‘One Pot’ Azidation of Chiral Secondary Alcohols.

By

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Dr. Salvatore A. Sanders, Dean of Graduate Studies Date

Thesis Abstract

This thesis employs the “one pot” synthesis in an attempt to synthesize azides from chiral secondary alcohols. The experimentation was unsuccessful in the azidation of this class of compounds, but the sulfonate ester intermediates were successfully synthesized, isolated and characterized. The steric environment on the structure of the starting material must have hindered the S_N2 reaction to yield desired product. All the findings within this research are strongly supported by previous literature, adequate yields and appropriate spectral data.

Acknowledgements

I would like to thank the Youngstown State University and the School of Graduate Studies for the study opportunity and support in my pursuit of my Master of Science degree. I would especially like to thank Dr. John A. Jackson and Dr. Sherri Lovelace-Cameron for being members of my thesis committee and for giving me advice and their time when I needed them.

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I am extremely grateful to my family and my immediate family for their invaluable support and understanding throughout my further studies. Lastly, I would like to thank all the people in the Norris Research Group for the support and teamwork that contributed to my success in the laboratory.

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Introduction

Organic azides.

Organic azides are a class of compounds with an azide ion (N_3) functional group attached to an alkyl, aryl or acyl group as shown in Figure 1 below.[1]

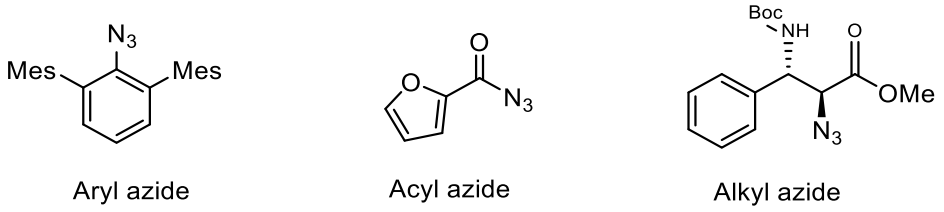
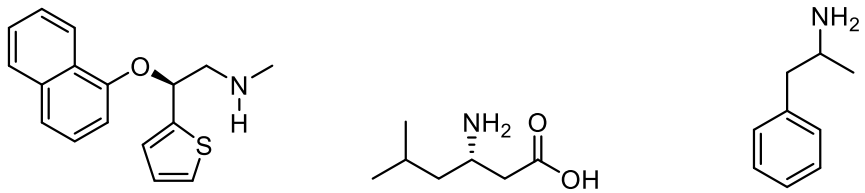


Figure 1: Different molecules containing azides.

Since the discovery of phenyl azides over 100 years ago by Peter Griess the chemistry of azides and nitrenes has attracted the attention of chemists.[2] Organic azides gained considerable attention in the 1950s and 1960s with new applications in chemistry of aryl, acyl and alkyl azides. Organic azides started to receive industrial interest due to their use of azides in the synthesis of heterocycles such as tetrazoles and triazolesas well as with their use as functional groups in pharmaceuticals and as blowing agents.[1] These group of compounds are useful intermediate components applied in the synthesis of drugs such as antipsychotics, antihistamines and acetaminophen. Lyrica®, Adderall® and Cymbalta® are some of the drugs that contain similar structures to the nitrogen containing compounds synthesized in this research (Figure 2).



Cymbalta® Lyrica® Adderall®

Figure 2: Some of the *N*-containing pharmaceuticals.

Synthesis.

Organic azides can be synthesized through five distinct methods: (1) cleavage of triazines and analogous compounds; (2) insertion of the N_3 group (addition or substitution), (3) insertion of a nitrogen atom (diazotization); (4) rearrangement of azides; and (5) introduction of an N_2 group (diazo transfer).[1]The synthesis and properties of aliphatic and aromatic azides vary to a great extent, therefore the two classes of compounds are discussed separately.[1]

Safety in Handling Azides.

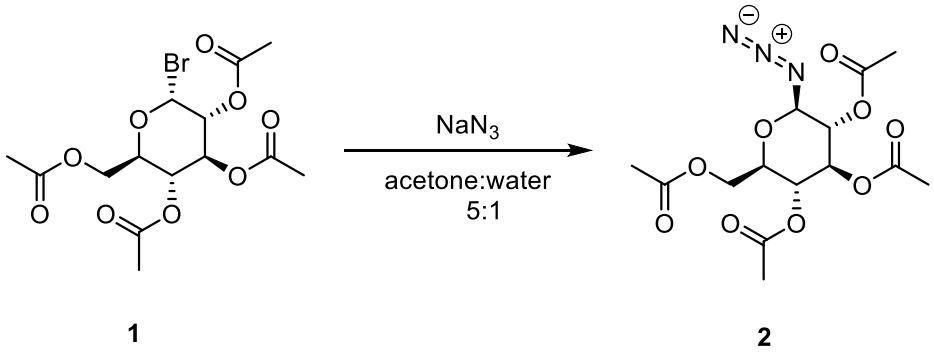
Some of the organic azides and other covalent azides are highly explosive[4] and very toxic,[1] and therefore safety measures must be taken always when handling them. Sodium azide is very toxic, it is easily absorbed into the body via the skin. It also decomposes on heating above 275 $^{\circ}$C. Sodium azide reacts vigorously with dimethyl sulfate, bromine, a series of metals such as lead and copper, nitric acid and CS_2. [1]

Classic Nucleophilic Substitution.

Aliphatic azides are readily accessible through nucleophilic substitution (S_N2) with the highly nucleophilic azide ion. Sodium azide is the main azide source, other

sources are tetraalkylammonium azides, alkali azides and polymer-bound azides[5] and the highly explosive silver azide.[3] Quite frequently halides,[6] carboxylates,[7] and (cyclic) sulfonates[8] as well as mesylates[1] and nosylates are chosen as leaving groups,[2] although sulfonium salts are possible substrates.[9]

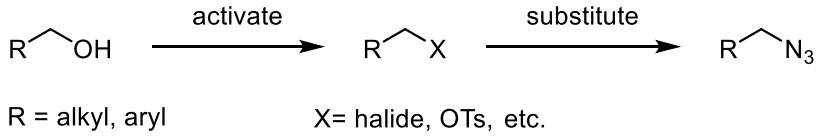
An example of such an S_N2 reaction can be seen in (Equation 1), where 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**) is reacted with sodium azide to form the glucosyl azide **2**.[10]



1 **2**

Equation 1.

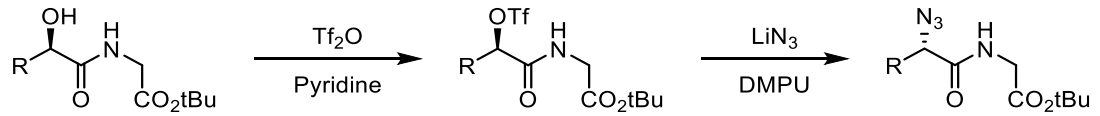
Classical Azide Synthesis.



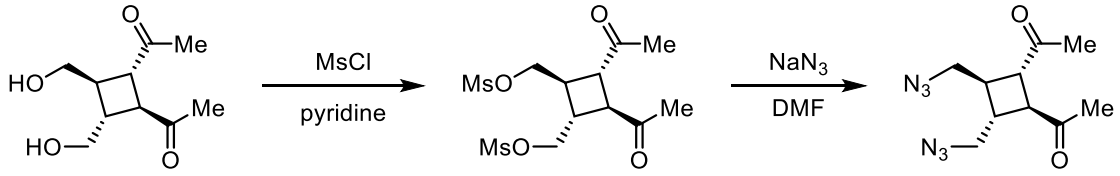
Scheme 1.

The main azide precursors of this research are alcohols, as alcohols are easily displaced by azides after addition of reagents that increase leaving capability of the hydroxyl group (Scheme 1).[11] Sulfur-containing reagents like mesyl chloride, triflic

anhydride and tosyl chloride react with both primary and secondary alcohols resulting in formation of sulfonate esters, which good are leaving groups. The sulfonate ester is usually readily substituted by an azide in a polar aprotic solvent to yield the desired product. Prior to S_N2 displacement by an azide nucleophile, intermediate triflate and mesylate esters are formed in examples shown in Scheme 2 and 3 below.[12, 13]



Scheme 2.

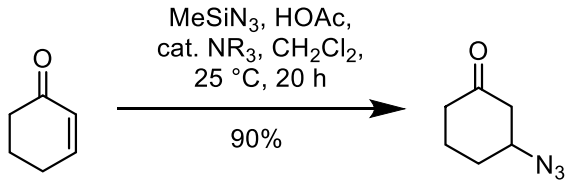


Scheme 3.

The classical method above is useful in synthesis of amines, peptides and heterocycles. The challenge with this method is that its time consuming because it takes place through two steps; it involves work up and separation to isolate the intermediate. There is also use of environmentally harmful halides as well as use of excessive (dangerous) azides.

Polar 1,4 addition reactions.

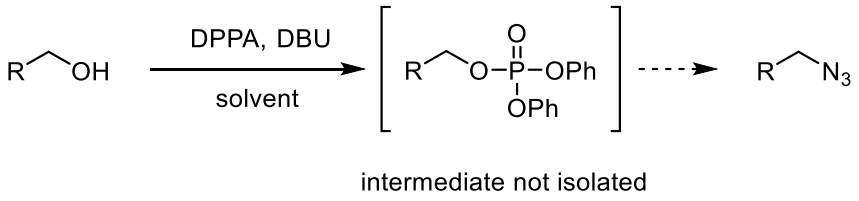
In 1999 Miller and co-workers described an alkyl azide synthesis from 2-cyclohexenone using an equimolar mixture of acetic acid and trimethylsilyl azide as the azide source.Tertiary amines as Lewis bases catalyze the reaction (Equation 2).[1]



Equation 2: Conjugate addition of azide ions to cyclohexanone.

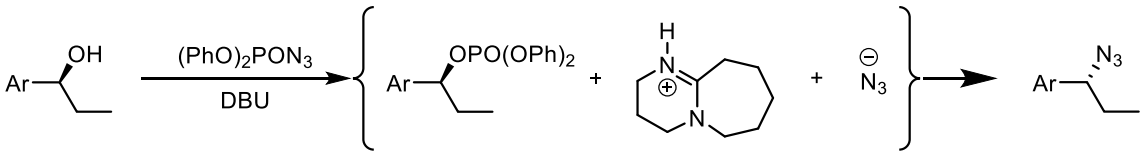
"One-pot" synthesis.

To overcome the challenges stated above, the use of the Mitsunobu method for synthesis of azides from primary and secondary alcohols has been reported.[14] The method is quite useful because it is more efficient, and it bypasses intermediate isolations. The general reaction is shown in Scheme 4.



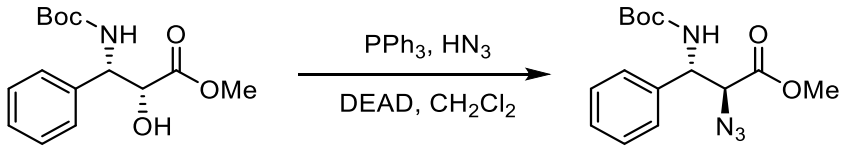
Scheme 4.

An example of such a process is the reaction between a secondary alcohol with diphenyl phosphorazidate (DPPA) and 1,8-diazobicyclo [5.4.0]undec-7-ene (DBU) to produce the desired azide (Equation 3).[15]



Equation 3.

Similarly, Mitsunobu reaction conditions can be used to transform a secondary alcohol to an azide, the product shows inversion of stereochemistry in that position (Equation 4).[1]



Equation 4.

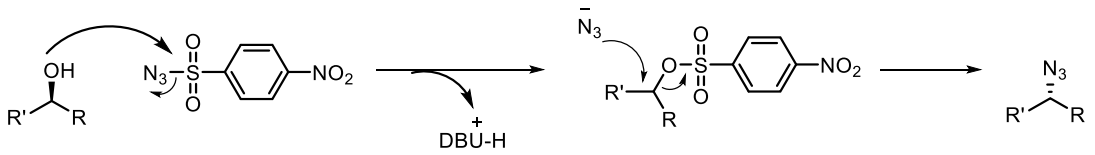
The major challenge with the method above is that it leads to creation of oxide by-products that are often strenuous to remove from reaction mixture as well as being troublesome to work with.[2]

Statement of the problem.

Nitrogen containing compounds are found in essential and natural processes in the disciplines of biological and medicinal chemistry. Organic azides constitute part of this group of compounds. The traditional synthesis methods are cumbersome and time consuming because they involve isolation steps and workups. The experimental design of this research involves exploring various reaction conditions to come up with optimal conditions for the “one-pot” azidation of chiral secondary alcohols.

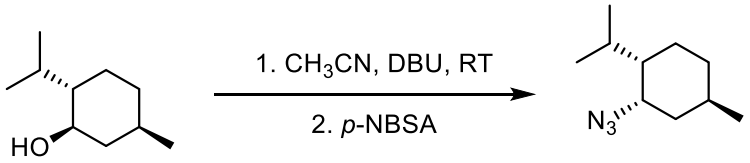
Results and Discussion.

The objective of the research was to come up with optimum conditions for the conversion of chiral secondary alcohols to the corresponding azides. Knowing that sulfonate esters are used in traditional azide synthesis the following reaction mechanism was hypothesized based on *in situ* synthesis of the azide nucleophile (Scheme 5).



Scheme 5: Mechanism for azide formation using *p*-NBSA, DBU, and secondary alcohol.

Attempted synthesis of menthol azide (4).

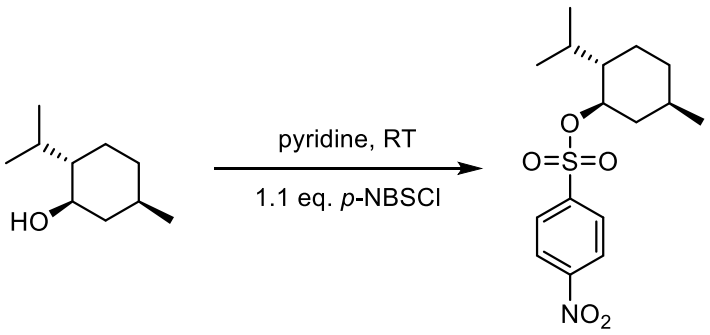


3 **4**

Equation 5.

The treatment of menthol (**3**) with *p*-NBSA and DBU in acetonitrile did not yield the expected outcome. TLC (1:1 hexane: ethyl acetate) of the reaction mixture showed no consumption of the starting material after twelve hours. The ^{1}H NMR and ^{13}C NMR of the extracted product showed data that matched the starting material. The steric environment on the structure of the starting material must have prevented formation of the sulfonate ester and an S_N2 attack of the azide nucleophile to produce the expected product.

Attempted synthesis of benzenesulfonic acid, 4-nitro-, 5-methyl-2-(1-methylethyl) cyclohexyl ester (5) from menthol (3).



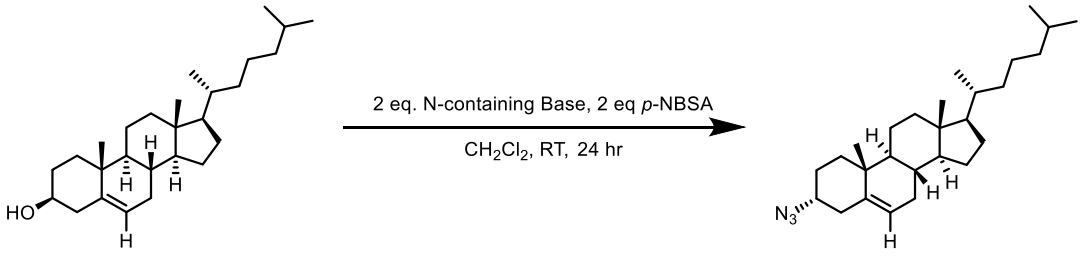
3 **5**

Equation 6.

The treatment of menthol (**3**) with *p*-NBSCl in pyridine did not yield the expected product. TLC (1:2 hexane: ethyl acetate) of the reaction mixture showed no consumption of the starting material after twelve hours. The ^{1}H NMR and ^{13}C NMR of the extracted product showed data that matched the starting material.

Attempted synthesis of Cholest-5-en-3β-ol azide (7) from Cholesterol (6).

Treatment of cholesterol (**6**) with *para*-Nitrobenzenesulfonyl azide (*p*-NBSA*)* in different solvents and nitrogen containing bases were observed and recorded. Table 1 and Table 2 shows the yields of the desired azide product.



6 **7**

Equation 7.

Table 1: Reaction of cholesterol with *p*-NBSA in different nitrogen-containing bases.

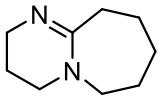
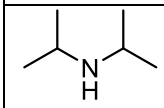
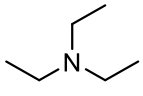
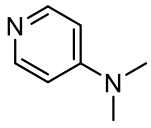
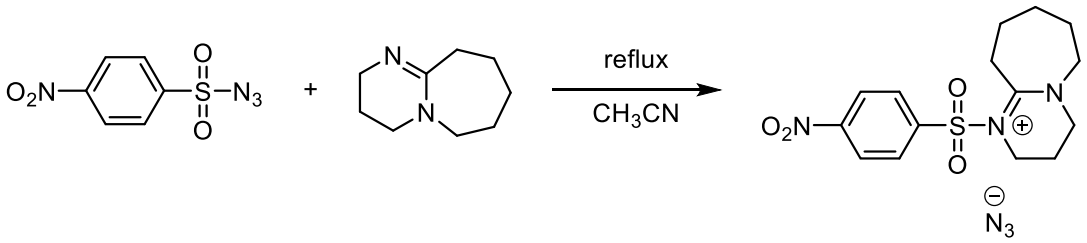
Structure	Name	(7) % Yield
	1,8-Diazabicyclo[5.4.0]undec-7-ene	0
	Pyridine	0
	Diisopropylamine	0
	Triethylamine	0
	4-dimethylaminopyridine	0

Table 2: Reaction of cholesterol with *p*-NBSA in different solvents.

Formula	**Name**	**(7) % Yield**
CH_2Cl_2	Methylene chloride	0
$(C_2H_5)_2O$	Diethyl ether	0
C_3H_6O	Acetone	0
CH_3Cl	Chloroform	0
C_3H_7NO	Dimethyl formamide	0

Table 1 and Table 2 shows that there was no conversion of cholesterol **6** to the corresponding azide in any of the bases and solvents tested. The unexpected outcome could be due to the bulky nature of cholesterol structure that hindered an S_N2 attack to yield the desired product. Previous work done by former YSU researcher; Charles Hartranft[2] indicated that attempts to form similar azide products stopped at the intermediate stage. The observation also signaled to the presence of a side reaction between the bases used and *p*-NBSA hindering the formation of the azide product. To support this conclusion *p*-NBSA and DBU were left to react in a flask in the absence of the hydroxyl group as shown in Equation 8.



8

Equation 8.

During the reflux, infrared spectroscopy was utilized to monitor the progress of the reaction after one hour. The IR data showed an azide absorption at 2022 cm^{-1} which was significantly lower than that of *p*-NBSA at 2122 cm^{-1}. The absorption shift towards the suspected anionic azide form is supported by the fact that NaN_3 has an absorption at 2000 cm^{-1}. The *in-situ* generation of the anionic azide supports the suggestion that a competing side reaction was hindering the azidation reaction.

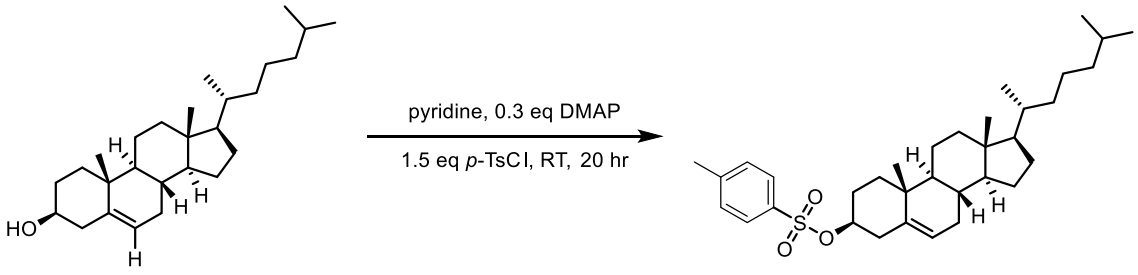
The second objective of the research was to synthesize and isolate sulfonate ester intermediate that were believed to be formed during this azidation reaction. The synthesized intermediates would then be reacted with *para*-nitrobenzene sulfonyl azide (*p*-NBSA*)* and DBU to yield the azide product.

Synthesis of sulfonate ester intermediates.

6 **9**

Equation 9.

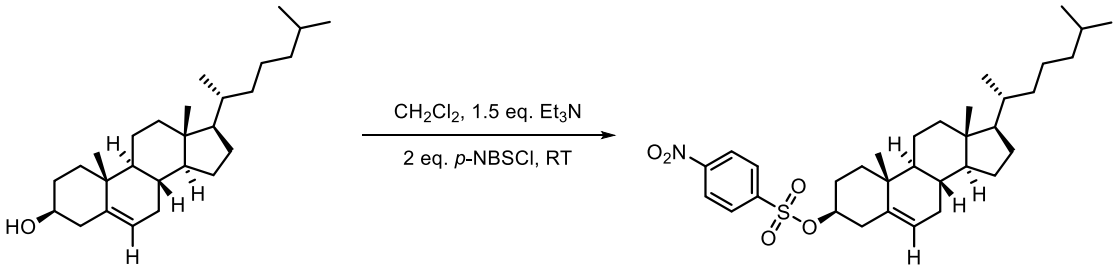
Preparation of cholest-5-en-3β-ol methanesulfonate **12** was achieved by substitution on cholesterol (**6)**. Once the triethylamine and **6** have been left to mix for 30 minutes, a solution of methane-sulfonyl chloride in dichloromethane was introduced into the reaction mixture to generate **9**. TLC (1:3 hexane: ethyl acetate) of the reaction mixture that was done after twelve hours showed complete consumption of **6**. ^{1}H NMR analysis of the needle-like solid (product **9**, 53% yield) indicates a three proton singlet peak at 2.99 ppm due to the new methyl group on the sulfonate ester.^{13}C NMR also supported this observation due to the existence of the new signal at 37.30 ppm and the change of signal on C-1 from 71.80 ppm to 80.99 ppm.



6 **10**

Equation 10.

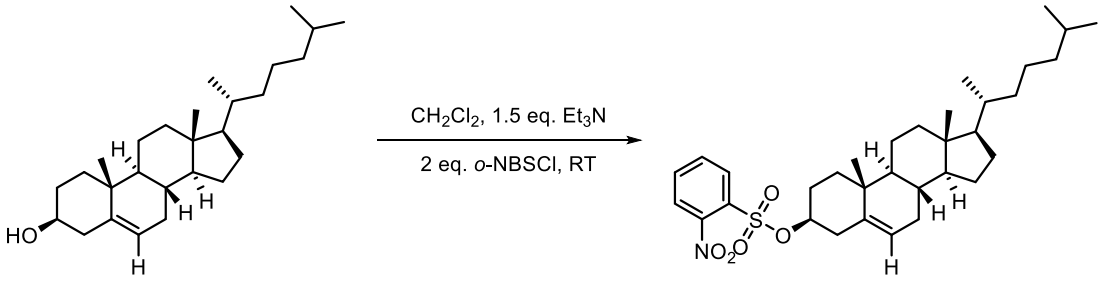
Synthesis of cholest-5-ene-3β-yl p-toluenesulfonate **10** was achieved by reaction of cholesterol (**6**) with and *p*-toluenesulfonyl chloride. Once *N,N'*-dimethylaminopyridine (DMAP) and **6** have been left to stir for 45 minutes, *p*-toluenesulfonyl chloride was introduced into the reaction mixture to generate **10**. TLC (5:1 hexane: ethyl acetate) showed complete consumption of **6** within twenty hours. The ^{1}H NMR data of the colorless needles (product **10**, 79%), indicates a three-proton singlet at 2.45 ppm as well as four proton multiplet in the range of 7.32-7.81 ppm. ^{13}C NMR also supported this observation due to the existence of the new signal at 21.68 ppm due to the *para*-methyl group on aromatic ring. The aromatic ring carbons have chemical shifts of 144.43 ppm, 138.87ppm, 134.66 ppm, 129.77 ppm, 127.67 ppm and the change of signal on C-1 from 71.80 ppm to 82.43 ppm.



6 **11**

Equation 11.

Synthesis of cholest-5-en-3-ol (3β)-4-nitrobenzenesulfonate **11** was achieved by reaction of cholesterol **6** with and 4-nitrobenzenesulfonyl chloride. Once triethylamine and **6** have been left to react for 30 minutes, 4-nitrobenzenesulfonyl chloride was introduced into the reaction mixture to generate **11**. TLC (1:2 hexane: ethyl acetate) showed complete consumption of **9** within four hours. The ^{1}H NMR data of the colorless crystals (product **11**, 86%), indicates four new one-proton doublets at 8.39 ppm, 8.37 ppm, 8.12 ppm, 8.09 ppm due to the benzene ring hydrogens. ^{13}C NMR also supported this observation due to the existence of the benzene ring carbons chemical shifts of 150.69 ppm, 143.65 ppm, 128.87 ppm, 124.33 ppm, 124.11 ppm and the change of signal on C-1 from 71.80 ppm to 84.21 ppm.

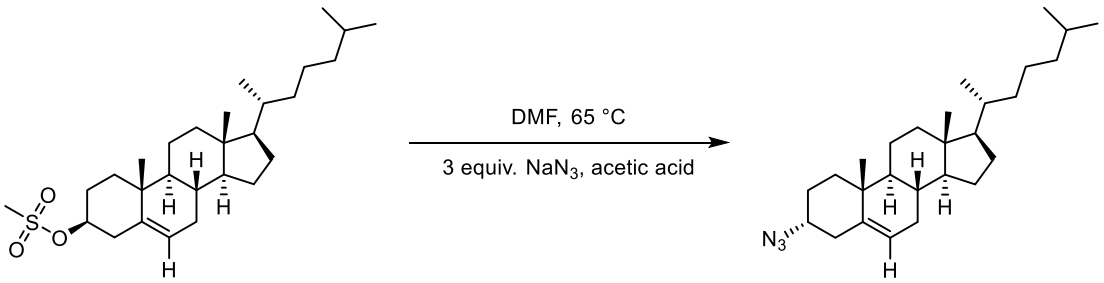


6 **12**

Equation 12.

Attempted synthesis of cholest-5-en-3-ol (3β)-2-nitrobenzenesulfonate **12** was tried by reaction of cholesterol (**6**) with 2-nitrobenzenesulfonyl chloride. Once triethylamine and **6** have been left to stir for 30 minutes, 2-nitrobenzenesulfonyl chloride was introduced into the reaction mixture to generate **12**. TLC (1:2 hexane: ethyl acetate) showed no consumption of **6** after twelve hours. The ^{1}H NMR and ^{13}C NMR of the extracted product showed data that matched the starting material.

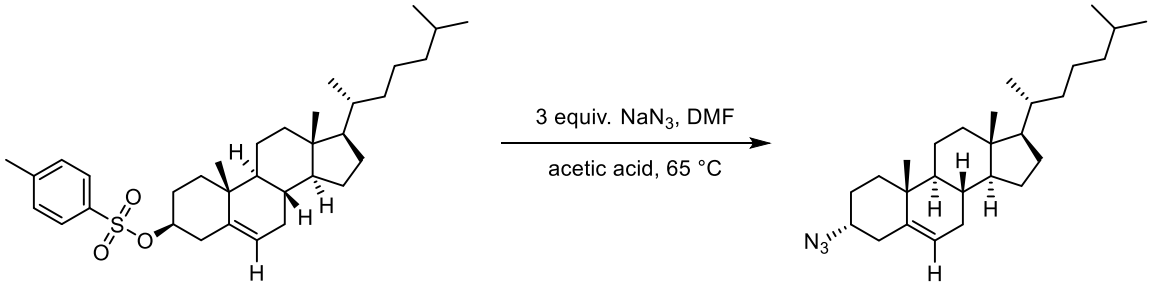
Attempted NaN_3-based azidation of sulfonate ester intermediates.



9 **7**

Equation 13.

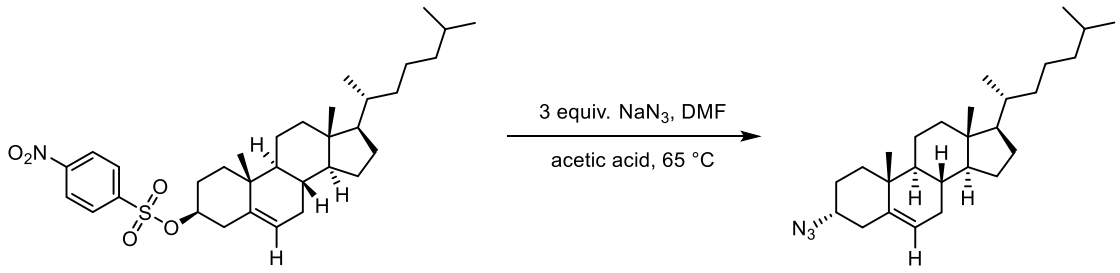
Attempted synthesis of cholest-5-en-3β-ol azide 7 was tried by reaction of cholest-5-en-3β-ol methanesulfonate **9** with sodium azide. Once cholest-5-en-3β-ol methanesulfonate **9** was dissolved in DMF, sodium azide in acetic acid was introduced into the reaction mixture to generate **7**. TLC (1:1 hexane: ethyl acetate) showed no consumption of **9** after twenty-four hours. The ^{1}H NMR and ^{13}C NMR of the extracted product showed data that matched the starting material.



10 **7**

Equation 14.

Attempted synthesis of cholest-5-en-3β-ol azide 7 was tried by reaction of cholest-5-ene-3β-yl p-toluenesulfonate **10** with sodium azide. Once cholest-5-ene-3β-yl p-toluenesulfonate **10** was dissolved in DMF, sodium azide in acetic acid was introduced into the reaction mixture to generate **7**. TLC (1:1 hexane: ethyl acetate) showed no consumption of **10** after twenty-four hours. The ^{1}H NMR and ^{13}C NMR of the extracted product showed data that matched the starting material.



11 **7**

Equation 15.

Attempted synthesis of cholest-5-en-3β-ol azide 7 was tried by reaction of cholest-5-en-3-ol (3β) -, 4-nitrobenzenesulfonate **11** with sodium azide. Once cholest-5-en-3-ol (3β) -, 4-nitrobenzenesulfonate **11** was dissolved in DMF, sodium azide in acetic acid was introduced into the reaction mixture to generate **7**. TLC (1:1 hexane: ethyl acetate) showed no consumption of **11** after twenty-four hours. The ^{1}H NMR and ^{13}C NMR of the extracted product showed data that matched the starting material.

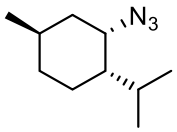
In conclusion, it was shown that the "one-pot" azidation was unsuccessful in converting chiral secondary alcohols to their corresponding azides. On the other hand, the synthesis of sulfonate ester intermediates which are used in traditional azide synthesis was successful. For further research, simple chiral secondary alcohols can be explored. Additionally, use of nonaflyl azide containing the nonaflate leaving group that is 120,000 times better leaving group than mesylate and twice as good as triflate, could be explored.

Experimental.

General procedures.

The apparatus used in the experiments was oven dried and kept in the desiccator to cool before use. The reactions were monitored via thin layer chromatography (TLC) to determine end point of the reactions. ^{1}H and ^{13}C nuclear magnetic resonance spectra of the samples were recorded in $CDCl_3$ solvent using Bruker Avance II and Avance III systems at a frequency of 400 MHZ. The chemical shifts were recorded in parts per million (ppm). Signals are labelled as follows; s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), m (multiplet) and coupling constants (*J*) are measured in Hertz. A Thermo Electron Corporation IR 200 spectrometer was used to record infrared spectra.

Attempted synthesis of menthol azide (4).



4

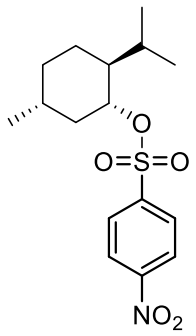
In a 100 mL round-bottom flask equipped with septum and magnetic stir bar, menthol (0.78 g, 5 mmol) was dissolved in acetonitrile (15.0 mL). The flask was flushed with nitrogen gas and DBU (0.83 g, 5.5 mmol) was added. After 30 minutes a solution of *p*-NBSA (1.27 g, 5.5 mmol) in acetonitrile (5 mL) was added dropwise for 30 minutes. The reaction mixture was left to stir overnight. TLC (1:1 hexane:ethyl acetate) showed that there was no consumption of the starting material. The reaction mixture was poured

into ethyl acetate (50 mL) and water (50 mL) in a separatory funnel. After separation the organic layer was washed with 5% HCl, washed with water, and then washed with saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed through rotary evaporation at 40 °C. NMR analysis of the extracted product confirmed that there was no formation of the desired azide product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37-3.43 (ddd, 1H, J = 4.15 Hz), 2.13-2.21 (m, 1H), 1.93-1.99 (m, 1H), 1.62-1.68 (m, 2H), 1.51 (s, -OH), 1.39-1.43 (m, 4H) 1.01-1.11 (m, 1H) 0.90-0.94 (m, 6H) 0.81-0.82 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 71.6, 50.16, 45.13, 34.59, 31.63, 25.90, 23.28, 22.04, 20.92, 16.15.

Attempted synthesis of benzenesulfonic acid, 4-nitro-, 5-methyl-2-(1-methylethyl) cyclohexyl ester (5) from menthol (3).



5

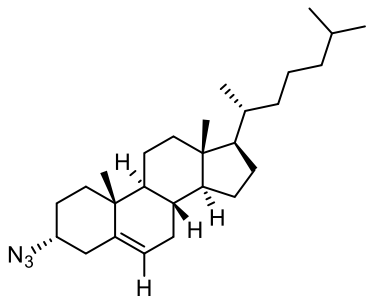
In a 100 mL round-bottom flask equipped with septum and magnetic stir bar, menthol (0.78 g, 5 mmol) was dissolved in pyridine (8.0 mL). The flask was flushed with nitrogen gas. After 30 minutes a solution of 4-nitrobenzene sulfonyl chloride (*p*-NBSCl)

(1.23 g, 5.5 mmol) in pyridine (5 mL) was added dropwise for 30 minutes. The reaction mixture was left to stir overnight. TLC (1:2 hexane:ethyl acetate) showed that there was no consumption of the starting material. The reaction mixture was poured into ethyl acetate (50 mL) and water (50 mL) in a separatory funnel. After separation the organic layer was neutralized with 5% HCl, washed with water, and then washed with saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed through rotary evaporation at 40 °C. NMR analysis confirmed that there was no formation of the desired product as depicted by TLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37-3.43 (ddd, 1H, J = 4.15 Hz), 2.13-2.21 (m, 1H), 1.93-1.99 (m, 1H), 1.62-1.68 (m, 2H), 1.51 (s, -OH), 1.39-1.43 (m, 4H) 1.01-1.11 (m, 1H) 0.90-0.94 (m, 6H) 0.81-0.82 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 71.6, 50.16, 45.13, 34.59, 31.63, 25.90, 23.28, 22.04, 20.92, 16.15.

Attempted synthesis of Cholest-5-en-3β-ol azide (7) from Cholesterol (6).



10

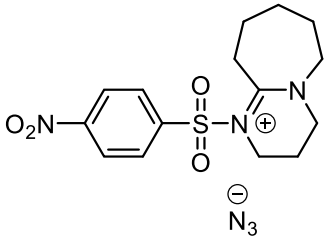
In a 100 mL round-bottom flask equipped with septum and magnetic stir bar, cholesterol (1.93 g, 5 mmol) was dissolved in anhydrous dichloromethane (16.2 mL) in

an ice bath. The flask was flushed with nitrogen gas and suitable nitrogen-containing base was added. After 30 minutes a solution of *p*-NBSA (2.3 g, 10 mmol) in dichloromethane (5 mL) was added dropwise for 30 minutes. The reaction was left to stir overnight. Increase in the amount of *p*-NBSA and the base tested did not result in significant azide formation. The same reaction was run using different organic solvents to try and determine a solvent that can yield the desired azide product under similar reagents and condition. Equally, there was no formation of the desired azide product. This observation led to the conclusion that a side reaction between the bases used and *p*-NBSA was occurring hindering the formation of the azide product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H), 3.47-3.55 (m, 1H), 2.26-2.28 (s, 2H), 2.02-2.03 (d, 2H, J = 4.67 Hz), 1.08-2.00 (m, 24H), 1.00 (s, 3H) 0.93 (s, 3H) 0.86-0.87 (m, 6H) 0.68 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.82, 121.66, 71.80, 56.83, 56.26, 50.23, 42.37, 39.85, 39.54, 37.30, 36.54, 36.23, 35.77, 31.97, 31.93, 31.72, 28.20, 28.00, 24.29, 23.85, 22.75, 22.51, 21.11, 19.36, 18.17, 11.85.

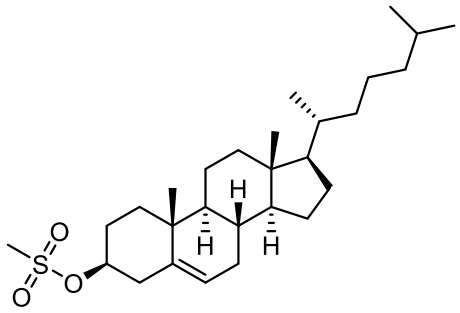
***In situ* generation of anionic azide from *p*-NBSA and DBU**.



8

In a 100 mL round-bottom flask equipped with septum and magnetic stir bar, *p*-NBSA (1.14 g, 5 mmol) was dissolved in acetonitrile (20 mL). The flask was flushed with nitrogen gas and immediately DBU (0.75 mL, 5 mmol) was added through a syringe into the reaction flask. IR spectroscopy was employed in monitoring the progress of the reaction after three hours and the samples used for the testing were not worked up. Data indicated azide absorption at 2020 cm^{-1} which suggests *in situ* generation of anionic azide.

Synthesis of sulfonate ester intermediates.



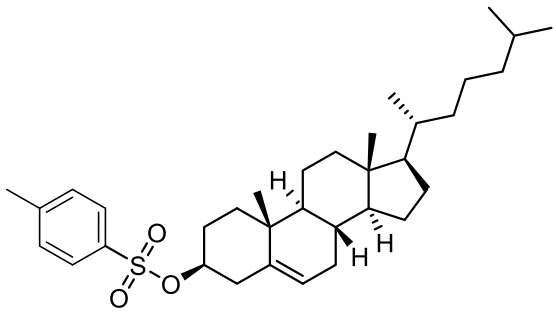
9

In a 100 mL round-bottom flask equipped with septum and magnetic stir bar, cholesterol (1.93 g, 5 mmol) was dissolved in anhydrous dichloromethane (16.2 mL) in an ice bath. Triethylamine (1.1 mL, 7.5 mmol) and a solution of methanesulfonyl chloride (0.42 mL, 5.3 mmol) in dichloromethane (3.3 mL) was added dropwise in 30 min. The reaction mixture left to stir overnight. The completion of the reaction was determined by TLC (1:3 hexane:ethyl acetate). The reaction mixture was poured into ethyl acetate (50 mL) and water (50 mL) in a separatory funnel. After separation the organic layer was neutralized with 5% HCl, washed with water, and then washed with

saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed through rotary evaporation at 40 °C. Recrystallization of the product from acetone-methanol mixture gave pure cholest-5-en-3β-ol methanesulfonate (1.23 g, 2.651 mmol) (**9**) in 53% yield. Melting point 114-117° C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (s, 1H), 4.51 (m, 1H), 2.99 (s, 3H),2.49 (s, 2H), 1.01-2.01 (m, 32H), 0.86 (m, 6H) 0.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.72, 123.77, 81.99, 56.68, 56.21, 50.03, 42.35, 39.72, 39.52, 39.20, 38.79, 36.95, 36.42, 36.20, 35.76, 31.89, 31.84, 29.01, 28.17, 27.99, 24.26,23.84, 22.75, 22.52, 21.05, 19.17, 18.72, 11.84.



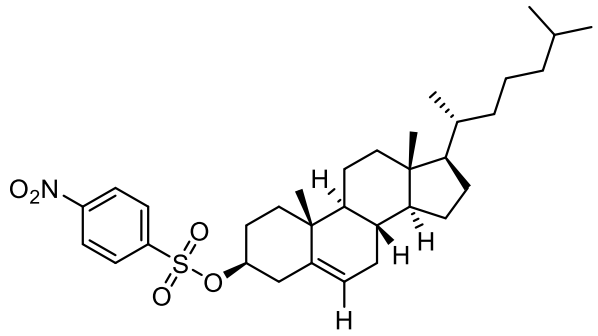
10

In a 100 mL round-bottom flask equipped with septum and magnetic stir bar, cholesterol (1.93 g, 5 mmol) was dissolved in dry pyridine (4 mL). *N,N'*-dimethylaminopyridine (DMAP, 0.193 g, 0.16 mmol) and *p*-toluenesulfonyl chloride (1.43g,7.50 mmol) were added to reaction mixture and stirred at ice temperature for 20 h until TLC (5:1 hexane: ethyl acetate) showed the consumption of the starting material. The solvent was evaporated under reduced pressure and the residue was dissolved ethyl acetate. The reaction mixture was added to 250 mL separatory funnel; washed with 5%

hydrochloric acid (60 mL), 5% $NaHCO_3$ (60 mL) and H_2O (60 mL). The separated ethyl acetate layer was collected, dried over $MgSO_4$, filtered and the solvent was removed through rotary evaporation at 40 °C. The residue was recrystallized from acetone-methanol mixture to give pure cholest-5-ene-3β-yl p-toluenesulfonate (2.291 g, 3.95 mmol) (**10**) as colorless needles in 79% yield. Melting point 128-131 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 1H) 7.79 (m, 1H) 7.34 (m, 1H) 7.32 (m, 1H), 5.41 (s, 1H), 4.51 (m, 1H), 2.45 (s, 3H), 2.24-2.28 (m, 2H), 1.01-2.01 (m, 32H), 0.86 (m, 6H) 0.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.43, 138.87, 134.66, 129.77, 127.67, 123.55, 82.43, 56.65, 56.09, 49.90, 42.29, 39.65, 39.52, 38.87, 36.89, 36.35, 36.17, 35.77, 31.86, 31.75, 28.63, 28.22, 28.03, 24.26, 23.81, 22.84, 22.58, 21.68, 21.00, 19.16, 18.11, 11.85.



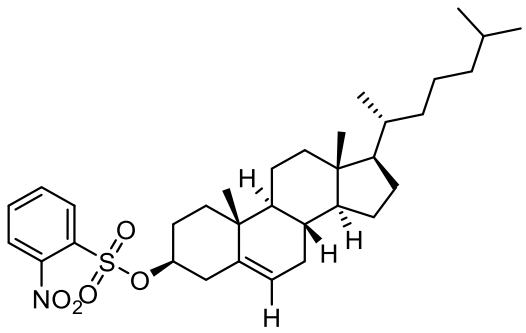
11

In a 100 mL round-bottom flask equipped with septum and magnetic stir bar, cholesterol (1.93 g, 5 mmol) was dissolved in anhydrous dichloromethane (16.2 mL) in an ice bath. Triethylamine (1.1 mL, 7.5 mmol) and a solution of 4-nitrobenzenesulfonyl chloride (2.3 g, 10.0 mmol) in dichloromethane (6.6 mL) was added dropwise in 30 min. The reaction was warmed up to room temperature and left to stir overnight. The

completion of the reaction was determined by TLC (1:2 hexane: ethyl acetate). The reaction mixture was poured into ethyl acetate (50 mL) and water (50 mL) in a separatory funnel. After separation the organic layer was neutralized with 5% HCl, washed with water, and then washed with saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed through rotary evaporation at 40 °C. The solid residue was recrystallized from methanol to give pure cholest-5-en-3-ol (3β)-, 4-nitrobenzenesulfonate (2.456 g, 4.301 mmol) (**11**) in 86% yield. Melting point 123-126 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H) 8.37 (s, 1H) 8.12 (s, 1H) 8.09 (s, 1H), 5.34 (s, 1H), 4.44-4.52 (m, 1H), 2.48 (d, 2H, *J* = 11.73 Hz) 2.30-2.34 (m, 2H), 1.01-2.01 (m, 32H), 0.86 (m, 6H) 0.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.69, 143.65, 138.39, 128.87, 124.33, 124.11, 84.21, 56.66, 56.20, 49.98, 42.33, 39.68, 39.52, 38.99, 36.87, 36.38, 36.19, 35.73, 31.85, 31.79, 28.81, 28.14, 27.98, 24.23, 23.82, 22.74, 22.51, 21.02, 19.10, 18.70, 11.82.



12

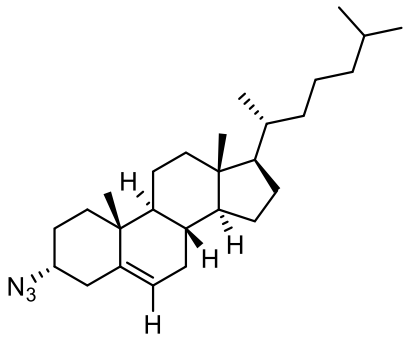
In a 100 mL round-bottom flask equipped with septum and magnetic stir bar, cholesterol (1.93 g, 5 mmol) was dissolved in anhydrous dichloromethane (16.2 mL) in

an ice bath. Triethylamine (1.1 mL, 7.5 mmol) and solution of 2-nitrobenzenesulfonyl chloride (2.3 g, 10.0 mmol) in dichloromethane (6.6 mL) was added dropwise in 30 min. The reaction mixture was left to stir overnight. TLC (1:2 hexane: ethyl acetate) showed that there was no consumption of starting material. The reaction mixture was poured into ethyl acetate (50 mL) and water (50 mL) in a separatory funnel. After separation the organic layer was neutralized with 5% HCl, washed with water, and then washed with saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed through rotary evaporation at 40 °C.NMR data confirmed that there was no formation of the desired intermediate product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H), 3.47-3.55 (m, 1H), 2.26-2.28 (s, 2H), 2.02-2.03 (s, 2H), 1.08-2.00 (m, 24H), 1.00 (s, 3H) 0.93 (s, 3H) 0.86-0.87 (m, 6H) 0.68 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.82, 121.66, 71.80, 56.83, 56.26, 50.23, 42.37, 39.85, 39.54, 37.30, 36.54, 36.23, 35.77, 31.97, 31.93, 31.72, 28.20, 28.00, 24.29, 23.85, 22.75, 22.51, 21.11, 19.36, 18.17, 11.85.

Attempted NaN_3-based azidation of sulfonate ester intermediates.

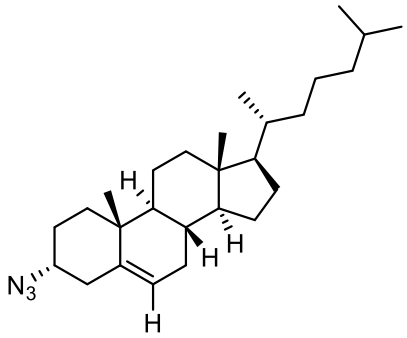


7

In a 100 mL round-bottom flask equipped with septum and magnetic stir bar, cholest-5-en-3β-ol methanesulfonate **9** (2.32 g, 5 mmol) was dissolved in dimethylformamide (DMF) (25.0 mL).Sodium azide (0.98 g, 15.0 mmol, 3 equiv) and acetic acid (2.0 mL) were added at room temperature while stirring. The reaction mixture was heated to 65 °C and stirred for twenty-four hours. TLC (1:1 hexane: ethyl acetate) showed that there was no consumption of starting material. The reaction mixture was cooled to room temperature and aqueous sodium hydrogen carbonate (100 mL) solution was added. The organic product was extracted using benzene (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. NMR data confirmed that there was no formation of the desired azide product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (s, 1H), 4.51 (m, 1H), 2.99 (s, 3H),2.49 (s, 2H), 1.01-2.01 (m, 32H), 0.86 (m, 6H) 0.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.72, 123.77, 81.99, 56.68, 56.21, 50.03, 42.35, 39.72, 39.52, 39.20, 38.79, 36.95, 36.42, 36.20, 35.76, 31.89, 31.84, 29.01, 28.17, 27.99, 24.26,23.84, 22.75, 22.52, 21.05, 19.17, 18.72, 11.84.

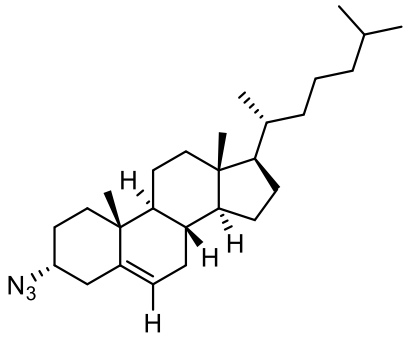


7

In a 100 mL round-bottom flask equipped with septum and magnetic stir bar, cholest-5-ene-3β-yl p-toluenesulfonate **10** (2.70 g, 5 mmol) was dissolved in dimethylformamide (DMF) (25.0 mL).Sodium azide (0.98 g, 15.0 mmol, 3 equiv) and acetic acid (2.0 mL) were added at room temperature while stirring. The reaction mixture was heated to 65 °C and stirred for twenty-four hours. TLC (1:1 hexane: ethyl acetate) showed that there was no consumption of starting material. The reaction mixture was cooled to room temperature and aqueous sodium hydrogen carbonate (100 mL) solution was added. The organic product was extracted using benzene (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. NMR data confirmed that there was no formation of the desired azide product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H) 7.79 (s, 1H) 7.34 (s, 1H) 7.32 (s, 1H), 5.41 (s, 1H), 4.51 (m, 1H), 2.45 (s, 3H), 2.24-2.28 (m, 2H), 1.01-2.01 (m, 32H), 0.86 (m, 6H) 0.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.43, 138.87, 134.66, 129.77, 127.67, 123.55, 82.43, 56.65, 56.09, 49.90, 42.29, 39.65, 39.52, 38.87, 36.89, 36.35, 36.17, 35.77, 31.86, 31.75, 28.63, 28.22, 28.03, 24.26, 23.81, 22.84, 22.58, 21.68, 21.00, 19.16, 18.11, 11.85.



7

In a 100 mL round-bottom flask equipped with septum and magnetic stir bar, cholest-5-en-3-ol (3β) -, 4-nitrobenzenesulfonate **11** (2.86 g, 5 mmol) was dissolved in dimethylformamide (DMF) (25.0 mL). Sodium azide (0.98 g, 15.0 mmol, 3 equiv) and acetic acid (2.0 mL) were added at room temperature while stirring. The reaction mixture was heated to 65 °C and stirred for twenty-four hours. TLC (1:1 hexane: ethyl acetate) showed that there was no consumption of starting material. The reaction mixture was cooled to room temperature and aqueous sodium hydrogen carbonate (100 mL) solution was added. The organic product was extracted using benzene (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. NMR data confirmed that there was no formation of the desired azide product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H) 8.37 (s, 1H) 8.12 (s, 1H) 8.09 (s, 1H), 5.34 (s, 1H), 4.44-4.52 (m, 1H), 2.48 (d, 2H, *J* = 11.73 Hz) 2.30-2.34 (m, 2H), 1.01-2.01 (m, 32H), 0.86 (s, 6H) 0.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.69, 143.65, 138.39, 128.87, 124.33, 124.11, 84.21, 56.66, 56.20, 49.98, 42.33, 39.68, 39.52, 38.99, 36.87, 36.38, 36.19, 35.73, 31.85, 31.79, 28.81, 28.14, 27.98, 24.23, 23.82, 22.74, 22.51, 21.02, 19.10, 18.70, 11.82.

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Appendix

NMR and IR spectra

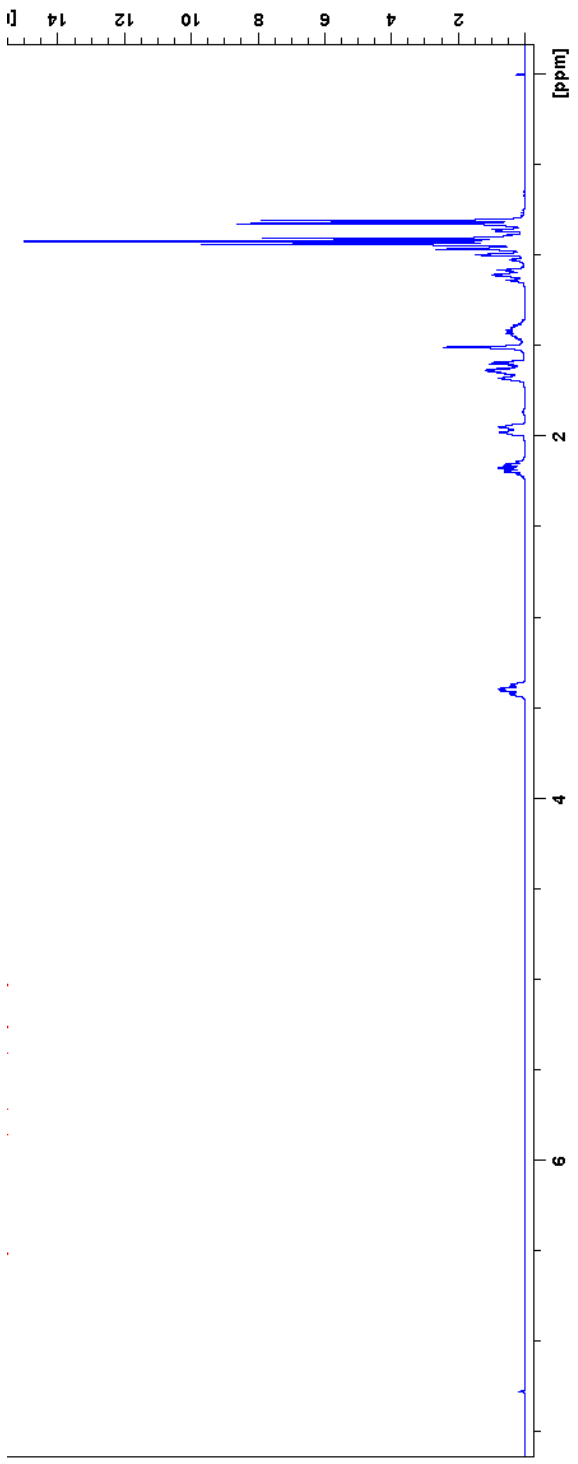

Figure 3: ^{1}H NMR spectrum of menthol (**3**).

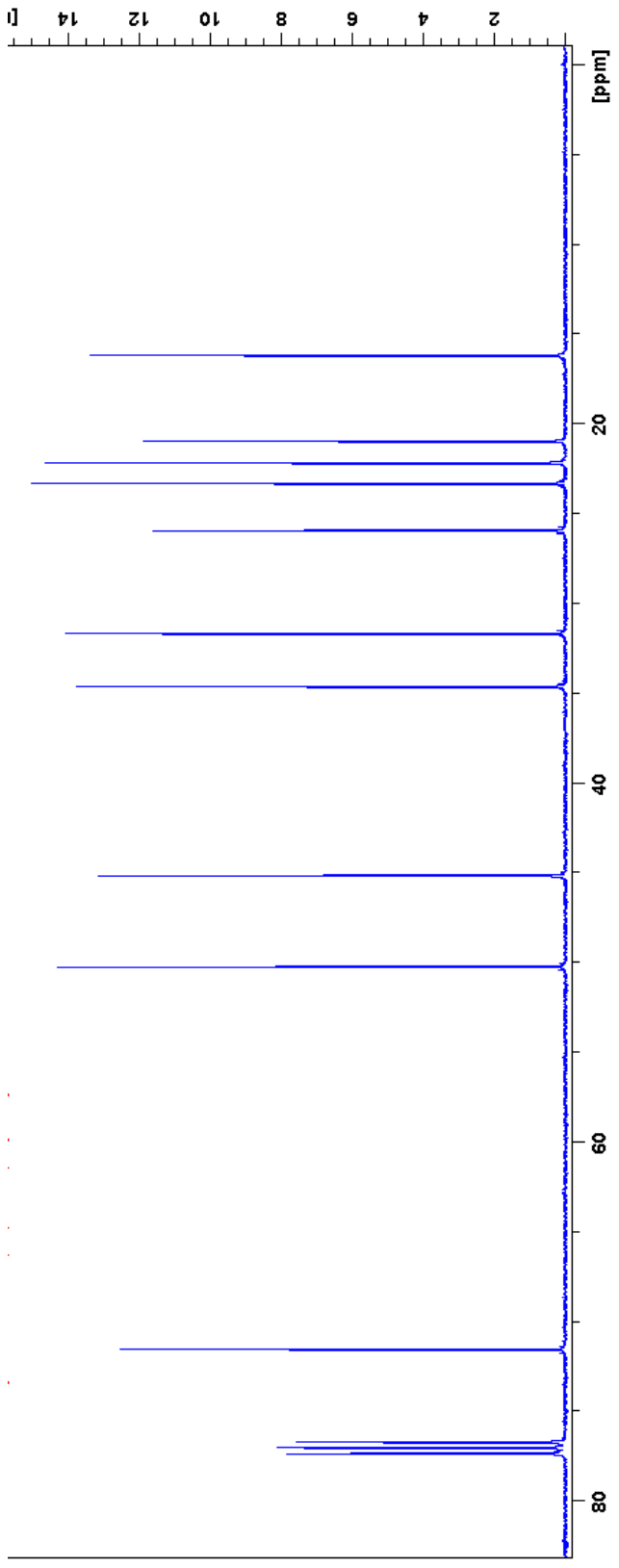

Figure 4: ^{13}C NMR spectrum of menthol (**3**).

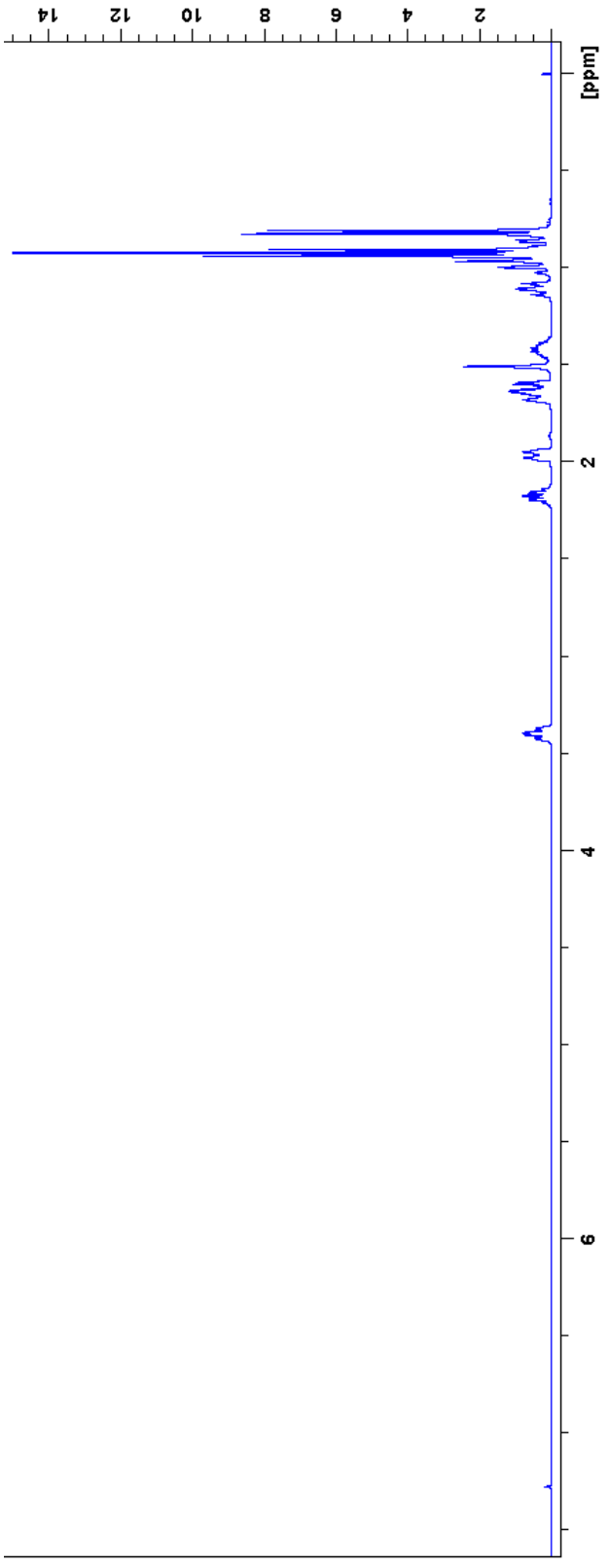

Figure 5: ^{1}H NMR spectrum of the attempted menthol azide **4** synthesis.

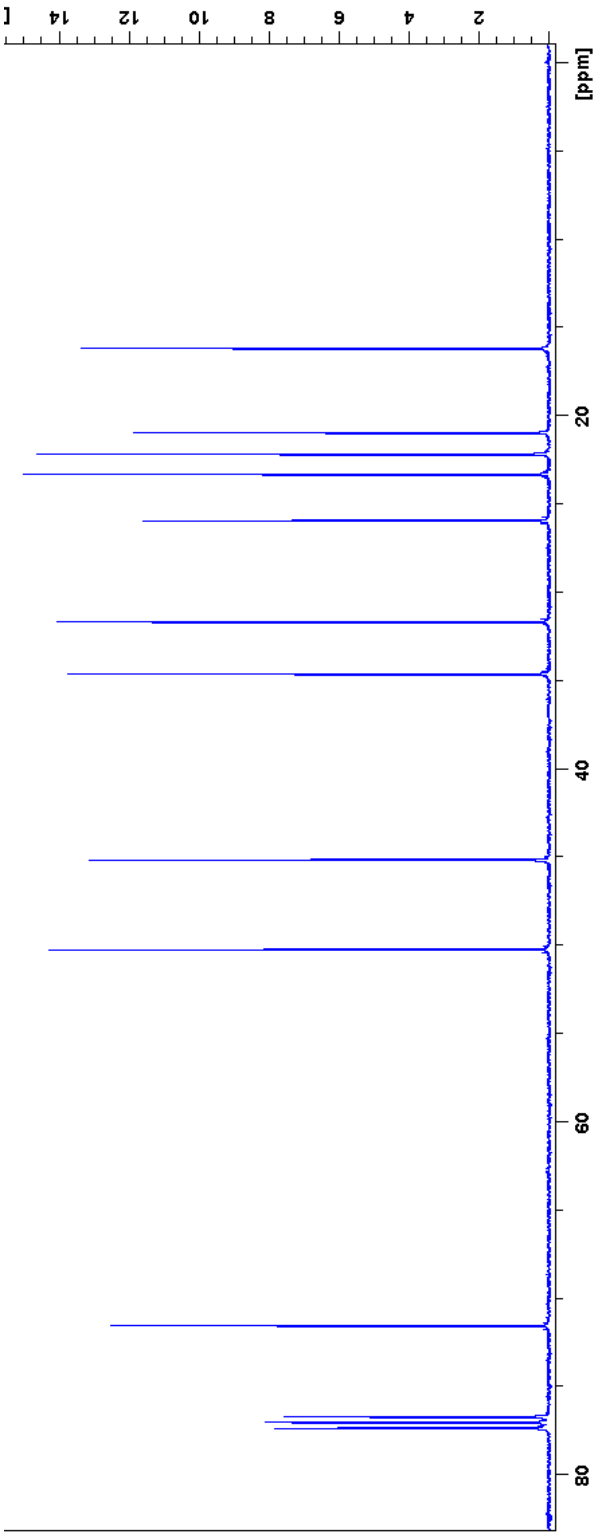

Figure 6: ^{13}C NMR spectrum of the attempted menthol azide **4** synthesis.

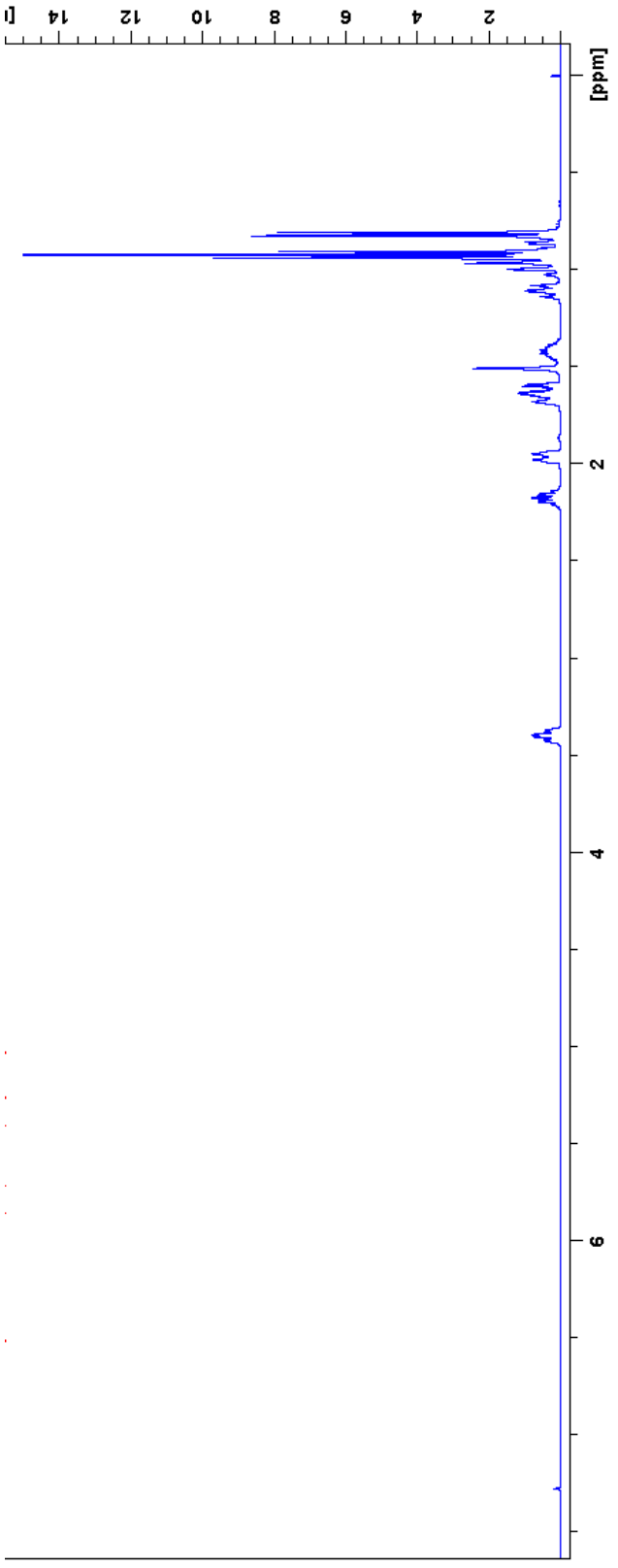

Figure 7: ^{1}H NMR spectrum of the attempted benzenesulfonic acid, 4-nitro-, 5-methyl-2-(1-methylethyl) cyclohexyl ester (**5**) synthesis.

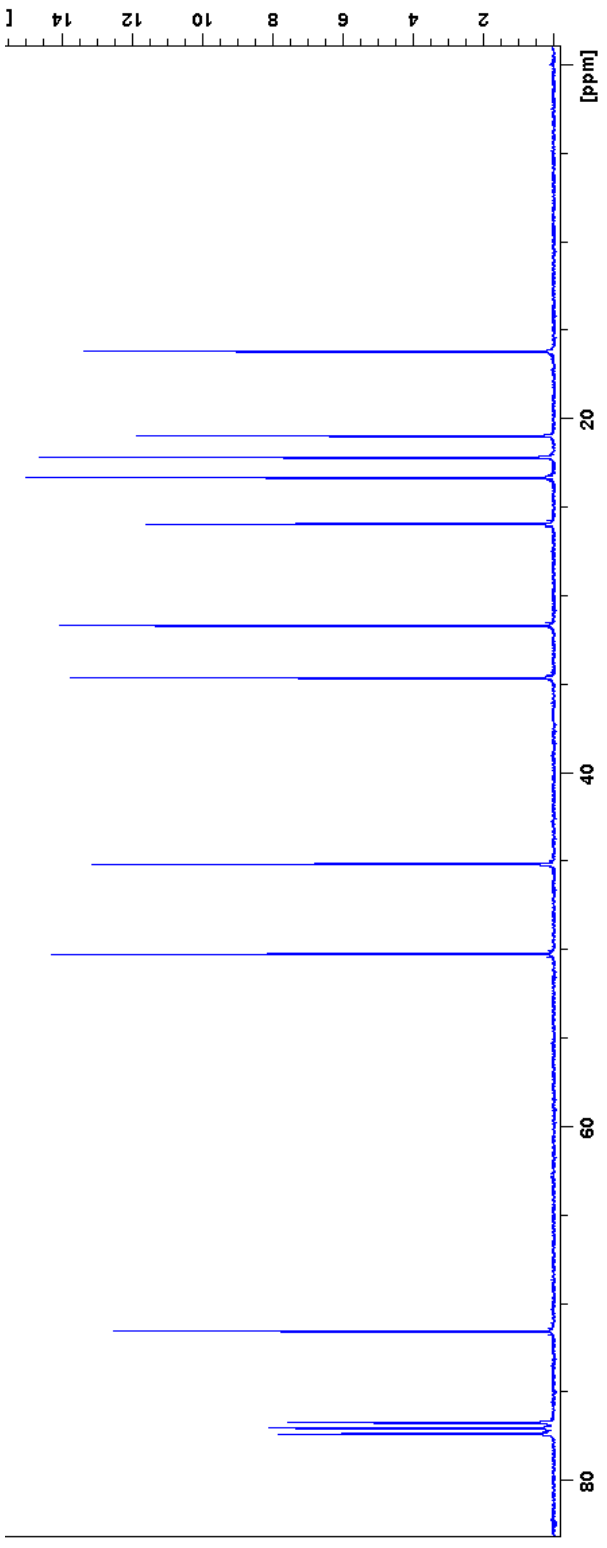

Figure 8: ^{13}C NMR spectrum of the attempted benzenesulfonic acid, 4-nitro-, 5-methyl-2-(1-methylethyl) cyclohexyl ester (**5**) synthesis.

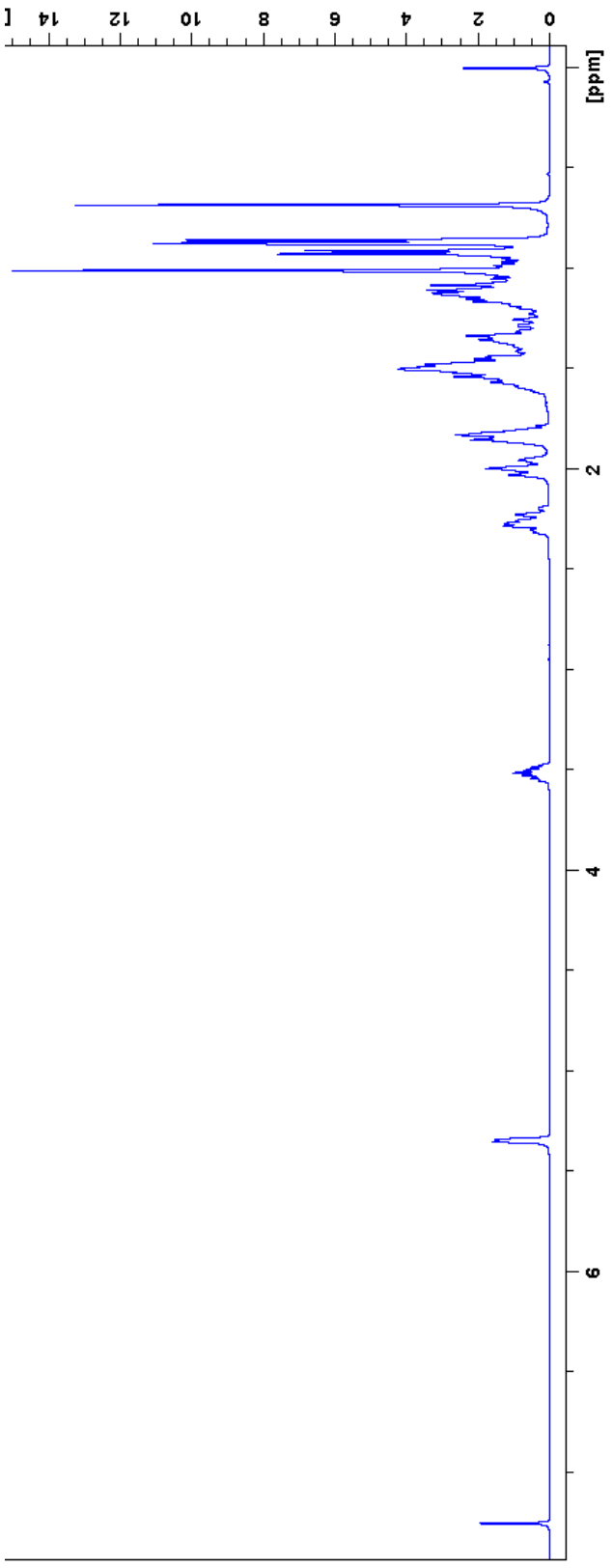

Figure 9: ^{1}H NMR spectrum of cholesterol (**6**).

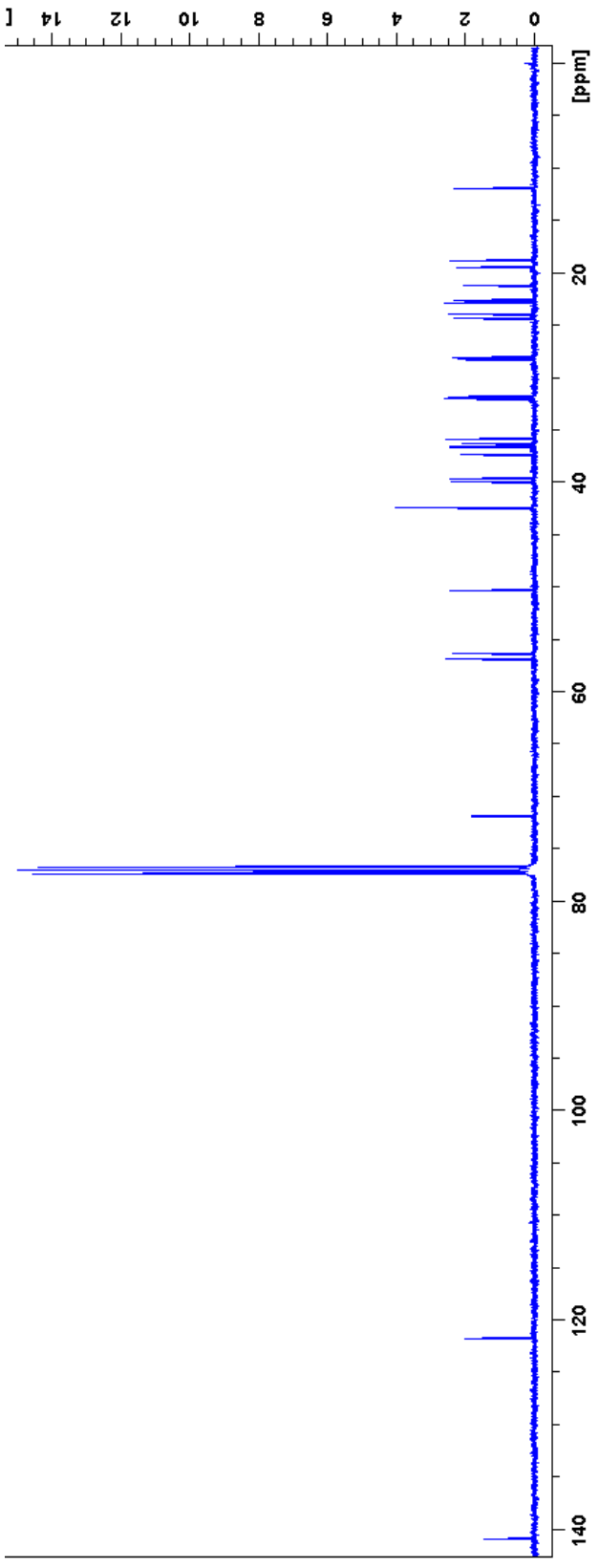

Figure 10: ^{13}C NMR spectrum of cholesterol (**6**).

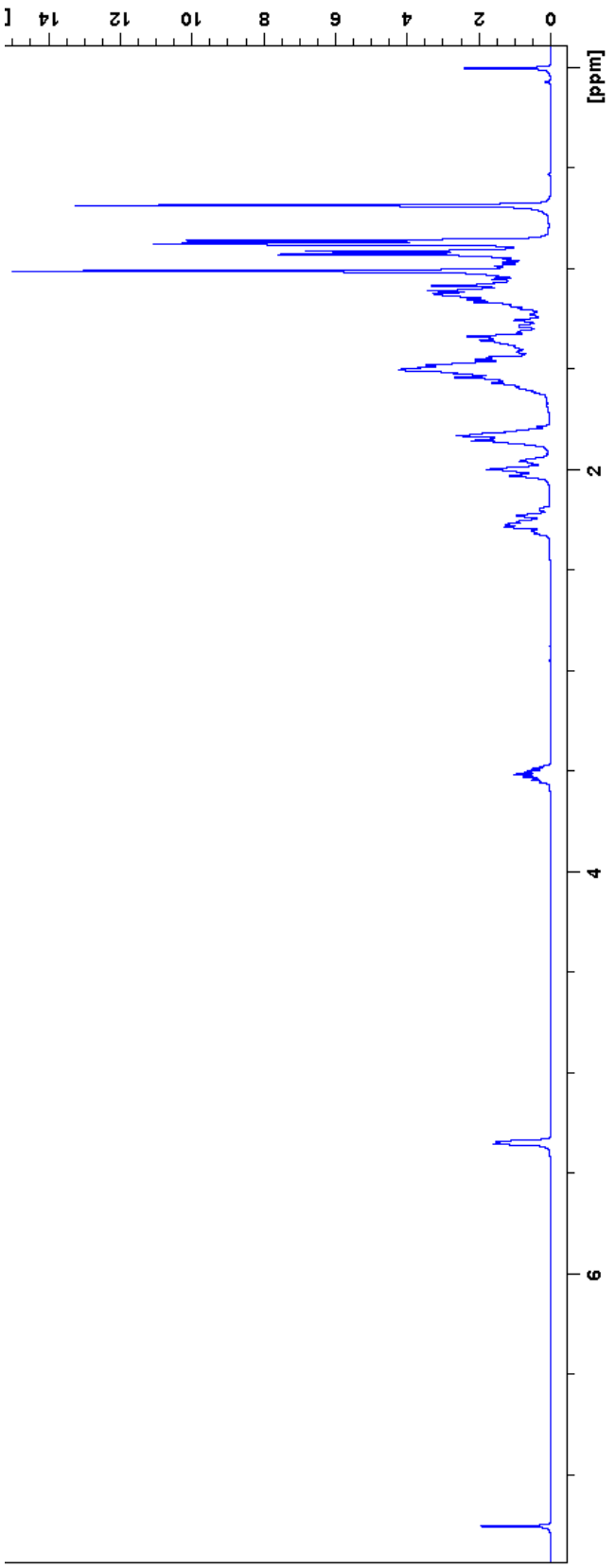

Figure 11: ^{1}H NMR spectrum of the attempted cholest-5-en-3β-ol azide (**7**) synthesis.

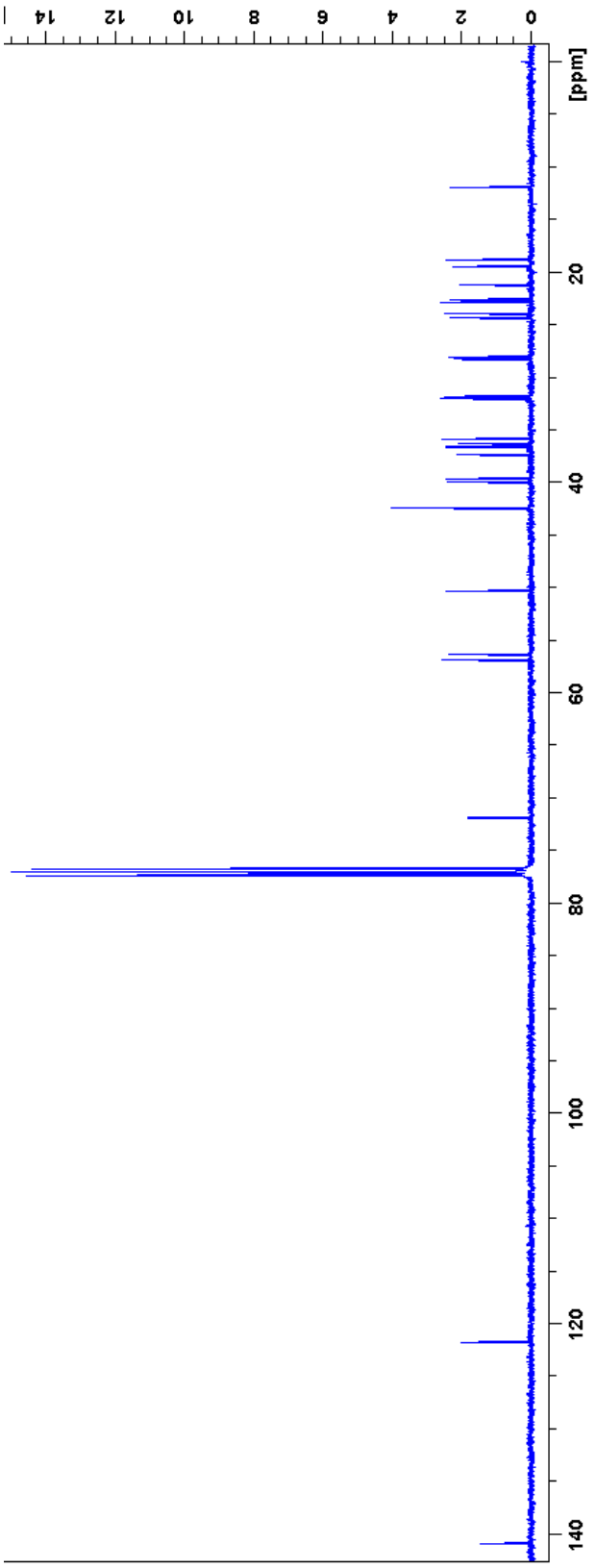

Figure 12: ^{13}C NMR spectrum of the attempted cholest-5-en-3β-ol azide (**7**) synthesis.

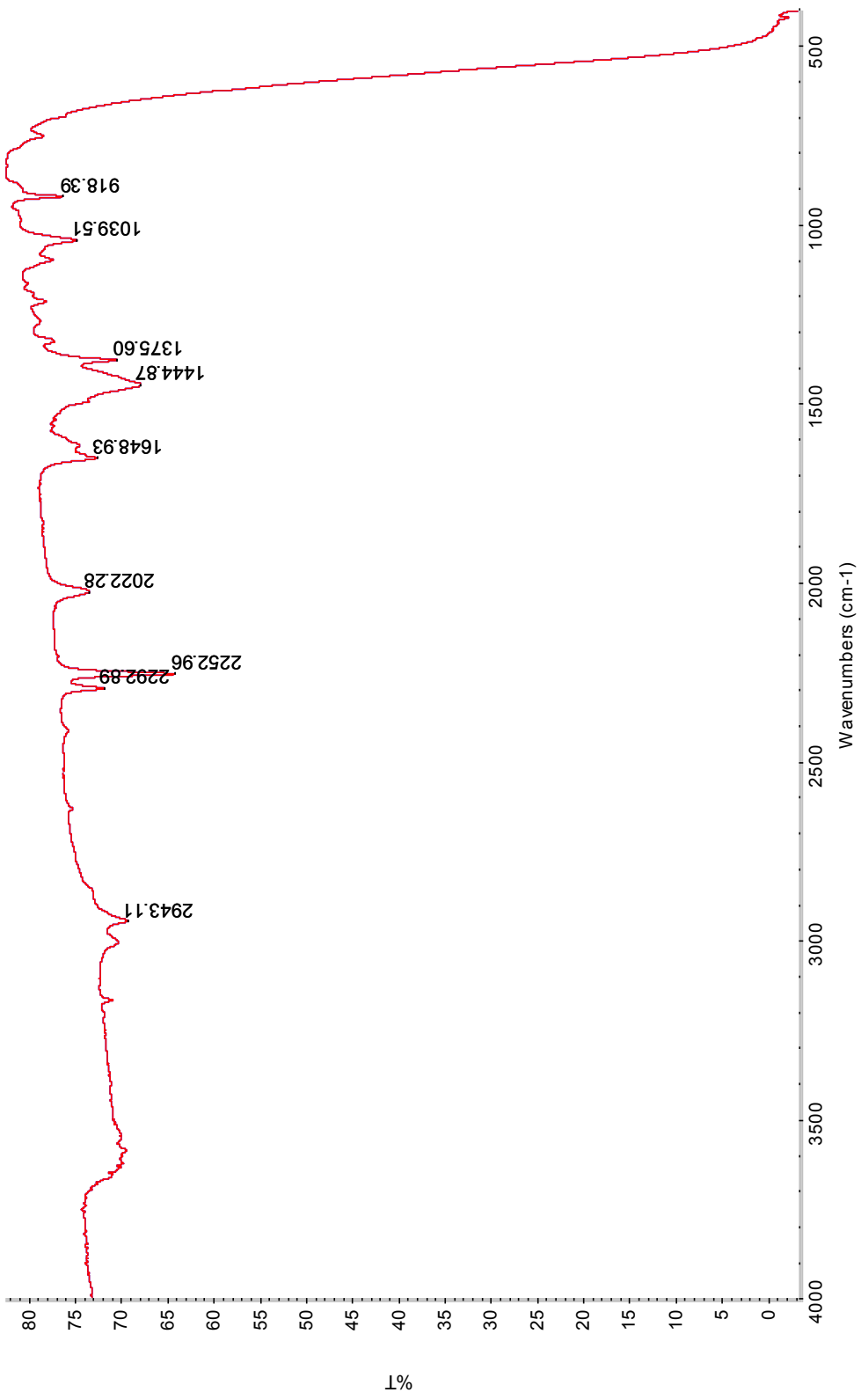

Figure 13: IR spectrum of the *in situ* product of *p*-NBSA and DBU **8**.

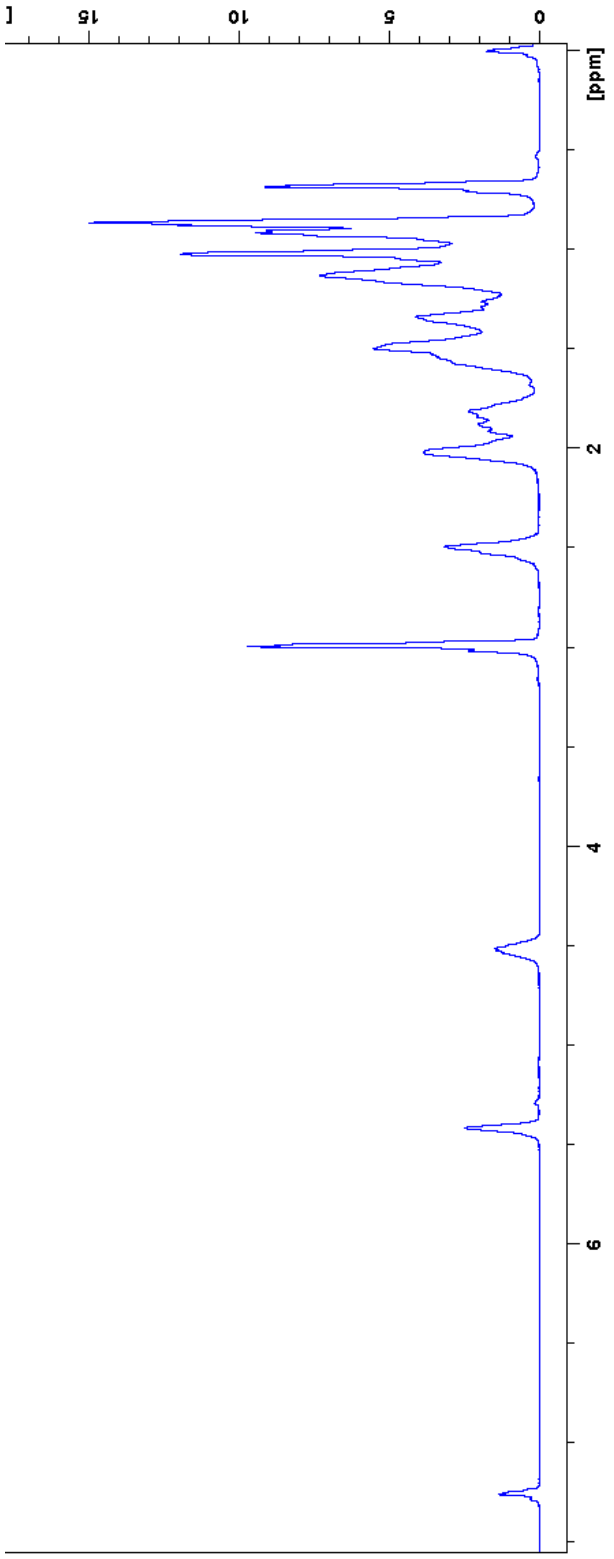

Figure 14: ^{1}H NMR spectrum of cholest-5-en-3β-ol methanesulfonate **(9)**.

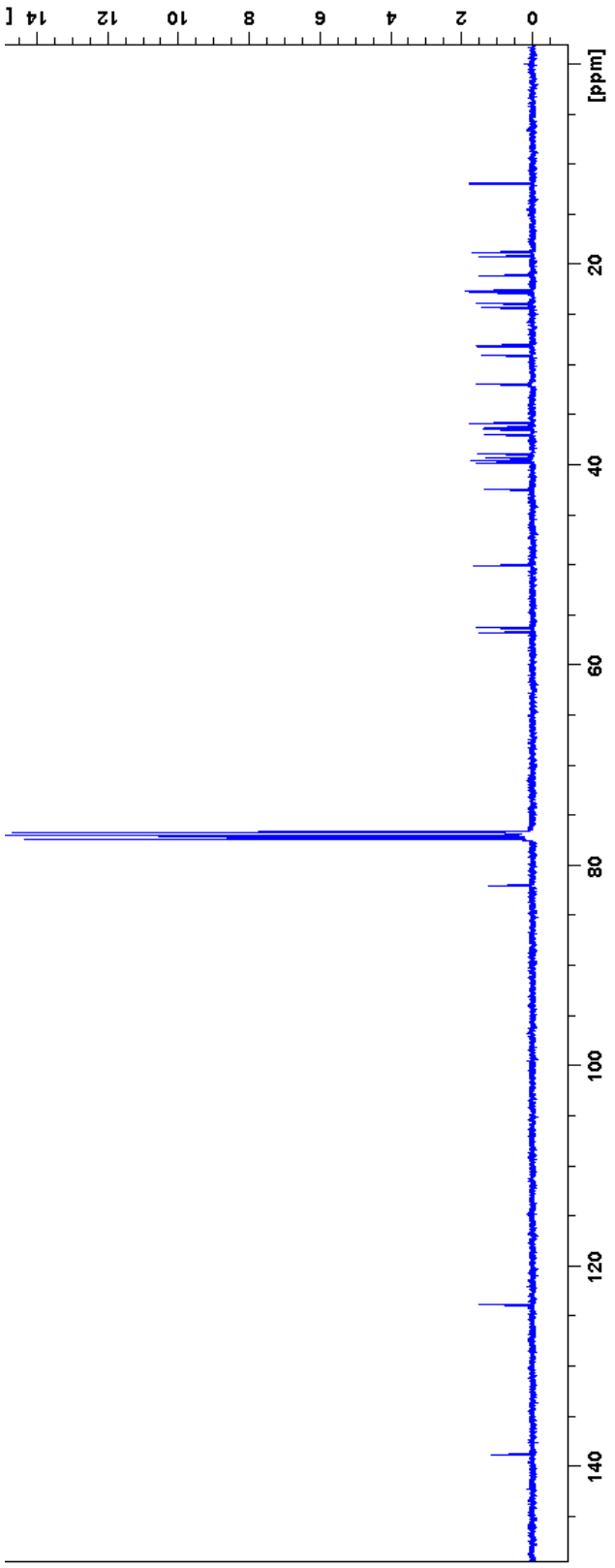

Figure 15: ^{13}C NMR spectrum of cholest-5-en-3β-ol methanesulfonate **(9)**.

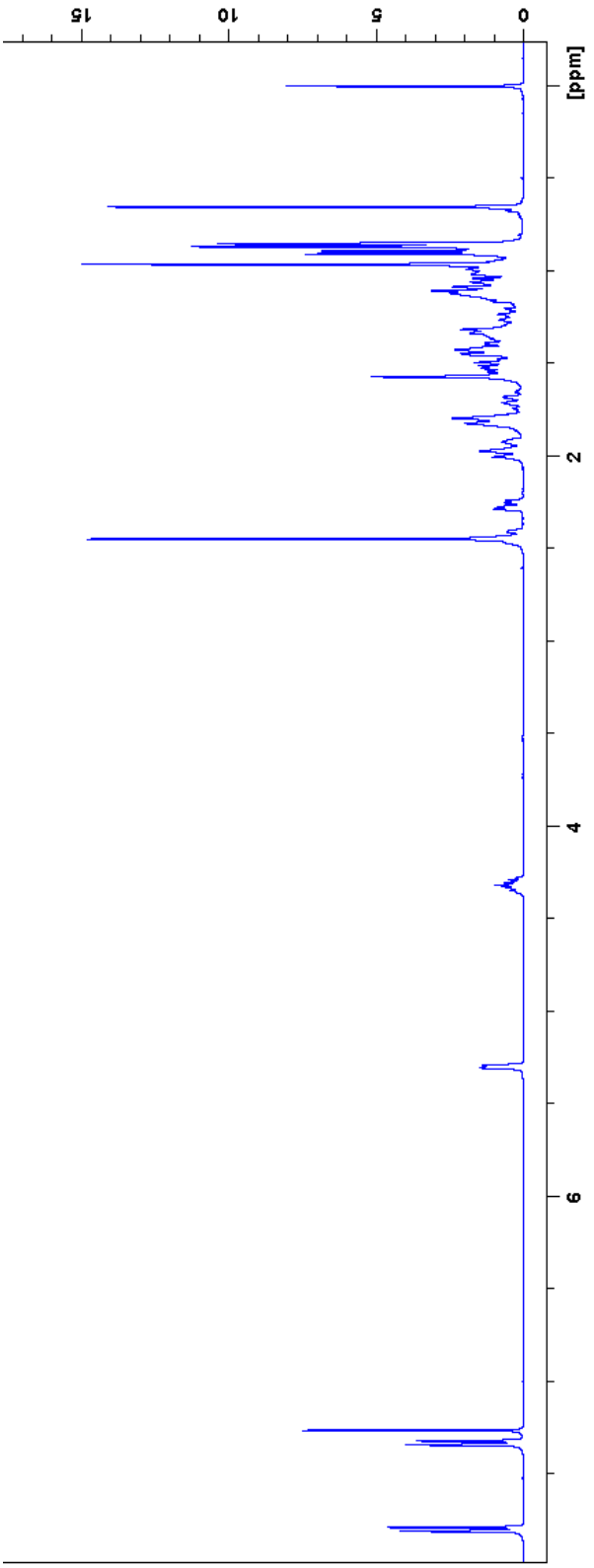

Figure 16: ^{1}H NMR spectrum of cholest-5-ene-3β-yl p-toluenesulfonate **(10)**.

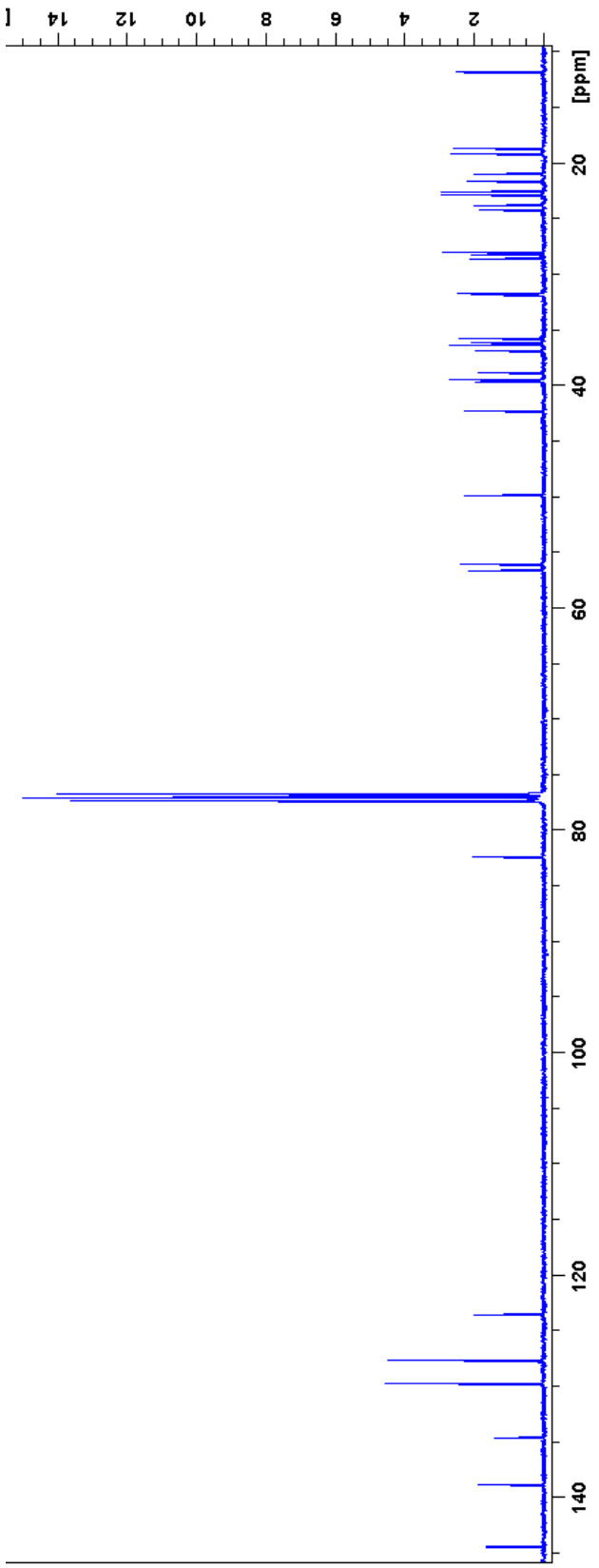

Figure 17: ^{13}C NMR spectrum of cholest-5-ene-3β-yl *p*-toluenesulfonate **(10)**.

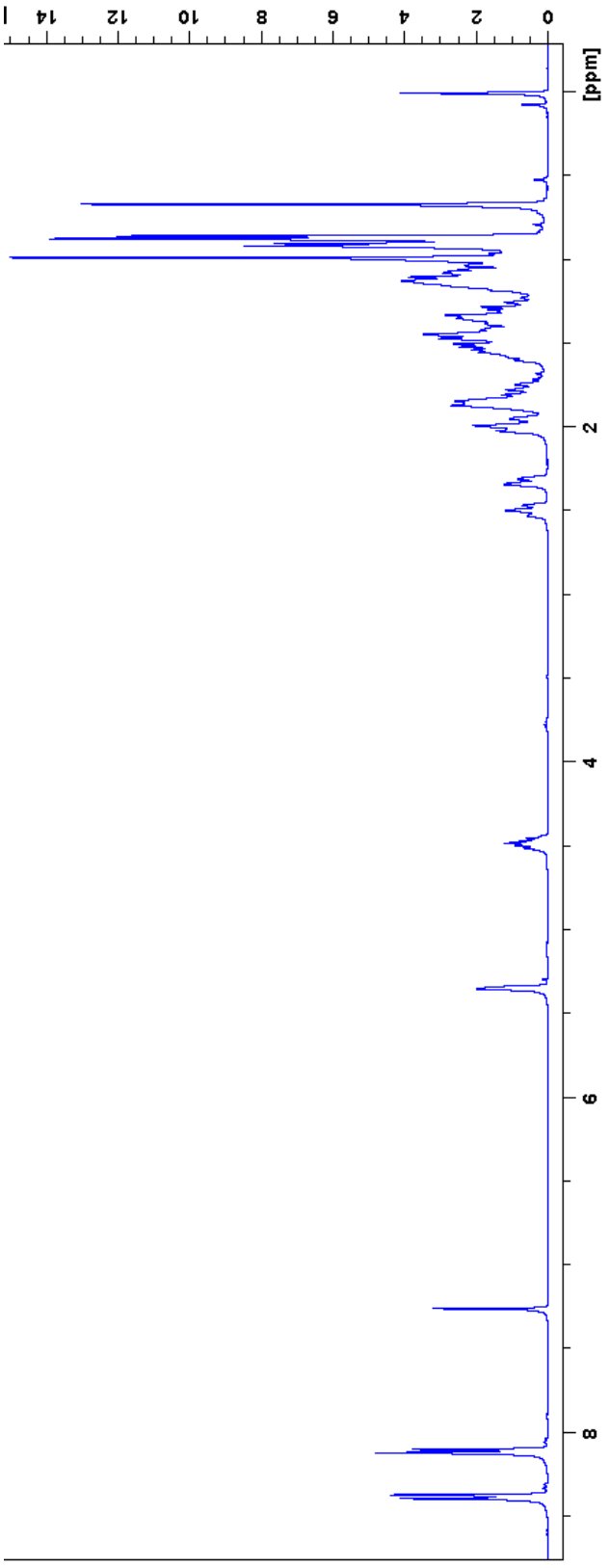

Figure 18: ^{1}H NMR spectrum of cholest-5-en-3-ol (3β)-4-nitrobenzenesulfonate **(11)**.

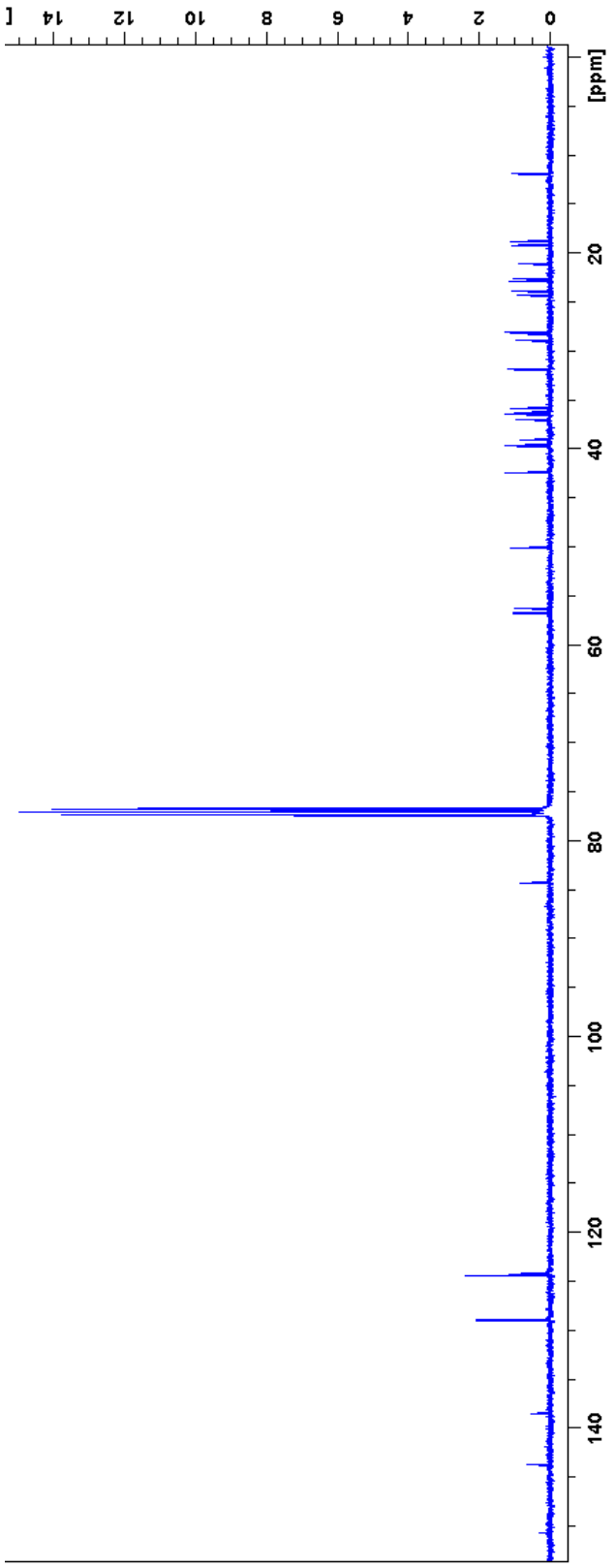

Figure 19: ^{13}C NMR spectrum of cholest-5-en-3-ol (3β)-4-nitrobenzenesulfonate **(11)**.

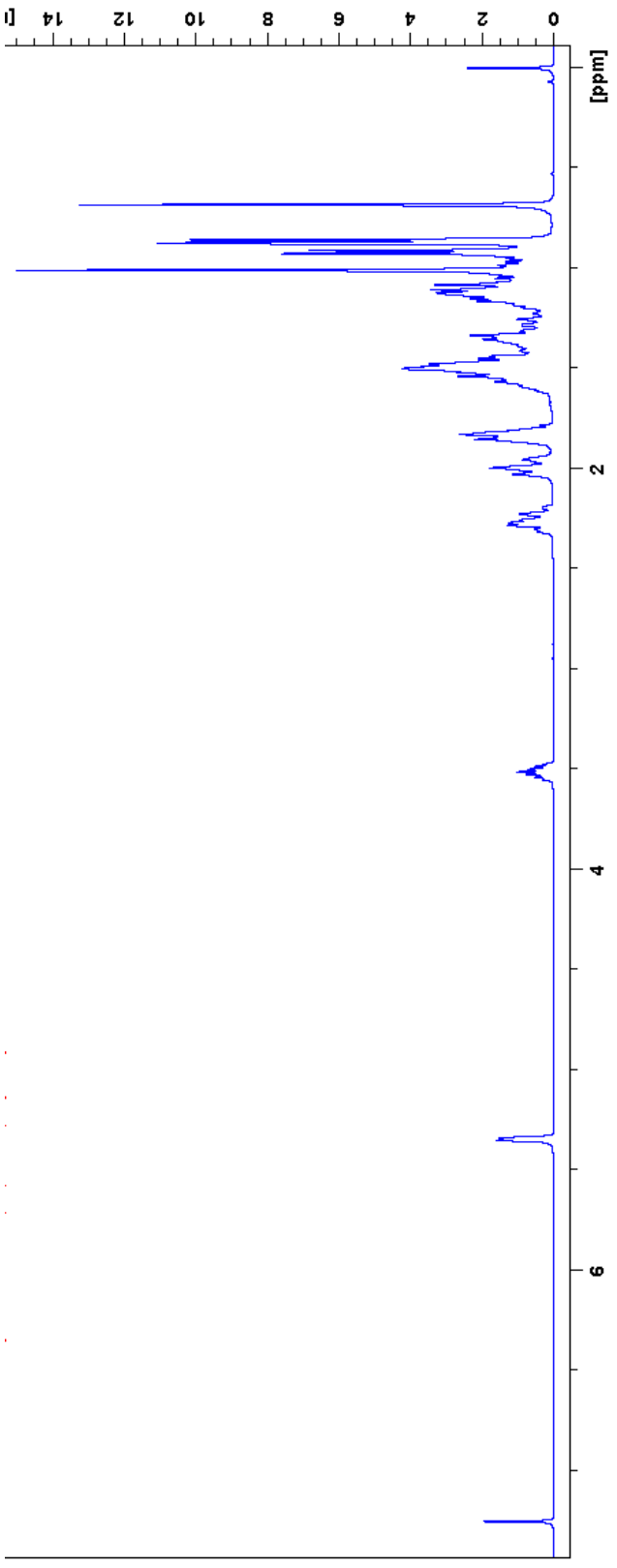

Figure 20: ^{1}H NMR spectrum of the attempted cholest-5-en-3-ol (3β)-2-nitrobenzenesulfonate **(12)** synthesis.

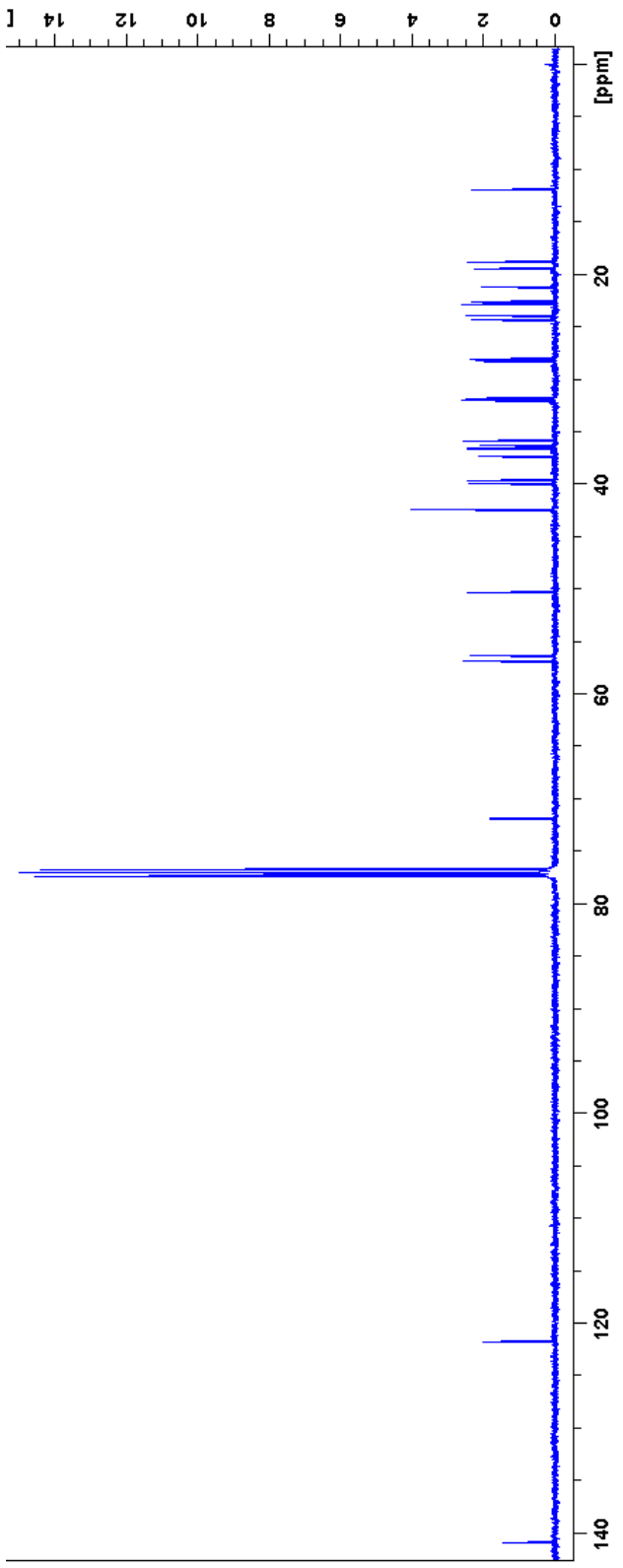

Figure 21: ^{13}C NMR spectrum of the attempted cholest-5-en-3-ol (3β)-2-nitrobenzenesulfonate **(12)** synthesis.