by the following considerations. Firstly, the plan was to develop the use of the new core molecules that were not sensitive to deprotection by mild acid or hydrogenolysis (Chapter 2). The next goal was to create dendrimers that were less easily hydrolyzed *in vivo* than the well-known bis-HMPA-based dendrimers. These latter dendrimers are hydrolyzed fairly slowly,⁸⁰ but even slower hydrolysis would improve lifetimes for use of these dendrimers as frameworks in applications such as antiadhesion drugs against urinary tract

infections or to support vaccines or as drug carriers. It was thought that incorporation of more branched dendrons would accomplish this goal.

6.2. The Use of 2,2-Bis(hydroxymethyl)propanoic Acid (bis-HMPA) Dendrons.

As part of a program to prepare polyester glycodendrimers, initial attempts were to assemble core molecules and dendrons (discussed in Chapter 2) into polyester dendrimers. Both the benzylidene-protected and the acetonide-protected dendrons of bis-HMPA (Figure 17) were prepared. As shown in Scheme 52, core **79** reacted with anhydride **44** in the presence of DMAP and pyridine to give the protected first generation dendrimer in excellent yield. Deprotection using hydrogenolysis also proceeded in excellent yield to give the deprotected first generation dendrimer. The two anhydrides **44** and **49** were then reacted with core **81** (Schemes 53 and 54). The divergent growth of a second generation dendrimer using **49** is illustrated in Scheme 53 and the synthesis of a third generation dendrimer using **44** is shown in Schemes 54 and 55.

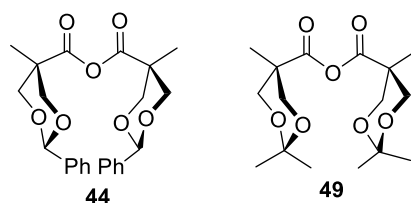
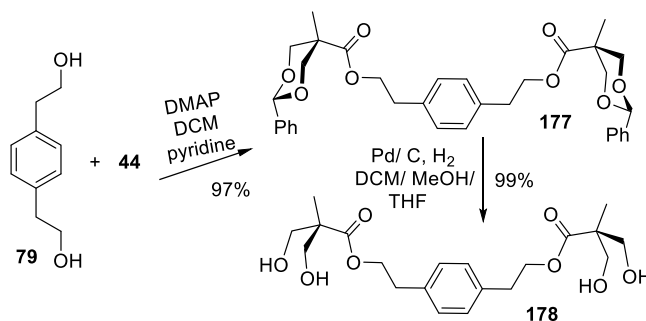
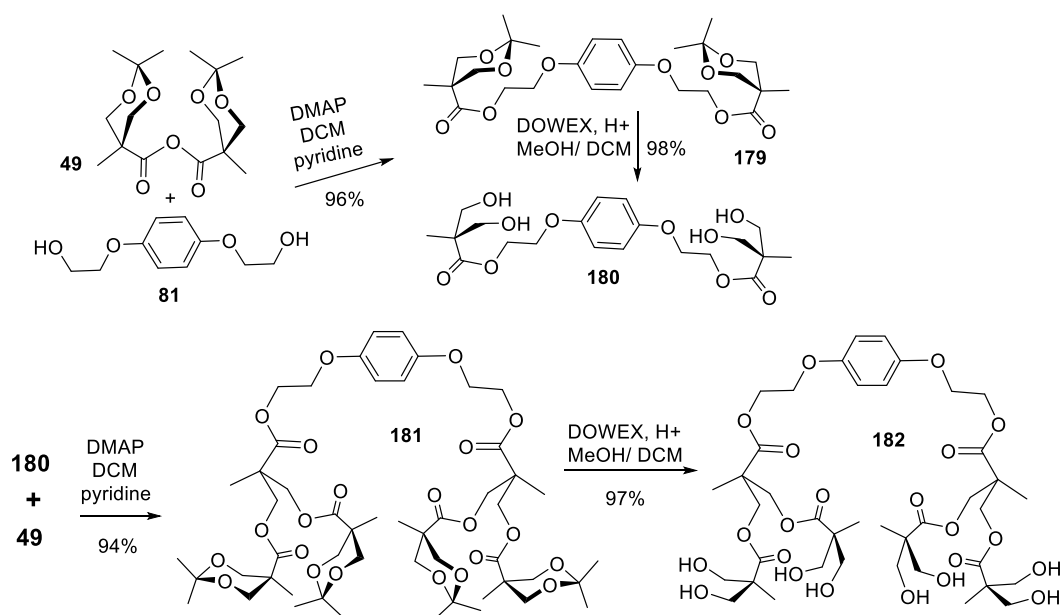


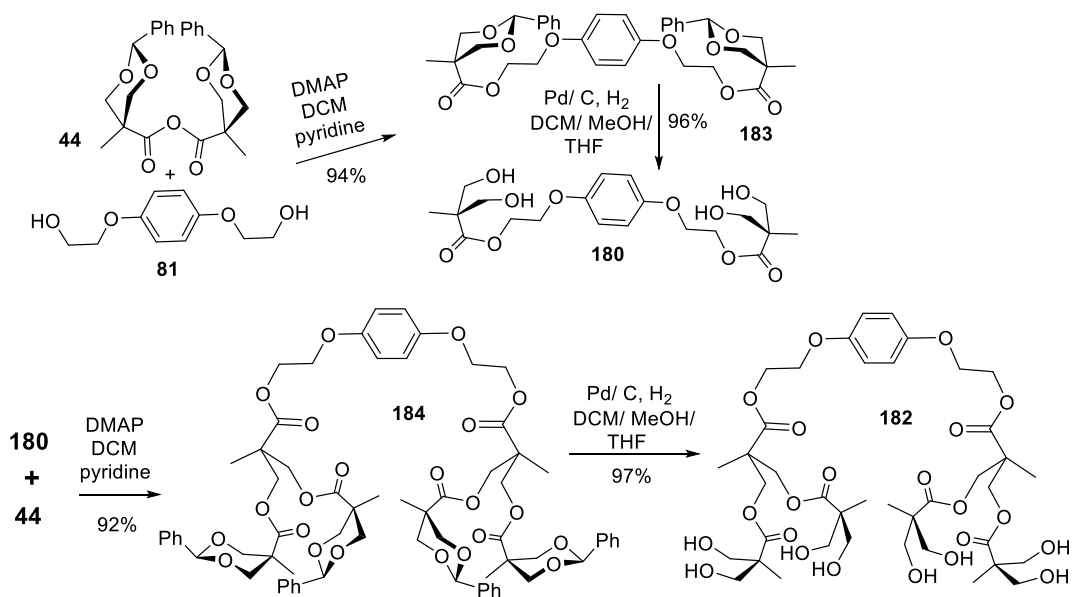
Figure 17 Benzylidene and acetonide-protected dendrons of bis-HMPA



Scheme 52 Preparation of a first-generation dendrimer with a hydroquinone core, a tetraol

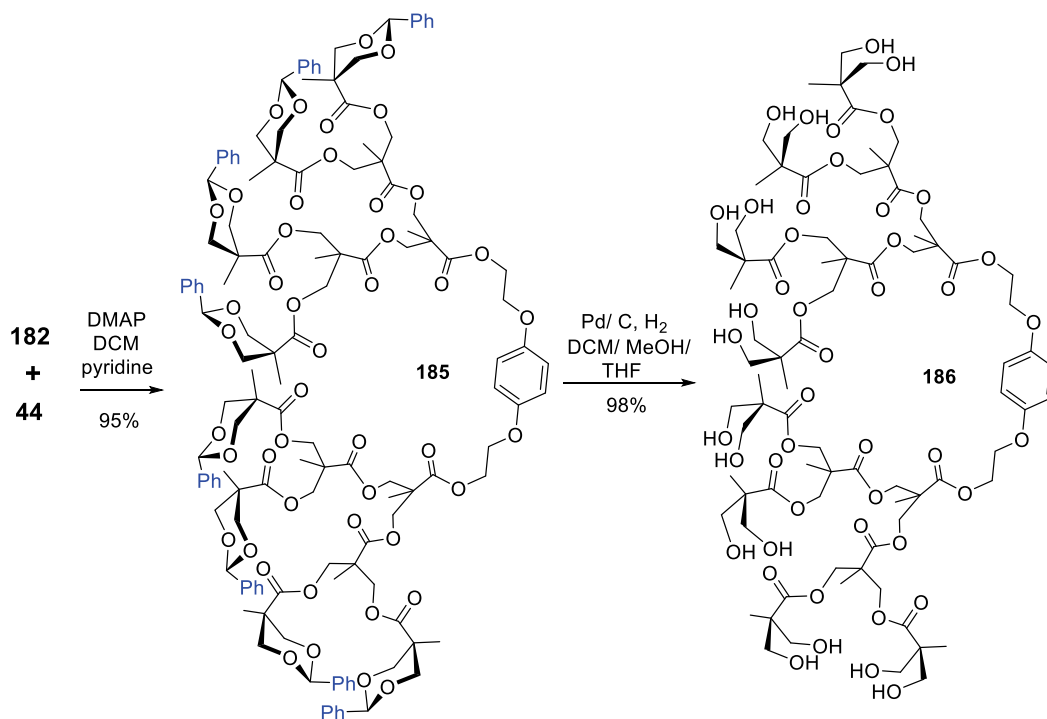


Scheme 53 Preparation of a second-generation dendrimer with a hydroquinone core, an octaol



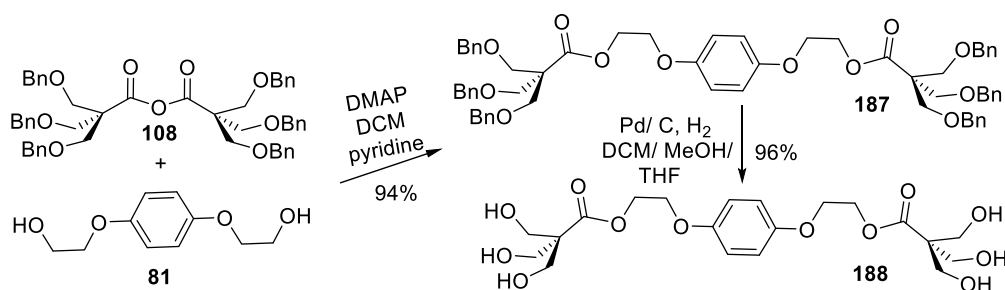
Scheme 54 An alternative route to second-generation dendrimer **182**

These dendrimers, both protected and hydroxyl-terminated are crystalline products, and were stable over a period of several months at room temperature.



Scheme 55 Elaboration of octaol **182** into G-3(OH)₁₆ **186**

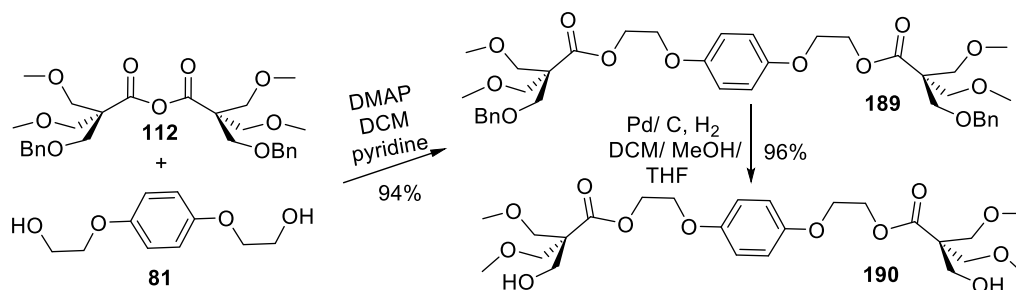
6.3. The Reactivity of Tribranched Dendrons



Scheme 56 Synthesis of 1st generation dendrimer (**188**), a hexaol, using a tribranched dendron

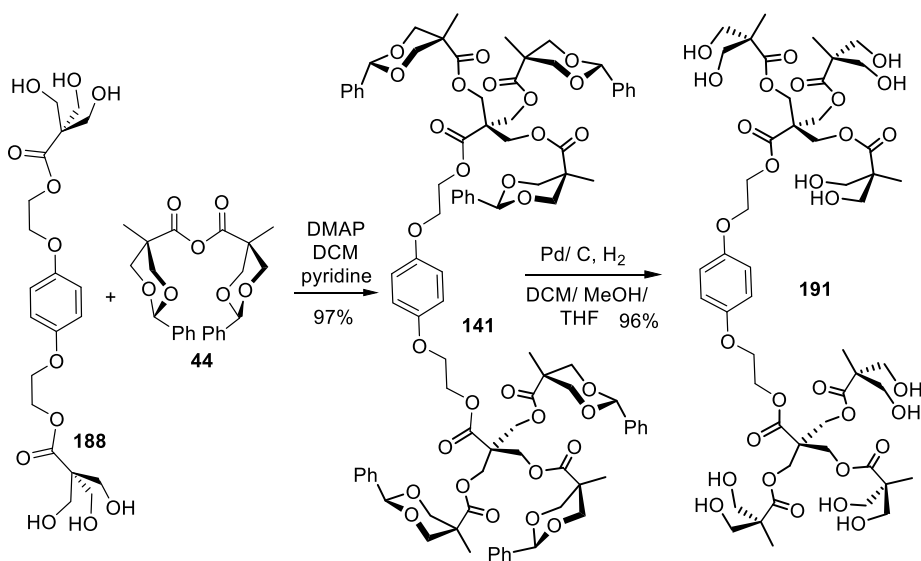
The successful preparation of new tribranched dendrons was discussed in Chapter 2. It was hoped that the use of these tribranched dendrons would lead to the preparation of new types of polyester dendrimers that hydrolyze more slowly. The AB₃ anhydride **108** reacted with core **81** under the standard conditions to give a protected first generation dendrimer in excellent yield.

Hydrogenolysis of the six *O*-benzyl groups occurred via reaction overnight under the same conditions used for removal of the benzylidene acetals to give a hexaol (Scheme 56). The same two steps using tribranched **112** produced **190**, a diol as shown in Scheme 57.



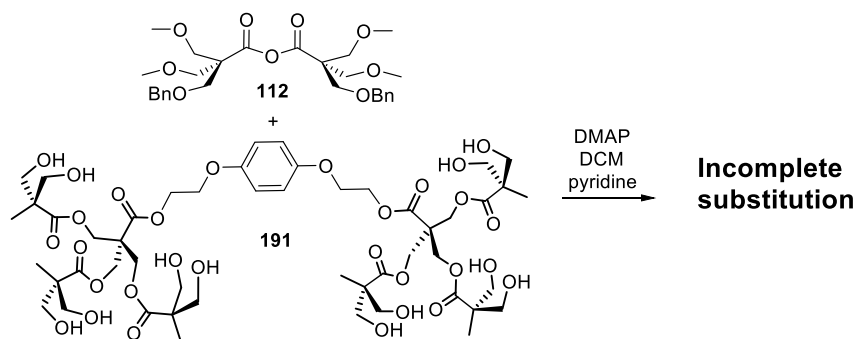
Scheme 57 Preparation of diol **190**

First generation dendrimer **188** was then reacted with excess amount of the benzyl-protected dendron **108** but unfortunately, most of the anhydride was recovered even after 24 hours. On the other hand, reaction of the hexaol with the dibranched anhydride **44**, followed by hydrogenolysis gave the second generation mixed polyester dendrimer **191**, again in excellent yield (Scheme 58).⁹¹

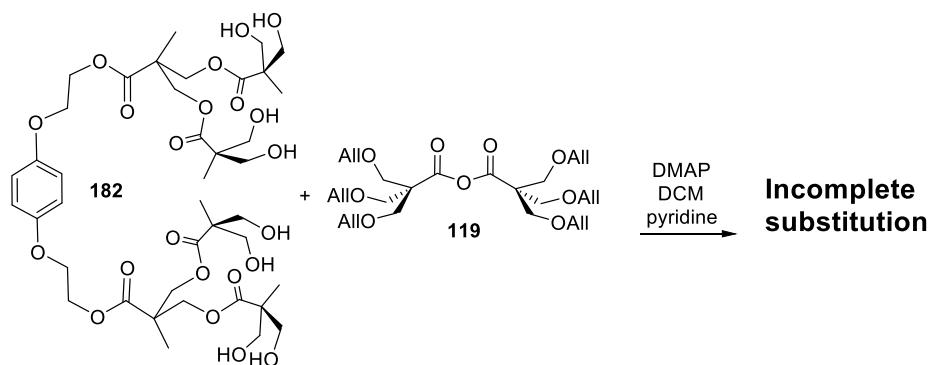


Scheme 58 Preparation of 2nd generation hydroquinone-cored dendrimer **191**, a dodecaol

The divergent growth of a dendrimer is self-limiting, and is governed by steric hindrance arising from the introduction of numerous surface groups, particularly when sterically congested dendrons are used. Various reactions using flexible tribranched dendrons **108**, **112**, and **119** beyond the first generation were attempted but they all gave unsatisfactory results. For example, when anhydride **112** was reacted with dendrimer **191** under standard conditions for dendrimer growth, most of the dendron was recovered after 24 hours (Scheme 59). Similarly, the reaction of the allyl-terminated anhydride **119** and the octaol **182** did not yield successful results as shown in Scheme 60. It seems that these flexible tribranched dendrons are not versatile dendrimer building blocks. The groups at the quaternary sp^3 center are flexible and can rotate around freely thereby blocking the reactive anhydride center.

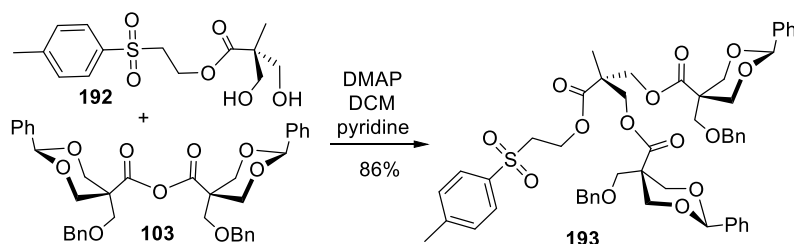


Scheme 59 Potential preparation of protected third generation dendrimer



Scheme 60 Potential preparation of allyl-terminated third generation dendrimer

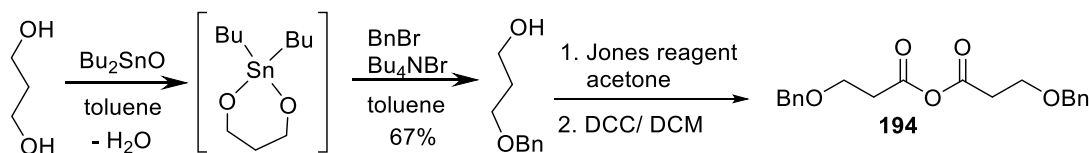
The other type of tribranched dendrons discussed in Chapter 2 has two hydroxyl groups of the starting pentaerythritol tied up using a benzylidene acetal linkage. Reducing the rotational freedom of the protected hydroxymethyl groups by ring formation reduces steric hindrance around the reactive center and consequently, this type of dendron has improved reactivity. For example, as shown in Scheme 61, anhydride **103** reacted with diol **192**³³⁶ under standard conditions for dendrimer growth to give protected second generation dendron **193** in 86% yield.



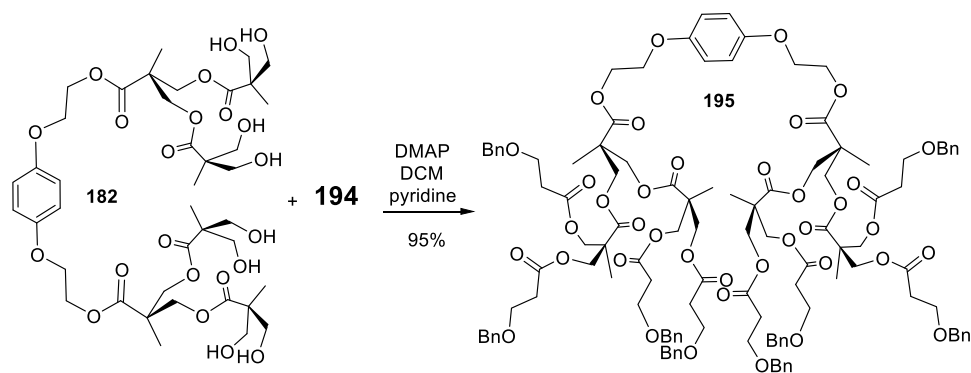
Scheme 61 Preparation of second generation mixed polyester dendron **193**

6.4. Dendrimer Surface Functionalization

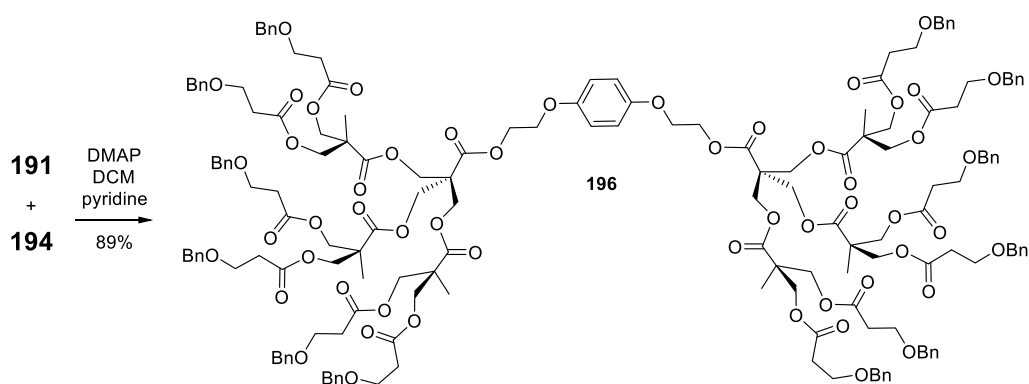
Following their synthesis, dendrimers are traditionally functionalized in accordance with the features the researcher wants them to display and the application they are intended for. The properties of dendrimers are heavily influenced by the type of functional groups at their periphery. For example, when water soluble crystalline dendrimers **182** and **191** were reacted with anhydride **194** (Schemes 63 and 64), the resulting compounds (**195** and **196** respectively) were syrups and they dissolved in non-polar solvents like diethyl ether and dichloromethane.



Scheme 62 Preparation of anhydride **194**



Scheme 63 Synthesis of benzyl-terminated dendrimer **195**



Scheme 64 Synthesis of benzyl-terminated dendrimer **196**

6.4.1. Polyester Glycodendrimers

The interactions of carbohydrates with different receptors displayed at the cell surface control a number of biological processes. The affinity of carbohydrate-receptor interactions is typically low for a single carbohydrate ligand but has been shown to increase significantly through multivalent ligand-receptor interactions.^{21,46,337-340} Consequently, several groups have attempted the development of well-defined macromolecules displaying a large number of carbohydrate ligands using dendrimers as carriers to achieve multivalent carbohydrate-receptor interactions and utilize them for recognition and targeting to specific cells.^{339,341-346} I am interested in the synthesis and the evaluation of polyester glycodendrimers as potential anti-

adhesion drugs. Initial work has focussed on urinary tract infections (UTIs) which are among the most frequently occurring bacterial diseases in humans.³⁴⁷⁻³⁴⁹

UTIs are mainly caused by strains of uropathogenic *Escherichia coli* (UPEC), a gram-negative bacterium present in most animals and humans.³⁴⁹ UPEC expose mannose-sensitive type 1 pili on their outer surface.^{350,351} Type 1 pili are heteropolymeric fibers that carry a two-domain adhesin, FimH, at their distal tip. FimH adheres via its lectin domain to terminal mannopyranose residues of uroplakin Ia and $\alpha_3\beta_1$ integrins, membrane glycoproteins that are abundantly expressed on superficial epithelial cells of the urinary tract.^{352,353} Early studies have shown that small compounds can hinder UPEC in different stages of their pathogenic cascade.³⁵⁴ Consequently, Type 1 pili and the FimH adhesion present an attractive target for the design of antibacterial species.^{351,355,356} It is known that to mimic the interactions of high-mannose glycans with the FimH receptor-binding site, mannosides must have α -linked hydrophobic aglycones of considerable length ((CH₂)₇ or biphenyl) to fit in the so-called tyrosine gate.^{339,357-364}

Following this guide, two mannose residues (**198** and **201**) were prepared as shown in Scheme 65, with the idea of attaching them to dendrimer surfaces using click chemistry. These particular derivatives were selected for the following reasons. As shown in Figure 18, the original *p*-nitrophenyl glycoside^{339,357} and the heptyl glycoside^{339,357} both had nM binding constants to FimH. The hexameric **197** shown in Figure 19 had a very good K_d of 3 nM (that is a per mannose binding constant of 18 nM).³³⁹ In view of the fact that the binding constant of the heptyl glycoside is considerably better than the butyl derivative, it was considered that the closeness of the branching point to the glycosidic centre of the derivative in Figure 19 considerably hindered its binding. This led to the first set of compounds (using **198**) which have

a longer chain after the triazole ring. The second set of compounds (using **201**) was derived to more closely mimic heptyl α -D-mannopyranoside.³⁵⁵

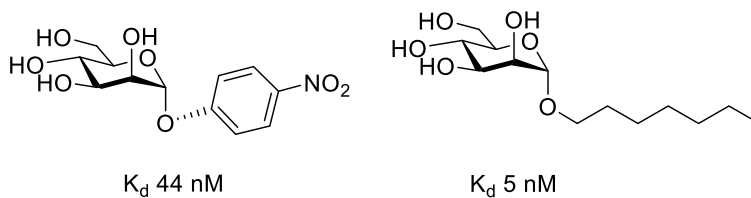


Figure 18 Binding constants of two monomeric mannosides with FimH

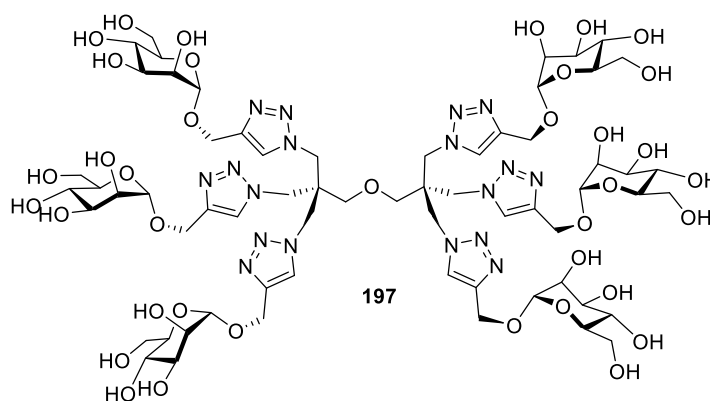
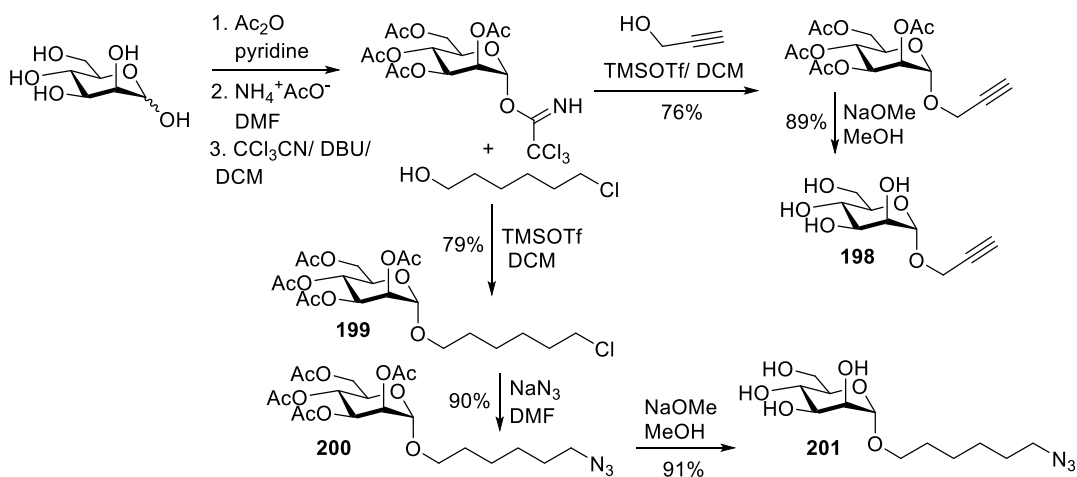


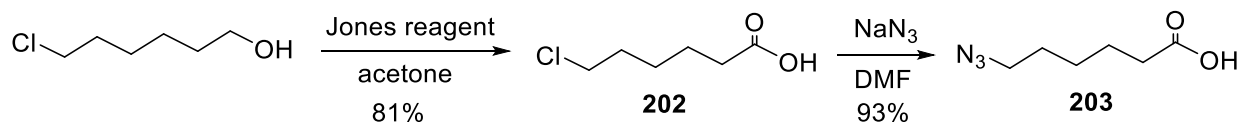
Figure 19 A hexameric compound with a K_d per mannose residue of 18 nM



Scheme 65 Synthesis of mannose residues **198** and **201**

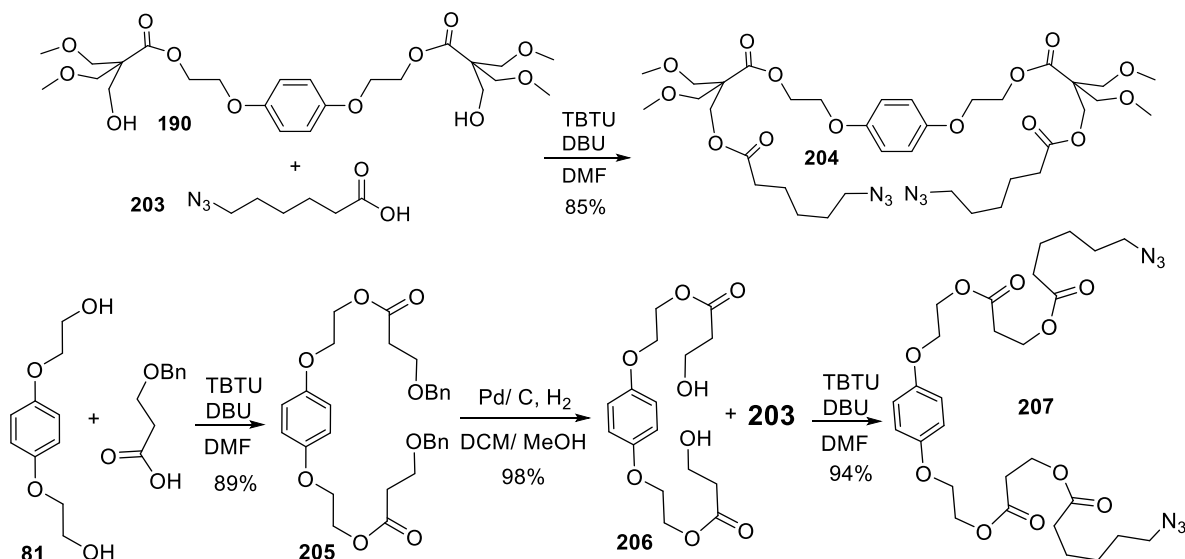
Per-*O*-acetylation then selective deprotection of the anomeric center followed by activation with trichloroacetonitrile gave trichloroacetimidate. Glycosylation with propargyl alcohol followed by deacetylation gave **198**. Glycosylation using 6-chlorohexanol afforded **199**, which was transformed into the corresponding azido mannoside **201** after sodium azide displacement of the chloride and deacetylation (Scheme 65).

In other reactions, 6-azidohexanoic acid was prepared for attachment to click coupling partners of **198**, which must be azide-terminated. Accordingly, 6-chlorohexanol was oxidized to the corresponding acid using Jones reagent followed by an S_N2 displacement with sodium azide.

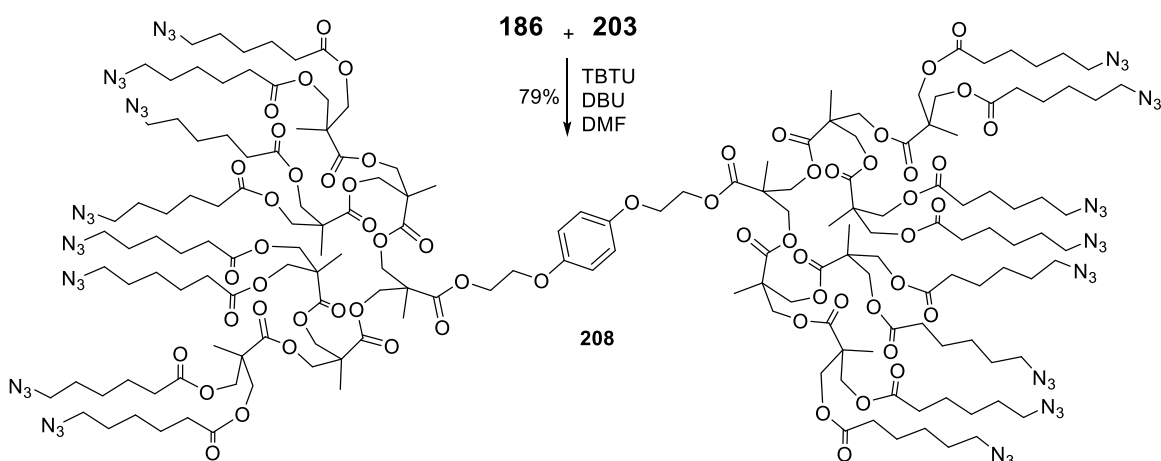


Scheme 66 Preparation of 6-azidohexanoic acid

The TBTU-promoted esterification using 6-azidohexanoic acid for the preparation of azide-terminated species worked well in DMF. In the case of diols, reactions were high yielding with short reaction times as expected based on the observations of Chapter 3, section 3.4. As illustrated in Scheme 67, diol **190** reacted for 4 hours to afford the corresponding azide **204** in 85% yield, while **206** yielded **207** in 94% yield after 2 hours. Similarly, third generation dendrimer **186** afforded **208** in 79% yield after reacting with 6-azidohexanoic acid for 12 hours as shown in Scheme 68.



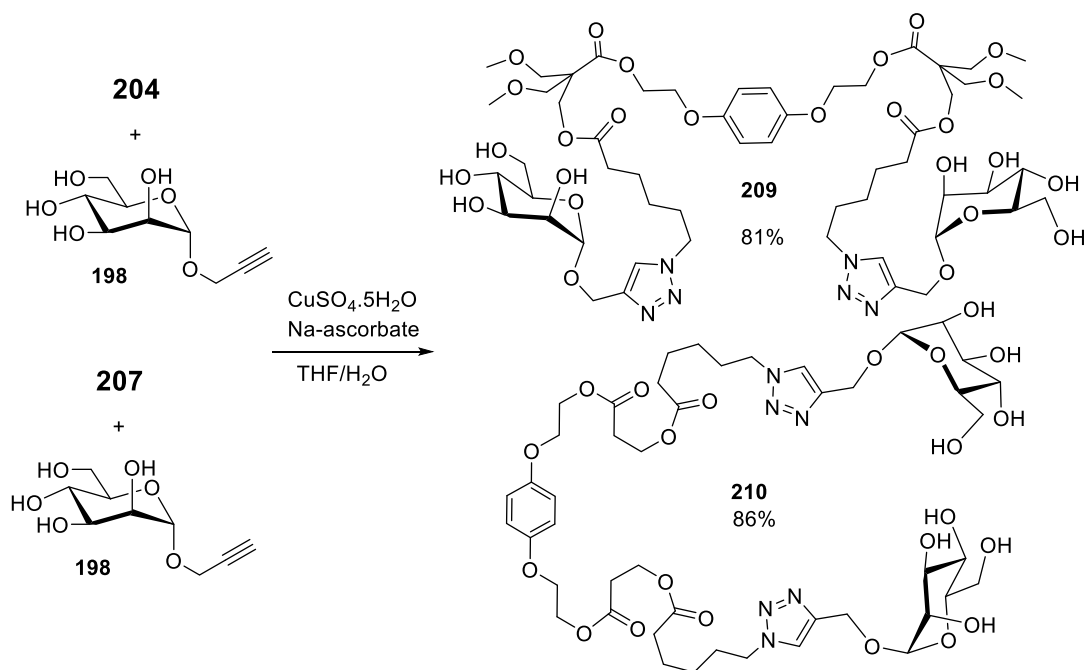
Scheme 67 Preparation of divalent azide compounds **204** and **207**



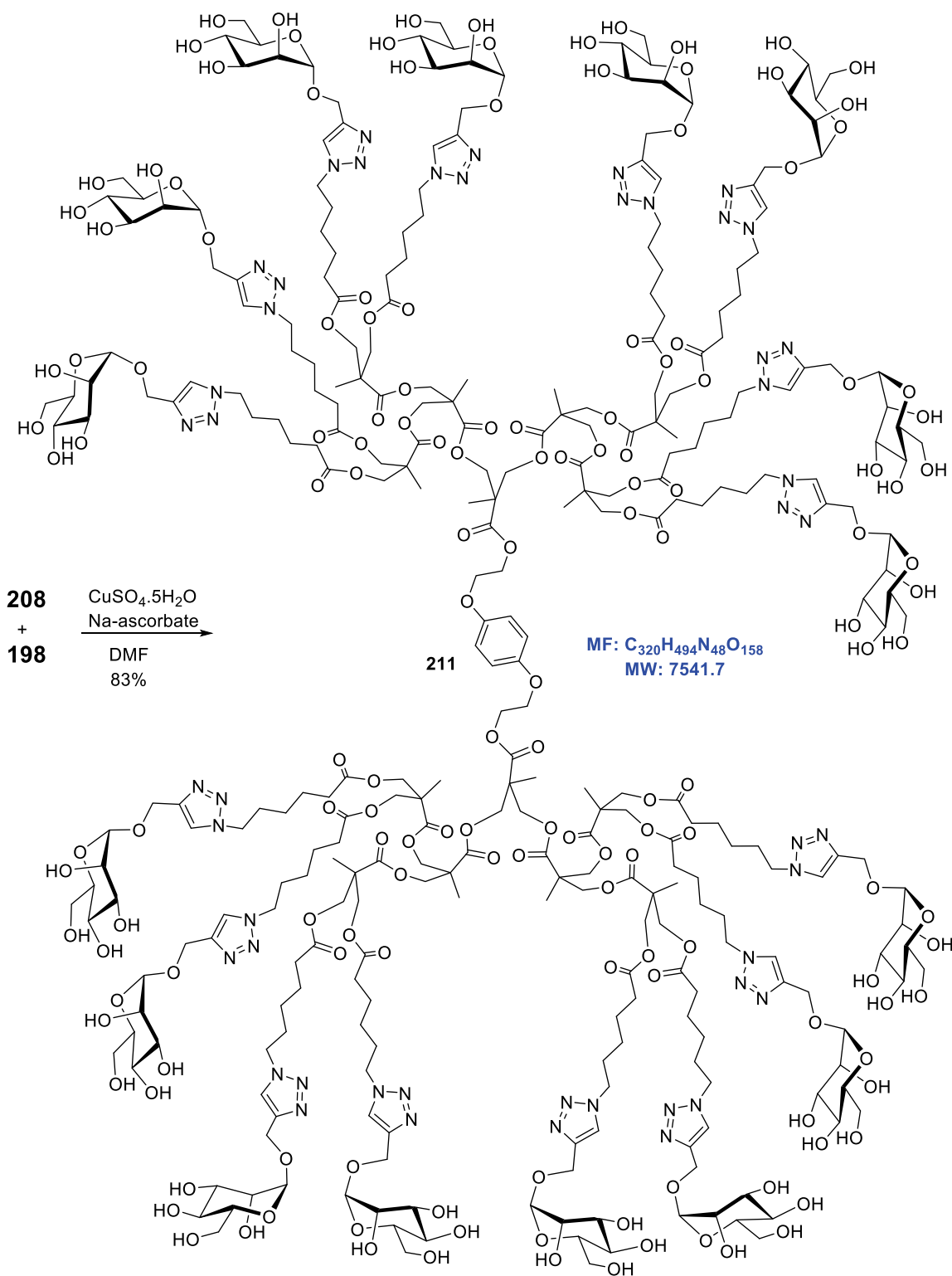
Scheme 68 Preparation of an azide-terminated third generation polyester dendrimer

Having successfully prepared both the alkyne functionalized mannoside **198** and the azide terminated species; the next step was to connect them using a click reaction. Modified versions of the click reaction have been developed that do not require toxic copper (I) so that these reactions can even be used in living cells.³⁶⁵⁻³⁶⁷ The reaction has also been used for the synthesis

of dendrons and dendrimer skeletons.^{58,368,369} Here, using this reaction, **204** and **207** reacted with mannoside **198** to give the corresponding divalent mannoside clusters **209** and **210**, respectively (Scheme 69). Most often, this reaction is carried out using a mixture of water and tetrahydrofuran and this system worked well for the preparation of divalent clusters. However, this solvent system did not work for the azide terminated third generation polyester dendrimer because it precipitated whenever water was introduced into the system. After few trials, it was found that the reaction worked well in DMF. As shown in Scheme 70, dendrimer **208** reacted with mannoside **198** to give a highly mannosylated system **211** in 83% yield.

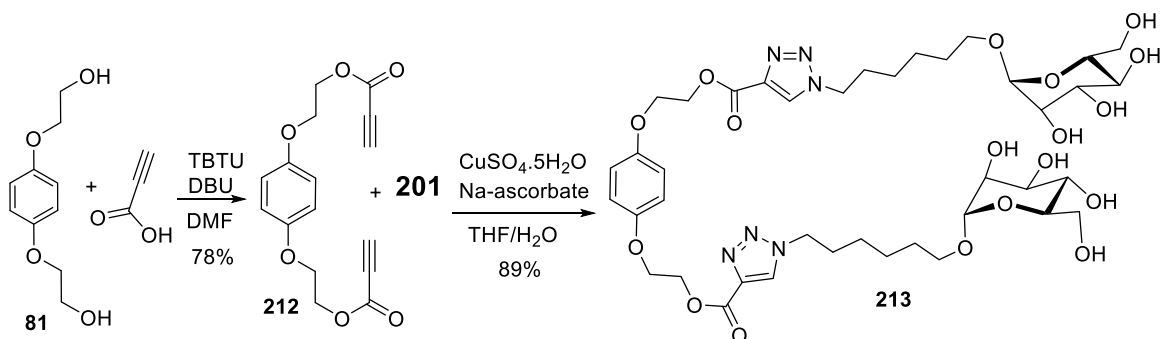


Scheme 69 Synthesis of divalent mannoside clusters **209** and **210**



Scheme 70 Synthesis of a highly mannosylated system **211**

We have used mannoside **201** (Scheme 65) for the synthesis of non-ester glycodendrimers in this lab but this work is not discussed in this thesis. One example using **201** and an ester **212** is shown in Scheme 71. Core molecule **81** was esterified with propynoic acid to give **212** that was transformed into crystalline divalent glycodendrimer **213**.



Scheme 71 Synthesis of divalent mannoside cluster **213**

6.5. Concluding Remarks

As previously known,⁹⁴ anhydride coupling was an efficient route for preparing polyester dendrimers from the core diols developed in Chapter 2. This method was used to synthesize various early generation dendritic polyols in excellent yields. The use of new cores allowed the preparation of dendrimers with new architectures. Anhydrides of the new flexible tribranched dendrons could be added to the core diols but not to first generation dendrimers bearing either dibranched or tribranched termini. Anhydrides of the new cyclic acetal protected tribranched dendrons could be added to the core diols and to dibranched termini but not to tribranched termini. It appears that dendrimers where tribranched dendrons are incorporated at one or more generations among dendrimers that are mainly formed from dibranched dendrons may be synthesized. These would meet the goal of having more slowly hydrolyzable polyester dendrimer frameworks.

TBTU-promoted esterification was an efficient method for preparing esters. Various dendrimers such as compounds **204**, **205**, **207**, and **208** were successfully prepared following this method. Using the well-known click reaction, a number of polyester glycodendrimers including compound **211** with 16 mannose residues were efficiently prepared and characterized. It would be interesting to test if TBTU-promoted esterification can be used for the preparation of dendrimers using hindered flexible tribranched dendrons. Even though TBTU is expensive which is a disadvantage especially for large scale preparations, the reactive intermediate here would be much less hindered in comparison to the anhydride reactive center of tribranched dendrons.

6.6. Experimental Section

6.6.1. General

^1H and ^{13}C NMR spectra were recorded on Bruker Avance 500 or Bruker Avance 300 NMR spectrometers operating at 500.13 and 125.7 MHz or 300.15 and 75.5 MHz respectively using the solvent resonances as secondary chemical shift references. The carbon and hydrogen atoms were assigned following analysis of their one dimensional (^1H , ^{13}C) and two dimensional (COSY, HSQC, HMBC, and TOCSY) NMR spectral data. Coupling constant (J) values are reported in Hertz. High-resolution mass spectra were recorded on a Bruker Micro-TOF mass spectrometer using electrospray ionization. Melting points were determined on a Fisher-John's melting point apparatus and are uncorrected. Acetone was refluxed over K_2CO_3 and distilled over molecular sieves. Dichloromethane was refluxed over calcium hydride and distilled onto molecular sieves. Methanol was refluxed over calcium oxide and distilled over molecular sieves. Tetrahydrofuran was refluxed over LiAlH_4 and distilled over molecular sieves. Unless otherwise noted, non-aqueous reactions were carried out under a nitrogen atmosphere. Jones reagent (0.56 M) was prepared by dissolving sodium dichromate dihydrate ($\text{Na}_2\text{Cr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$, 300 g, 1.01 mol)

in 1.5 L of water followed by slowly adding conc. sulfuric acid (300 mL) to the cooled solution (0 °C). Compounds were visualized/ located by spraying the TLC plate with a solution of 2 % ceric ammonium sulfate in 0.5 M H₂SO₄ followed by heating on a hot plate until color developed. Solid compounds were purified on silica gel using flash column chromatography and specified eluents, or by crystallization. Liquids and oils were purified using flash column chromatography. Water soluble compounds were purified using size exclusion chromatography on a Sephadex LH-20 gel column with water as the eluent.

6.6.2. Synthesis

6.6.2.1. General procedures

Formation of dendritic esters (anhydride coupling): To an oven-dried round-bottomed flask equipped with a magnetic stir bar under nitrogen atmosphere, the benzylidene, acetonide or benzyl protected anhydride, the hydroxyl-terminated dendrimer or core, and *N,N*-dimethyl-4-aminopyridine (DMAP) were dissolved in a 3:1 mixture of CH₂Cl₂: pyridine (v/v). The reaction mixture was stirred at rt for 4 to 12 h and diluted with water (3 mL) in pyridine (3 mL). Stirring was continued overnight to quench the excess anhydride. The mixture was diluted with CH₂Cl₂ (150 mL) and washed using NaHCO₃ (1 M, 30 mL × 3), 10% aq. Na₂CO₃ (30 mL × 3), brine (30 mL × 2), and water (30 mL), then dried (MgSO₄), filtered, and concentrated. The crude solid was then purified using precipitation out of hexanes/ EtOAc or column chromatography to give the desired product. The NaHCO₃ layers were combined, acidified (pH = 5 – 6), and the carboxylic acid by-product was recovered. However, a different workup procedure was used for the synthesis of dendrimer **141**.

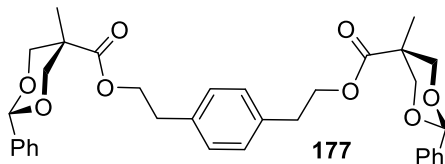
Deprotection using hydrogenolysis: To an oven-dried round-bottomed flask equipped with a magnetic stir bar, the benzylidene or benzyl protected dendrimer was dissolved in a 1:2:1

mixture of CH₂Cl₂ : MeOH : THF (v/v/v) and a catalytic amount of Pd/C was added. The flask was evacuated and back-filled with hydrogen three times. After stirring the mixture overnight under a H₂ atmosphere, the catalyst was filtered off using celite and this celite was washed with MeOH. The filtrate was concentrated to dryness to afford the product as a colorless solid.

Removal of isopropylidene acetals: An acetonide-protected dendrimer was dissolved in CH₂Cl₂ (5 mL) and the mixture was diluted using methanol (15 mL). A tea spoon of DOWEX, H⁺ resin was added and the mixture was stirred for 3 h at rt when TLC confirmed complete removal of the protective groups. The resin was filtered off and carefully washed with methanol. Methanol was removed under vacuum to give hydroxyl-terminated products as colorless crystalline products.

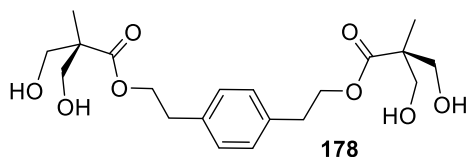
Esterification procedure using TBTU: In an oven-dried round-bottomed flask equipped with a magnetic stir bar, an acid (1.20 mmol), TBTU (0.387 g, 1.20 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.37 mL, 2.40 mmol) were dissolved in anhydrous DMF (3 mL) and the resulting mixture was stirred at rt for 30 min under a nitrogen atmosphere. An alcohol (1.00 mmol of hydroxyl groups) in DMF (1 mL) was then injected into the reaction mixture via syringe, and stirring was continued at rt until TLC confirmed the completion of the reaction (1 – 12 h). The reaction mixture was diluted with CH₂Cl₂ (15 mL) and the resulting mixture was washed with 5% HCl (2 x 3 mL), 1M NaHCO₃ (3 x 3 mL) and water (2 x 3 mL). The organic layer was collected, dried (MgSO₄), filtered and concentrated to give a crude ester product, which was purified using column chromatography and specified eluents.

6.6.2.2. Benzylidene-protected first-generation dendrimer (177)



1,4-Benzenediethanol **79** (0.630 g, 3.79 mmol), dry pyridine (11 mL), CH_2Cl_2 (33 mL), DMAP (0.203 g, 1.66 mmol) and the anhydride **44** (3.88 g, 9.09 mmol) were stirred at rt for 5 h under nitrogen. After work up and purification as described above, the product was obtained as colorless flakes (2.1 g, 97% yield): mp 138 – 140 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 0.95 (s, 6H, CH_3), 2.95 (t, $J = 7$ Hz, 4H, PhCH_2), 3.62 (d, $J = 11.5$ Hz, 4H, H-4_{ax}, H-6_{ax}), 4.38 (t, $J = 7$ Hz, 4H, CH_2O), 4.63 (d, $J = 11.5$ Hz, 4H, H-4_{eq}, H-6_{eq}), 5.44 (s, 2H, H-2), 7.13 (s, 4H, PhH), 7.32 – 7.34 (m, 6H, PhH), 7.42 – 7.46 (m, 4H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 173.9 (C=O), 137.9, 136, 129.1, 129, 128.2, 126.2 (PhC), 101.8 (C-2), 73.5 (C-4, C-6), 65.5 (CH_2O), 42.4 (C_{quat}), 34.7 (PhCH_2), 17.9 (CH_3). HR ESI MS: m/z calcd for $\text{C}_{34}\text{H}_{38}\text{NaO}_8$ 597.2459, found 597.2413.

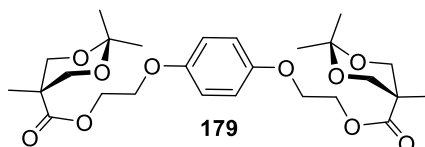
6.6.2.3. First generation dendrimer (178)



Compound **177** (1.22 g, 2.12 mmol) dissolved in dry CH_2Cl_2 (15 mL), dry methanol (30 mL) and dry THF (15 mL) was deprotected as in the general method to afford hydroxyl-terminated **178** as a colorless crystalline solid (0.84 g, 99% yield): mp 118 – 120 °C; ^1H NMR (500.13 MHz, methanol- d_4) δ 1.09 (s, 6H, CH_3), 2.92 (t, $J = 7$ Hz, 4H, PhCH_2), 3.61 (AB q, $\Delta\nu_{\text{AB}} = 22.3$ Hz, $J_{\text{AB}} = 10.5$ Hz, 8H, CH_2OH), 4.27 (t, $J = 7$ Hz, 4H, CH_2O), 7.19 (s, 4H, PhH); ^{13}C

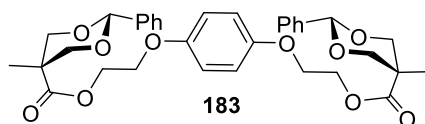
NMR (125.7 MHz, methanol-*d*₄) δ 176.6 (C=O), 137.7, 130.1 (PhC), 66.3 (CH₂O), 65.8 (CH₂OH), 51.5 (C_{quat}), 35.6 (PhCH₂), 17.3 (CH₃). HR ESI MS: *m/z* calcd for C₂₀H₃₀NaO₈ 421.1833, found 421.1830.

6.6.2.4. Acetonide-protected hydroquinone-cored first-generation dendrimer (179)



1,4-Bis-(2-hydroxyethoxy)benzene **81** (0.750 g, 3.78 mmol), dry pyridine (11 mL), CH₂Cl₂ (33 mL), DMAP (0.203 g, 1.66 mmol) and the anhydride **49** (3.00 g, 9.08 mmol) were stirred at rt for 4 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless crystalline solid (1.85 g, 96% yield): R_f 0.50 (hexanes/EtOAc; 1:1); mp 75 – 77 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 1.17 (s, 6H, CH₃), 1.35 (s, 6H, CH_{3ax}), 1.40 (s, 6H, CH_{3eq}), 3.62 (d, *J* = 12 Hz, 4H, H-4_{ax}, H-6_{ax}), 4.12 (t, *J* = 5 Hz, 4H, PhOCH₂), 4.17 (d, *J* = 11.5 Hz, 4H, H-4_{eq}, H-6_{eq}), 4.44 (t, *J* = 4.5 Hz, 4H, CH₂OC=O), 6.82 (s, 4H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 174.2 (2 C=O), 153.1, 115.9 (PhC), 98.1 (C-2), 66.7 (PhOCH₂), 66.0 (C-4, C-6), 63.2 (CH₂OC=O), 41.9 (C_{quat}), 24.6 (CH_{3eq}), 22.8 (CH_{3ax}), 18.7 (CH₃). HR EI MS: *m/z* calcd for C₂₆H₃₈NaO₁₀ 533.2357, found 533.2371.

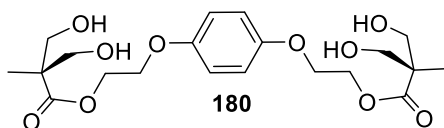
6.6.2.5. Benzylidene-protected hydroquinone-cored first-generation dendrimer (183)



Compound **183** was synthesized as described above in the general procedure for dendritic ester formation. 1,4-Bis-(2-hydroxyethoxy)benzene **81** (0.500 g, 2.52 mmol), dry pyridine (6

mL), CH₂Cl₂ (18 mL), DMAP (0.135 g, 1.11 mmol) and the anhydride **44** (2.58 g, 6.05 mmol) were stirred at rt for 4 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless solid (1.48 g, 97% yield): mp 143 - 145 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 1.04 (s, 6H, CH₃), 3.65 (d, *J* = 11.5 Hz, 4H, H-4_{ax}, H-6_{ax}), 4.16 (t, *J* = 5 Hz, 4H, PhOCH₂O), 4.53 (t, *J* = 5 Hz, 4H, OCH₂CH₂O), 4.68 (d, *J* = 11.5 Hz, 4H, H-4_{eq}, H-6_{eq}), 5.45 (s, 2H, H-2), 6.81 (s, 4H, PhH), 7.28 – 7.44 (m, 10H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 174.1 (C=O), 153.2, 138, 129.1, 128.3, 126.4, 116.1 (PhC), 102 (C-2), 73.7 (C-4, C-6), 66.9 (OCH₂CH₂O), 63.6 (OCH₂CH₂O), 42.7 (C_{quat}), 18.0 (CH₃). HR ESI MS: *m/z* calcd for C₃₄H₃₈NaO₁₀ 629.2357, found 629.2352.

6.6.2.6. Hydroquinone-cored first-generation dendrimer (**180**)



Method A: removal of isopropylidene acetals

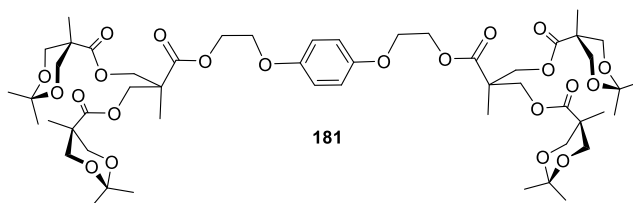
Acetonide-protected first generation dendrimer **179** (1.50 g, 2.94 mmol) was deprotected as described above in the general procedure for the removal of isopropylidene acetals to give **180** as colorless crystals (1.24 g, 98% yield).

Method B: deprotection using hydrogenolysis

Using the general procedure for hydrogenolysis described above, compound **183** (1.18 g, 1.95 mmol) dissolved in dry CH₂Cl₂ (15 mL), dry methanol (30 mL) and dry THF (15 mL) afforded hydroxyl-terminated **180** as a colorless solid (0.83 g, 99% yield): mp 155 – 156 °C; ¹H NMR (500.13 MHz, methanol-*d*₄) δ 1.16 (s, 6H, CH₃), 3.66 (AB q, Δ*v*_{AB} = 29.5 Hz, *J*_{AB} = 11 Hz, 8H, CH₂OH), 4.16 (t, *J* = 5 Hz, 4H, OCH₂CH₂O), 4.40 (t, *J* = 5 Hz, 4H, OCH₂CH₂O), 6.89 (s,

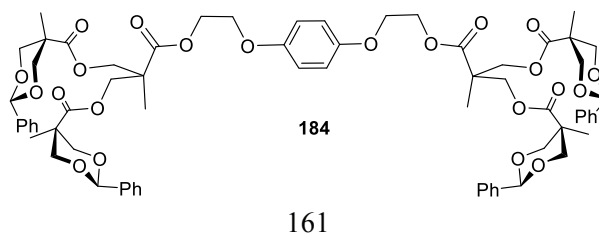
4H, PhH); ^{13}C NMR (125.7 MHz, methanol- d_4) δ 176.5 (C=O), 154.6, 116.9 (PhC), 67.9 (OCH₂CH₂O), 65.8 (CH₂OH), 64.3 (OCH₂CH₂O), 51.6 (C_{quat}), 17.3 (CH₃). HR ESI MS: m/z calcd for C₂₀H₃₀NaO₁₀ 453.1731, found 453.1740.

6.6.2.7. Acetonide-protected hydroquinone-cored second-generation dendrimer (181)



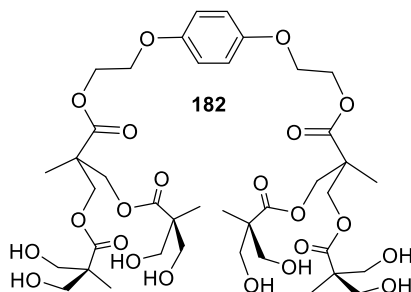
First generation dendrimer **180** (0.650 g, 1.51 mmol), dry pyridine (10 mL), CH₂Cl₂ (30 mL), DMAP (0.162 g, 1.33 mmol) and anhydride **49** (2.40 g, 7.26 mmol) were stirred at rt for 5 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless crystalline solid (1.50 g, 94% yield); mp 110 - 112 °C; ^1H NMR (500.13 MHz, CDCl₃) δ 1.12 (s, 12H, 4 CH₃), 1.30 (s, 6H, 2 CH₃), 1.34 (s, 12H, 4 CH_{3ax}), 1.40 (s, 12H, 4 CH_{3eq}), 3.60 (d, J = 13 Hz, 8H, H-4_{ax}, H-6_{ax}), 4.11 - 4.15 [(m, 8H (H-4_{eq}, H-6_{eq}) and 4H (PhOCH₂)], 4.33 (s, 8H, 4 CH₂), 4.43 (t, J = 5 Hz, 4H, CH₂OC=O), 6.81 (s, 4H, PhH); ^{13}C NMR (125.7 MHz, CDCl₃) δ 173.7 (4 C=O), 172.7 (2 C=O), 153.1, 115.9 (PhC), 98.2 (C-2), 66.4 (PhOCH₂), 66.10, 66.06 (C-4, C-6), 65.4 (4 CH₂), 63.8 (OCH₂CH₂OC=O), 46.9 (2 C_{quat}), 42.2 (4 C_{quat}), 25.3 (4 CH_{3eq}), 22.2 (4 CH_{3ax}), 18.6 (4 CH₃), 17.8 (2 CH₃). HR EI MS: m/z calcd for C₅₂H₇₈NaO₂₂ 1077.4877, found 1077.4873.

6.6.2.8. Benzylidene-protected hydroquinone-cored second-generation dendrimer (184)



Compound **184** was synthesized as described above in the general procedure for dendritic ester synthesis. Compound **180** (0.800 g, 1.86 mmol), dry pyridine (5 mL), CH₂Cl₂ (15 mL), DMAP (0.200 g, 1.64 mmol) and the anhydride **44** (3.80 g, 8.91 mmol) were stirred at rt for 10 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless solid (2.13 g, 92% yield): mp 115 - 116 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 0.94 (s, 12H, 4CH₃), 1.28 (s, 6H, 2CH₃), 3.59 (d, *J* = 11.5 Hz, 8H, H-4_{ax}, H-6_{ax}), 3.89 (t, *J* = 5 Hz, 4H, OCH₂CH₂O), 4.27 (t, *J* = 5 Hz, 4H, OCH₂CH₂O), 4.41 (AB q, Δ*v*_{AB} = 6 Hz, *J*_{AB} = 11 Hz, 8H, 4CH₂OC=O), 4.58 (m, 8H, H-4_{eq}, H-6_{eq}), 5.42 (s, 4H, H-2), 6.69 (s, 4H, PhH), 7.28 – 7.42 (m, 20H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 173.4 (4C=O), 172.8 (2C=O), 153.0, 138, 129.0, 128.3, 126.3, 115.8 (PhC), 101.8 (C-2), 73.7, 73.6 (C-4, C-6), 66.3 (OCH₂CH₂O), 65.7 (4CH₂O), 63.8 (OCH₂CH₂O), 47.0 (2C_{quat}), 42.7 (4C_{quat}), 17.9 (CH₃). HR ESI MS: *m/z* calcd for C₆₈H₇₈Na₂O₂₂ 1269.4877, found 1269.4877.

6.6.2.9. Second generation hydroquinone-cored dendrimer (**182**)



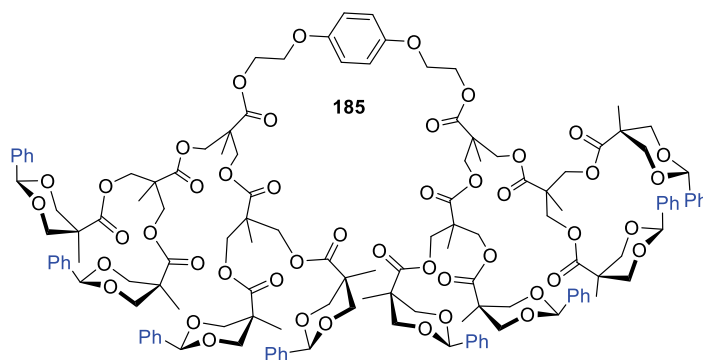
Method A: removal of isopropylidene acetals

Protected second generation dendrimer **181** (1.49 g, 1.41 mmol) was deprotected as described above in the general procedure for the removal of isopropylidene acetals to give the product as colorless crystals (1.24 g, 98% yield).

Method B: deprotection using hydrogenolysis

Using the general procedure for hydrogenolysis described above, protected second generation dendrimer **184** (1.95 g, 1.56 mmol) dissolved in dry CH_2Cl_2 (15 mL), dry methanol (30 mL), and dry THF (15 mL) afforded **182** as a colorless solid (1.36 g, 97% yield): mp 114 – 115 °C; ^1H NMR (500.13 MHz, methanol- d_4) δ 1.12 (s, 12H, 4 CH_3), 1.28 (s, 6H, CH_3), 3.62 (m, 16H, CH_2OH), 4.17 (br m, 4H, $\text{PhOCH}_2\text{CH}_2$), 4.27 (AB q, $\Delta\nu_{\text{AB}} = 19$ Hz, $J_{\text{AB}} = 11$ Hz, 8H, 4 $\text{CH}_2\text{OC}=\text{O}$), 4.43 (br m, 4H, $\text{CH}_2\text{CH}_2\text{OC}=\text{O}$), 6.88 (s, 4H, PhH); ^{13}C NMR (125.7 MHz, methanol- d_4) δ 175.8 (4 $\text{C}=\text{O}$), 174.4 (2 $\text{C}=\text{O}$), 154.4, 116.9 (PhC), 67.6 ($\text{OCH}_2\text{CH}_2\text{O}$), 66.3 (4 $\text{CH}_2\text{OC}=\text{O}$), 65.7 (CH_2OH), 65.0 ($\text{OCH}_2\text{CH}_2\text{O}$), 51.7 (4 C_{quat}), 47.7 (2 C_{quat}), 18.1 (2 CH_3), 17.2 (4 CH_3). HR ESI MS: m/z calcd for $\text{C}_{40}\text{H}_{62}\text{NaO}_{22}$ 917.3625, found 917.3629.

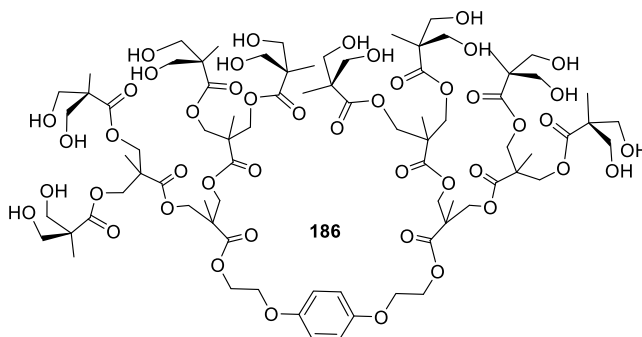
6.6.2.10. Benzylidene-protected hydroquinone-cored third-generation dendrimer (**185**)



Compound **185** was synthesized as described above in the general procedure for dendritic ester synthesis. Compound **182** (1.01 g, 1.13 mmol), dry pyridine (5 mL), CH_2Cl_2 (15 mL), DMAP (0.330 g, 2.71 mmol) and the anhydride **44** (4.81 g, 11.3 mmol) were stirred at rt for 10 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless solid (2.71 g, 95% yield): mp 112 - 114°C; ^1H NMR (500.13 MHz, CDCl_3) δ 0.92 (s, 24H, 8 CH_3), 1.04 (s, 6H, 2 CH_3), 1.19 (s, 12H, 4 CH_3), 3.57 (d, $J = 11.5$ Hz, 16H, H-4 $_{\text{ax}}$, H-6 $_{\text{ax}}$),

3.97 (t, $J = 5$ Hz, 4H, ArOCH₂), 4.07 (AB q, $\Delta\nu_{AB} = 11$ Hz, $J_{AB} = 11$ Hz, 8H, 4CH₂OC=O), 4.31 – 4.37 (m, 20H, 8CH₂OC=O, 2CH₂OC=O), 4.55 – 4.57 (m, 16H, H-4_{eq}, H-6_{eq}), 5.39 (s, 8H, H-2), 6.75 (s, 4H, PhH), 7.27 – 7.40 (m, 40H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 173.3, 172.3, 172.0 (C=O), 153.0, 137.9, 129.0, 128.3, 126.3, 115.8 (PhC), 101.8 (C-2), 73.63, 73.56 (C-4, C-6), 66.3 (ArOCH₂), 66.0 (4CH₂OC=O), 65.3 (8CH₂OC=O), 63.8 (OCH₂CH₂O), 47.0 (4C_{quat}), 46.6 (2C_{quat}), 42.7 (C-5), 17.82 (8CH₃), 17.78 (4CH₃), 17.4 (2CH₃). HR ESI MS: m/z calcd for C₁₃₆H₁₅₈Na₂O₄₆ 1286.4904, found 1286.4887.

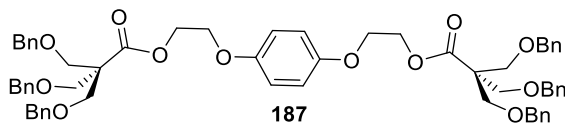
6.6.2.11. Third generation hydroquinone-cored dendrimer (186)



Using the general procedure for hydrogenolysis described above, protected third generation dendrimer **185** (1.55 g, 0.613 mmol) dissolved in dry CH₂Cl₂ (15 mL), dry methanol (30 mL), and dry THF (15 mL) afforded **186** as a colorless solid (1.10 g, 98% yield): mp 109 – 111 °C; ¹H NMR (500.13 MHz, DMSO-*d*₆) δ 1.00 (s, 24H, 8CH₃), 1.14 (s, 12H, 4CH₃), 1.20 (s, 6H, CH₃), 3.39 – 3.46 (m, 32H, 16CH₂OH), 4.08 – 4.23 (m, 28H, 8CH₂O, 4CH₂O, 2ArOCH₂), 4.36 (br, 4H, OCH₂CH₂O), 4.66 (br, 16H, OH), 4.86 (s, PhH); ¹³C NMR (125.7 MHz, DMSO-*d*₆) δ 174.1 (6C=O), 172.1 (2C=O), 171.9 (4C=O), 152.5, 115.6 (PhC), 66.0 (OCH₂CH₂O), 65.8 (OCH₂CH₂O), 64.5 (4CH₂OC=O), 63.7 (CH₂OH, 8CH₂OC=O), 50.3 (8C_{quat}), 46.4 (4C_{quat}), 46.2

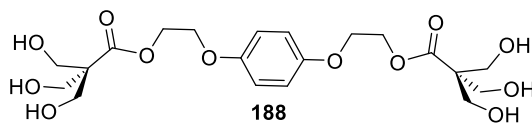
(2C_{quat}), 17.2 (4CH₃), 17.0 (2CH₃), 16.8 (8CH₃). HR ESI MS: *m/z* calcd for C₈₀H₁₂₆Na₂O₄₆ 934.3652, found 934.3654.

6.6.2.12. Benzyl-protected tribranched first-generation dendrimer (**187**)



Compound **187** was synthesized as described above in the general procedure for formation of dendritic esters. The core molecule **81** (0.630 g, 3.18 mmol), dry pyridine (6 mL), CH₂Cl₂ (18 mL), DMAP (0.210 g, 1.72 mmol) and the anhydride **108** (6.15 g, 7.47 mmol) were stirred at rt for 12 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless crystalline solid (hexanes/ EtOAc; 3:1; R_F 0.35) (2.99 g, 94 %): mp 70 – 71 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 3.71 (s, 12H, 6C_{quat}CH₂O), 4.01 (t, *J* = 5 Hz, 4H, 2PhOCH₂), 4.42 (t, *J* = 5 Hz, 4H, 2CH₂OC=O), 4.46 (s, 12H, 6CH₂ benzylic), 6.69 (s, 4H, PhH), 7.21 – 7.27 (m, 30H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 172.6 (C=O), 153.1, 138.5, 128.4, 127.52, 127.46, 115.8 (PhC), 73.3 (6CH₂ benzylic), 68.0 (6C_{quat}CO), 66.6 (2PhOC), 63.0 (2COC=O), 53.9 (C_{quat}). HR ESI MS: *m/z* calcd for C₆₂H₆₆NaO₁₂ 1025.4446, found 1025.4429.

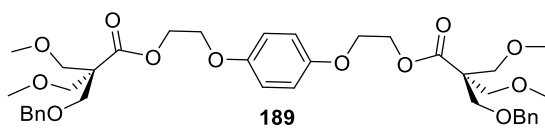
6.6.2.13. First generation tribranched dendrimer (**188**)



Using the general procedure for hydrogenolysis described above, compound **187** (1.74 g, 1.73 mmol), dissolved in dry CH₂Cl₂ (15 mL), dry MeOH (30 mL), and dry THF (15 mL) afforded **188** as a colorless crystalline solid (0.77 g, 96 % yield): mp 150 – 151 °C; ¹H NMR

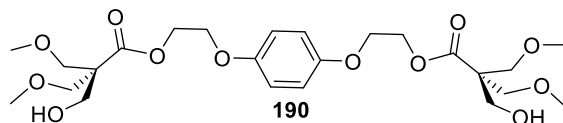
(500.13 MHz, methanol- d_4) δ 3.77 (s, 12H, 6CH₂O), 4.17 (t, J = 5 Hz, 4H, 2PhOCH₂), 4.42 (t, J = 5 Hz, 4H, 2CH₂OC=O), 6.90 (s, 4H, PhH); ¹³C NMR (125.7 MHz, methanol- d_4) δ 175.4 (C=O), 154.7, 116.5 (PhC), 71.1 (2PhOC), 61.8 (2COC=O), 61.5 (6COH), 57.1 (C_{quat}). HR ESI MS: m/z calcd for C₂₀H₃₀NaO₁₂ 485.1629, found 485.1656.

6.6.2.14. Methyl and benzyl-protected hydroquinone-cored first-generation dendrimer (189)



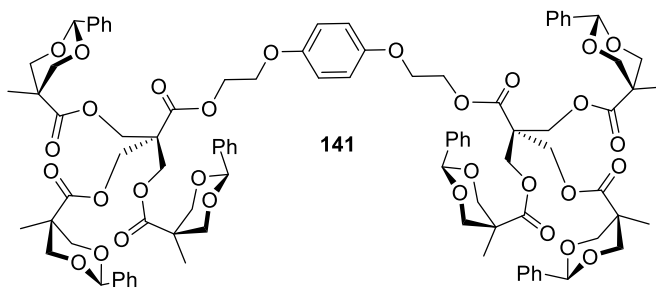
Compound **189** was synthesized as described above in the general procedure for formation of dendritic esters. The core molecule **81** (0.50 g, 2.52 mmol), dry pyridine (5 mL), CH₂Cl₂ (15 mL), DMAP (0.185 g, 1.51 mmol) and the anhydride **112** (3.14 g, 6.05 mmol) were stirred at rt for 12 h under nitrogen. After work up and purification using column chromatography (hexanes/EtOAc; 2:1; R_F 0.26), the product was obtained as colorless syrup (1.66 g, 94 % yield): ¹H NMR (500.13 MHz, CDCl₃) δ 3.31 (s, 12H, 4OCH₃), 3.62 (s, 8H, 4CH₂O), 3.69 (s, 4H, 2CH₂O), 4.09 (t, J = 5 Hz, 4H, ArOCH₂), 4.47 (t, J = 5 Hz, 4H, 2CH₂OC=O), 4.52 (s, 4H, 2CH₂ benzylic), 6.82 (s, 4H, PhH), 7.27 – 7.35 (m, 10H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 172.4 (C=O), 153.0, 138.4, 128.2, 127.4, 127.2, 115.6 (PhC), 73.1 (2CH₂ benzylic), 70.2 (4C_{quat}CO), 67.8 (2CH₂OBn), 66.5 (2PhOC), 62.9 (2COC=O), 59.2 (4OCH₃), 53.5 (2C_{quat}). HR ESI MS: m/z calcd for C₃₈H₅₀NaO₁₂ 721.3194, found 721.3170.

6.6.2.15. Methyl and hydroxyl-terminated first-generation dendrimer (**190**)



Using the general procedure for hydrogenolysis described above, compound **189** (1.45 g, 2.08 mmol), dissolved in dry CH_2Cl_2 (10 mL), dry MeOH (30 mL), and dry THF (15 mL) afforded **190** as a colorless syrup (1.05 g, 98% yield): ^1H NMR (500.13 MHz, acetone- d_6) δ 3.24 (s, 12H, 4OCH₃), 3.51 – 3.55 (m, 8H, 4CH₂O), 3.73 (d, $J = 6$ Hz, 4H, 2CH₂O), 3.80 (t, $J = 6$ Hz, 2H, OH), 4.14 (t, $J = 5$ Hz, 4H, ArOCH₂), 4.39 (t, $J = 5$ Hz, 4H, 2CH₂OC=O), 6.90 (s, 4H, PhH); ^{13}C NMR (125.7 MHz, acetone- d_6) δ 173.0 (2C=O), 153.9, 116.4 (PhC), 71.0 (4C_{quat}CO), 67.3 (2PhOC), 63.4 (2COC=O), 61.0 (2CH₂OH), 59.3 (4OCH₃), 54.9 (2C_{quat}). HR ESI MS: m/z calcd for $\text{C}_{24}\text{H}_{38}\text{NaO}_{12}$ 541.2255, found 541.2254.

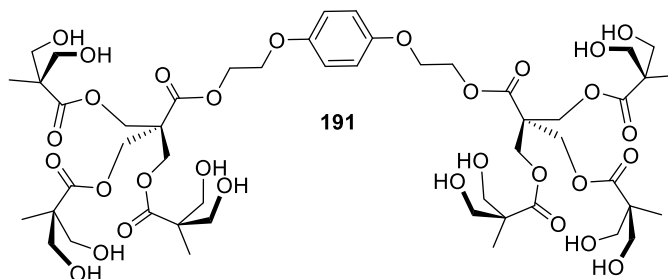
6.6.2.16. Benzylidene-protected second-generation dendrimer with mixed branching (**141**)



Compound **141** was synthesized as described above in the general procedure for dendritic ester formation. Dendrimer **188** (0.550 g, 1.19 mmol), dry pyridine (4 mL), CH_2Cl_2 (12 mL), DMAP (0.262 g, 2.14 mmol) and the anhydride **44** (3.80 g, 8.91 mmol) were stirred at rt for 7 h under nitrogen. Water (4 mL) was added and the ester product precipitated out of solution immediately. The product was collected using suction filtration and was washed with methanol

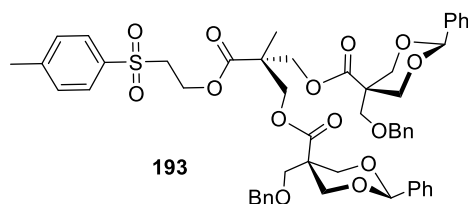
(3 x 5 mL) to afford a colorless crystalline solid (1.95 g, 97 % yield): mp 183 – 185 °C; ^1H NMR (500.13 MHz, acetone- d_6 / DMSO- d_6) δ 3.70 (d, J = 11.5 Hz, 12H, 6H-4_{ax}, 6H-6_{ax}), 3.93 (t, J = 4.5 Hz, 4H, 2PhOCH₂), 4.27 (t, J = 4.5 Hz, 4H, 2CH₂OC=O), 4.44 (d, J = 11.5 Hz, 12H, 6H-4_{eq}, 6H-6_{eq}), 4.47 (s, 12H, 2C_{quat}(CH₂)₃), 5.50 (s, 6H, H-2), 6.73 (s, 4H, PhH), 7.30 – 7.38 (m, 30H, PhH); ^{13}C NMR (125.7 MHz, acetone- d_6 / DMSO- d_6) δ 173.4 (6C=O), 170.5 (2C=O), 153.2, 138.9, 129.1, 128.4, 126.7, 116.0 (PhC), 101.5 (6C-2), 73.2 (6C-4, 6C-6), 66.4 (2PhOC), 64.4 (2CH₂OC=O), 62.0 (2C_{quat}(CH₂)₃), 51.4 (2C_{quat}), 42.9 (6C-5), 17.5 (6CH₃). HR ESI MS: m/z calcd for C₉₂H₁₀₂Na₂O₃₀ 866.3120, found 866. 3048.

6.6.2.17. Second generation hydroquinone-cored dendrimer with mixed branching (191)



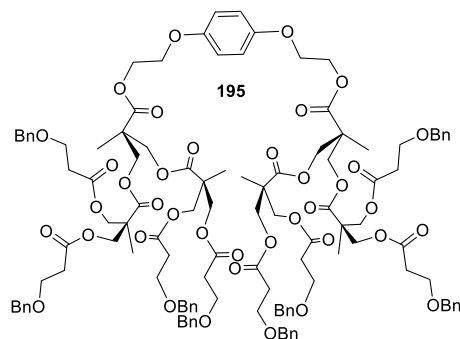
Using the general procedure for hydrogenolysis described above, compound **141** (1.50 g, 0.889 mmol), dissolved in dry CH₂Cl₂ (30 mL), dry MeOH (15 mL), and dry THF (15 mL) afforded **191** as a colorless crystalline solid (0.99 g, 96 % yield): mp 151 – 152 °C; ^1H NMR (500.13 MHz, DMSO- d_6) δ 3.38 – 3.46 (m, 24H, 12CH₂OH), 4.12 (t, J = 5 Hz, 4H, 2PhOCH₂), 4.23 (s, 12H, 2C_{quat}(CH₂)₃), 4.37 (t, J = 5 Hz, 4H, 2CH₂OC=O), 4.67 (t, J = 5.5 Hz, 12H, 12OH), 6.87 (s, 4H, PhH); ^{13}C NMR (125.7 MHz, DMSO- d_6) δ 174.0 (6C=O), 170.2 (2C=O), 152.5, 115.6 (PhC), 65.9 (2PhOCH₂), 63.8 (2CH₂OC=O), 63.6 (12CH₂OH), 61.1 (2C_{quat}(CH₂)₃), 50.4 (6CCH₂OH), 50.3 (2C_{quat}), 16.7 (6CH₃). HR ESI MS: m/z calcd for C₅₀H₇₈NaO₃₀ 1181.4470, found 1181.4470.

6.6.2.18. Protected second generation dendron with mixed branching (193)



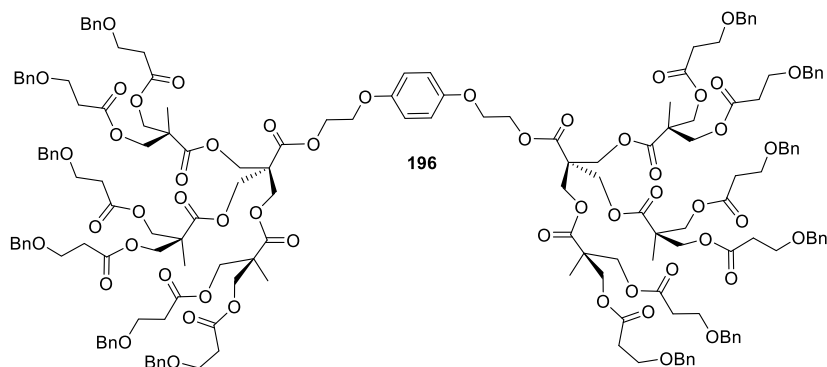
Compound **193** was synthesized as described above in the general procedure for formation of dendritic esters. Compound **192** (1.35 g, 4.27 mmol), dry pyridine (5 mL), CH₂Cl₂ (15 mL), DMAP (0.230 g, 1.88 mmol) and the anhydride **103** (6.54 g, 10.2 mmol) were stirred at rt for 12 h under nitrogen. After work up and purification using column chromatography (hexanes/EtOAc; 2:1; R_F 0.29), the product was obtained as colorless solid (3.44 g, 86% yield): mp 131 – 133 °C ¹H NMR (500.13 MHz, acetone-*d*₆) δ 1.06 (s, 3H, CH₃), 2.35 (s, 3H, PhCH₃), 3.28 (t, *J* = 5.5 Hz, 2H, SCH₂), 3.41 (s, 4H, 2C_{quat}CH₂O), 3.88 (d, *J* = 11.5 Hz, 4H, 2H-4_{ax}, 2H-6_{ax}), 4.19 (s, 4H, C_{quat}2CH₂O), 4.25 (t, *J* = 5.5 Hz, 2H, CH₂O), 4.40 (s, 4H, benzylic), 4.56 – 4.60 (m, 4H, 2H-4_{eq}, 2H-6_{eq}), 5.46 (s, 2H, H-2), 7.25 – 7.39 and 7.65 – 7.71 (m, 24H, PhH); ¹³C NMR (125.7 MHz, acetone-*d*₆) δ 172.1, 171.4 (C=O), 145.1, 137.9, 137.5, 136.4, 130.1, 129.1, 128.6, 128.3, 128.2, 128.0, 127.7 (PhC), 101.8 (C-2), 73.6 (benzylic), 70.5 (C_{quat}2CH₂O), 70.4 (C-4, C-6), 65.6 (2C_{quat}CH₂O), 58.4 (SCH₂CH₂O), 54.7 (SCH₂CH₂O), 47.8 (2C_{quat}), 46.9 (C_{quat}), 21.7 (ArCH₃), 17.3 (CH₃). HR ESI MS: *m/z* calcd for C₅₂H₅₆O₁₄NaS 959.3287, found 959.3283.

6.6.2.19. Benzyl-functionalized hydroquinone-cored second-generation dendrimer (195)



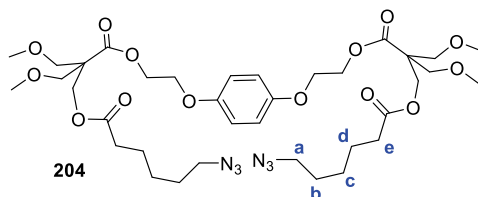
Compound **195** was synthesized as described above in the general procedure for formation of dendritic esters. Second generation dendrimer **182** (0.779 g, 0.860 mmol), dry pyridine (4 mL), CH₂Cl₂ (12 mL), DMAP (0.250 g, 2.07 mmol) and the anhydride **194** (2.95 g, 8.62 mmol) were stirred at rt for 4 h under nitrogen. After work up and purification using column chromatography (hexanes/ EtOAc; 1:1; R_F 0.31), the product was obtained as colorless syrup (1.79 g, 95% yield): ¹H NMR (500.13 MHz, CDCl₃) δ 1.27 (s, 12H, 4CH₃), 1.29 (s, 6H, 2CH₃), 2.68 (t, *J* = 6.5 Hz, 16H, 8CH₂OBn), 3.78 (t, *J* = 6.5 Hz, 16H, 8CH₂C=O), 4.14 (t, *J* = 4.5 Hz, 4H, 2OCH₂CH₂OC=O), 4.29 – 4.33 (m, 24H, C_{quat}CH₂O), 4.48 (t, *J* = 4.5 Hz, 4H, ArOCH₂), 4.58 (s, 16H, benzylic), 6.89 (s, 4H, PhH), 7.33 – 7.42 (m, 40H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 172.1 (2C=O), 172.0 (4C=O), 171.0 (8C=O), 152.9, 138.0, 128.4, 127.6, 115.7 (PhC), 73.0 (8CH₂, benzylic), 66.2 (ArOCH₂), 65.6 (2C_{quat}2CH₂), 65.4 (8CH₂OBn), 65.2 (4C_{quat}2CH₂), 46.6 (2C_{quat}), 46.4 (4C_{quat}), 34.9 (8CH₂C=O), 17.7 (4CH₃), 17.5 (2CH₃). HR ESI MS: *m/z* calcd for C₁₂₀H₁₄₂NaKO₃₈ 1126.4351, found 1126.4393.

6.6.2.20. Benzyl-functionalized second-generation dendrimer with mixed branching (196)



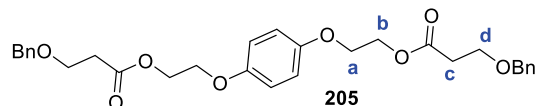
Compound **196** was synthesized as described above in the general procedure for formation of dendritic esters. Second generation dendrimer **191** (0.350 g, 0.302 mmol), dry pyridine (4 mL), CH₂Cl₂ (12 mL), DMAP (0.133 g, 1.09 mmol) and the anhydride **194** (1.55 g, 4.53 mmol) were stirred at rt for 4 h under nitrogen. After work up and purification using column chromatography (hexanes/ EtOAc; 1:1; R_F 0.21), the product was obtained as colorless syrup (0.834 g, 89% yield): ¹H NMR (500.13 MHz, CDCl₃) δ 1.20 (s, 6CH₃), 2.62 (t, *J* = 6.5 Hz, 24H, 12CH₂OBn), 3.72 (t, *J* = 6.5 Hz, 24H, 12CH₂C=O), 4.07 (t, *J* = 4.0 Hz, 4H, 2OCH₂CH₂OC=O), 4.25 (s, 24H, 6C_{quat}2CH₂O), 4.32 (s, 12H, 2C_{quat}3CH₂O), 4.44 (t, *J* = 4.0 Hz, 4H, ArOCH₂), 4.51 (s, 24H, benzylic), 6.83 (s, 4H, PhH), 7.27 – 7.36 (m, 60H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 171.7 (6C=O), 170.9 (12C=O), 169.3 (2C=O), 152.8, 138.0, 128.4, 128.3, 127.6, 115.6 (PhC), 72.9 (12CH₂, benzylic), 65.9 (ArOCH₂), 65.3 (12CH₂OBn), 65.0 (6C_{quat}2CH₂), 64.3 (2CH₂OC=O), 61.3 (2C_{quat}3CH₂O), 50.8 (2C_{quat}), 46.4 (6C_{quat}), 34.8 (12CH₂C=O), 17.5 (6CH₃).

6.6.2.21. Azide-functionalized divalent first-generation dendrimer (**204**)



Compound **204** was synthesized using the general esterification procedure using TBTU. 6-Azidohexanoic acid **203** (0.190 g, 1.20 mmol) and diol **190** (0.260 g, 1.00 mmol (OH)) reacted for 4 h to give **204** (0.34 g, 85% yield) as a colorless syrup after purification using column chromatography (hexanes/ EtOAc; 3:2; R_F 0.36): ¹H NMR (300.15 MHz, CDCl₃) δ 1.28 – 1.35 (m, 4H, H_c), 1.47 – 1.59 (m, 8H, H_b, H_d), 2.21 (t, *J* = 7 Hz, 4H, H_e), 3.19 (t, *J* = 7 Hz, 4H, H_a), 3.24 (s, 12H, 4OCH₃), 3.50 (s, 8H, 2C_{quat}2CH₂O), 4.05 (t, *J* = 4.5 Hz, 4H, ArOCH₂), 4.23 (s, 4H, C_{quat}CH₂OC=O), 4.39 (t, *J* = 4.5 Hz, 4H, CH₂OC=O), 6.77 (s, 4H, PhH); ¹³C NMR (75.5 MHz, CDCl₃) δ 172.6, 171.5 (C=O), 153.0, 115.7 (PhC), 70.2 (4COMe), 66.5 (ArOCH₂), 63.1 (OCH₂CH₂O), 62.0 (CH₂OC=O), 59.3 (4OCH₃), 52.4 (2C_{quat}), 51.1 (C_a), 33.8 (C_e), 28.4, 26.1 (C_b, C_d), 24.3 (C_c). HR ESI MS: *m/z* calcd for C₃₆H₅₆N₆NaO₁₄ 819.3747, found 819.3743.

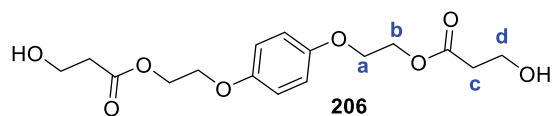
6.6.2.22. Benzyl-functionalized divalent dendrimer (**205**)



Compound **205** was synthesized using the general esterification procedure using TBTU. 3-Benzyloxypropanoic acid (0.216 g, 1.20 mmol) and diol **81** (0.100 g, 1.00 mmol (OH)) reacted for 1.5 h to give **205** (0.23 g, 89% yield) as a colorless solid after purification using column

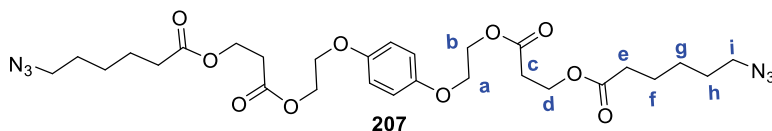
chromatography (hexanes/ EtOAc; 2:1; R_F 0.29): mp 105 – 107 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 2.69 (t, $J = 6.5$ Hz, 4H, H_c), 3.78 (t, $J = 6.5$ Hz, 4H, H_d), 4.12 (t, $J = 4.5$ Hz, 4H, H_a), 4.44 (t, $J = 4.5$ Hz, 4H, H_b), 4.54 (s, 4H, benzylic), 6.85 (s, 4H, PhH), 7.29 – 7.35 (m, 10H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 171.5 (C=O), 153.0, 138.0, 128.4, 127.6, 115.6 (PhC), 73.0 (CH_2 , benzylic), 66.5 (C_a), 65.5 (C_d), 62.9 (C_b), 35.0 (C_c). HR ESI MS: m/z calculated for $\text{C}_{30}\text{H}_{34}\text{NaO}_8$ 545.2146, found 545.2139.

6.6.2.23. Hydroxyl-terminated divalent dendrimer (206)



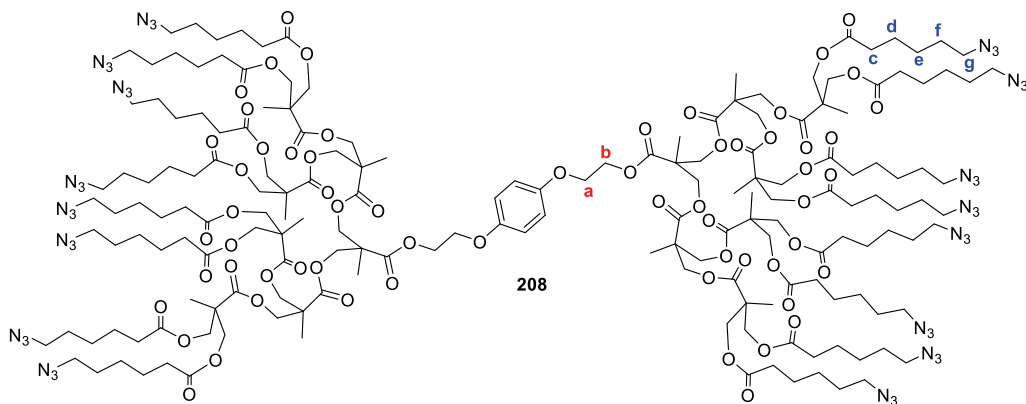
Using the general procedure for hydrogenolysis described above, compound **205** (0.75 g, 1.44 mmol), dissolved in dry CH_2Cl_2 (5 mL), dry MeOH (10 mL), and dry THF (5 mL) afforded **206** as a colorless crystalline solid (0.48 g, 98% yield): mp 118 – 120 °C ^1H NMR (500.13 MHz, methanol- d_4) δ 2.56 (t, $J = 6.5$ Hz, 4H, H_c), 3.82 (t, $J = 6.5$ Hz, 4H, H_d), 4.13 (t, $J = 4.5$ Hz, 4H, H_a), 4.40 (t, $J = 4.5$ Hz, 4H, H_b), 6.87 (s, 4H, PhH); ^{13}C NMR (125.7 MHz, methanol- d_4) δ 173.5 (C=O), 154.5, 116.7 (PhC), 67.7 (C_a), 64.2 (C_b), 58.7 (C_d), 38.4 (C_c). HR ESI MS: m/z calcd for $\text{C}_{16}\text{H}_{22}\text{NaO}_8$ 365.1207, found 365.1205.

6.6.2.24. Azide-functionalized divalent dendrimer (207)



Compound **207** was synthesized using the general esterification procedure using TBTU. 6-Azidohexanoic acid **203** (0.190 g, 1.20 mmol) and diol **206** (0.170 g, 1.00 mmol (OH)) reacted for 2 h to give **207** (0.29 g, 94% yield) as a colorless solid after purification using precipitation from diethyl ether. Purification was also achieved using column chromatography (hexanes/EtOAc; 1:1; R_F 0.53): mp 102 – 105 °C; ^1H NMR (300.15 MHz, CDCl_3) δ 1.36 – 1.40 (m, 4H, H_g), 1.51 – 1.65 (m, 8H, H_f and H_h), 2.27 (t, $J = 7.4$ Hz, 4H, H_e), 2.69 (t, $J = 6.2$ Hz, 4H, H_c) 3.23 (t, $J = 6.8$ Hz, 4H, H_i), 4.10 (t, $J = 4.5$ Hz, 4H, H_a), 4.33 (t, $J = 6.2$ Hz, 4H, H_d), 4.42 (t, $J = 4.5$ Hz, 4H, H_b), 6.82 (s, 4H, PhH); ^{13}C NMR (75.5 MHz, CDCl_3) δ 173.1, 170.7 (C=O), 153.1, 115.8 (PhC), 66.6 (C_a), 63.2 (C_b), 59.7 (C_d), 51.2 (C_i), 33.9 (C_c , C_e), 28.6 (C_h), 26.2 (C_f), 24.4 (C_g). HR ESI MS: m/z calcd for $\text{C}_{28}\text{H}_{40}\text{N}_6\text{NaO}_{10}$ 643.2696, found 643.2701.

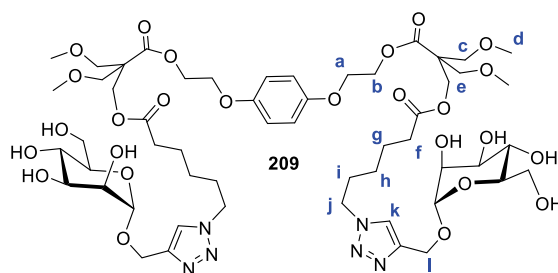
6.6.2.25. Azide-functionalized hydroquinone-cored third-generation dendrimer (**208**)



Compound **208** was synthesized using the general esterification procedure using TBTU. 6-Azidohexanoic acid **203** (0.190 g, 1.20 mmol) and dendrimer **186** (0.114 g, 1.00 mmol (OH)) reacted for 12 h to give **208** (0.20 g, 79% yield) as a colorless syrup after purification using column chromatography (hexanes/EtOAc; 3:2; R_F 0.16): ^1H NMR (500.13 MHz, CDCl_3) δ 1.20 (s, 24H, 8 CH_3), 1.21 (s, 12H, 4 CH_3), 1.28 (s, 6H, 2 CH_3), 1.33 - 1.40 (m, 32H, H_e), 1.55 - 1.63

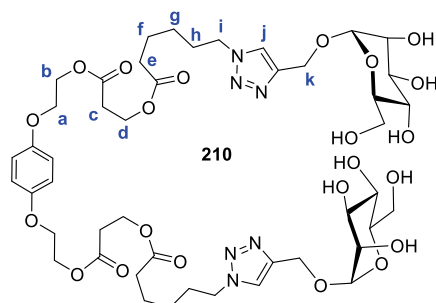
(m, 64H, H_d, H_f), 2.30 (t, $J = 7.5$ Hz, 32H, H_c), 3.25 (t, $J = 6.9$ Hz, 32H, H_g), 4.11 - 4.28 (m, 60H, H_b, 28CH₂), 4.42 (t, $J = 4.5$ Hz, 4H, H_a), 6.81 (s, 4H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 172.8, 172.03, 172.01, 171.5 (C=O), 153.0, 115.7 (PhC), 66.3 (C_a), 66.1 (2C_{quat}2CH₂O), 65.2 (4C_{quat}2CH₂O), 64.9 (8C_{quat}2CH₂O), 63.9 (C_b), 51.2 (C_g), 46.7 (4C_{quat}), 46.6 (2C_{quat}), 46.4 (8C_{quat}), 33.8 (C_c), 28.6 (C_f), 26.2 (C_d), 24.4 (C_e), 17.8 (8CH₃), 17.6 (4CH₃), 17.5 (2CH₃).

6.6.2.26. Divalent α -D-mannopyranoside-terminated dendrimer (209)



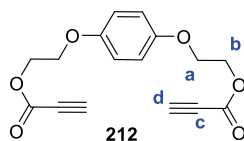
The azide functionalized divalent dendrimer **204** (0.440 g, 0.552 mmol) and propargyl α -D-mannopyranoside **198** (0.280 g, 1.28 mmol) were dissolved in THF (15 mL). To the clear solution was added sodium ascorbate (0.060 g, 0.303 mmol) and a solution of copper(II) sulfate pentahydrate (0.030 g, 0.120 mmol) in water (15 mL). The mixture was then vigorously stirred overnight and concentrated under reduced pressure. Purification using size exclusion chromatography on Sephadex LH-20 column gave the product as a thick colorless syrup (0.55 g, 81% yield). ¹H NMR (500.13 MHz, D₂O) δ 1.14 (br, 4H, H_h), 1.44 (br, 4H, H_g), 1.60 – 1.80 (br, m, 4H, H_i), 2.18 (br, 4H, H_f), 3.17 – 4.92 (m, 54H, H_a, H_b, H_c, H_d, H_e, H_j, H_l, H-1, H-2, H-3, H-4, H-5, H-6), 6.88 (s, 4H, PhH), 8.05 (br, 2H, H_k). HR ESI MS: m/z calcd for C₅₄H₈₄N₆Na₂O₂₆ 639.2610, found 639.2628.

6.6.2.27. Extended α -D-mannopyranoside-terminated dendrimer (210)



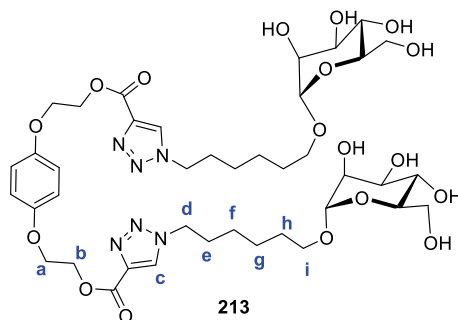
The azide functionalized divalent dendrimer **207** (0.700 g, 1.13 mmol) and propargyl α -D-mannopyranoside **198** (0.570 g, 2.61 mmol) were dissolved in THF (20 ml). To the clear solution was added sodium ascorbate (0.120 g, 0.606 mmol) and a solution of copper(II) sulfate pentahydrate (0.060 g, 0.240 mmol) in water (15 mL). The mixture was then vigorously stirred overnight and concentrated under reduced pressure. Purification using size exclusion chromatography on Sephadex LH-20 column gave the product as a thick colorless syrup (1.03 g, 86% yield): ^1H NMR (500.13 MHz, methanol- d_4) δ 1.13 – 1.28 (q, $J = 7.5$ Hz, 4H, H_g), 1.52 – 1.61 (q, $J = 7.5$ Hz, 4H, H_f), 1.81 – 1.88 (q, $J = 7.5$ Hz, 4H, H_h), 2.25 (t, $J = 7.5$ Hz, 4H, H_e), 2.69 (t, $J = 6$ Hz, 4H, H_c), 3.55 – 3.89 (m, 12H, H-2, H-3, H-4, H-5, H-6), 4.23 (t, $J = 4.5$ Hz, 4H, H_a), 4.30 (t, $J = 6$ Hz, 4H, H_d), 4.37 (t, $J = 7$ Hz, 4H, H_i), 4.41 (t, $J = 4.5$ Hz, 4H, H_b), 4.64 (d, $J = 12.5$ Hz, 2H, H_k), 4.79 (d, $J = 12.5$ Hz, 2H, H_{k'}), 4.86 (br, 2H, H-1), 6.86 (s, 4H, PhH), 8.00 (s, 2H, C=CH, triazole); ^{13}C NMR (125.7 MHz, methanol- d_4) δ 174.8, 172.5 (C=O), 154.4 (PhC), 145.2 (C_{sp2}), 125.3 (CH_{sp2}), 116.6 (PhC), 100.7 (C-1), 74.9 (C-5), 72.5 (C-3), 71.9 (C-2), 68.5 (C-4), 67.8 (C_a), 64.5 (C-6), 62.9 (C_b), 61.1 (C_k), 60.7 (C_d), 51.1 (C_i), 34.6 (C_c), 34.5 (C_e), 30.8 (C_h), 26.8 (C_f), 25.2 (C_g). HR ESI MS: m/z calcd for C₄₆H₆₈N₆NaO₂₂ 1079.4279, found 1079.4246.

6.6.2.28. Alkyne-terminated divalent dendrimer (212)



Compound **212** was synthesized using the general esterification procedure using TBTU. Propynoic acid (0.084 g, 1.20 mmol) and diol **81** (0.099 g, 1.00 mmol (OH)) reacted for 1 h to give the product (0.12 g, 78% yield) as a colorless solid after purification using column chromatography (hexanes/ EtOAc; 3:1; R_F 0.18): mp 99 – 102 °C; ^1H NMR (500.13 MHz, CDCl_3) δ 2.92 (s, 2H, H_d), 4.16 9 (t, $J = 4.5$ Hz, 4H, H_a) 4.52 (t, $J = 4.5$ Hz, 4H, H_b), 6.85 (s, 4H, PhH); ^{13}C NMR (125.7 MHz, CDCl_3) δ 153.1 (C=O), 152.7, 115.9 (PhC), 75.5 (C_d), 74.5 (C_c), 66.2 (C_a), 64.6 (C_b). HR ESI MS: m/z calcd for $\text{C}_{16}\text{H}_{14}\text{NaO}_6$ 325.0683, found 325.0678.

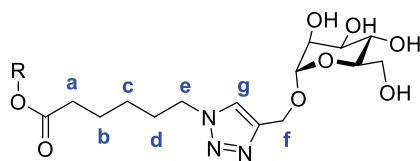
6.6.2.29. A divalent α -D-mannopyranoside-terminated dendrimer with a hexyl linker (213)



The dialkyne **212** (0.260 g, 0.860 mmol) and 6-azidohexyl α -D-mannopyranoside **201** (0.550 g, 1.80) were dissolved in THF (15 ml). To the clear solution was added sodium ascorbate (0.090 g, 0.454) and a solution of copper(II) sulfate pentahydrate (0.045 g, 0.180 mmol) in water (15 mL). The mixture was then vigorously stirred overnight and concentrated under reduced

pressure. Purification using size exclusion chromatography on Sephadex LH-20 column gave the product as a colorless solid (0.72 g, 89% yield): mp 132 – 134 °C ^1H NMR (500.13 MHz, DMSO- d_6 / methanol- d_4) δ 1.11 – 1.40 (m, 8H, H_f, H_g), 1.41 – 1.50 (m, 4H, H_h), 1.75 – 1.85 (quint, J = 7 Hz, 4H, H_e), 3.26 – 3.67 (m, 16H, H_i, H-2, H-3, H-4, H-5, H-6), 4.18 (br, 4H, H_a), 4.36 (t, J = 7 Hz, H_d), 4.54 (br, 4H, H_b), 4.58 (br, 2H, H-1), 6.85 (s, 4H, PhH), 8.58 (s, 2H, H_c); ^{13}C NMR (125.7 MHz, DMSO- d_6 / methanol- d_4) δ 161.9 (C=O), 154.2 (PhC), 140.2 (C_{sp2} triazole), 130.2 (C_c), 116.9 (PhC), 101.4 (C-1), 75.0 (C-5), 72.5 (C-3), 72.0 (C-2), 68.5 (C-4), 67.9 (C_i), 67.7 (C_a), 64.7 (C_b), 62.8 (C-6), 51.4 (C_d), 31.0 (C_h), 30.3 (C_e), 27.1 (C_f), 26.7 (C_g). HR ESI MS: m/z calcd for C₄₀H₆₀N₆NaO₁₈ 935.3856, found 935.3848.

6.6.2.30. Third generation dendrimer bearing 16 mannose residues (211)



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The azide functionalized dendrimer **208** (1.40 g, 0.346 mmol) and propargyl α -D-mannopyranoside **198** (1.51 g, 6.92 mmol) were dissolved in DMF (35 ml). To the clear solution was added sodium ascorbate (0.290 g, 1.46 mmol) and a solution of copper(II) sulfate pentahydrate (0.145 g, 0.581 mmol) in water (3 mL). The mixture was then vigorously stirred overnight and concentrated under reduced pressure. Purification using size exclusion chromatography on Sephadex LH-20 column gave the product as a thick colorless syrup (2.16 g, 83% yield): ^1H NMR (500.13 MHz, D₂O) δ 1.09 – 1.30 (br, 74H, 14CH₃, 16CH₂ (H_c)), 1.50 (br, 32H, 16CH₂ (H_b)), 1.79 (br, 32H, 16CH₂ (H_d)), 2.25 (br, 32H, 16CH₂ (H_a)), 3.57 – 4.89 ((br, m,

240H (32H, 16CH₂, H_e), (32H, 16CH₂, H_f), (112H, 16sugar x 7H), (8H, OCH₂CH₂O), (8H, 2C_{quat}2CH₂O), (16H, 4C_{quat}2CH₂O), (32H, 8C_{quat}2CH₂O)), 6.82 (br, 4H, PhH), 8.04 (br, 16H, H_g); ¹³C NMR (125.7 MHz, D₂O) δ 174.0, 172.7, 172.0 (C=O), 152.8 (PhC), 144.1 (C_{sp2} triazole), 125.1 (C_g), 115.9 (PhC), 99.4 (C-1), 73.0 (C-5), 70.6 (C-3), 70.0 (C-2), 66.6 (C-4), 65.3 (2C, OCH₂CH₂O), 60.8 (C-6), 59.7 (C_f), 50.1 (C_e), 46.5, 46.3 (C_{quat}), 33.3 (C_a), 29.3 (C_d), 25.4 (C_b), 23.8 (C_c).

Chapter 7: Conclusions

7.1. Achievements Described in the Thesis

The results in Chapter 2 of this thesis detailed the preparation of core molecules.⁹¹ Selected cores are aromatic with non-benzylic and non-phenolic hydroxyl groups for ester stability that will not be cleaved under mild acid (for selective removal of isopropylidene acetals) or hydrogenolysis conditions (for reductive removal of benzylidene acetals and benzyl ethers). Because the selected cores (Figure 2.1) all have terminal CH₂CH₂OH groups, a single convenient route was employed for their synthesis.⁹¹ Chapter 2 also discussed the manipulation of the hydroxyl groups of pentaerythritol using various chemical transformations and various protection/ deprotection strategies for the preparation of new types of tribranched dendrons.

Chapter 3 described an efficient esterification procedure between carboxylic and all types of alcohols using coupling reagents COMU, TBTU, and TATU in the presence of organic bases.^{274,275} Esterification of secondary alcohols promoted by TBTU and TATU required a base, such as DBU, that is stronger than tertiary amines. Only COMU was effective for the preparation of esters from tertiary alcohols, and then only when the still stronger base, MTBD was used. The base sensitivity of the TBTU and TATU promoted reactions was used for the regioselective esterification of primary hydroxyls in diols and polyols.²⁷⁵

The results detailed in Chapters 4 and 5 of this thesis illustrated a facile synthesis of a library of Lyme disease glycolipid antigens³¹⁹ and the direct synthesis of maradolipids and other trehalose 6-monoesters and 6,6'-diesters.³⁷⁰ These short syntheses were possible because of the base sensitivity of the TBTU-promoted reactions (Chapter 3), which allowed selective esterifications of primary hydroxyl groups of unprotected carbohydrates under mild conditions.

Chapter 6 discussed the assembly of cores and dendrons into polyester dendrimers.^{91,371} Various species were isolated here. However, dendrimers incorporating only tribranched dendrons could not be synthesized beyond the first generation because of steric hindrance. It appears that dendrimers where tribranched dendrons are incorporated at one or more generations among dendrimers that are mainly formed from dibranched dendrons can be synthesized. These would meet the goal of having more slowly hydrolyzable polyester dendrimer frameworks. The preparation of this type of layered polyester dendrimers is currently underway.

7.2. Future Work

7.2.1. Synthesis

Another avenue of investigation we are interested in is the preparation of dendronized polymers tipped with biologically active compounds and their evaluation as potential anti-adhesion drugs. Dendronized polymers are typically formed by a backbone of a linear polymer with pendant reactive anchor groups, from each of which emerges a dendron. These macromolecules are multivalent systems that integrate the two-dimensional structure of polymers and the three-dimensional structure of dendrons, to create polymers with optimized binding to the bacterial carbohydrate receptors,³⁷² among other important applications.^{373,374} Herein, dendrons like the azide-functionalized acid shown in Figure 20 have been prepared for the synthesis of functionalized dendronized polymers with polyvinyl alcohol (PVA) using the “graft-to” approach. The use of PVA is advantageous because it is commercially available in a range of molar masses, it is non-toxic, and the large number of hydroxyl groups can be readily functionalized in a variety of ways to produce diverse multivalent systems.³⁷⁵⁻³⁸⁰

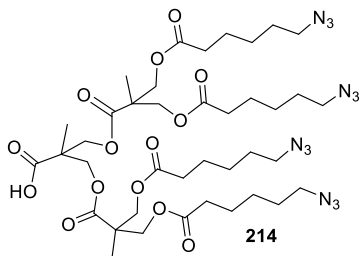


Figure 20 Azide-functionalized acid dendron

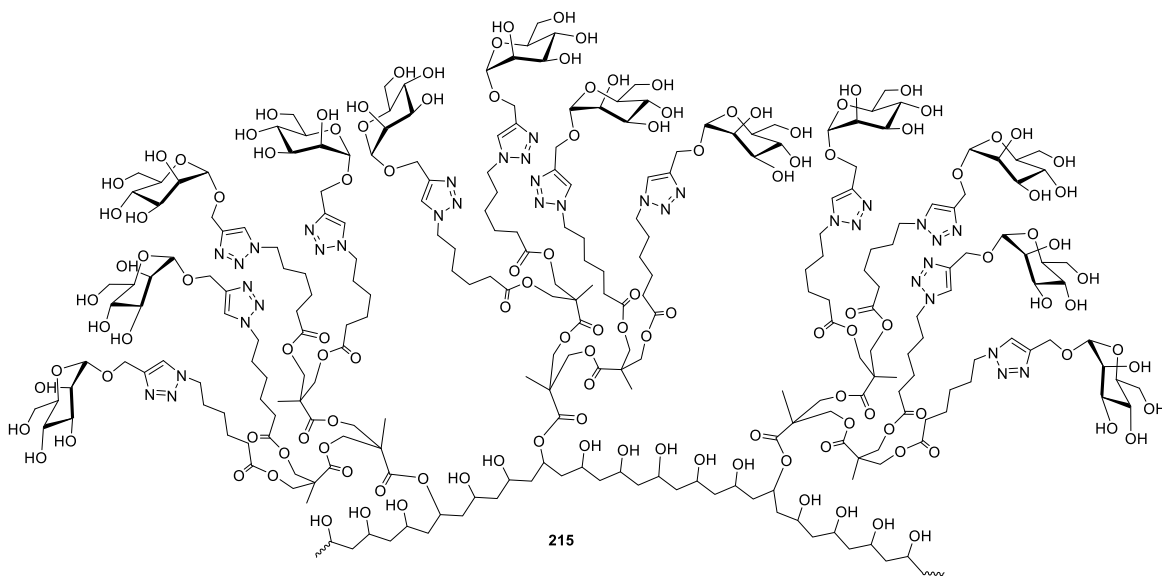


Figure 21 A potential mannose-tipped dendronized polymer based on PVA

Esterification between acid dendron **214** and PVA would result in azide-terminated dendronized polymers, which can easily be tipped with sugar residues using click chemistry. Figure 21 depicts a potential mannose-tipped dendronized polymer based on PVA. This type of compound is designed to interact with the FimH receptors at the tip of the pili of uropathogenic *E. coli* strains. The dendrons can provide the high local concentrations of α -linked-D-mannopyranoside residues with glycosidic linkages favorable³⁵¹ for binding. High local concentrations provide an entropic advantage for binding.³⁴⁰ The polymer provides a framework

spanning the 100 nm distance between pili³⁸¹ increasing the binding effectiveness to single bacteria and will also allow simultaneous binding of many bacteria.

7.2.2. Testing

Professor Beat Ernst of the Department of Pharmaceutical Sciences of the University of Basel in Switzerland has agreed to evaluate the polyester glycodendrimers discussed in Chapter 6 and also these mannose-tipped dendronized polymers against urinary tract infections. Professor Ernst has developed an extensive program of developing antiadhesion drugs against UTIs focusing on small molecules, and he has developed several methods for evaluating their effectiveness.^{361,362,382-384}

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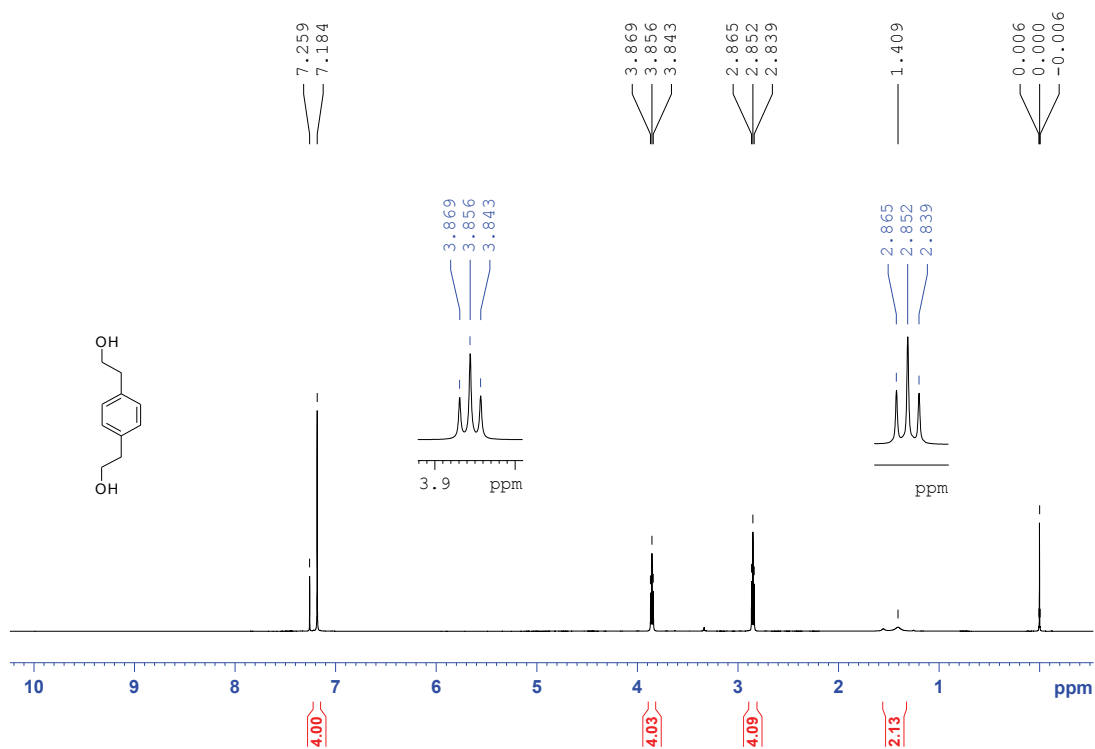
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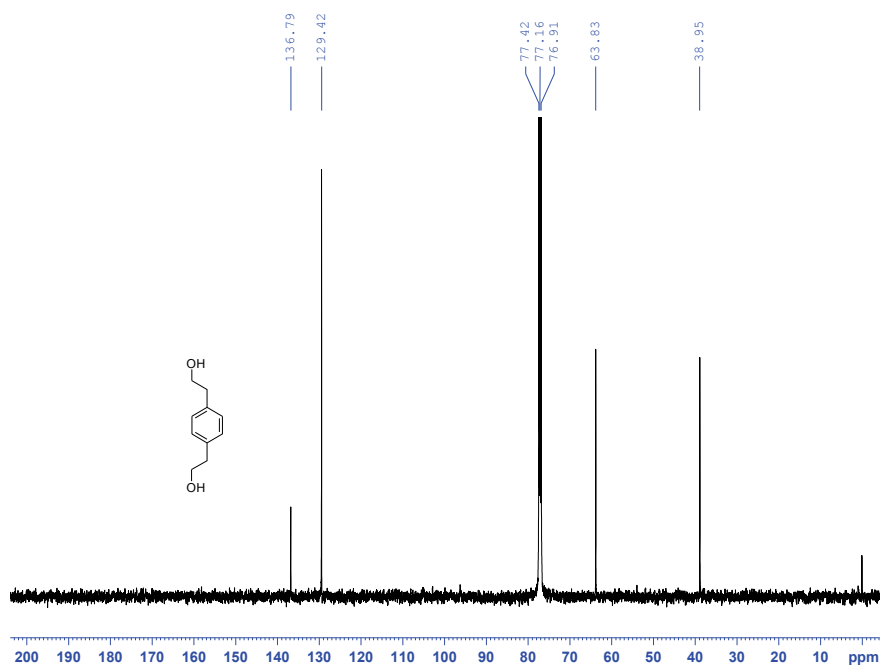
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APPENDIX B: NMR SPECTRAL DATA

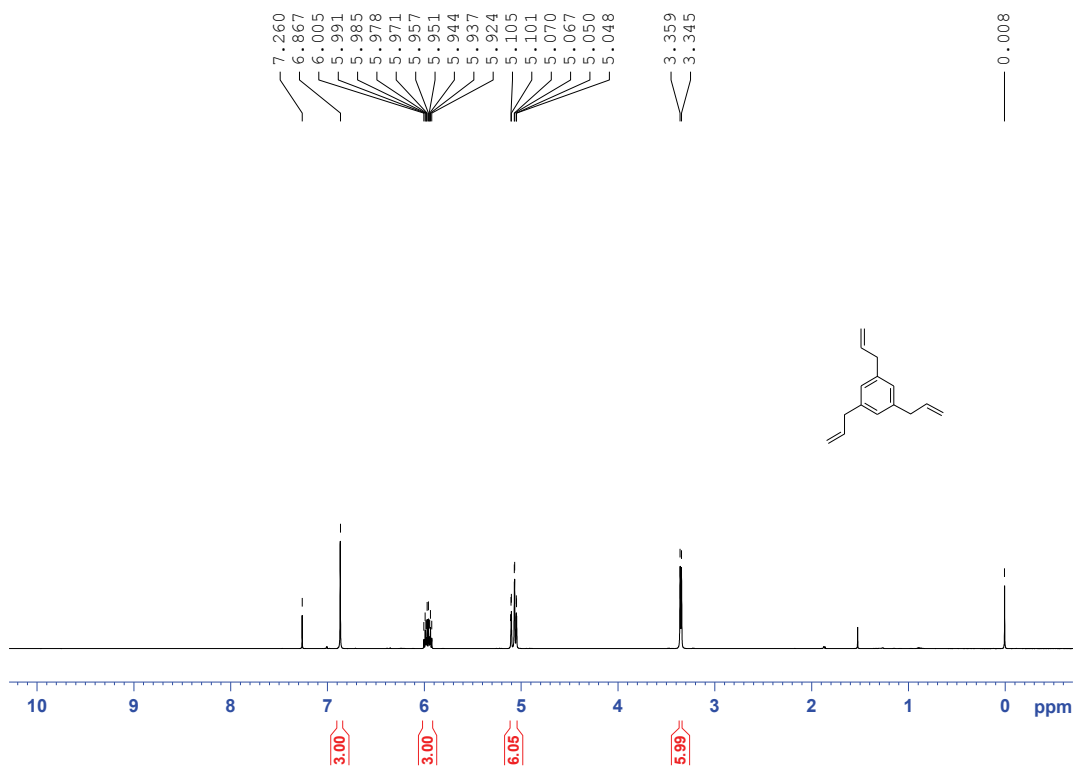
500.13 MHz ^1H NMR spectrum of 1,4-benzenediethanol (79) in chloroform-*d*



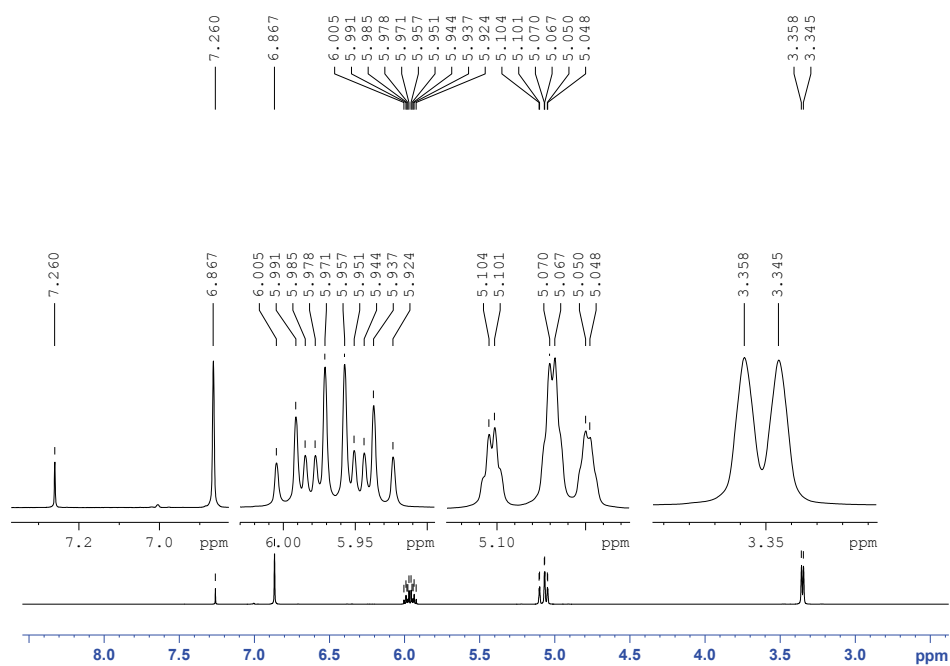
125.7 MHz ^{13}C NMR spectrum of 1,4-benzenediethanol (79) in chloroform-*d*



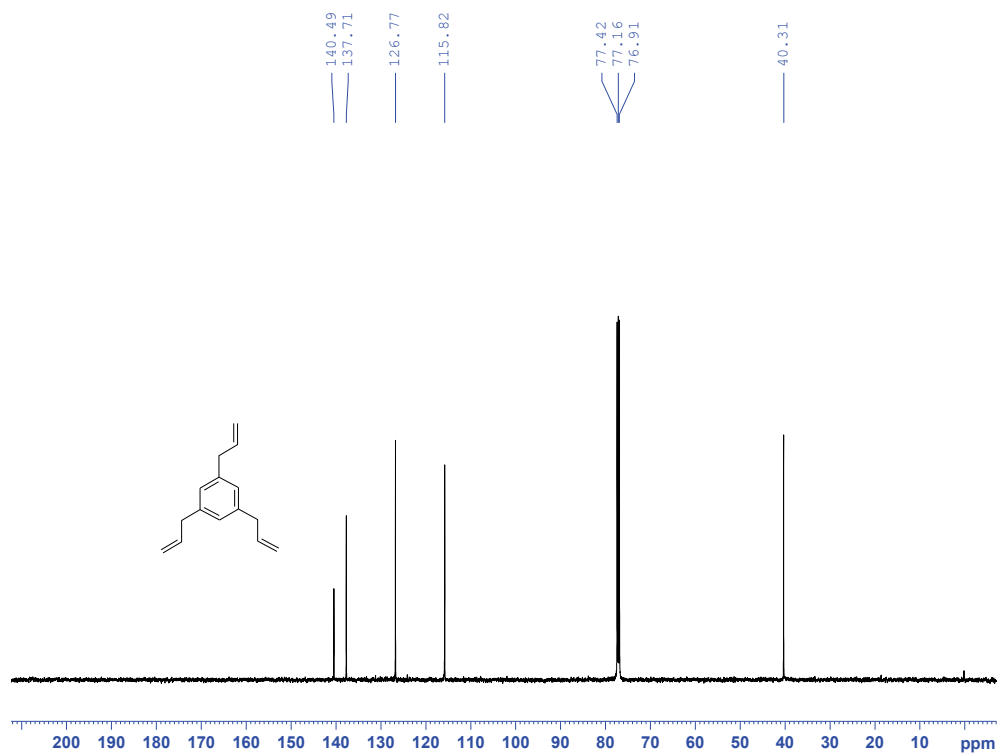
500.13 MHz ^1H NMR spectrum of 1,3,5-triallylbenzene (89) in chloroform-*d*



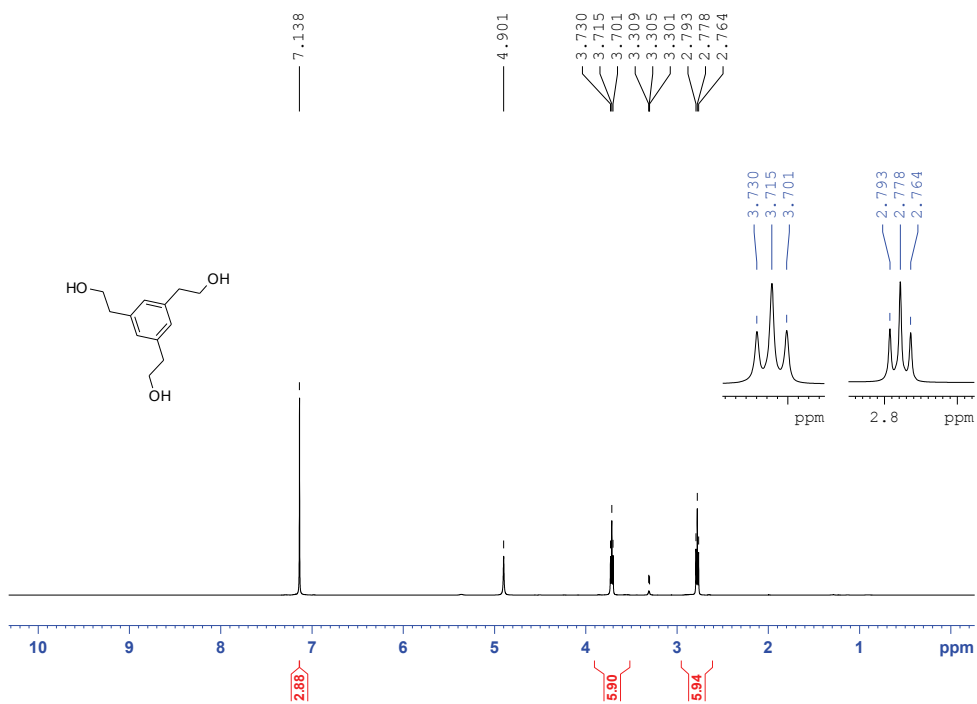
Expansions of the 500.13 MHz ^1H NMR spectrum of 1,3,5-triallylbenzene (89) in chloroform-*d*



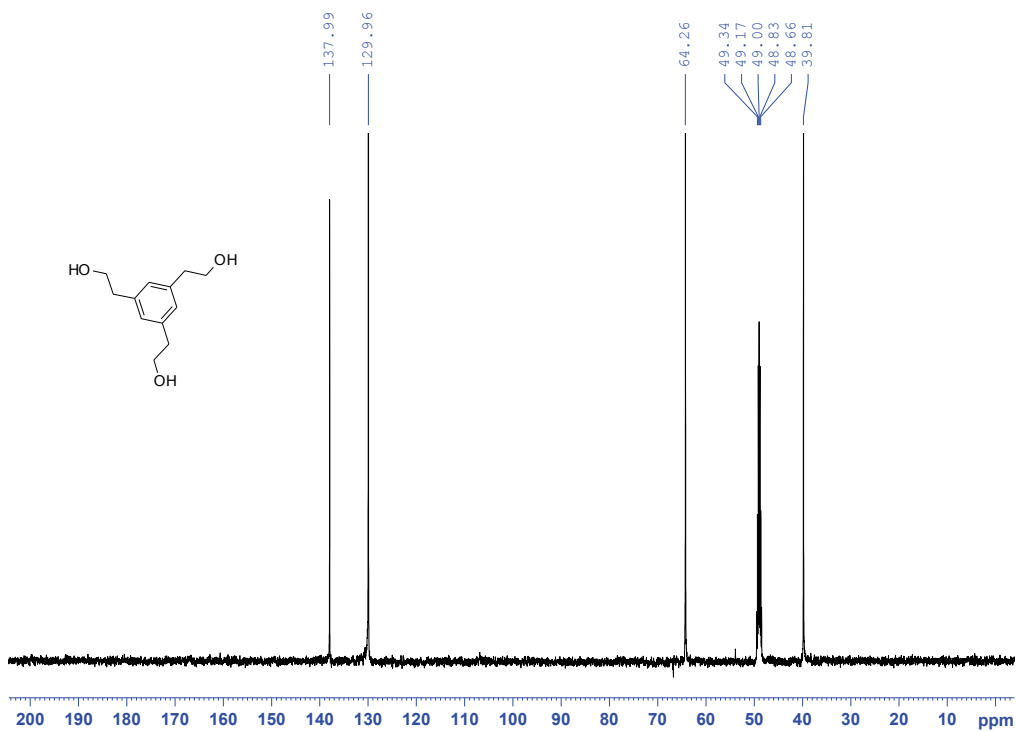
125.7 MHz ^{13}C NMR spectrum of 1,3,5-triallylbenzene (89) in chloroform-*d*



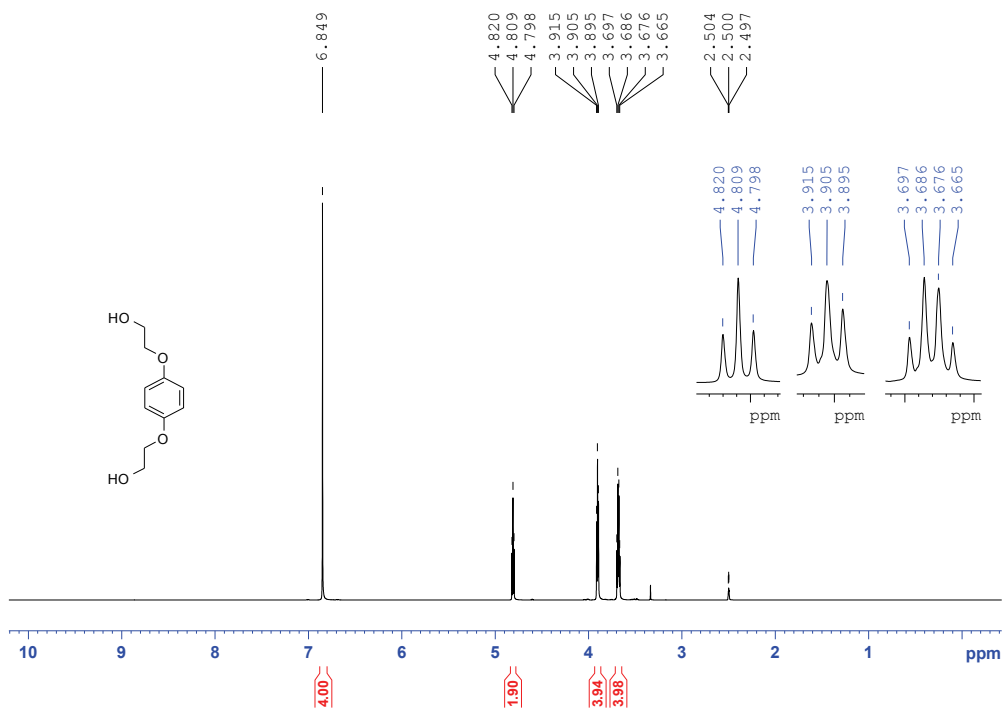
500.13 MHz ^1H NMR spectrum of 1,3,5-benzenetriethanol (80) in methanol-*d*₄



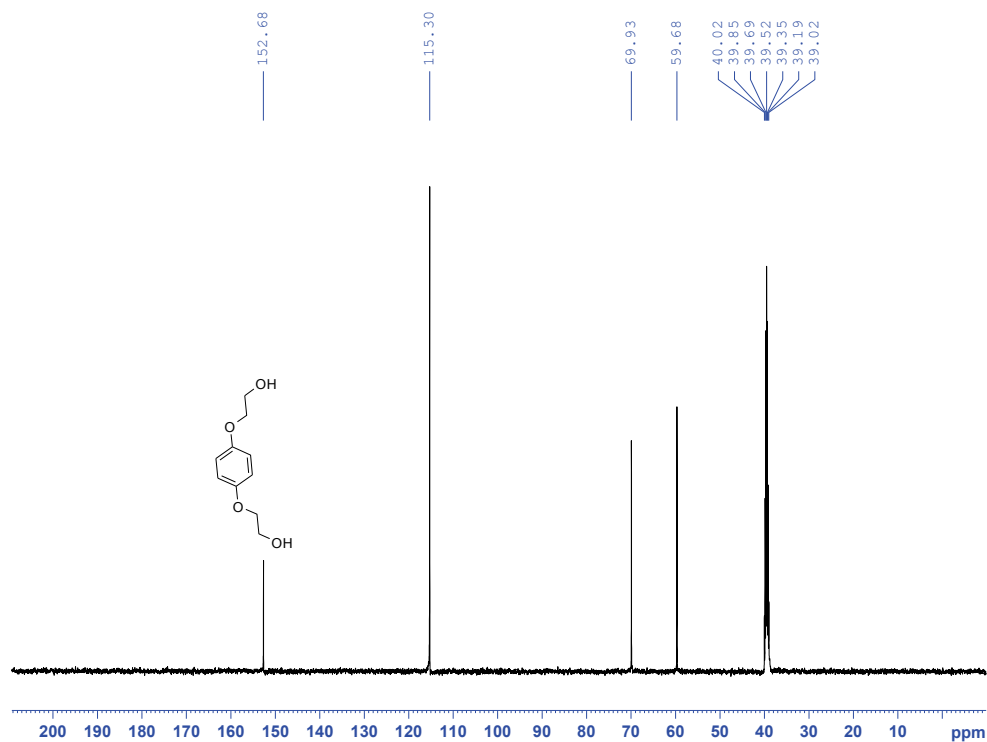
125.7 MHz ^{13}C NMR spectrum of 1,3,5-triethanolbenzene (80) in methanol- d_4



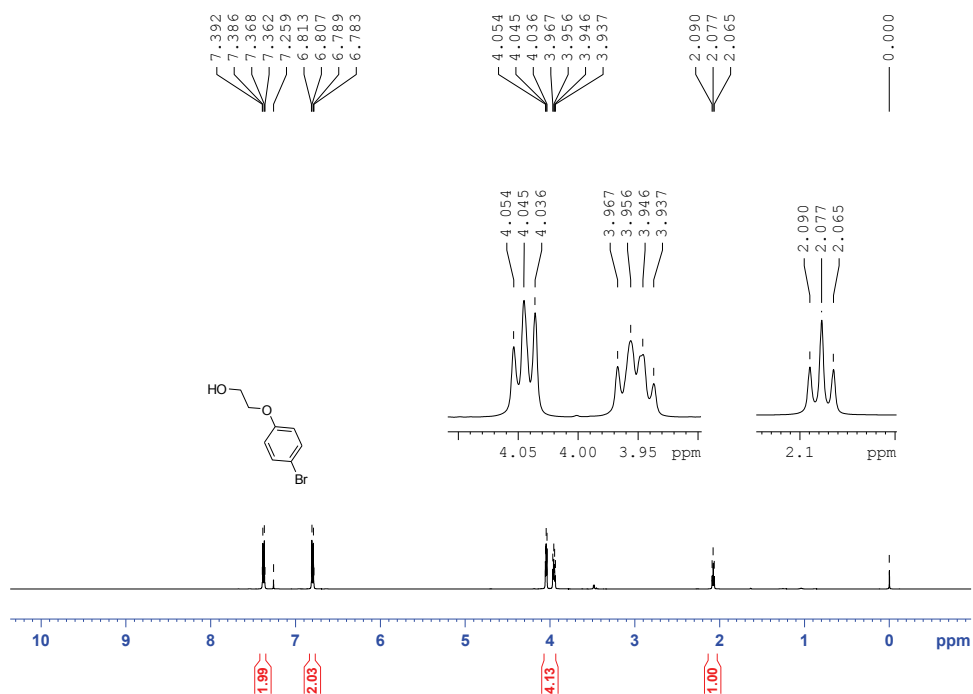
500.13 MHz ^1H NMR spectrum of 1,4-bis-(2-hydroxyethoxy)benzene (81) in DMSO- d_6



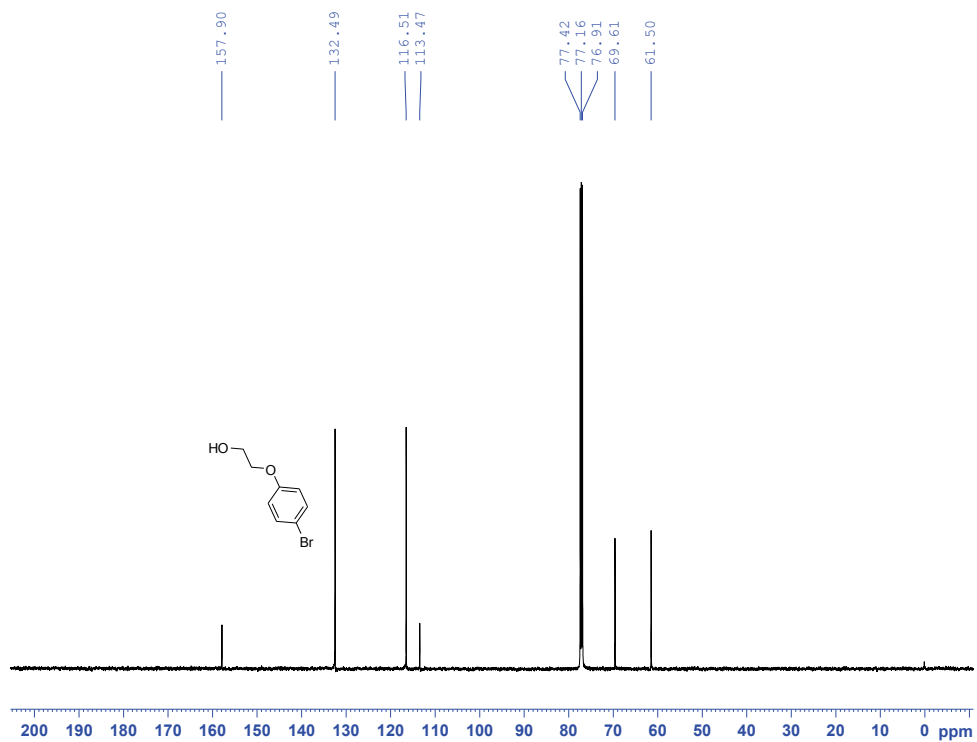
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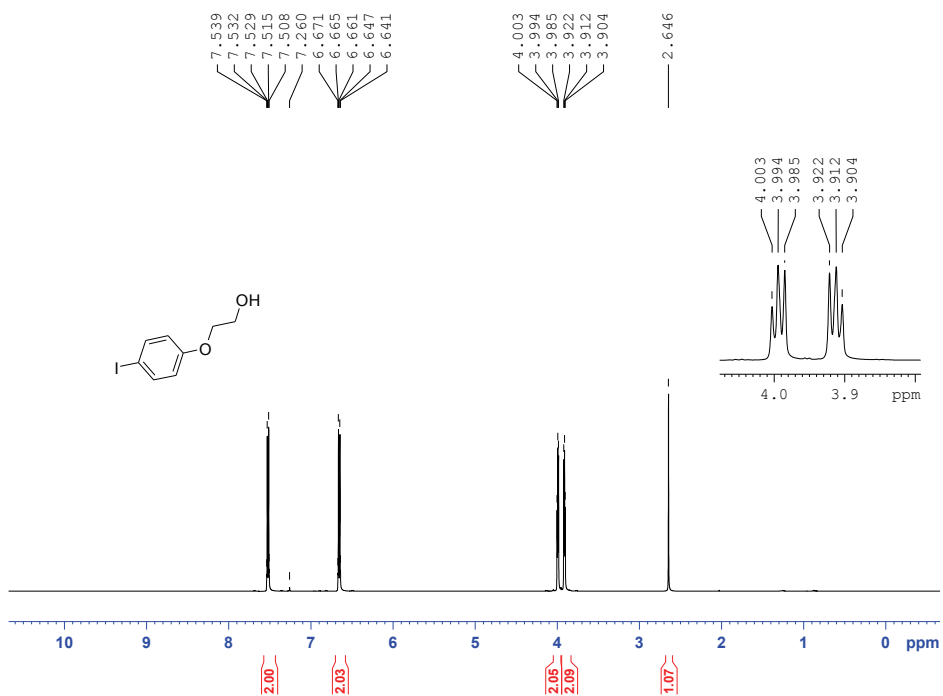
500.1 MHz ^1H NMR spectrum of 2-(4-bromophenoxy)ethanol (82) in $\text{chloroform-}d$



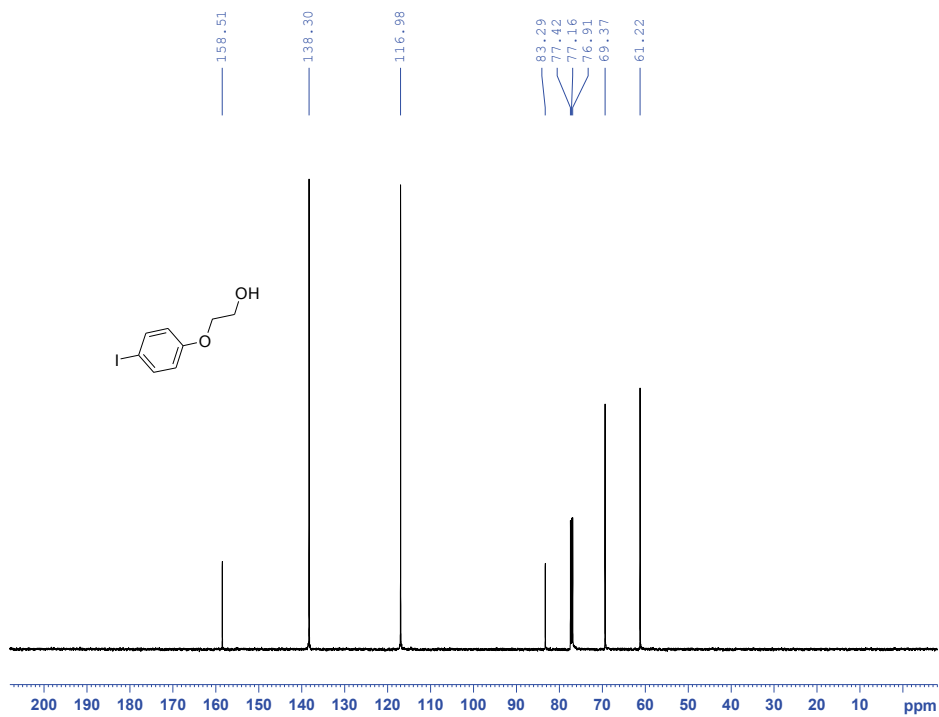
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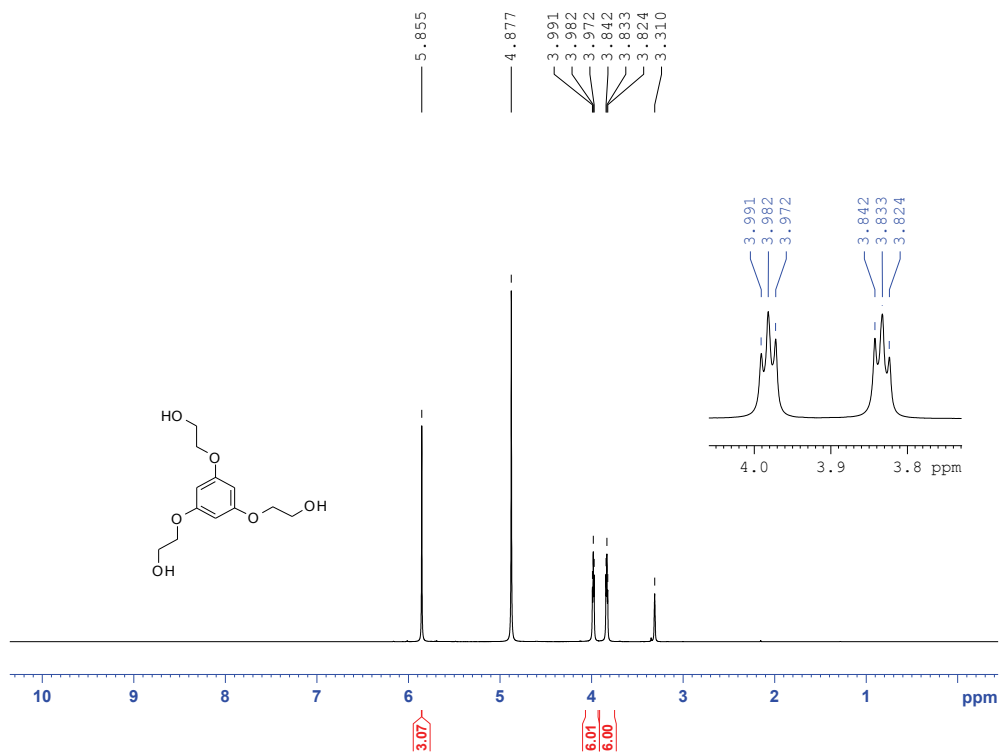
500.13 MHz ^1H NMR spectrum of 2-(4-iodophenoxy)ethanol (83) in chloroform-*d*



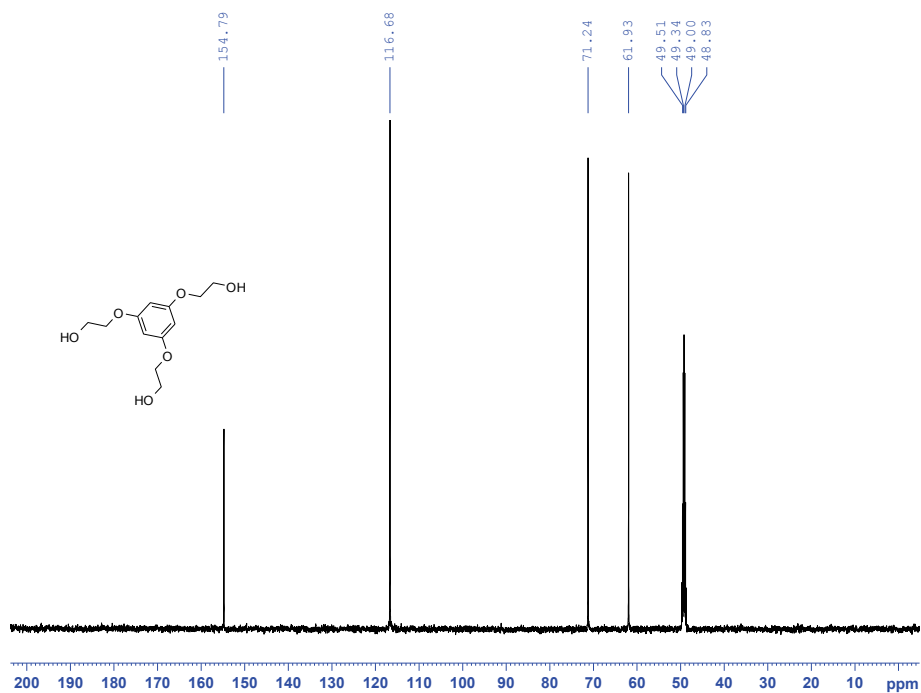
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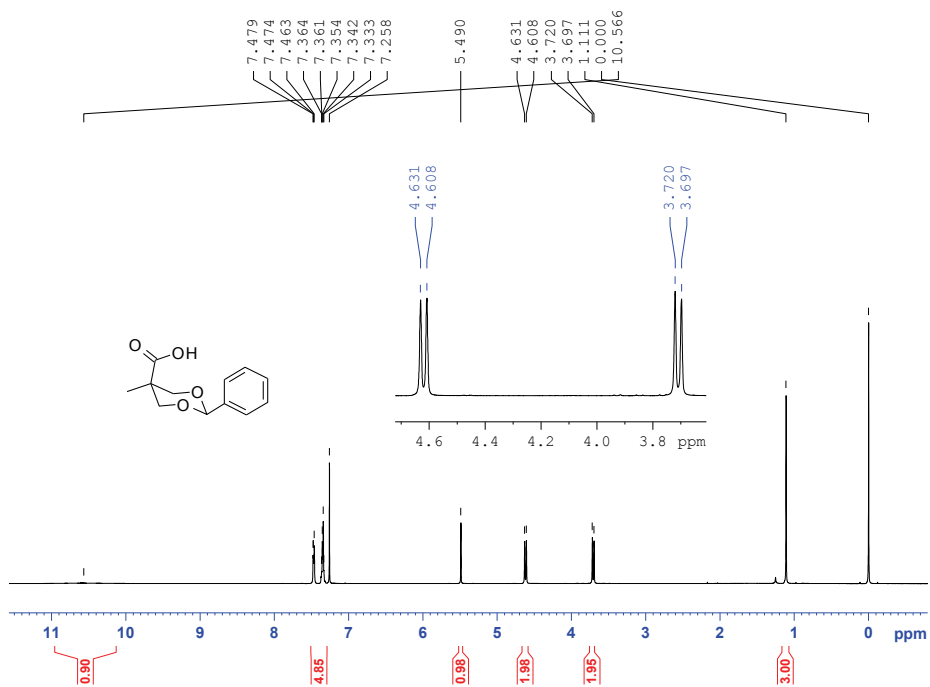
500.13 MHz ^1H NMR spectrum of 1,3,5-tris-(2-hydroxyethoxy)benzene (84) in methanol- d_4



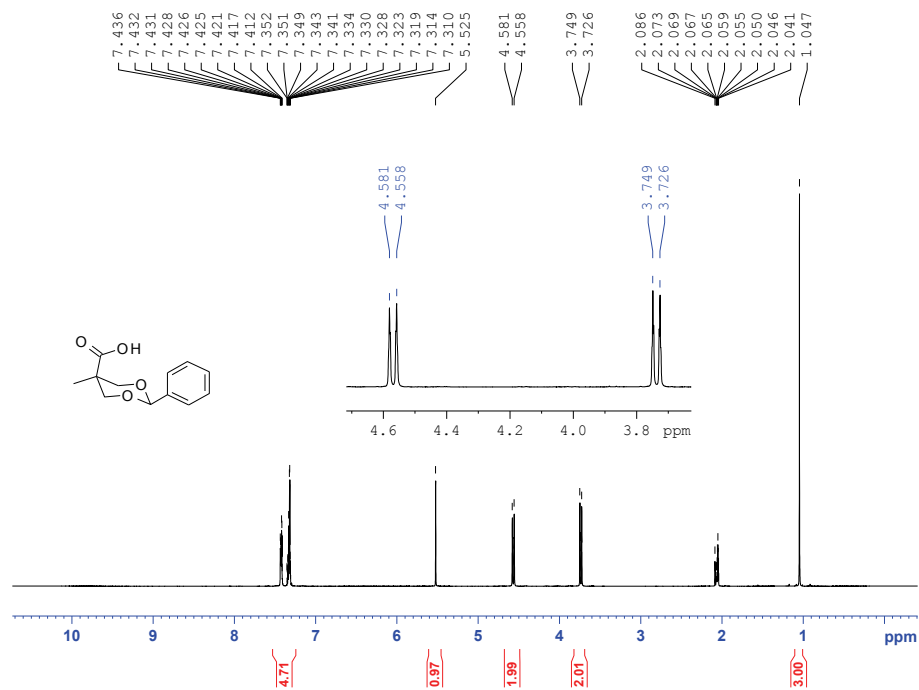
125.7 MHz ^{13}C NMR spectrum of 1,3,5-tris-(2-hydroxyethoxy)benzene (84) in methanol- d_4



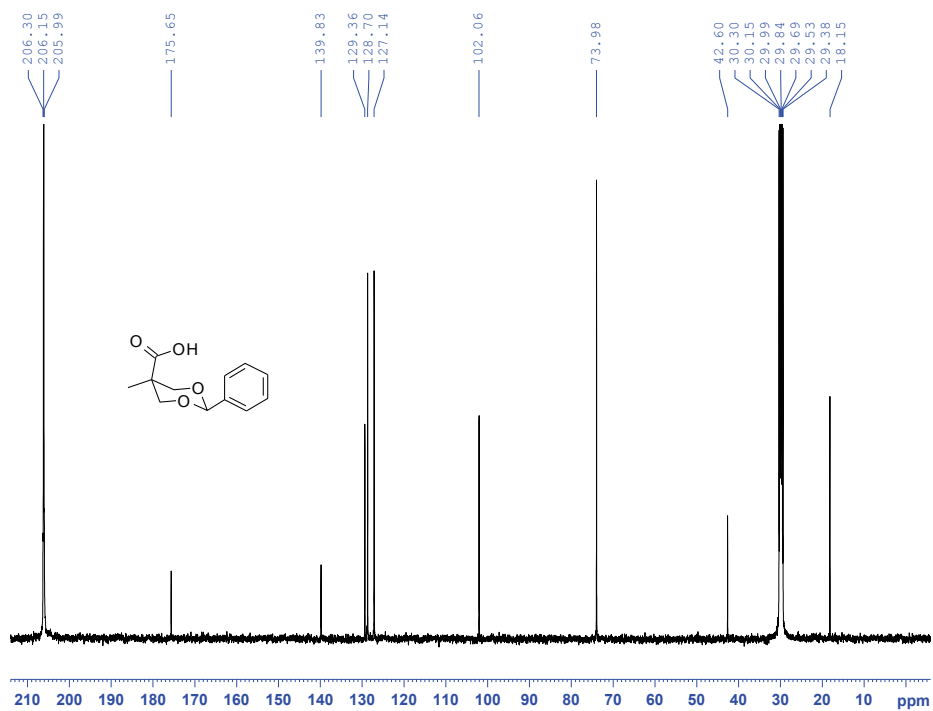
500.13 MHz ^1H NMR spectrum of 5-methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (43) in chloroform- d .



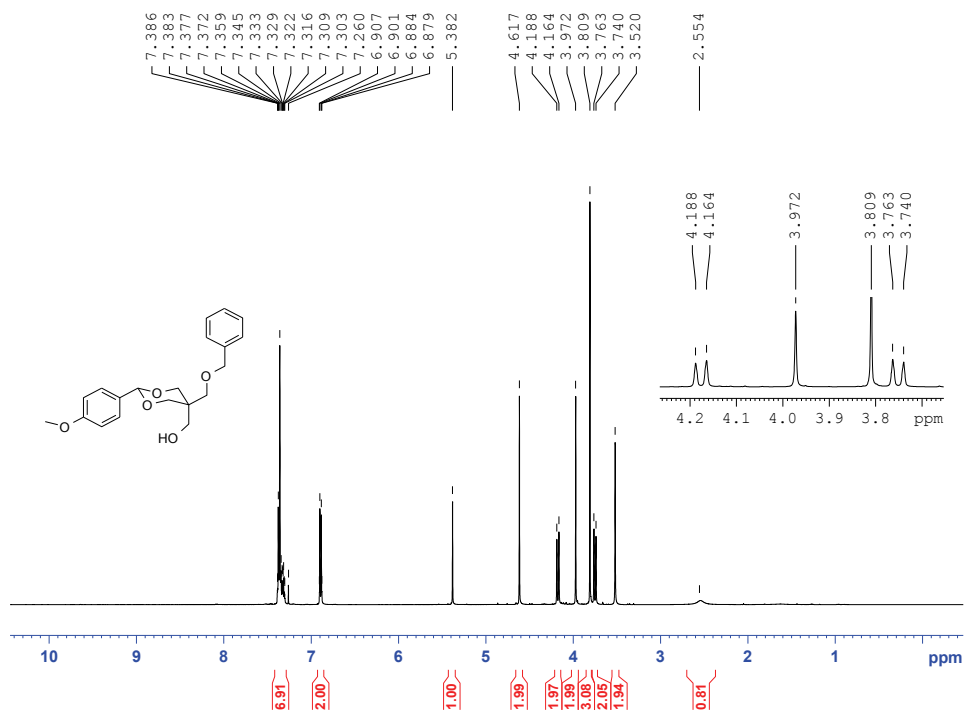
500.13 MHz ^1H NMR spectrum of 5-methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (43) in acetone- d_6 .



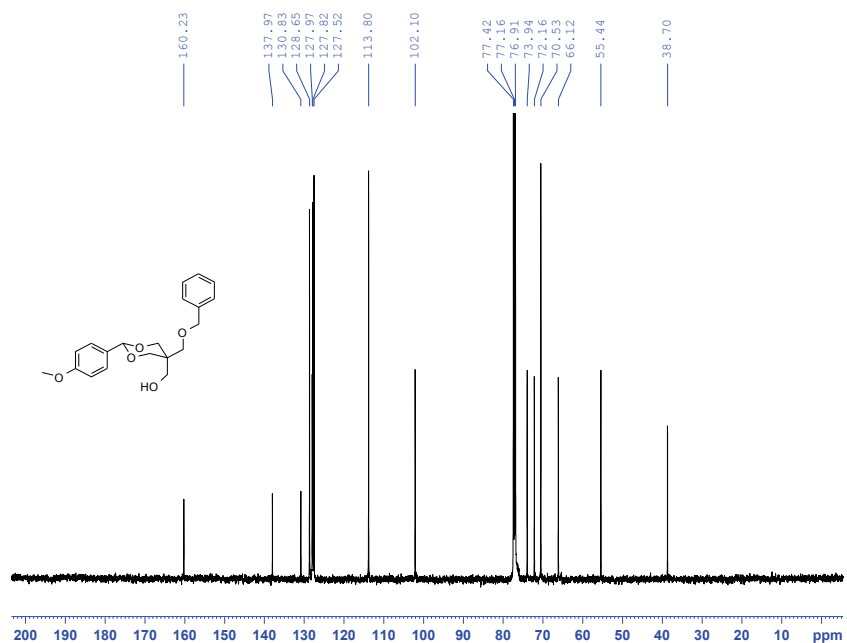
125.7 MHz ^{13}C NMR spectrum of 5-methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (43) in acetone- d_6 .



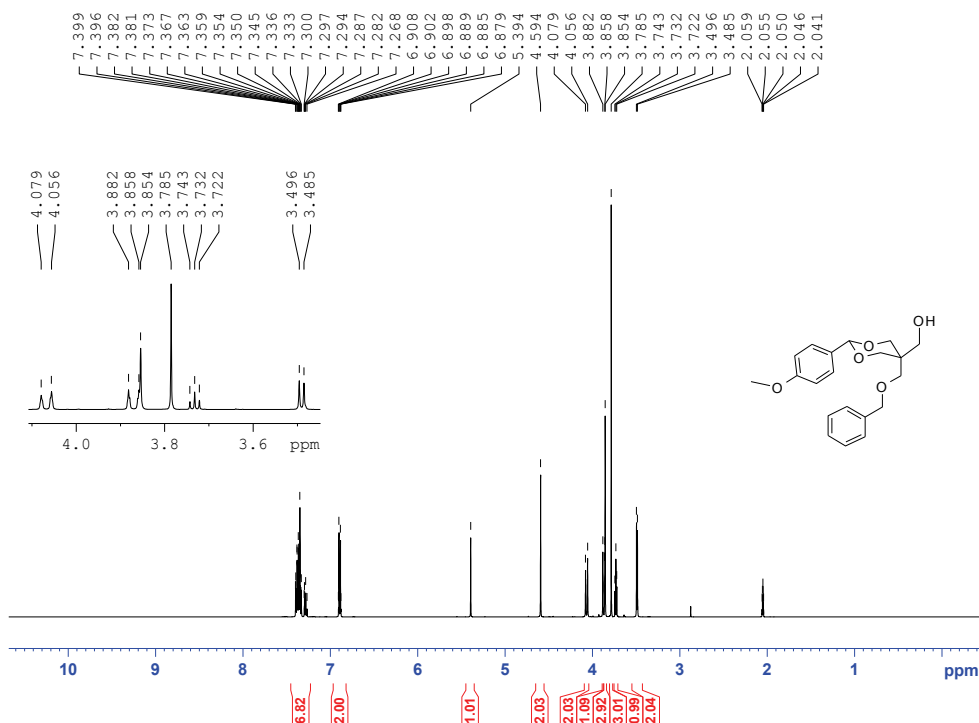
500.13 MHz ^1H NMR spectrum of *trans*-5-benzyloxymethyl-*cis*-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (98) in chloroform-*d*



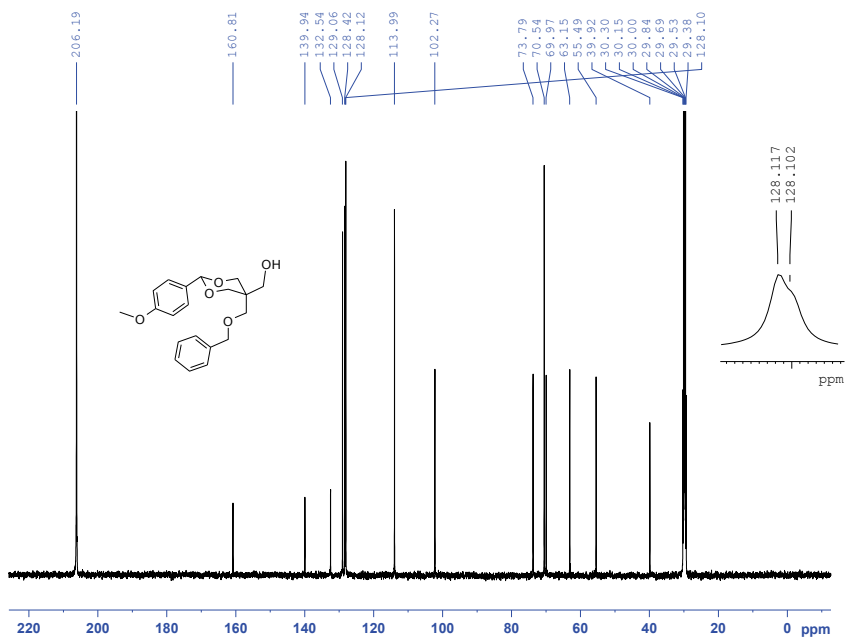
125.7 MHz ^{13}C NMR spectrum of *trans*-5-benzyloxymethyl-*cis*-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (98) in chloroform-*d*



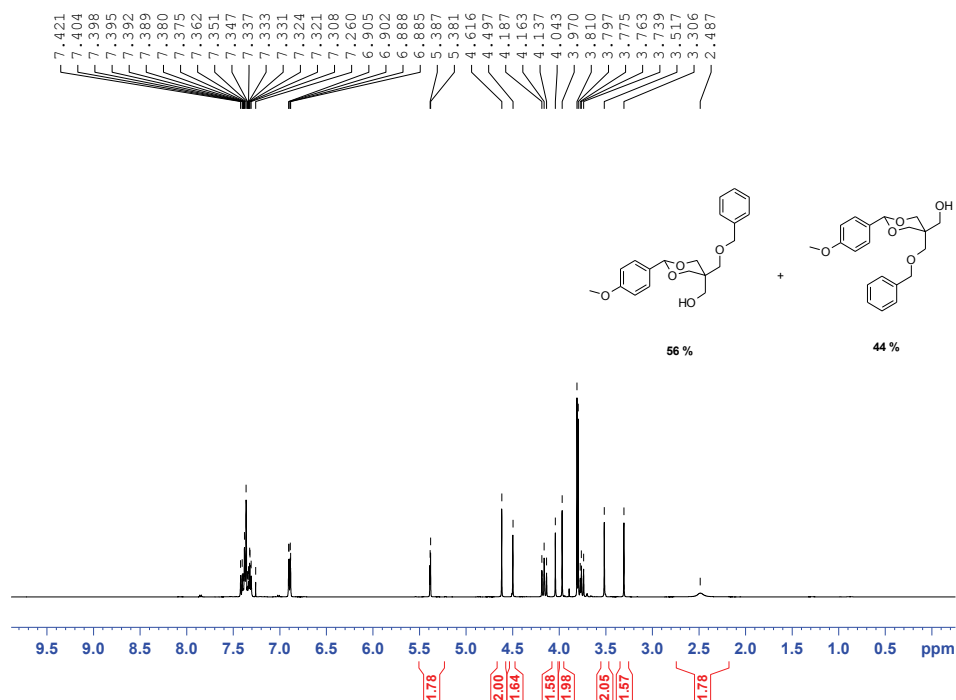
500.13 MHz ^1H NMR spectrum of *cis*-5-benzyloxymethyl-*trans*-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (99) in acetone- d_6



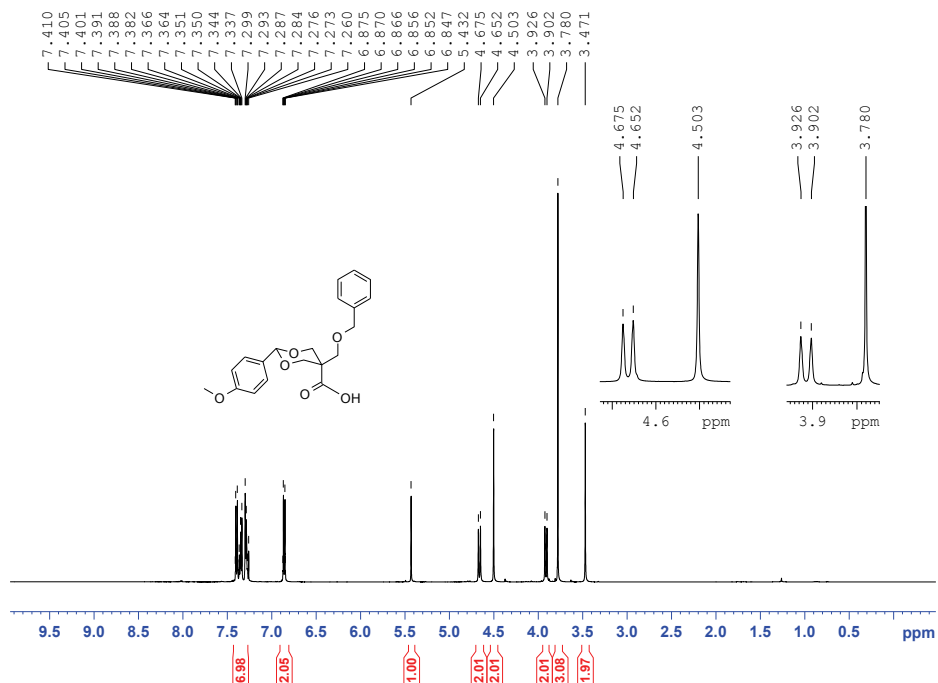
125.7 MHz ^{13}C NMR spectrum of *cis*-5-benzyloxymethyl-*trans*-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (99) in acetone- d_6



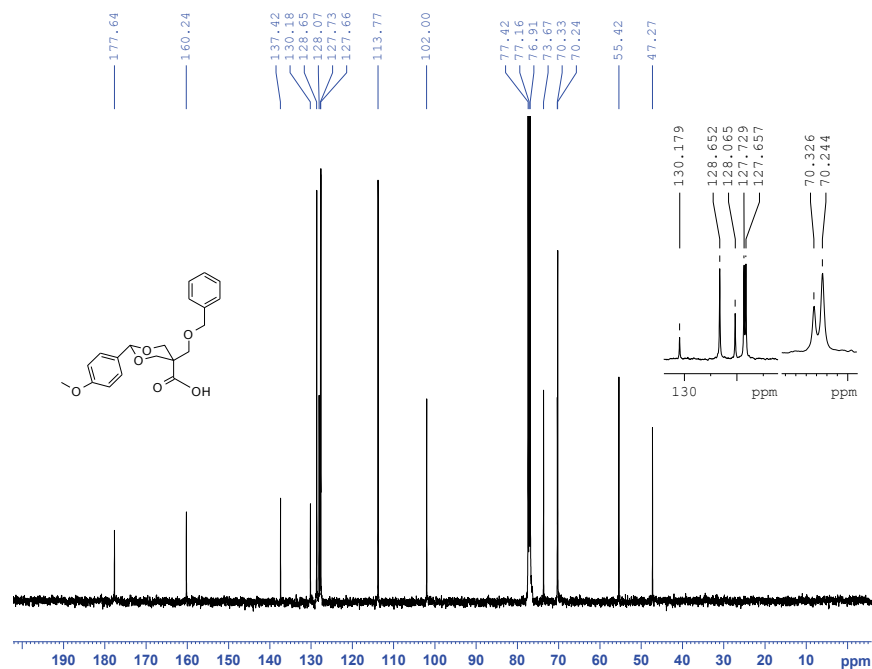
500.13 MHz ^1H NMR spectrum of *cis*-5-benzyloxymethyl-*trans*-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (99) dissolved in chloroform-*d* for 36 hours



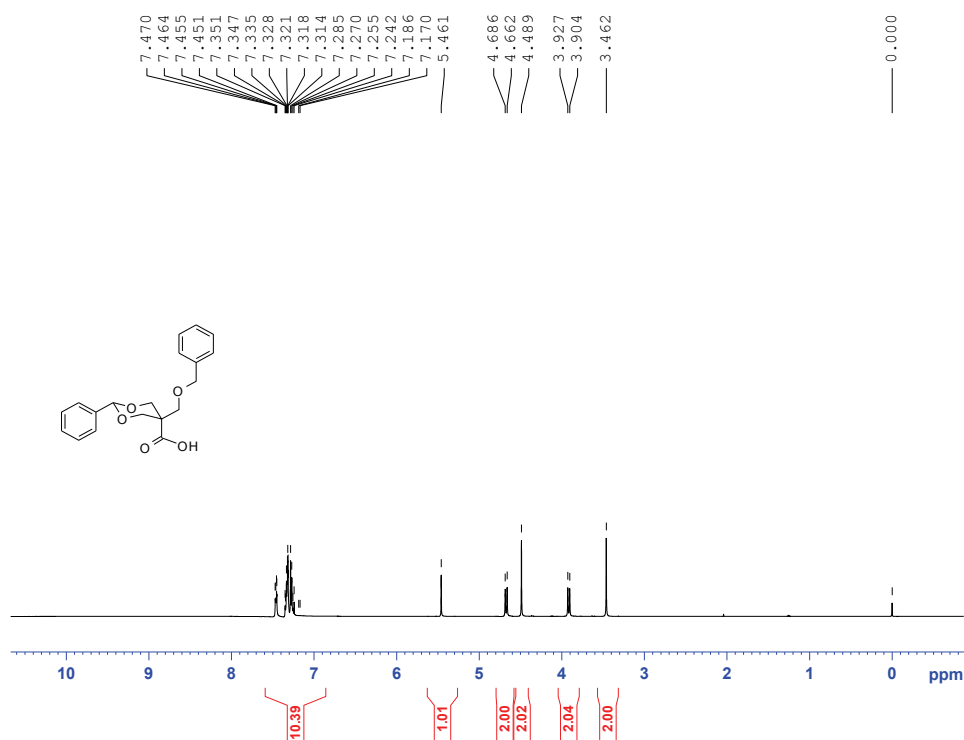
500.13 MHz ^1H NMR spectrum of *trans*-5-benzyloxymethyl-*cis*-2-(4-methoxyphenyl)-1,3-dioxane-5-carboxylic acid (102) in chloroform-*d*



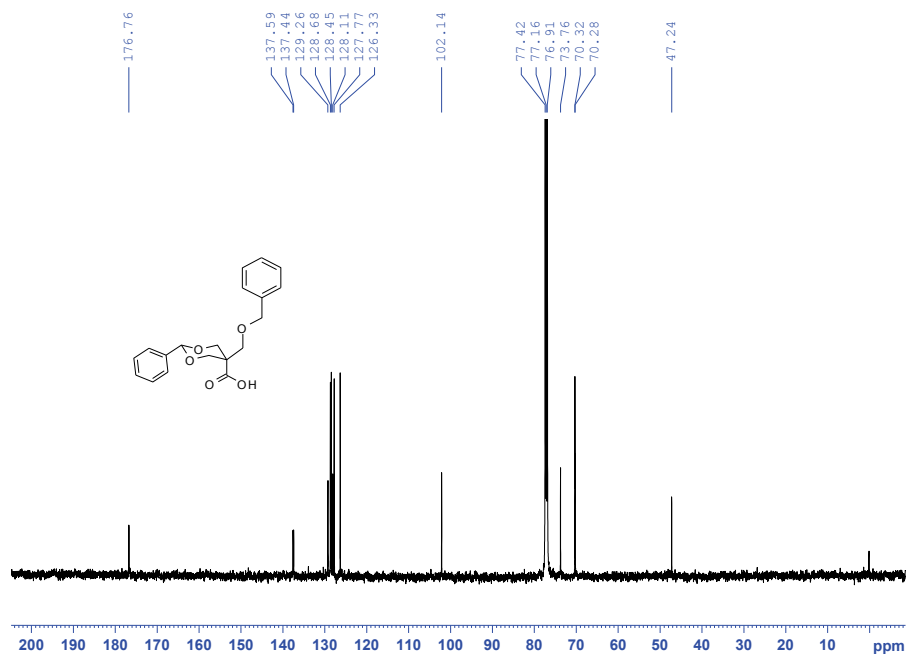
125.7 MHz ^{13}C NMR spectrum of *trans*-5-benzyloxymethyl-*cis*-2-(4-methoxyphenyl)-1,3-dioxane-5-carboxylic acid (102) in chloroform-*d*



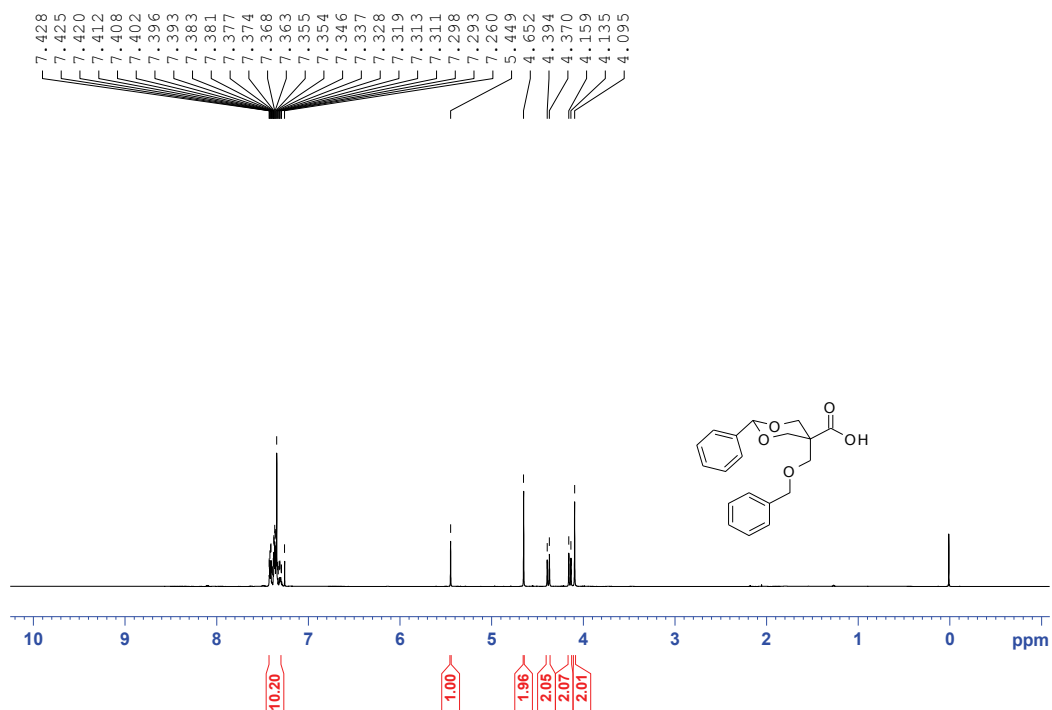
500.13 MHz ^1H NMR spectrum of *trans*-5-benzyloxymethyl-*cis*-2-phenyl-1,3-dioxane-5-carboxylic acid (100) in chloroform-*d*



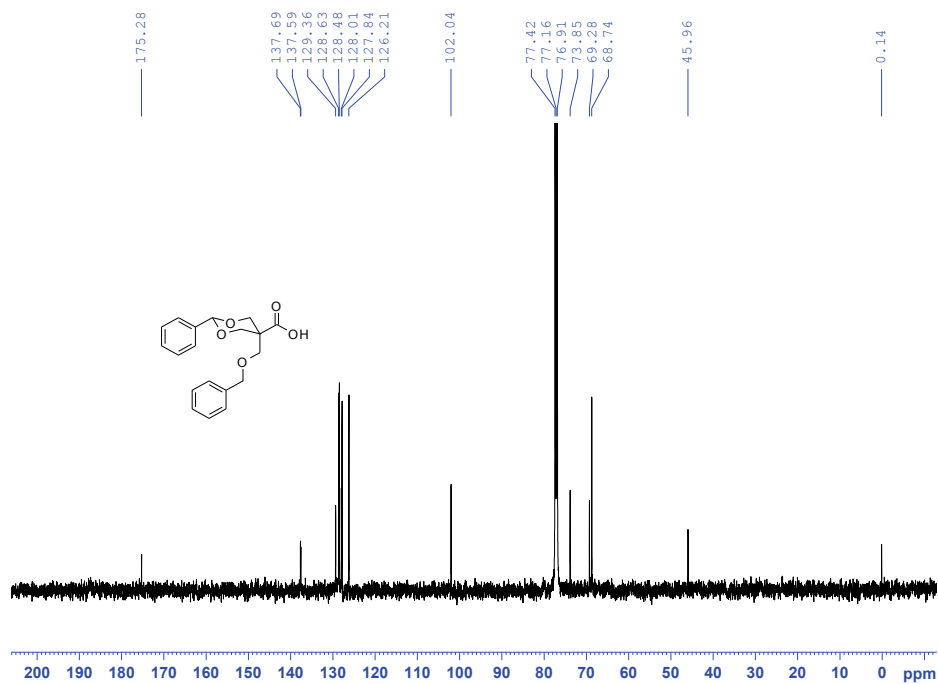
125.7 MHz ^{13}C NMR spectrum of *trans*-5-benzyloxymethyl-*cis*-2-phenyl-1,3-dioxane-5-carboxylic acid (100) in chloroform-*d*



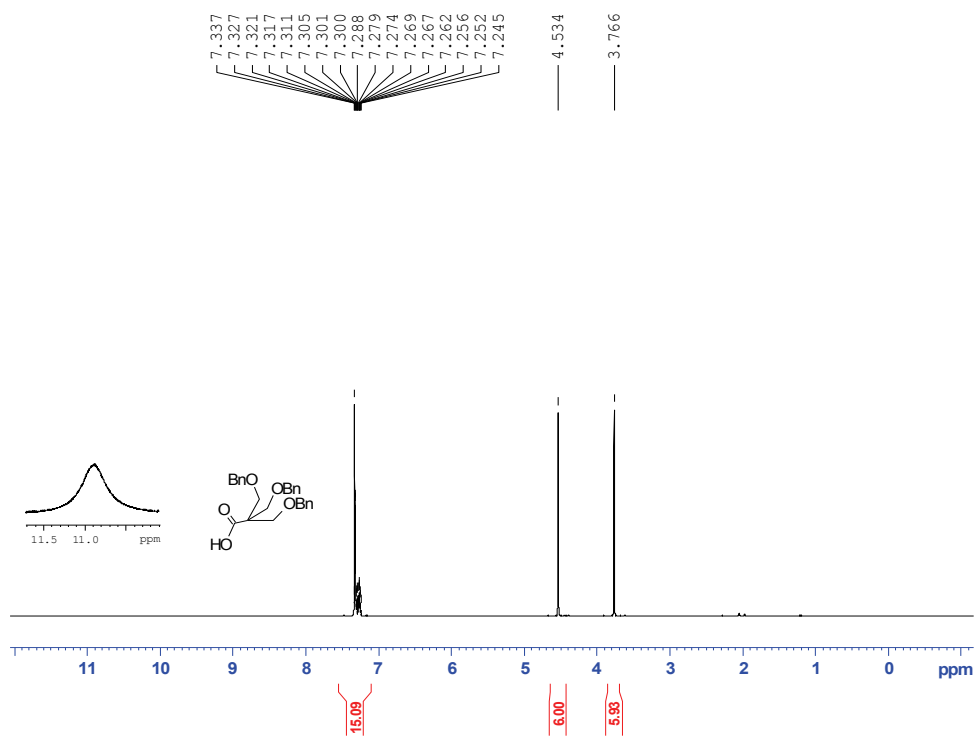
500.13 MHz ^1H NMR spectrum of *cis*-5-benzyloxymethyl-*trans*-2-phenyl-1,3-dioxane-5-carboxylic acid (101) in chloroform-*d*



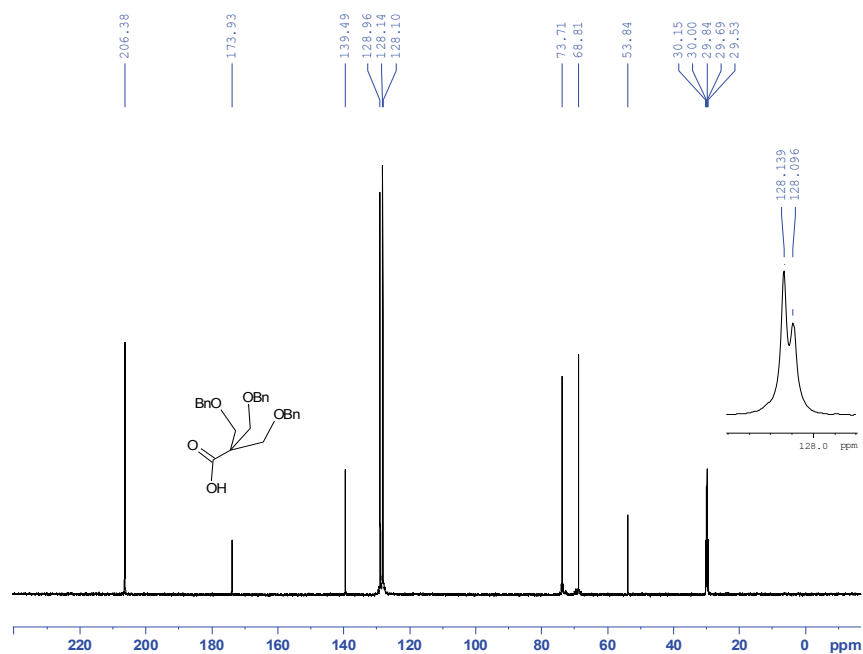
125.7 MHz ^{13}C NMR spectrum of *cis*-5-benzyloxymethyl-*trans*-2-phenyl-1,3-dioxane-5-carboxylic acid (101) in chloroform-*d*



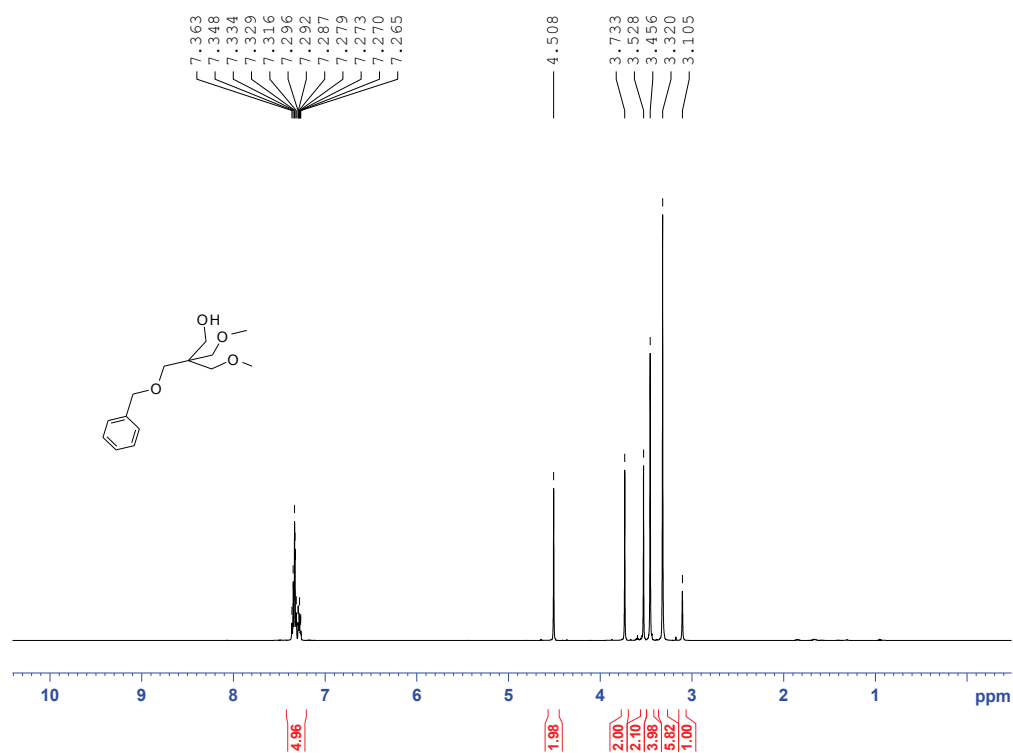
500.13 MHz ^1H NMR spectrum of 3-(benzyloxy)-2,2-bis(benzyloxymethyl)propanoic acid (107) in acetone- d_6



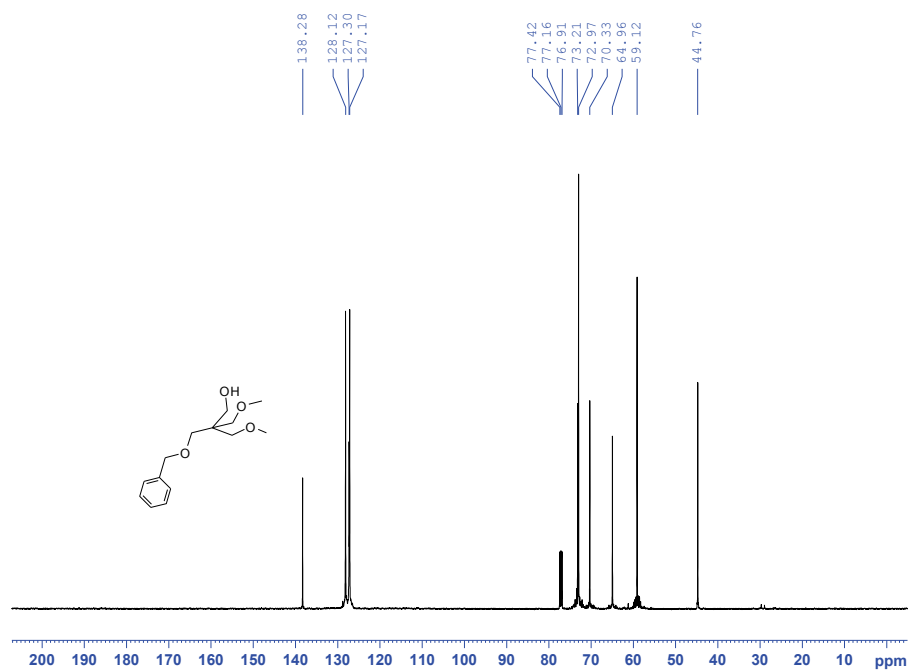
125.7 MHz ^{13}C NMR spectrum of 3-(benzyloxy)-2,2-bis(benzyloxymethyl)propanoic acid (107) in acetone- d_6



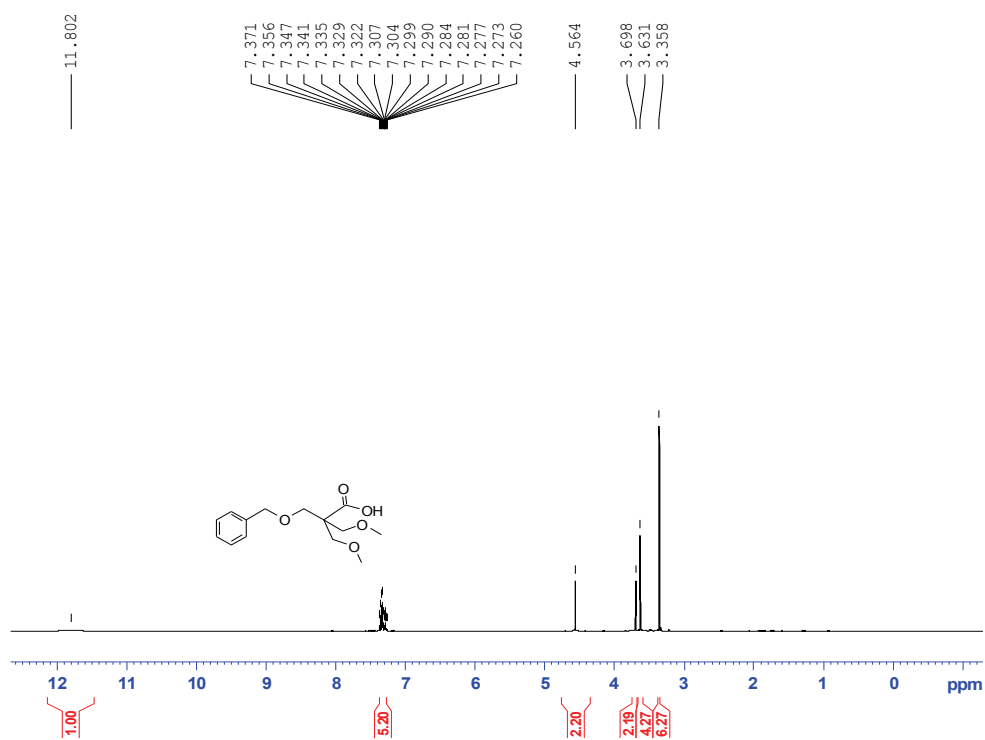
500.13 MHz ^1H NMR spectrum of 3-(benzyloxy)-2,2-bis(methyloxymethyl)propan-1-ol (110) in chloroform- d



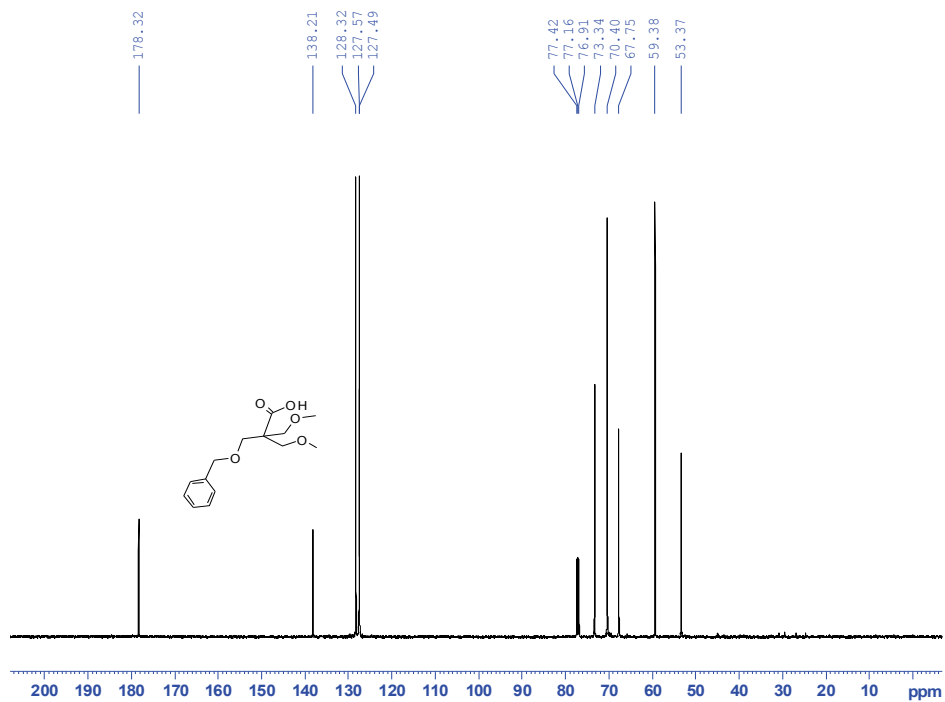
125.7 MHz ^{13}C NMR spectrum of 3-(benzyloxy)-2,2-bis(methoxymethyl)propan-1-ol (110) in chloroform-*d*



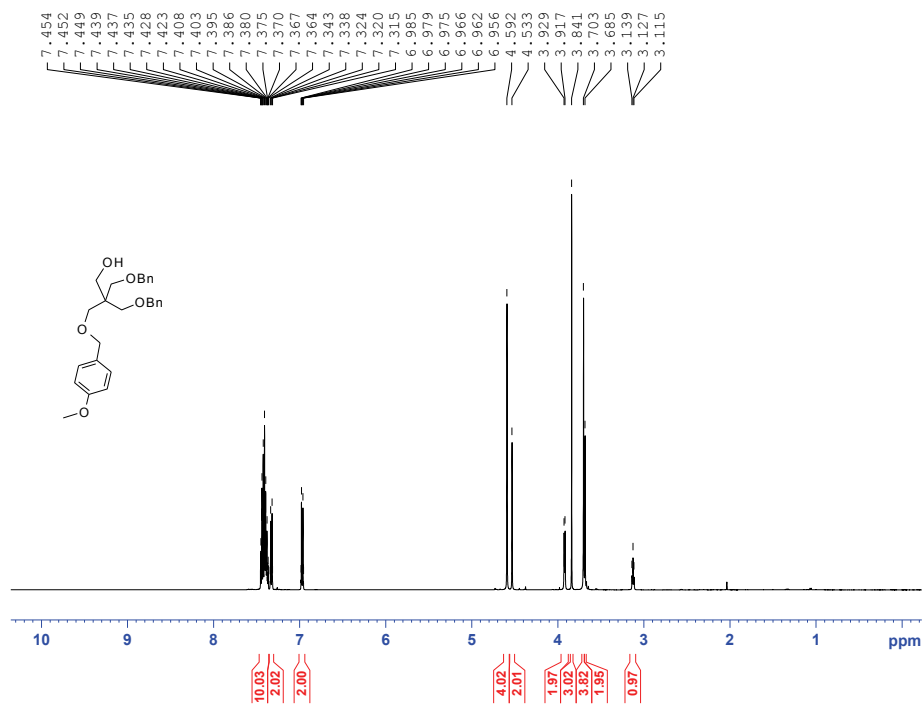
500.13 MHz ^1H NMR spectrum of 3-(benzyloxy)-2,2-bis(methoxymethyl)propanoic acid (111) in chloroform-*d*



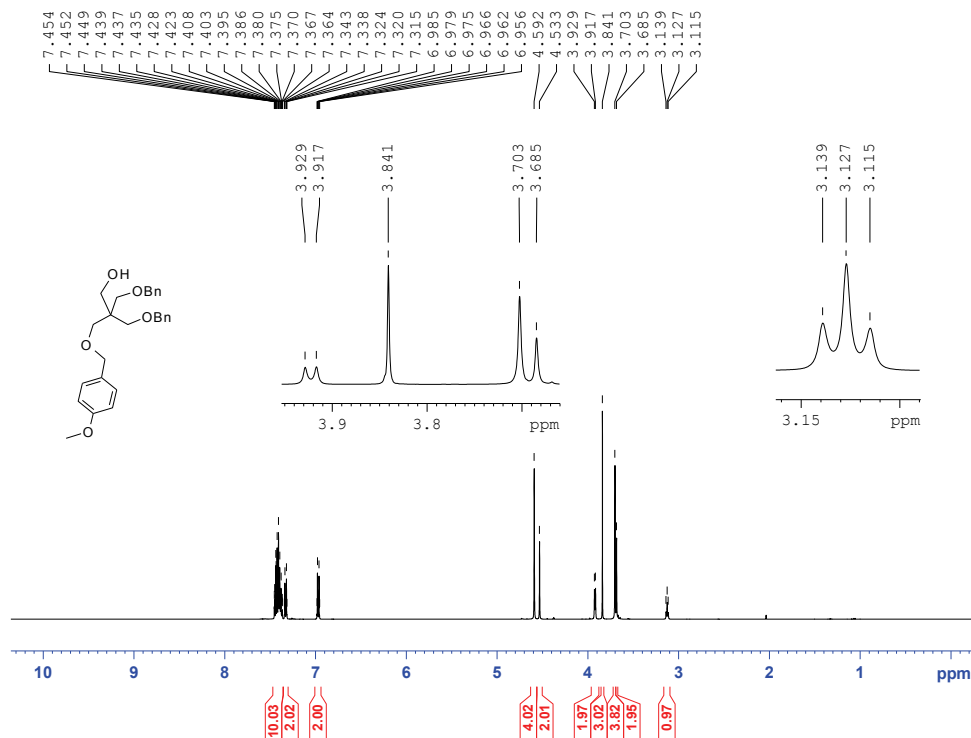
125.7 MHz ^{13}C NMR spectrum of 3-(benzyloxy)-2,2-bis(methoxymethyl)propanoic acid (111) in chloroform-*d*



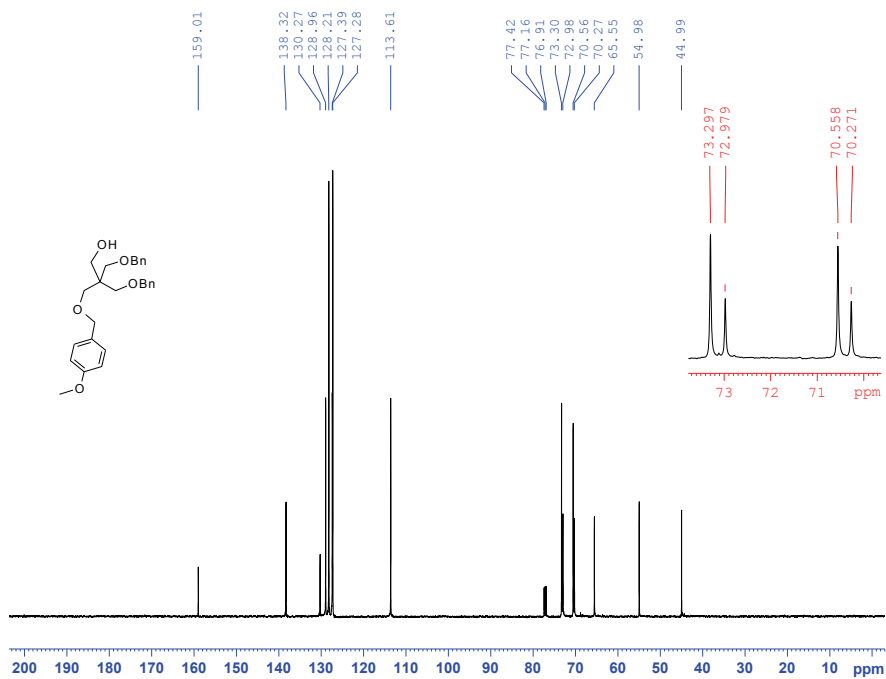
500.13 MHz ^1H NMR spectrum of 3-(benzyloxy)-2-(benzyloxymethyl)-2-((4-methoxybenzyloxy)methyl)propan-1-ol (115) in chloroform-*d*



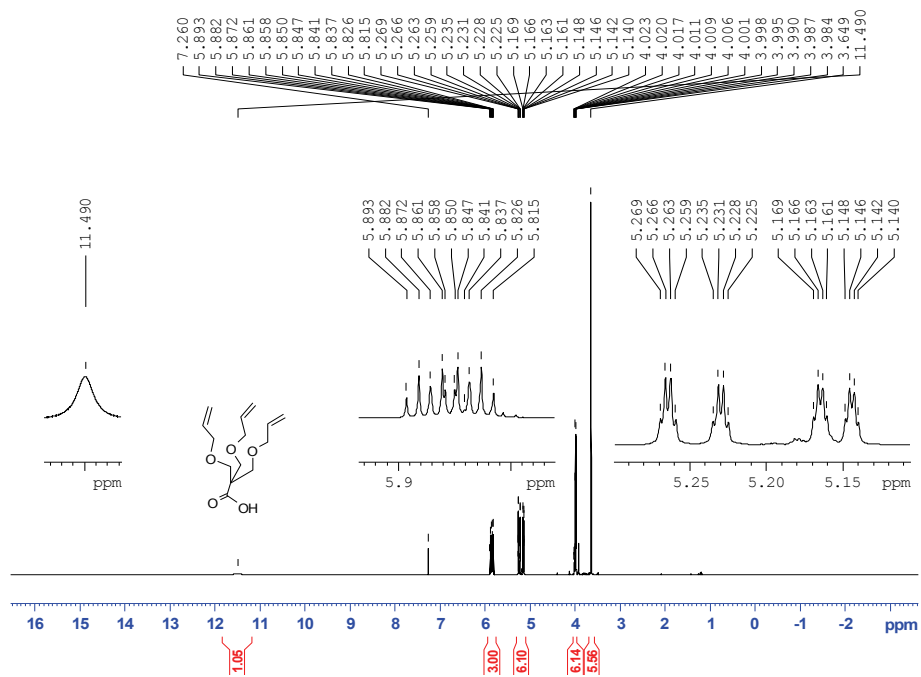
Expansions of the 500.13 MHz ^1H NMR spectrum of 3-(benzyloxy)-2-(benzyloxymethyl)-2-((4-methoxybenzyloxy)methyl)propan-1-ol (115) in chloroform-*d*



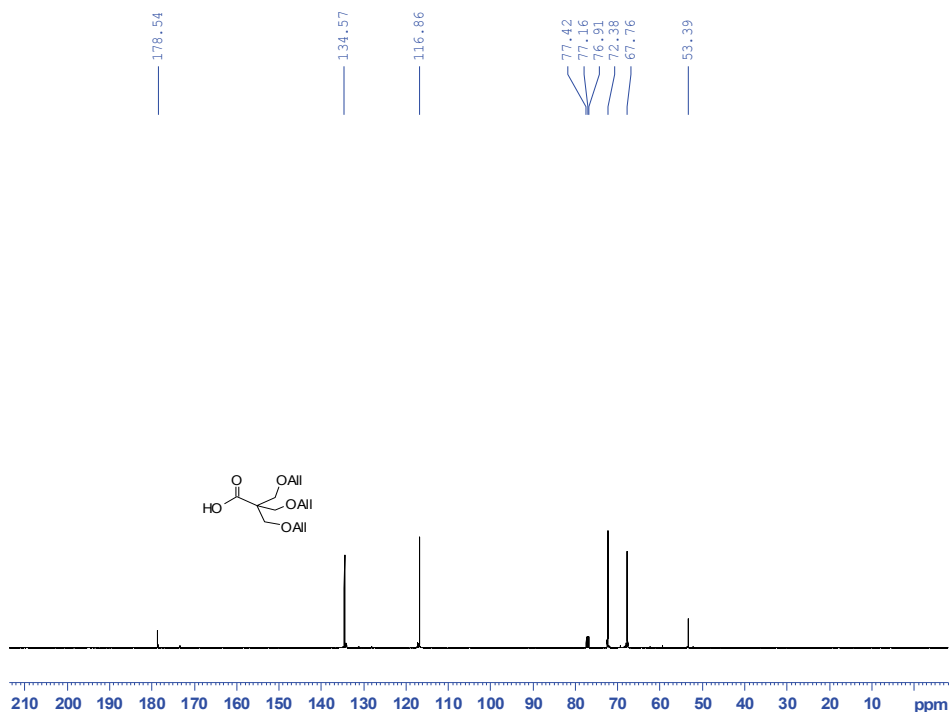
125.7 MHz ^{13}C NMR spectrum of 3-(benzyloxy)-2-(benzyloxymethyl)-2-((4-methoxybenzyloxy)methyl)propan-1-ol (115) in chloroform-*d*



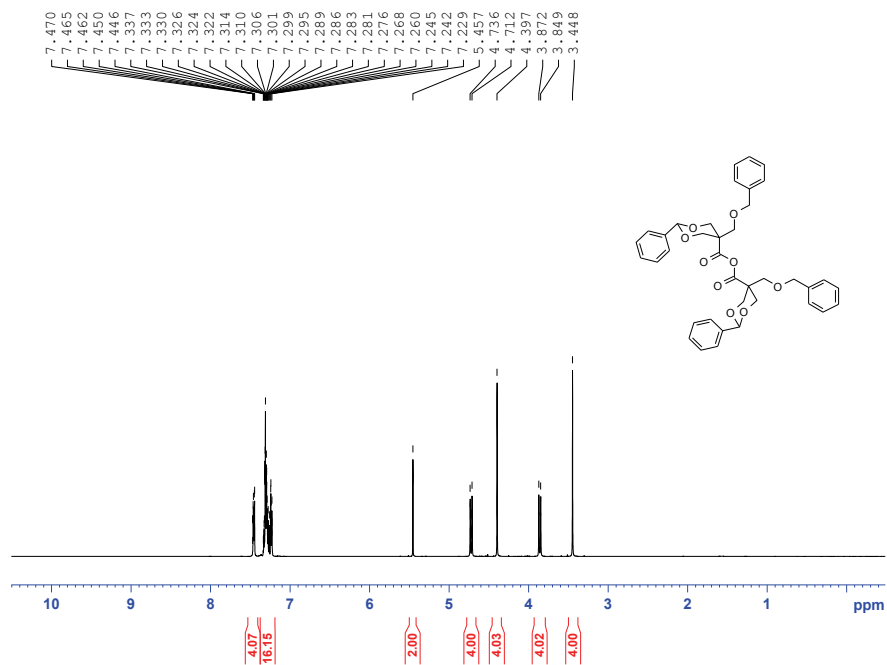
500.13 MHz ^1H NMR spectrum of 3-(allyloxy)-2,2-bis(allyloxymethyl)propanoic acid (118) in chloroform-*d*



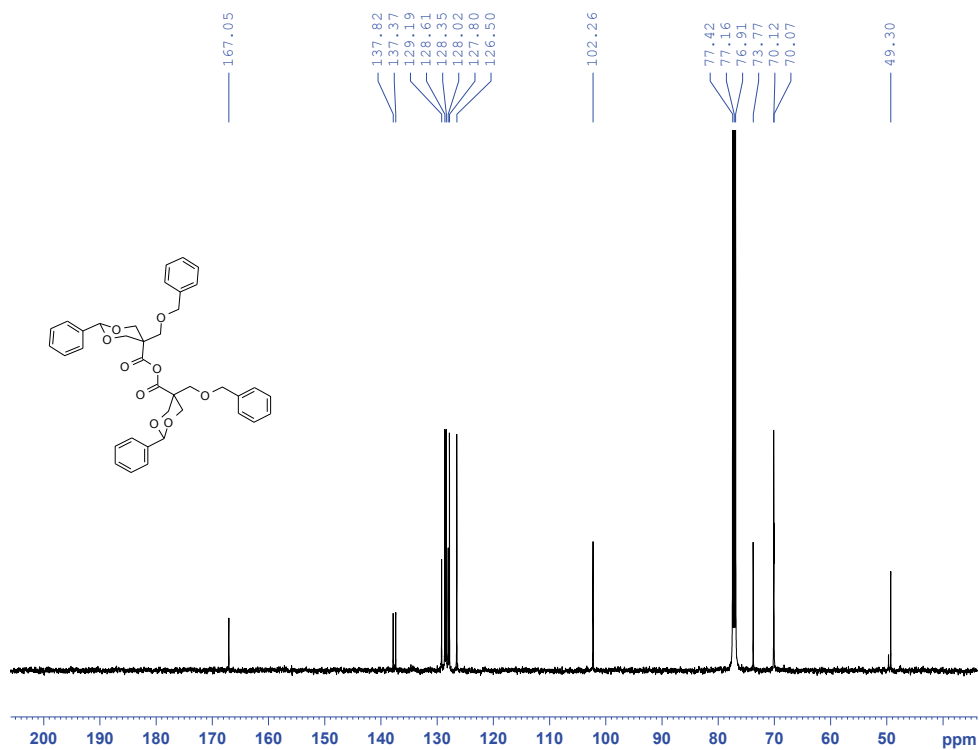
125.7 MHz ^{13}C NMR spectrum of 3-(allyloxy)-2,2-bis(allyloxymethyl)propanoic acid (118) in chloroform-*d*



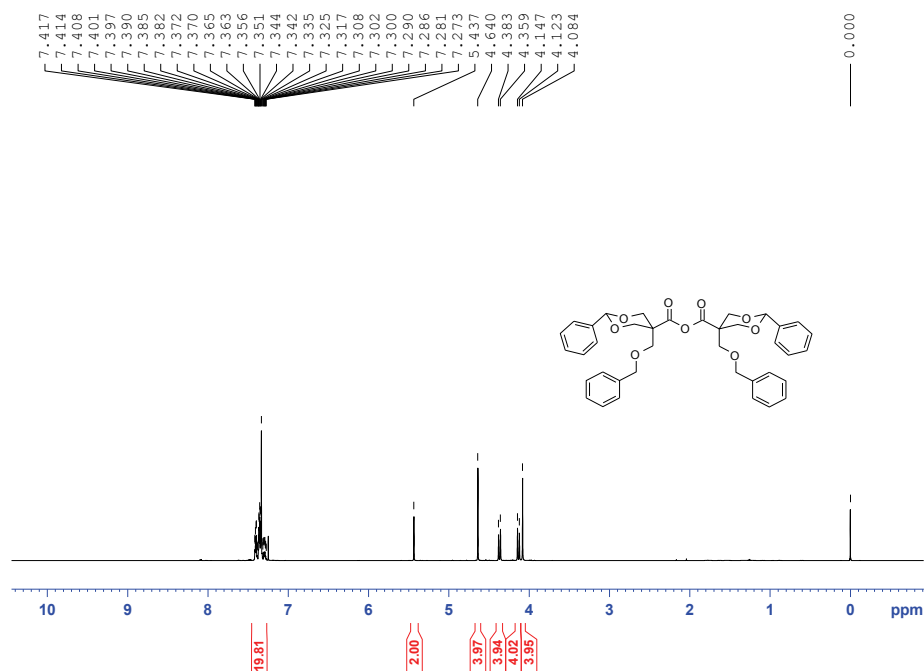
500.13 MHz ^1H NMR spectrum of *trans*-5-benzyloxymethyl-*cis*-2-phenyl-1,3-dioxane-5-carboxylic anhydride (103) in chloroform-*d*



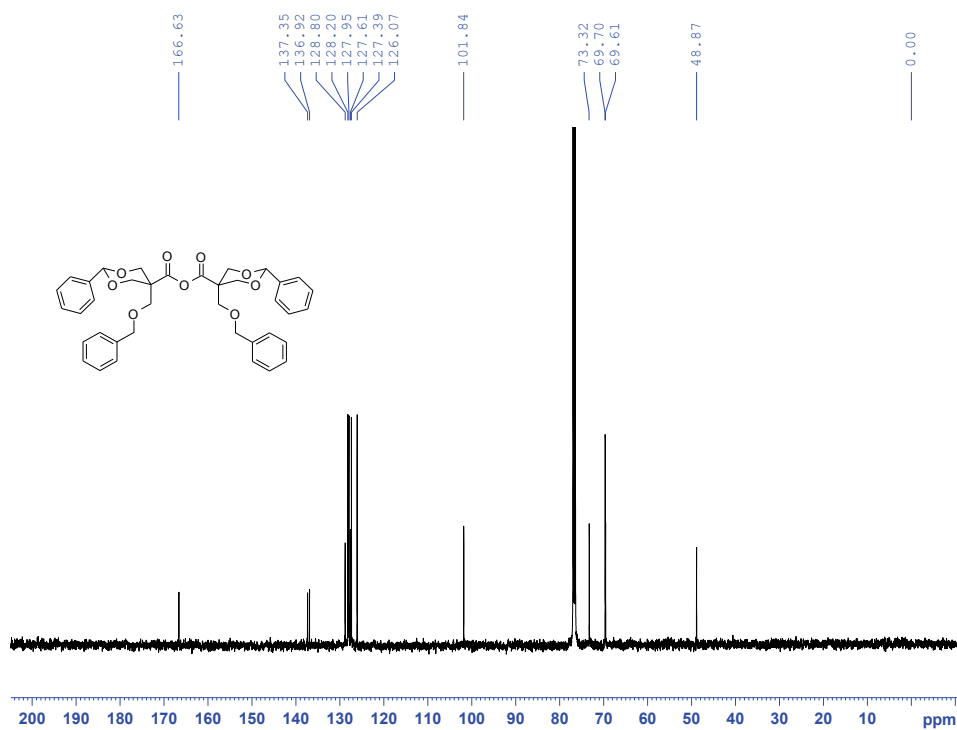
125.7 MHz ^{13}C NMR spectrum of *trans*-5-benzyloxymethyl-*cis*-2-phenyl-1,3-dioxane-5-carboxylic anhydride (103)



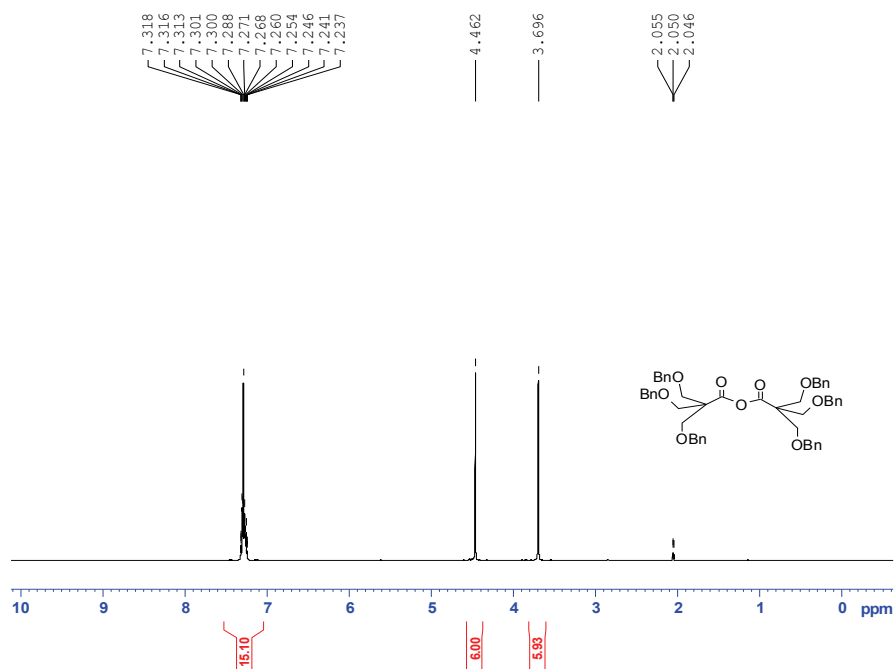
500.13 MHz ^1H NMR spectrum of *cis*-5-benzyloxymethyl-*trans*-2-phenyl-1,3-dioxane-5-carboxylic anhydride (104) in chloroform-*d*



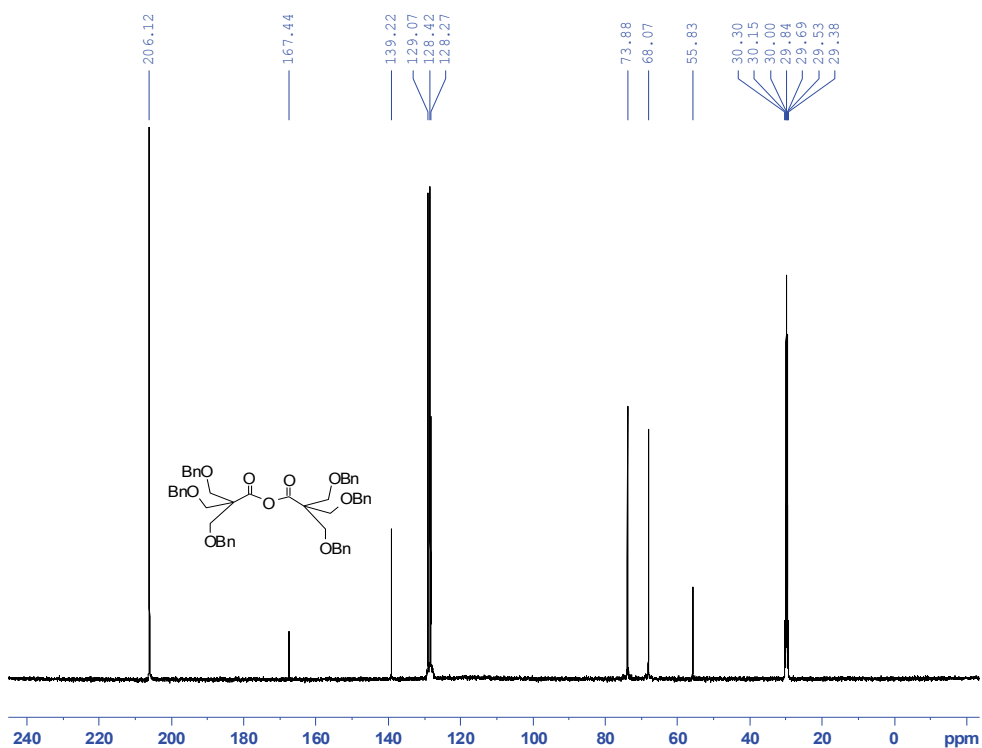
125.7 MHz ^{13}C NMR spectrum of *cis*-5-benzyloxymethyl-*trans*-2-phenyl-1,3-dioxane-5-carboxylic anhydride (104) in chloroform-*d*



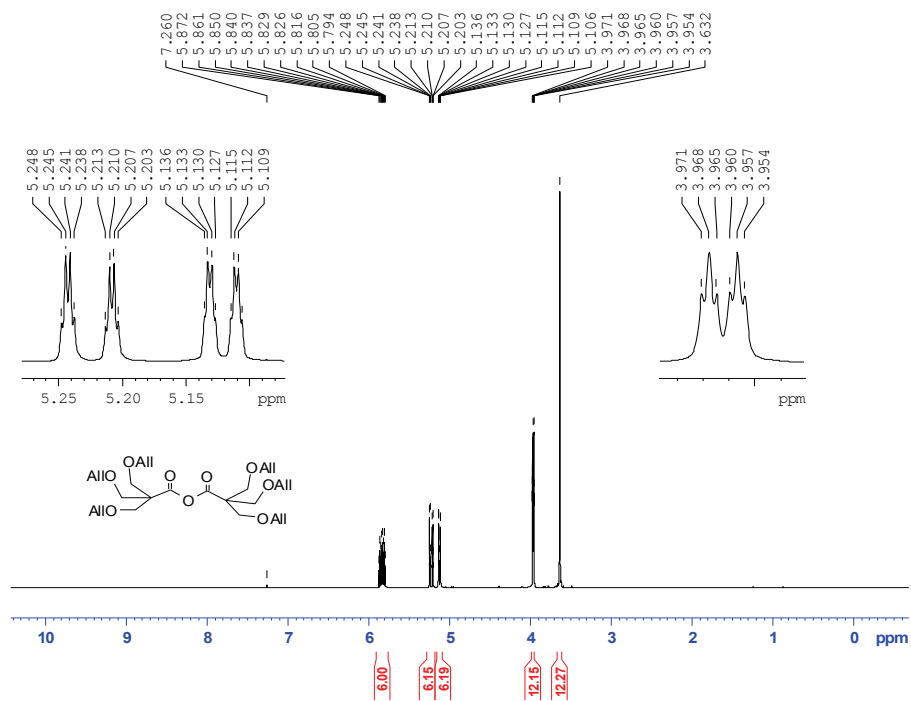
500.13 MHz ^1H NMR spectrum of 3-(benzyloxy)-2,2-bis(benzyloxymethyl)propanoic anhydride (108) in acetone- d_6 .



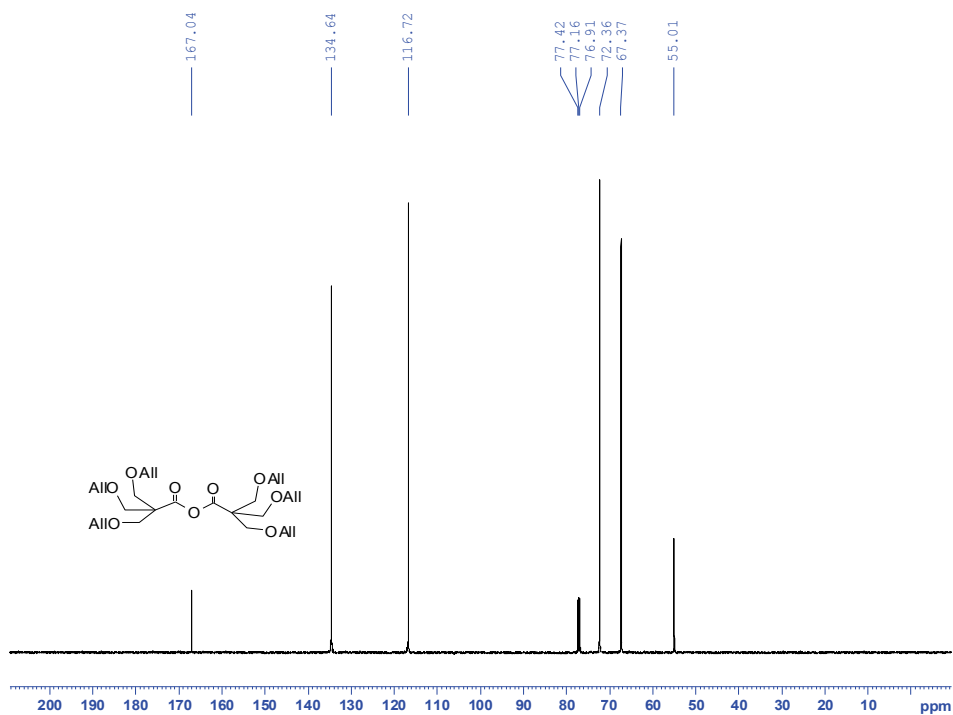
125.7 MHz ^{13}C NMR spectrum of 3-(benzyloxy)-2,2-bis(benzyloxymethyl)propanoic anhydride (108) in acetone- d_6 .



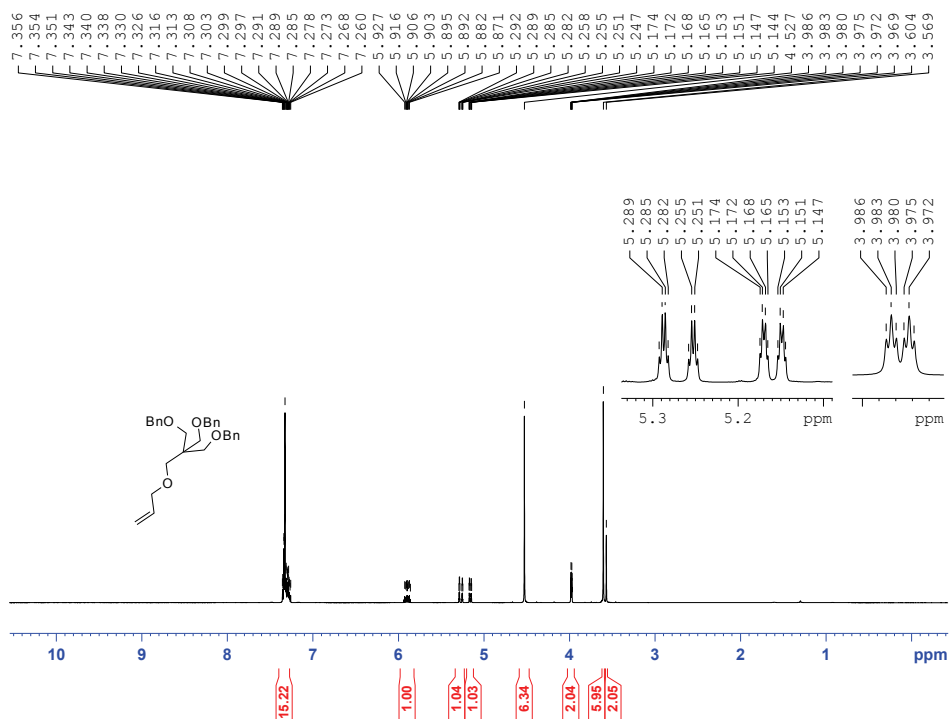
500.13 MHz ^1H NMR spectrum of 3-(allyloxy)-2,2-bis(allyloxymethyl)propanoic anhydride (119) chloroform-*d*



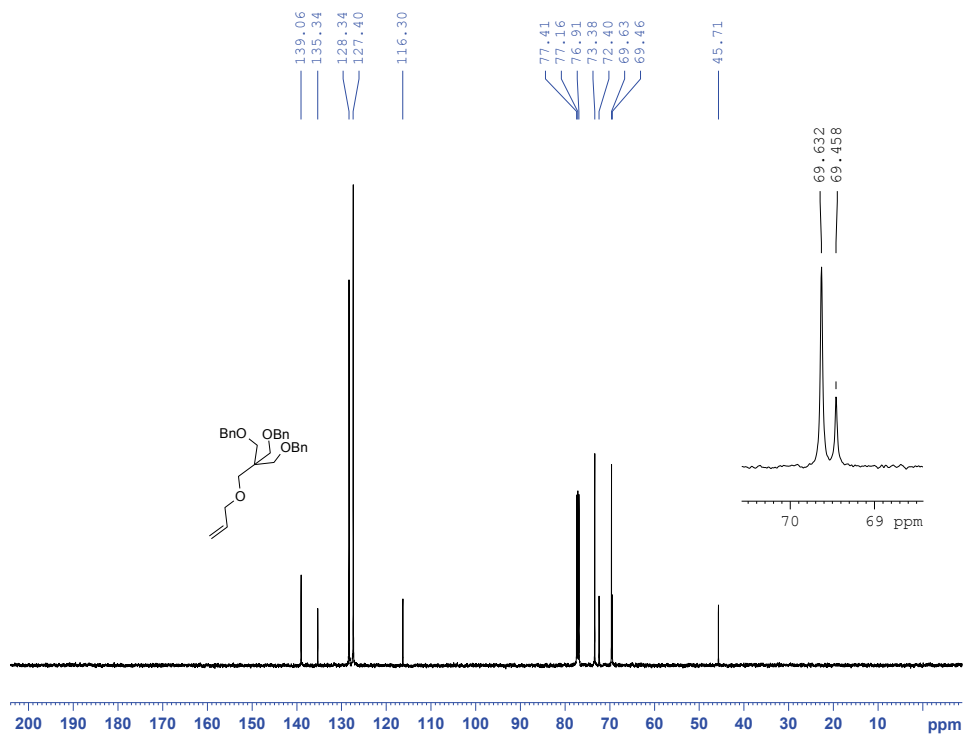
125.7 MHz ^{13}C NMR spectrum of 3-(allyloxy)-2,2-bis(allyloxymethyl)propanoic anhydride (119) chloroform-*d*



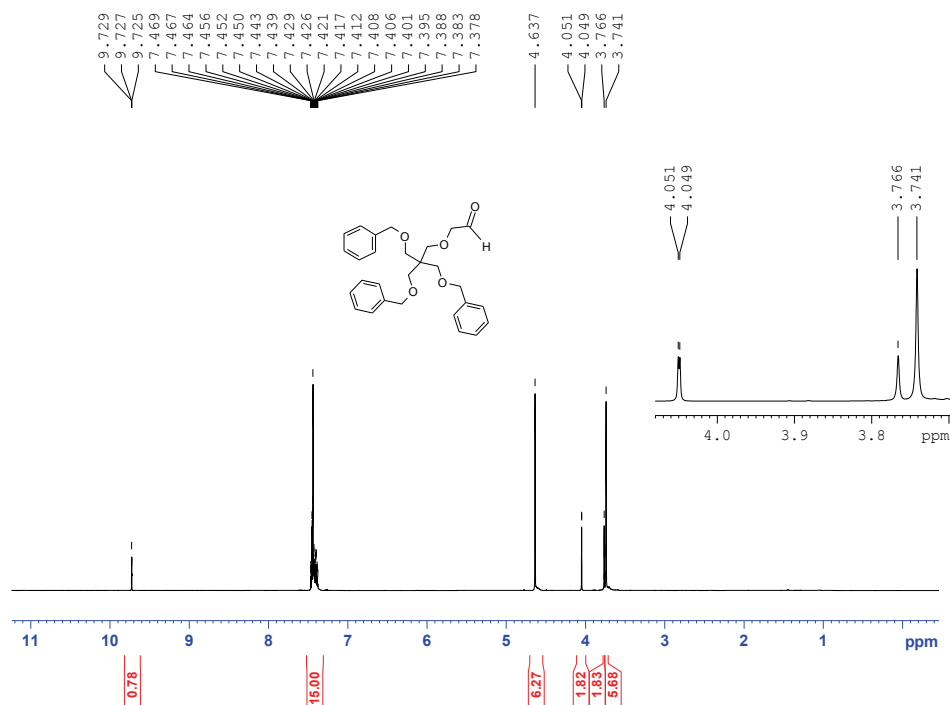
500.13 MHz ^1H NMR spectrum of allyl tribenzylpentaerythritol (149) in chloroform-*d*



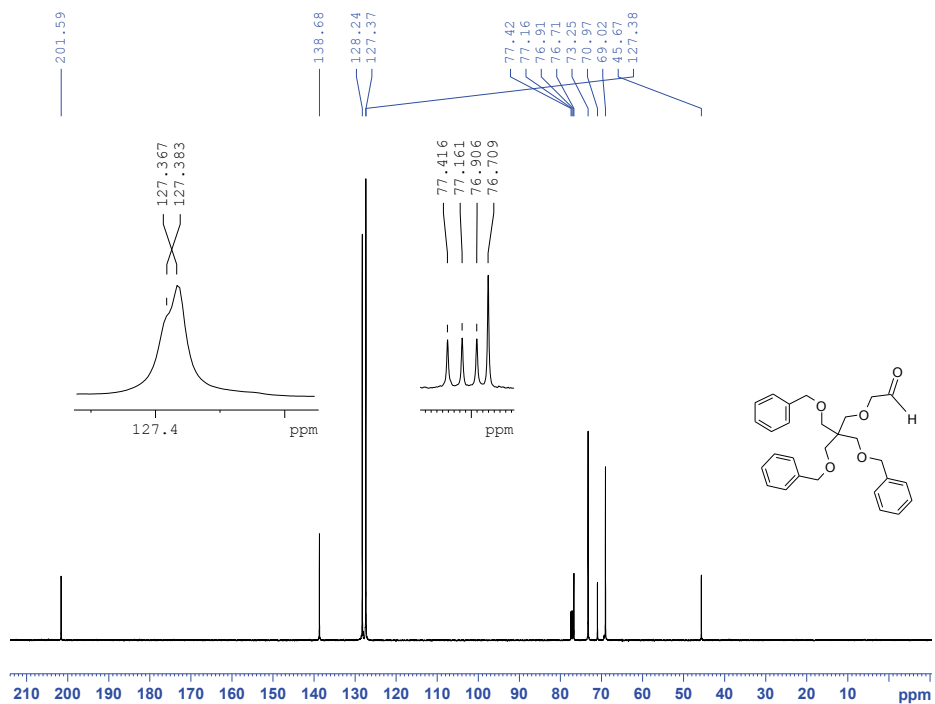
125.7 MHz ^{13}C NMR spectrum of allyl tribenzylpentaerythritol (149) in chloroform-*d*



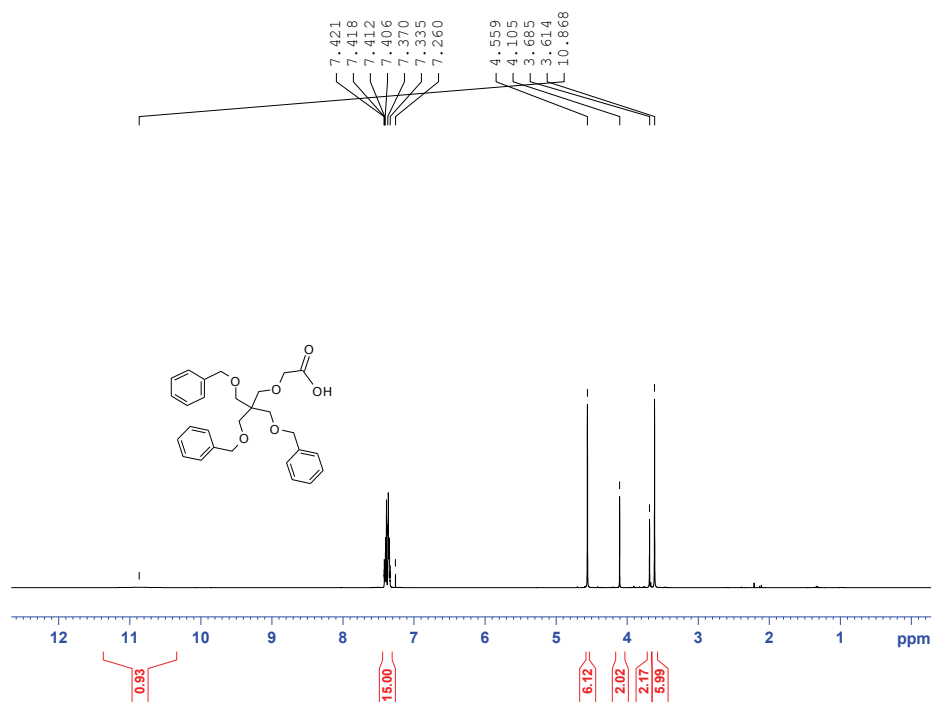
500.13 MHz ^1H NMR spectrum of (3-benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetaldehyde (150) in chloroform-*d*



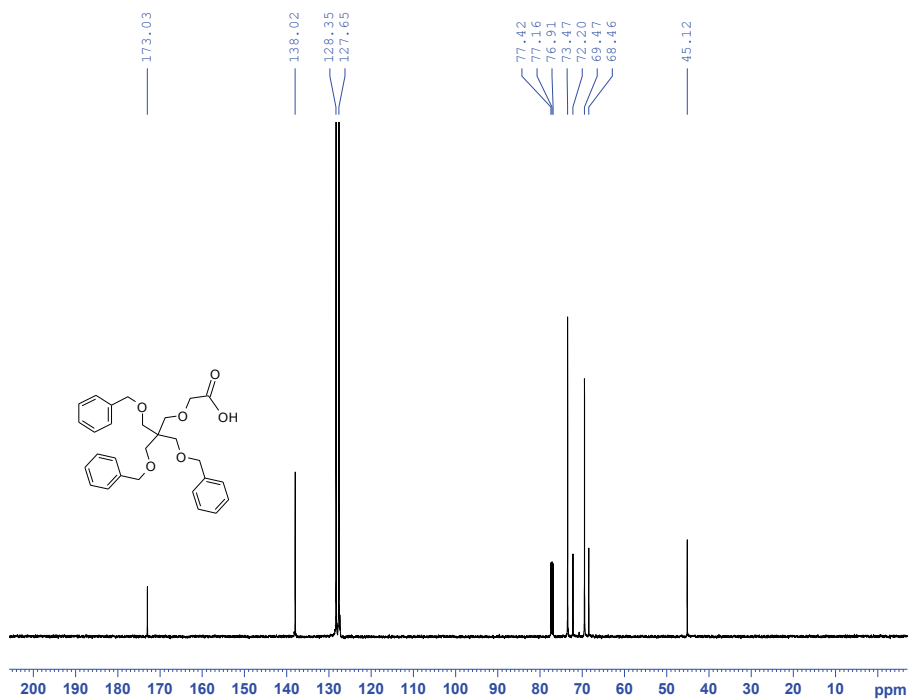
125.7 MHz ^{13}C NMR spectrum of (3-benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetaldehyde (150) in chloroform-*d*



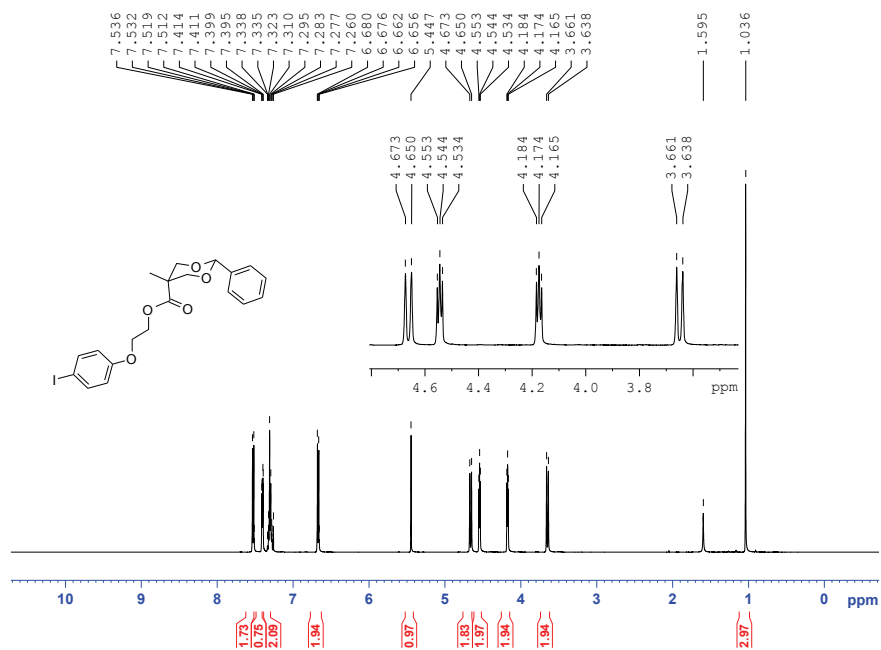
500.13 MHz ^1H NMR spectrum of (3-benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetic acid (126) in chloroform-*d*



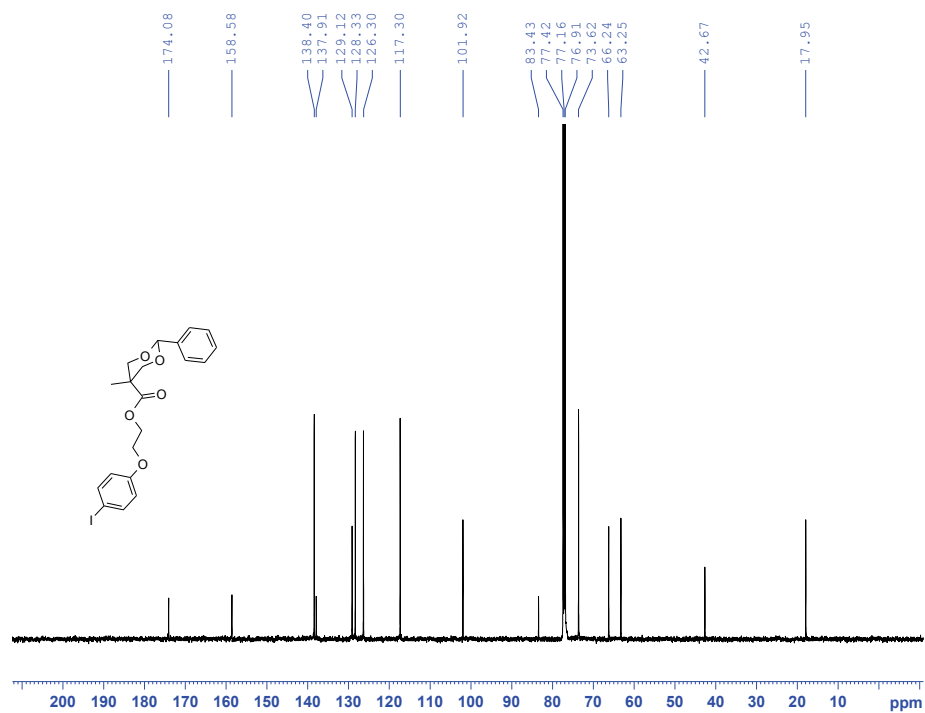
125.7 MHz ^{13}C NMR spectrum of (3-benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetic acid (126) in chloroform-*d*



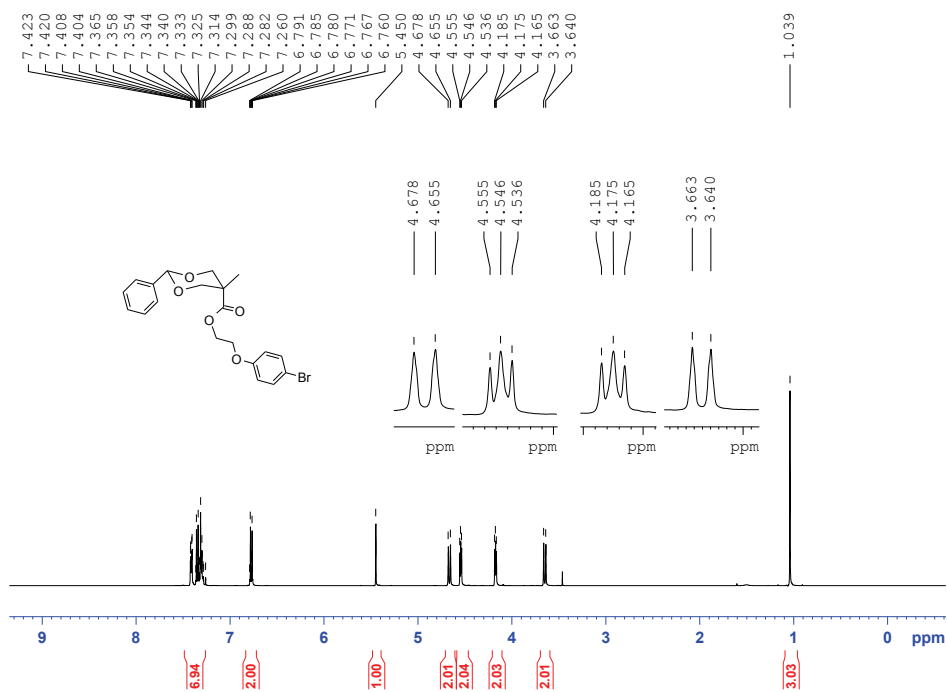
500.13 MHz ^1H NMR spectrum of 2-(4-iodophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (151) in chloroform-*d*



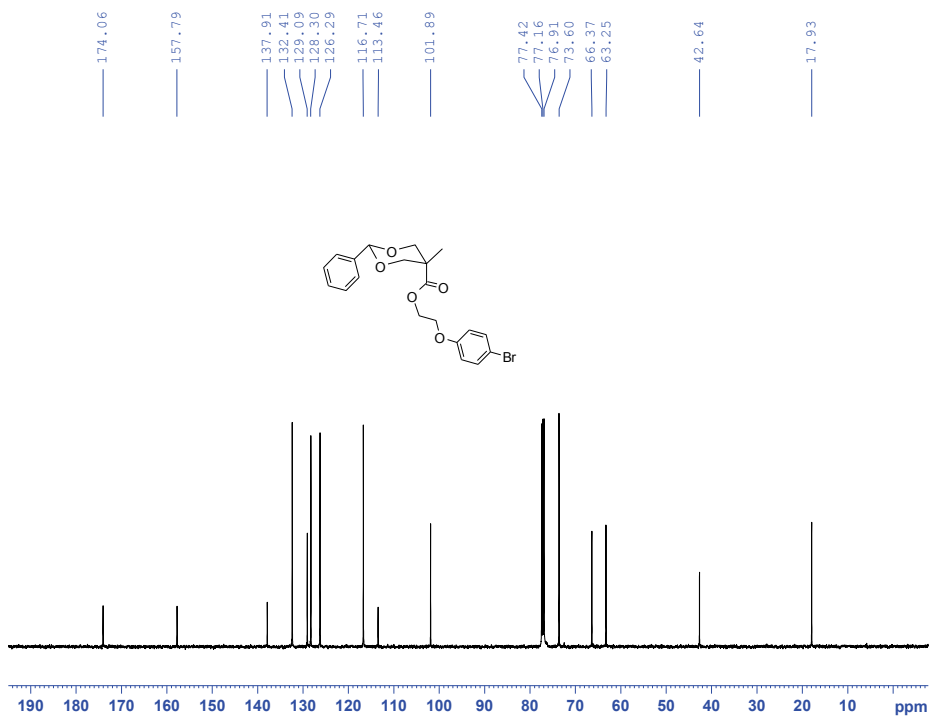
125.7 MHz ^{13}C NMR spectrum of 2-(4-iodophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (151) in chloroform-*d*



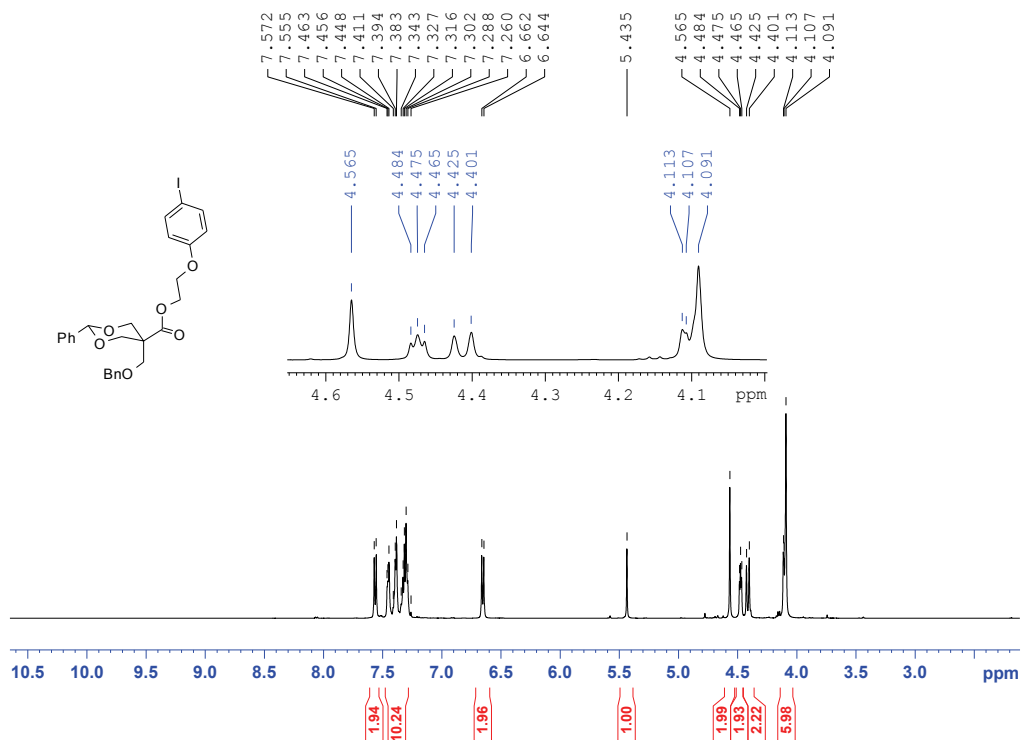
500.13 MHz ^1H NMR spectrum of 2-(4-bromophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (152) in chloroform-*d*



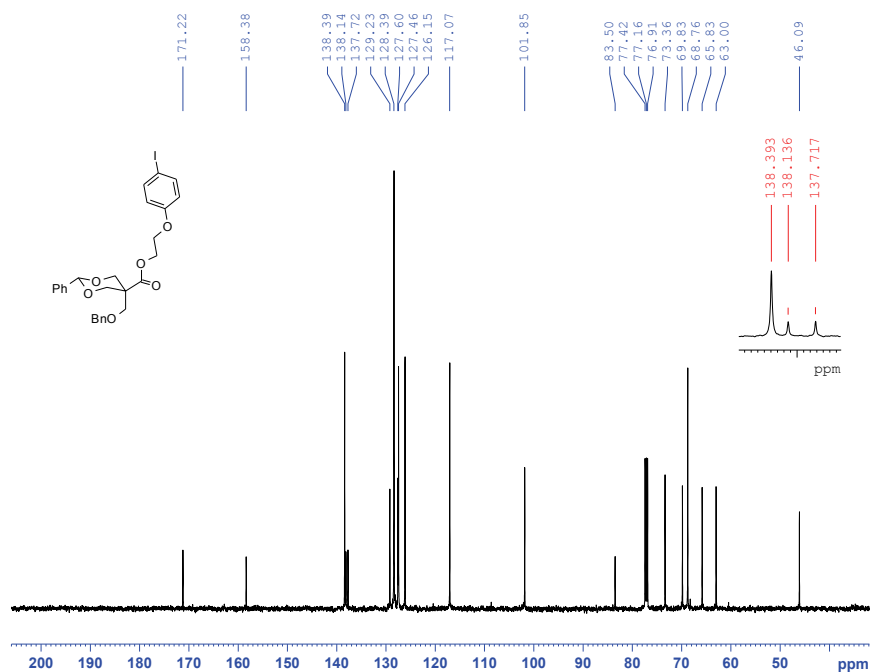
125.7 MHz ^{13}C NMR spectrum of 2-(4-bromophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (152) in chloroform-*d*



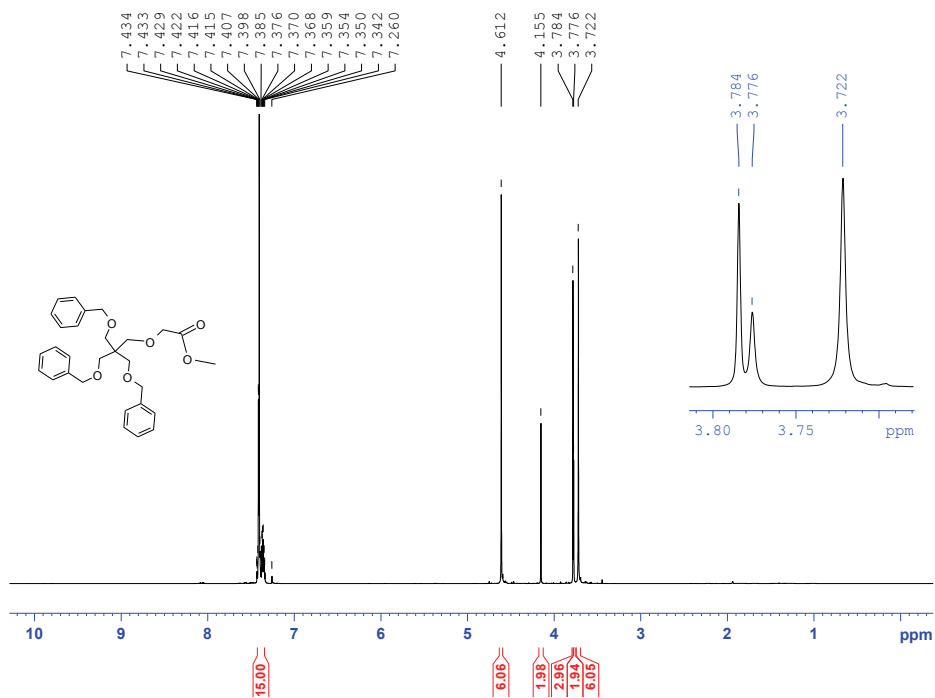
500.13 MHz ^1H NMR spectrum of 2-(4-iodophenoxy)ethyl 5-benzyloxymethyl-2-phenyl-1,3-dioxane-5-carboxylate (153) in chloroform-*d*



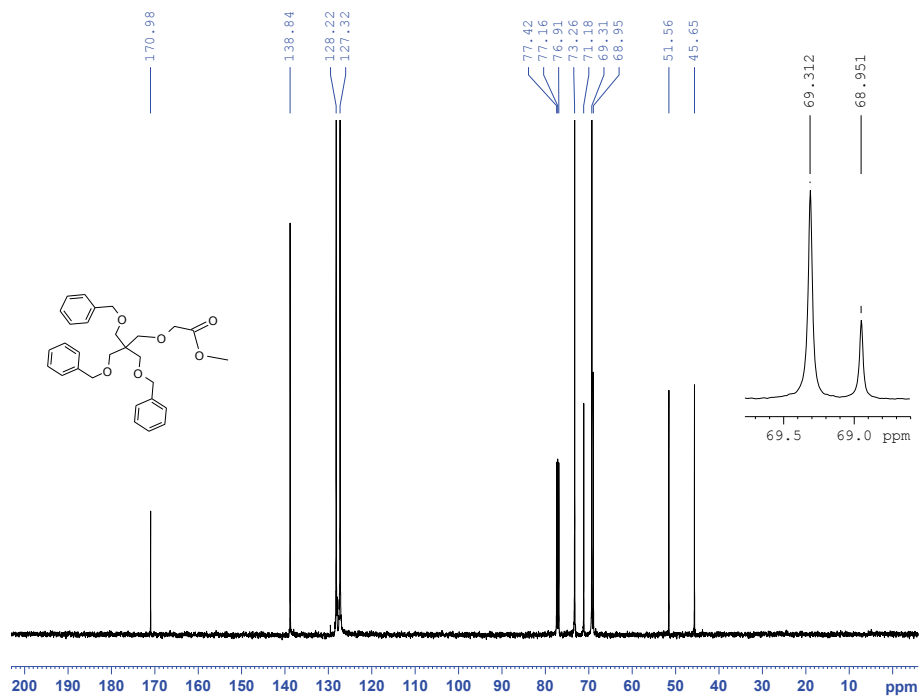
125.7 MHz ^{13}C NMR spectrum of 2-(4-iodophenoxy)ethyl 5-benzyloxymethyl-2-phenyl-1,3-dioxane-5-carboxylate (153) in chloroform-*d*



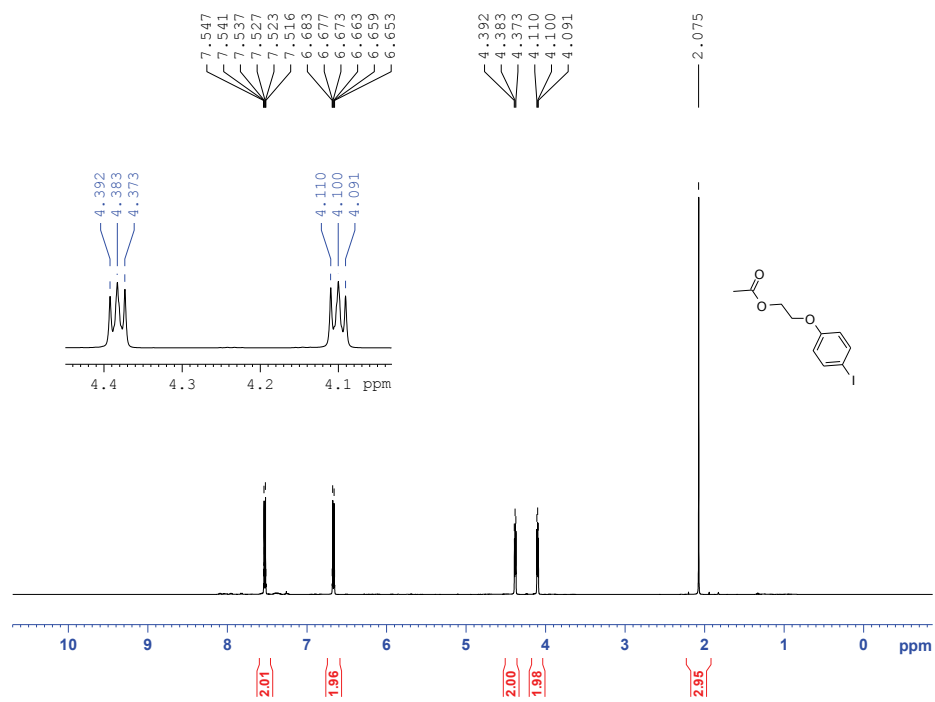
500.13 MHz ^1H NMR spectrum of methyl 2-(3-(benzyloxy)-2,2-bis(benzyloxymethyl)propoxy)acetate (154) in chloroform-*d*



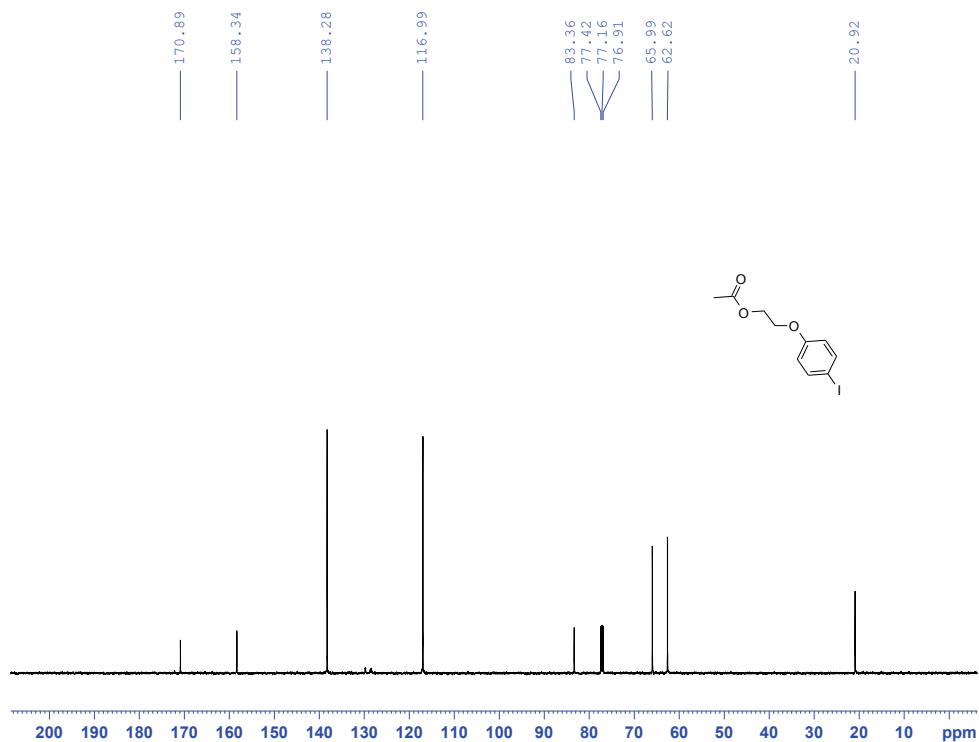
125.7 MHz ^{13}C NMR spectrum of methyl 2-(3-(benzyloxy)-2,2-bis(benzyloxymethyl)propoxy)acetate (154) in chloroform-*d*



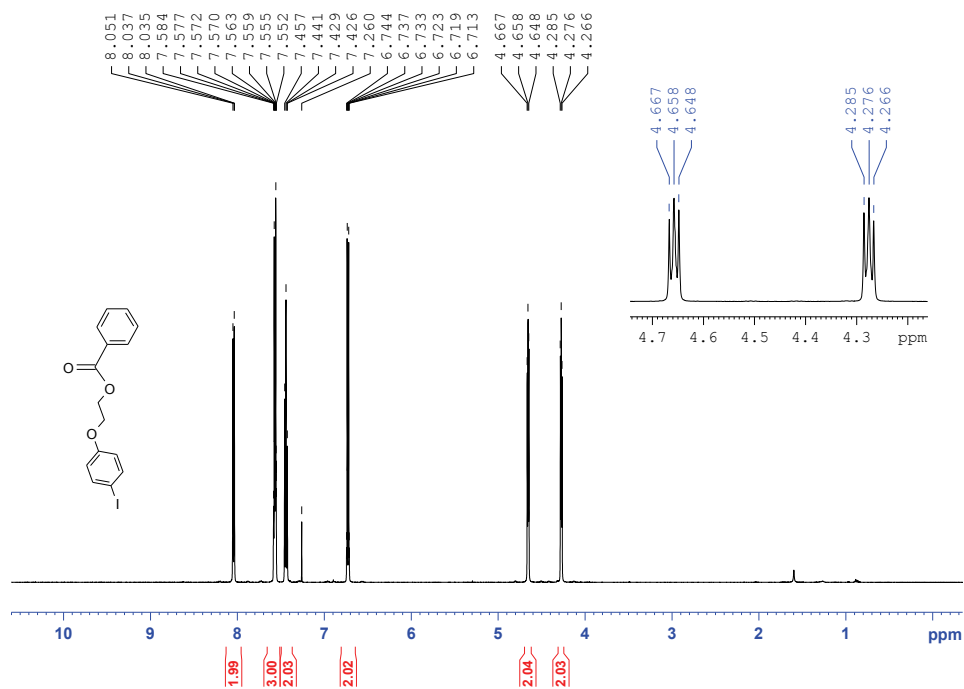
500.13 MHz ^1H NMR spectrum of 2-(4-iodophenoxy)ethyl acetate (155) in chloroform-*d*



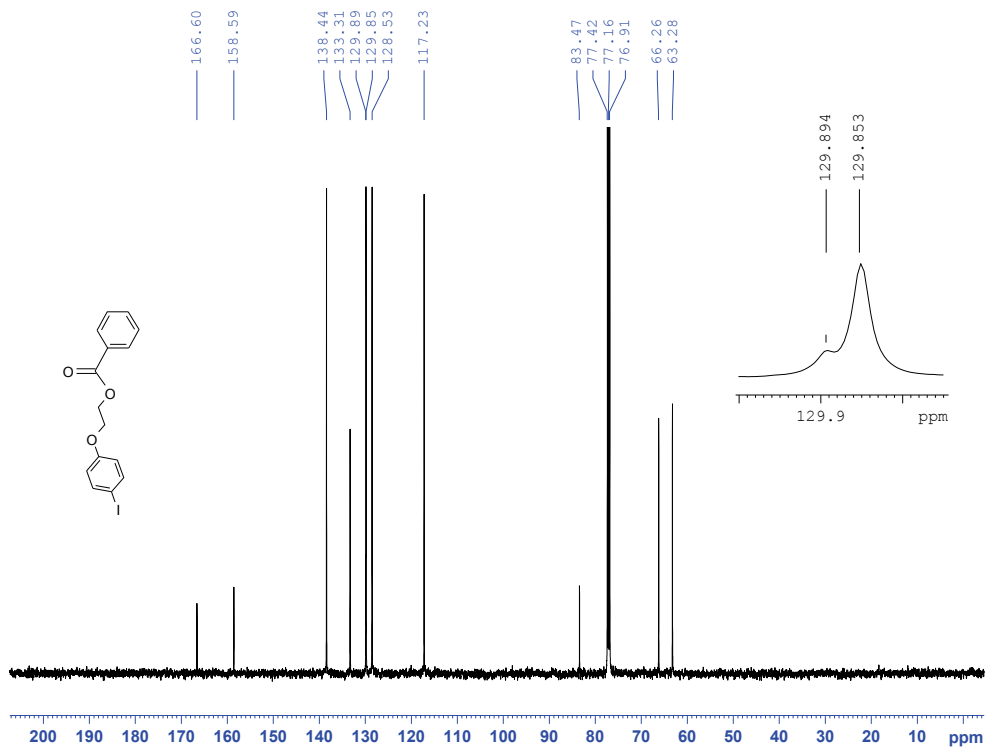
125.7 MHz ^{13}C NMR spectrum of 2-(4-iodophenoxy)ethyl acetate (155) in chloroform-*d*



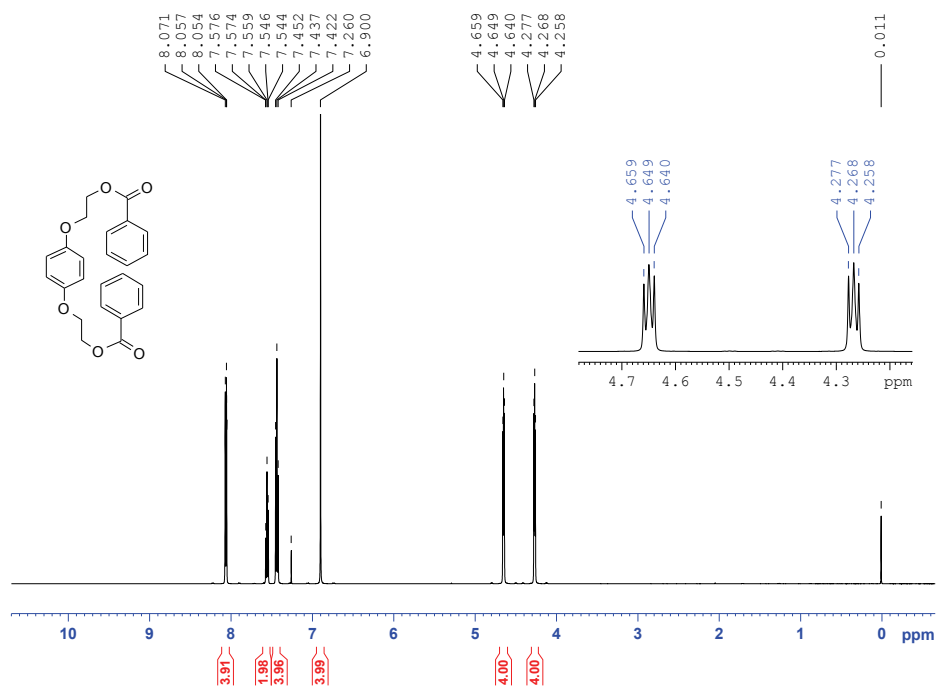
500.13 MHz ^1H NMR spectrum of 2-(4-iodophenoxy)ethyl benzoate (156) in chloroform-*d*



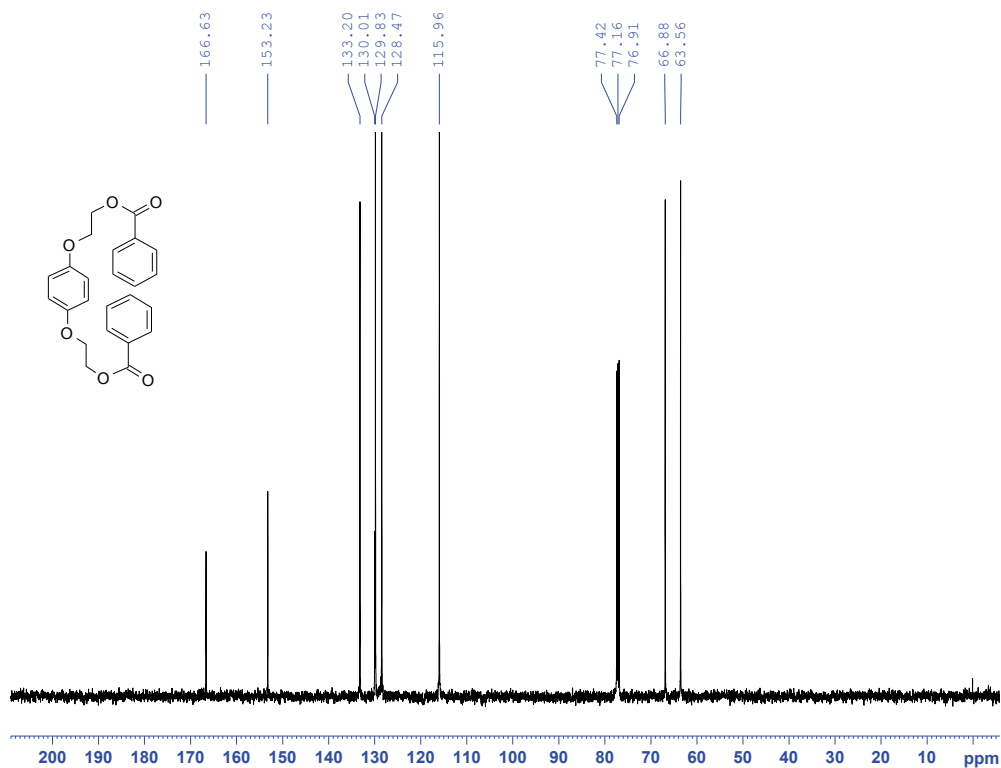
125.7 MHz ^{13}C NMR spectrum of 2-(4-iodophenoxy)ethyl benzoate (156) in chloroform-*d*



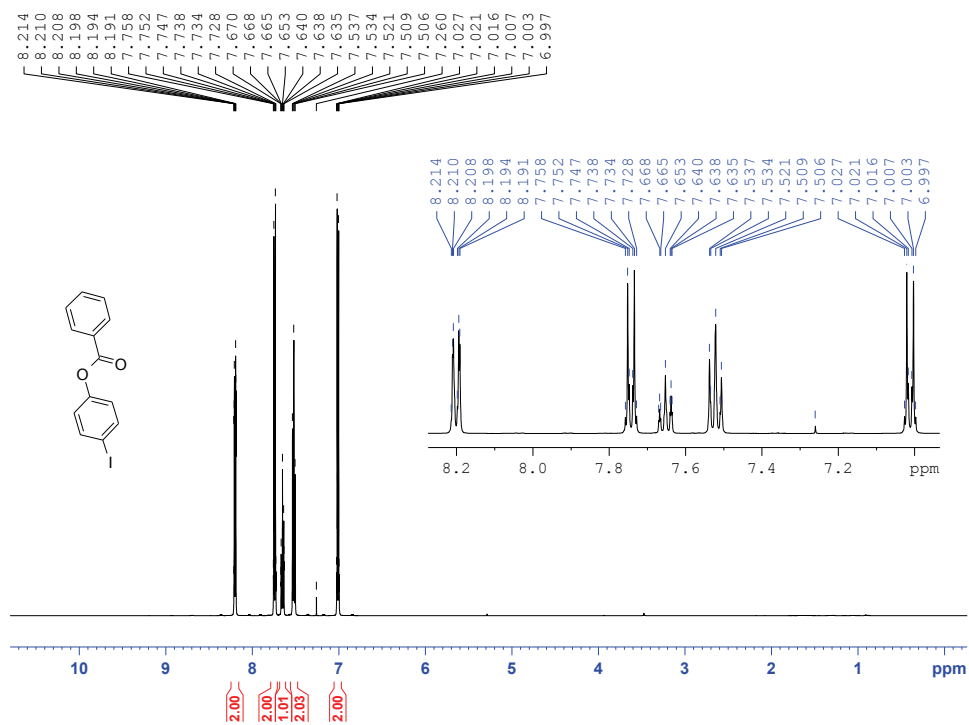
500.13 MHz ^1H NMR spectrum of 1,4-bis(2-benzoyloxyethoxy)benzene (157) in CDCl_3



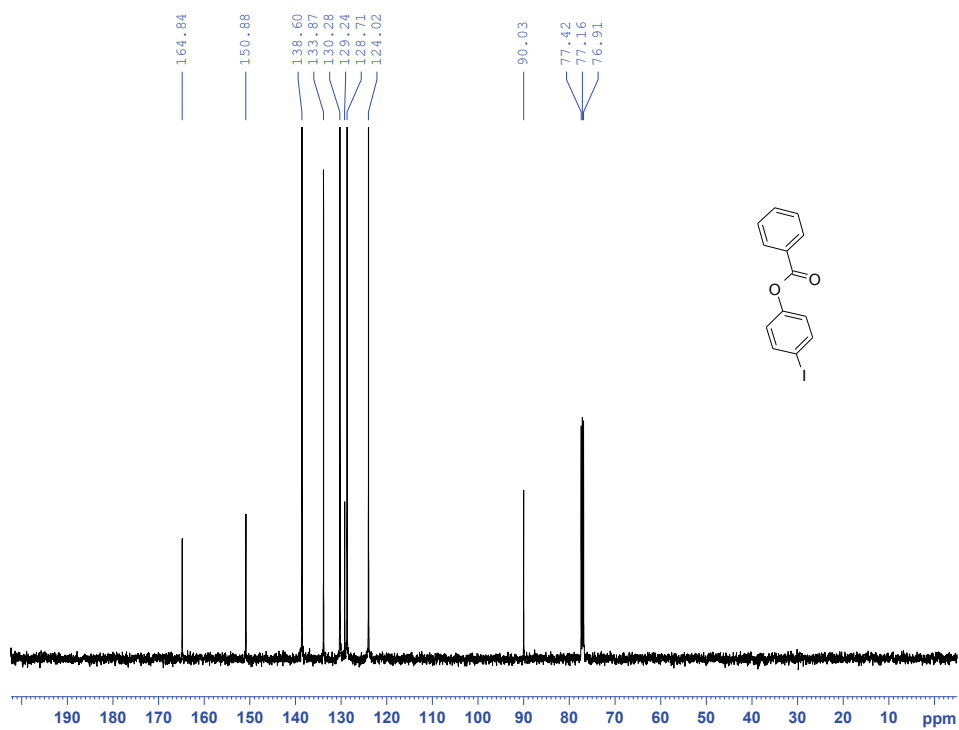
125.7 MHz ^{13}C NMR spectrum of 1,4-bis(2-benzoyloxyethoxy)benzene (157) in CDCl_3



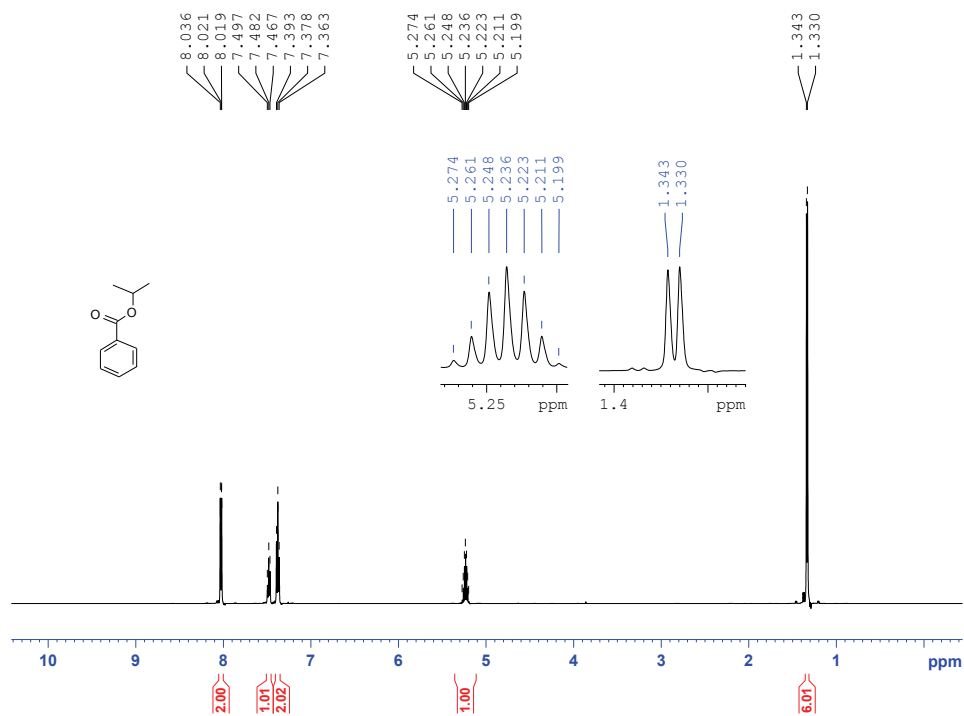
500.13 MHz ^1H NMR spectrum of 4-iodophenyl benzoate (158) in chloroform-*d*



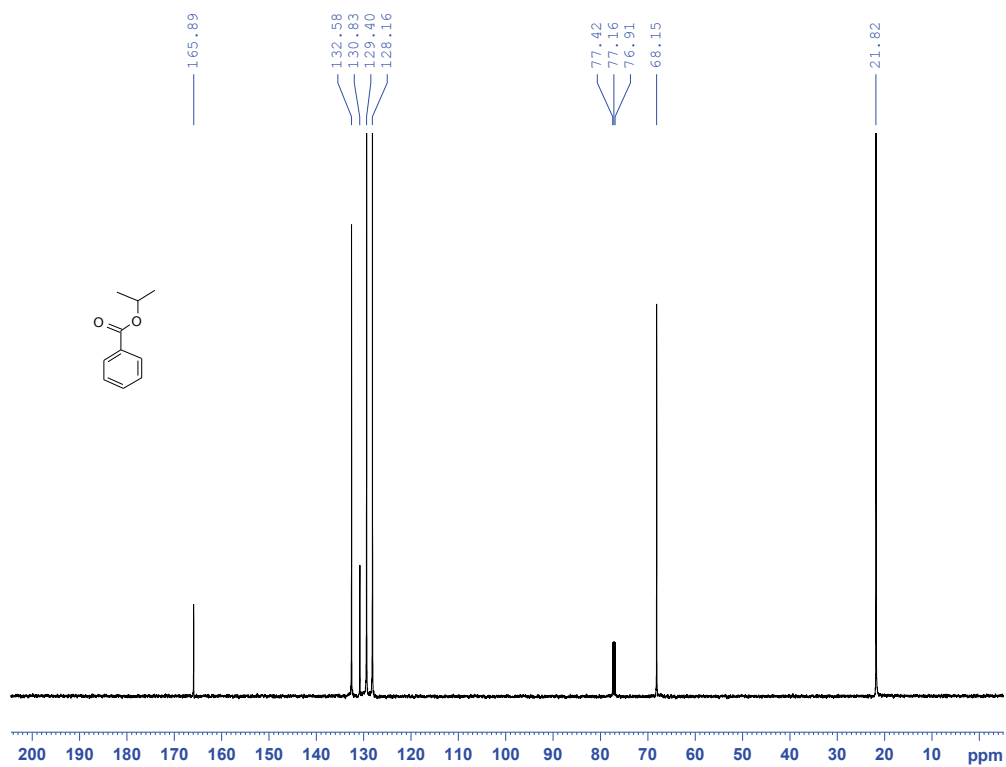
125.7 MHz ^{13}C NMR spectrum of 4-iodophenyl benzoate (158) in chloroform-*d*



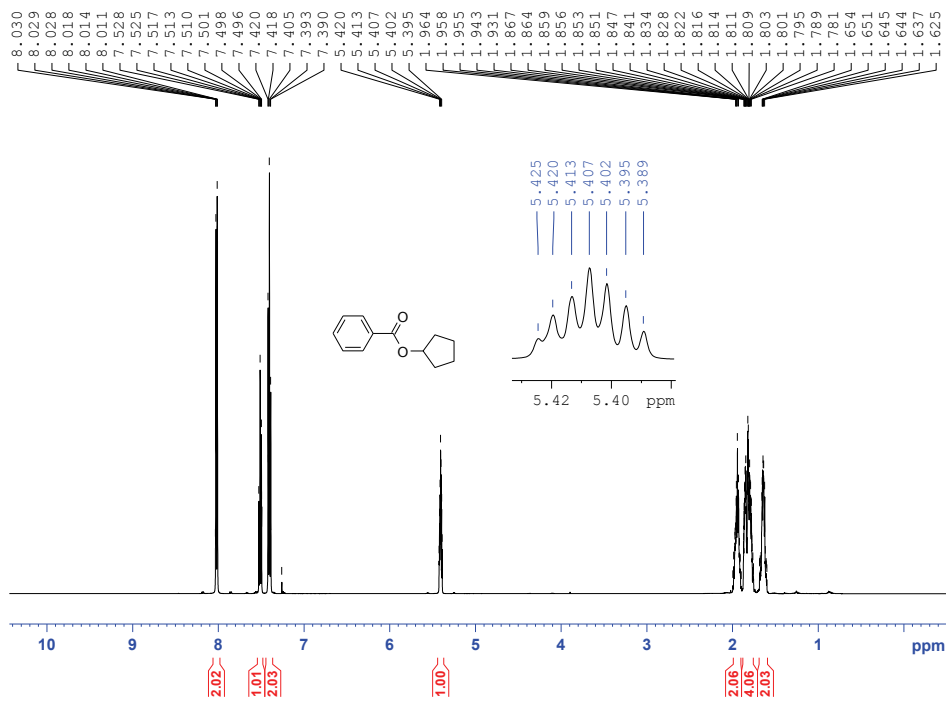
500.13 MHz ^1H NMR spectrum of isopropyl benzoate (159) in chloroform-*d*



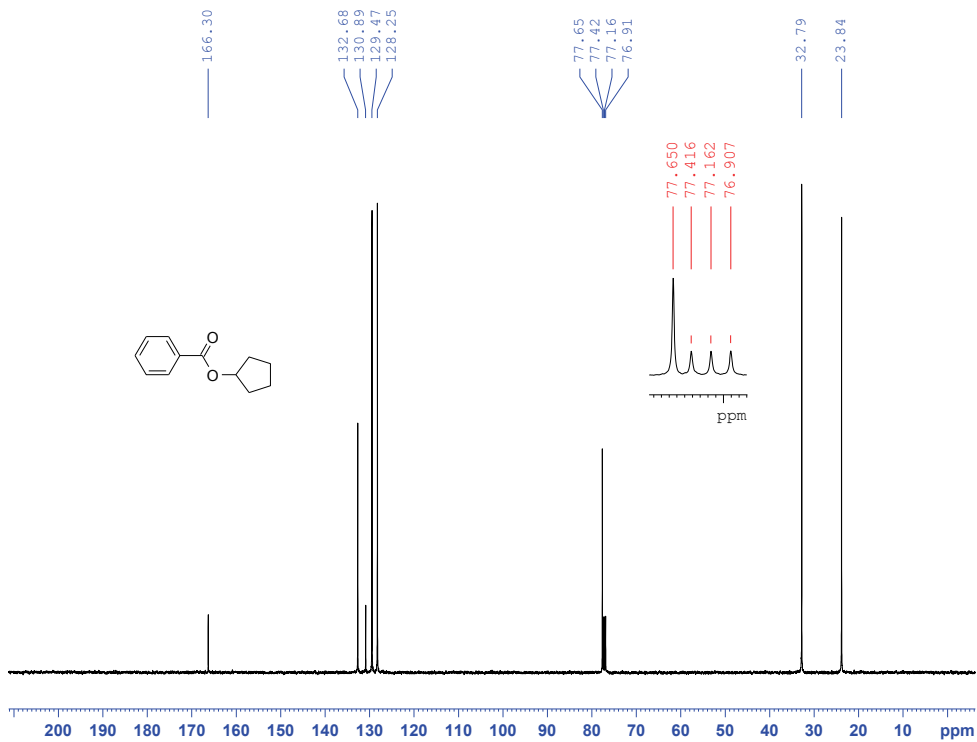
125.7 MHz ^{13}C NMR spectrum of isopropyl benzoate (159) in chloroform-*d*



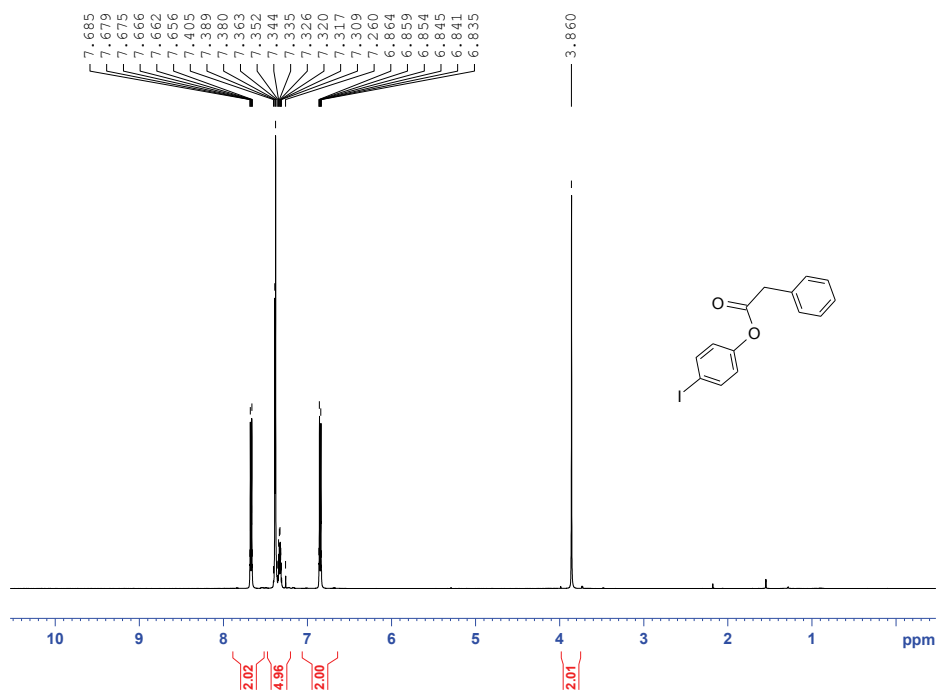
500.13 MHz ^1H NMR spectrum of cyclopentyl benzoate (160) in chloroform-*d*



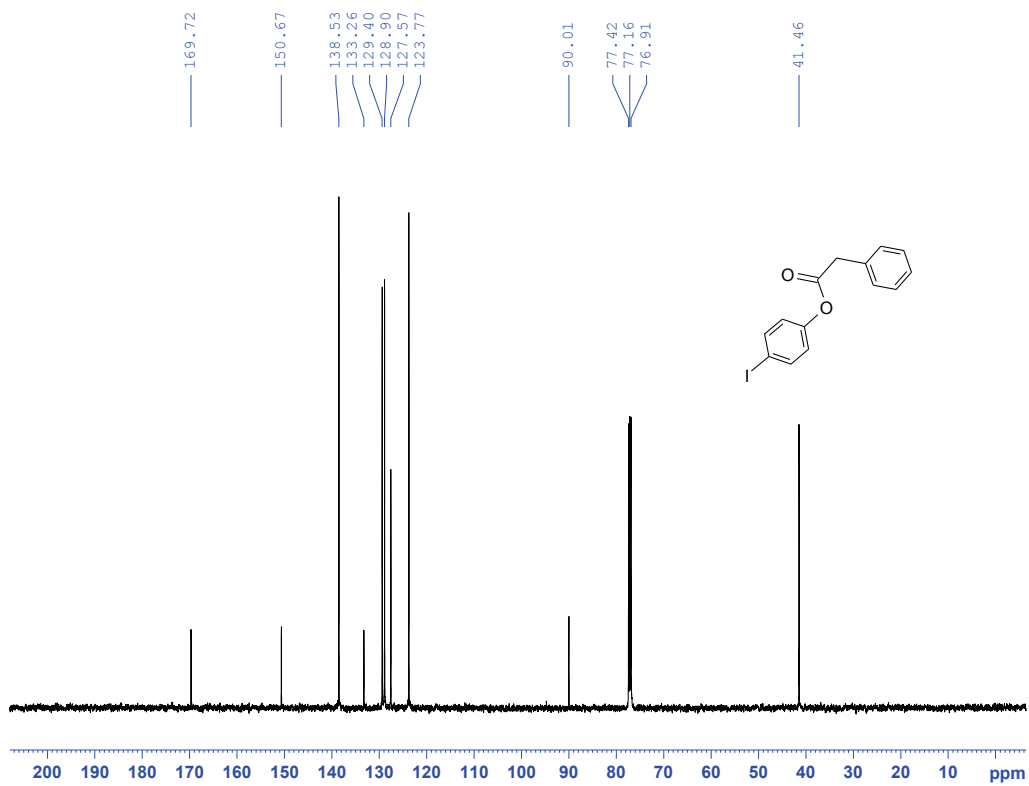
125.7 MHz ^{13}C NMR spectrum of cyclopentyl benzoate (160) in chloroform-*d*



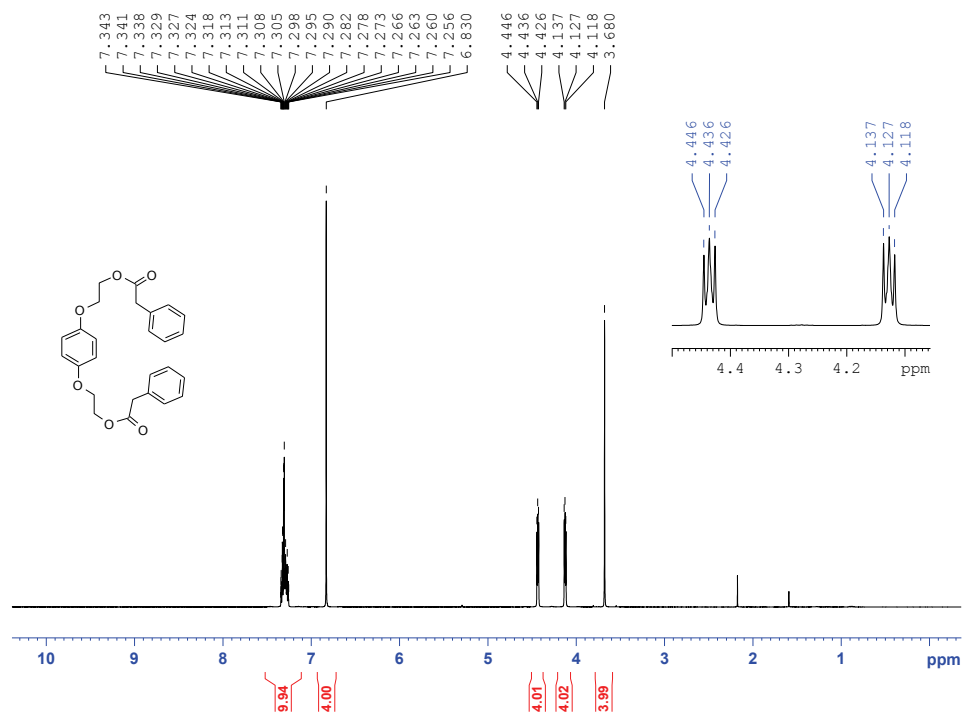
500.13 MHz ^1H NMR spectrum of 4-iodophenyl 2-phenylacetate (161) in chloroform-*d*



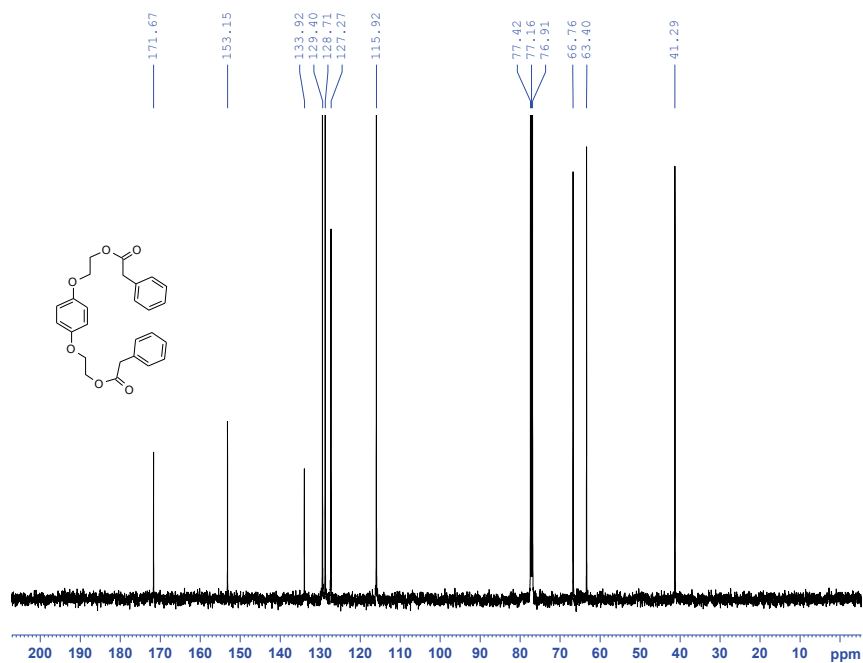
125.7 MHz ^{13}C NMR spectrum of 4-iodophenyl 2-phenylacetate (161) in chloroform-*d*



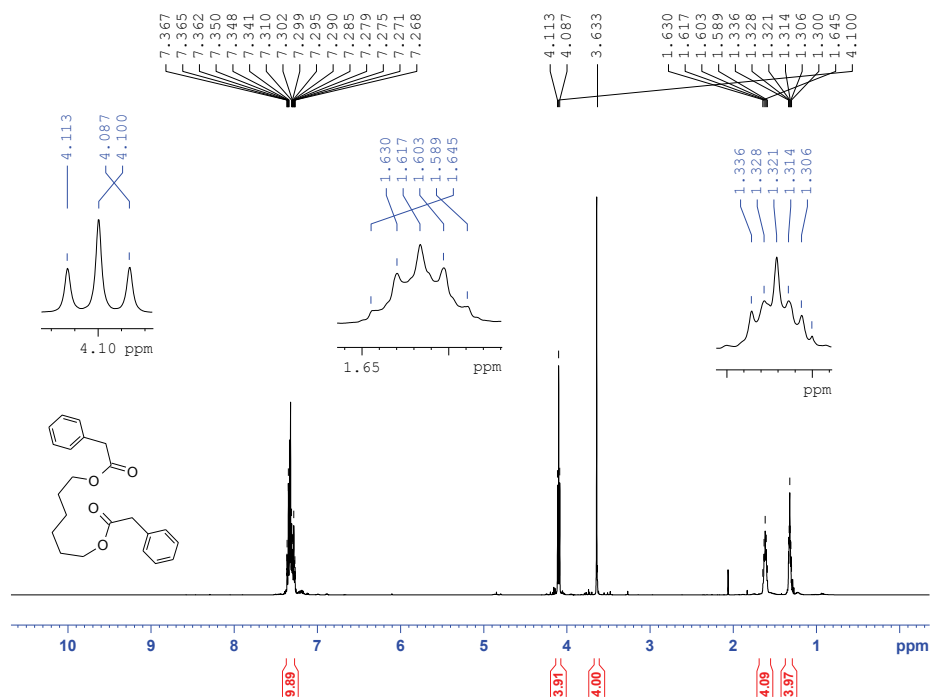
500.13 MHz ^1H NMR spectrum of 1,4-bis(2-(2-phenylacetyloxy)ethoxy)benzene (162) in chloroform-*d*



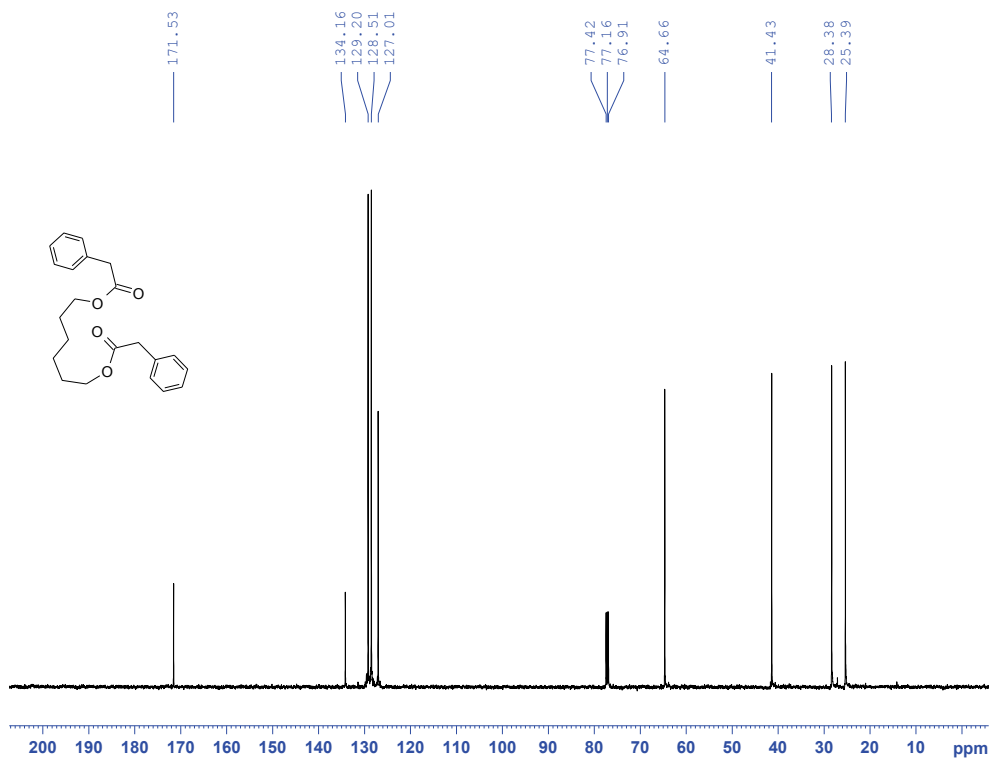
125.7 MHz ^{13}C NMR spectrum of 1,4-bis(2-(2-phenylacetyloxy)ethoxy)benzene (162) in chloroform-*d*



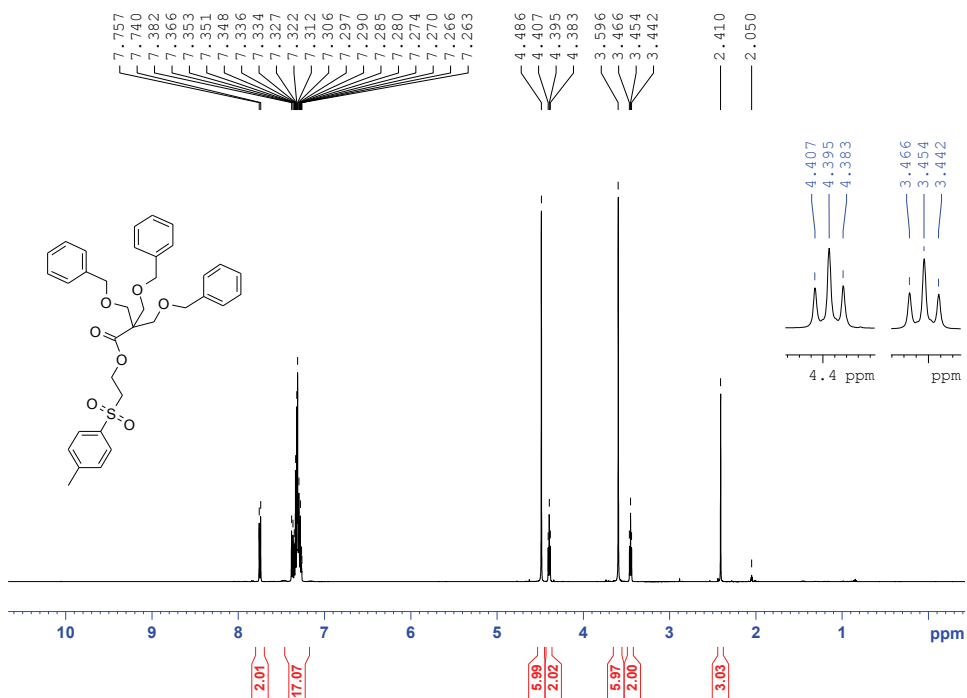
500.13 MHz ^1H NMR spectrum of 1,6-bis(2-phenylacetyloxy)hexane (163) in chloroform-*d*



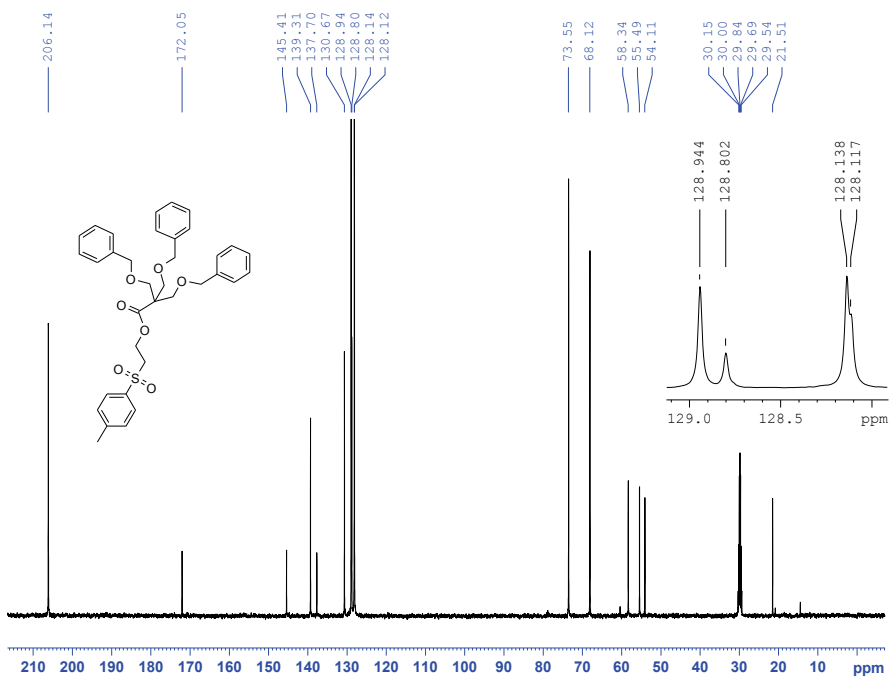
125.7 MHz ^{13}C NMR spectrum of 1,6-bis(2-phenylacetyloxy)hexane (163) in chloroform-*d*



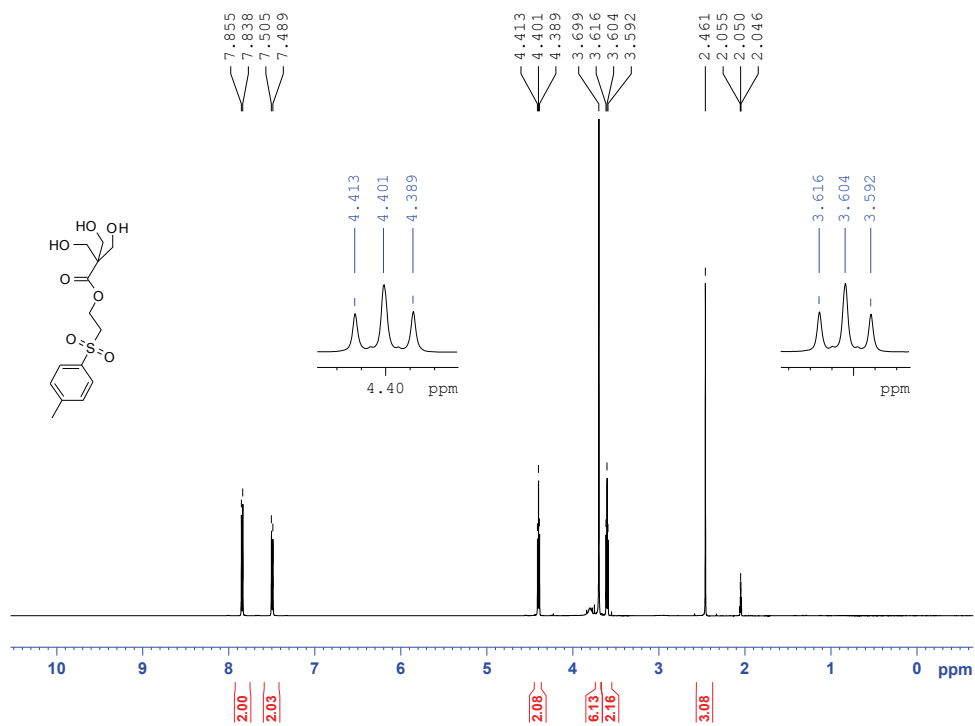
500.13 MHz ^1H NMR spectrum of 2-toluenesulfonylethyl 3-(benzyloxy)-2,2-bis(benzyloxymethyl)propanoate (137) in acetone- d_6



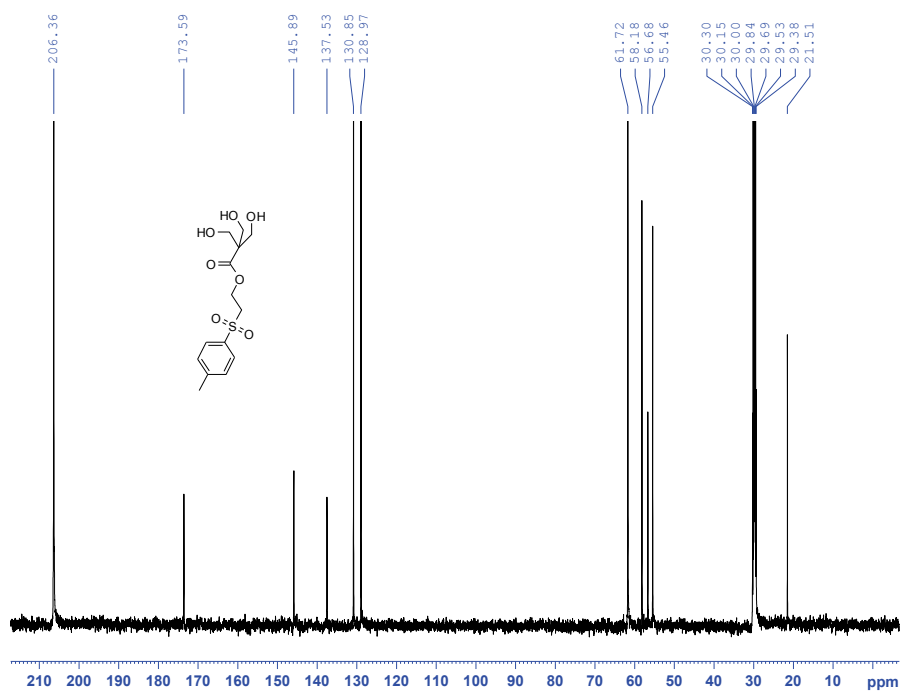
125.7 MHz ^{13}C NMR spectrum of 2-toluenesulfonylethyl 3-(benzyloxy)-2,2-bis(benzyloxymethyl)propanoate (137) in acetone- d_6



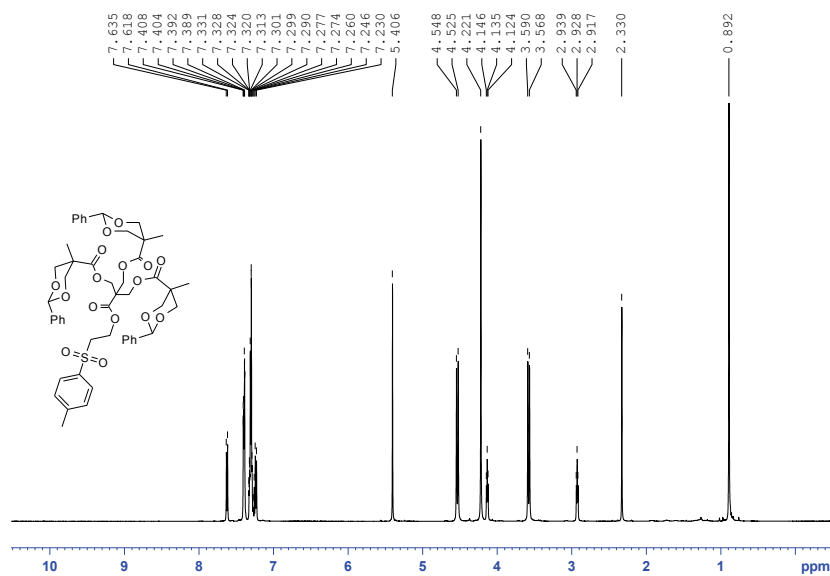
500.13 MHz ^1H NMR spectrum of 2-toluenesulfonylethyl 3-hydroxy-2,2-bis(hydroxymethyl)-propanoate (138) in acetone- d_6



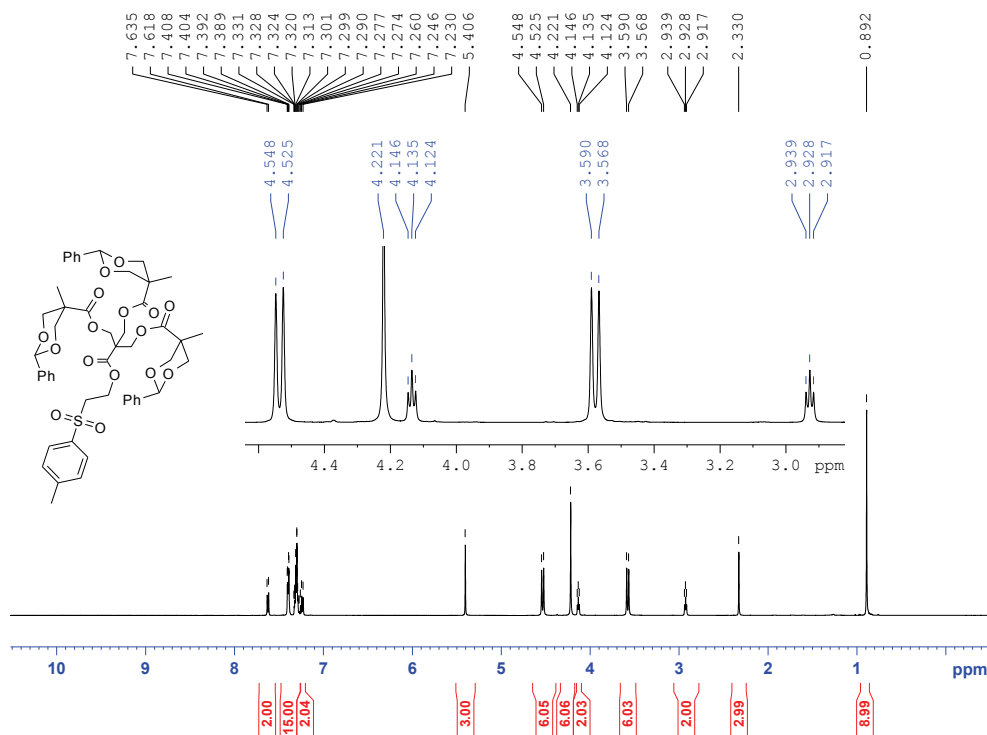
125.7 MHz ^{13}C NMR spectrum of 2-toluenesulfonylethyl 3-hydroxy-2,2-bis(hydroxymethyl)-propanoate (138) in acetone- d_6



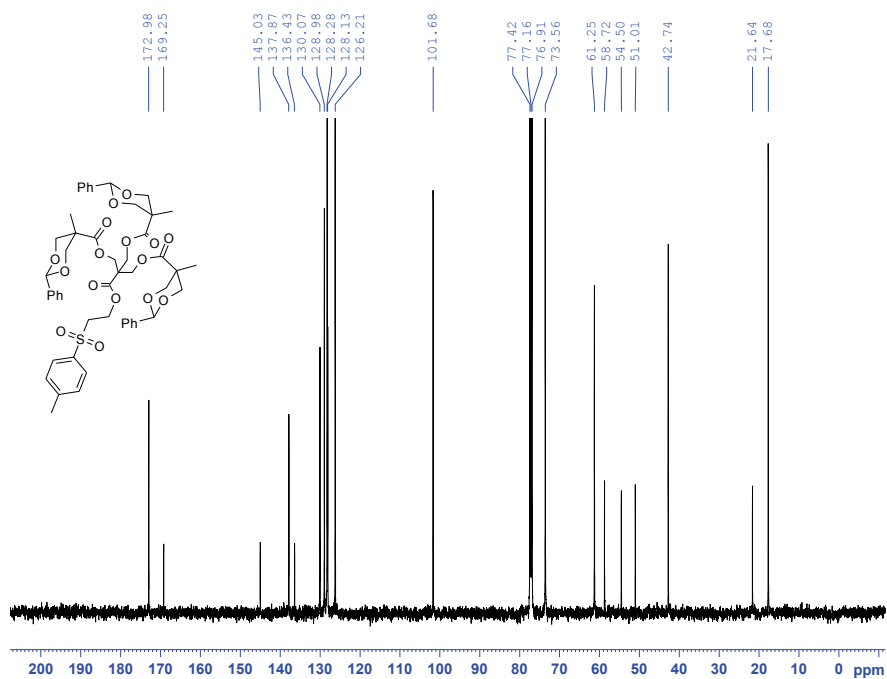
500.13 MHz ^1H NMR spectrum of 2-(toluenesulfonyl)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (139) in chloroform-*d*



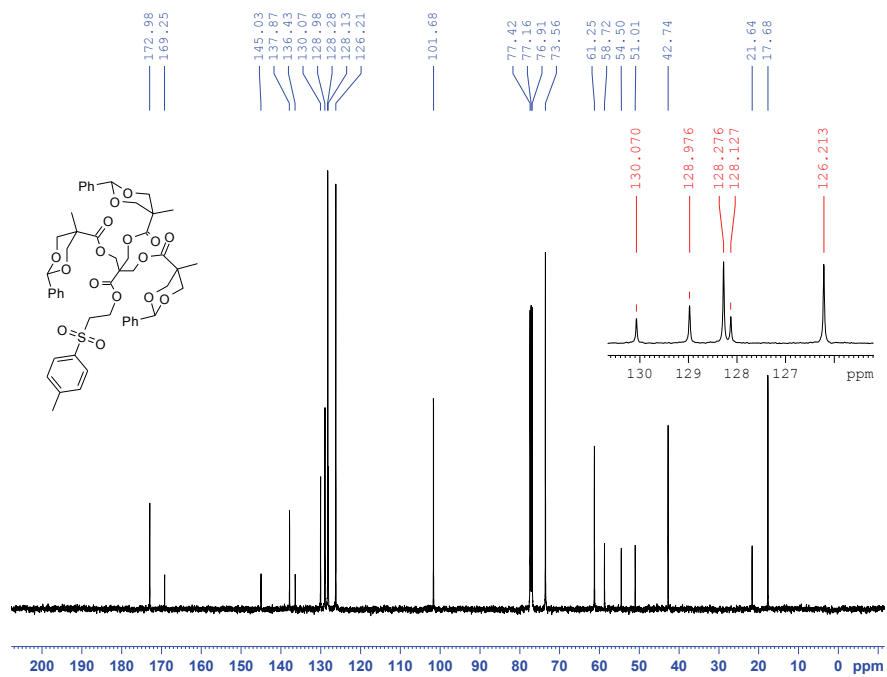
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of 2-(toluenesulfonyl)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (139) in chloroform-*d*



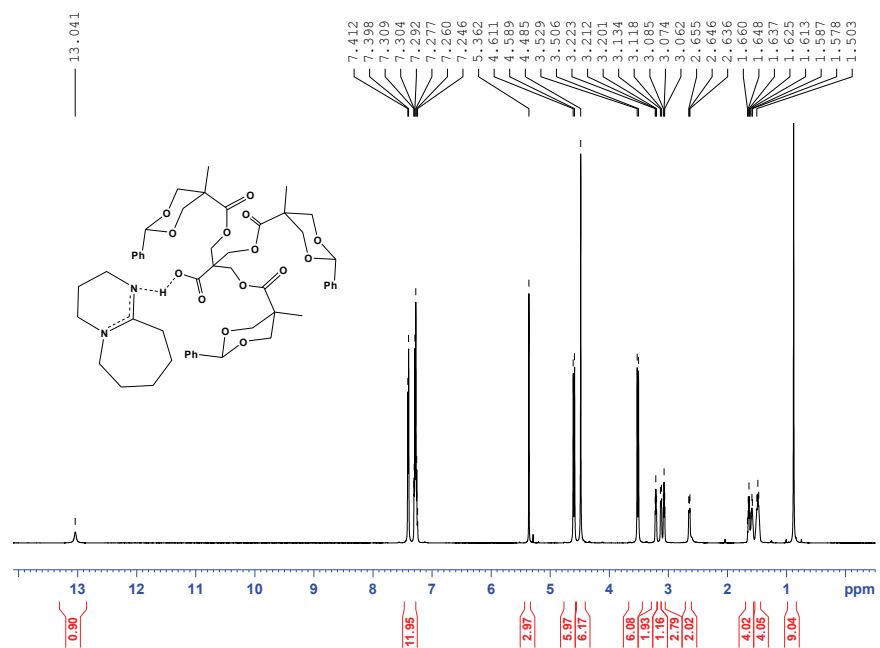
125.7 MHz ^{13}C NMR spectrum of 2-(toluenesulfonyl)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (139) in chloroform-*d*



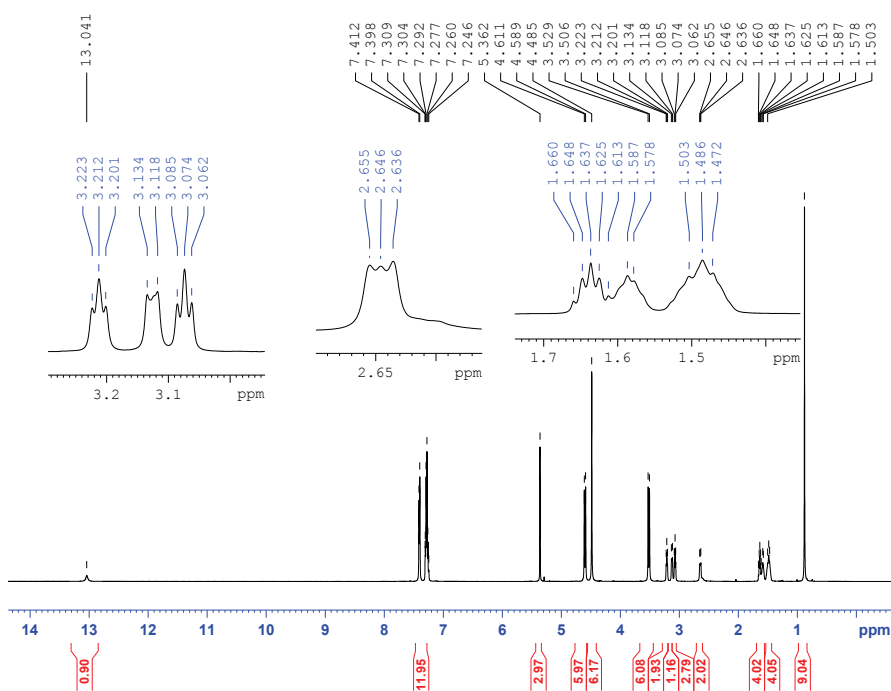
Expansions of part of the 125.7 MHz ^{13}C NMR spectrum of 2-(toluenesulfonyl)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (139) in chloroform-*d*



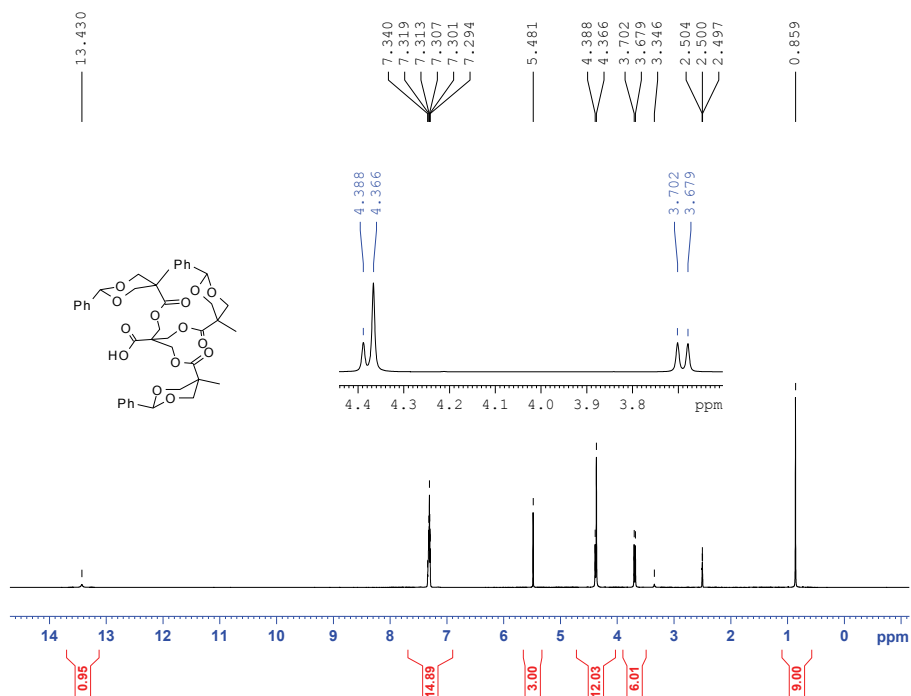
500.13 MHz ^1H NMR spectrum of 1,8-diazabicyclo[5.4.0]undec-7-ene-8-ium bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (140) in chloroform-*d*



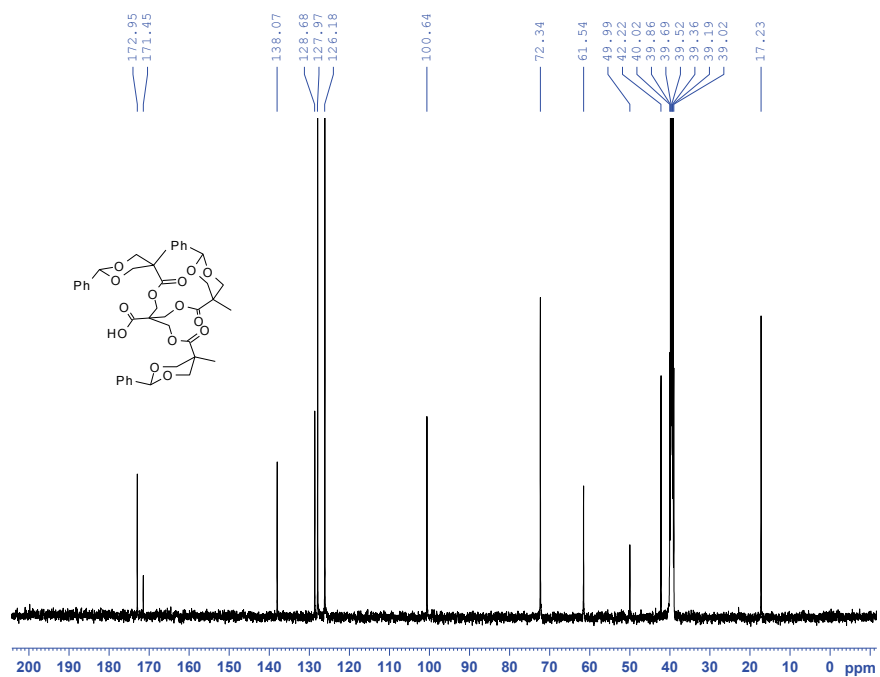
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of 1,8-diazabicyclo[5.4.0]undec-7-ene-8-ium bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (140) in chloroform-*d*



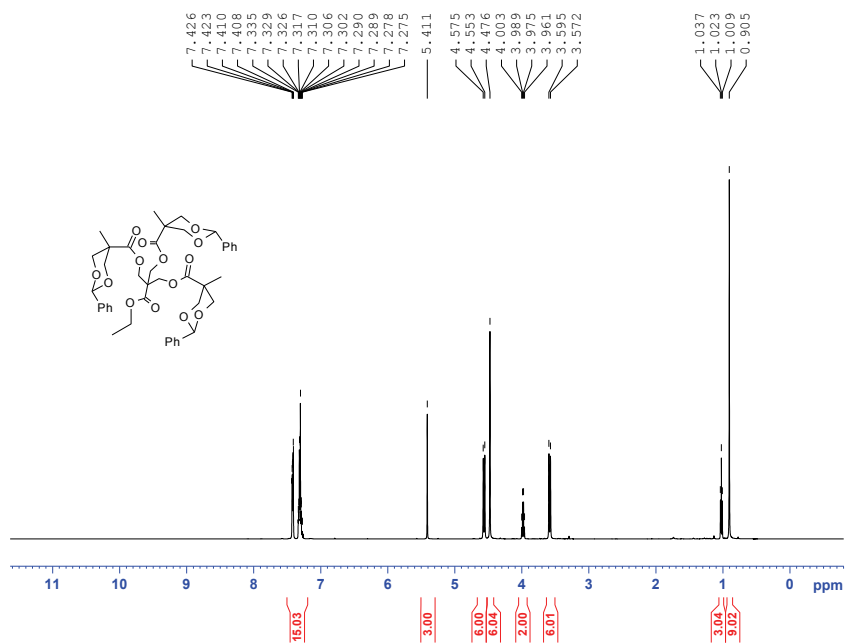
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoic acid (136) in $\text{DMSO-}d_6$



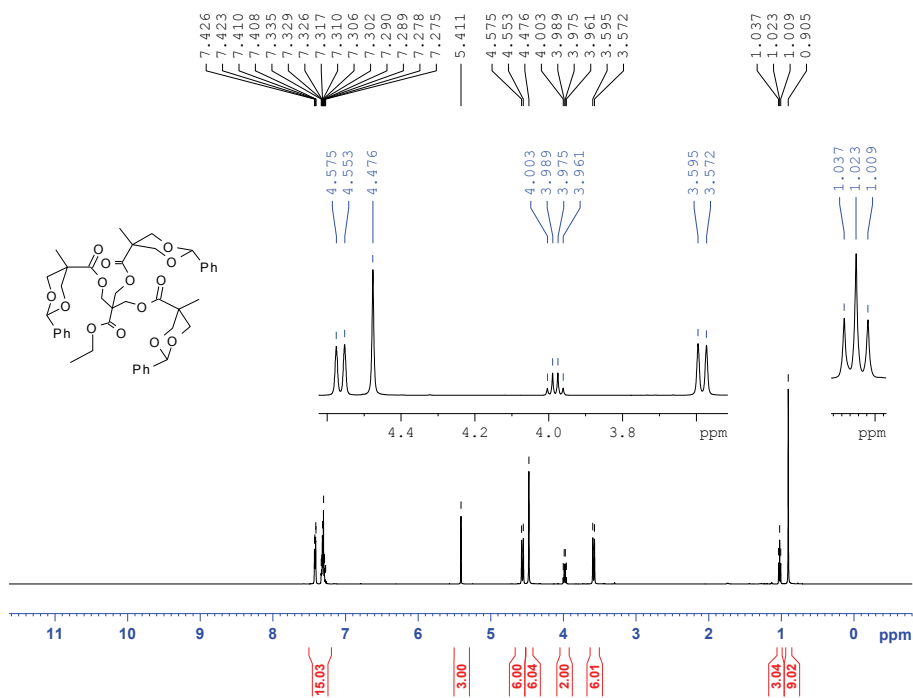
125.7 MHz ^1H NMR spectrum of bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoic acid (136) in $\text{DMSO-}d_6$



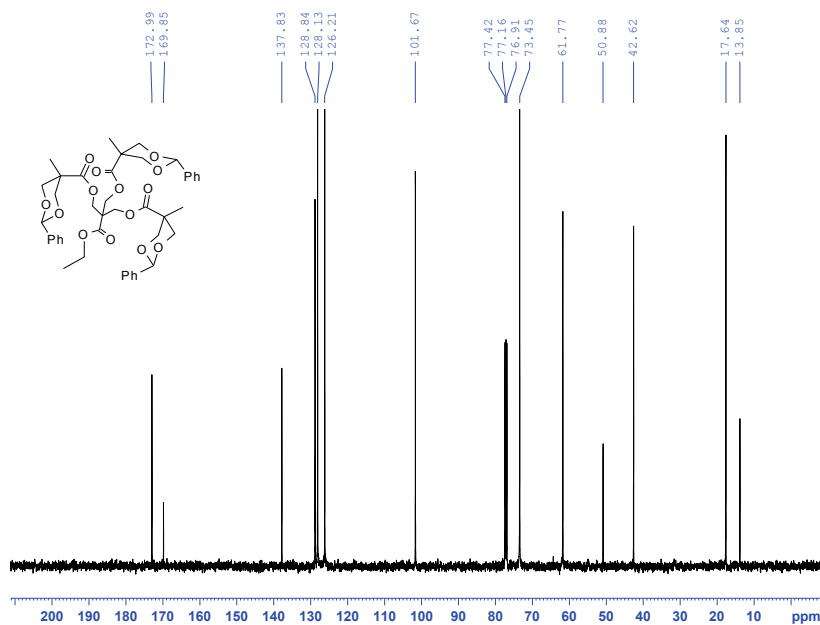
500.13 MHz ^1H NMR spectrum of ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (142) in chloroform-*d*



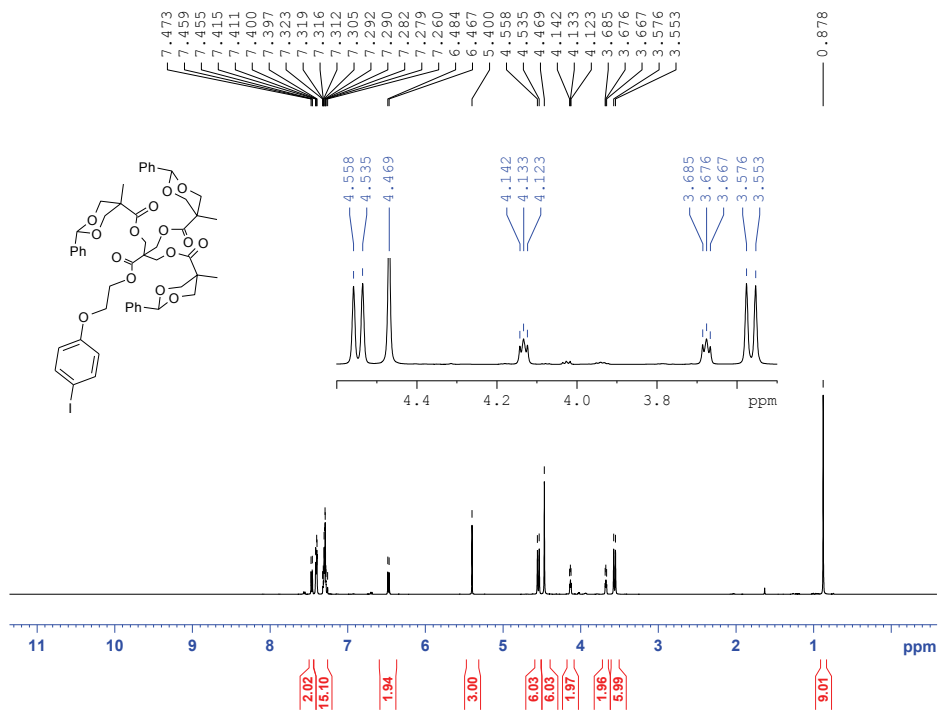
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (142) in chloroform-*d*



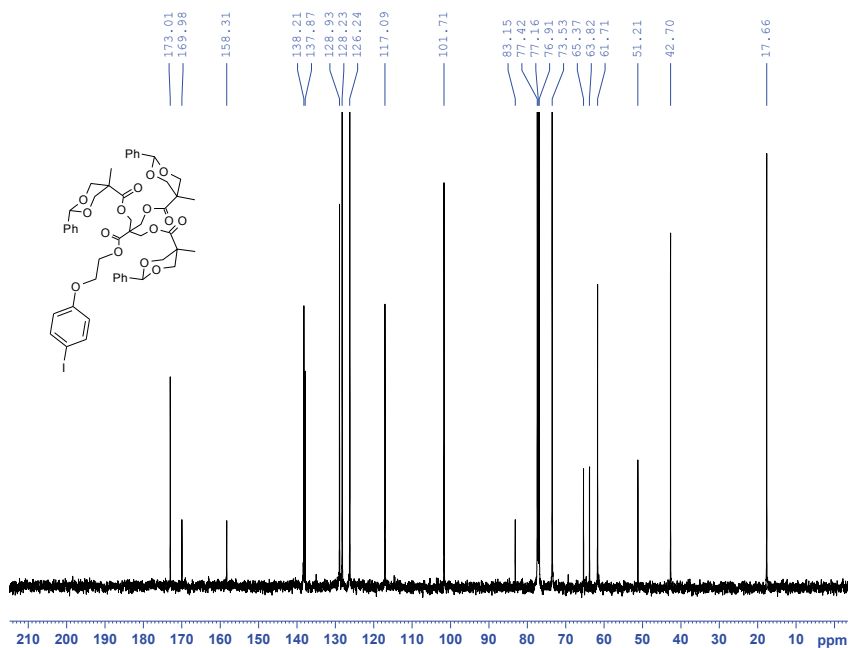
125.7 MHz ^1H NMR spectrum of ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (142) in chloroform-*d*



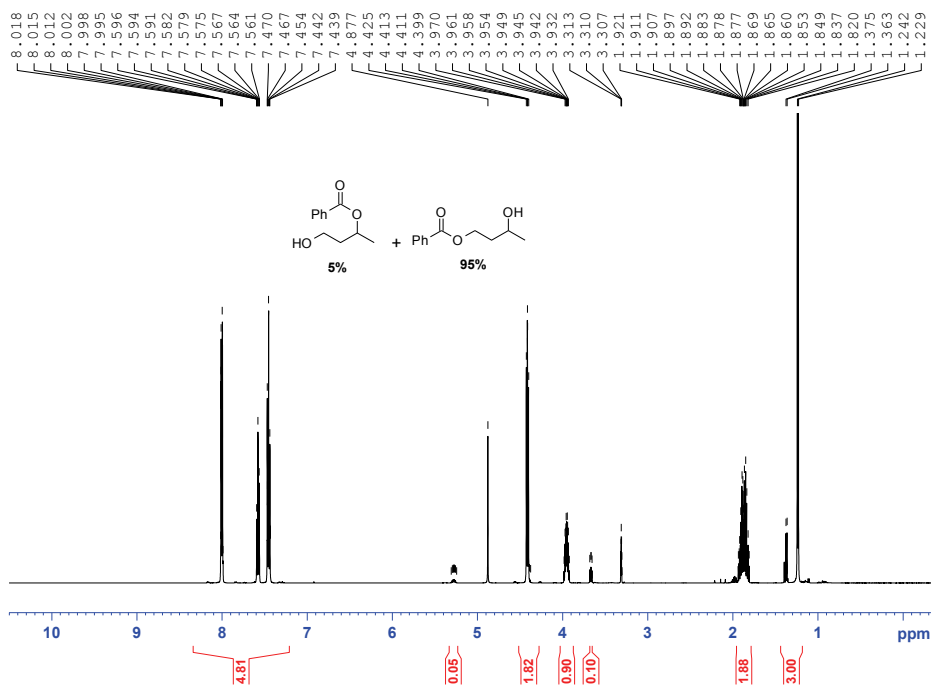
500.13 MHz ^1H NMR spectrum of 2-(4-iodophenoxy)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (143) in chloroform-*d*



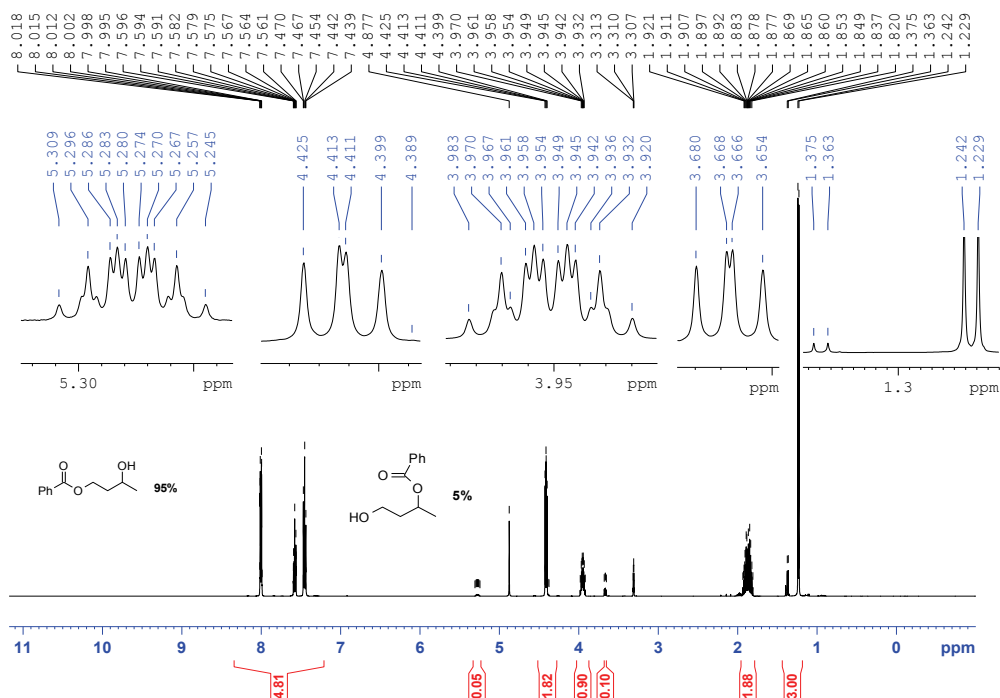
125.7 MHz ^{13}C NMR spectrum of 2-(4-iodophenoxy)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carboxyloxy)propanoate (143) in chloroform-*d*



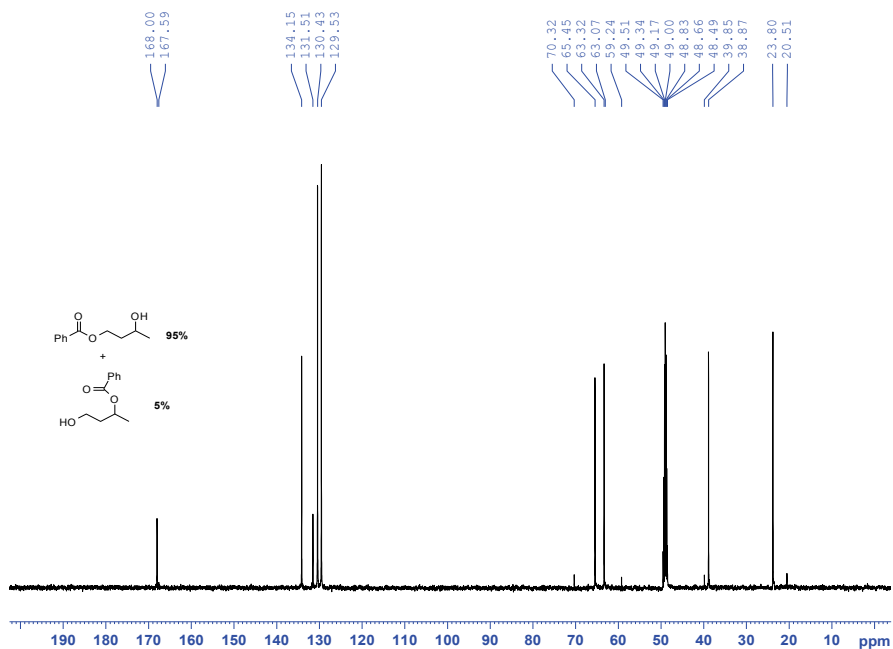
500.13 MHz ^1H NMR spectrum of 3-hydroxybutyl benzoate (144) with 5% of the secondary product in methanol-*d*₄



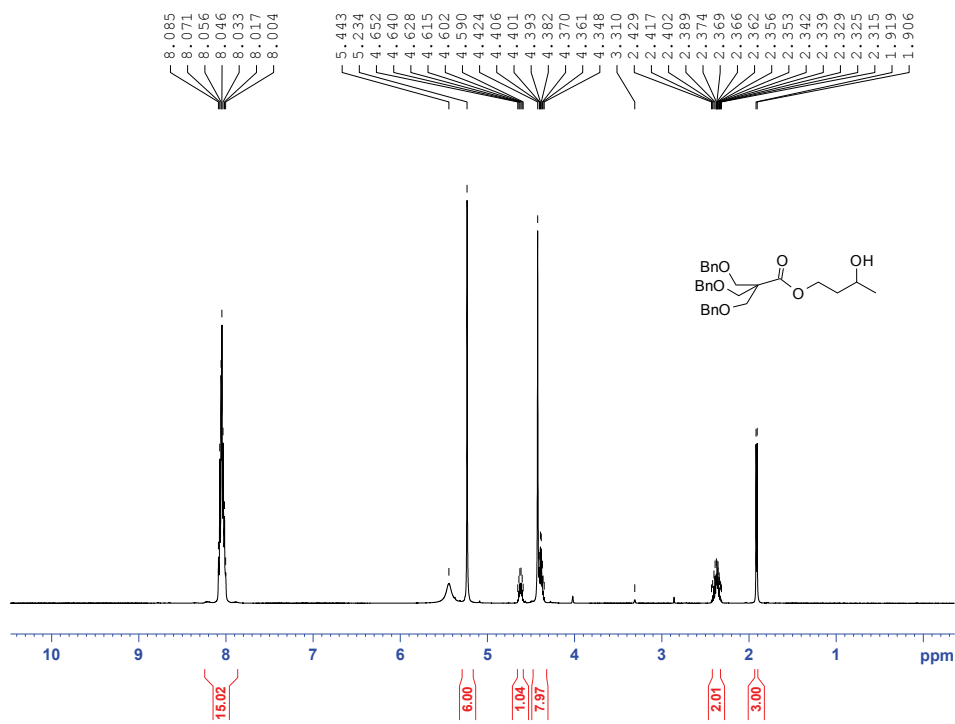
Expansions of the 500.13 MHz ^1H NMR spectrum of 3-hydroxybutyl benzoate (144) with 5% of the secondary product in methanol- d_4



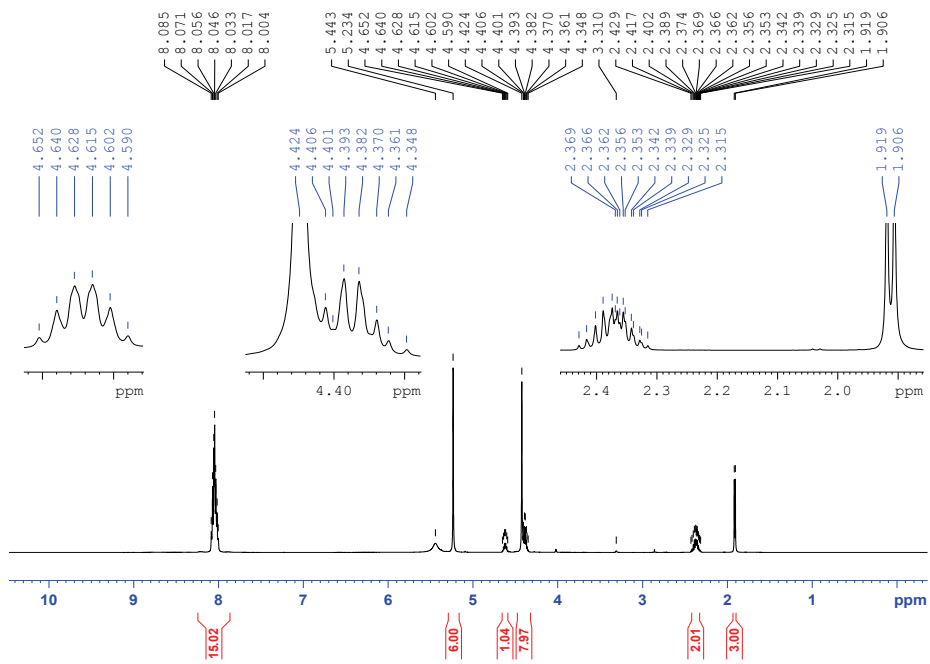
125.7 MHz ^{13}C NMR spectrum of 3-hydroxybutyl benzoate (144) with 5% of the secondary product in methanol- d_4



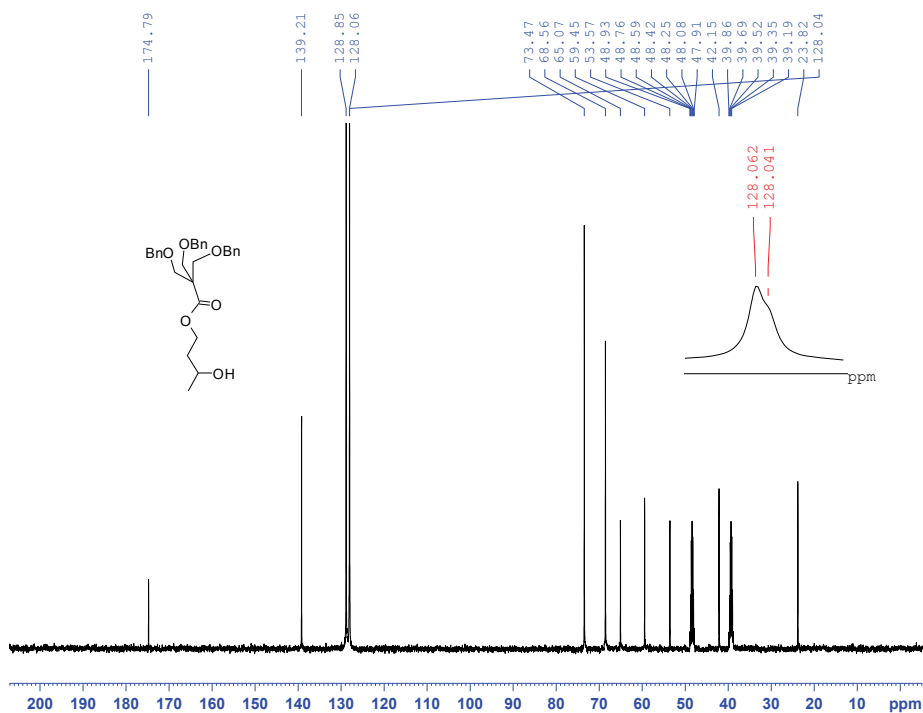
500.13 MHz ^1H NMR spectrum of 3-hydroxybutyl 3-benzyloxy-2,2'-bis(benzyloxymethyl)propanoate (145) in $\text{DMSO-}d_6/\text{methanol-}d_4$



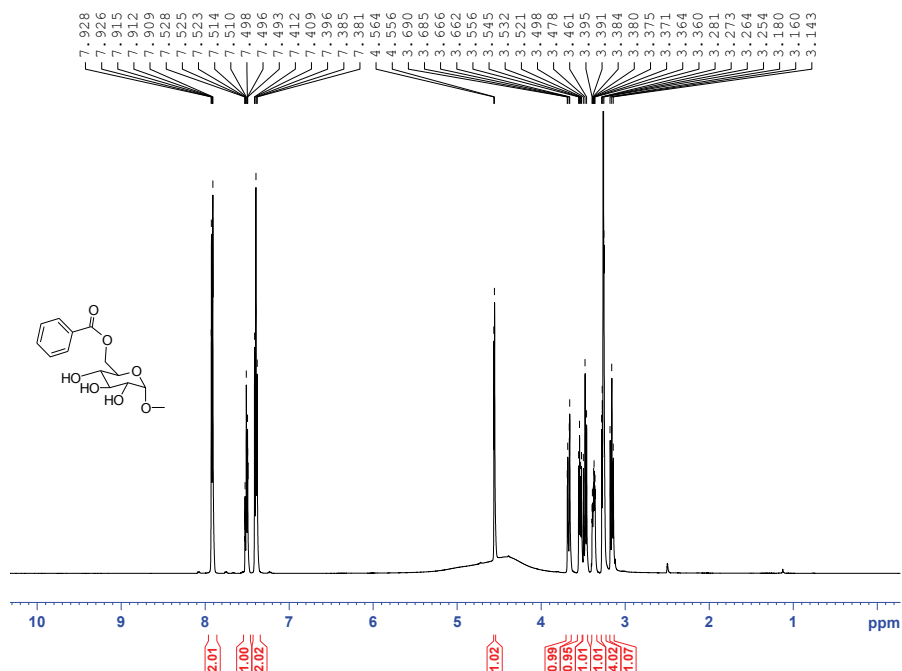
Expansions of the 500.13 MHz ^1H NMR spectrum 3-hydroxybutyl 3-benzyloxy-2,2'-bis(benzyloxymethyl)propanoate (145) in $\text{DMSO-}d_6/\text{methanol-}d_4$



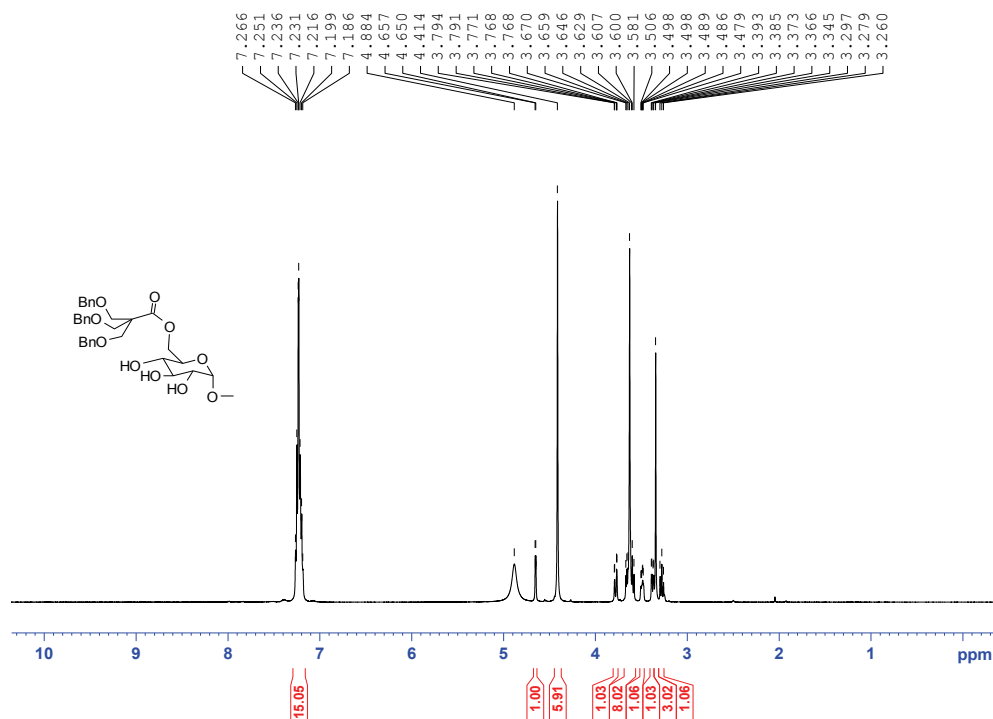
125.7 MHz ^{13}C NMR spectrum of 3-hydroxybutyl 3-benzyloxy-2,2'-bis(benzyloxymethyl)propanoate (145) in DMSO- d_6 / methanol- d_4



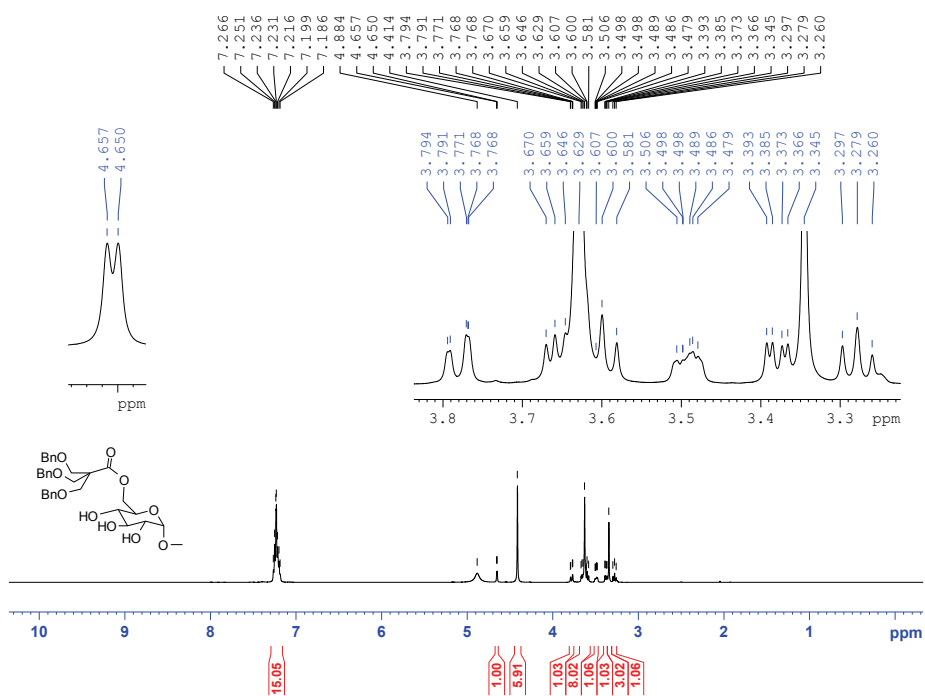
500.13 MHz ^1H NMR spectrum of methyl 6-O-benzoyl- α -D-glucopyranoside (146) in DMSO- d_6 / methanol- d_4



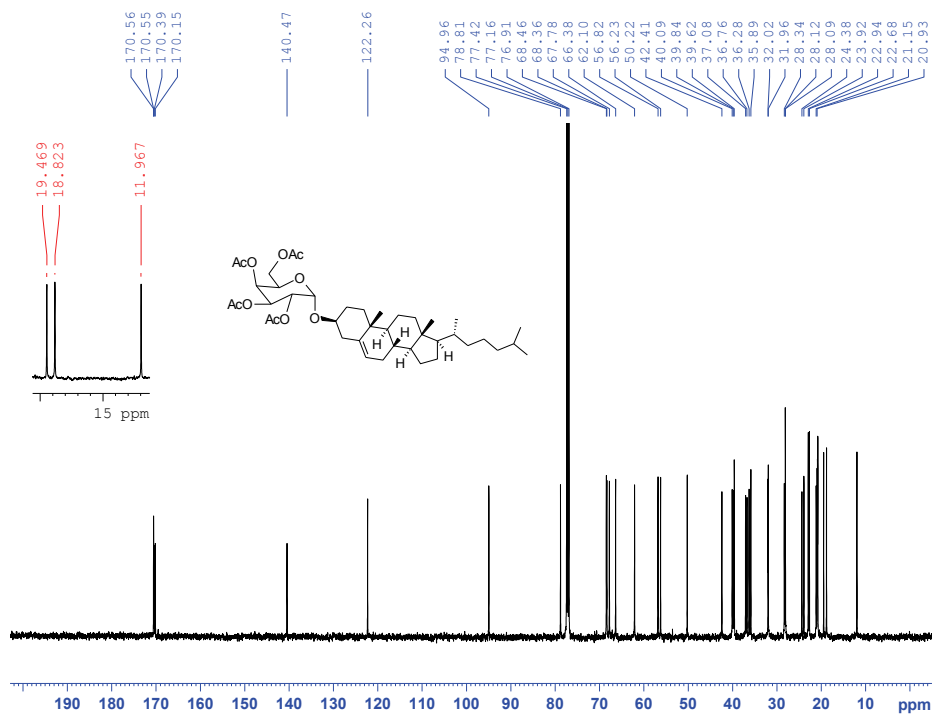
500.13 MHz ^1H NMR spectrum of methyl 6-*O*-(3-benzyloxy-2,2'-bis(benzyloxymethyl)propanoyloxy)- α -D-glucopyranoside (147) in DMSO- d_6 / methanol- d_4



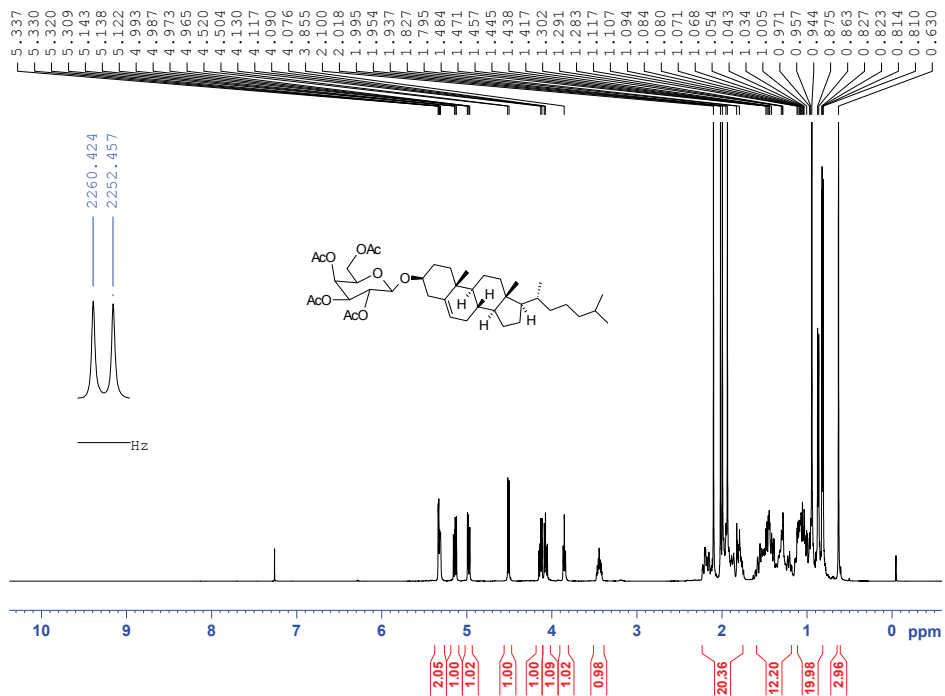
Expansions of the 500.13 MHz ^1H NMR spectrum methyl 6-*O*-(3-benzyloxy-2,2'-bis(benzyloxymethyl)propanoyloxy)- α -D-glucopyranoside (147) in DMSO- d_6 / methanol- d_4



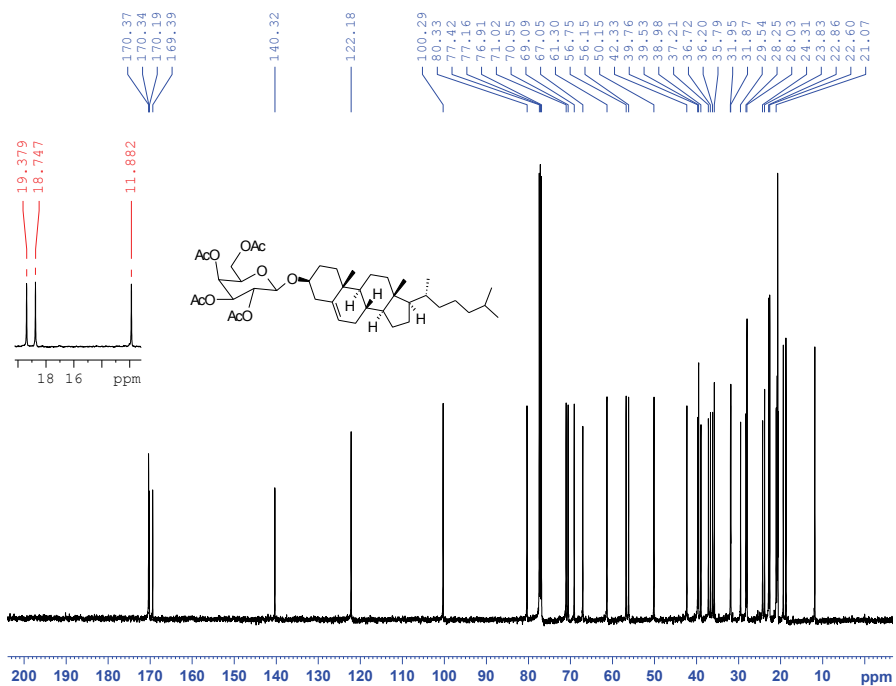
125.7 ¹³C NMR spectrum of cholesteryl 2,3,4,6-tetra-*O*-acetyl- α -D-galactopyranoside (170) in chloroform-*d*



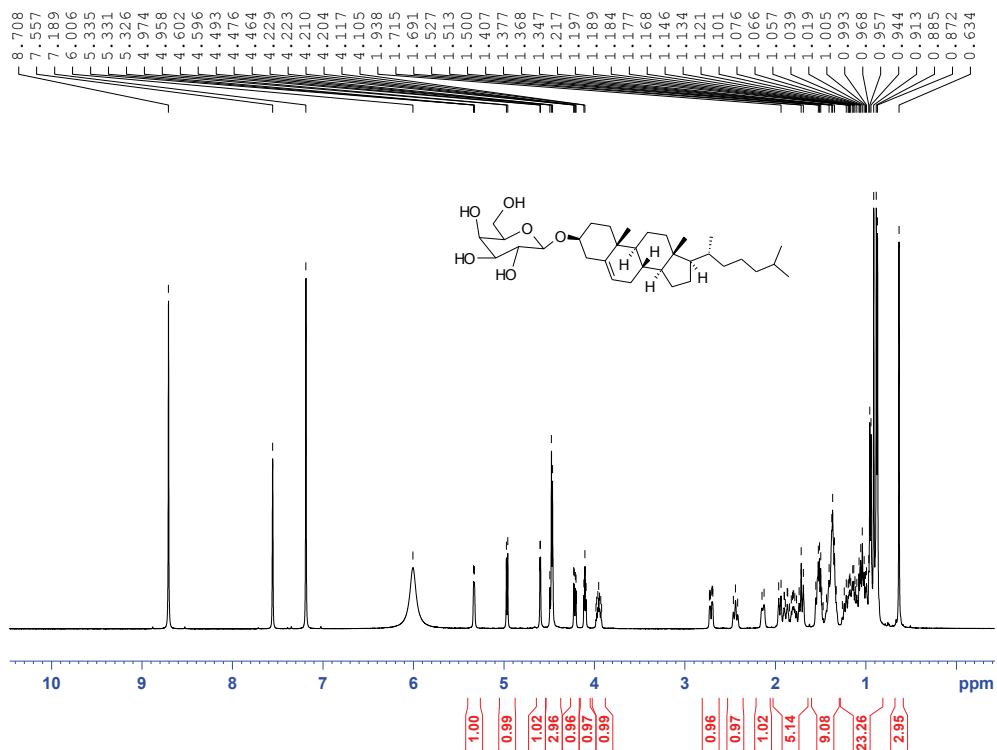
500.13 MHz ¹H NMR spectrum of cholesteryl 2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranoside (171) in chloroform-*d*



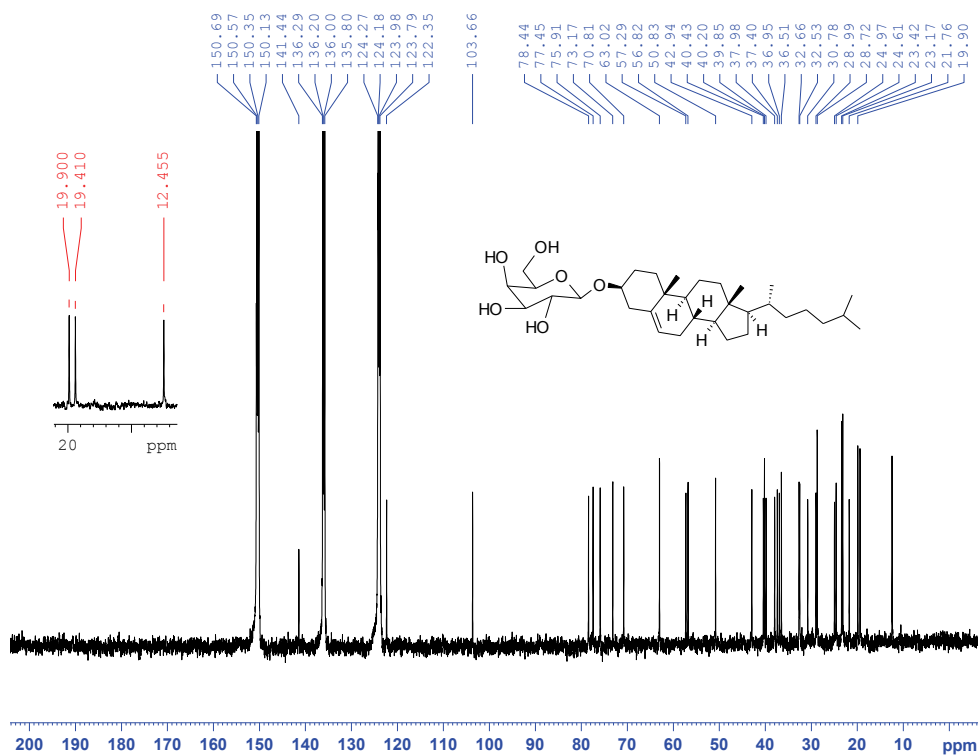
125.7 ¹³C NMR spectrum of cholesteryl 2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranoside (171) in chloroform-*d*



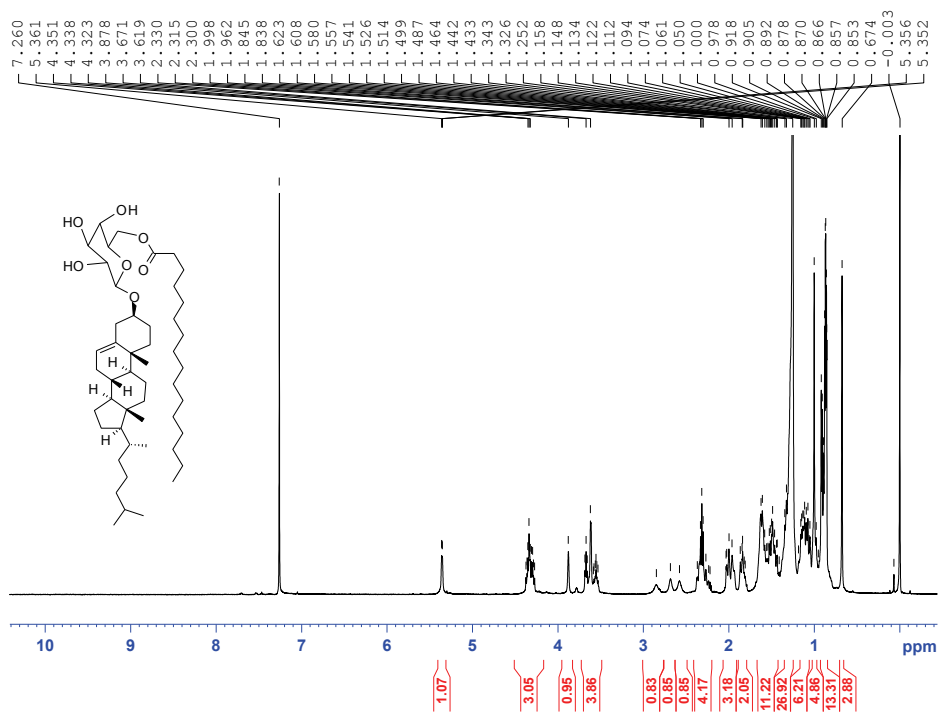
500.13 MHz ¹H NMR spectrum of cholesteryl β -D-galactopyranoside (168) in pyridine-*d*₅



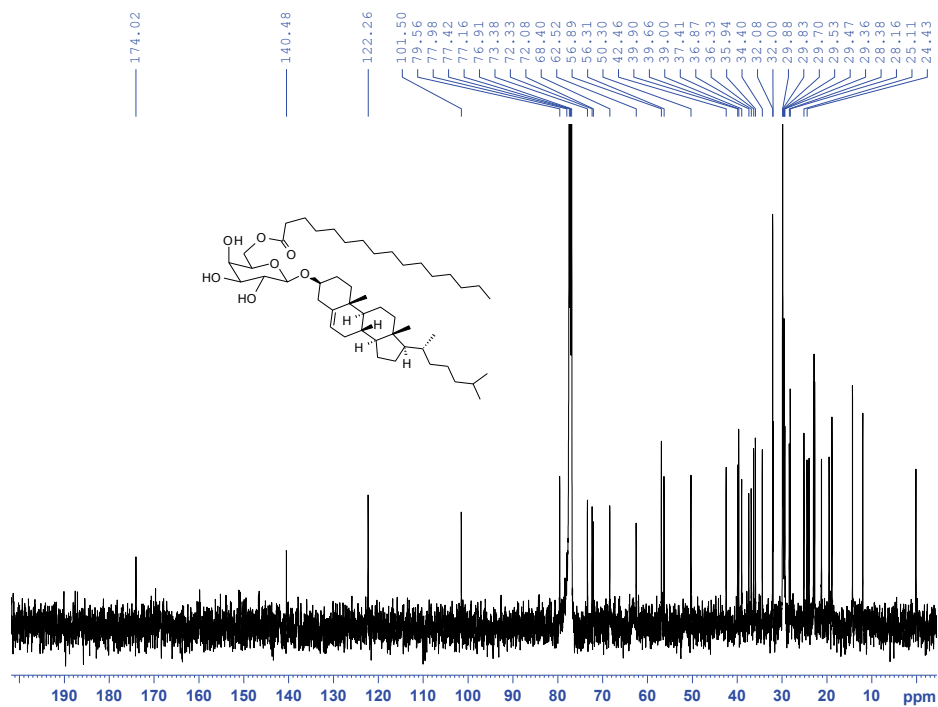
125.7 MHz ^{13}C NMR spectrum of cholesteryl β -D-galactopyranoside (168) in pyridine- d_5



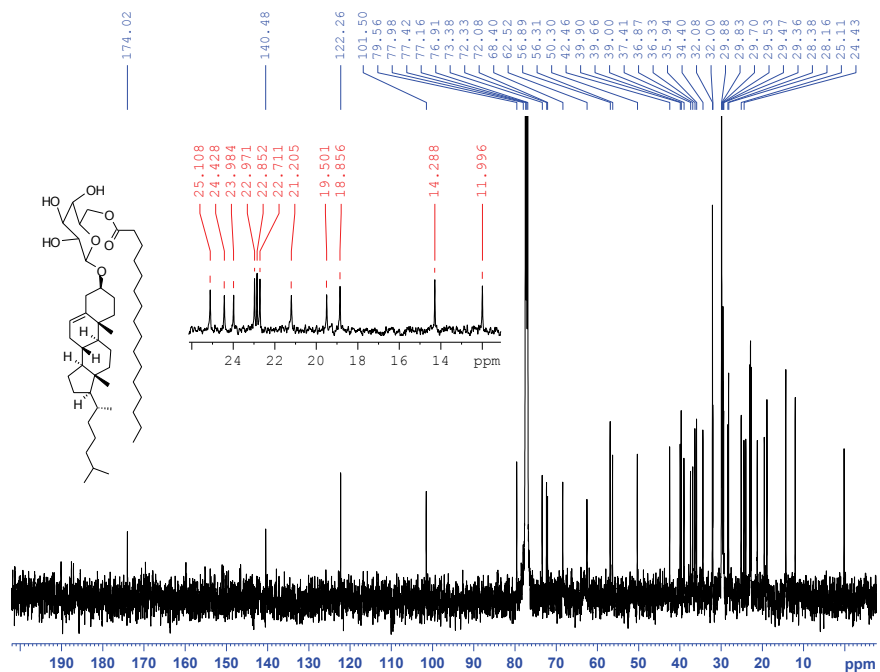
500.13 MHz ^1H NMR spectrum of cholesteryl 6-O-palmitoyl- β -D-galactopyranoside (169a) in chloroform- d



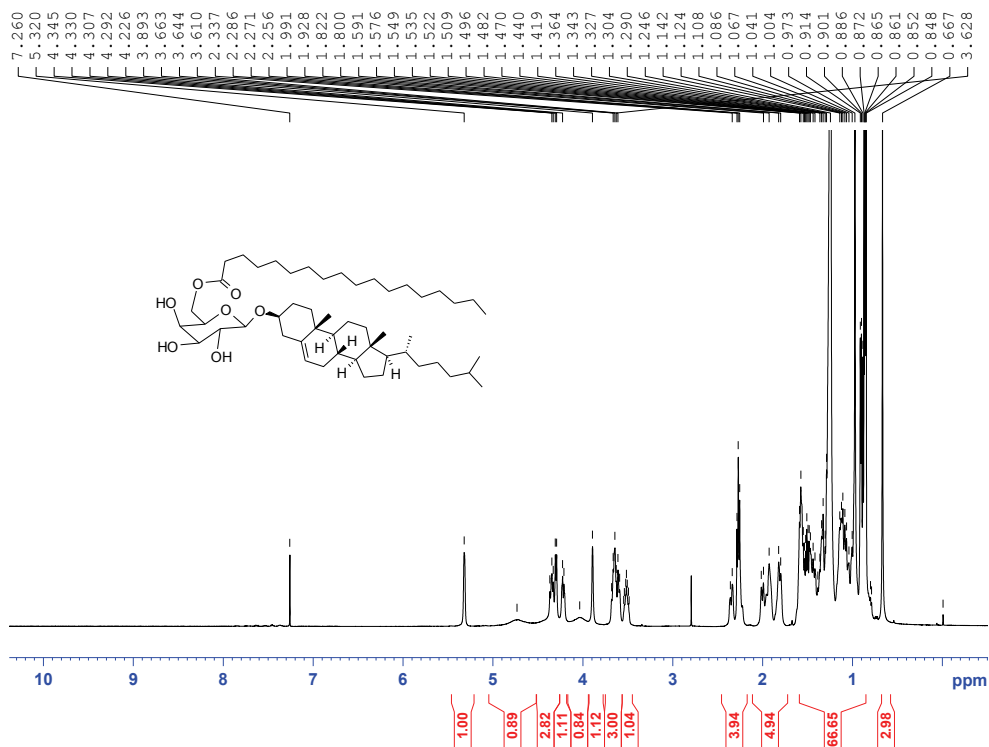
125.7 MHz ^{13}C NMR spectrum of cholesteryl 6-*O*-palmitoyl- β -D-galactopyranoside (169a) in chloroform-*d*



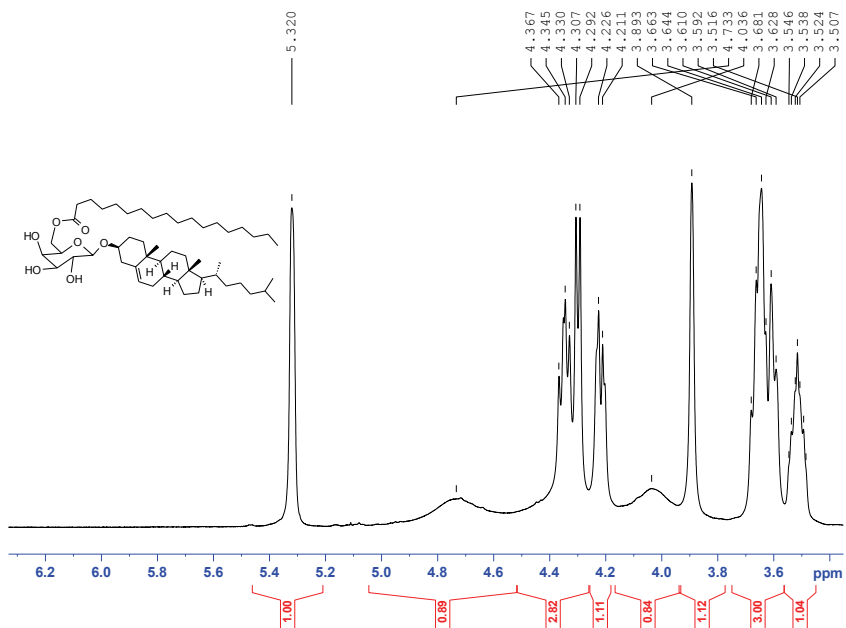
Expansions of parts of the 125.7 MHz ^{13}C NMR spectrum of cholesteryl 6-*O*-palmitoyl- β -D-galactopyranoside (169a) in chloroform-*d*



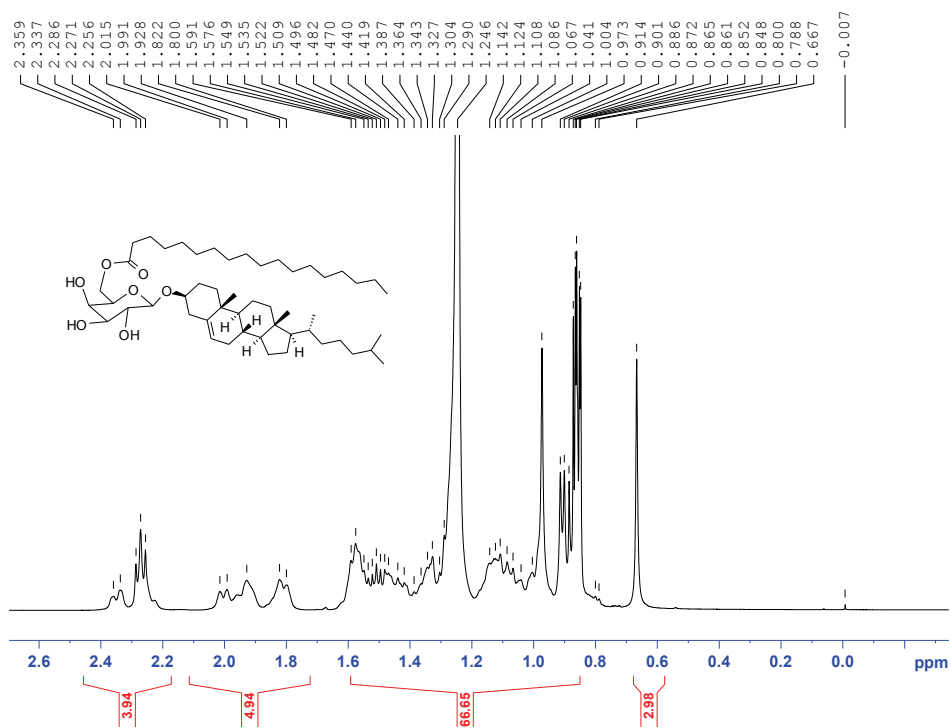
500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-stearoyl- β -D-galactopyranoside (169b) in chloroform-*d*



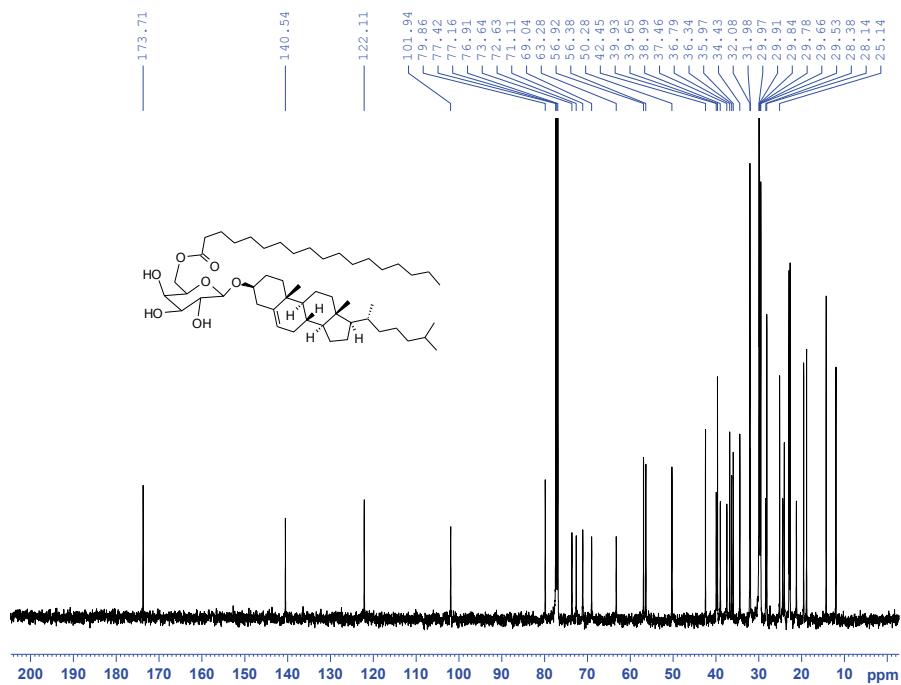
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-stearoyl- β -D-galactopyranoside (169b) in chloroform-*d*



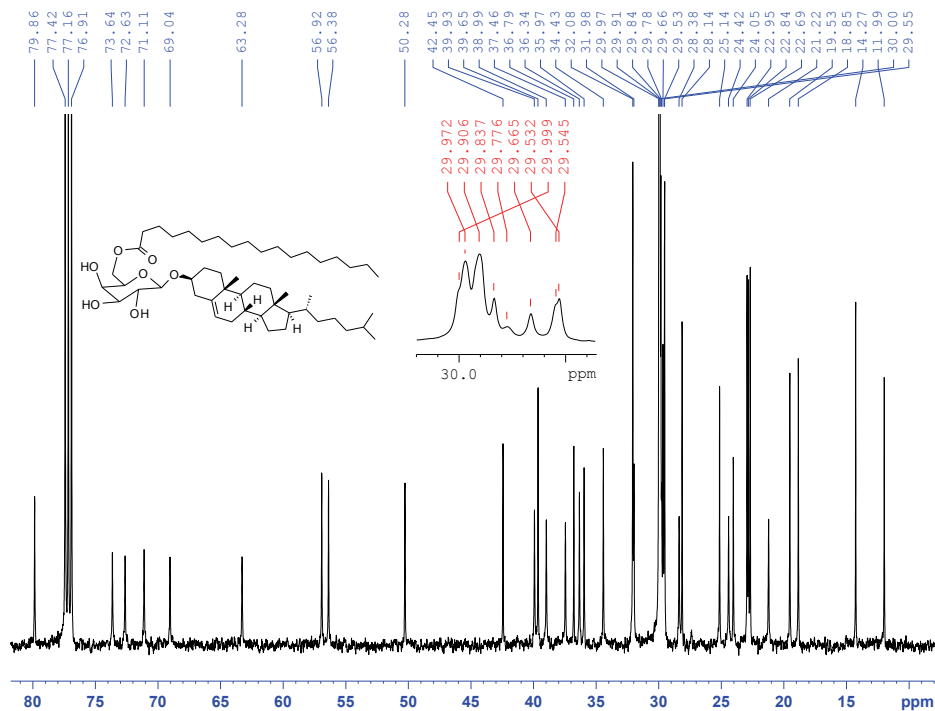
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-stearoyl- β -D-galactopyranoside (169b) in chloroform-*d*



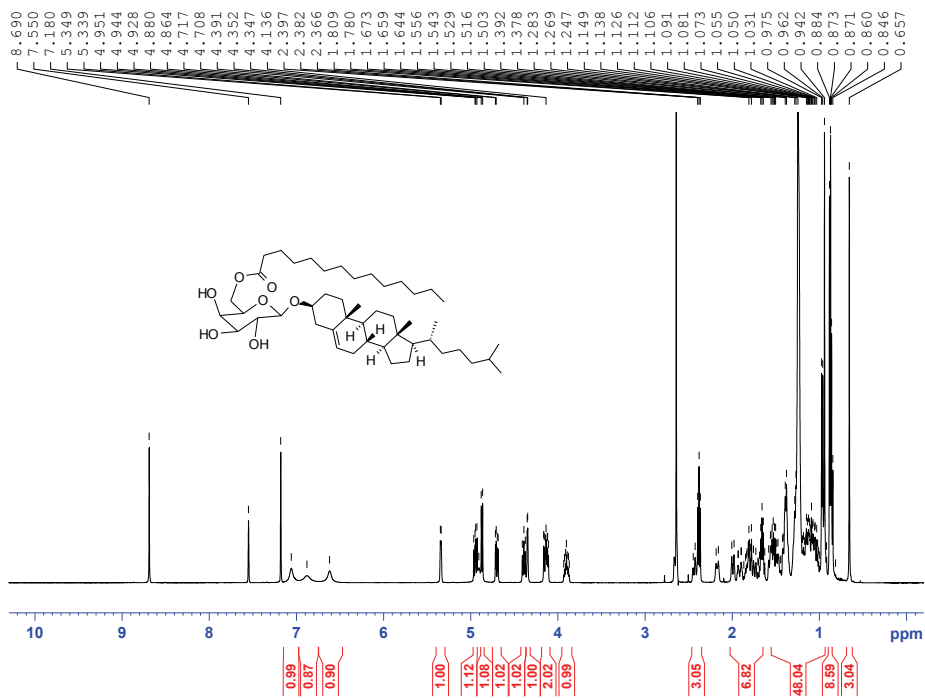
125.7 MHz ^{13}C NMR spectrum of cholesteryl 6-*O*-stearoyl- β -D-galactopyranoside (169b) in chloroform-*d*



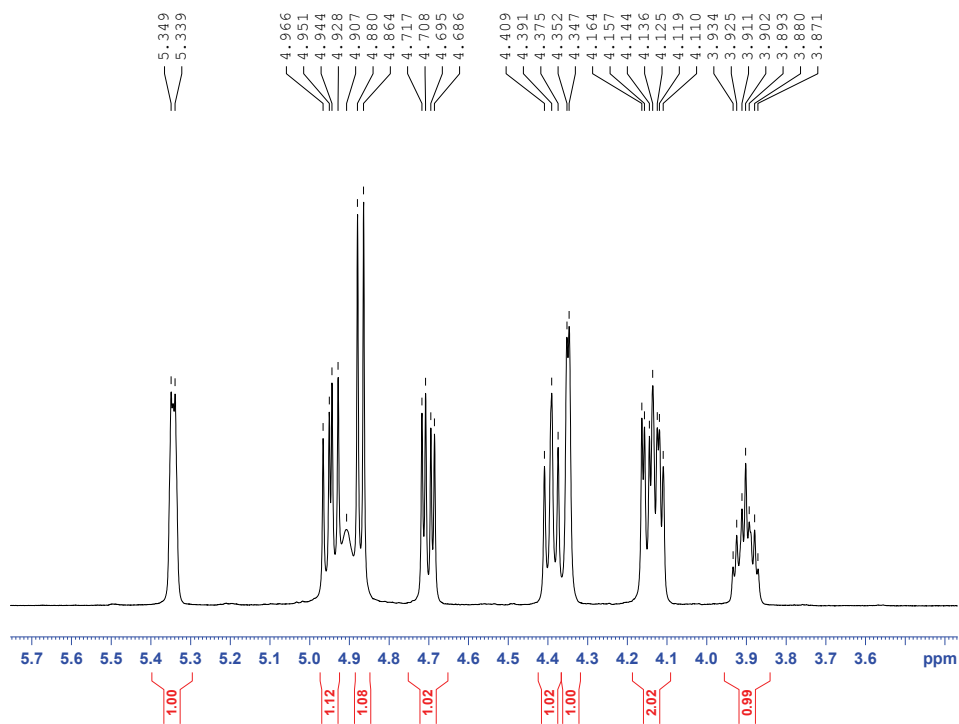
Expansions of parts of the 125.7 MHz ^{13}C NMR spectrum of cholesteryl 6-*O*-stearoyl- β -D-galactopyranoside (169b) in chloroform-*d*



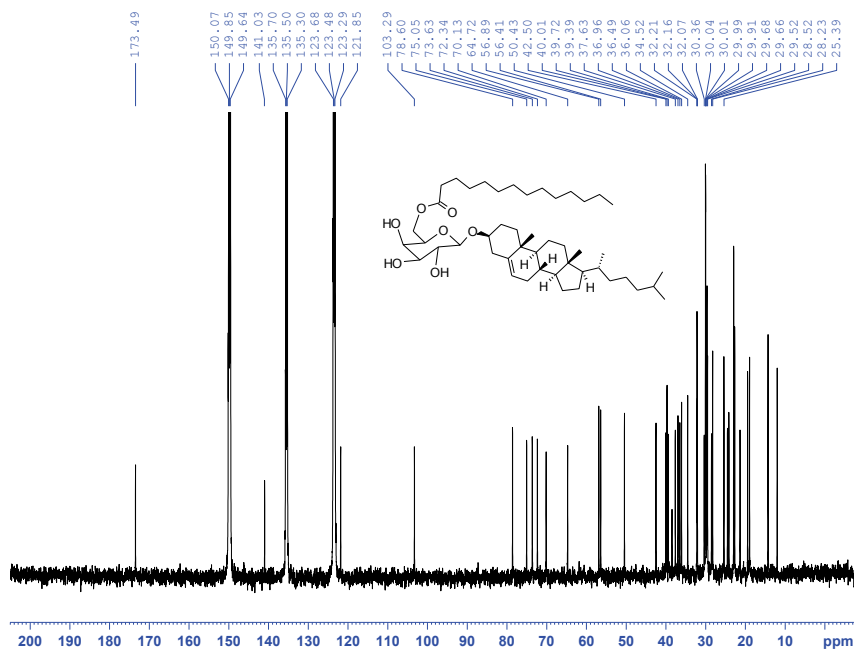
500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-myristoyl- β -D-galactopyranoside (169c) in pyridine-*d*₅



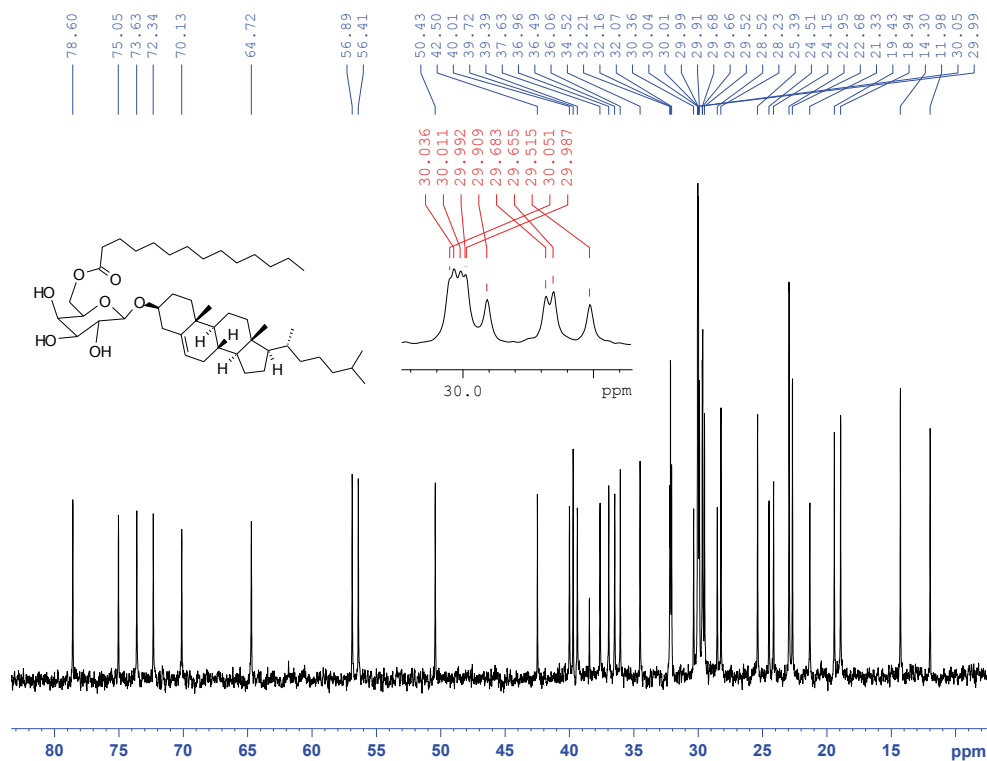
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-myristoyl- β -D-galactopyranoside (169c) in pyridine- d_5



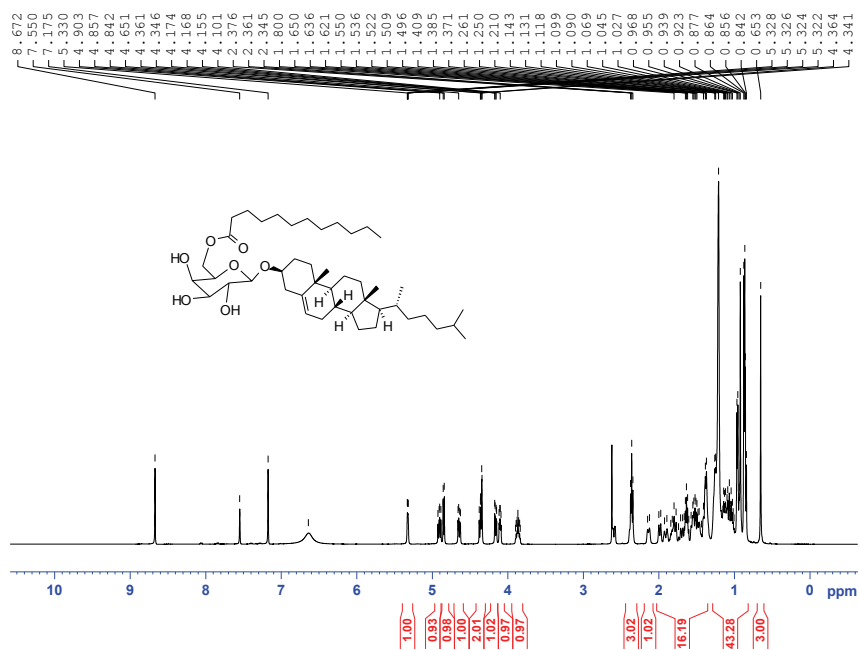
125.7 MHz ^{13}C NMR spectrum of cholesteryl 6-*O*-myristoyl- β -D-galactopyranoside (169c) in pyridine- d_5



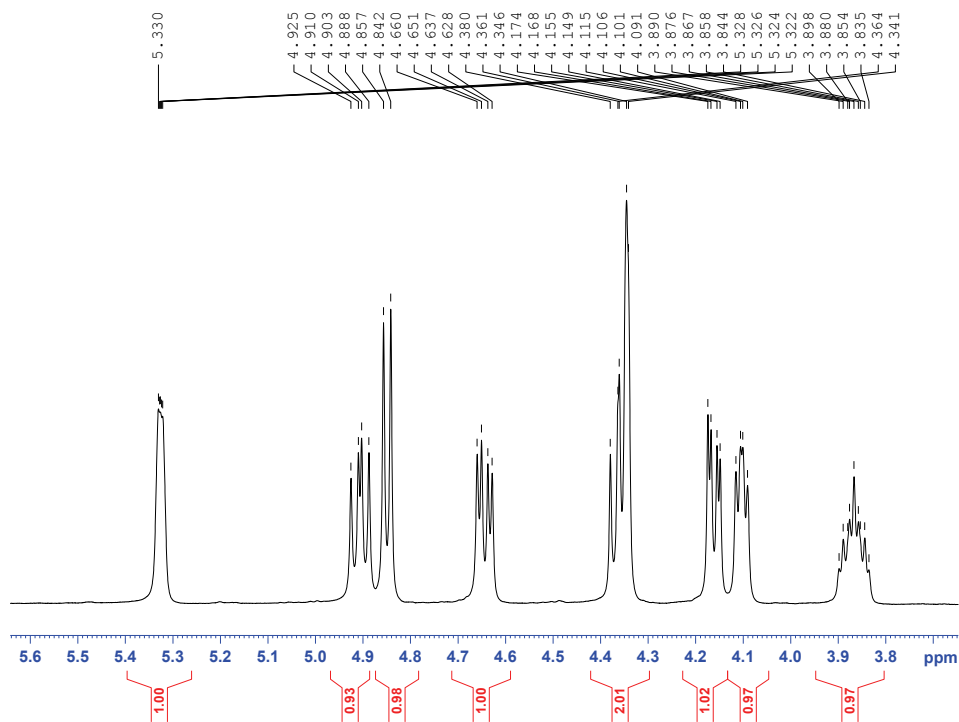
Expansions of parts of the 125.7 MHz ^{13}C NMR spectrum of cholesteryl 6-*O*-myristoyl- β -D-galactopyranoside (169c) in pyridine- d_5



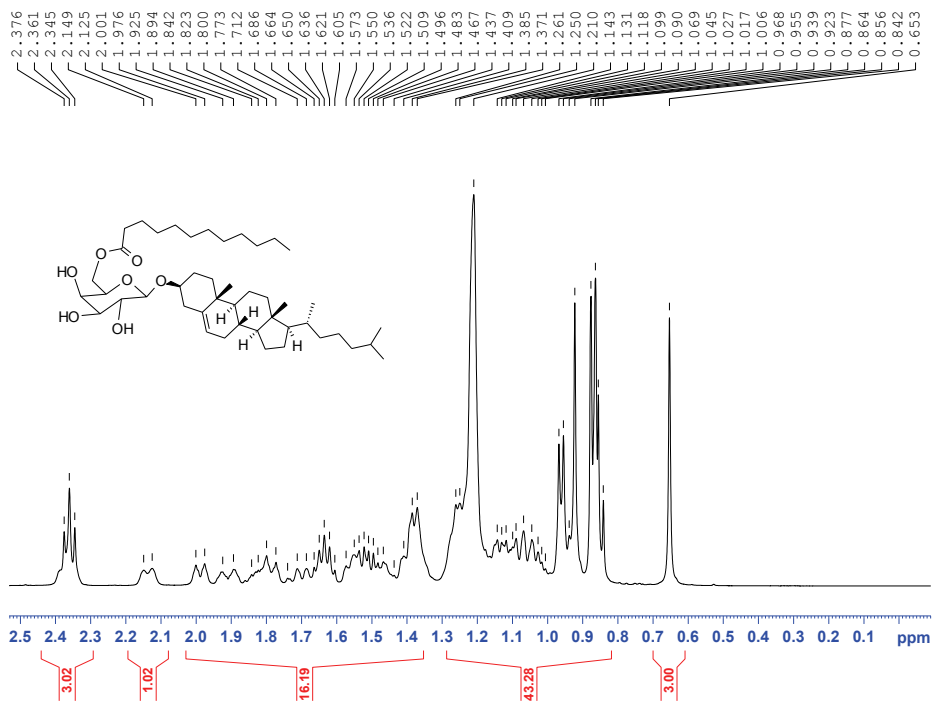
500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-lauroyl- β -D-galactopyranoside (169d) in pyridine- d_5



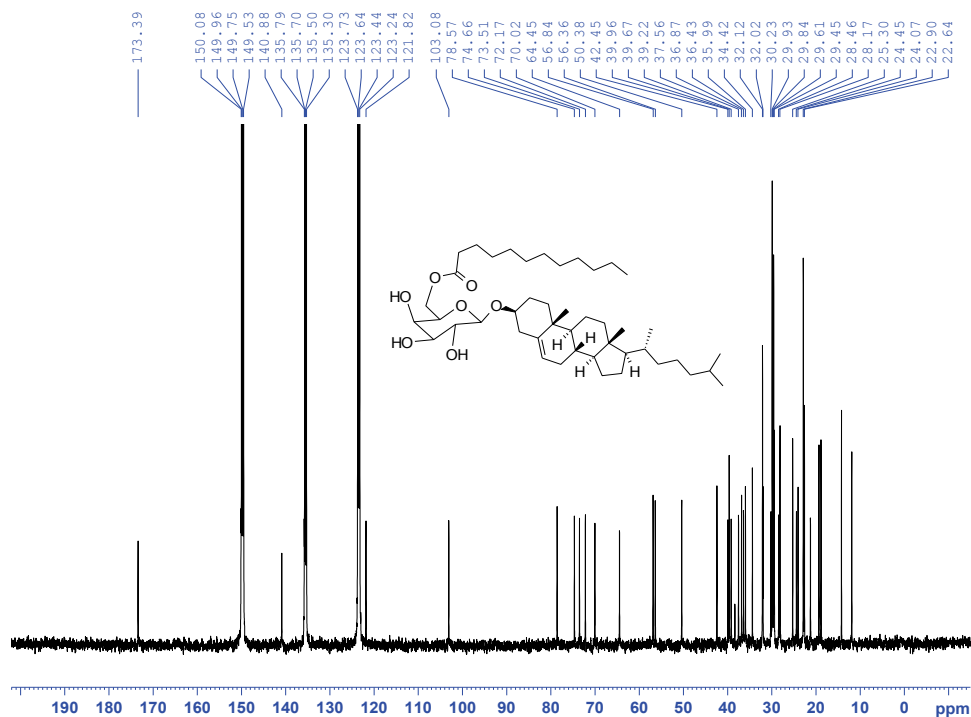
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-lauroyl- β -D-galactopyranoside (169d) in pyridine- d_5



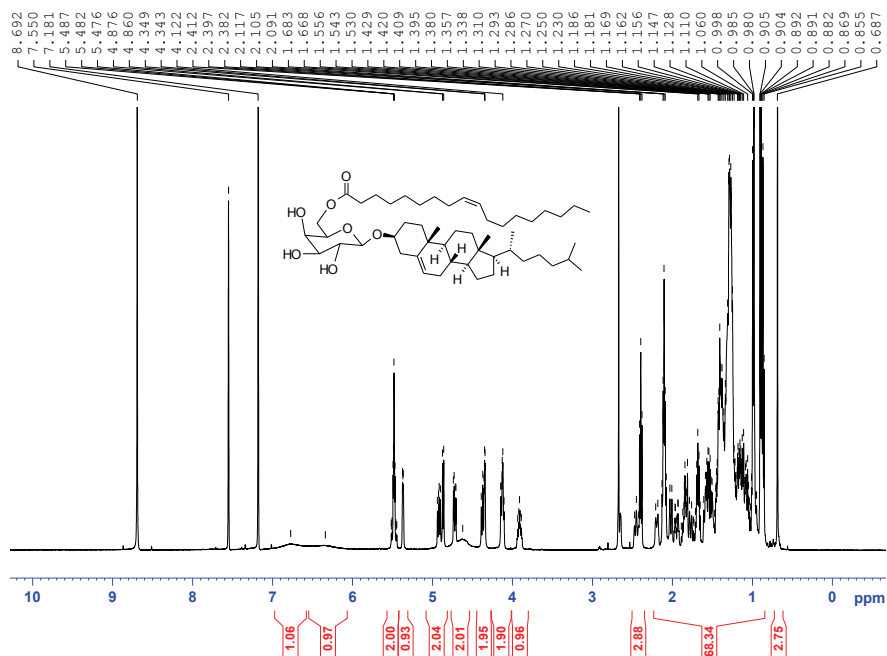
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-lauroyl- β -D-galactopyranoside (169d) in pyridine- d_5



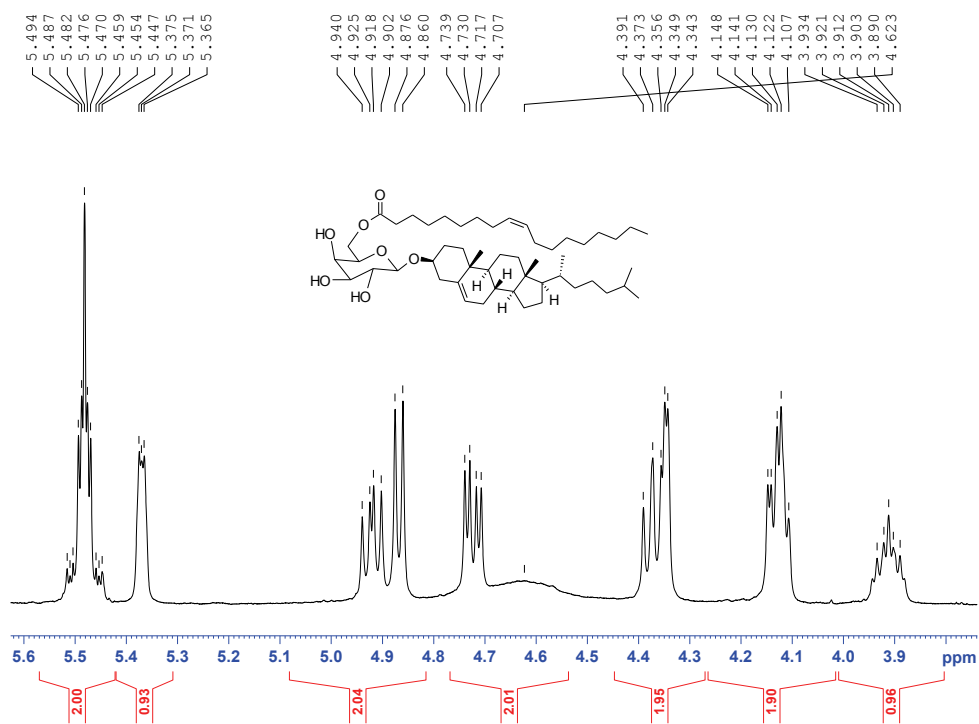
125.7 MHz ^{13}C NMR spectrum of cholesteryl 6-*O*-lauroyl- β -D-galactopyranoside (169d) in pyridine- d_5



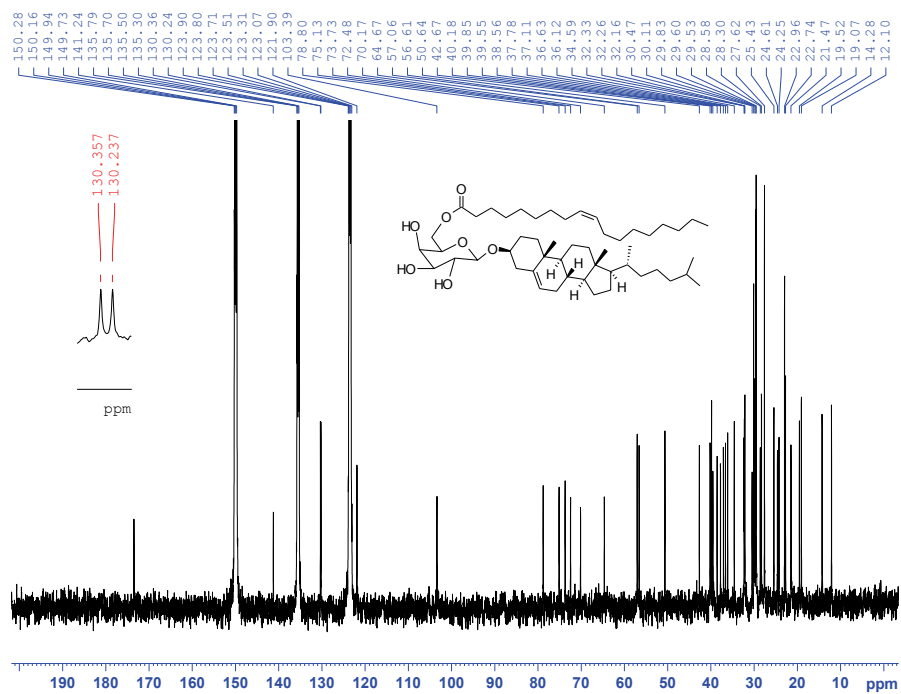
500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-oleoyl- β -D-galactopyranoside (169e) in pyridine- d_5



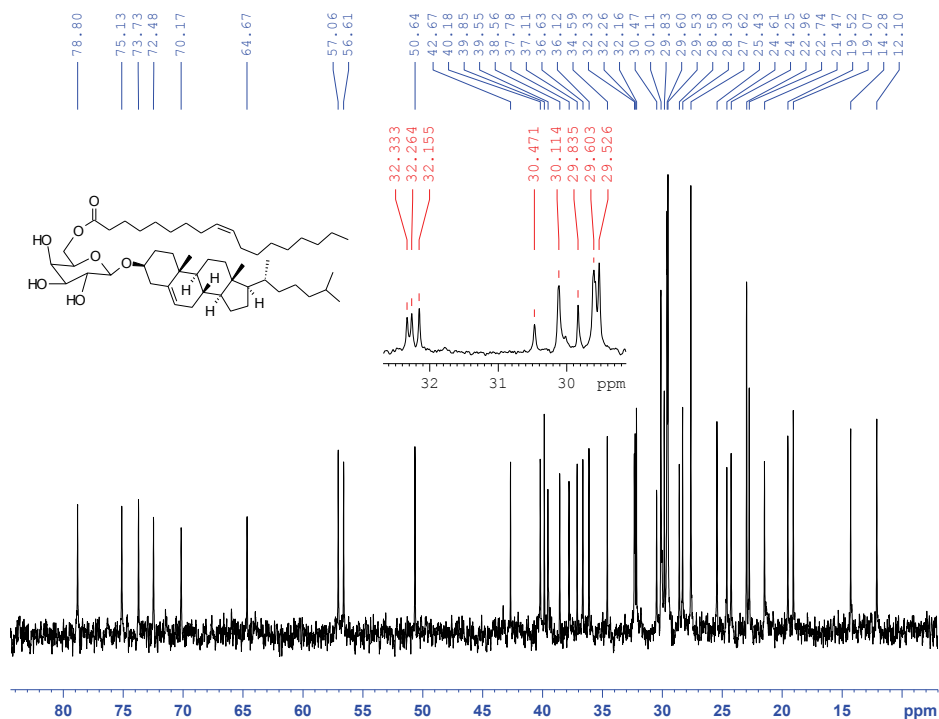
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-oleoyl- β -D-galactopyranoside (169e) in pyridine- d_5



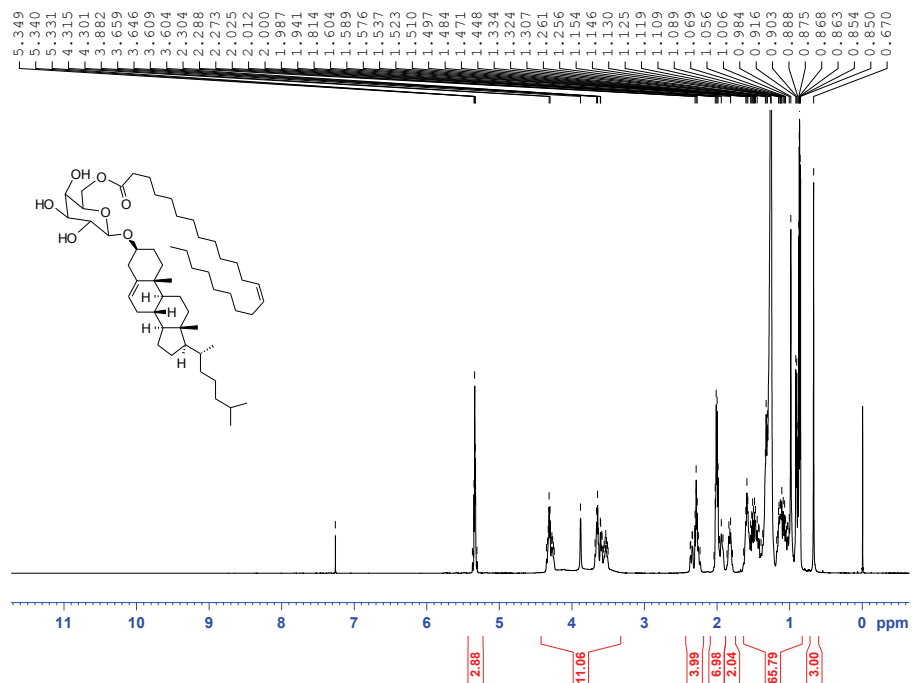
125.7 MHz ^{13}C NMR spectrum of cholesteryl 6-*O*-oleoyl- β -D-galactopyranoside (169e) in pyridine- d_5



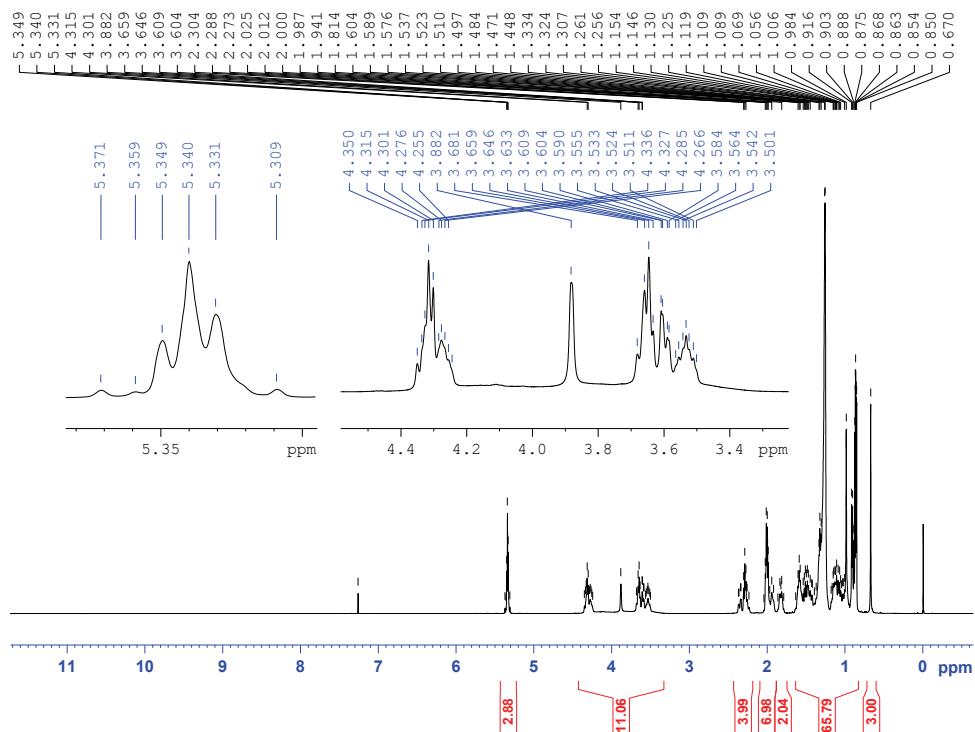
Expansions of parts of the 125.7 MHz ^{13}C NMR spectrum of cholesteryl 6-*O*-oleoyl- β -D-galactopyranoside (169e) in pyridine- d_5



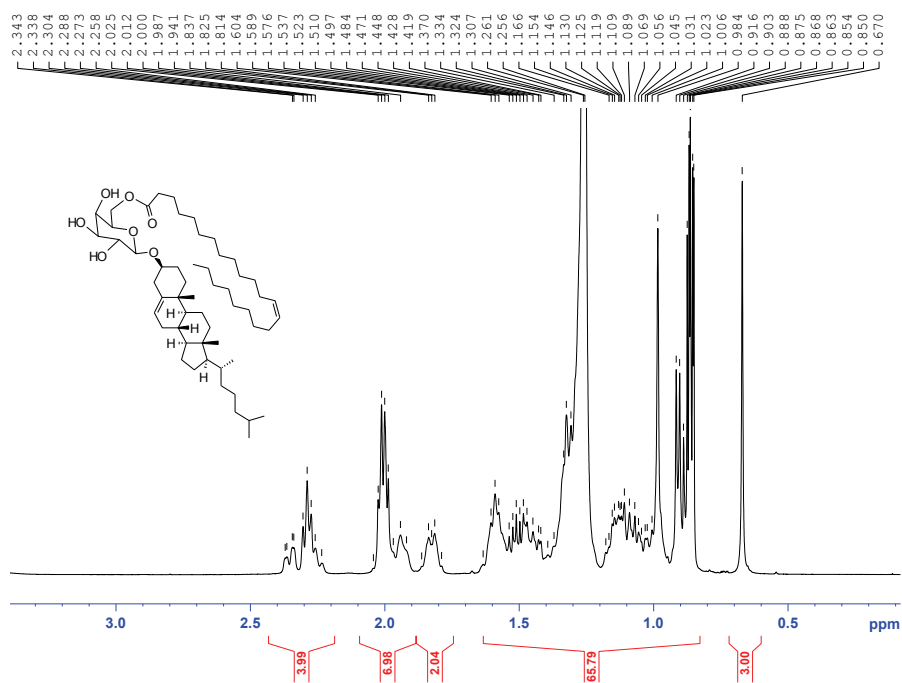
500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-erucoyl- β -D-galactopyranoside (169f) in chloroform- d



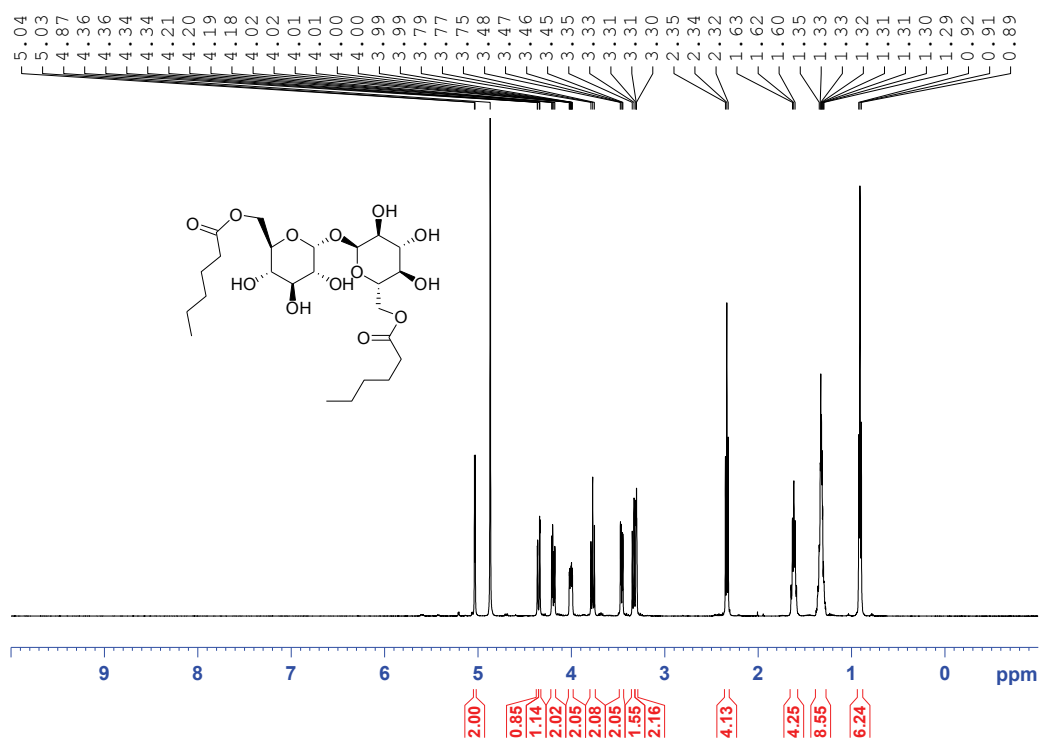
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-erucoyl- β -D-galactopyranoside (169f) in chloroform-*d*



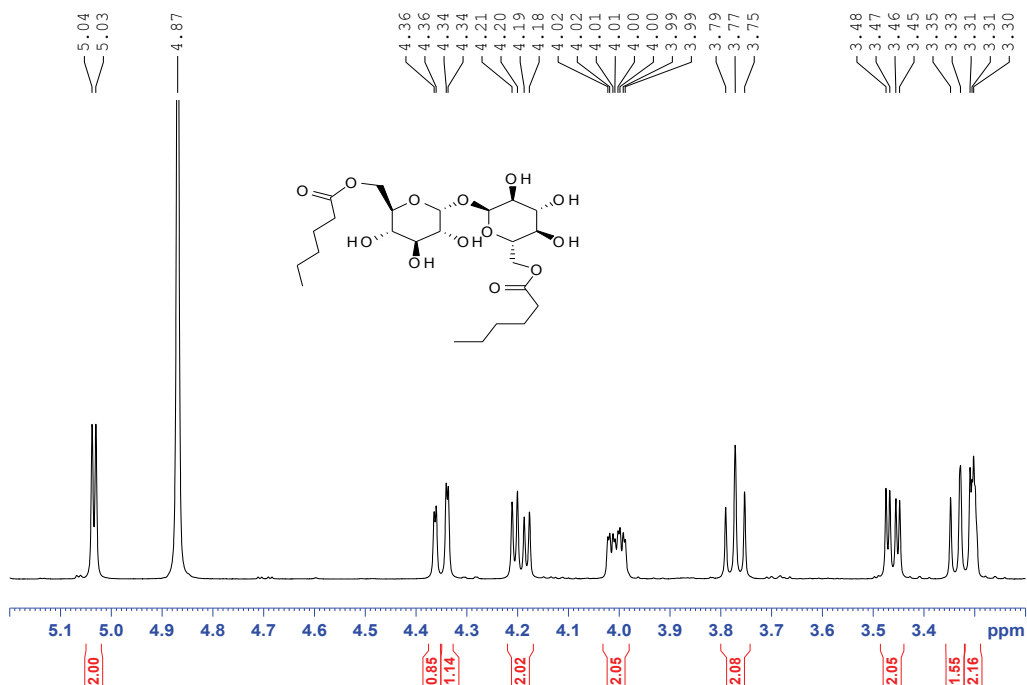
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of cholesteryl 6-*O*-erucoyl- β -D-galactopyranoside (169f) in chloroform-*d*



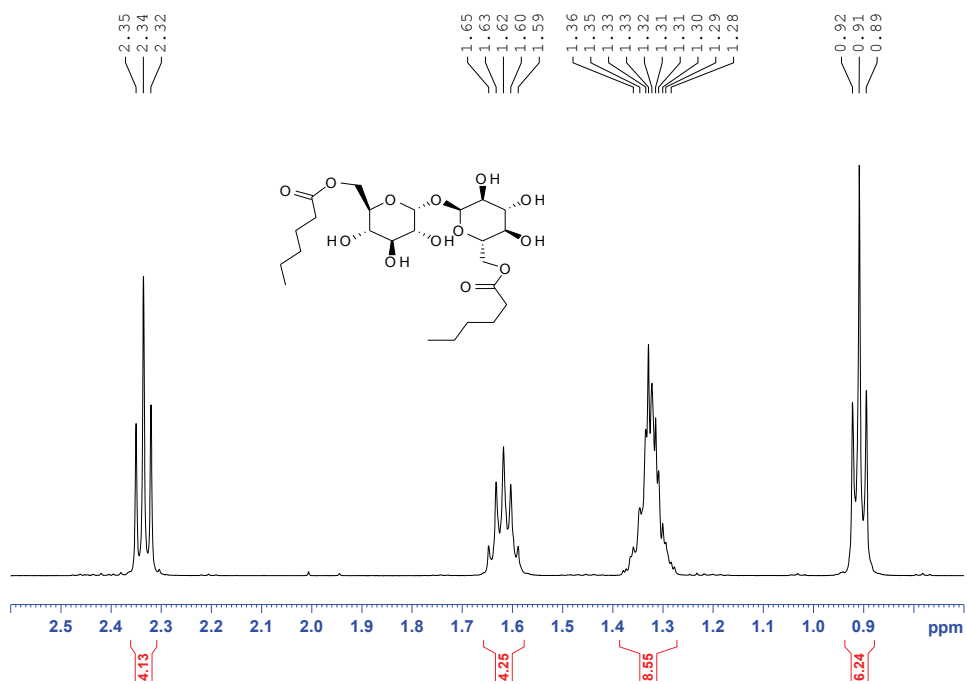
500.13 MHz ^1H NMR spectrum of 6,6'-di-*O*-hexanoyl- α,α -trehalose (174a) in methanol- d_4



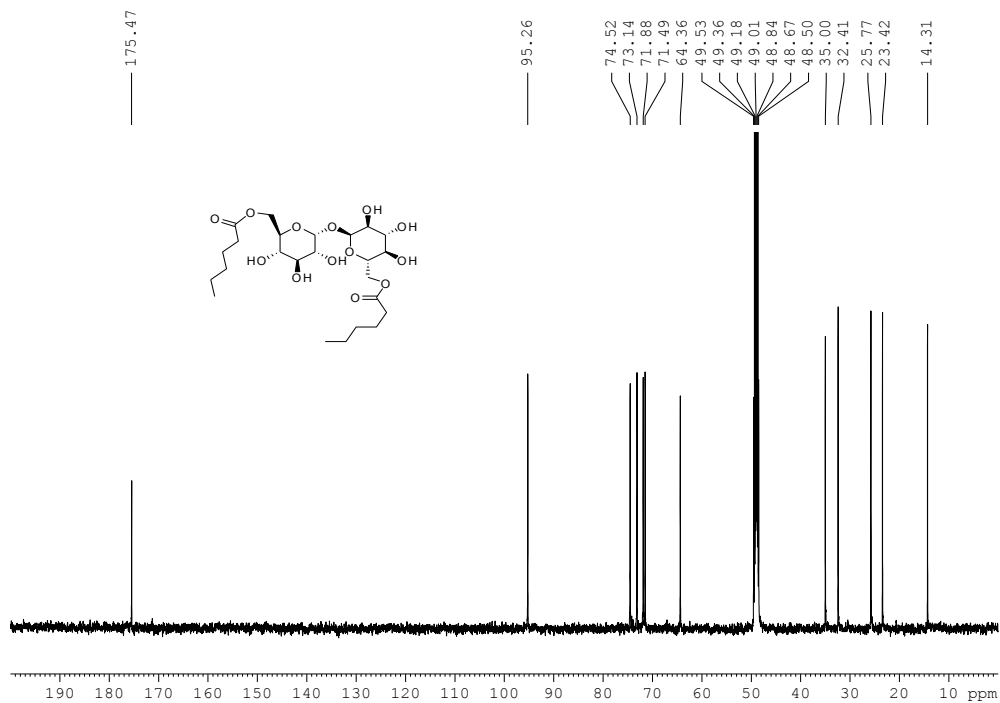
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6,6'-di-*O*-hexanoyl- α,α -trehalose (174a) in methanol- d_4



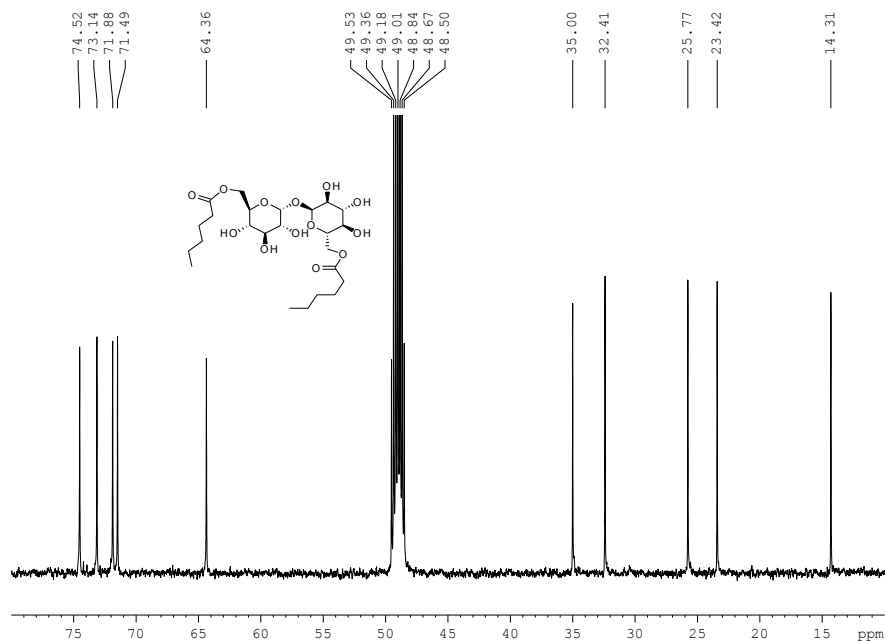
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6,6'-di-*O*-hexanoyl- α,α -trehalose (174a) in methanol- d_4



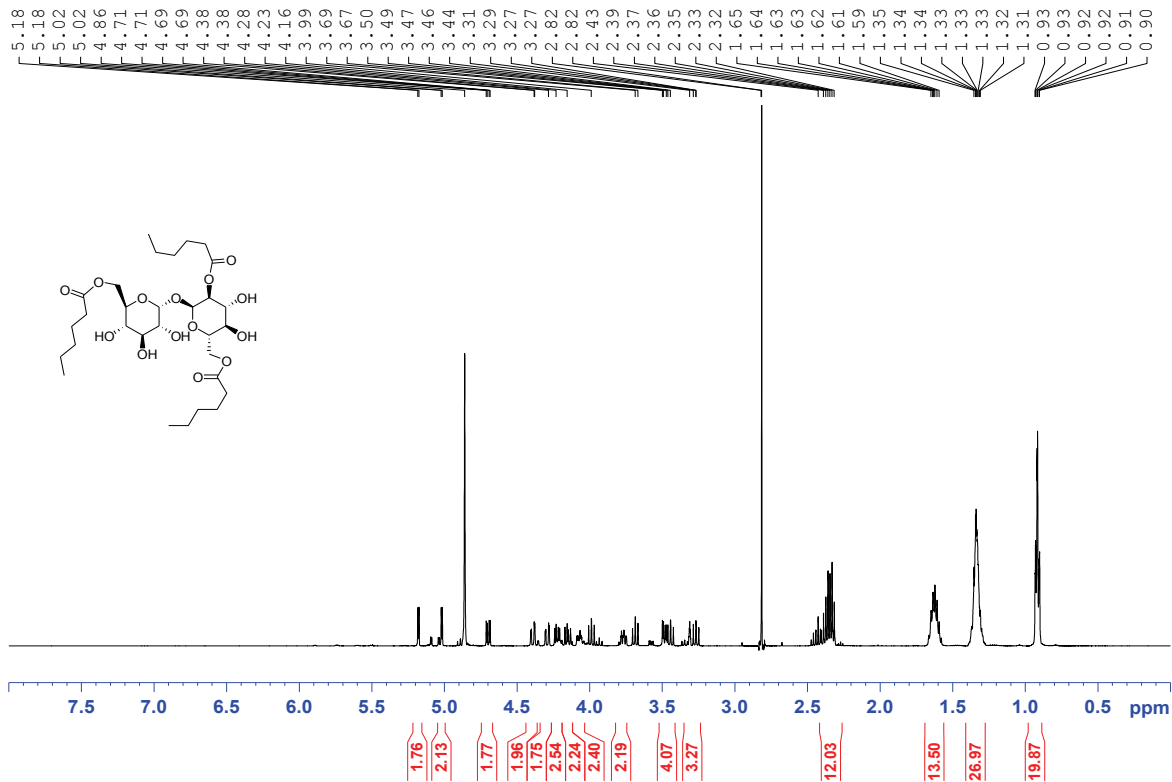
125.7 MHz ^{13}C NMR spectrum of 6,6'-di-*O*-hexanoyl- α,α -trehalose (174a) in methanol- d_4



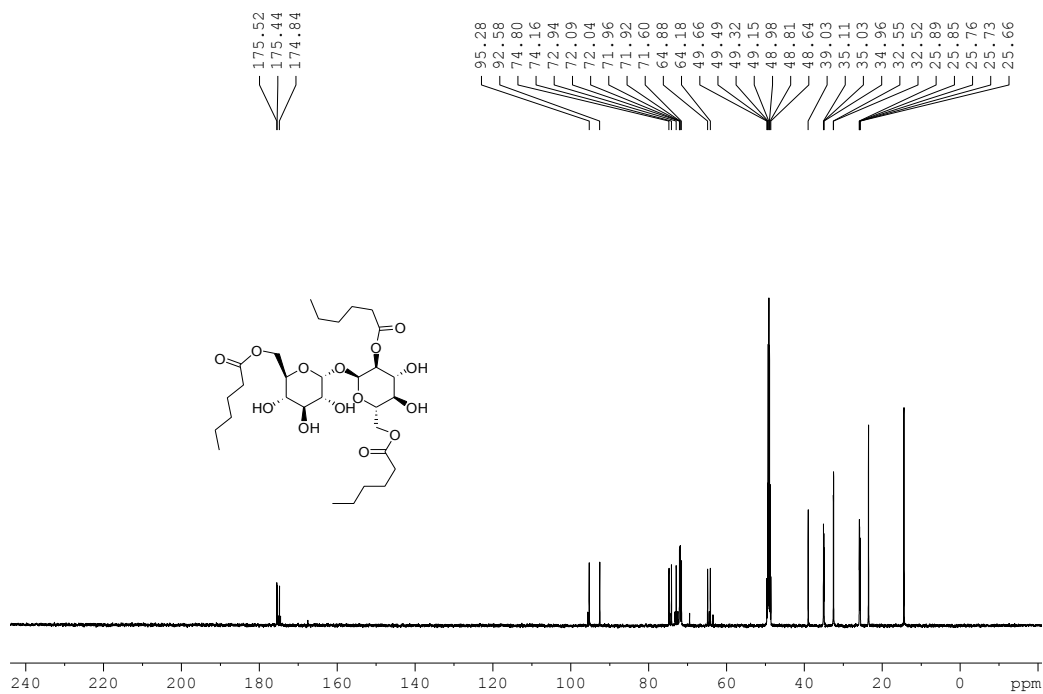
Expansion of part of the 125.7 MHz ^{13}C NMR spectrum of 6,6'-di-*O*-hexanoyl- α,α -trehalose (174a) in methanol- d_4



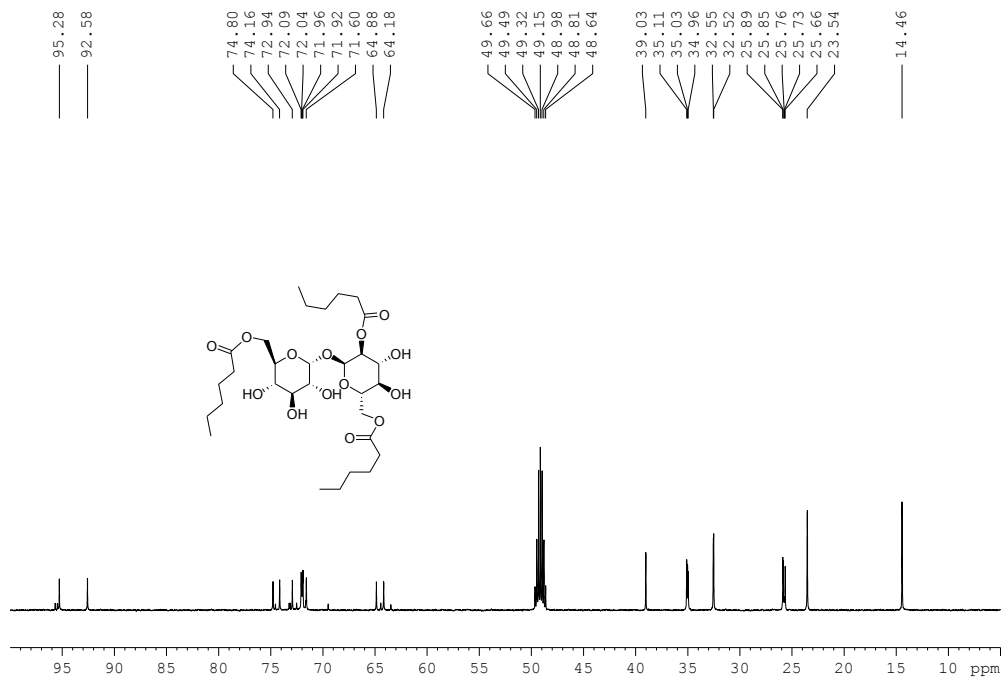
500.13 MHz ^1H NMR spectrum of 2,6,6'-tri-*O*-hexanoyl- α,α -trehalose (175a) in methanol- d_4



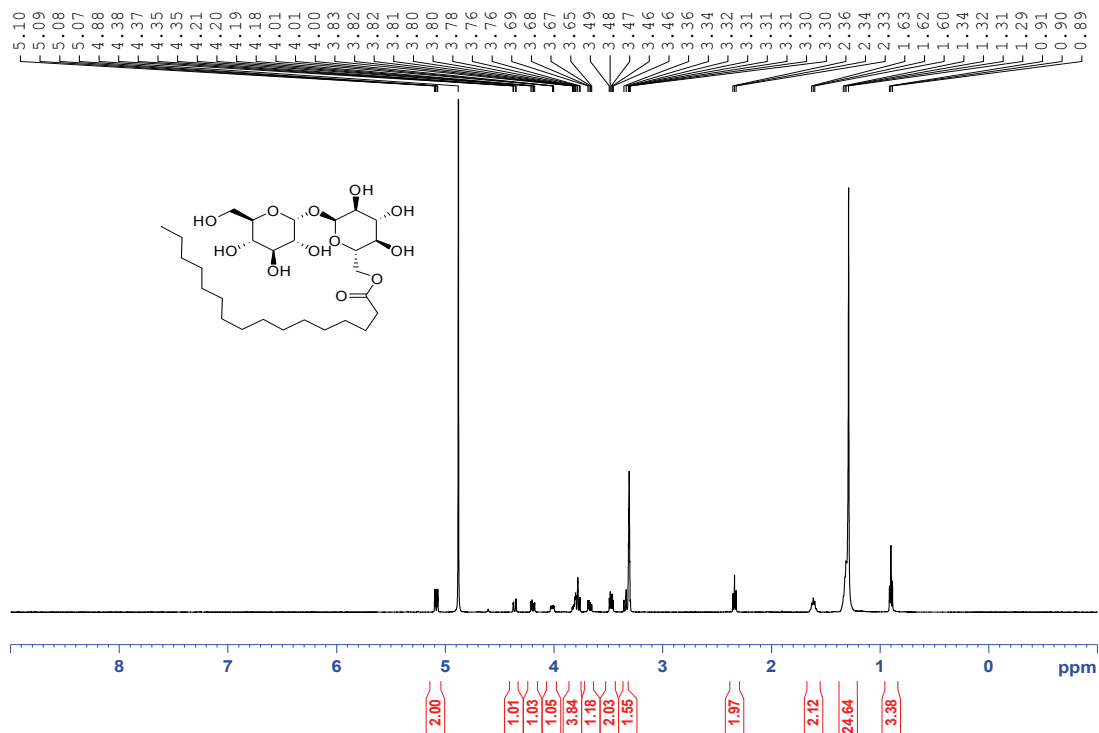
125.713 MHz ^{13}C NMR spectrum of 2,6,6'-tri-*O*-hexanoyl- α,α -trehalose (175a) in methanol- d_4



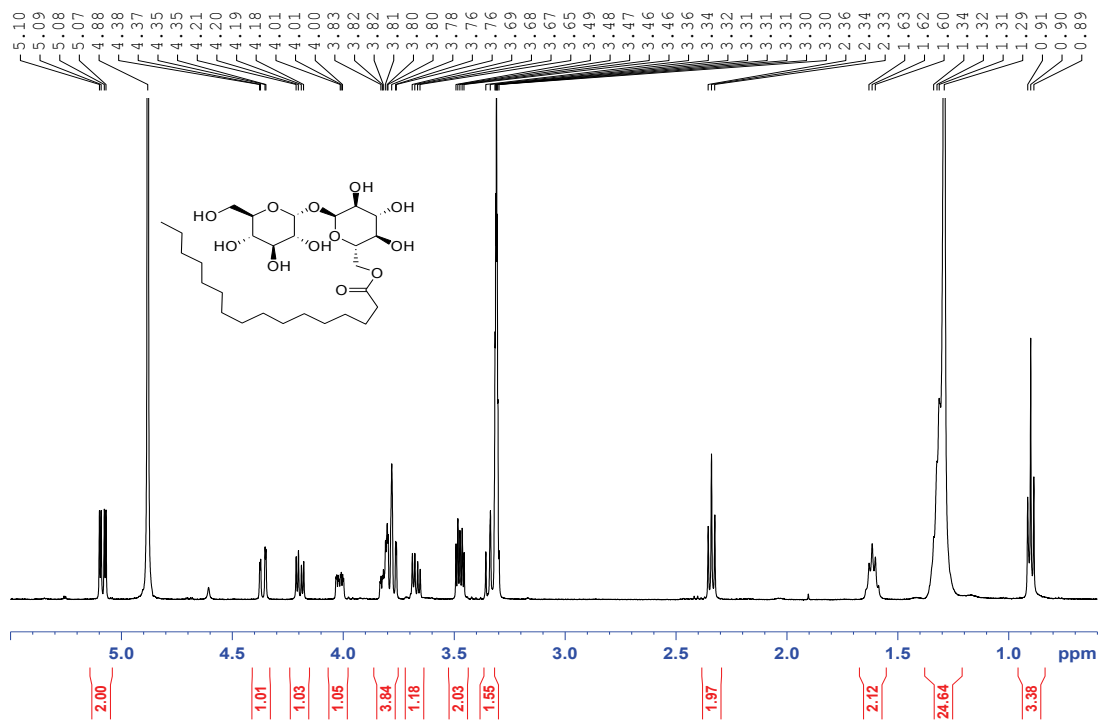
Expansion of part of the 125.7 MHz ^{13}C NMR spectrum of 2,6,6'-tri-*O*-hexanoyl- α,α -trehalose (175a) in methanol- d_4



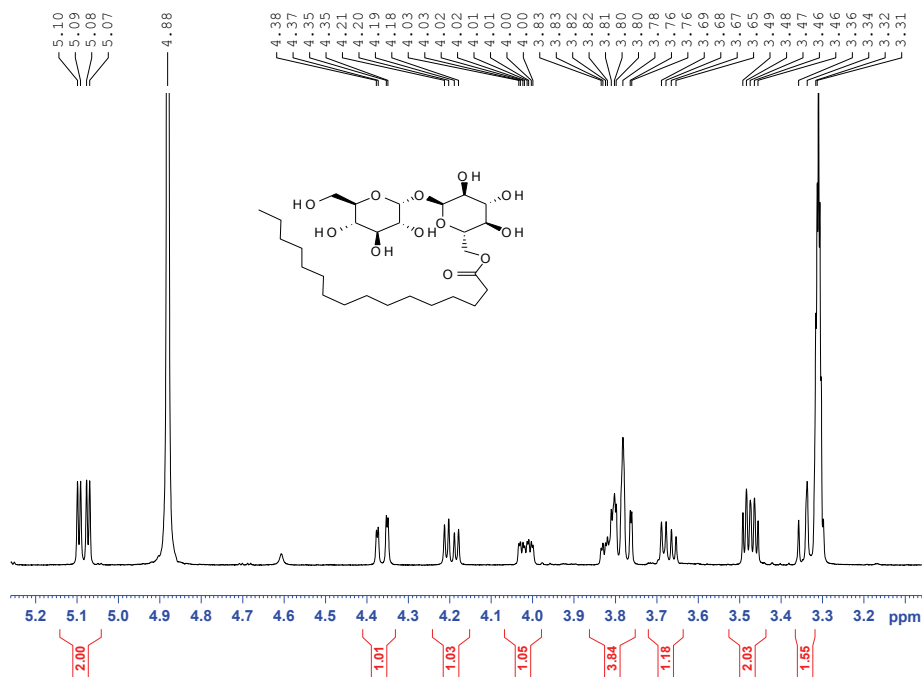
500.13 MHz ^1H NMR spectrum of 6-*O*-palmitoyl- α,α -trehalose (173b) in methanol- d_4



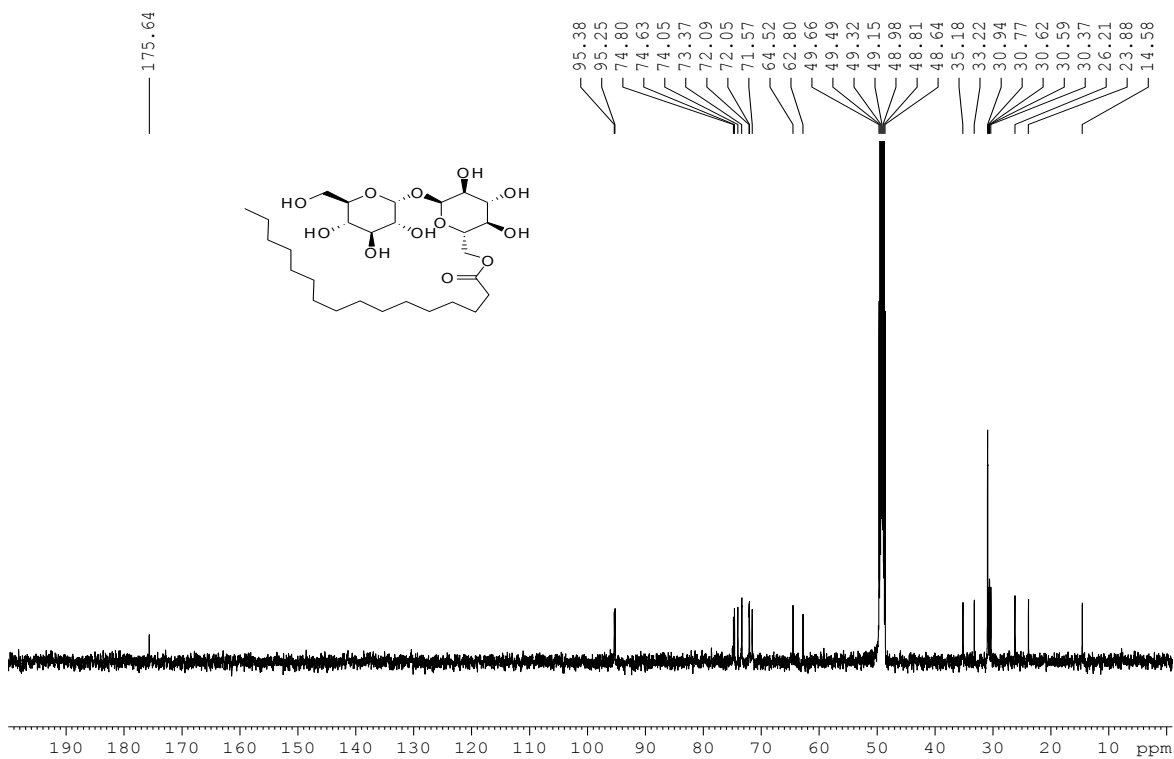
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6-*O*-palmitoyl- α,α -trehalose (173b) in methanol- d_4



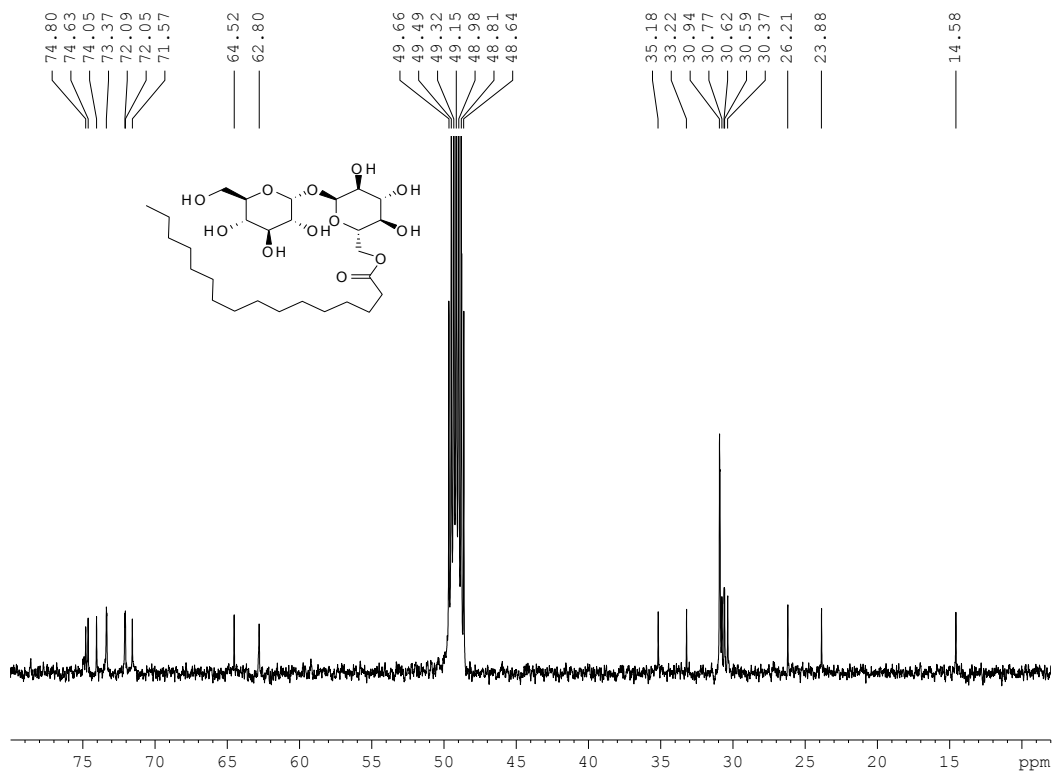
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6-*O*-palmitoyl- α,α -trehalose (173b) in methanol- d_4



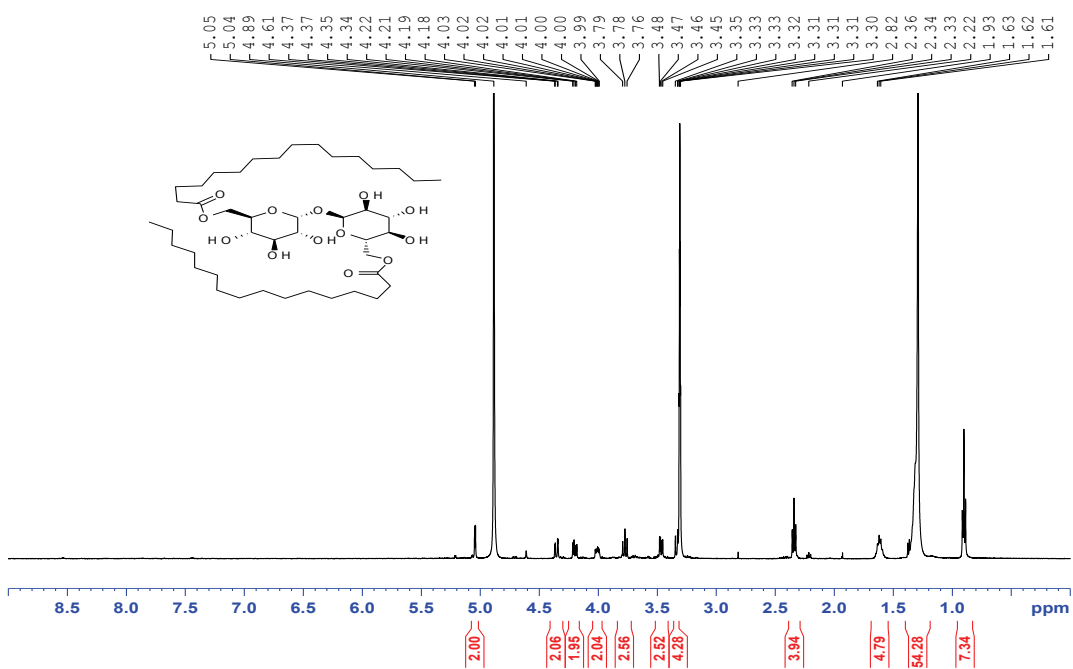
125.7 MHz ^{13}C NMR spectrum of 6-*O*-palmitoyl- α,α -trehalose (173b) in methanol- d_4



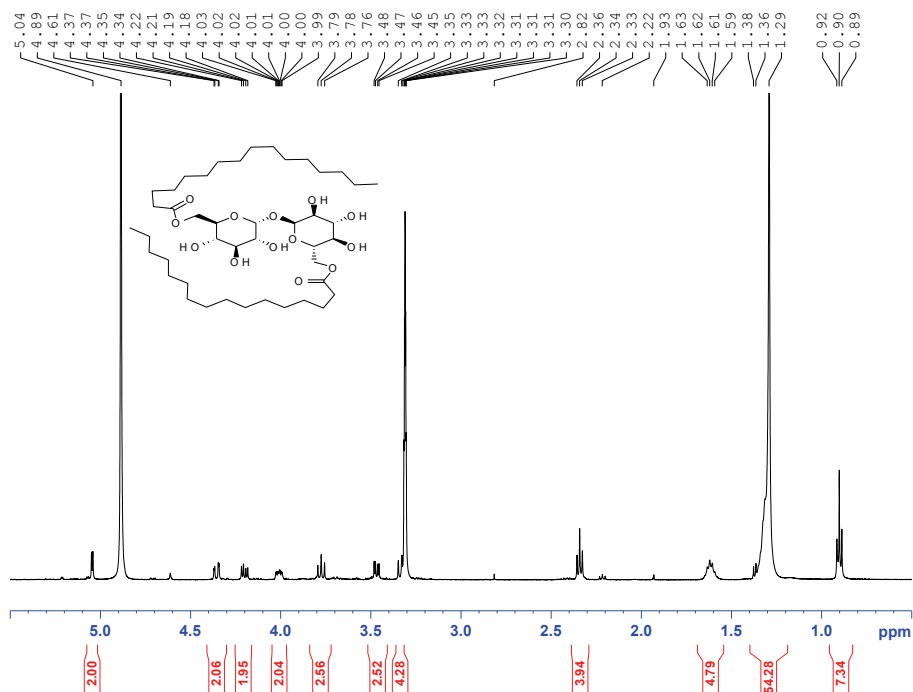
Expansion of part of the 125.7 MHz ^{13}C NMR spectrum of 6-*O*-palmitoyl- α,α -trehalose (173b) in methanol- d_4



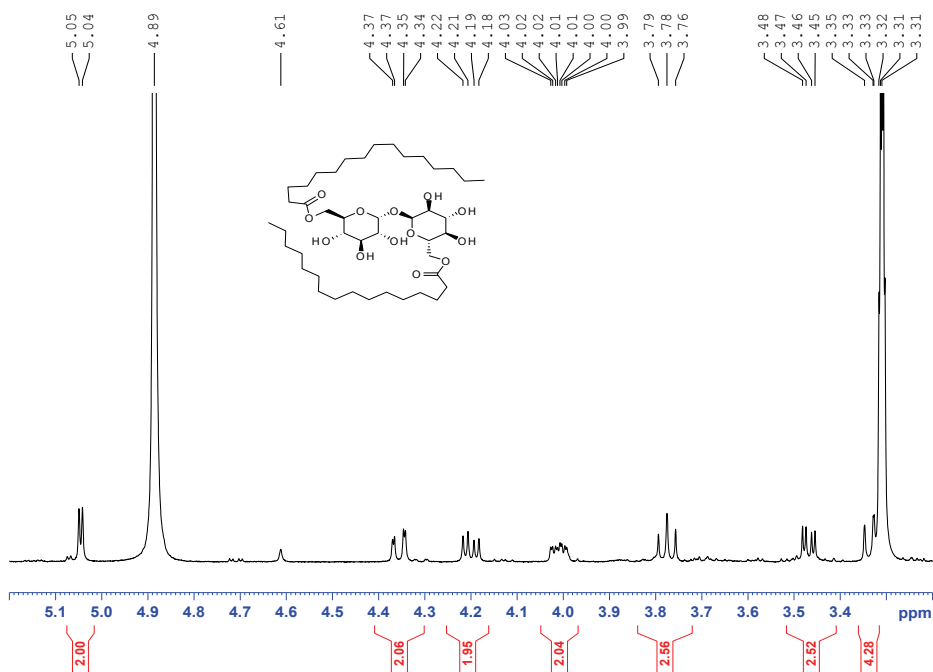
500.13 MHz ^1H NMR spectrum of 6,6'-*O*-palmitoyl- α,α -trehalose (174b) in methanol- d_4



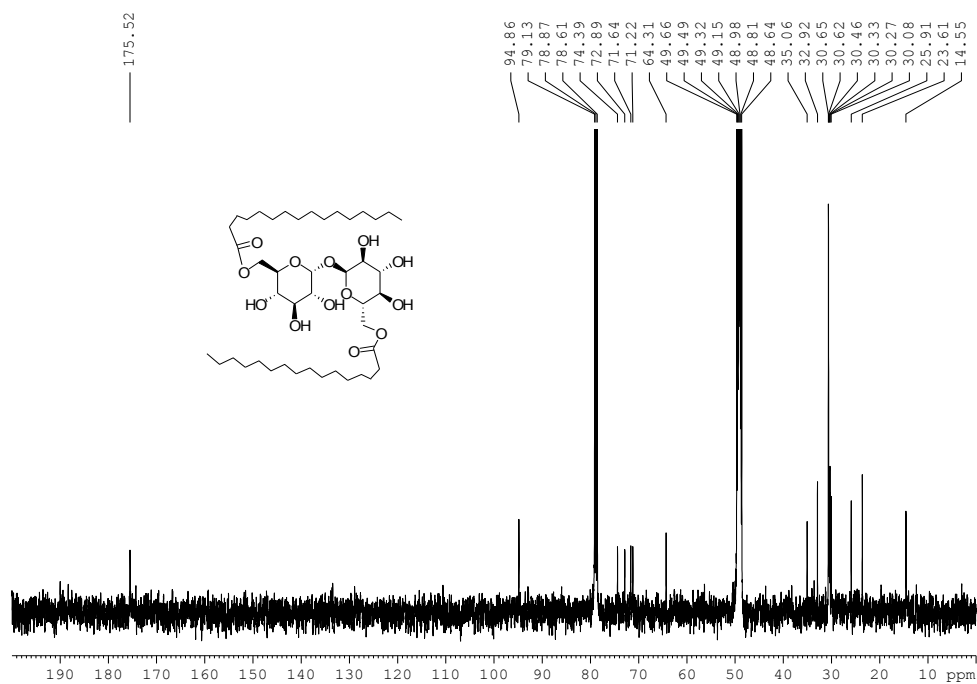
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6,6'-di-*O*-palmitoyl- α,α -trehalose (174b) in methanol- d_4



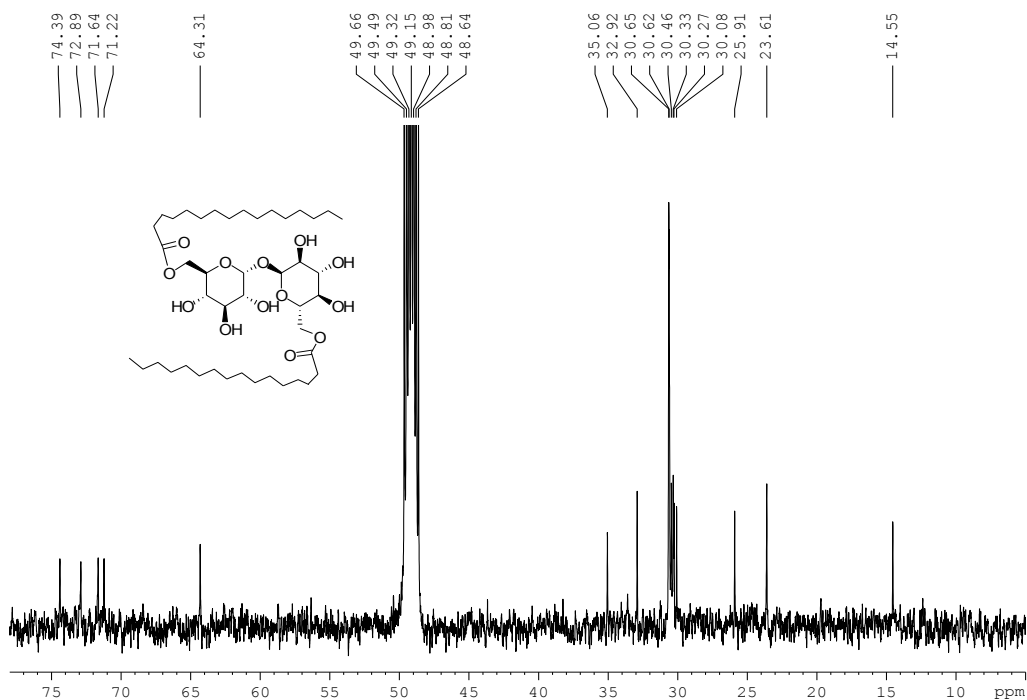
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6,6'-di-*O*-palmitoyl- α,α -trehalose (174b) in methanol- d_4



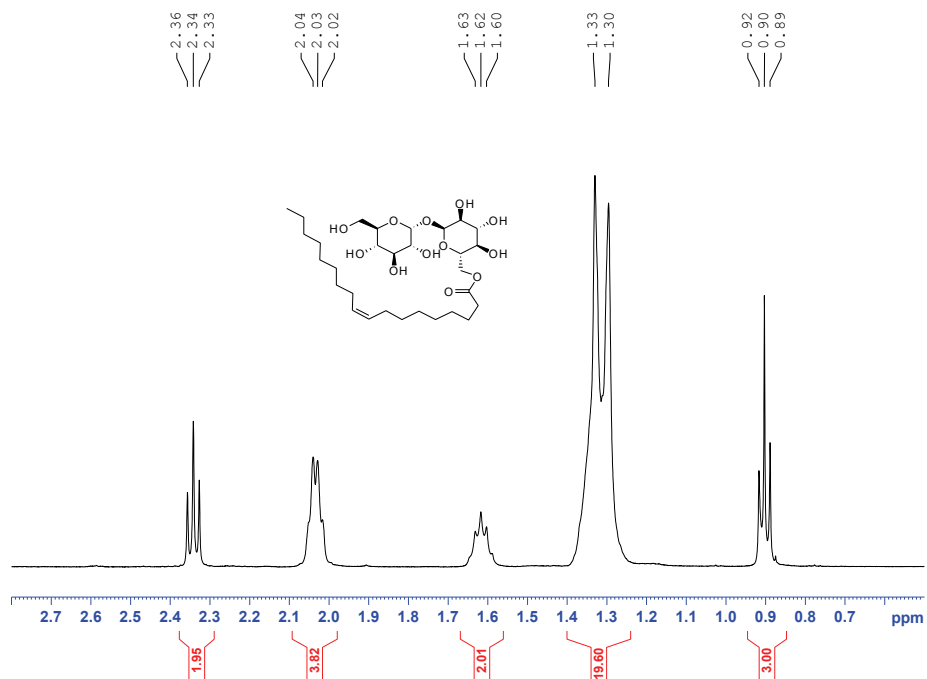
125.7 MHz ^{13}C NMR spectrum of 6,6'-di-*O*-palmitoyl- α,α -trehalose (174b) in chloroform-*d* and methanol-*d*₄



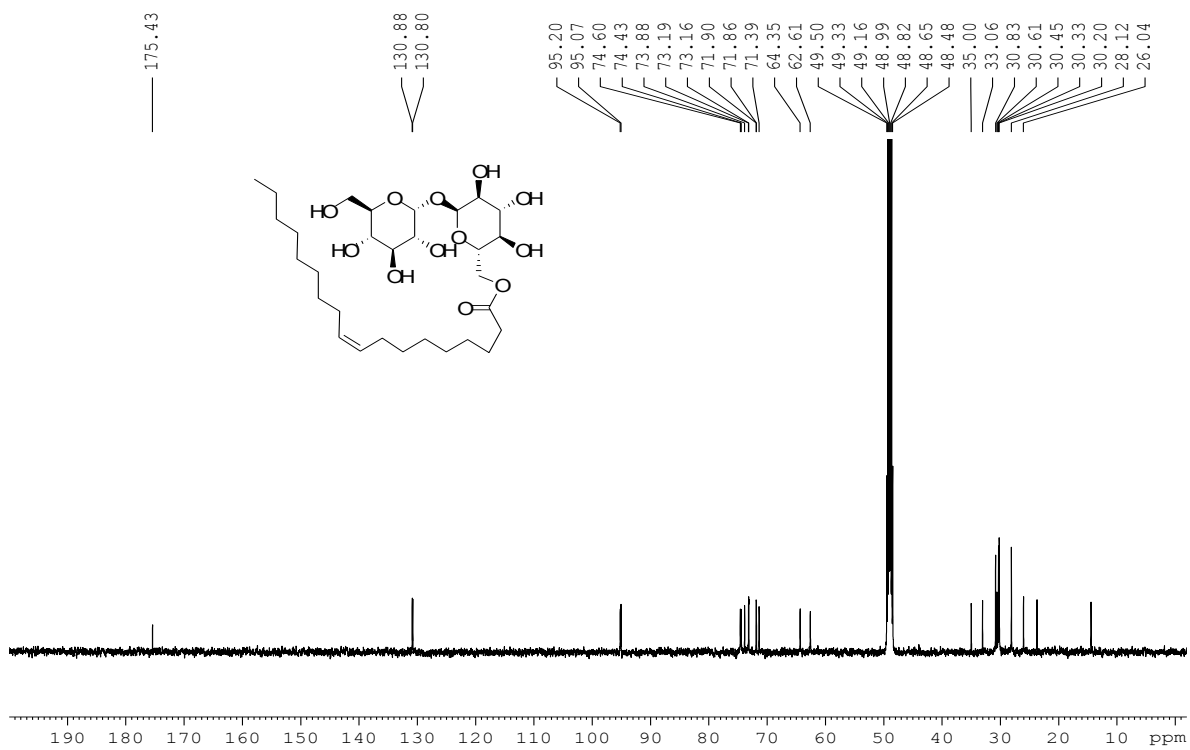
Expansion of part of the 125.7 MHz ^{13}C NMR spectrum of 6,6'-di-*O*-palmitoyl- α,α -trehalose (174b) in chloroform-*d* and methanol-*d*₄



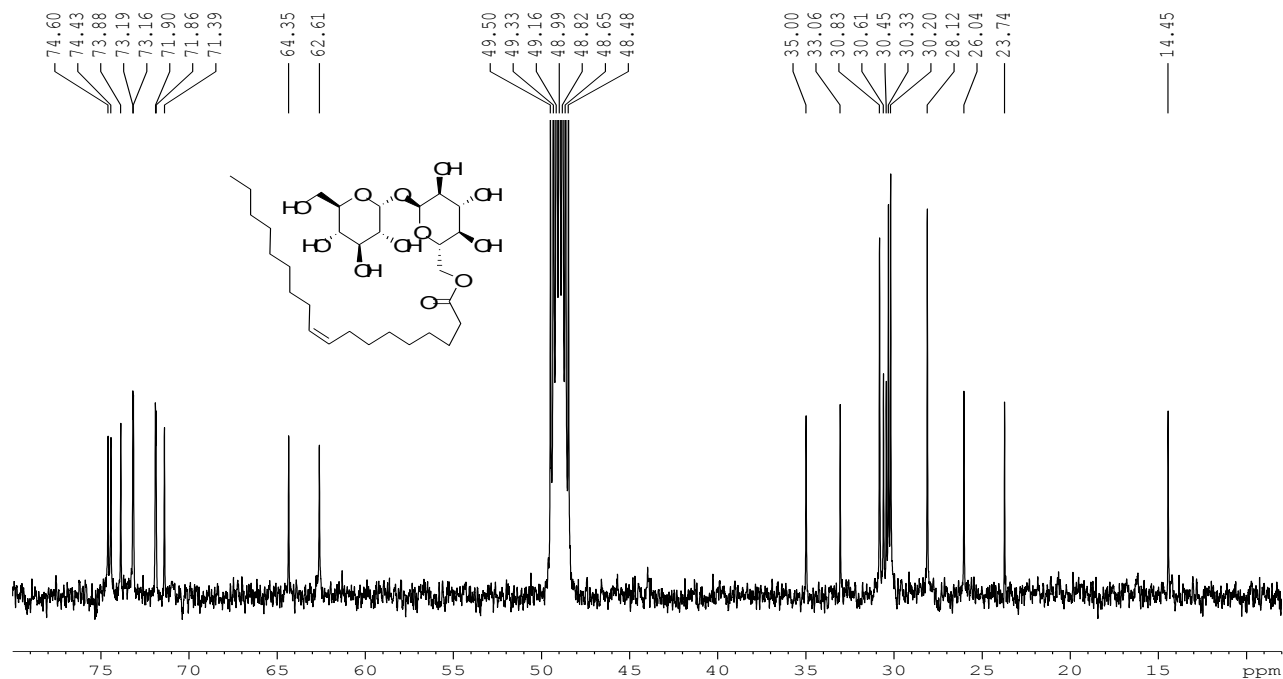
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6-*O*-oleoyl- α,α -trehalose (173c) in methanol- d_4



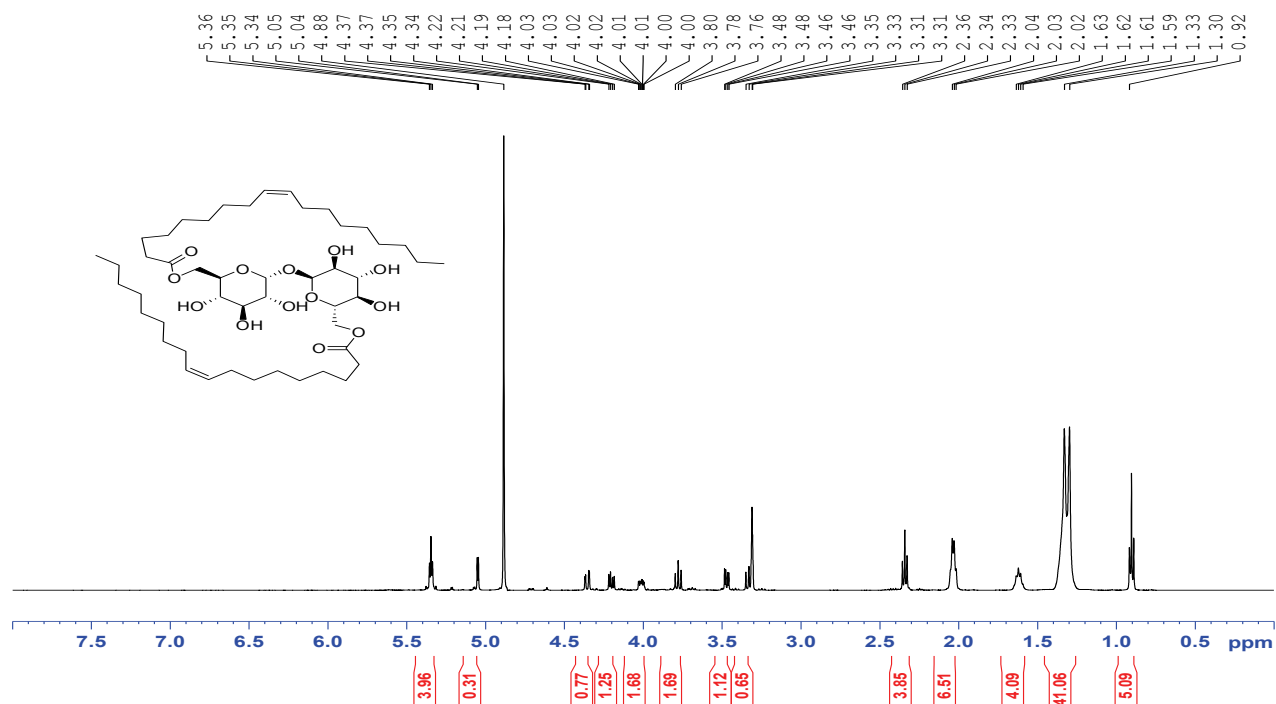
125.7 MHz ^{13}C NMR spectrum of 6-*O*-oleoyl- α,α -trehalose (173c) in methanol- d_4



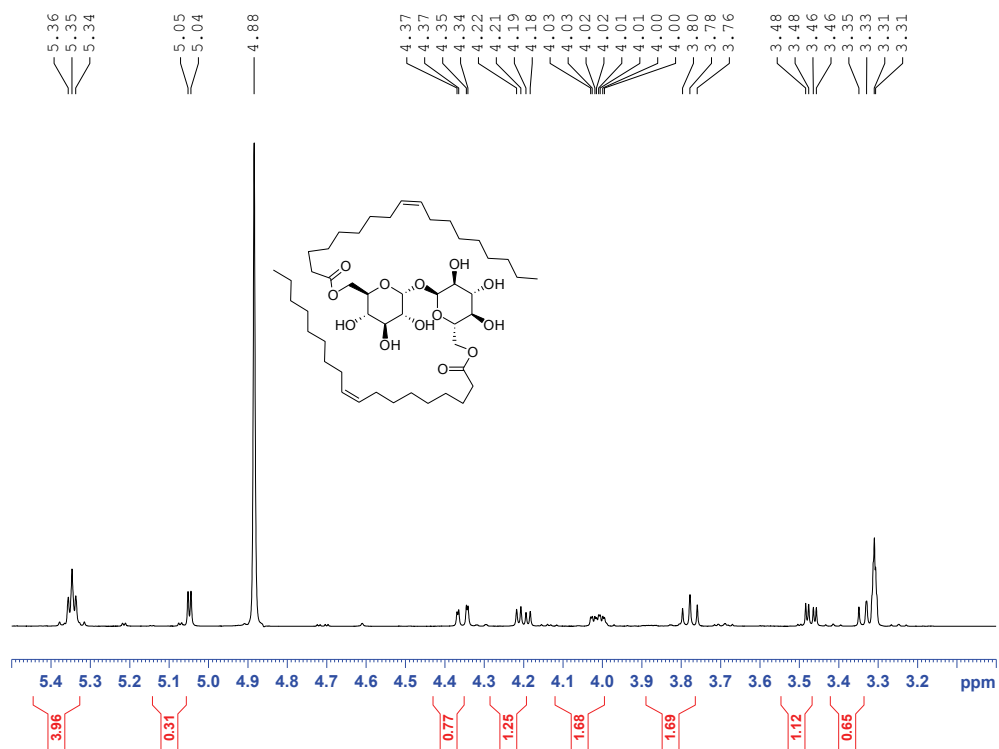
Expansion of part of the 125.7 MHz ^{13}C NMR spectrum of 6-*O*-oleoyl- α,α -trehalose (173c) in methanol- d_4



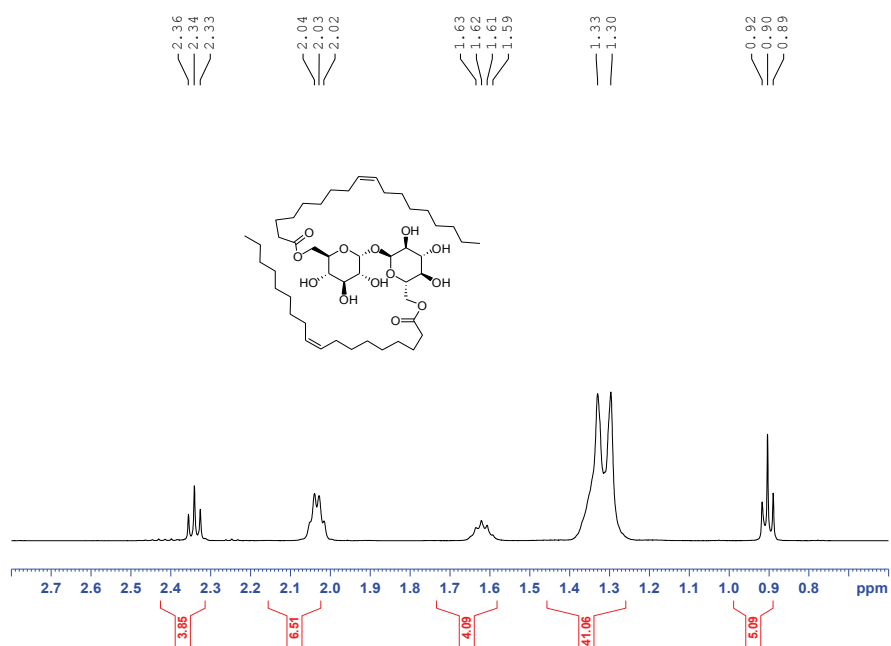
500.13 MHz ^1H NMR spectrum of 6,6'-di-*O*-oleoyl- α,α -trehalose (174c) in methanol- d_4



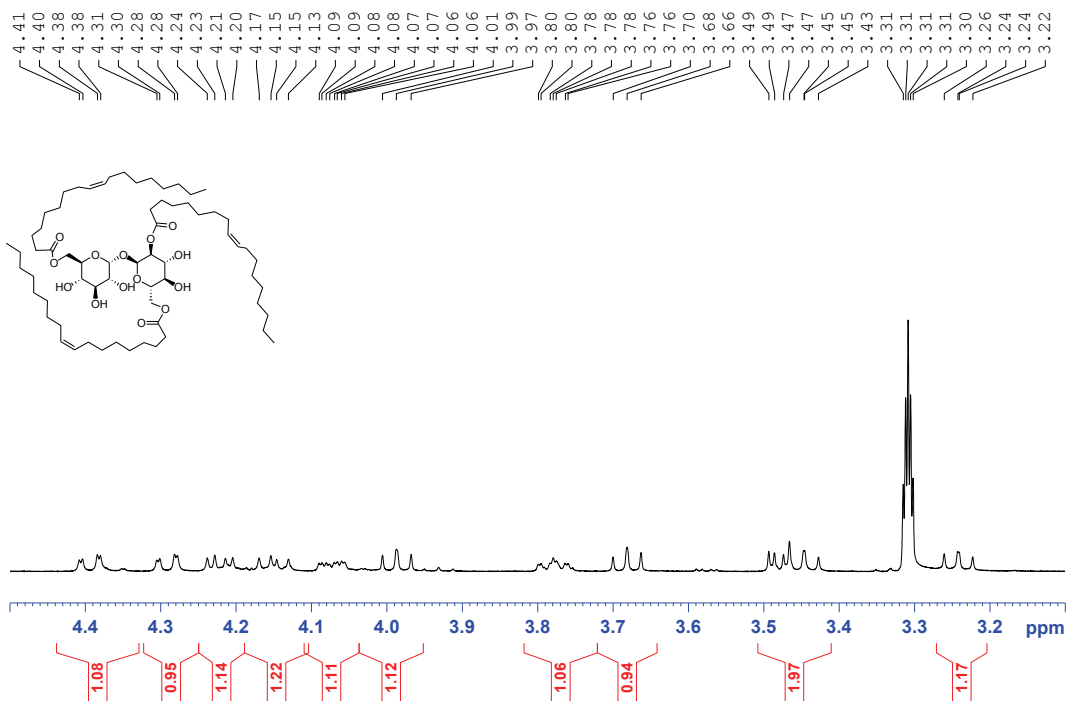
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6,6'-di-*O*-oleoyl- α,α -trehalose (174c) in methanol- d_4



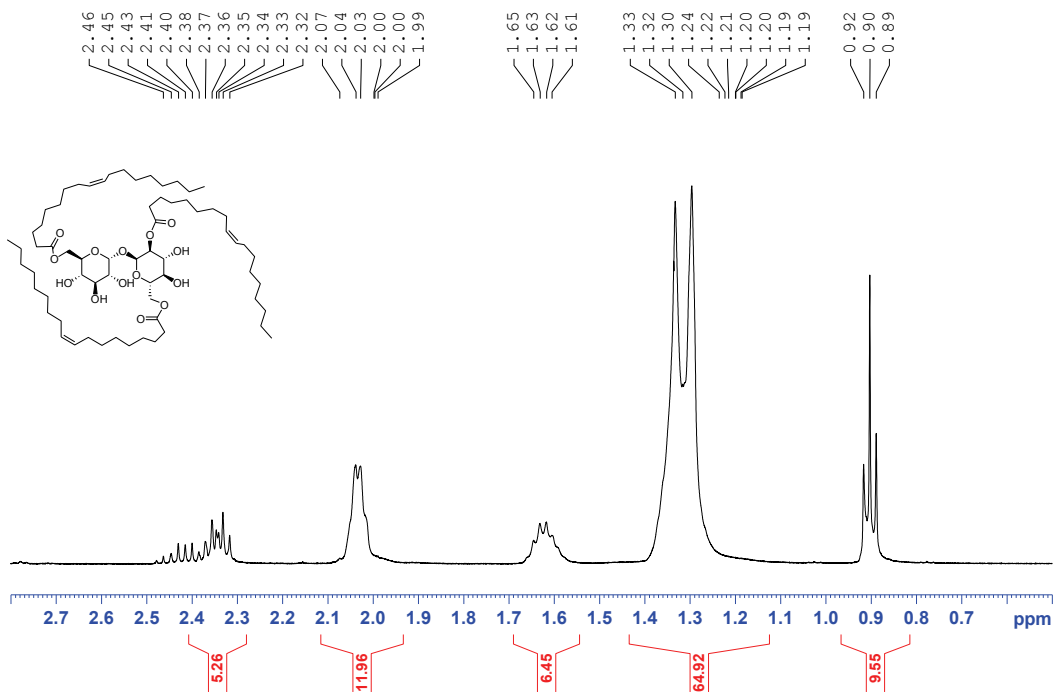
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6,6'-di-*O*-oleoyl- α,α -trehalose (174c) in methanol- d_4



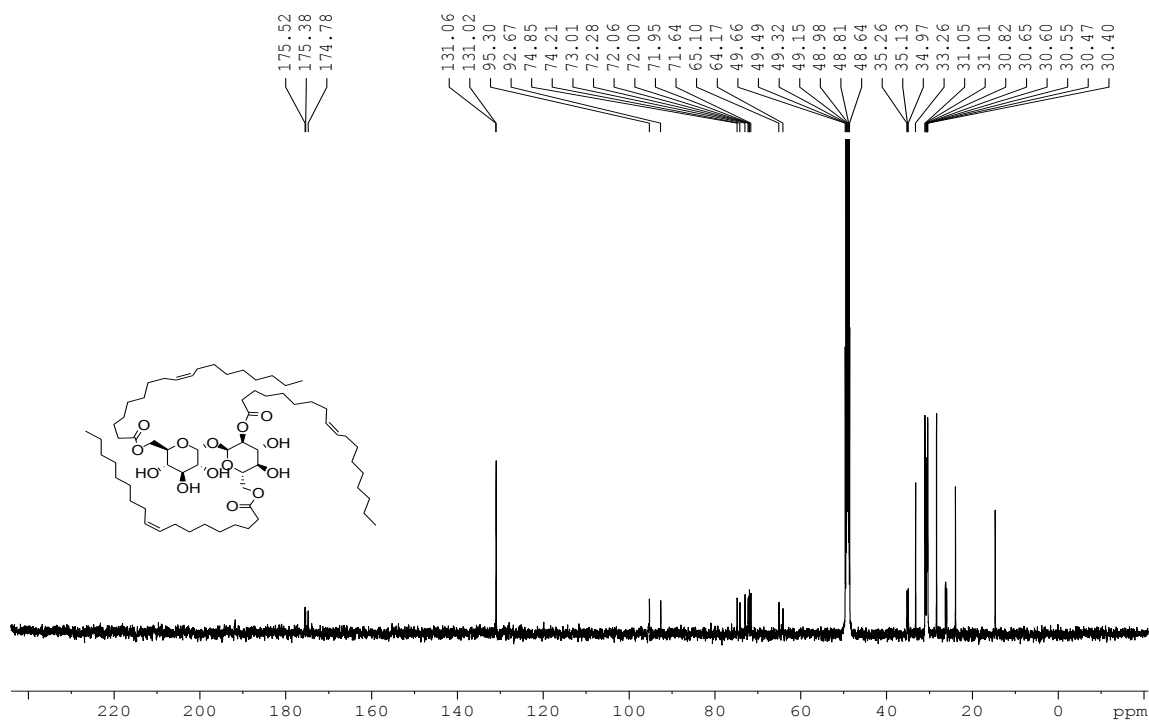
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 2,6,6'-tri-*O*-oleoyl- α,α -trehalose (175c) in methanol- d_4



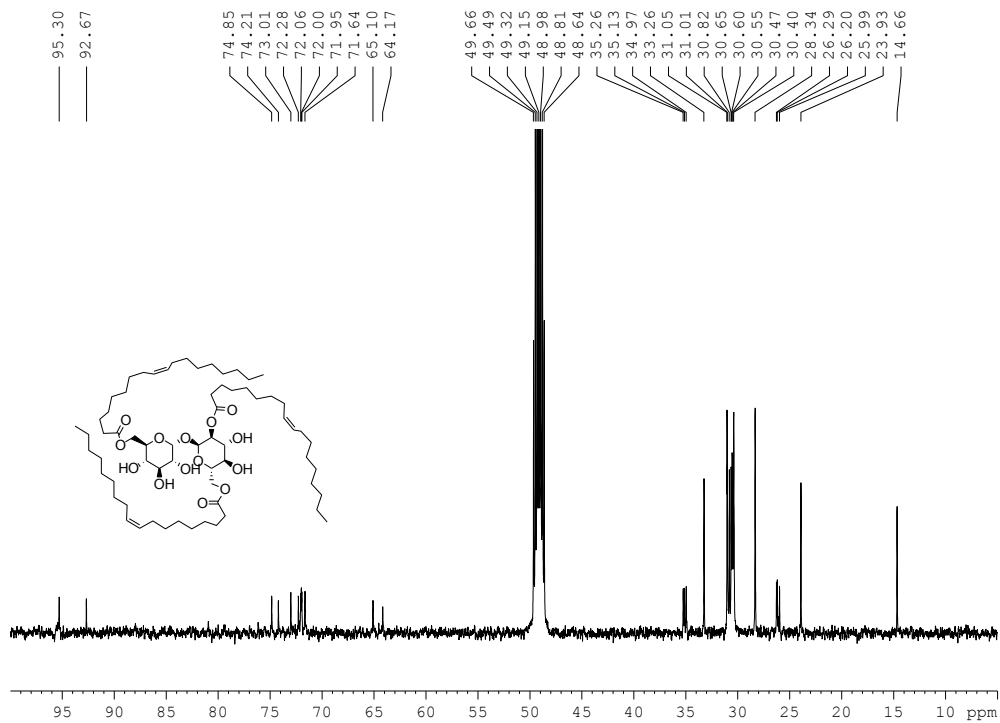
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 2,6,6'-tri-*O*-oleoyl- α,α -trehalose (175c) in methanol- d_4



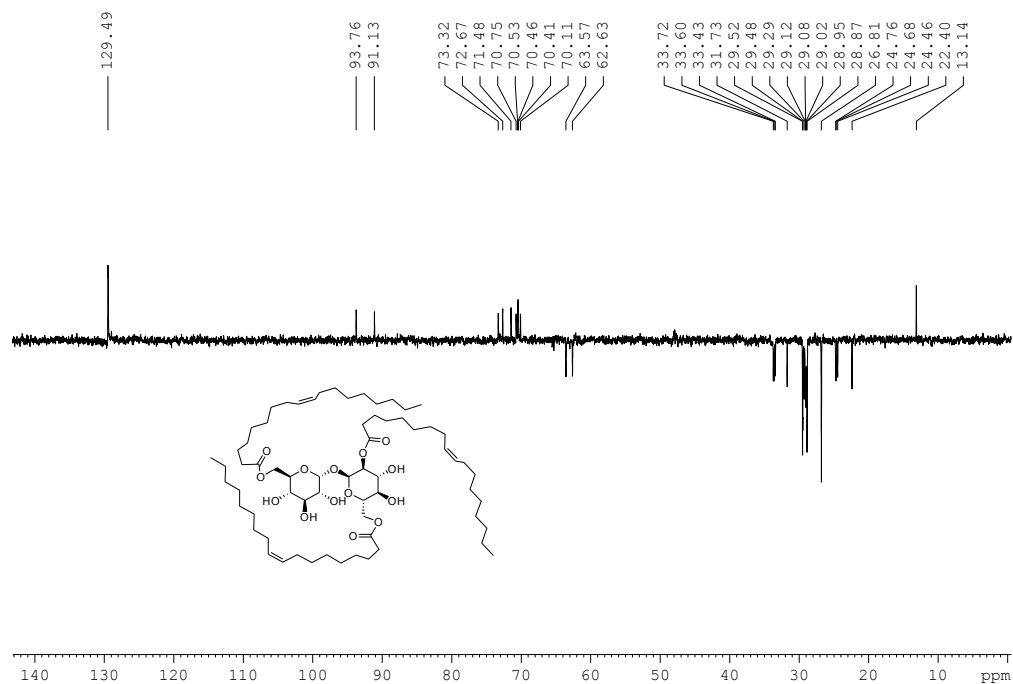
125.713 MHz ^{13}C NMR spectrum of 2,6,6'-tri-*O*-oleoyl- α,α -trehalose (175c) in methanol- d_4



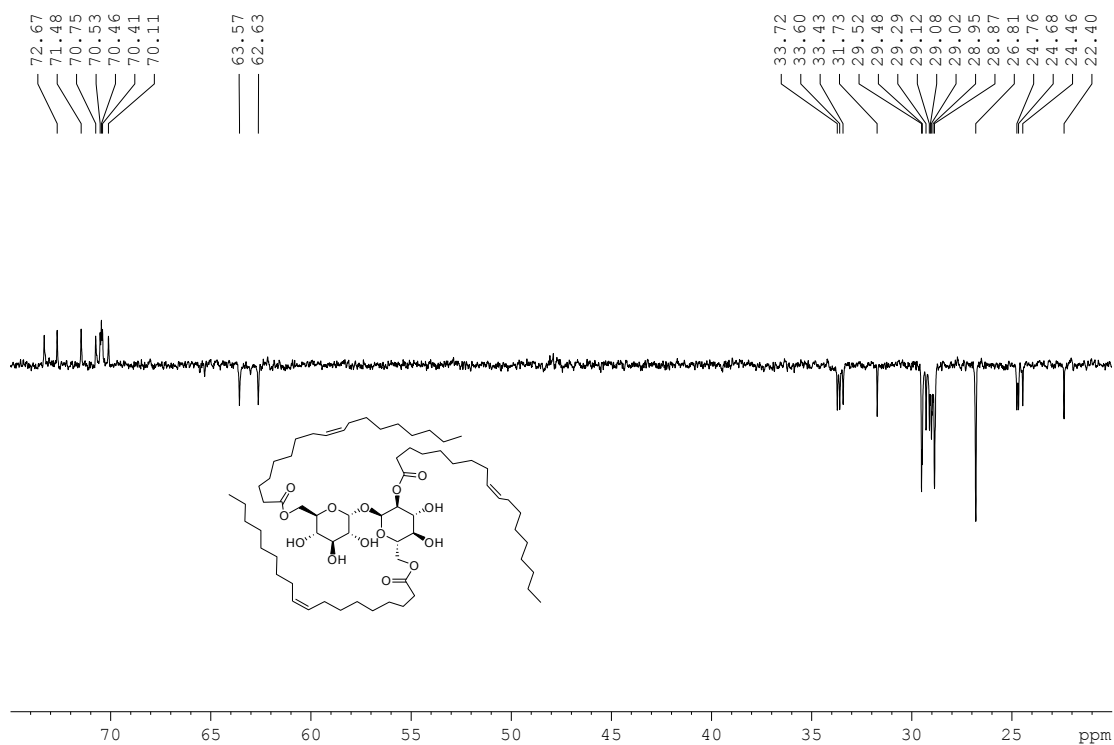
Expansion of part of the 125.7 MHz ^{13}C NMR spectrum of 2,6,6'-tri-*O*-oleoyl- α,α -trehalose (175c) in methanol- d_4



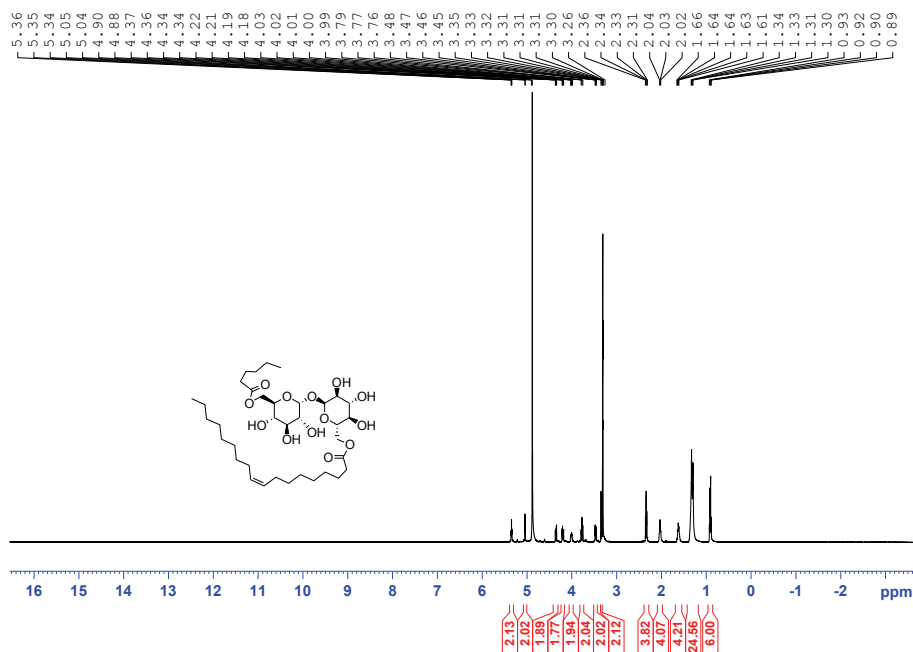
125.7 MHz DEPT spectrum of 2,6,6'-tri-*O*-oleoyl- α,α -trehalose (175c) in methanol- d_4



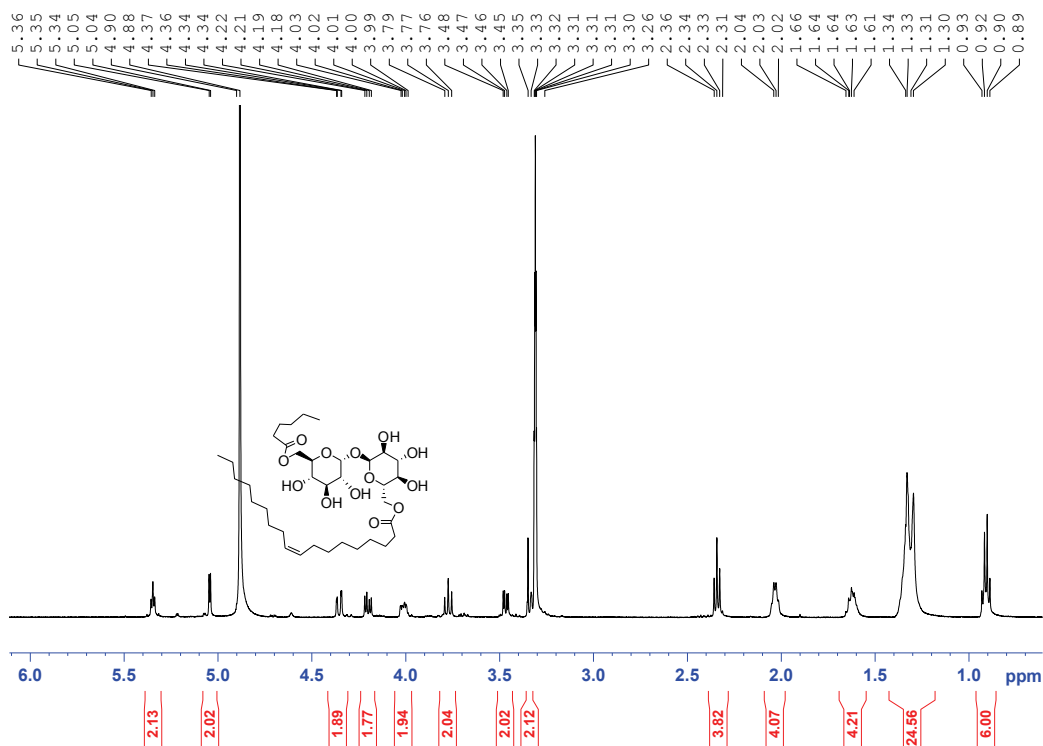
Expansion of part of the 125.7 MHz DEPT spectrum of 2,6,6'-tri-*O*-oleoyl- α,α -trehalose (175c) in methanol- d_4



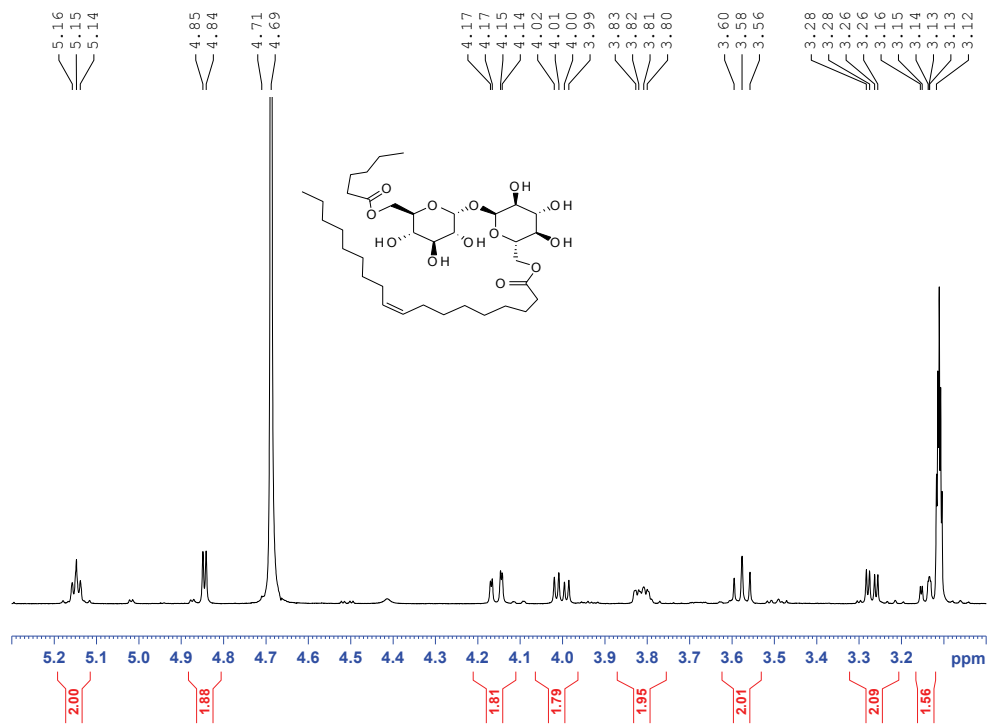
500.13 MHz ^1H NMR spectrum of 6-*O*-hexanoyl-6'-*O*-oleoyl- α,α -trehalose (176a) in methanol- d_4



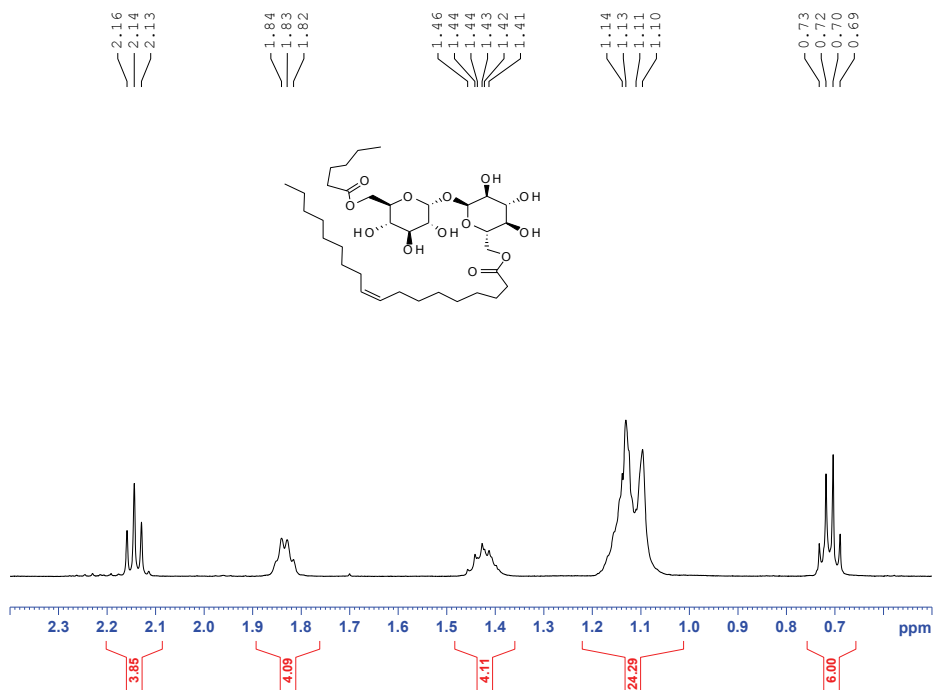
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6-*O*-hexanoyl-6'-*O*-oleoyl- α,α -trehalose (176a) in methanol- d_4



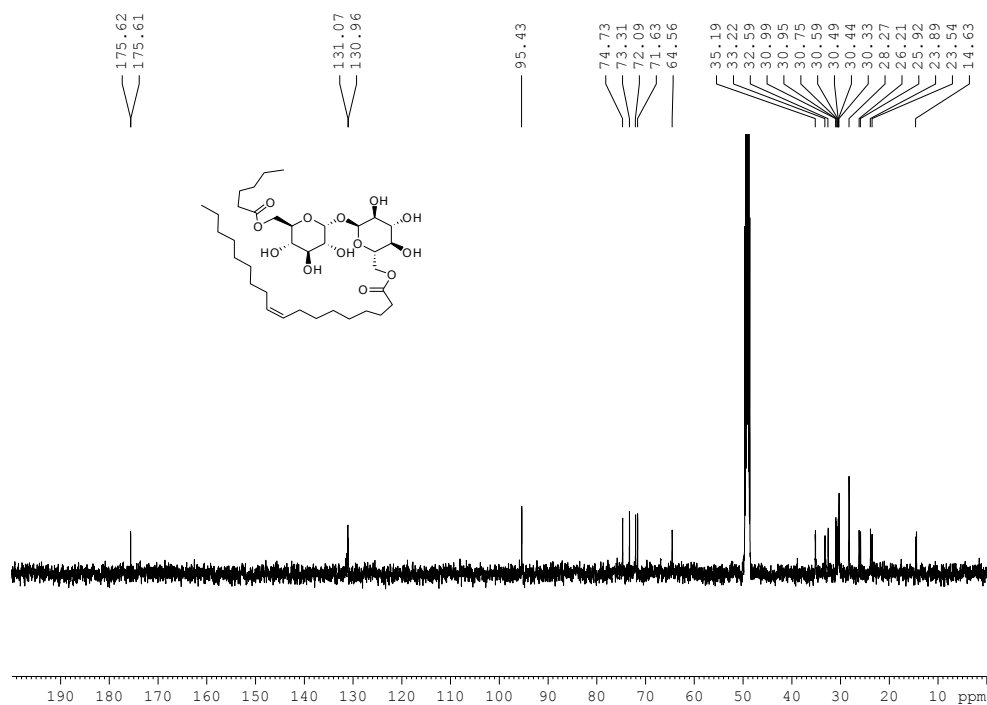
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6-*O*-hexanoyl-6'-*O*-oleoyl- α,α -trehalose (176a) in methanol- d_4



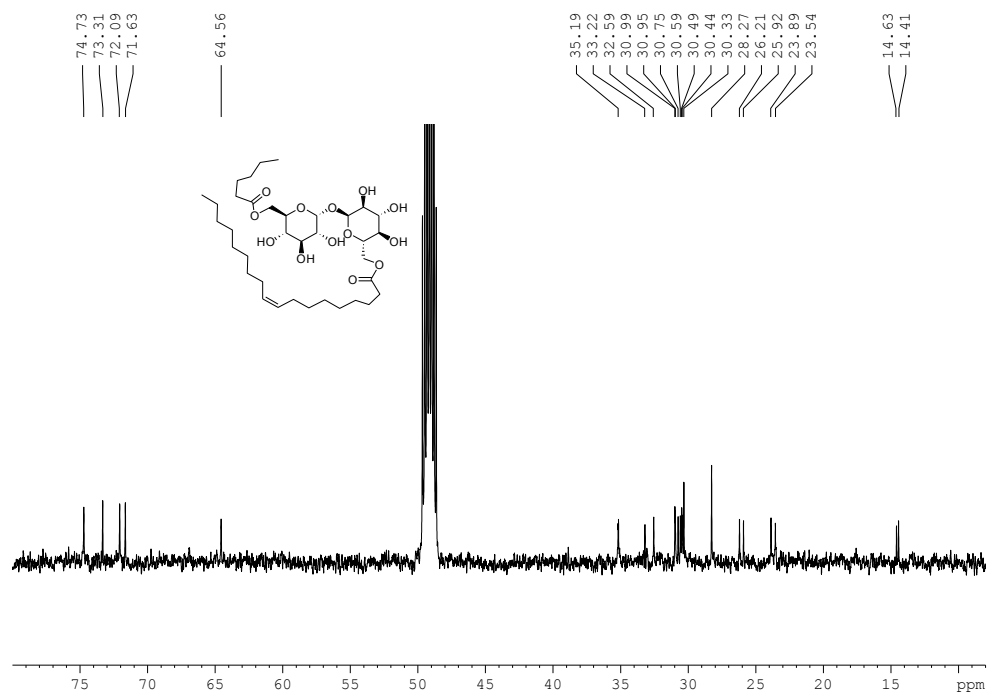
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6-*O*-hexanoyl-6'-*O*-oleoyl- α,α -trehalose (176a) in methanol- d_4



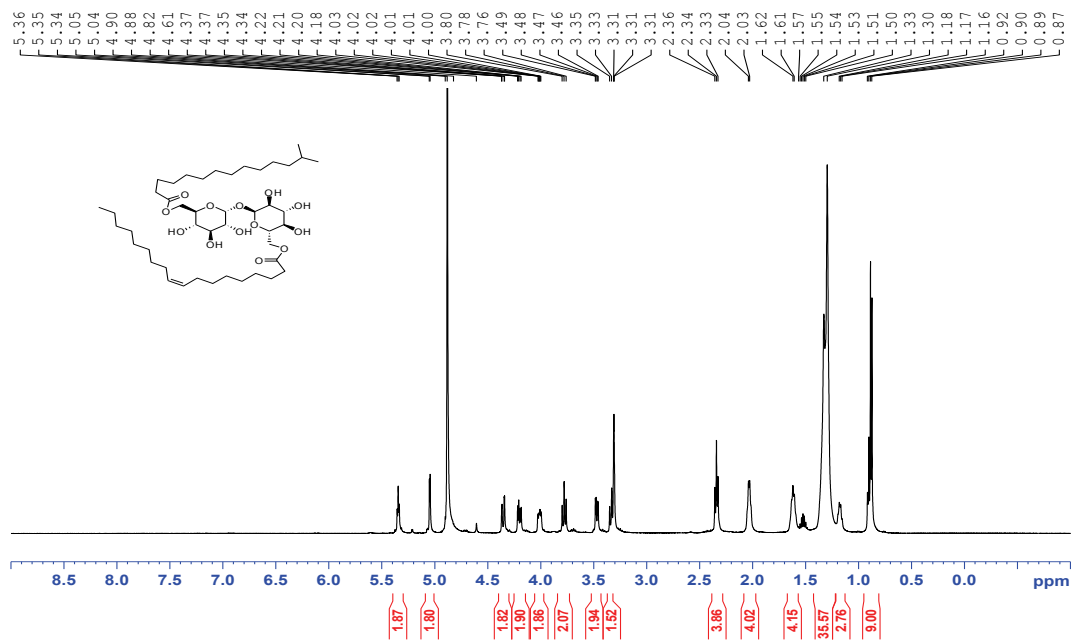
125.7 MHz ^{13}C NMR spectrum of 6-*O*-hexanoyl-6'-*O*-oleoyl- α,α -trehalose (176a) in methanol- d_4



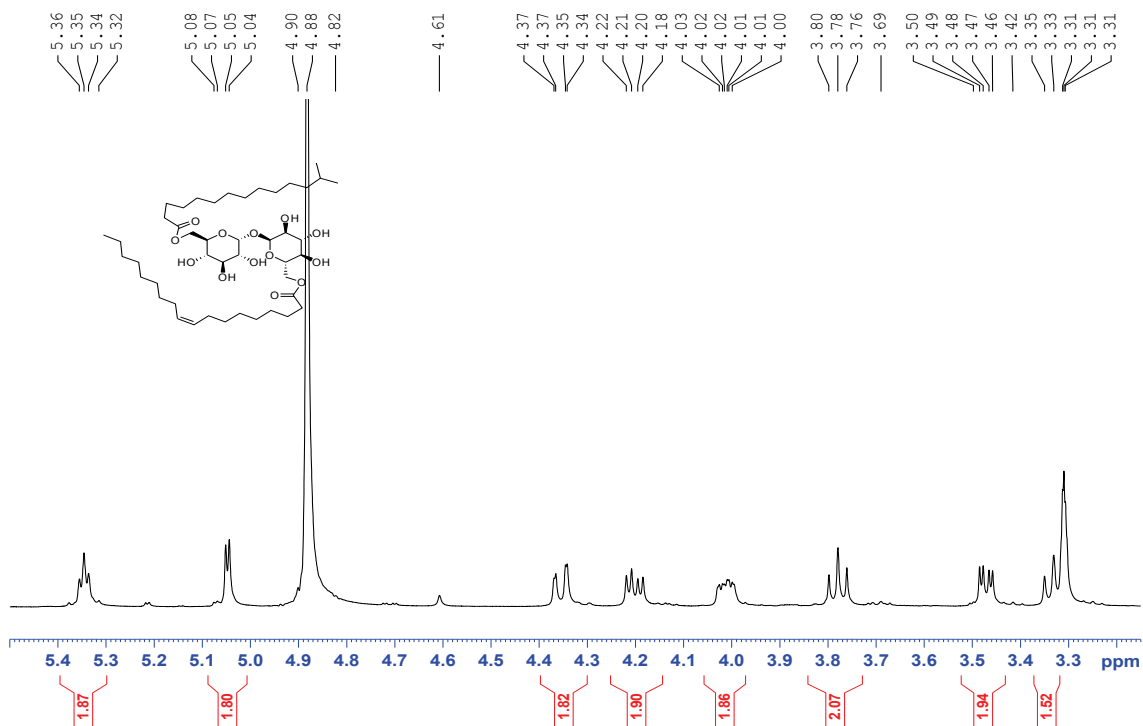
Expansion of part of the 125.7 MHz ^{13}C NMR spectrum of 6-*O*-hexanoyl-6'-*O*-oleoyl- α,α -trehalose (176a) in methanol- d_4



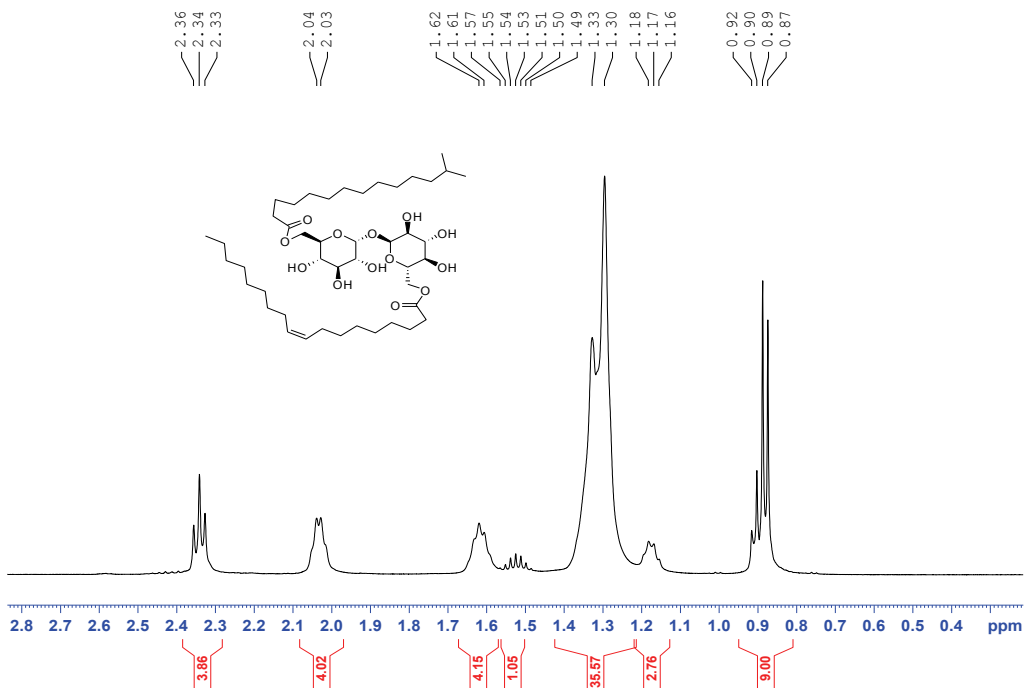
500.13 MHz ^1H NMR spectrum of 6-*O*-(13-methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (176b) in methanol- d_4



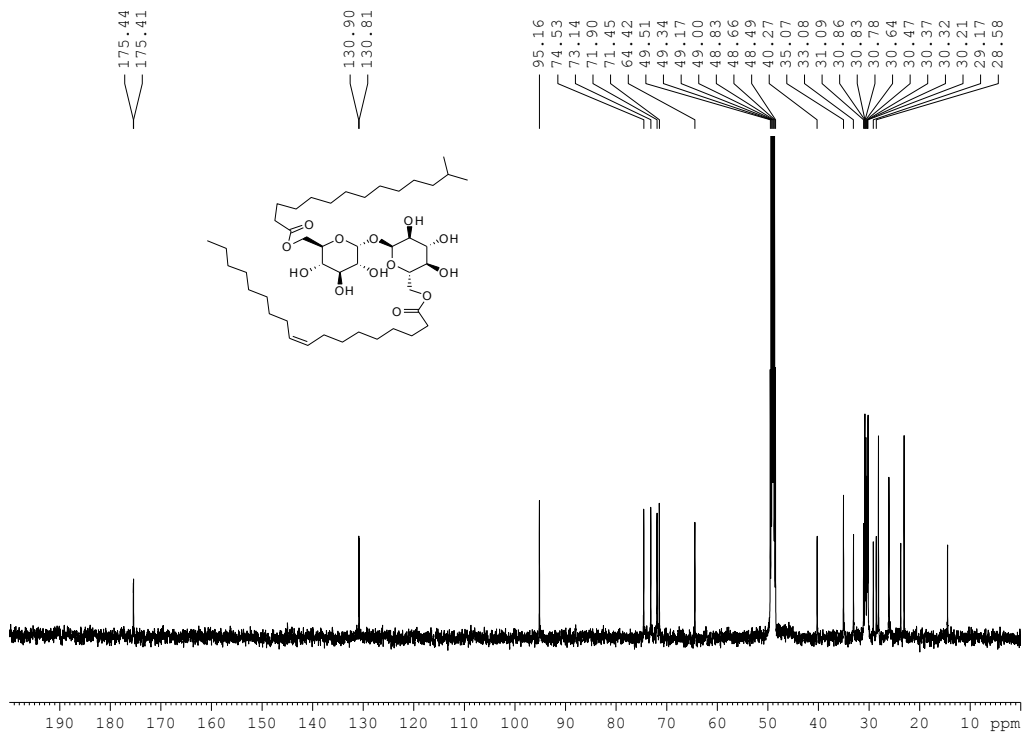
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6-*O*-(13-methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (176b) in methanol- d_4



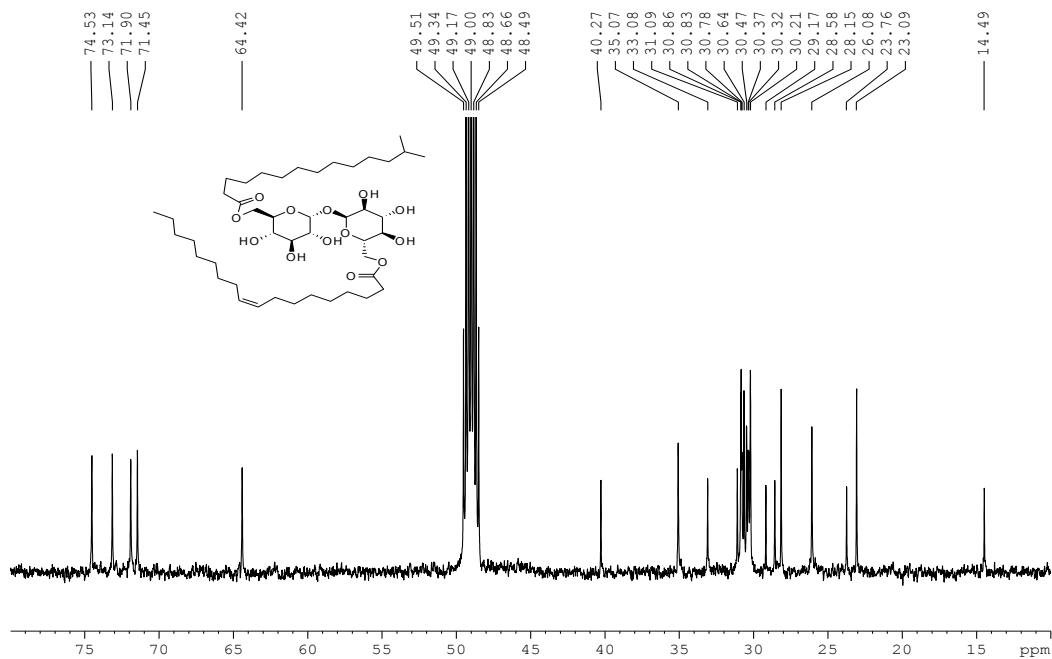
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6-*O*-(13-methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (176b) in methanol- d_4



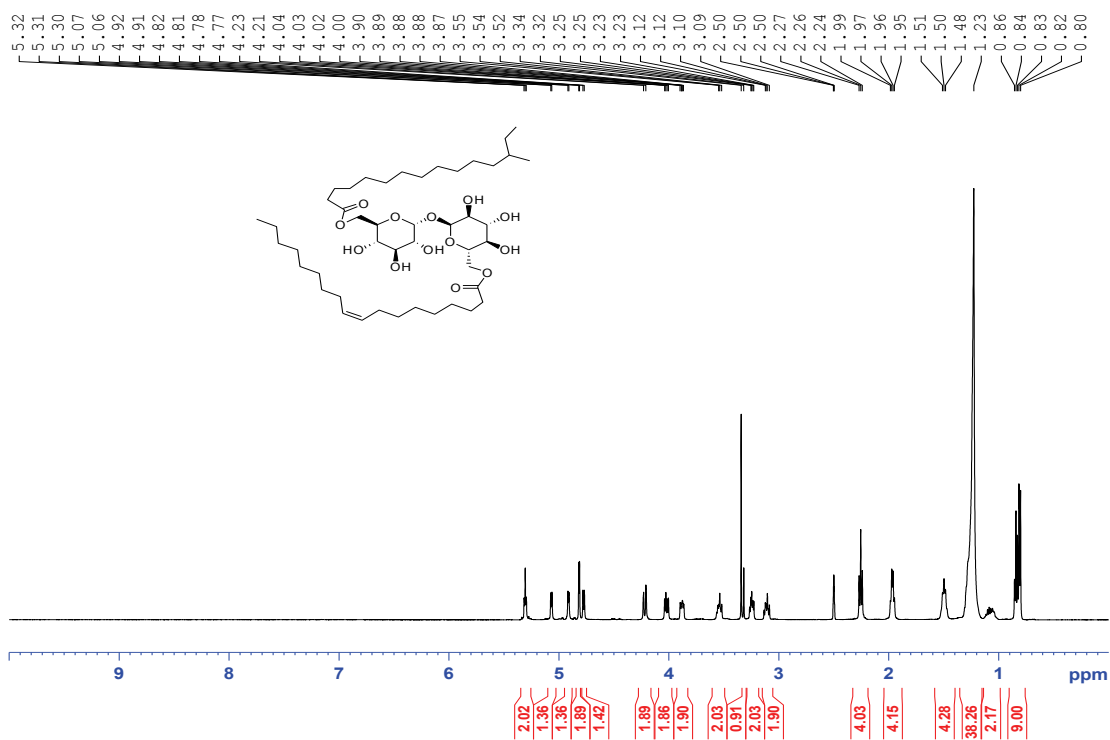
125.7 MHz ^{13}C NMR spectrum of 6-*O*-(13-methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (176b) in methanol- d_4



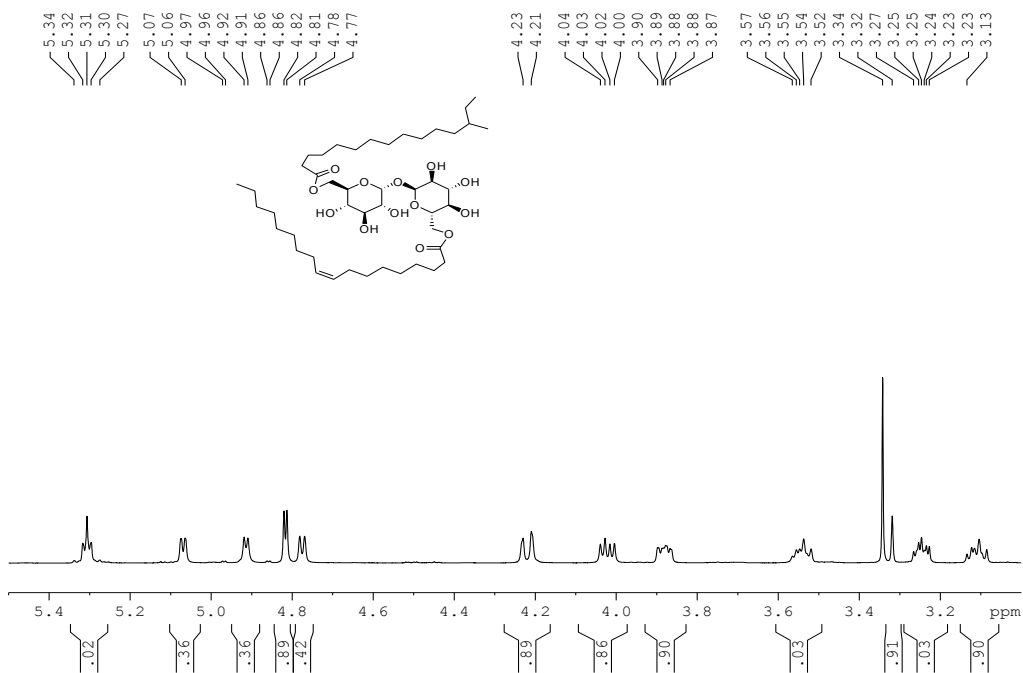
Expansion of part of the 125.7 MHz ^{13}C NMR spectrum of 6-*O*-(13-methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (176b) in methanol- d_4



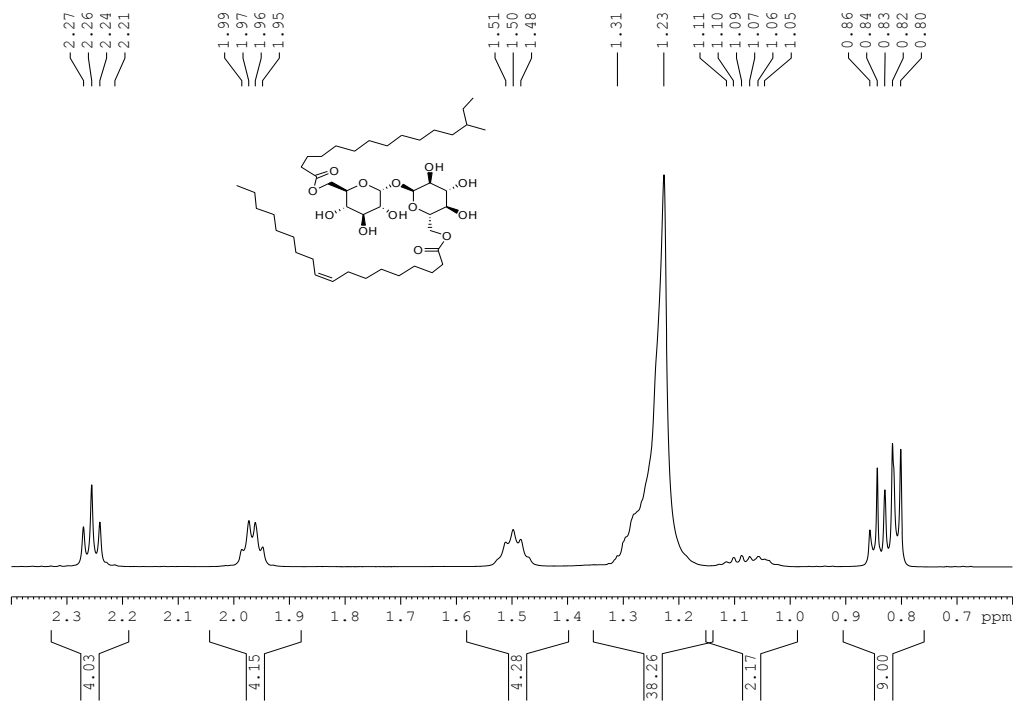
500.13 MHz ^1H NMR spectrum of 6-*O*-(12-methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (176c) in methanol- d_4



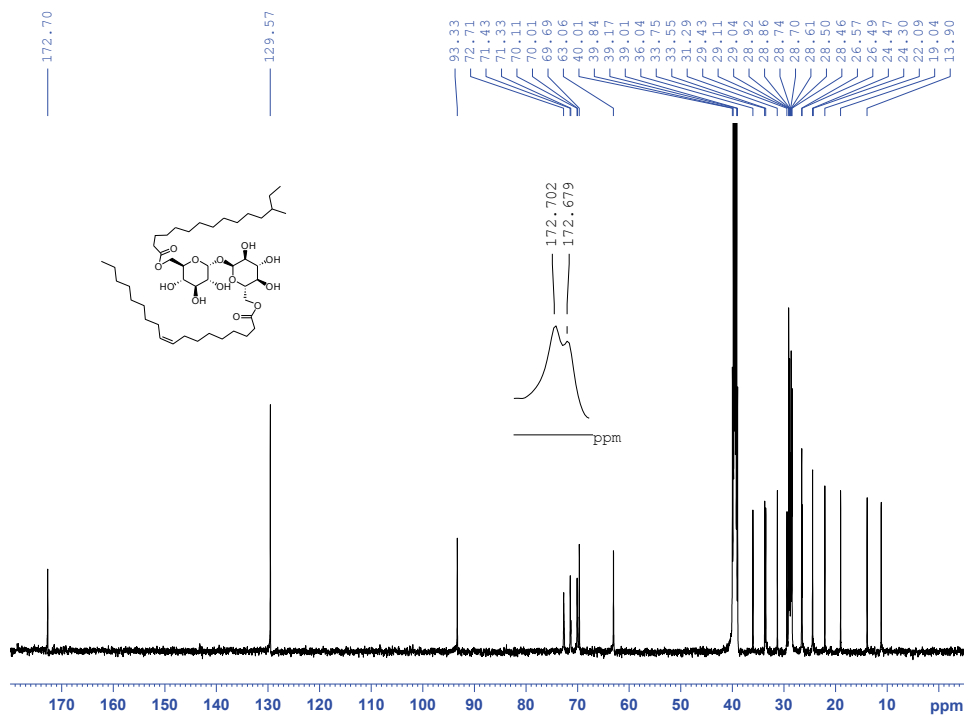
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6-*O*-(12-methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (176c) in methanol- d_4



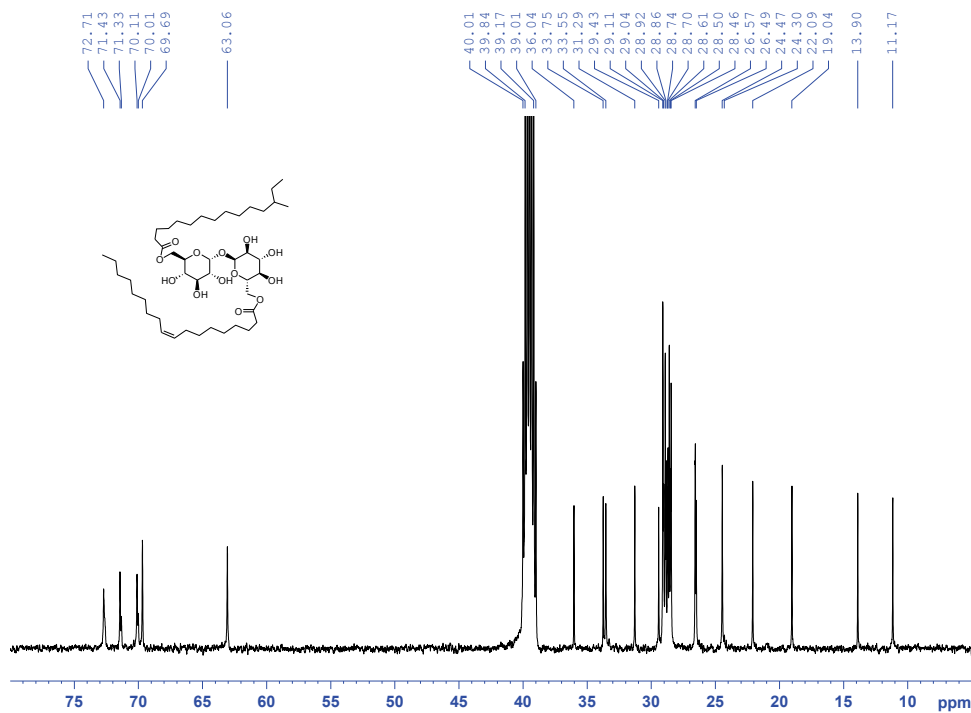
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6-*O*-(12-methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (176c) in methanol- d_4



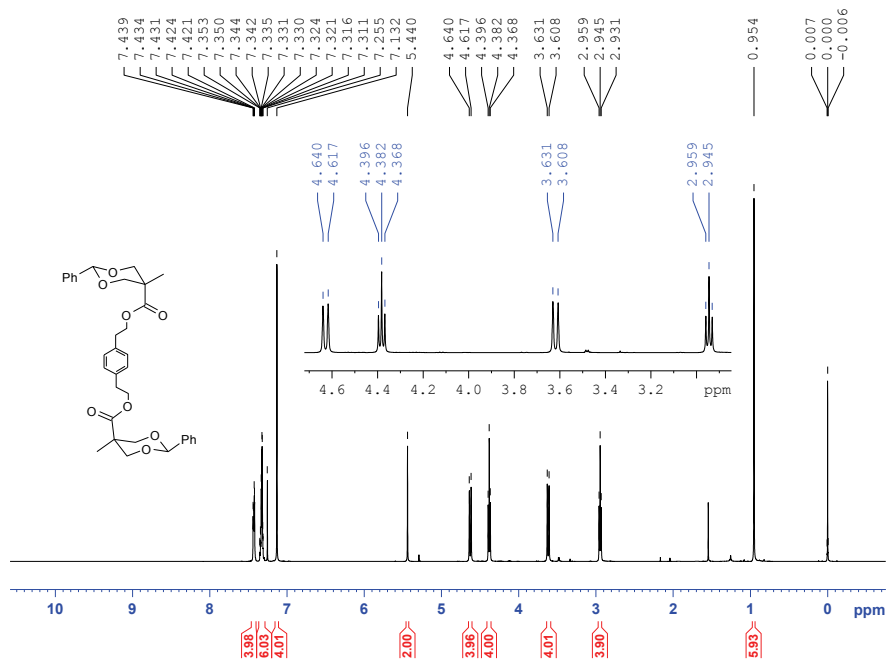
125.7 MHz ^{13}C NMR spectrum of 6-*O*-(12-methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (176c) in methanol- d_4



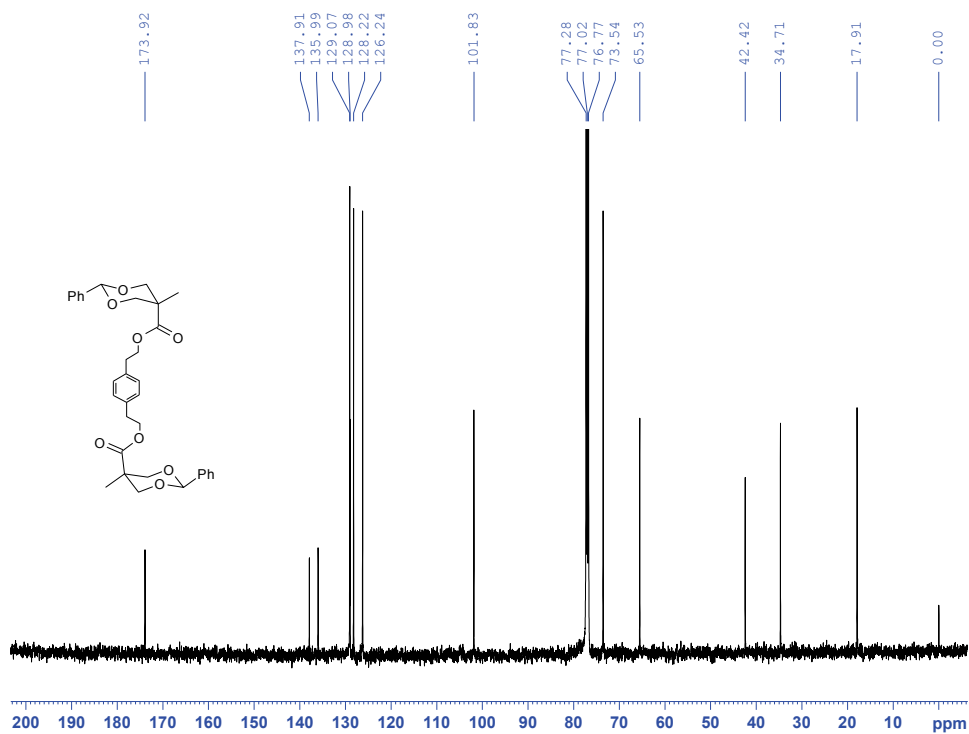
Expansion of part of the 125.713 MHz ^{13}C NMR spectrum of 6-*O*-(12-methyltetradecanoyl)-6'-*O*-oleoyl- α,α -trehalose (176c) in methanol- d_4



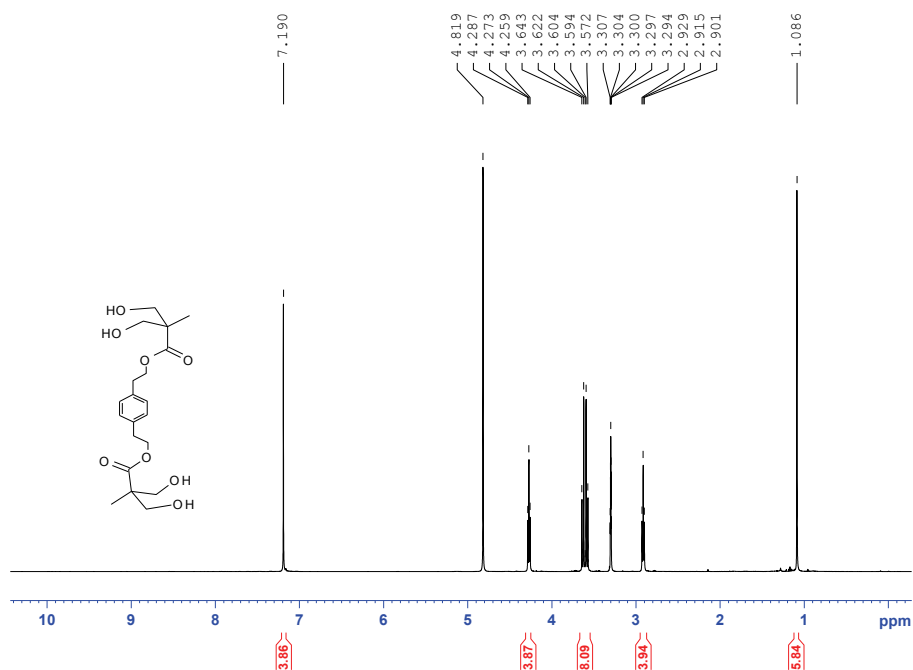
500.13 MHz ^1H NMR spectrum of benzylidene-protected first generation dendrimer (177) in chloroform-*d*.



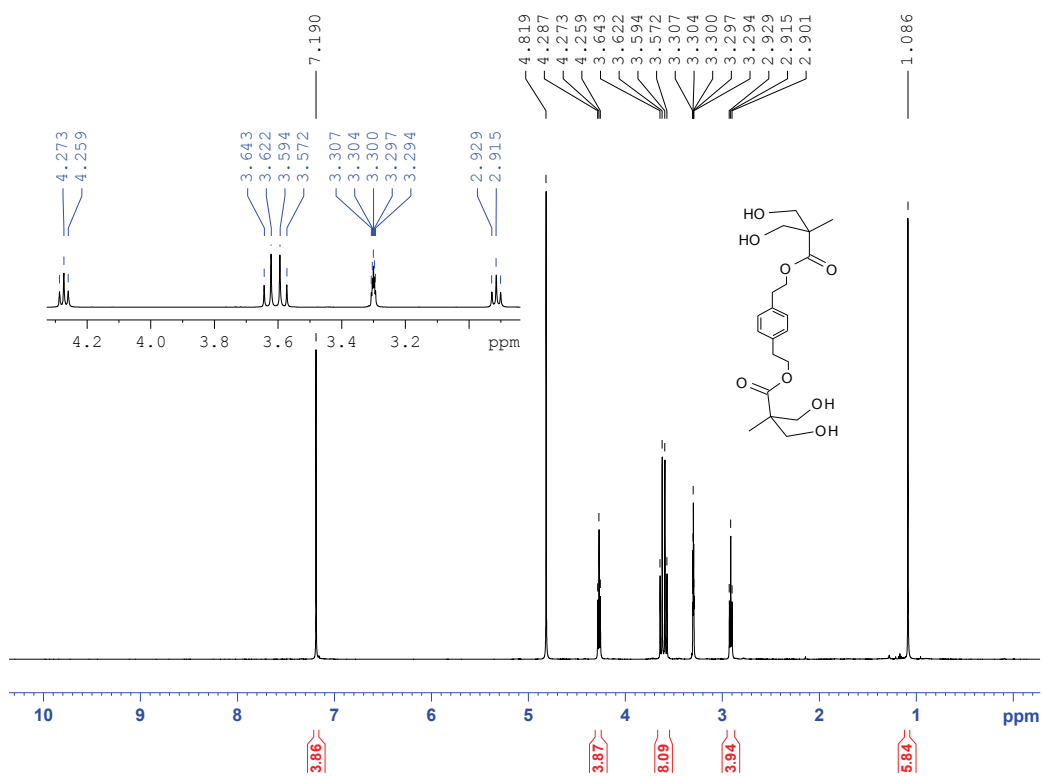
125.7 MHz ^{13}C NMR spectrum of benzylidene-protected first generation dendrimer (177) in chloroform-*d*.



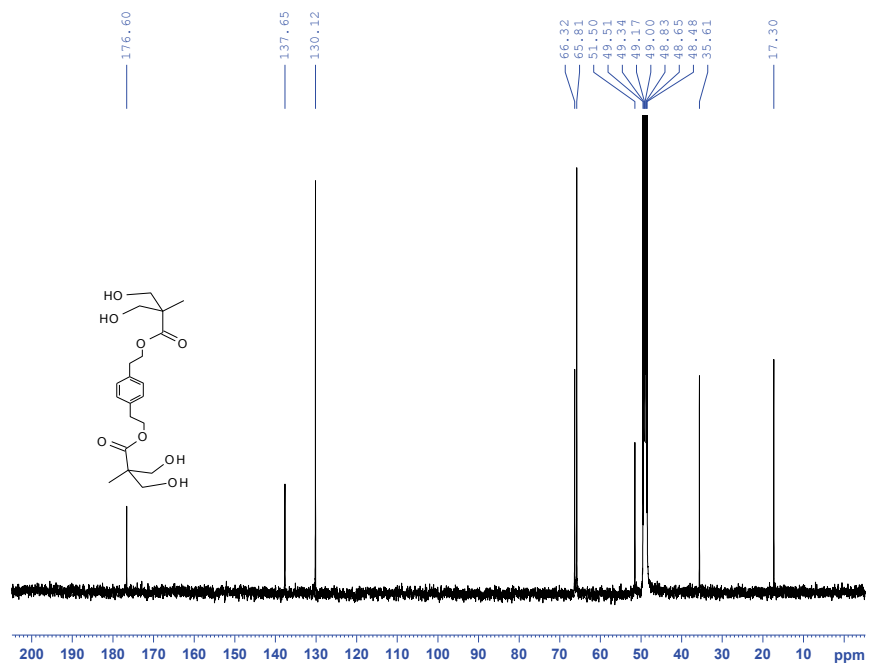
500.13 MHz ^1H NMR spectrum of first generation dendrimer (178) in methanol- d_4 .



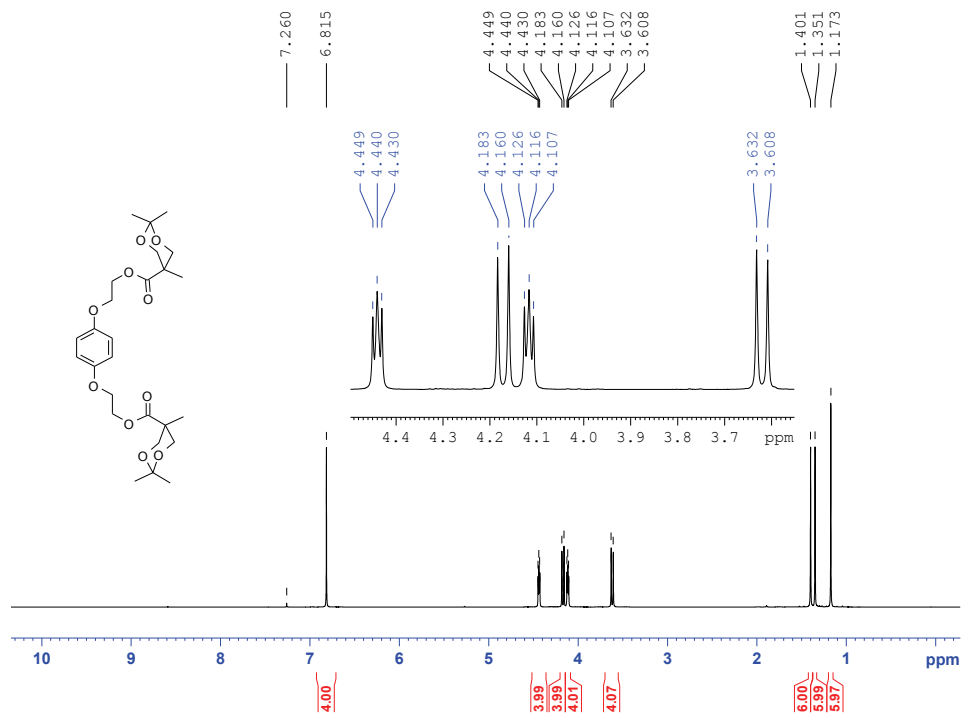
Expansion of part of the 500.13 MHz ^1H NMR spectrum of first generation dendrimer (178) in methanol- d_4 .



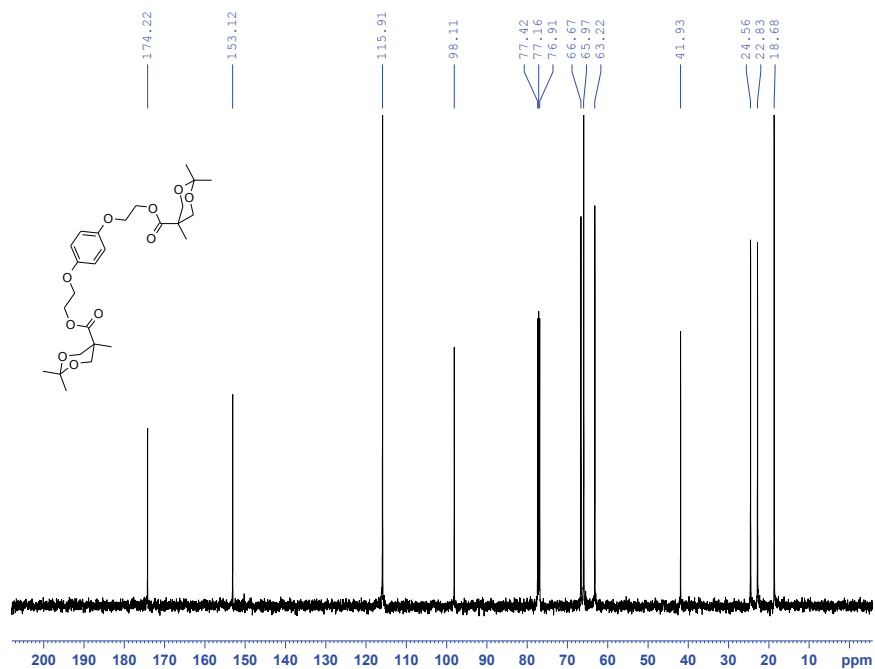
125.7 MHz ^{13}C NMR spectrum of first generation dendrimer (178) in methanol- d_4 .



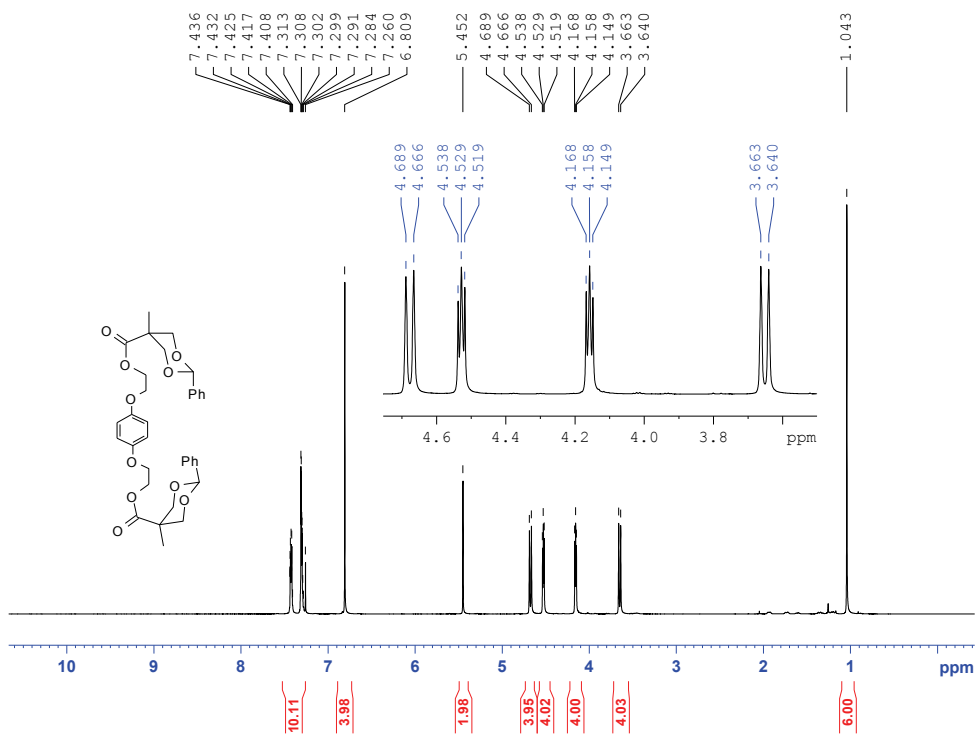
500.13 MHz ^1H NMR spectrum of acetonide-protected hydroquinone-cored first generation dendrimer (179) in chloroform- d



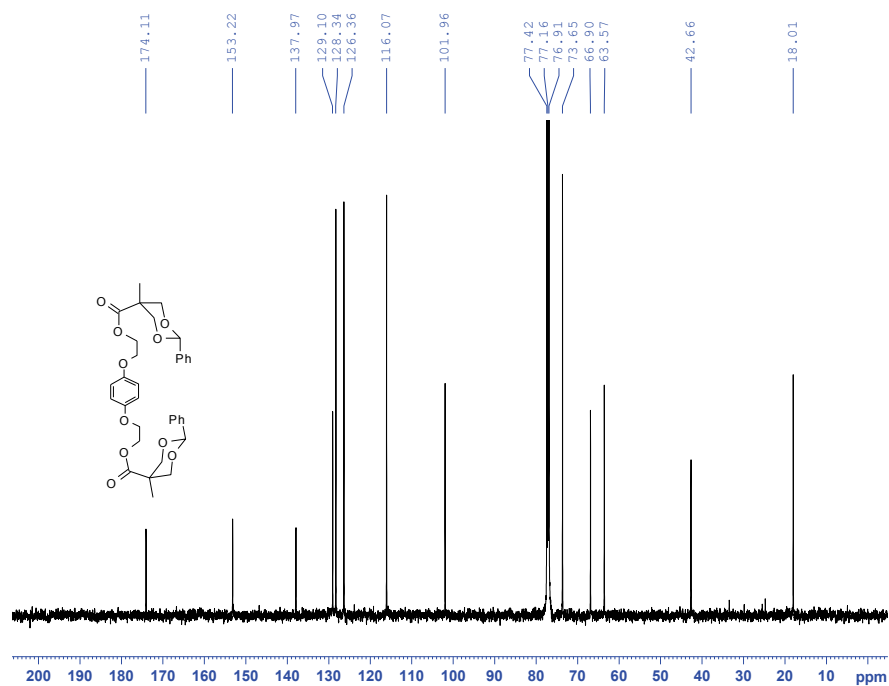
125.7 MHz ^{13}C NMR spectrum of acetonide-protected hydroquinone-cored first generation dendrimer (179) in chloroform-*d*



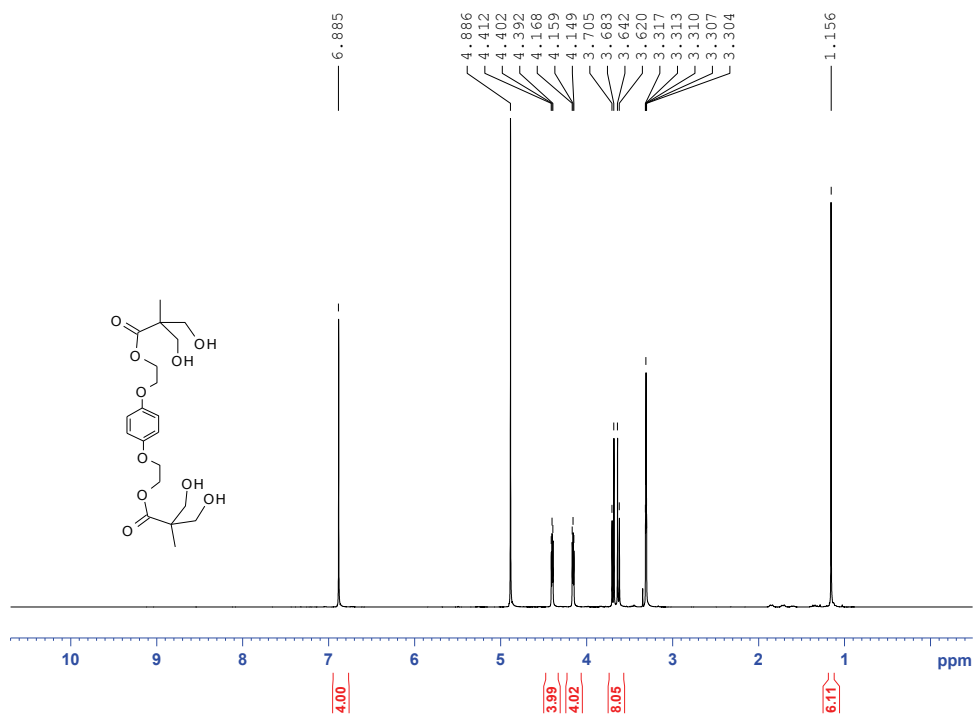
500.13 MHz ^1H NMR spectrum of benzylidene-protected hydroquinone-cored first generation dendrimer (183) in chloroform-*d*



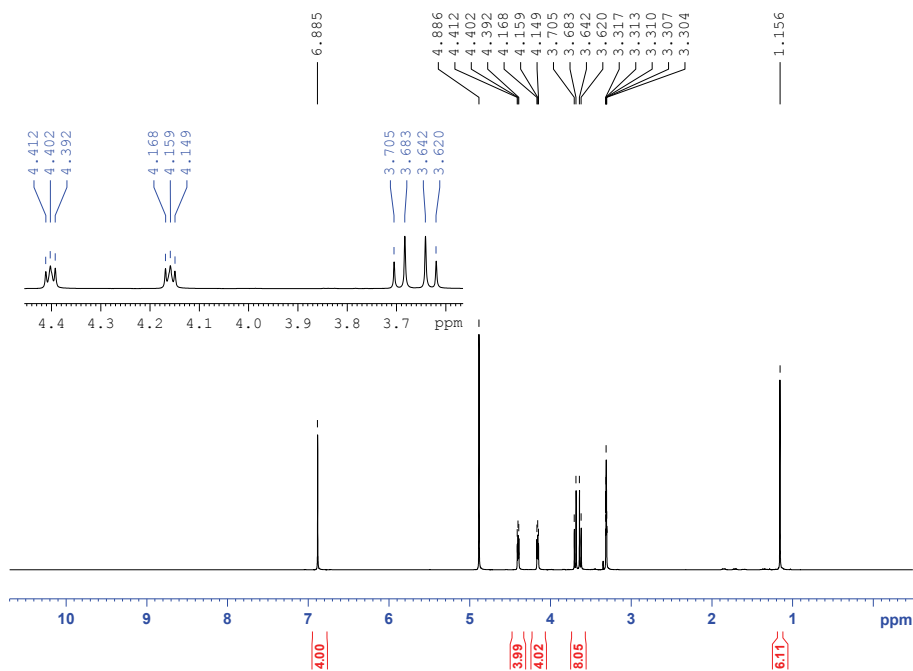
125.7 MHz ^{13}C NMR spectrum of benzylidene-protected hydroquinone-cored first generation dendrimer (183) in chloroform-*d*



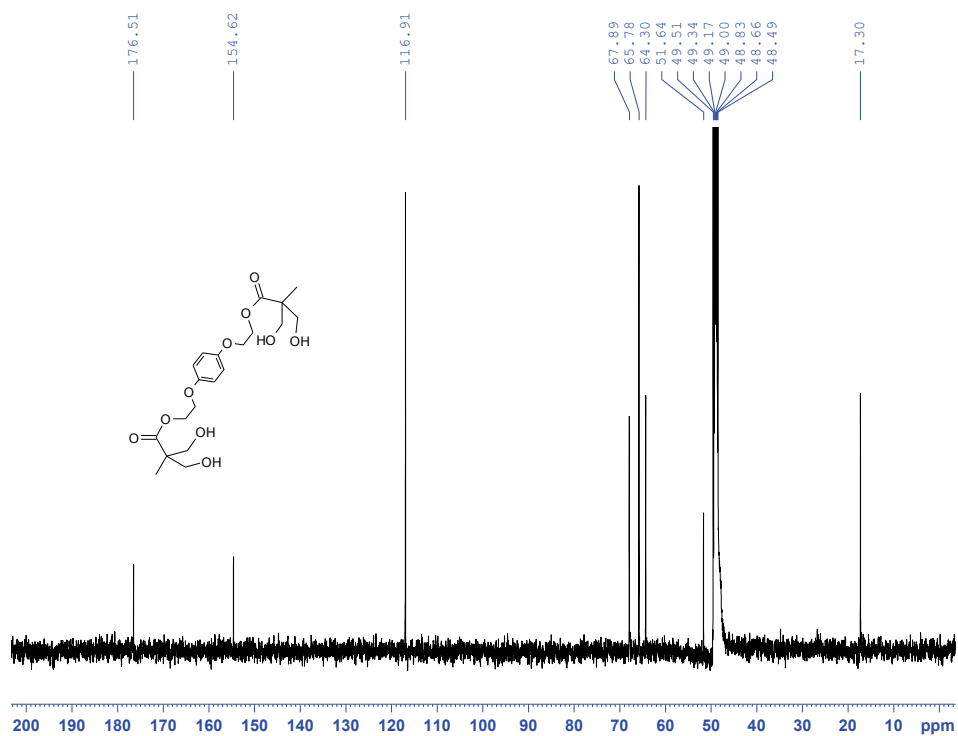
500.13 MHz ^1H NMR spectrum of hydroquinone-cored first generation dendrimer (180) in methanol-*d*₄.



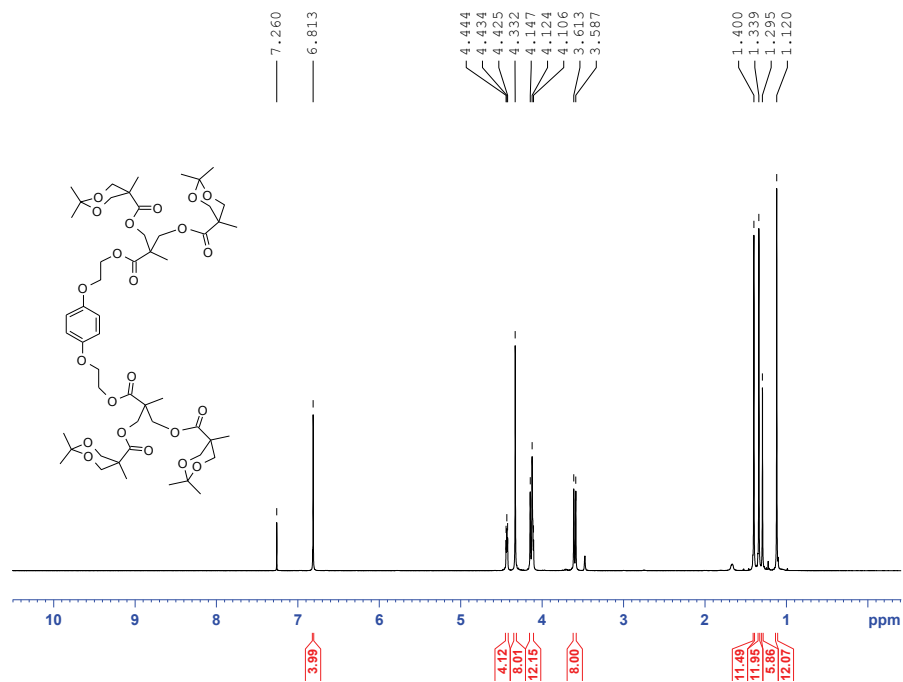
Expansion of part of the 500.13 MHz ^1H NMR spectrum of hydroquinone-cored first generation dendrimer (180) in methanol- d_4 .



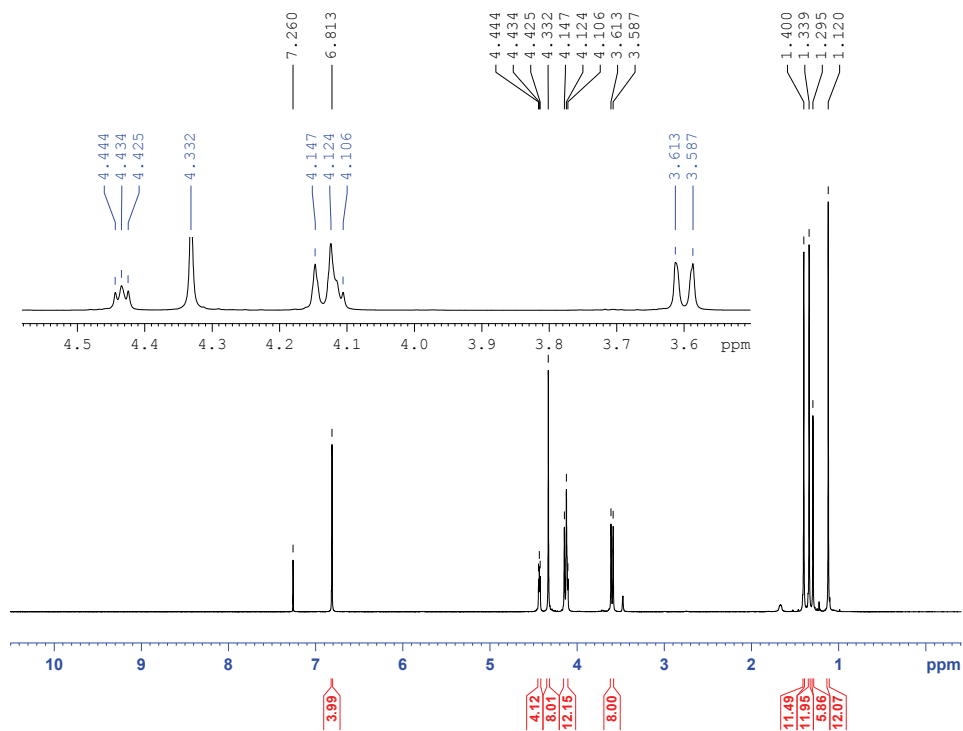
125.7 MHz ^{13}C NMR spectrum of hydroquinone-cored first generation dendrimer (180) in methanol- d_4 .



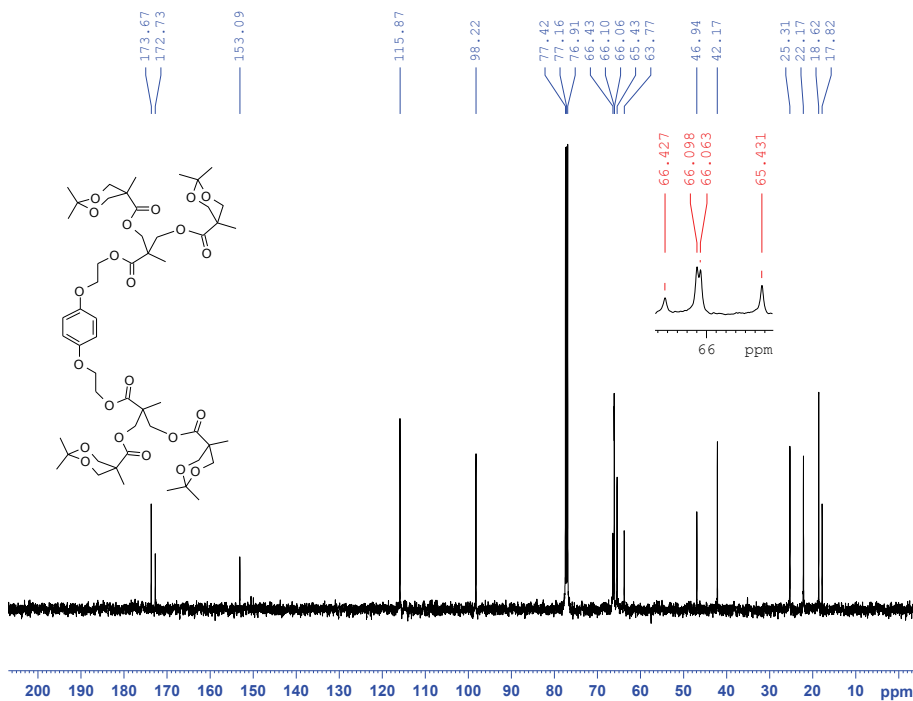
500.13 MHz ^1H NMR spectrum of acetonide-protected hydroquinone-cored second generation dendrimer (181) in chloroform-*d*



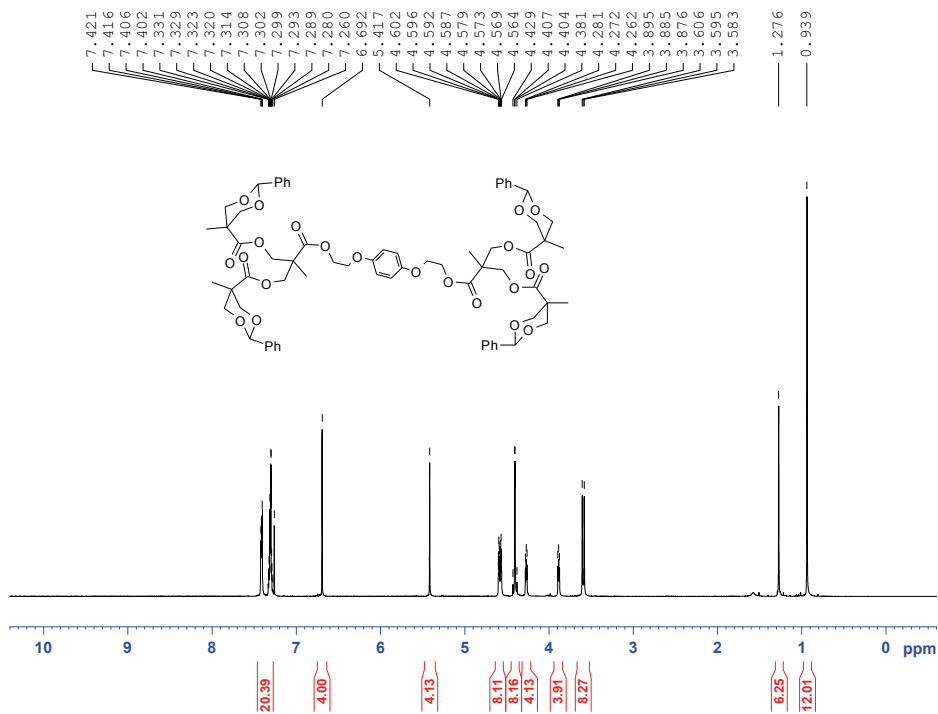
Expansion of part of the 500.13 MHz ^1H NMR spectrum of acetonide-protected hydroquinone-cored second generation dendrimer (181) in chloroform-*d*



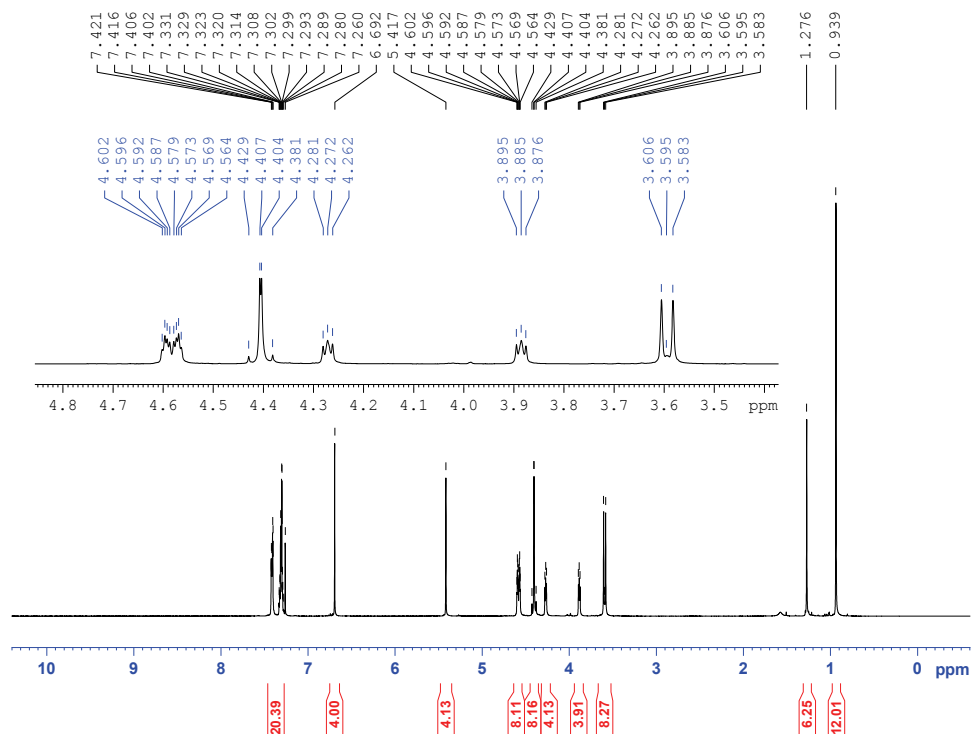
125.7 MHz ^{13}C NMR spectrum of acetonide-protected hydroquinone-cored second generation dendrimer (181) in chloroform-*d*



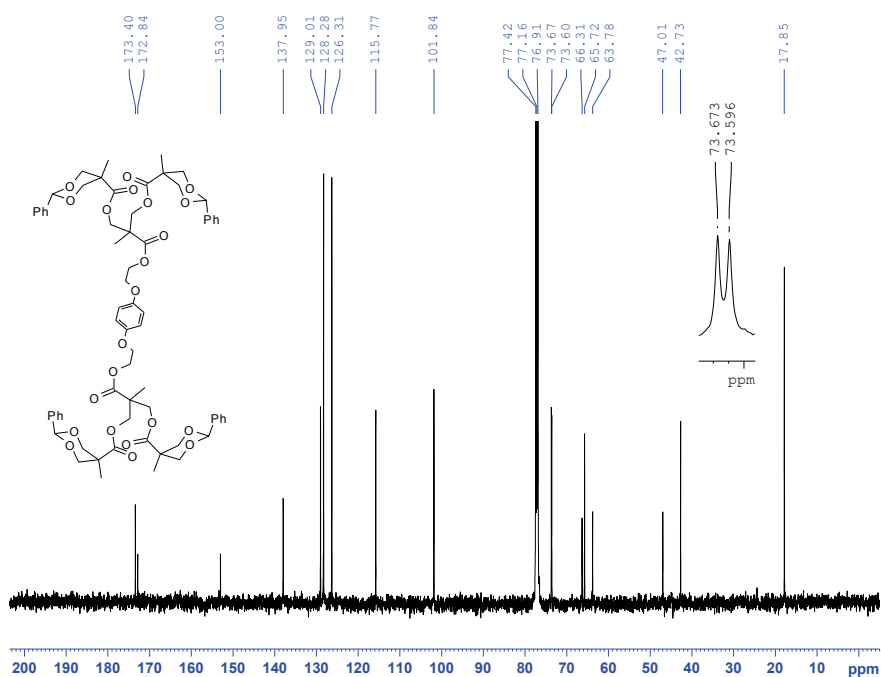
500.13 MHz ^1H NMR spectrum of benzylidene-protected hydroquinone-cored second generation dendrimer (184) in chloroform-*d*



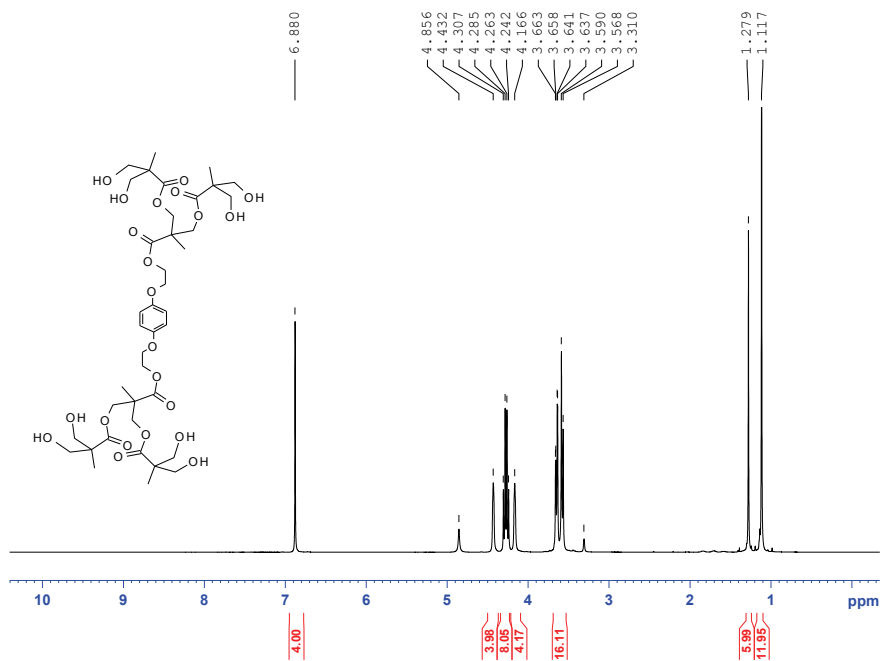
Expansion of part of the 500.13 MHz ^1H NMR spectrum of benzylidene-protected hydroquinone-cored second generation dendrimer (184) in chloroform-*d*



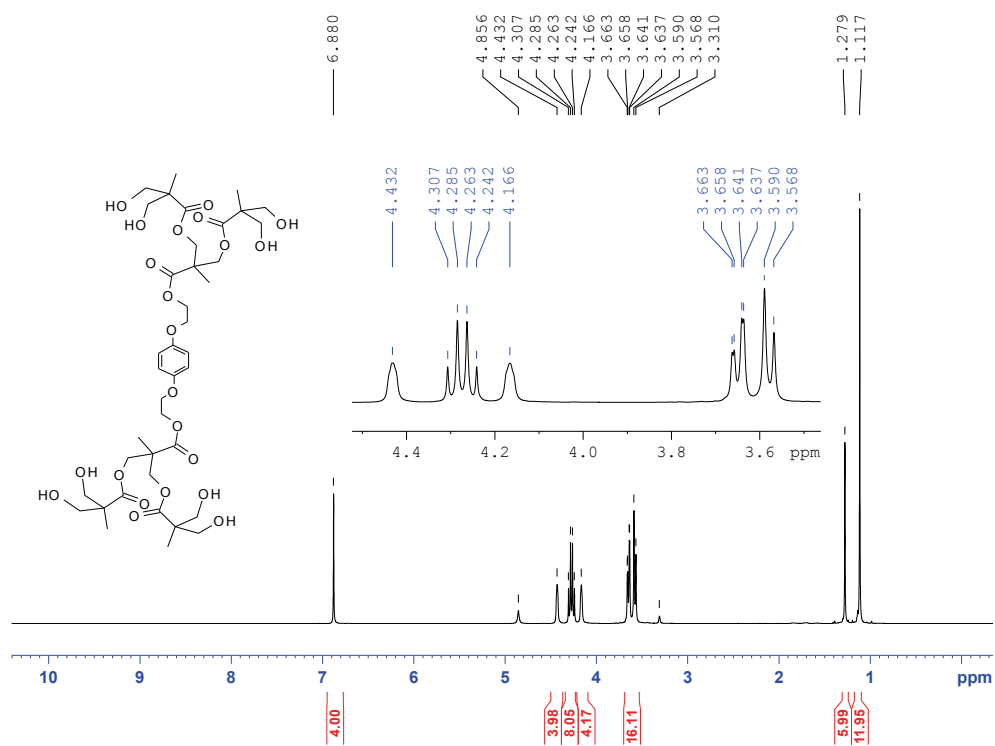
125.7 MHz ^{13}C NMR spectrum of benzylidene-protected hydroquinone-cored second generation dendrimer (184) in chloroform-*d*



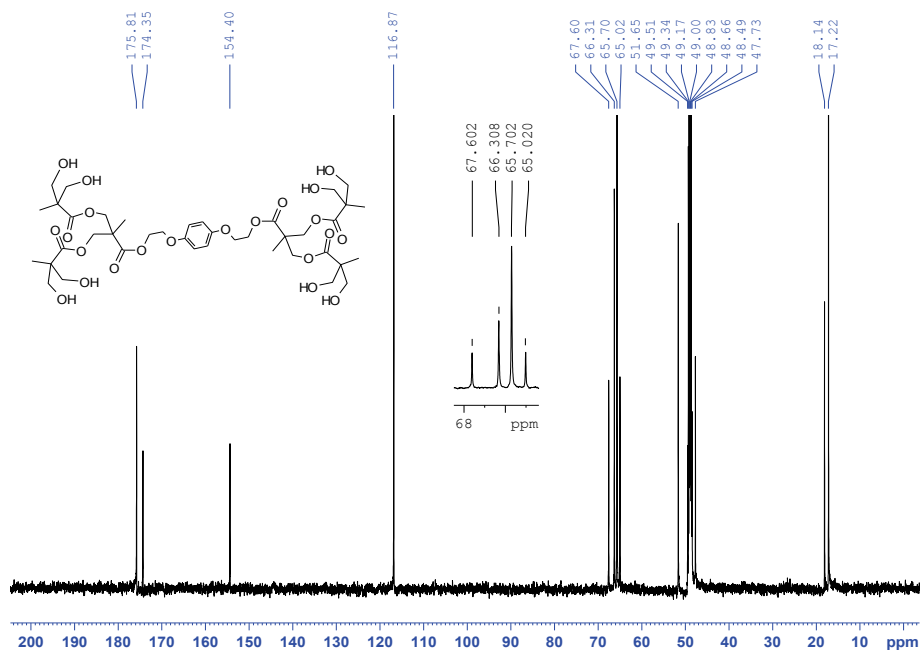
500.13 MHz ^1H NMR spectrum of hydroquinone-cored second generation dendrimer (182) in methanol- d_4



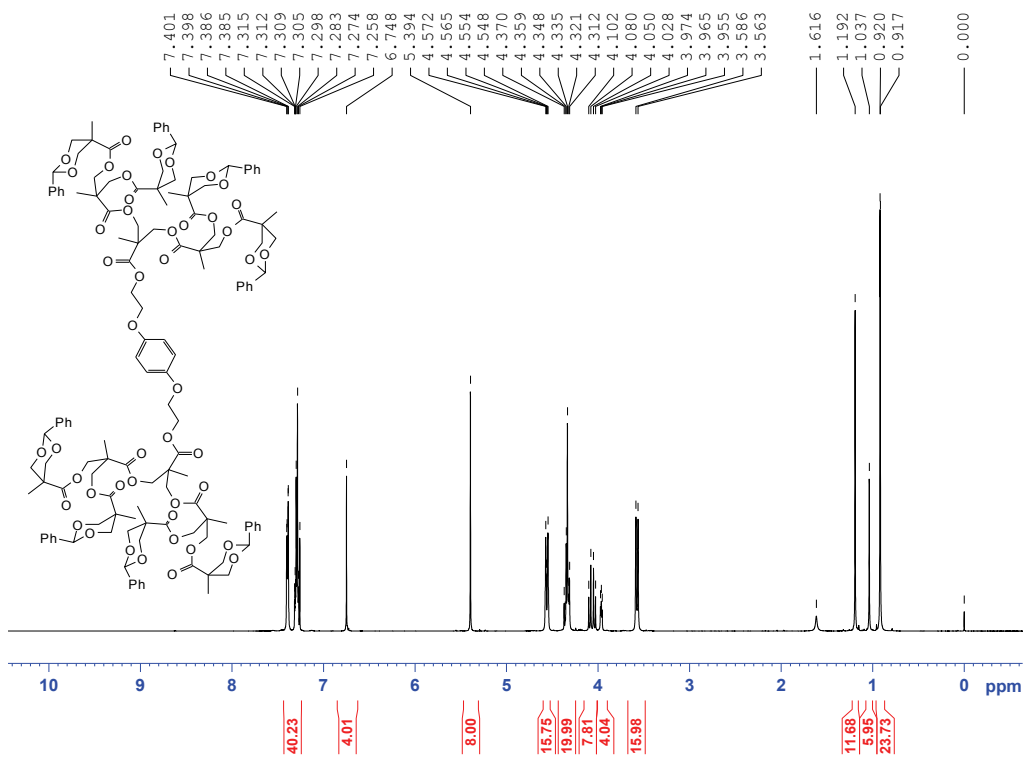
Expansion of part of the 500.13 MHz ^1H NMR spectrum of hydroquinone-cored second generation dendrimer (182) in methanol- d_4



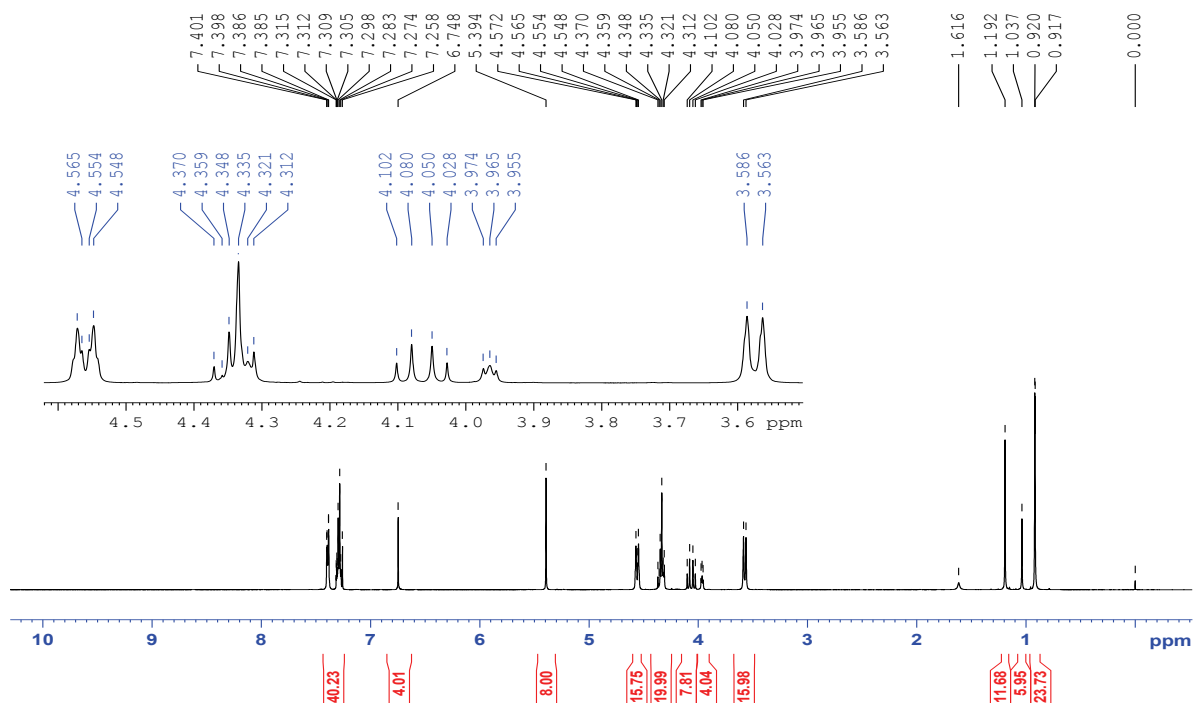
125.7 MHz ^{13}C NMR spectrum of hydroquinone-cored second generation dendrimer (182) in methanol- d_4



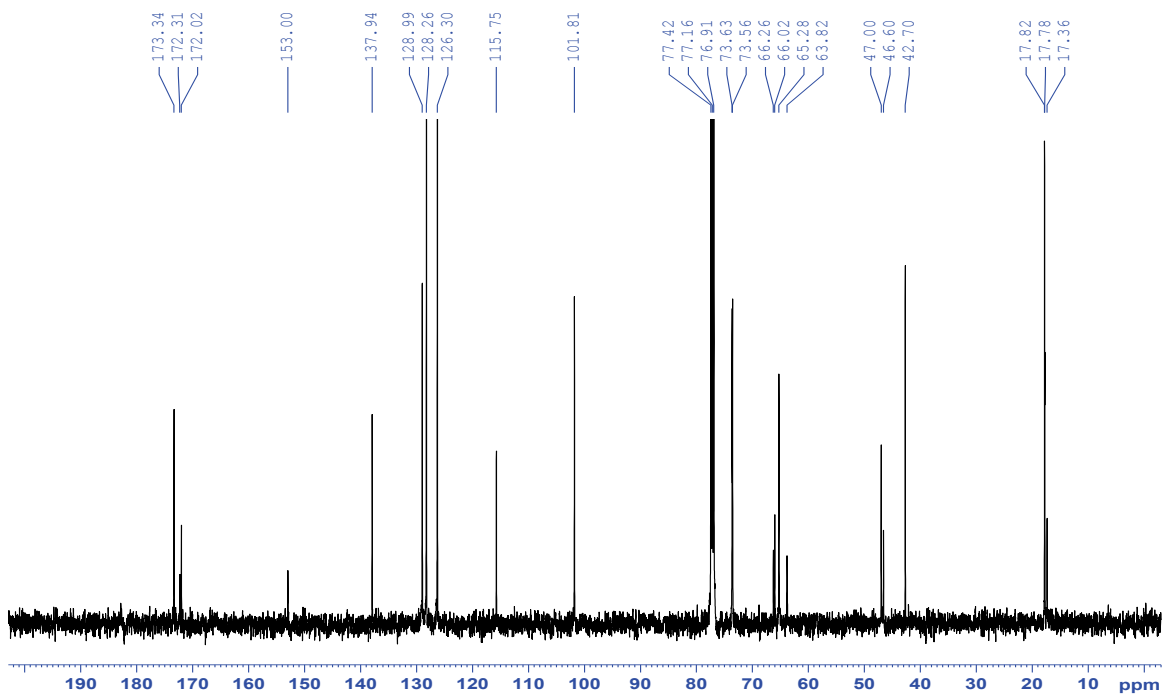
500.13 MHz ^1H NMR spectrum of benzylidene-protected hydroquinone-cored third generation dendrimer (185) in chloroform- d



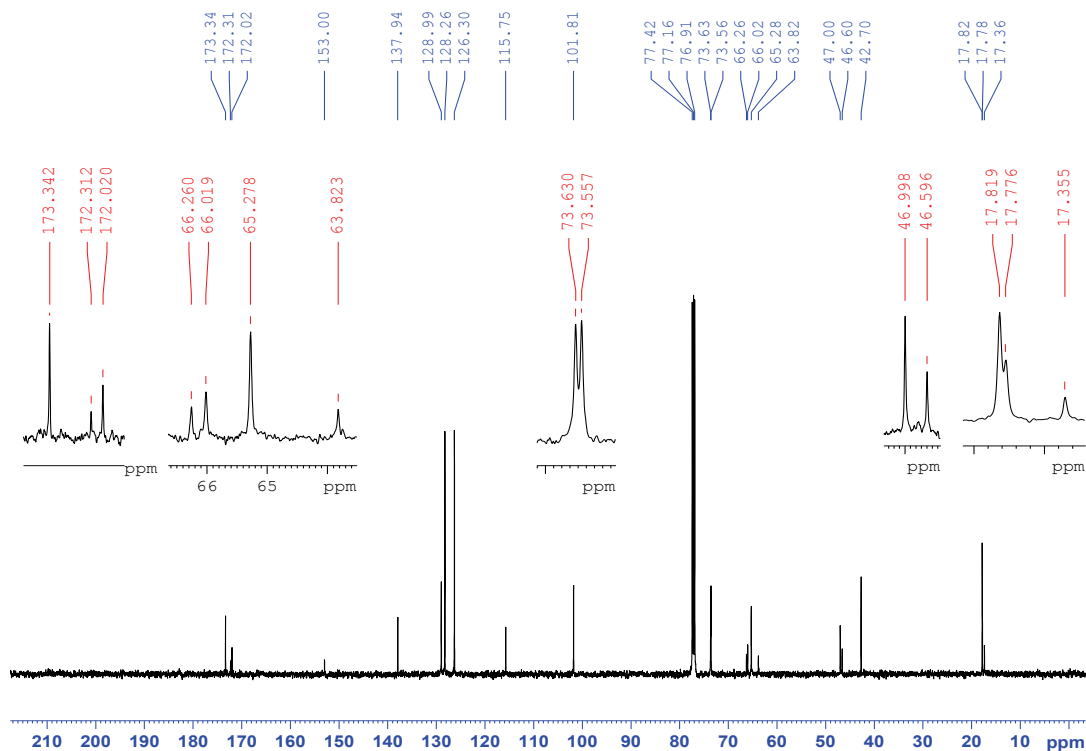
Expansion of part of the 500.13 MHz ^1H NMR spectrum of benzylidene-protected hydroquinone-cored third generation dendrimer (185) in chloroform-*d*



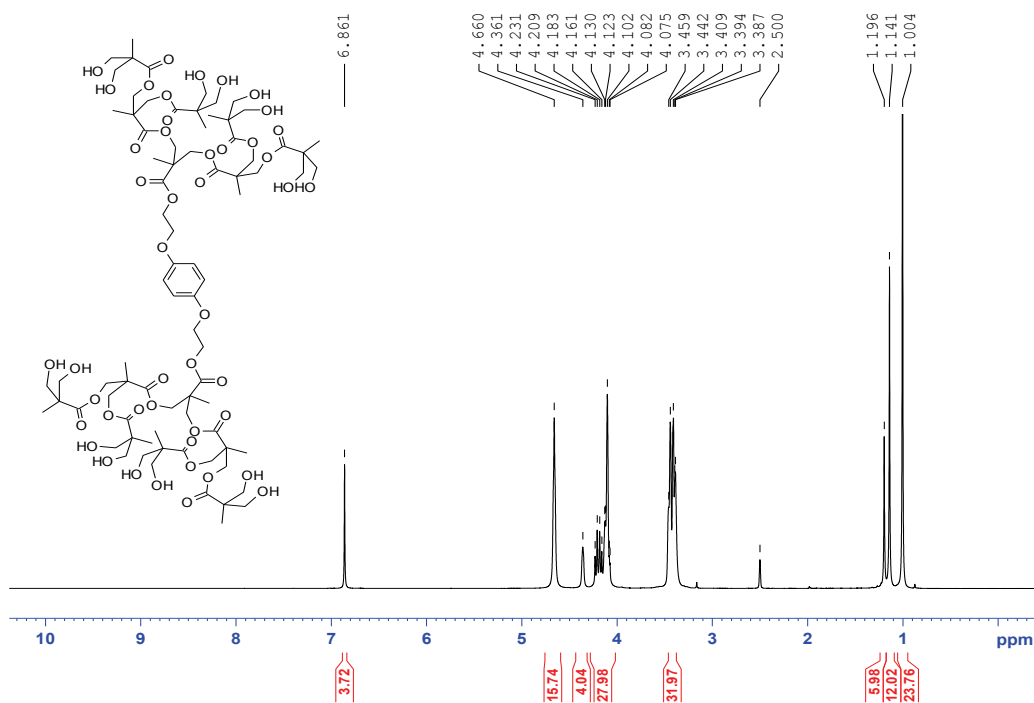
125.7 MHz ^{13}C NMR spectrum of benzylidene-protected hydroquinone-cored third generation dendrimer (185) in chloroform-*d*



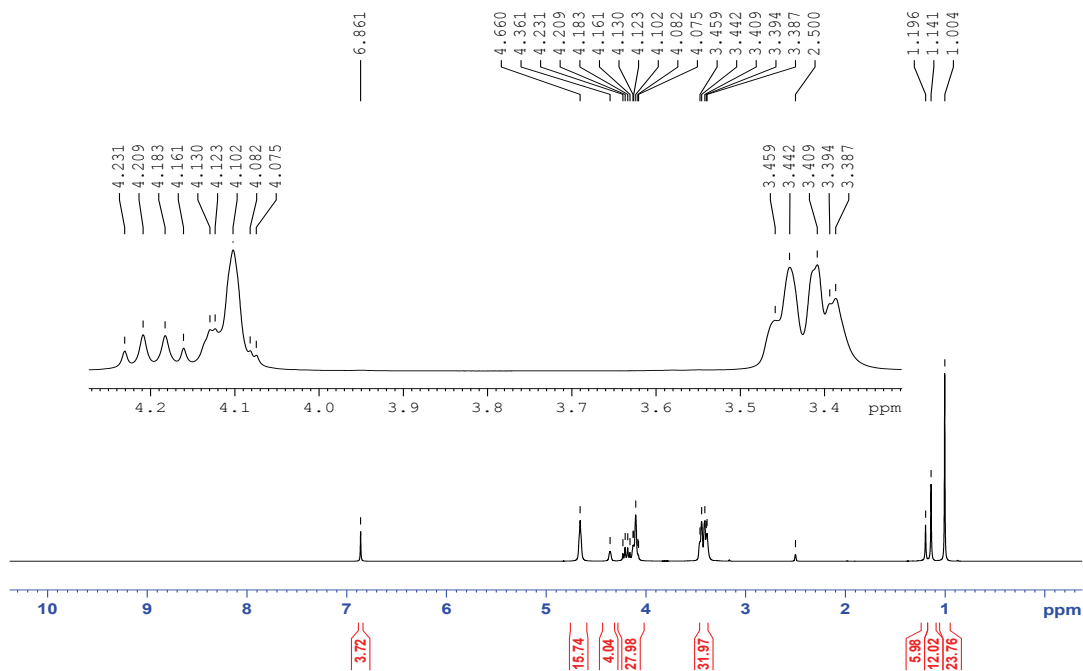
Expansions of parts of the 125.7 MHz ^{13}C NMR spectrum of benzylidene-protected hydroquinone-cored third generation dendrimer (185) in chloroform-*d*



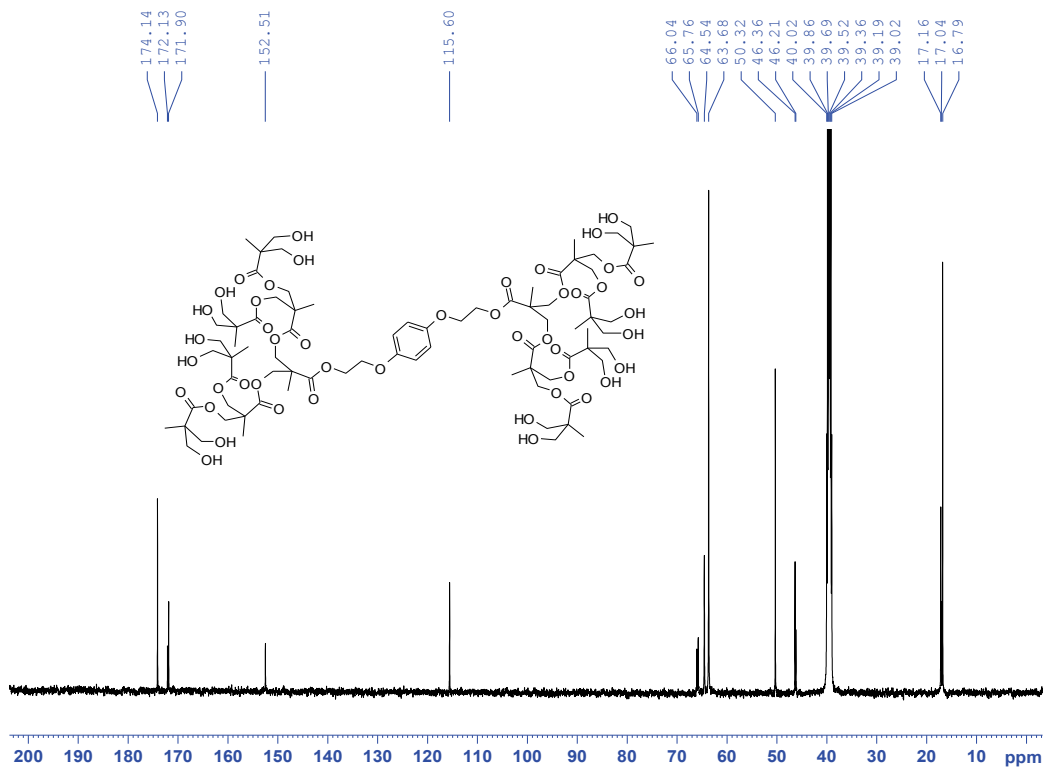
500.13 MHz ^1H NMR spectrum of third generation dendrimer (186) in DMSO-*d*₆



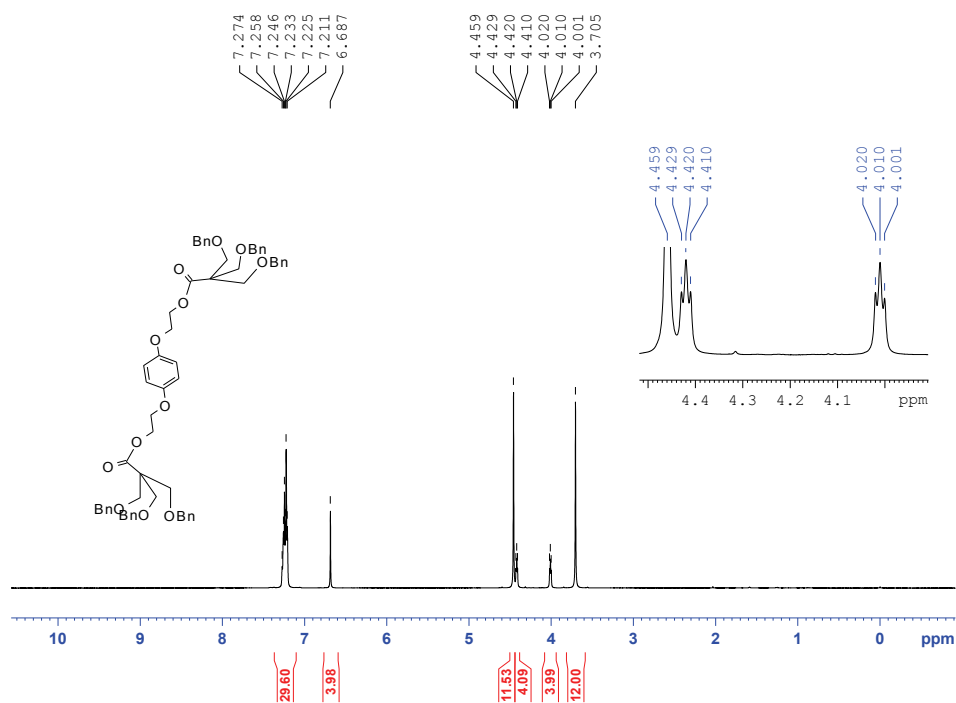
Expansion of part of the 500.13 MHz ^1H NMR spectrum of third generation dendrimer (186) in $\text{DMSO-}d_6$



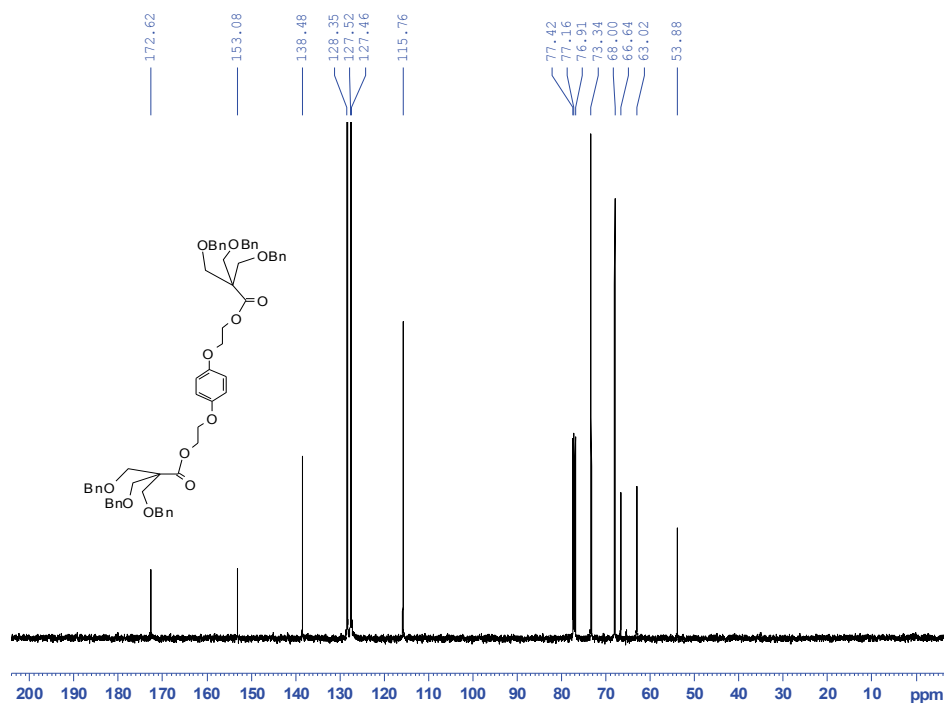
125.7 MHz ^{13}C NMR spectrum of third generation dendrimer (186) in $\text{DMSO-}d_6$



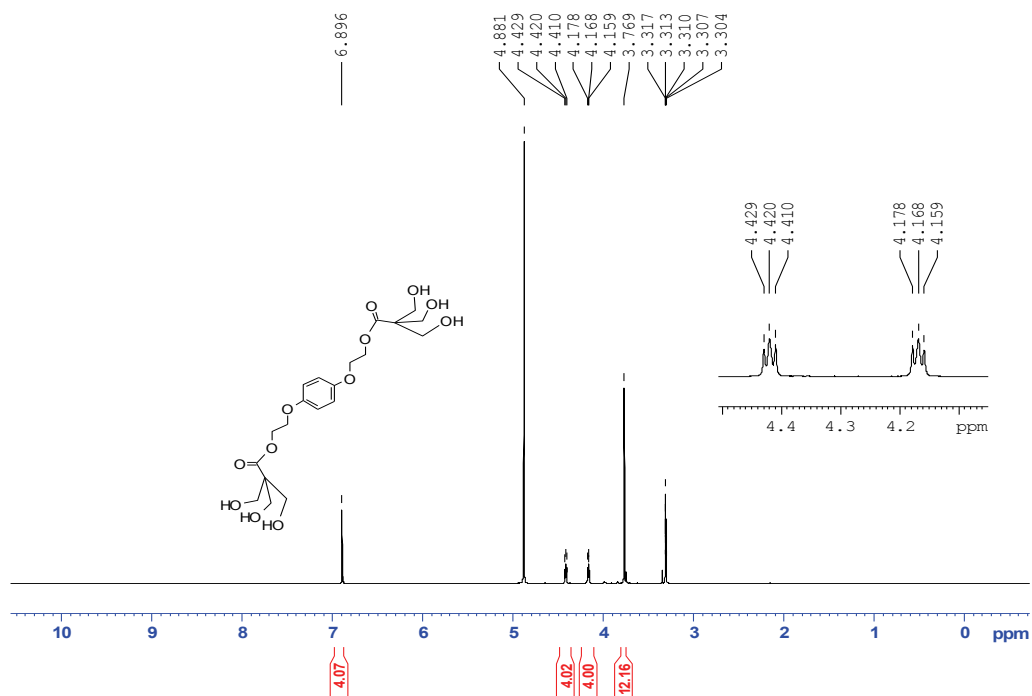
500.13 MHz ^1H NMR spectrum of benzyl-protected tribranched first generation dendrimer (187) in chloroform-*d*



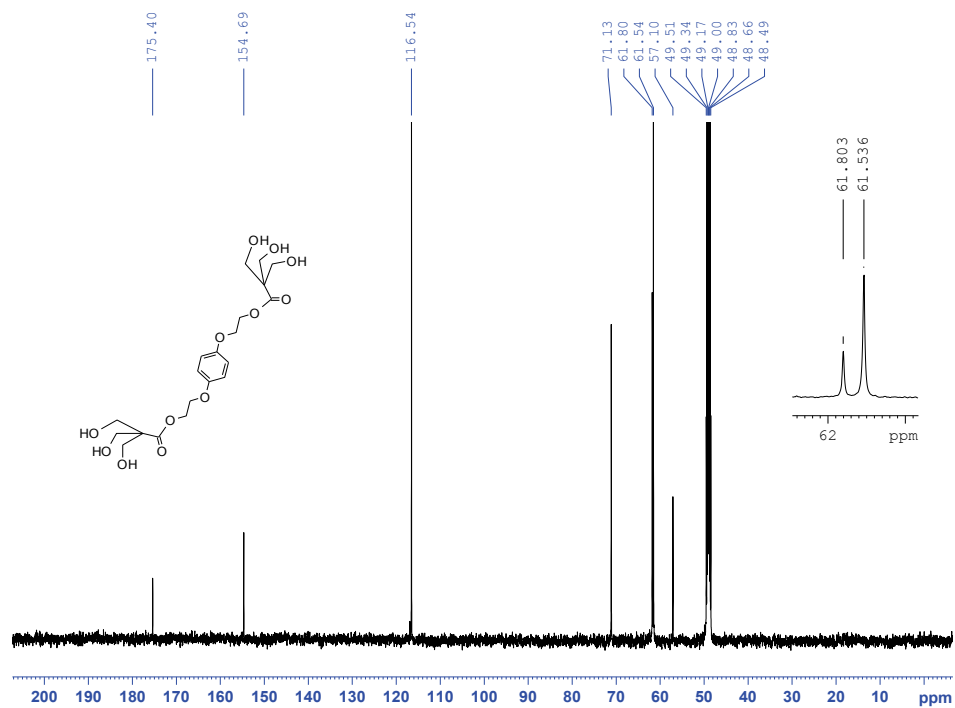
125.7 MHz ^{13}C NMR spectrum of benzyl-protected tribranched first generation dendrimer (187) in chloroform-*d*



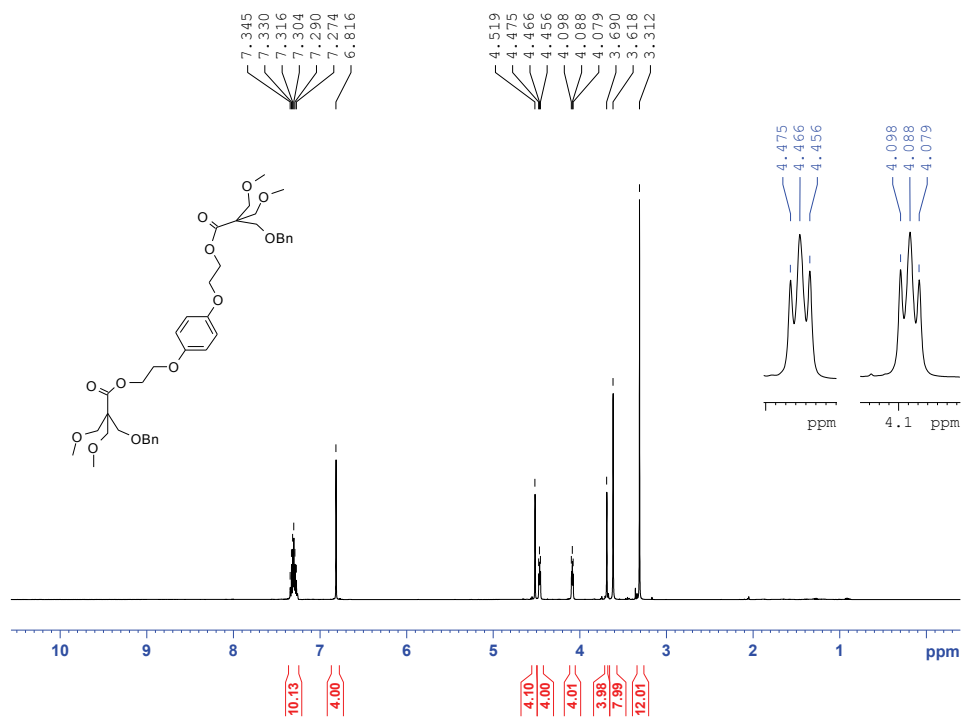
500.13 MHz ^1H NMR spectrum of tribranched first generation dendrimer (188) in methanol- d_4



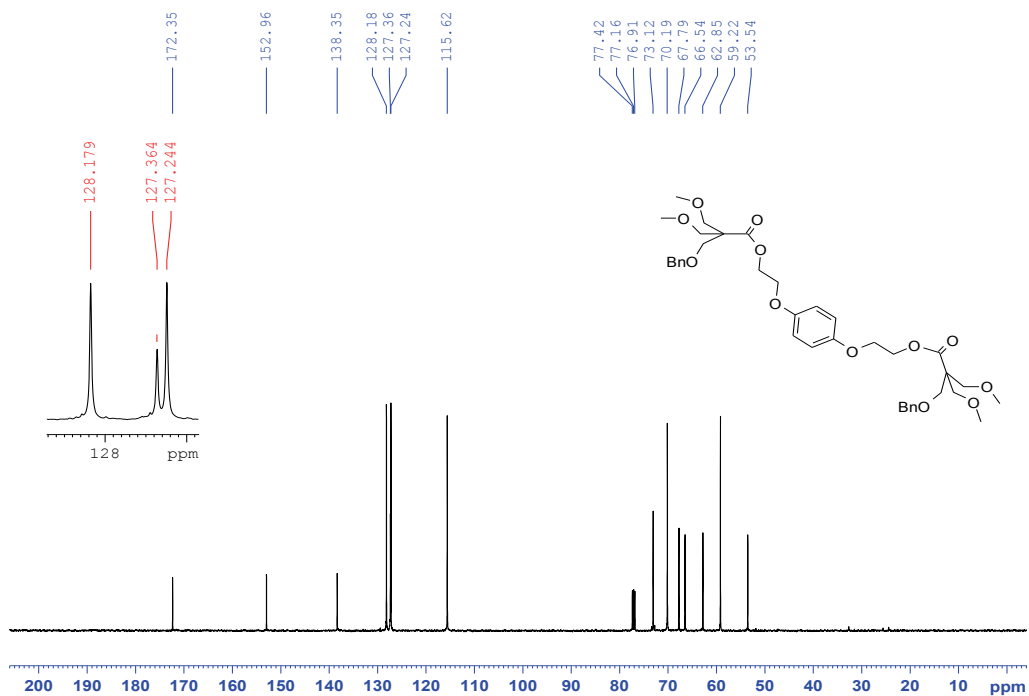
125.7 MHz ^{13}C NMR spectrum of tribranched first generation dendrimer (188) in methanol- d_4



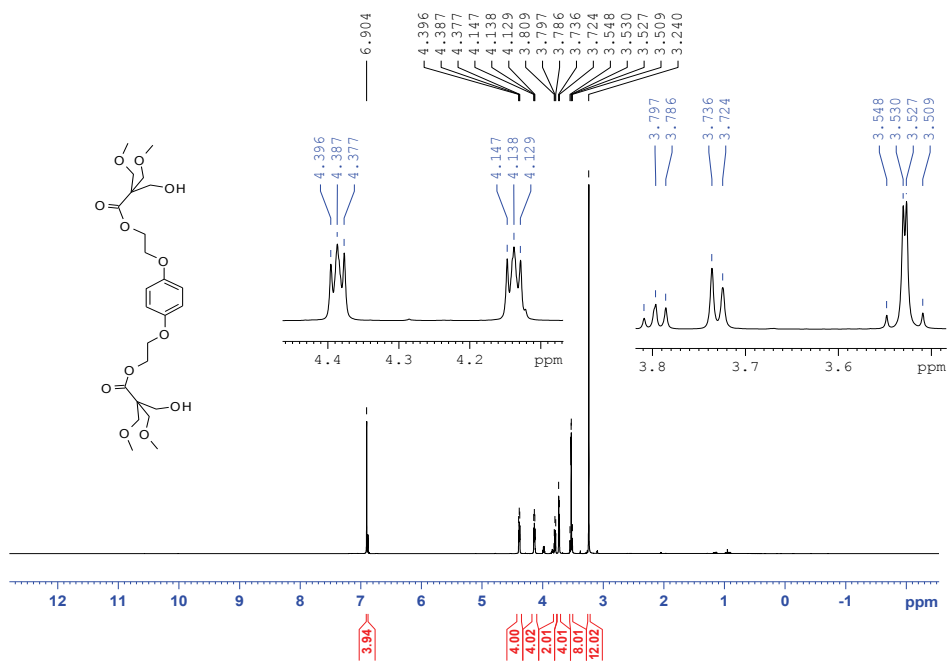
500.13 MHz ^1H NMR spectrum of methyl and benzyl-protected hydroquinone-cored first generation dendrimer (189) in chloroform-*d*



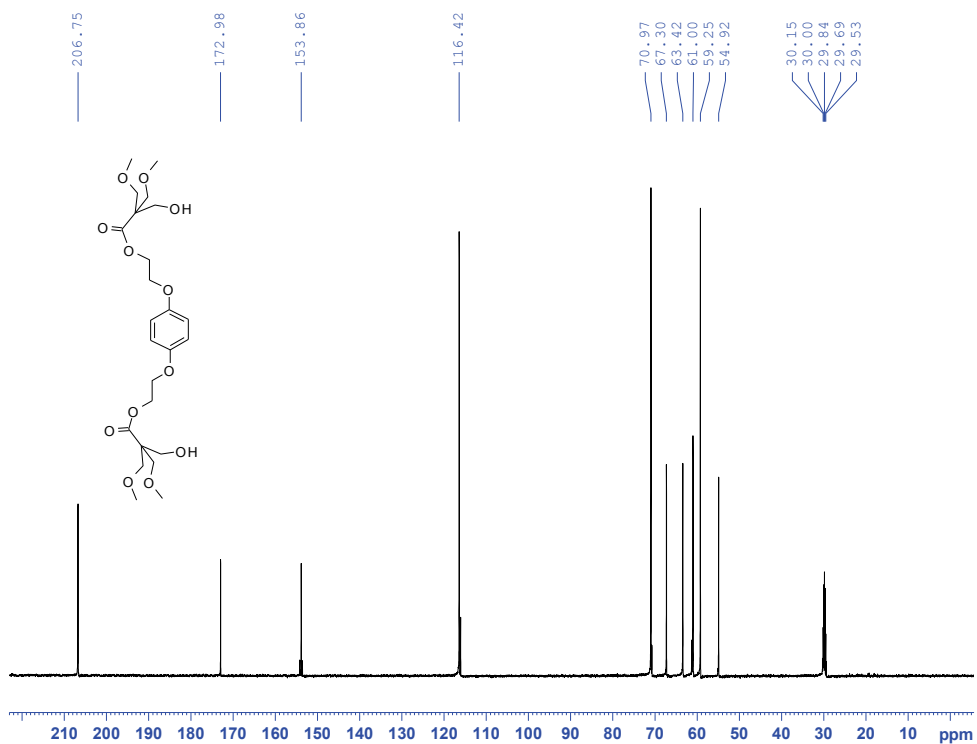
125.7 MHz ^{13}C NMR spectrum of methyl and benzyl-protected hydroquinone-cored first generation dendrimer (189) in chloroform-*d*



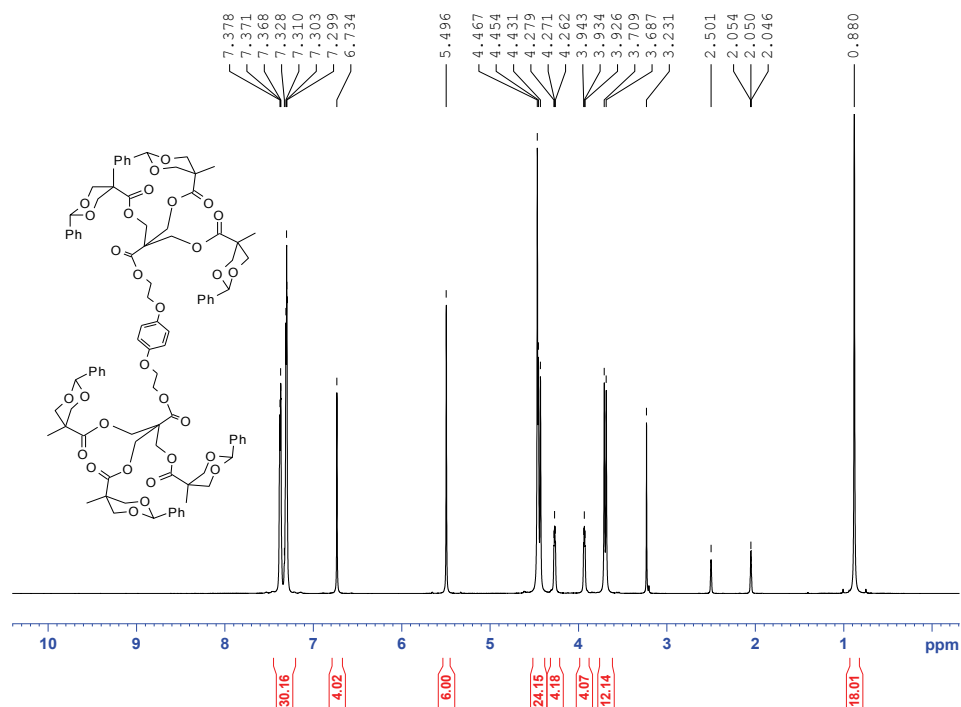
500.13 MHz ^1H NMR spectrum of hydroquinone-cored first generation dendrimer (190) in acetone- d_6



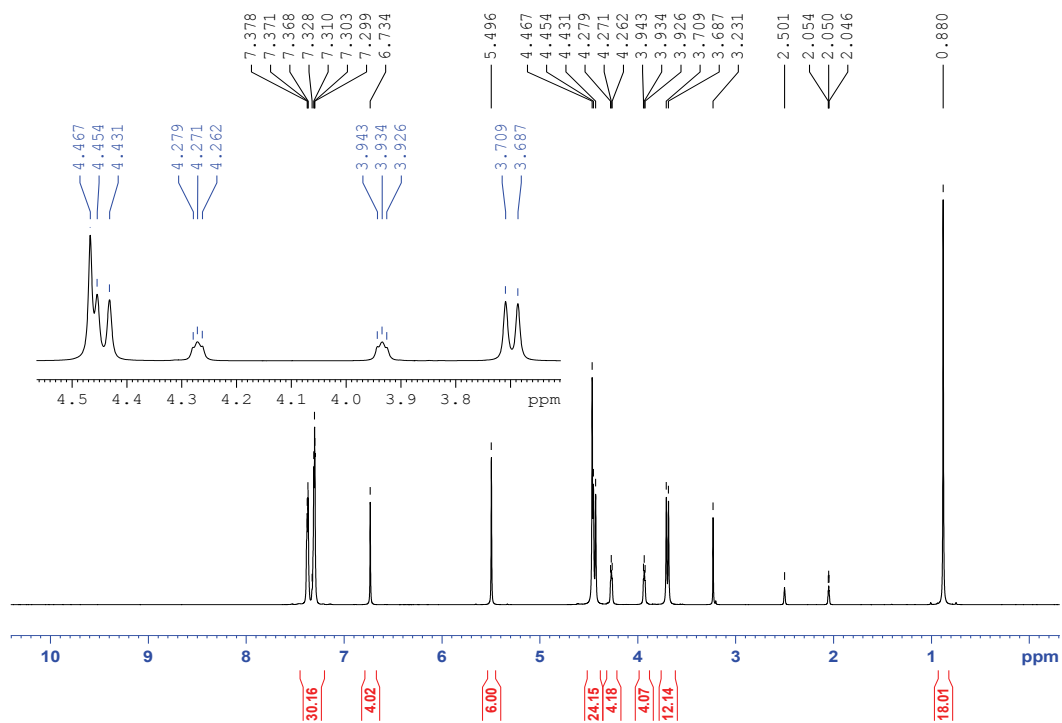
500.13 MHz ^1H NMR spectrum of hydroquinone-cored first generation dendrimer (190) in acetone- d_6



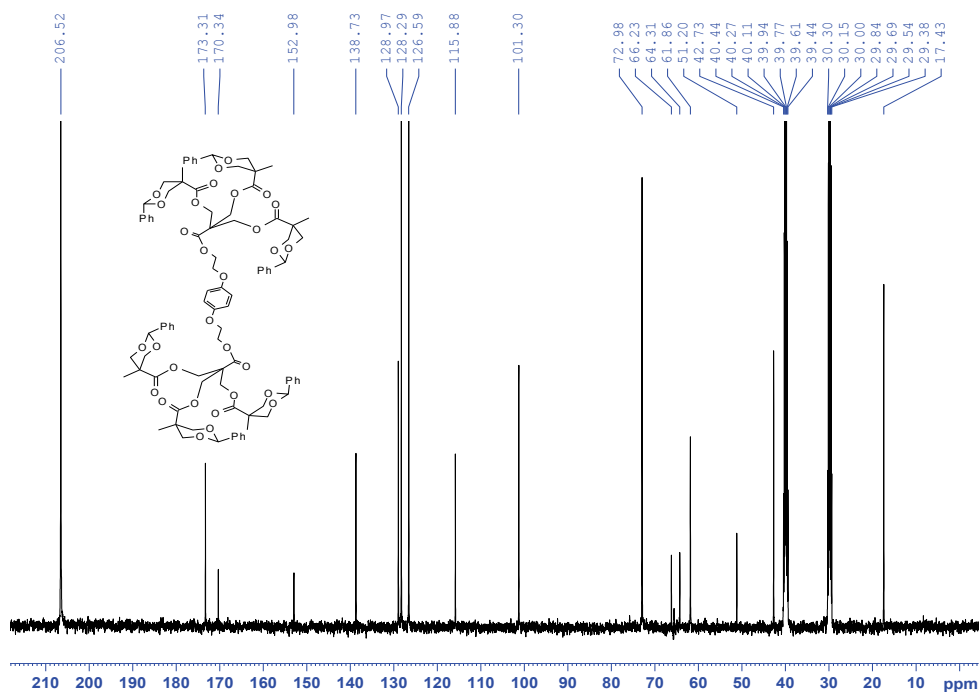
500.13 MHz ^1H NMR spectrum of benzylidene-protected second generation dendrimer with mixed branching (141) in acetone- d_6 / DMSO- d_6



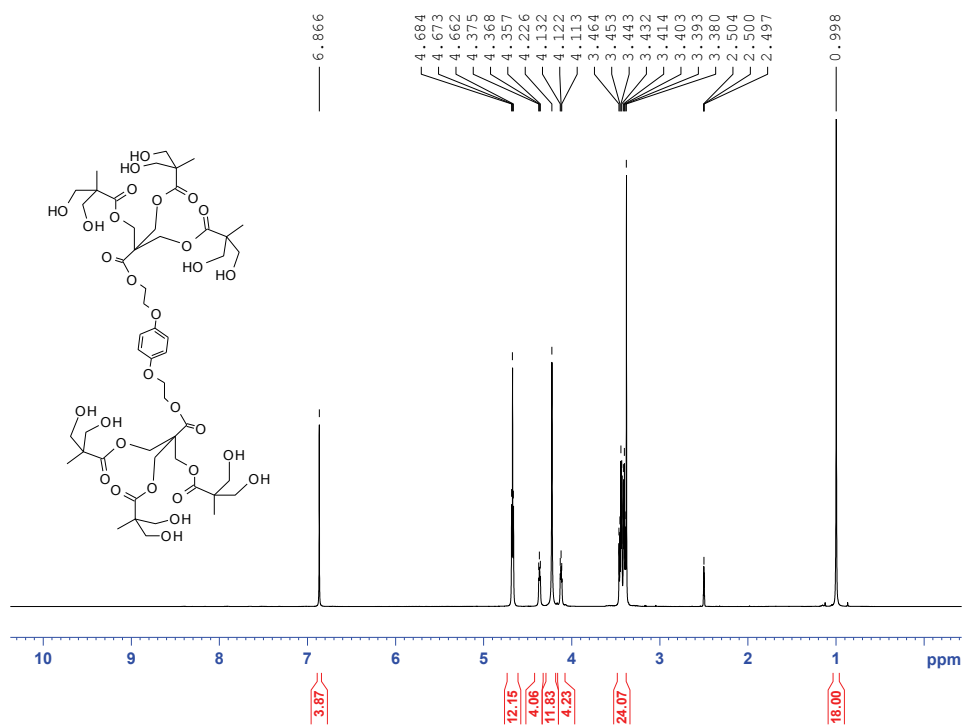
Expansion of part of the 500.13 MHz ^1H NMR spectrum of benzylidene-protected second generation dendrimer with mixed branching (141) in acetone- d_6 / DMSO- d_6



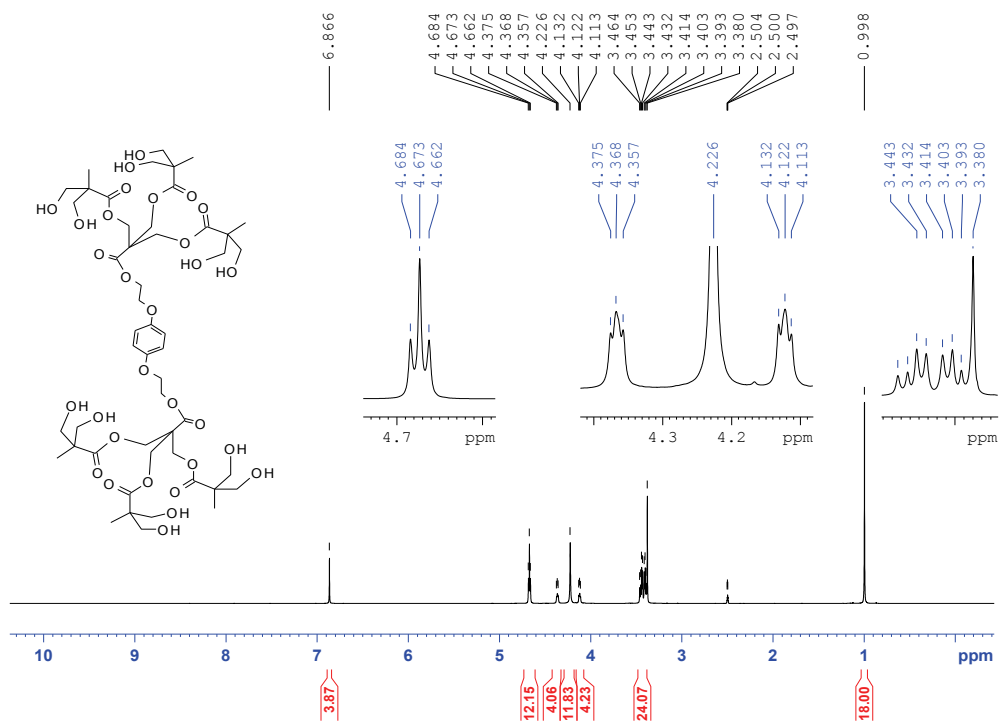
125.7 MHz ^{13}C NMR spectrum of benzylidene-protected second generation dendrimer with mixed branching (141) in acetone- d_6 / DMSO- d_6



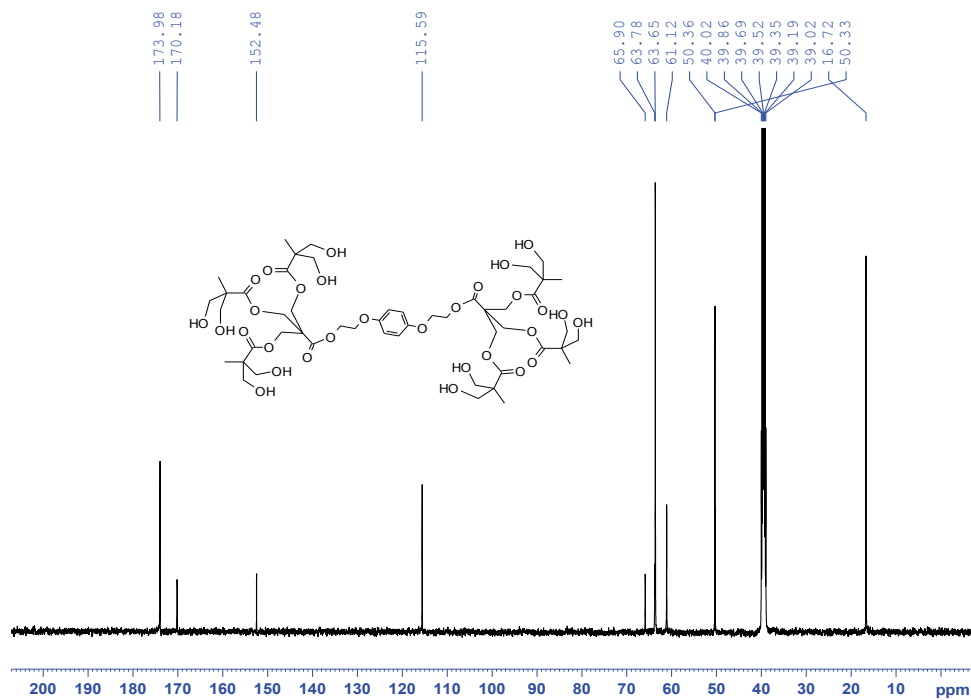
500.13 MHz ^1H NMR spectrum of second generation dendrimer with mixed branching (191) in DMSO- d_6



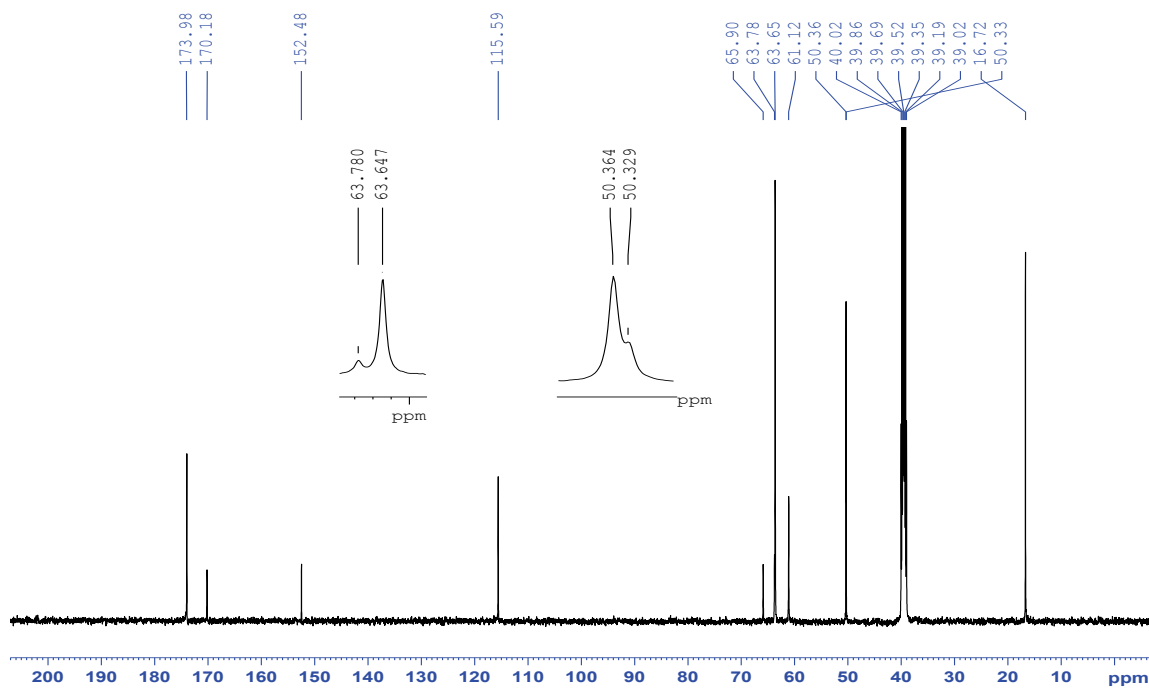
Expansions of parts of the the 500.13 MHz ^1H NMR spectrum of second generation dendrimer with mixed branching (191) in $\text{DMSO-}d_6$



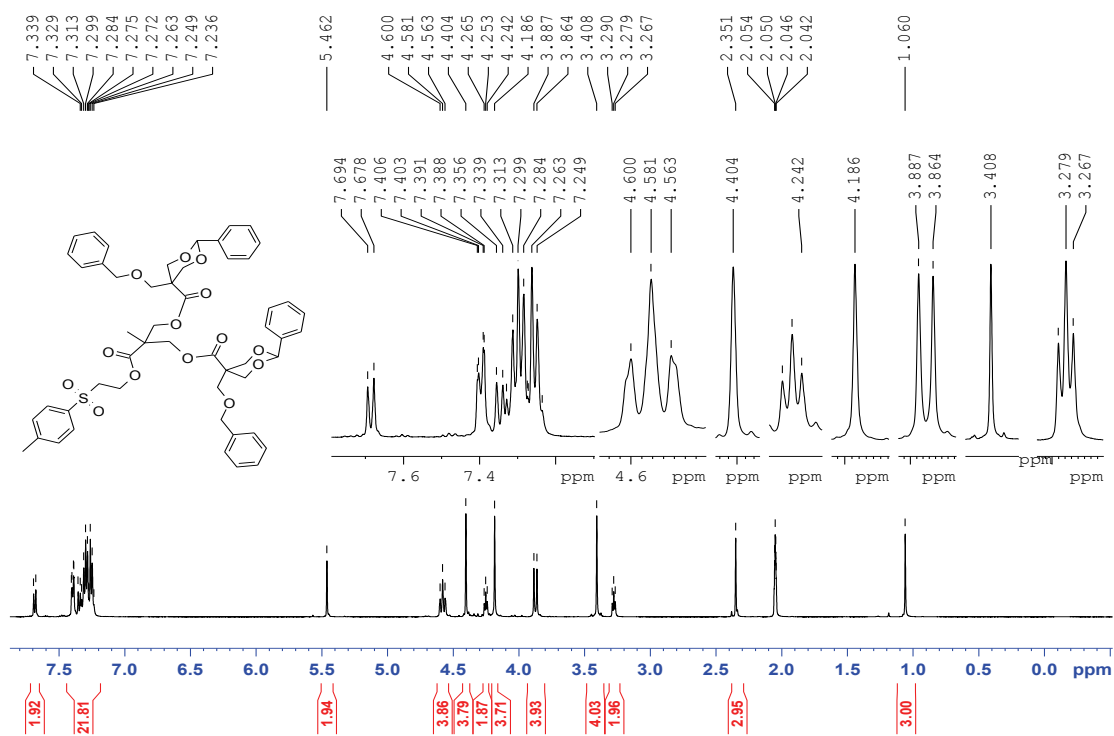
125.7 MHz ^{13}C NMR spectrum of second generation dendrimer with mixed branching (191) in $\text{DMSO-}d_6$



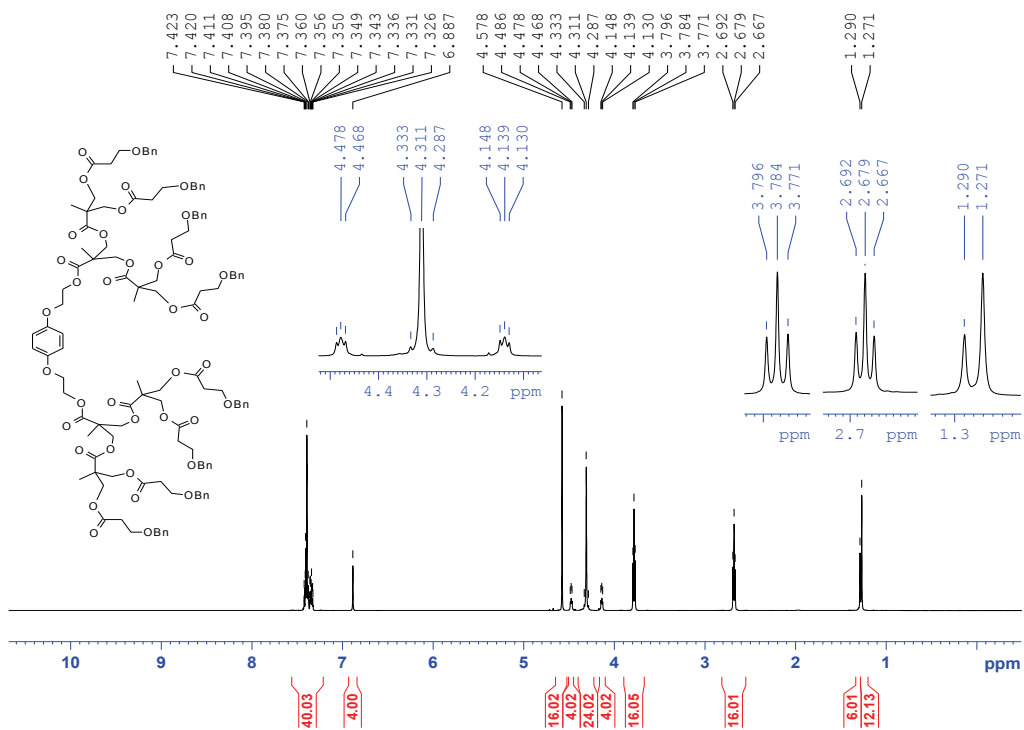
Expansion of parts of the 125.7 MHz ^{13}C NMR spectrum of second generation dendrimer with mixed branching (191) in $\text{DMSO-}d_6$



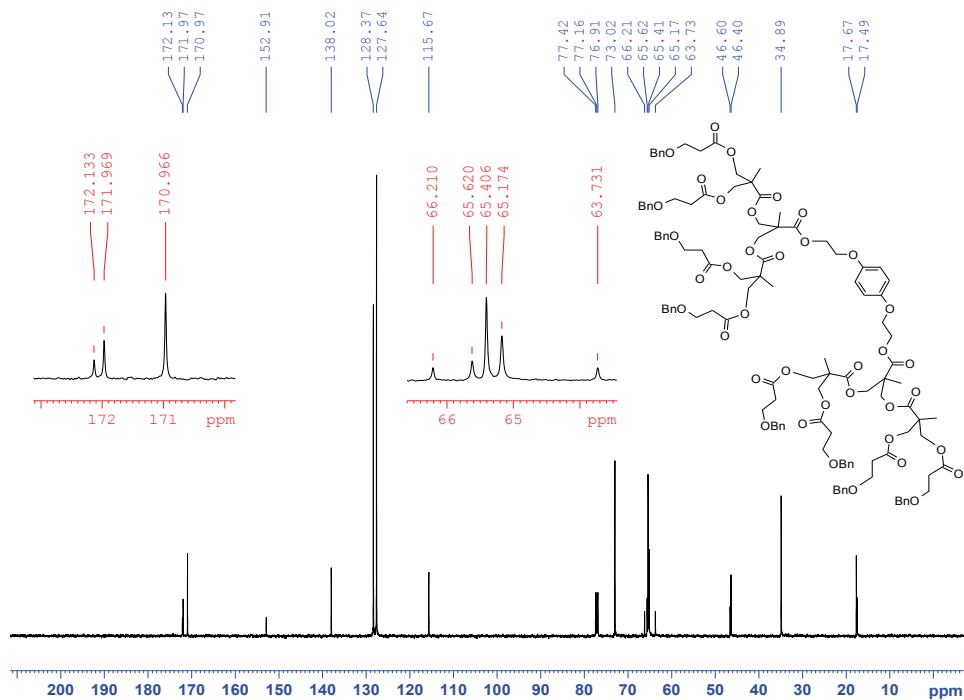
500.13 MHz ^1H NMR spectrum of protected second generation dendron with mixed branching (193) in $\text{acetone-}d_6$



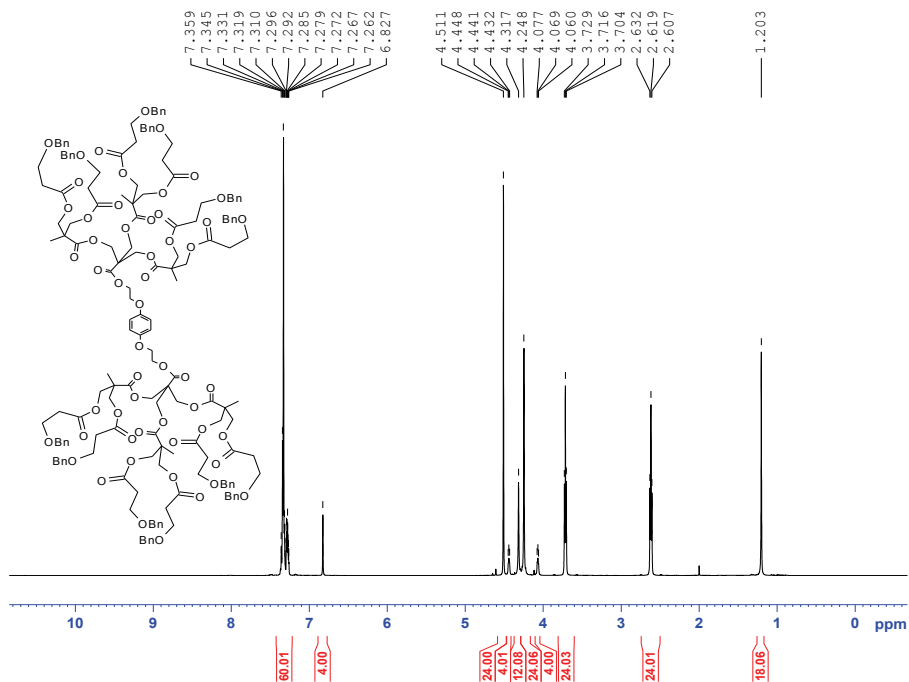
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of benzyl-functionalized hydroquinone-cored second generation dendrimer (195) in chloroform-*d*



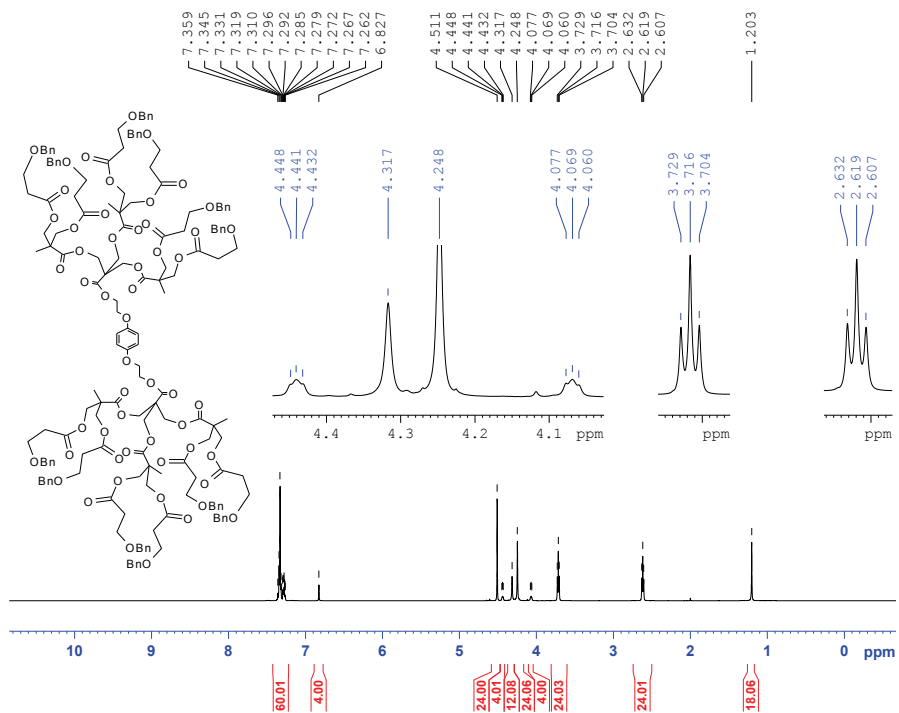
125.7 MHz ^{13}C NMR spectrum of benzyl-functionalized hydroquinone-cored second generation dendrimer (195) in chloroform-*d*



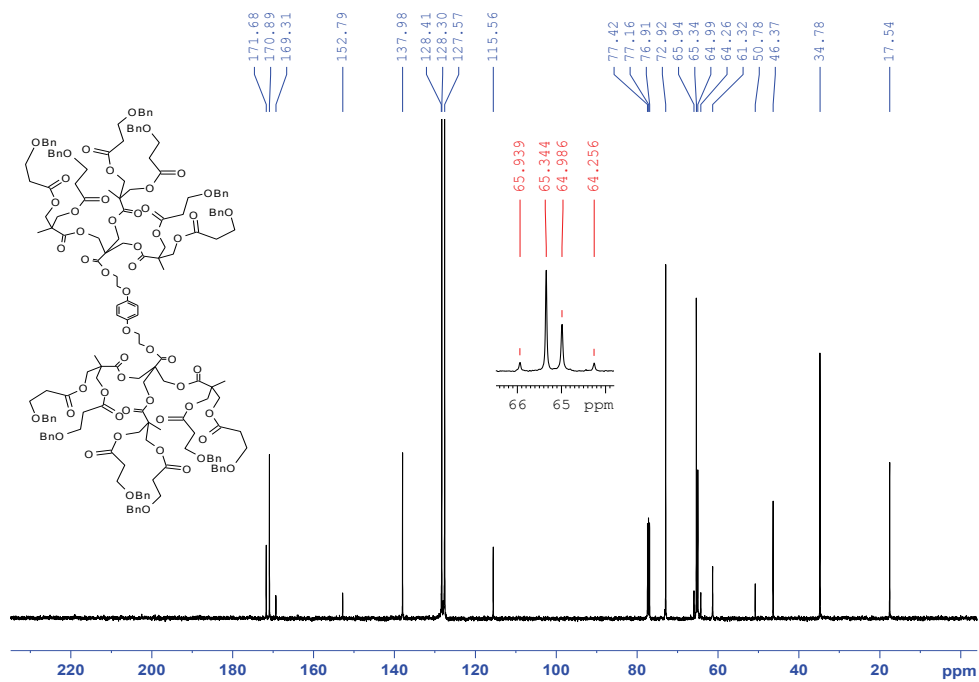
500.13 MHz ^1H NMR spectrum of benzyl-functionalized hydroquinone-cored second generation dendrimer with mixed branching (196) in chloroform-*d*



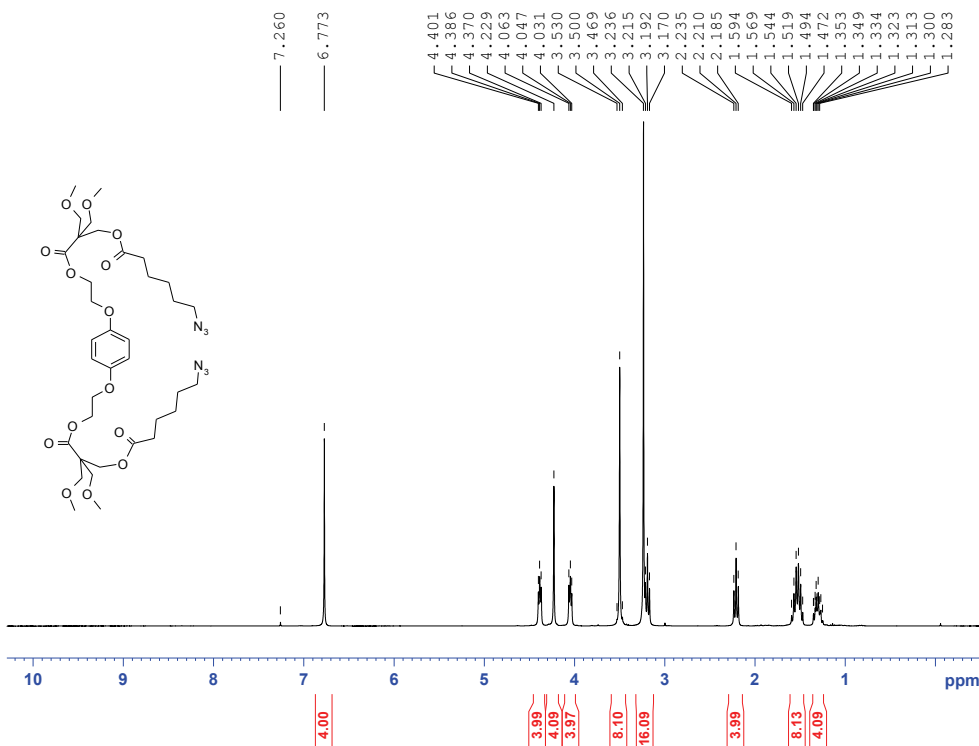
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of benzyl-functionalized hydroquinone-cored second generation dendrimer with mixed branching (196) in chloroform-*d*



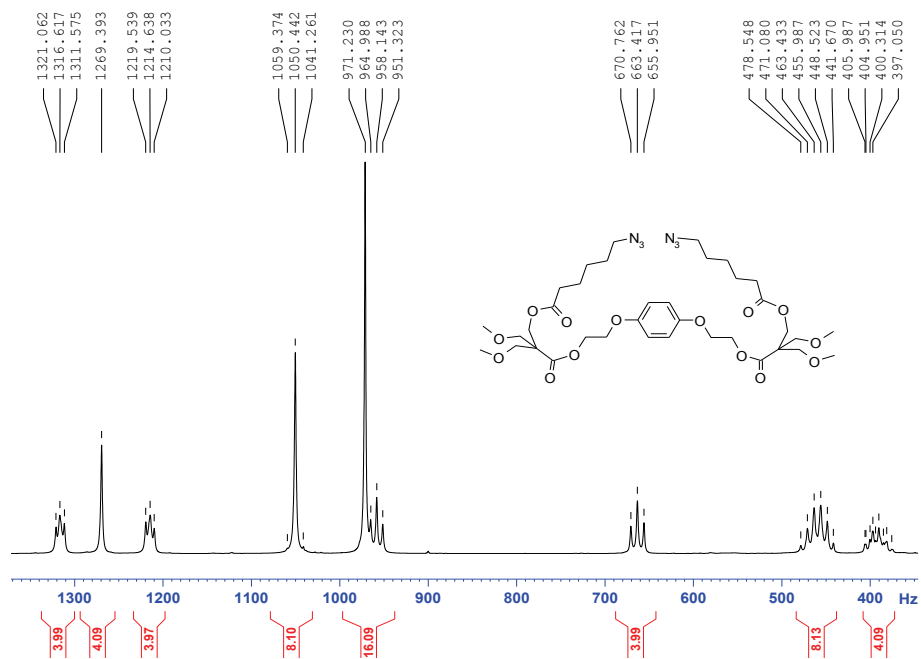
125.7 MHz ^{13}C NMR spectrum of benzyl-functionalized hydroquinone-cored second generation dendrimer (196) in chloroform-*d*



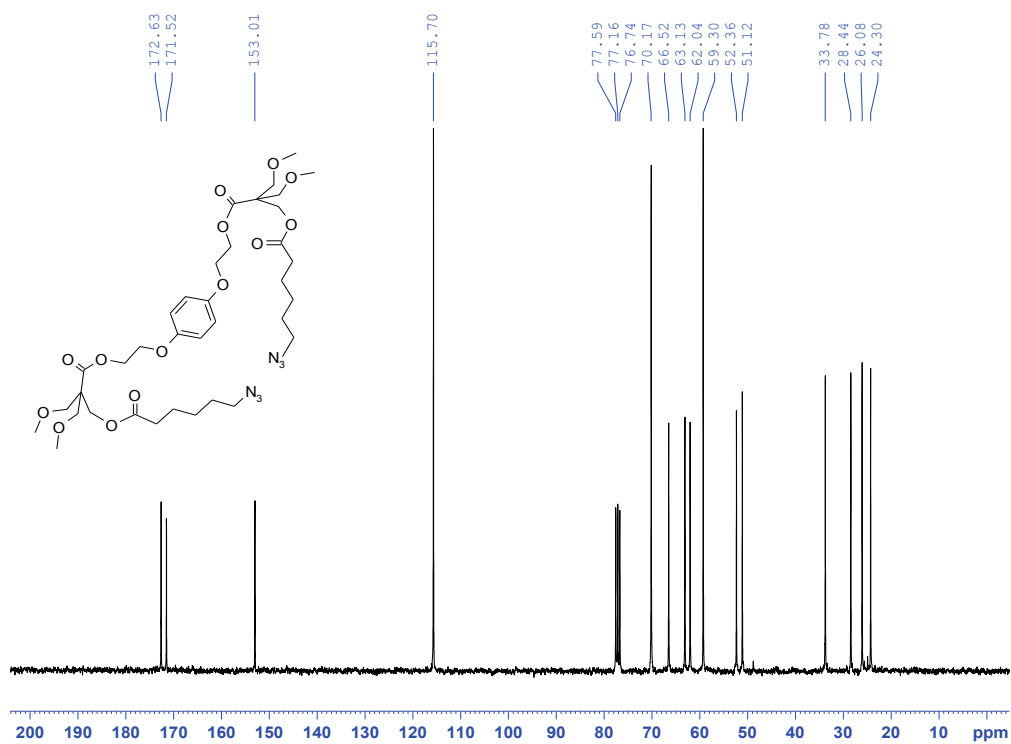
300.15 MHz ^1H NMR spectrum of azide-functionalized divalent first generation dendrimer (204) in chloroform-*d*



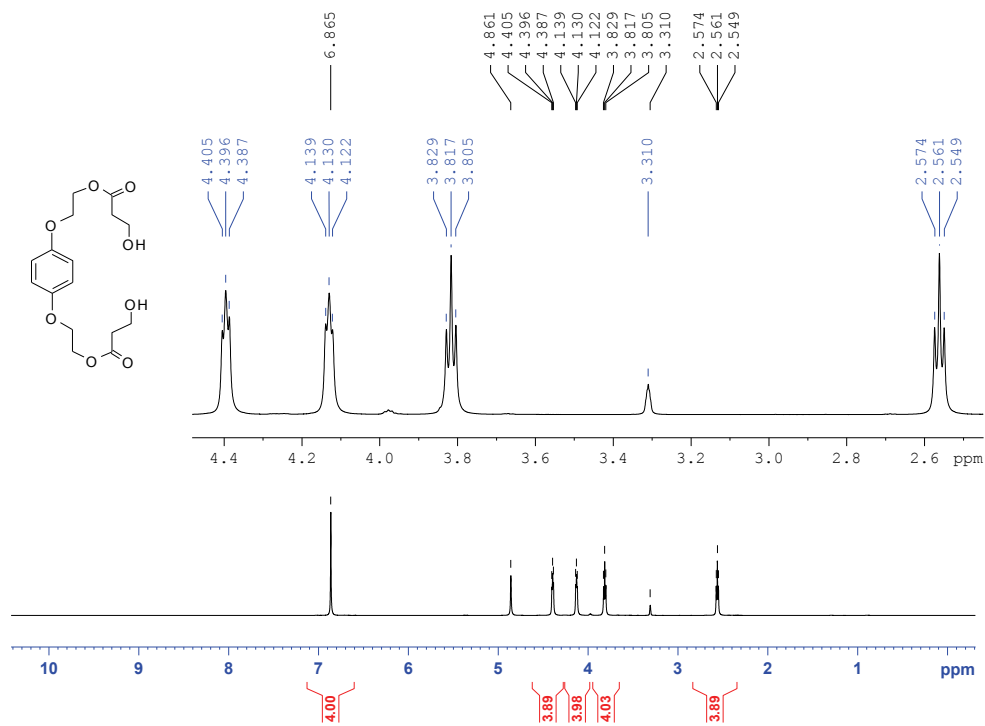
Expansion of part of the 300.15 MHz ^1H NMR spectrum of azide-functionalized divalent first generation dendrimer (204) in chloroform-*d*



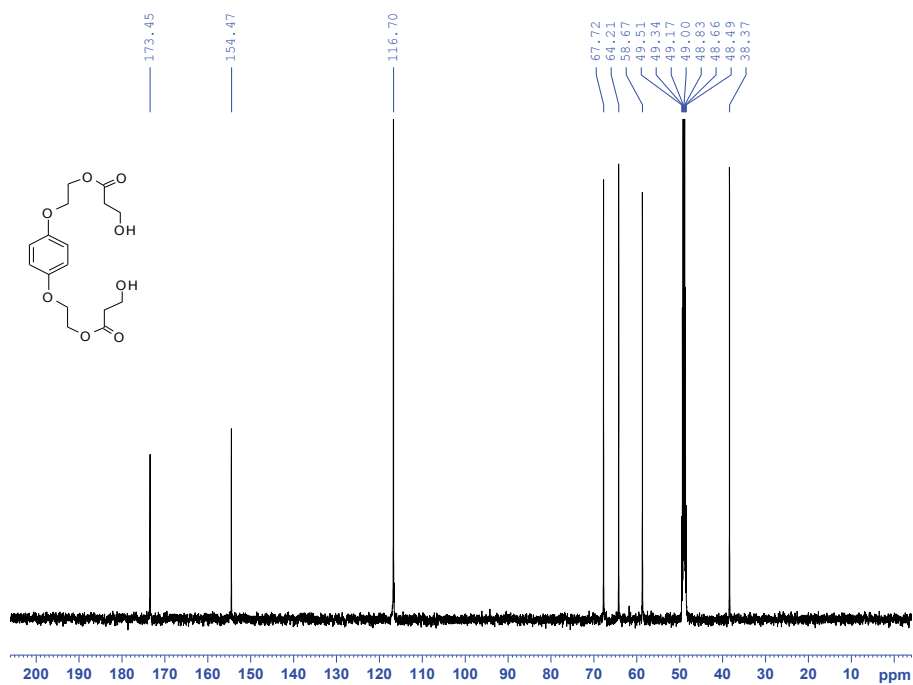
75.5 MHz ^{13}C NMR spectrum of azide-functionalized divalent first generation dendrimer (204) in chloroform-*d*



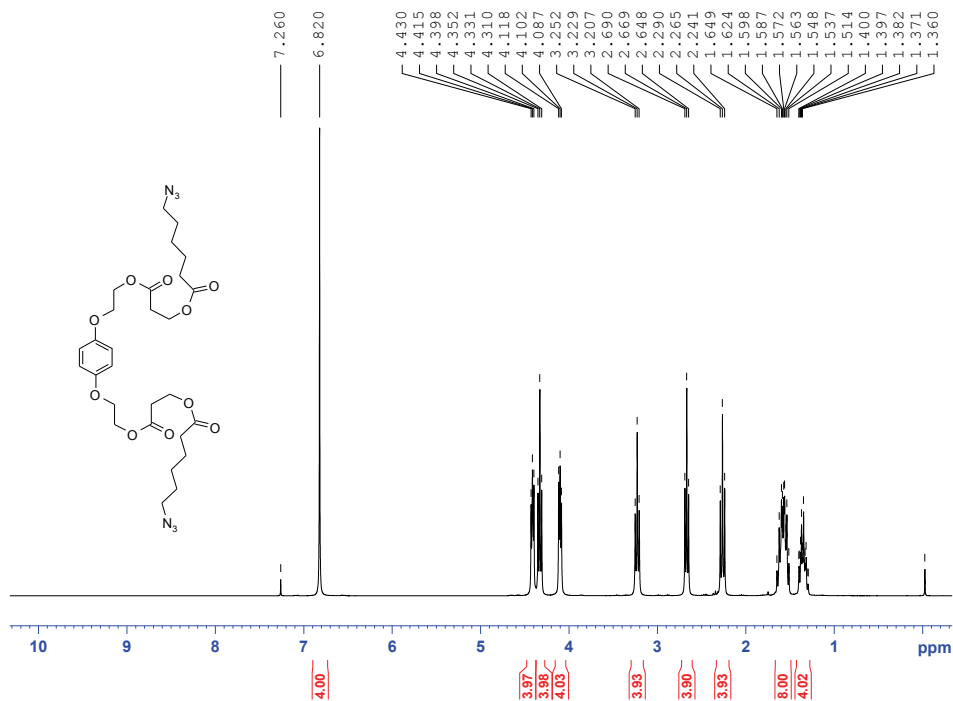
Expansion of part of the 500.13 MHz ^1H NMR spectrum of hydroxyl-terminated divalent dendrimer (206) in methanol- d_4



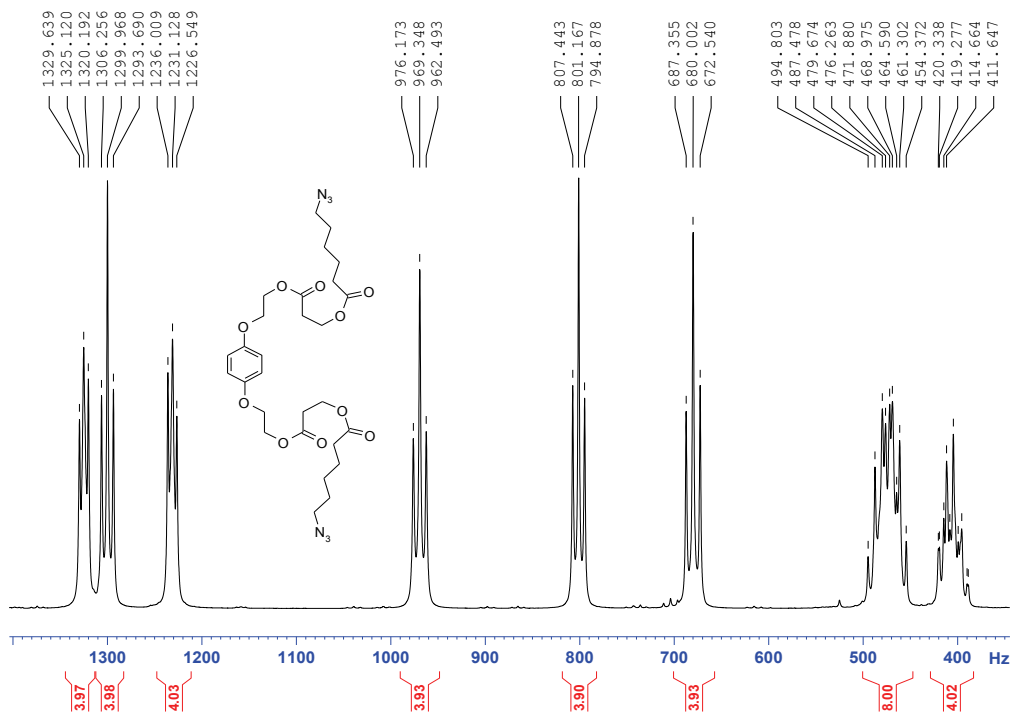
125.7 MHz ^{13}C NMR spectrum of hydroxyl-terminated divalent dendrimer (206) in methanol- d_4



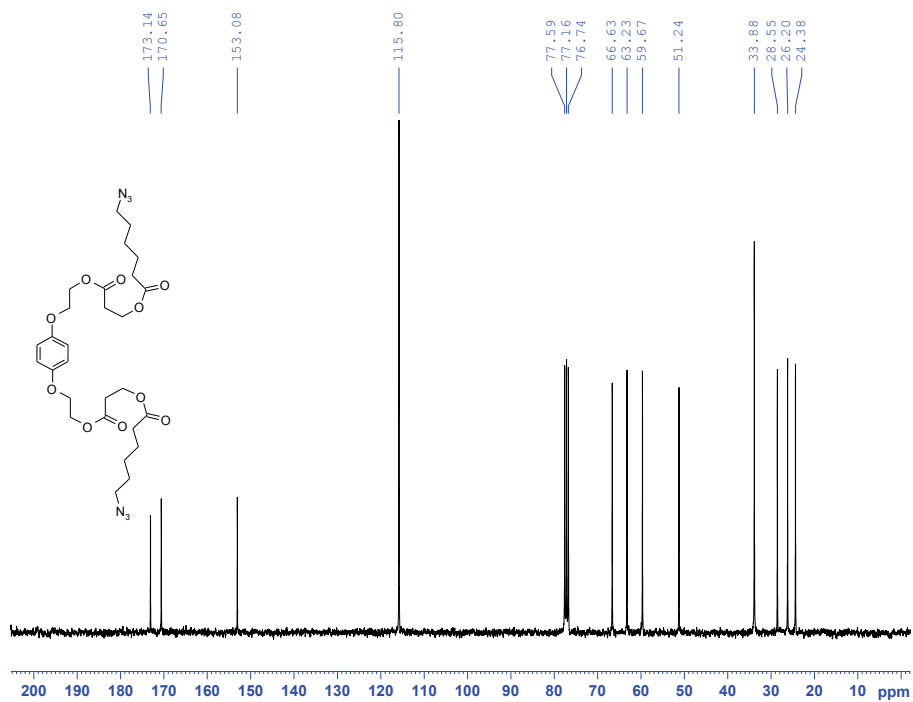
300.15 MHz ^1H NMR spectrum of azide-functionalized divalent dendrimer (207) in chloroform-*d*



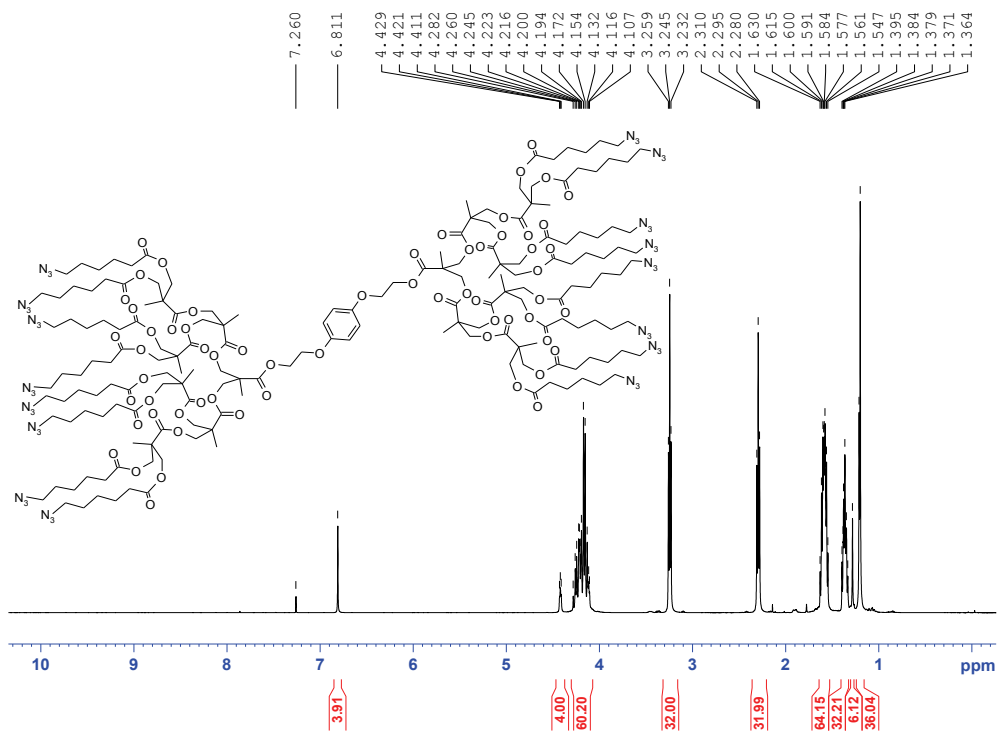
Expansion of part of the 300.15 MHz ^1H NMR spectrum of azide-functionalized divalent dendrimer (207) in chloroform-*d*



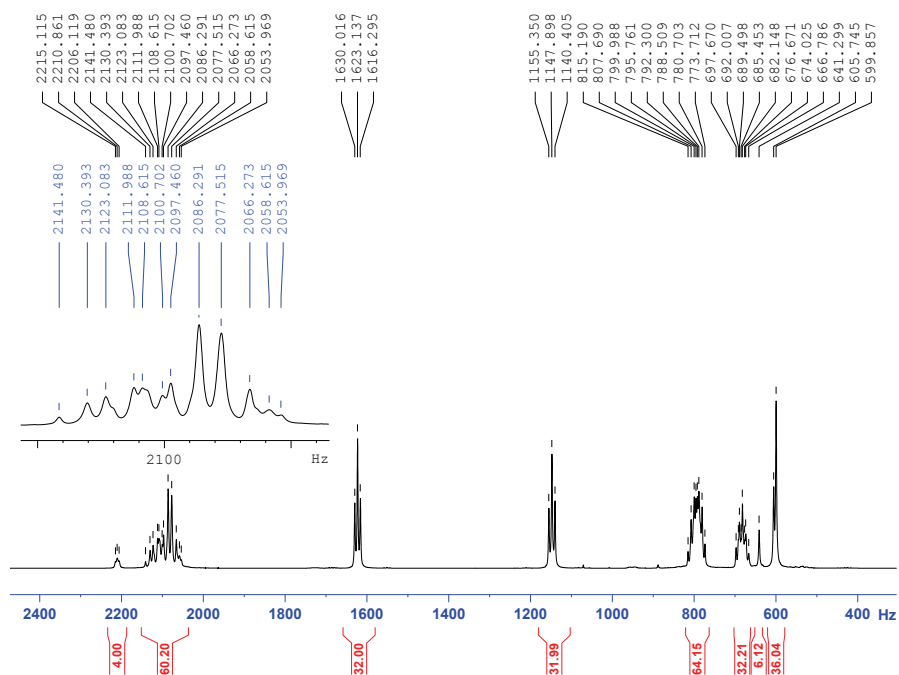
75.5 ^{13}C NMR spectrum of azide-functionalized divalent dendrimer (207) in chloroform-*d*



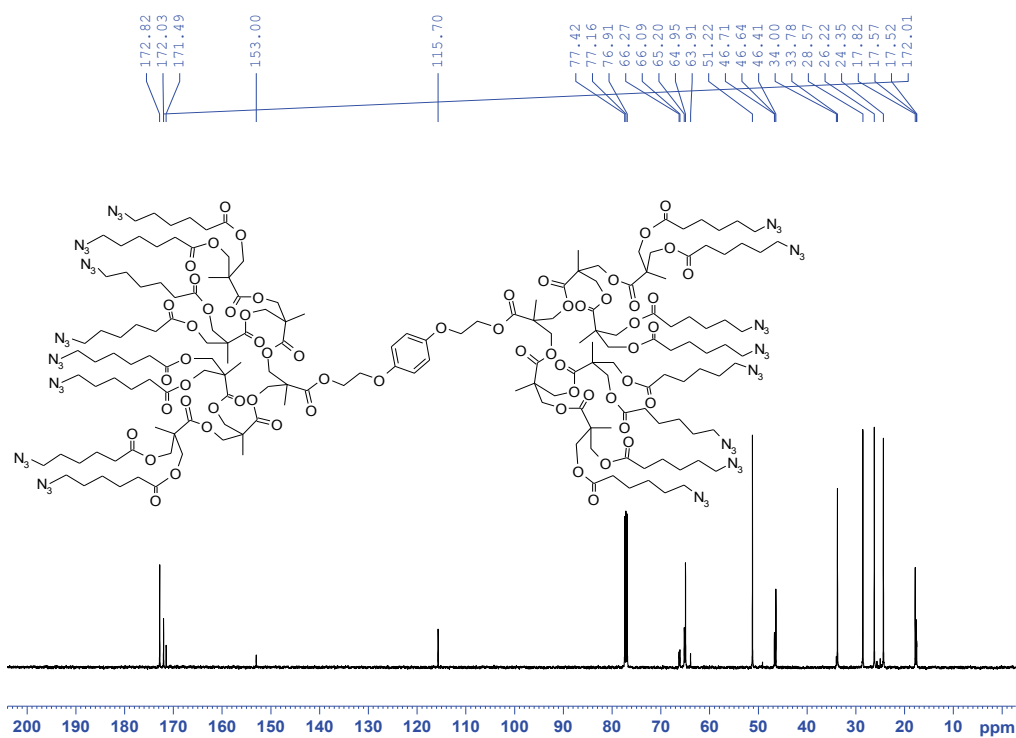
500.13 MHz ^1H NMR spectrum of azide-functionalized hydroquinone-cored third generation dendrimer (208) in chloroform-*d*



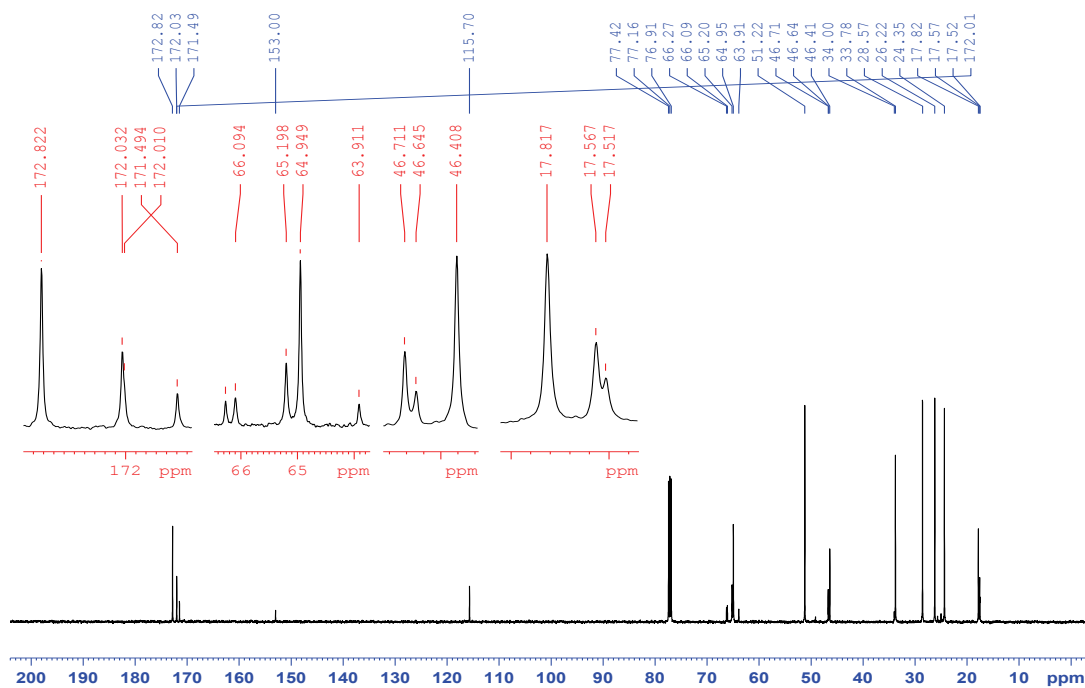
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of azide-functionalized hydroquinone-cored third generation dendrimer (208) in chloroform-*d*



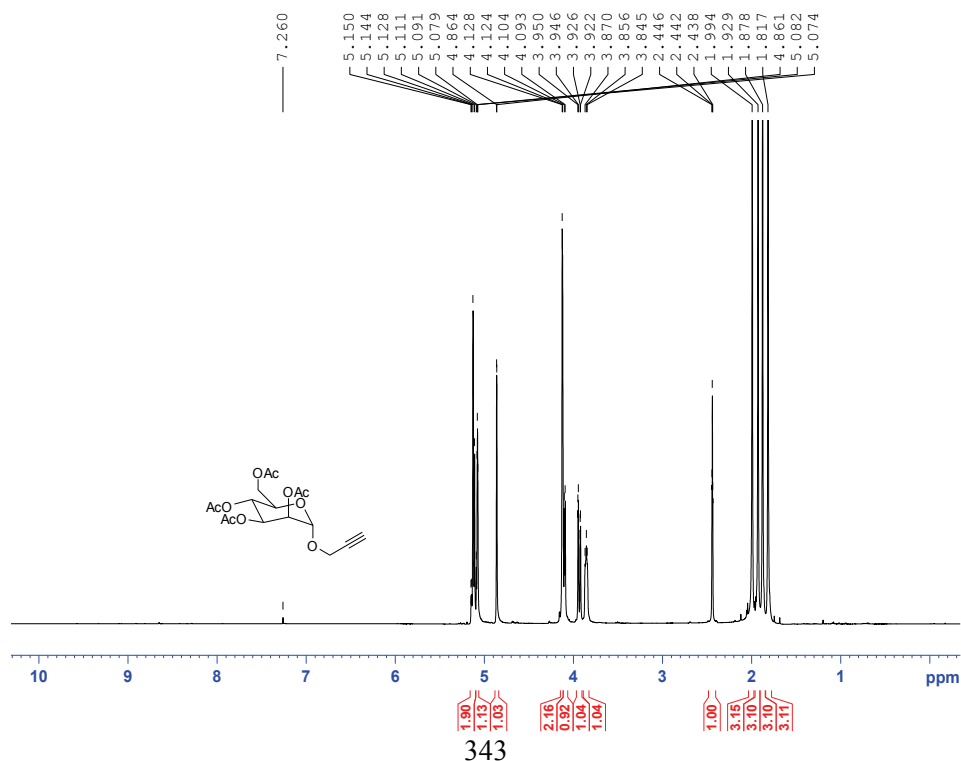
125.7 MHz ^{13}C NMR spectrum of azide-functionalized hydroquinone-cored third generation dendrimer (208) in chloroform-*d*



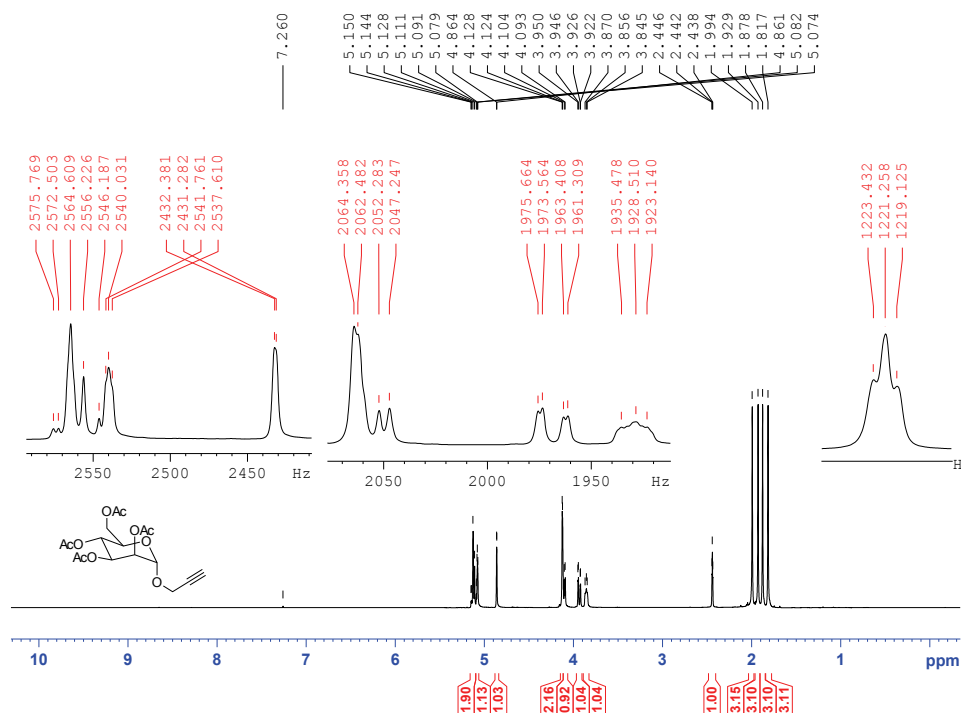
Expansions of the 125.7 MHz ^{13}C NMR spectrum of azide-functionalized hydroquinone-cored third generation dendrimer (208) in chloroform-*d*



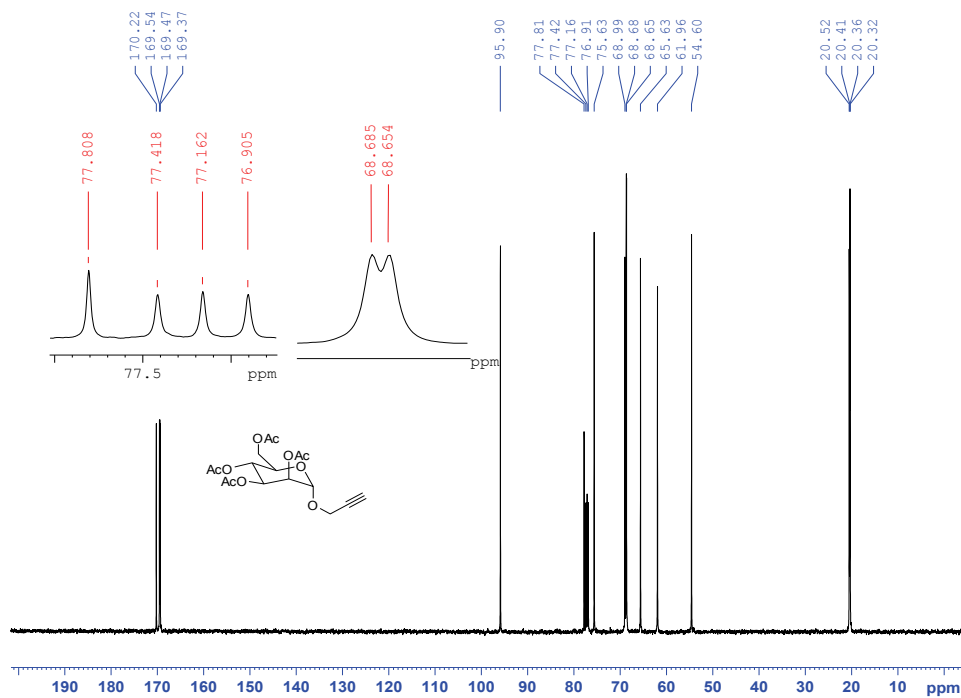
500.13 MHz ^1H NMR spectrum of 2-propynyl 2,3,4,6-tetra-*O*-acetyl- α -D-mannopyranoside in chloroform-*d*



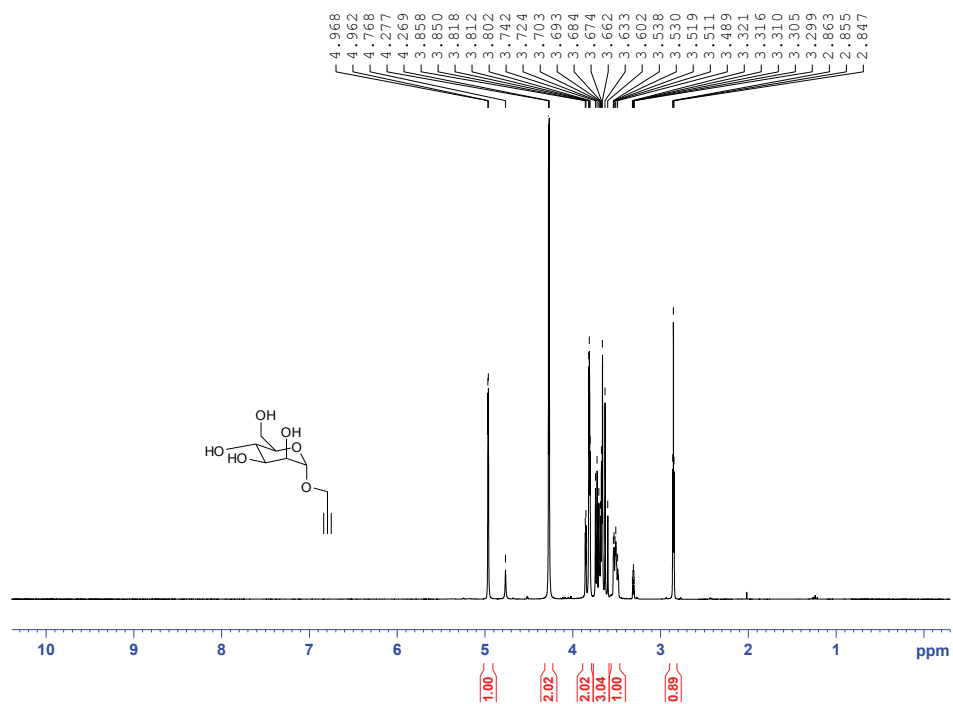
Expansions of parts of the 500.13 MHz ^1H NMR spectrum of 2-propynyl 2,3,4,6-tetra-*O*-acetyl- α -D-mannopyranoside in chloroform-*d*



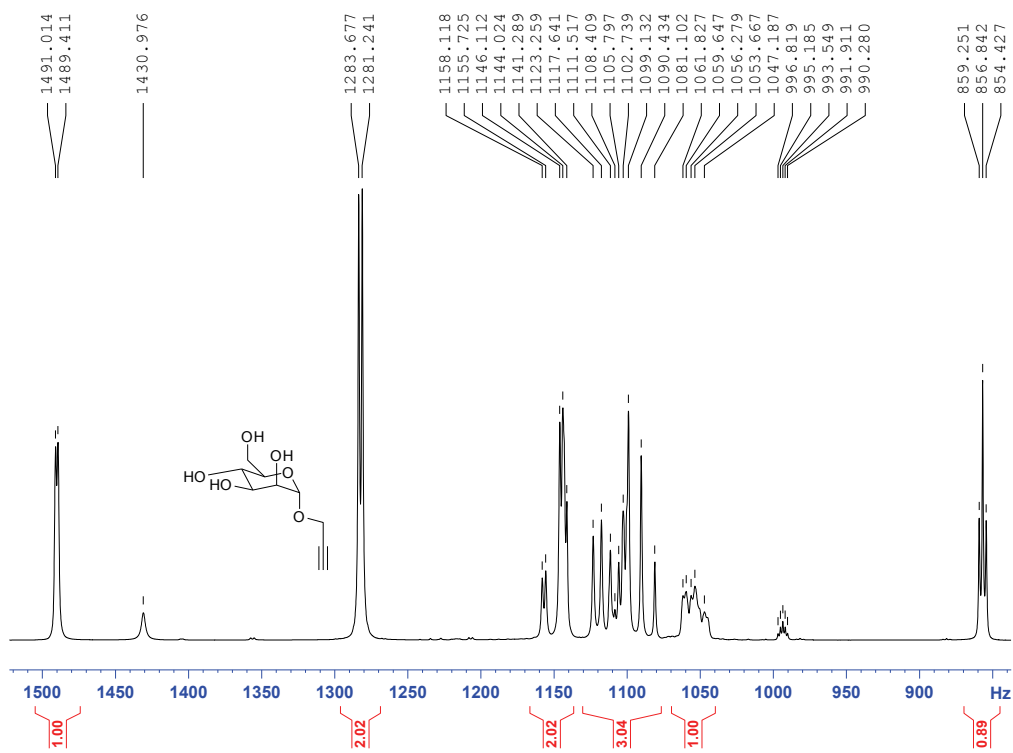
125.7 MHz ^{13}C NMR spectrum of 2-propynyl 2,3,4,6-tetra-*O*-acetyl- α -D-mannopyranoside in chloroform-*d*



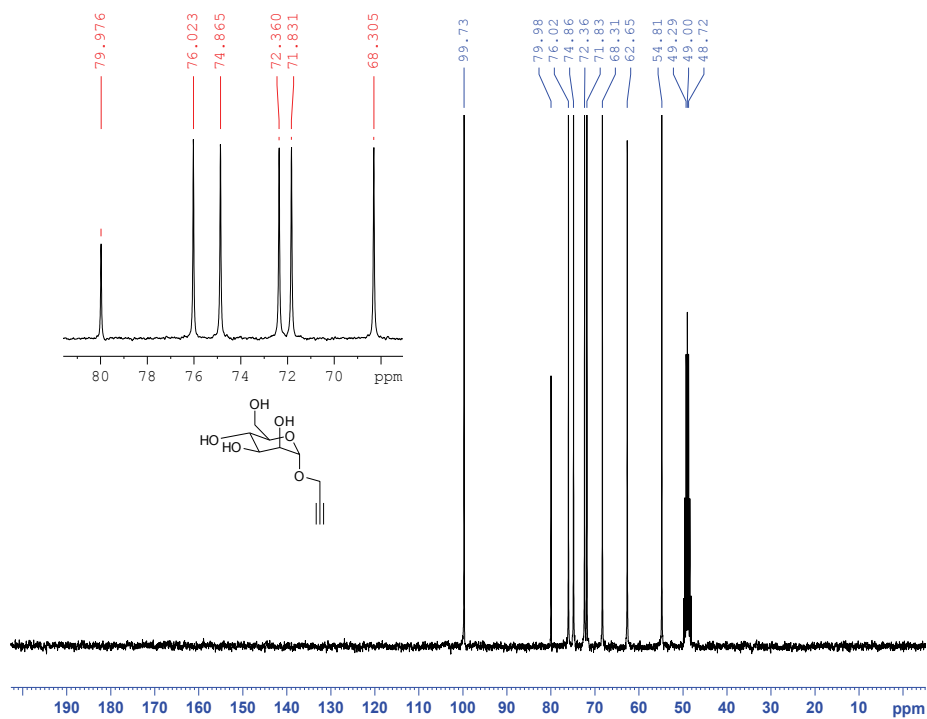
300.15 MHz ^1H NMR spectrum of 2-propynyl α -D-mannopyranoside (198) in methanol- d_4



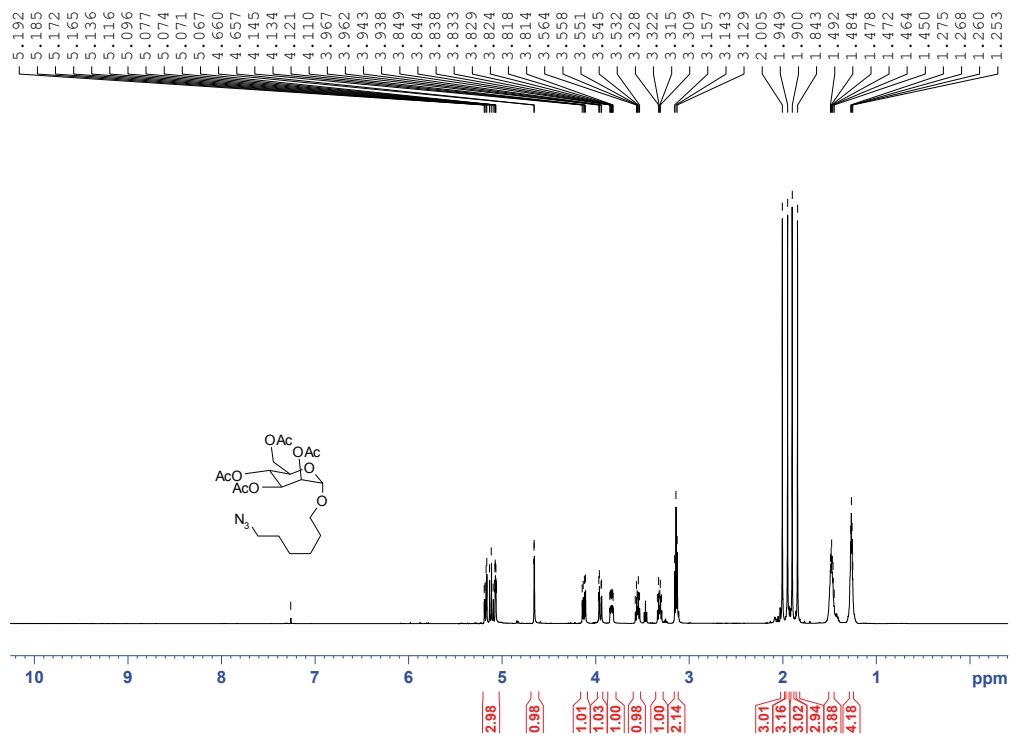
Expansions of part of the 300.15 MHz ^1H NMR spectrum of 2-propynyl α -D-mannopyranoside (198) in methanol- d_4



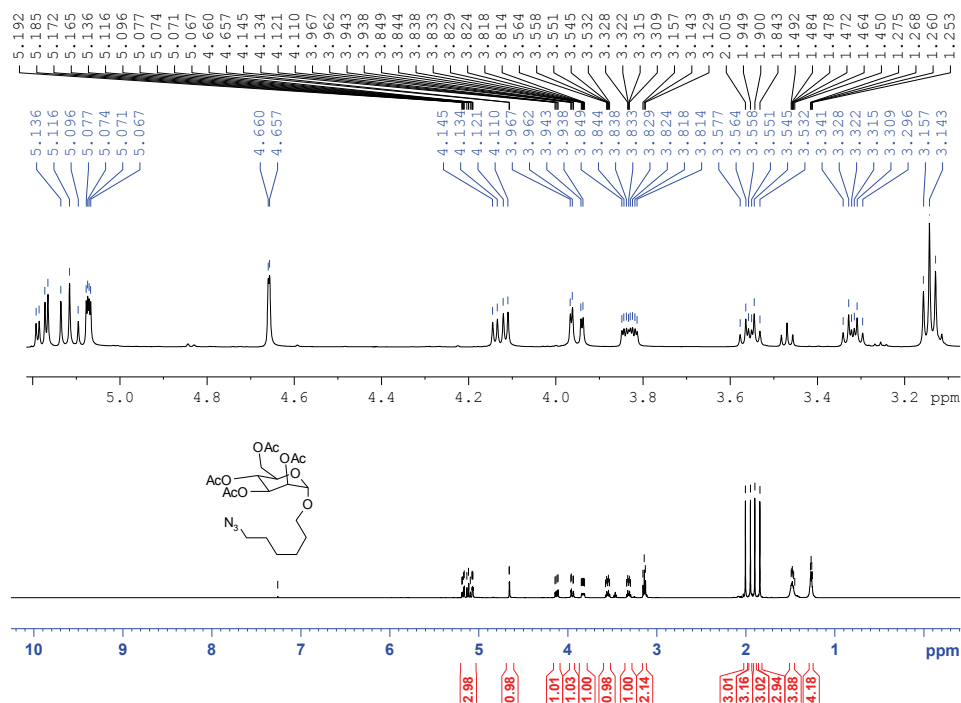
75.5 MHz ^{13}C NMR spectrum of 2-propynyl α -D-mannopyranoside (198) in methanol- d_4



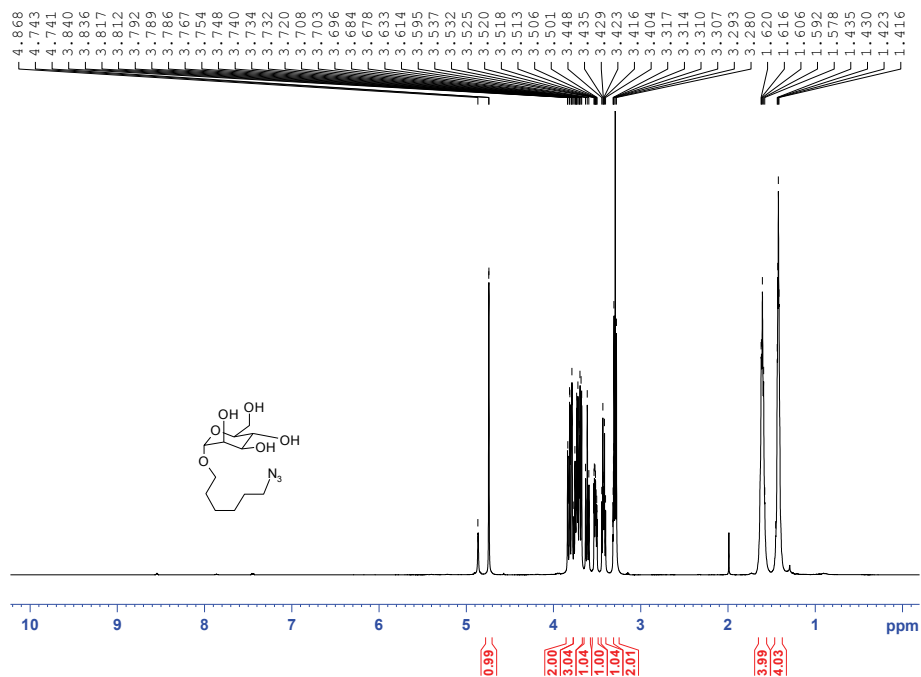
500.13 MHz ^1H NMR spectrum of 6-azidohexyl 2,3,4,6-tetra-*O*-acetyl- α -D-mannopyranoside (200) in chloroform- d



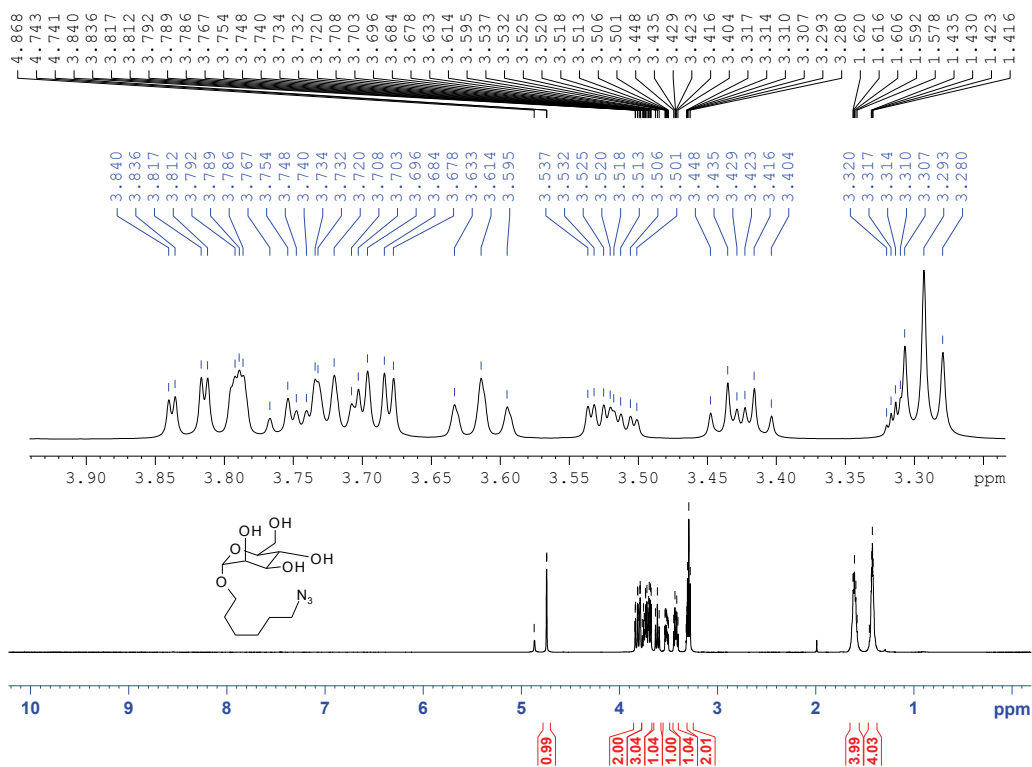
Expansions of part of the 500.13 MHz ^1H NMR spectrum of 6-azidohexyl 2,3,4,6-tetra-*O*-acetyl- α -D-mannopyranoside (200) in chloroform-*d*



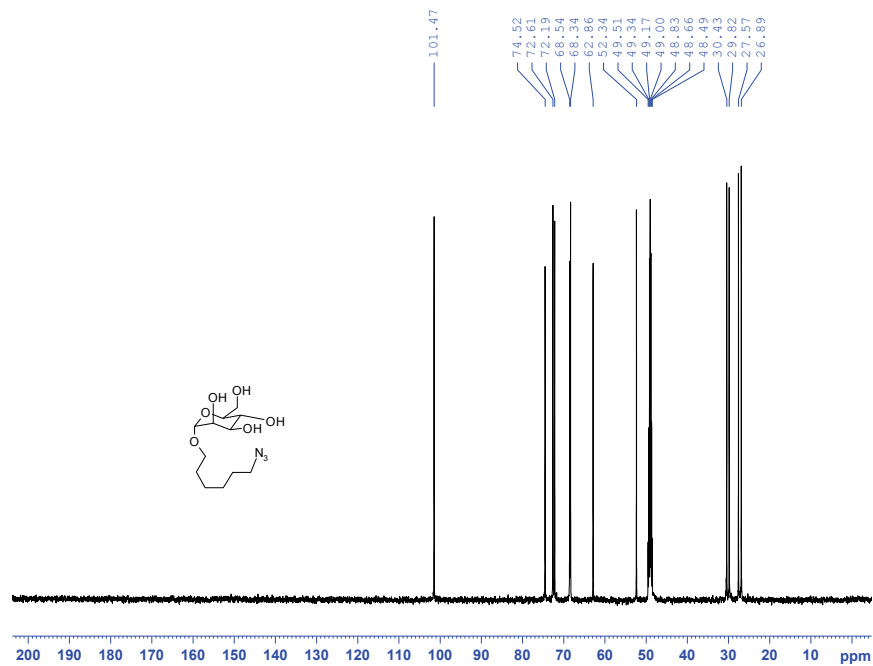
500.13 MHz ^1H NMR spectrum of 6-azidohexyl α -D-mannopyranoside (201) in methanol-*d*



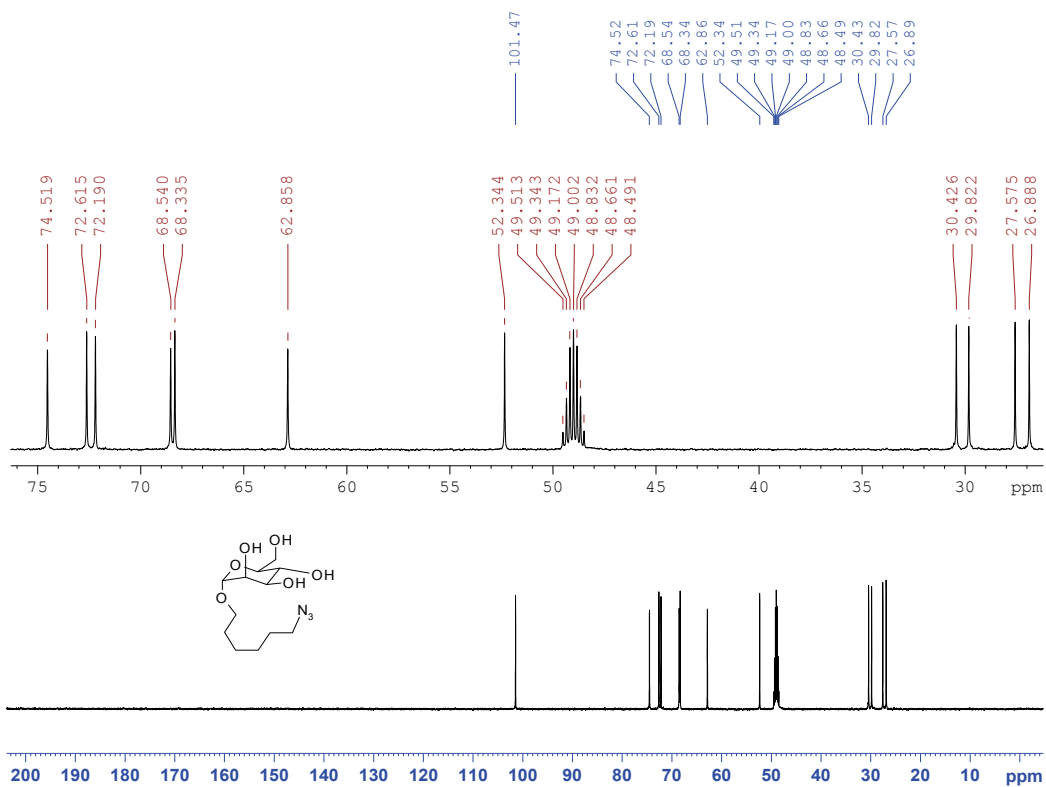
Expansion of part of the 500.13 MHz ^1H NMR spectrum of 6-azidohexyl α -D-mannopyranoside (201) in methanol-*d*



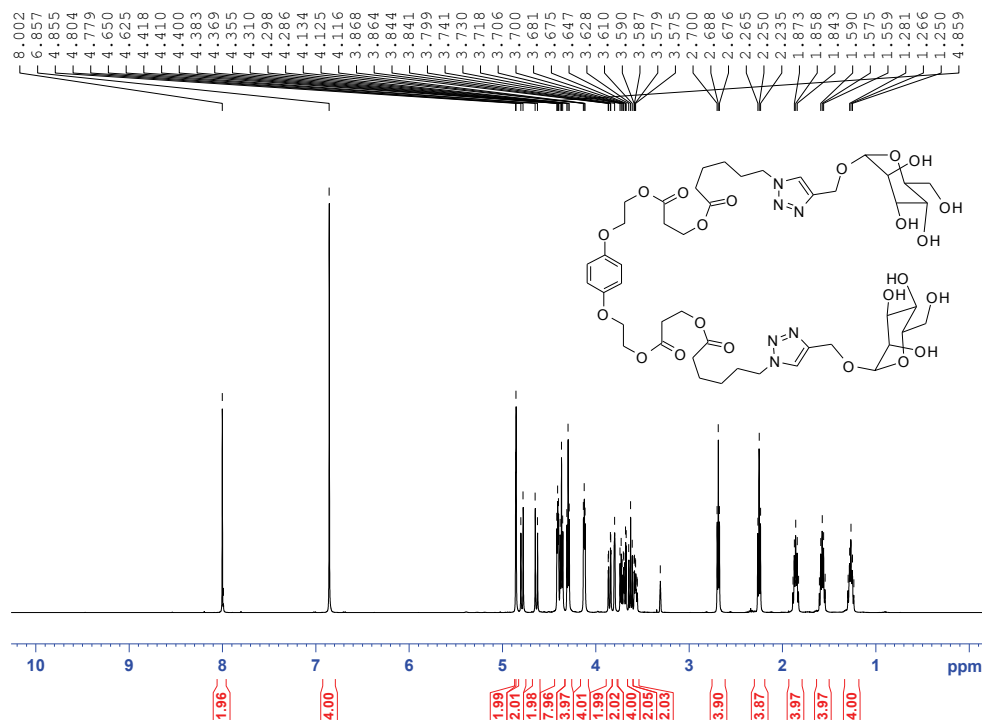
125.7 MHz ^{13}C NMR spectrum of 6-azidohexyl α -D-mannopyranoside (201) in methanol-*d*



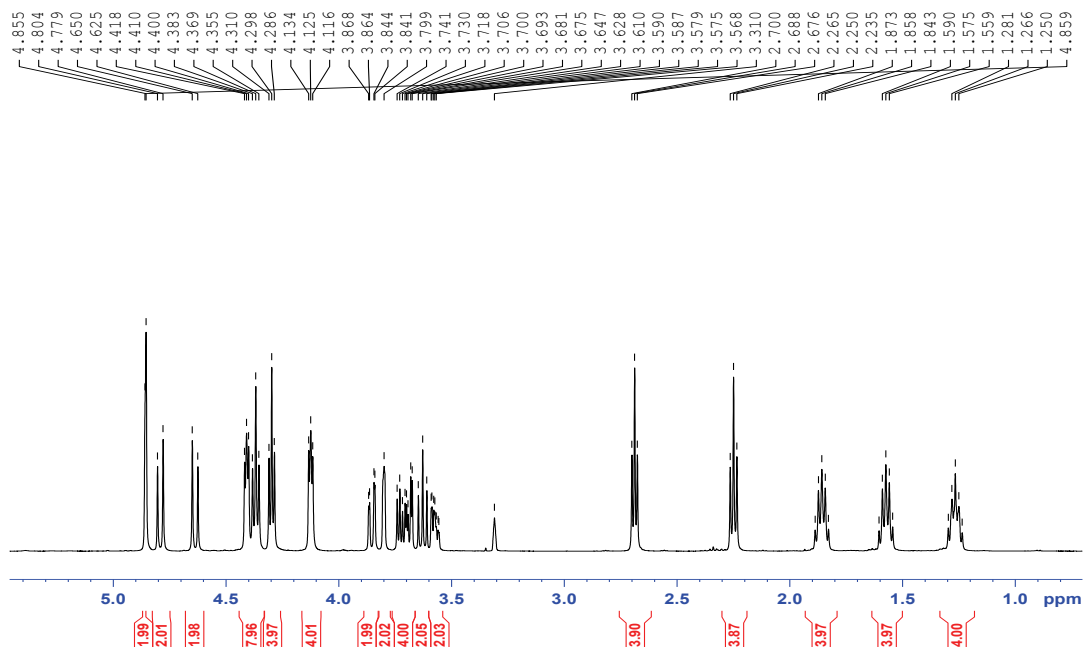
Expansion of part of the 125.7 MHz ^{13}C NMR spectrum of 6-azidohexyl α -D-mannopyranoside (201) in methanol-*d*



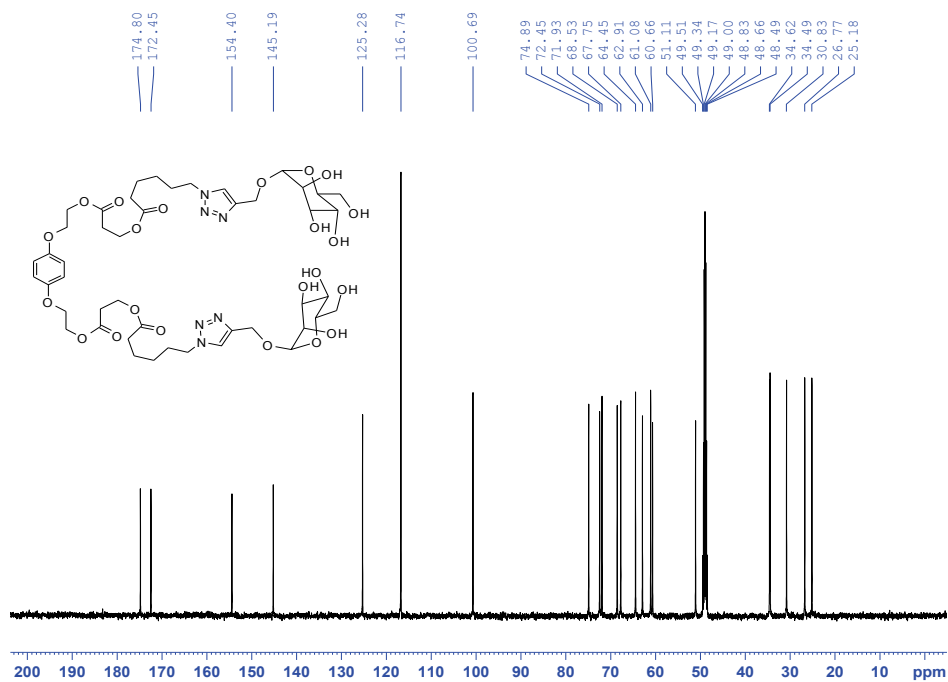
500.13 MHz ^1H NMR spectrum of extended divalent α -D-mannopyranoside-terminated dendrimer (210) in methanol- d_4



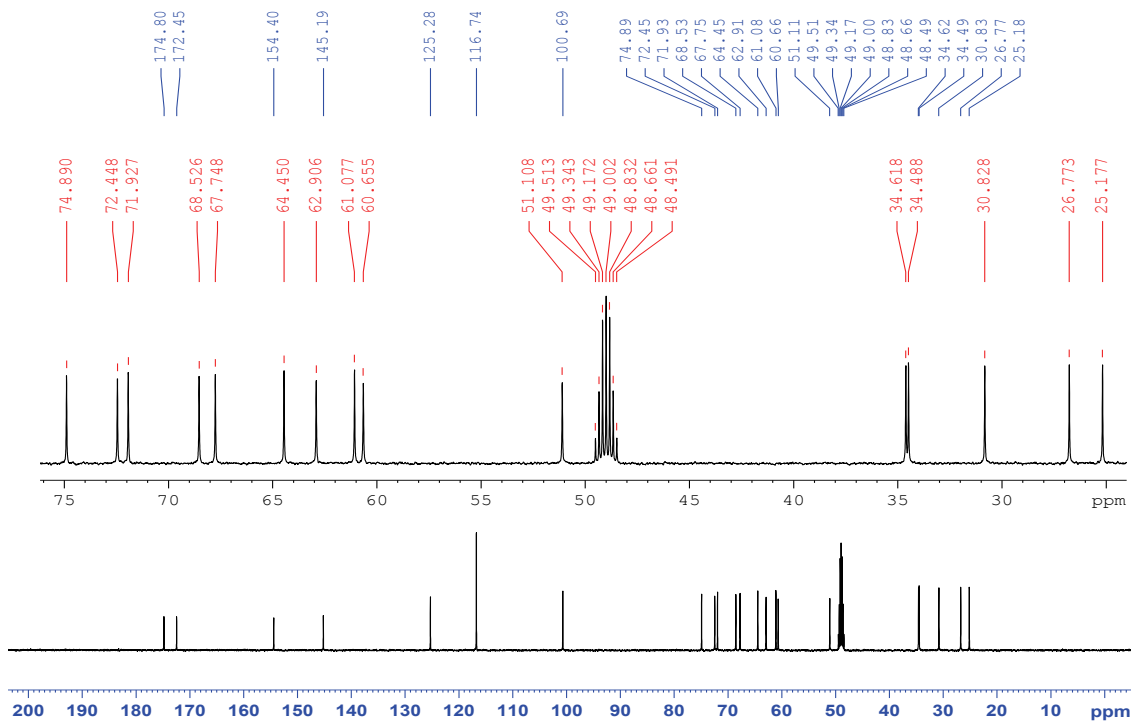
Expansion of part of the 500.13 MHz ^1H NMR spectrum of extended divalent α -D-mannopyranoside-terminated dendrimer (210) in methanol- d_4



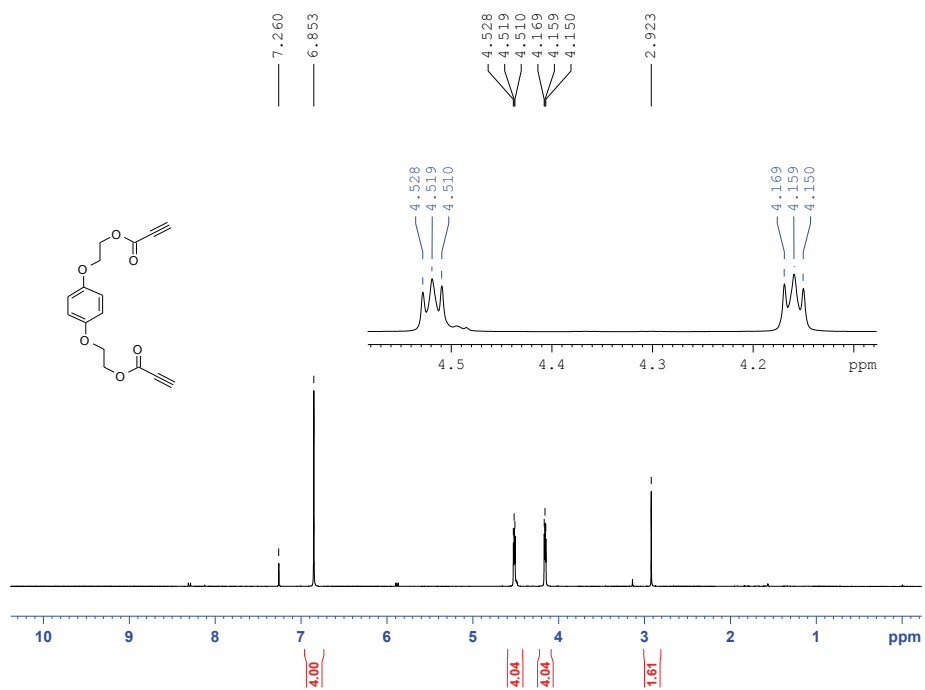
125.7 MHz ^{13}C NMR spectrum of extended divalent α -D-mannopyranoside-terminated dendrimer (210) in methanol- d_4



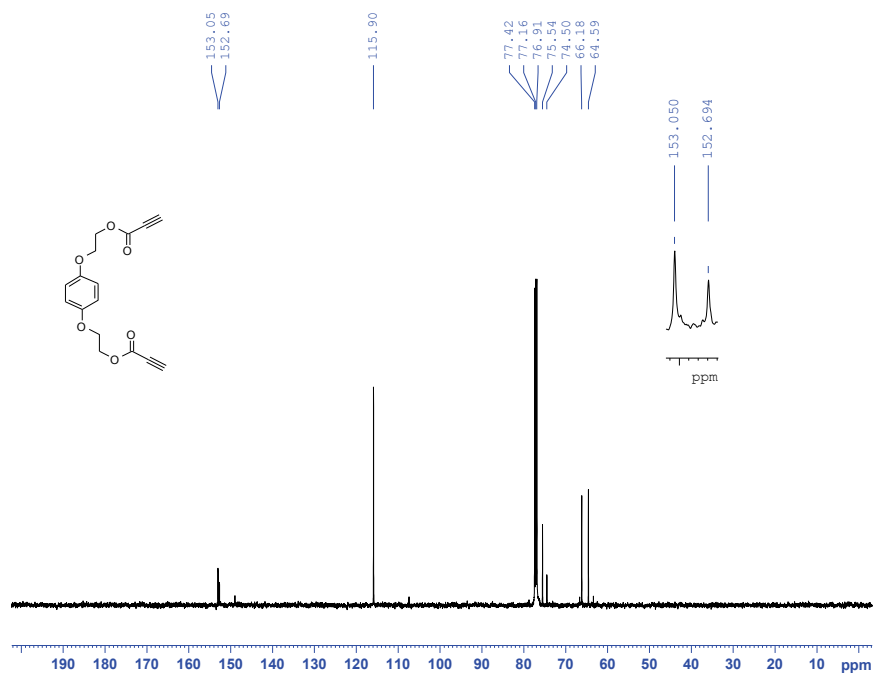
Expansion of part of the 125.7 MHz ^{13}C NMR spectrum of extended divalent α -D-mannopyranoside-terminated dendrimer (210) in methanol- d_4



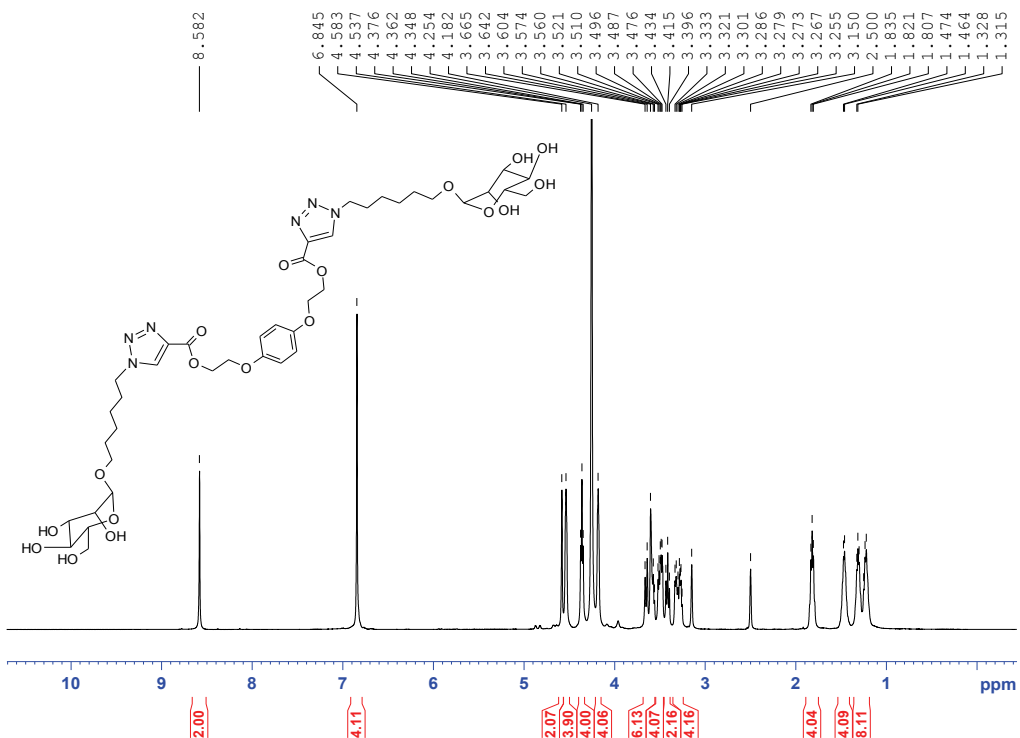
500.13 MHz ^1H NMR spectrum of alkyne-terminated divalent dendrimer (212) in chloroform-*d*



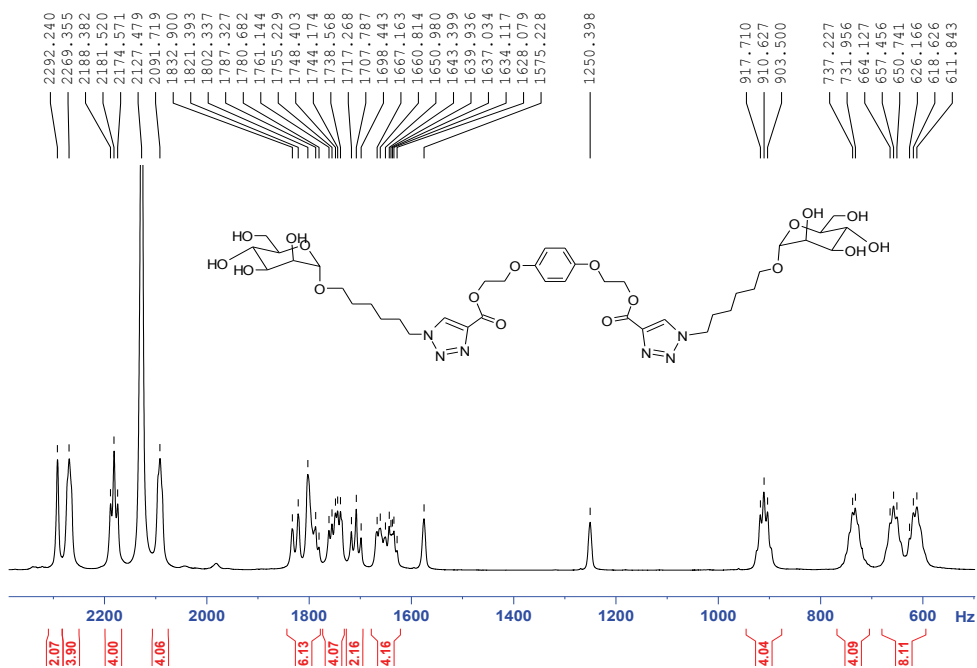
125.7 MHz ^{13}C NMR spectrum of alkyne-terminated divalent dendrimer (212) in chloroform-*d*



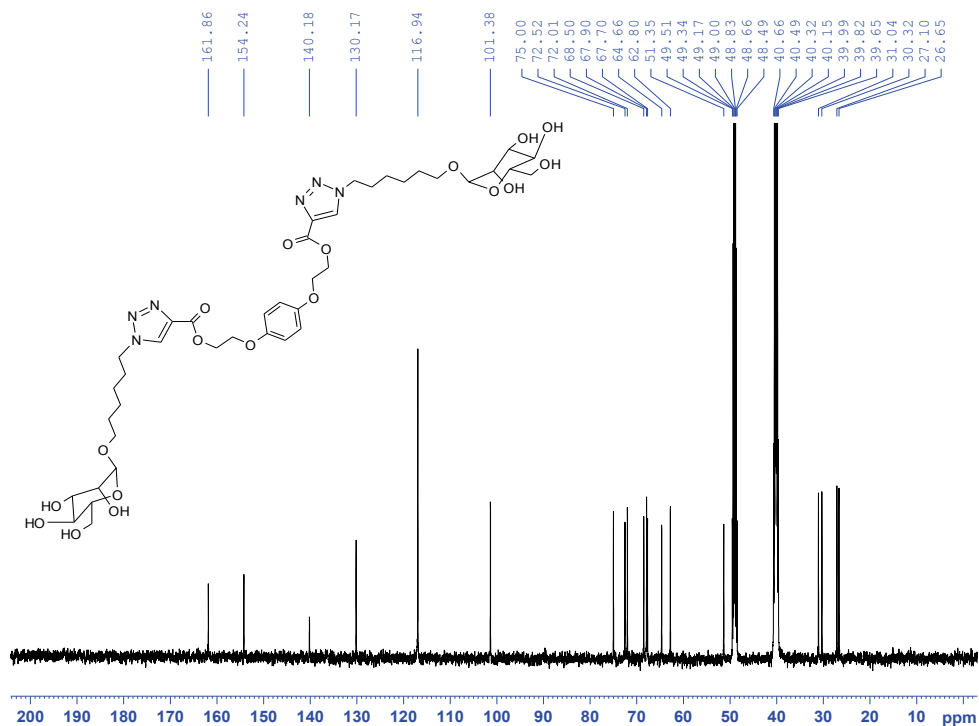
500.13 MHz ^1H NMR spectrum of divalent α -D-mannopyranoside-terminated dendrimer with a hexyl linker (213) in $\text{DMSO-}d_6/\text{methanol-}d_4$



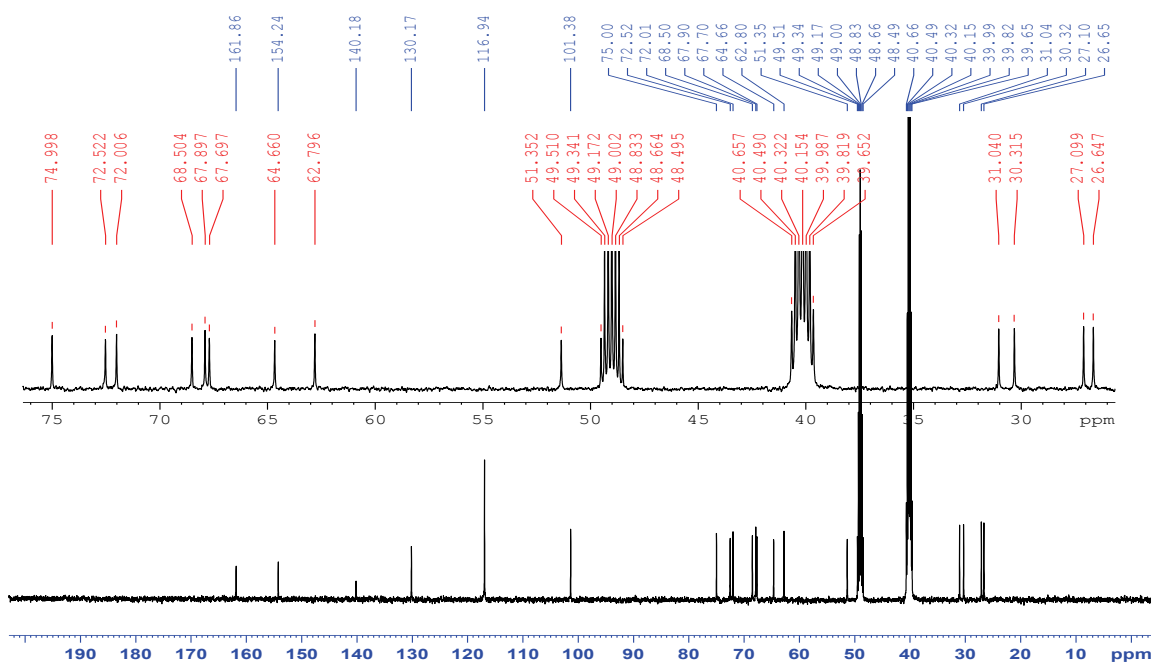
Expansion of part of the 500.13 MHz ^1H NMR spectrum of divalent α -D-mannopyranoside-terminated dendrimer with a hexyl linker (213) in $\text{DMSO-}d_6/\text{methanol-}d_4$



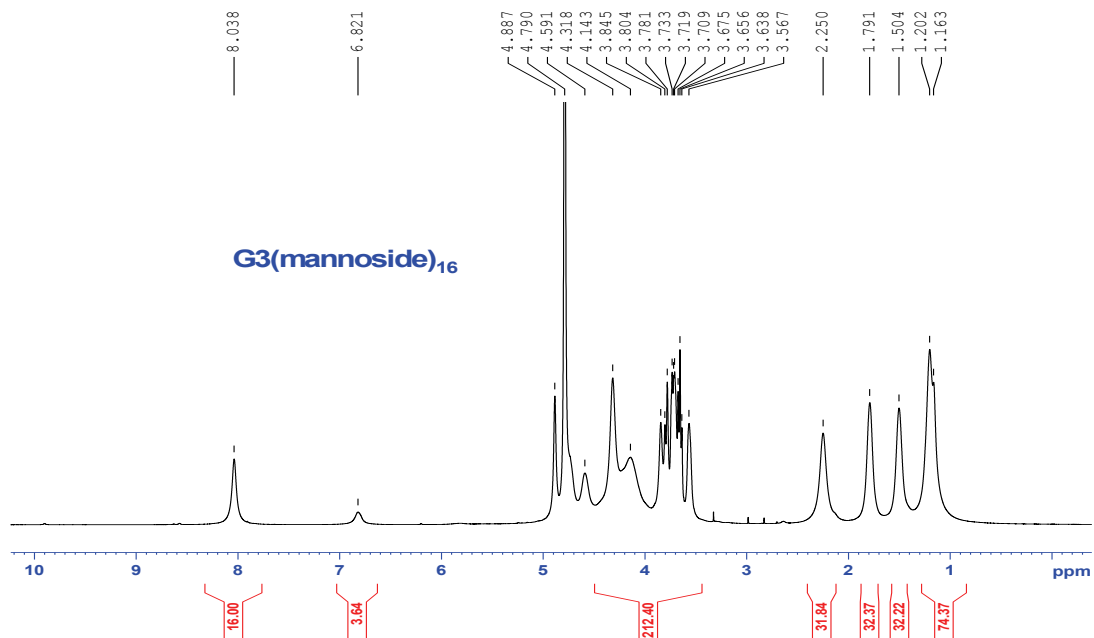
125.7 MHz ^{13}C NMR spectrum of divalent α -D-mannopyranoside-terminated dendrimer with a hexyl linker (213) in DMSO- d_6 / methanol- d_4



125.7 MHz ^{13}C NMR spectrum of divalent α -D-mannopyranoside-terminated dendrimer with a hexyl linker (213) in DMSO- d_6 / methanol- d_4



500.13 MHz ^1H NMR spectrum of third generation dendrimer bearing 16 mannose residues (211) in water- d_2



125.7 MHz ^{13}C NMR spectrum of third generation dendrimer bearing 16 mannose residues (211) in water- d_2

