A NOVEL DESYMMETRISATION APPROACH TOWARDS CHIRAL MOLECULES, USING "CLICK" CHEMISTRY

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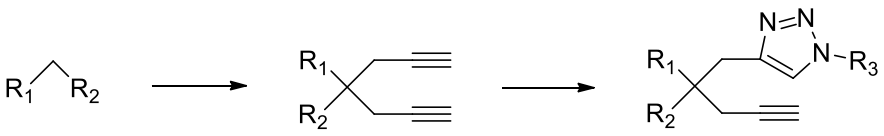
ABSTRACT

Typically, the popular click reaction between an alkyne and an azide forms a triazole in very high yield, but since this process does not produce a stereogenic centre, its use with chiral ligands has not been thoroughly investigated. Choosing a prochiral diyne as the starting material allows the click process to perform a desymmetrisation step. Desymmetrisation of prochiral molecules using click chemistry is a method that has had little attention in the past. Herein is described progress into a novel synthetic route to chiral molecules using this process.

The first part of this thesis introduces the concept of chirality, why it is important, and how molecules with chirality are synthesised. Then, the importance of the click reaction and similar reactions are discussed.

The second part of this thesis reports on the formation and characterisation of the *bis*-alkyne precursors, which are used in the key click chemistry step. Next, several azide compounds are discussed, as these are also required for the key step.

The third part of this thesis is concerned with the main click chemistry step. There are sub-sections for the original racemic trial reactions, as well as a series of reactions assessing various ligands, culminating in a tuning of conditions for the best ligand. A general reaction scheme for the project is given below.



Next follows the fourth part, which consists of some reactions performed in conjunction with a visiting project student. Whilst these are not key to my research, they are related to the main aim of a chiral click reaction.

The final part of this thesis is the experimental section and the appendix.

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PREFACE

The research described within this thesis is, to the best of my knowledge, original and all my own work, except where due reference has been made.

Alexander Sheldon

ACKNOWLEDGEMENTS

I would like to thank Prof. Phil Page and Dr G.R. Stephenson for allowing me the use of their laboratories and equipment for the duration of my PhD, and also to Prof. Annie-Claude Gaumont at the Université de Caen Basse Normandie for allowing me the same courtesy in her lab for my six-month exchange as part of the EU Interreg IVA (project 4061) research project, which I would also like to thank for the financial support. Special thanks go to Fabien Le Cavalier for performing my HPLC separations and Jean-François Lohier for obtaining my X-ray diffraction experiments whilst I was in France.

I would like to thank the countless lab members from both universities over the many years for their support over the decade I have been at the university, since my first visit back in early 2005 while searching for something to do after school. Who could have thought I would still be here after this long?

Finally, I would like to thank my friends and family for their (almost) unwavering support over the years. Without them, I would not have been able to get to where I am now.

This thesis is dedicated to the memory of my Nanna and Grandad, Queenie and Elijah (Reginald) Sheldon, and my Grandad, George Curtis.

ABBREVIATIONS

(*R*)-Tol-BINAP	(*R*)-(+)-2,2'-*bis*(di-p-tolylphosphino)-1,1'-binaphthyl
(*R*)-Xyl-BINAP	(*R*)-(+)-2,2'-*bis*[di(3,5-xylyl)phosphino]-1,1'-binaphthyl
(*R*,*R*)-BDPP	(2*R*,4*R*)-(+)-2,4-*bis*(diphenylphosphino)pentane
(*R*,*R*)-*i*Pr-PyBOX	(+)-2,6-*bis*[(4*R*)-4-(*iso*-propyl)-2-oxazolin-2-yl]pyridine
(*R*,*R*)-NORPHOS	(2*R*,3*R*)-(−)-2,3-*bis*(diphenylphosphino)-bicyclo[2.2.1]hept-5-ene
(*S*)-*i*Pr-Oxazoline-TPP	(*S*)-(−)-2-(2-diphenylphosphino-phenyl)-4-*iso*-propyl-4,5-dihydrooxazole
(*S*)-SYNPHOS	(*S*)-(−)-6,6'-*bis*(diphenylphosphino)-2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin
(*S*)-*t*Bu-*Bis*Oxazoline	(−)-2,2'-*iso*propylidene*bis*((*S*)-4-tert-butyl-2-oxazoline)
(*S*)-*t*Bu-Thiazoline-TPP	(*S*)-2-(2-diphenylphosphino-phenyl)-4-*tert*-butyl-4,5-dihydrothiazole
(*S*)-Tol-BINAP	(*S*)-(−)-2,2'-*bis*(di-p-tolylphosphino)-1,1'-binaphthyl
(*S*)-Xyl-BINAP	(*S*)-(−)-2,2'-*bis*[di(3,5-xylyl)phosphino]-1,1'-binaphthyl
(*S*,*S*)-Chiraphos	(2*S*,3*S*)-(+)-2,3-*bis*(diphenylphosphino)butane

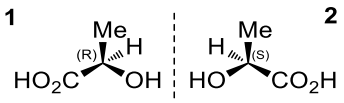
(*S*,*S*)-Me-DUPHOS	(+)-1,2-*bis*((2*S*,5*S*)-2,5-dimethylphospholano)benzene
Bn	Benzyl
BOX	*bis*(oxazoline)
CDA	Chiral Derivatising Agent
CLSR	Chiral Lanthanide Shift Reagent
CS	Proton NMR spectroscopy in the presence of a chiral lanthanide shift reagent
CuAAC	Copper-catalysed azide-alkyne cycloaddition
d	Doublet
DMF	*N,N*-Dimethylformamide
DMSO	dimethyl sulphoxide
ee	enantiomeric excess
equiv	Equivalent
Et	Ethyl
EtOAc	ethyl acetate
FT	Fourier transform
GC	Gas Chromatography
HPLC	High-Performance Liquid Chromatography
h	Hours
Hz	Hertz
IR	infra-red spectroscopy

J	coupling constant
m	Multiplet
min	minute(s)
mp	melting point
NMR	nuclear magnetic resonance
^{O}C	degrees Celsius
ppm	Parts per million
p-TSA	*para*-toluenesulfonyl acid
PyBOX	*bis*(oxazolinyl)pyridine
RT	room temperature
s	Singlet
SM	starting materials
t	Triplet
t-Bu	*tert*-butyl
THF	Tetrahydrofuran
TLC	thin layer chromatography
UV	Ultraviolet

CHIRALITY

WHAT IS CHIRALITY?

Chirality occurs in chemistry when a molecule has a non-superimposable mirror image. Such isomers are known as enantiomers. They have the same bond linkages, but exhibit a different 3D orientation of them. All the physical properties, and therefore reactivities of enantiomers are the same, apart from their ability to rotate the plane of plane polarised light. One enantiomer will rotate it one way, and the other will rotate it the other. Therefore, in a 50:50 mixture of both enantiomers, called a racemic mixture, the overall net rotation is zero. This is because the rotations cancel out.

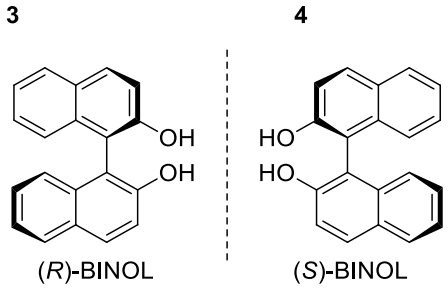


Structure 1,2 - Example of two enantiomers

Structures 1 and 2 are the two different enantiomers of lactic acid. The carbon atom at the centre is asymmetric, because it has four different groups attached to it. Each of the structures is a non-superimposable mirror image of the other.

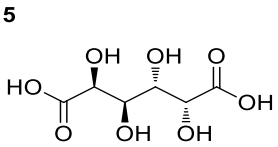
Perhaps the easiest way to explain this concept is to use one's hands. It is not possible to orient your left hand so that it looks like your right hand, and because of this, a left-handed glove does not fit on a right hand.

In organic compounds, chirality often arises from an asymmetric carbon atom, although this is not always the case. There are several examples of compounds with no asymmetric centres, yet they exhibit chirality, such as BINOL, which exhibits axial chirality.



Structure 3,4 - Both enantiomers of BINOL

In contrast, there are molecules which contain more than one asymmetric centre, but they are not overall chiral, because the mirror image is now identical, and is superimposable. These are known as *meso*-compounds. One example used in this thesis is mucic acid.



Structure 5 - Mucic acid. A meso-compound

Chirality is useful in chemical synthesis, but to be able to reliably discuss the enantiomers with fellow scientists a naming convention is required. The *R / S* system is one of several conventions, and is the one preferred by chemists. For each asymmetric centre, the four substituents are ordered, in line with the Cahn-Ingold-Prelog rules.[1] The molecule is moved round so that the lowest priority substituent is placed away from the viewer. The remaining three substituents, starting with the highest priority, will then be ordered in either a clockwise (*R*), or anti-clockwise (*S*) direction. This process is repeated for every asymmetric centre in the molecule.

For axial chirality, a similar method of defining their chirality is used, but the chiral axis is used as the viewing point, rather than a chiral atom, as in the process above. Using the Cahn-Ingold-Prelog rules, the two groups on the front of the bond are ordered 1 and 2, then the groups on the rear of the bond are ordered. Again, the ordering of these substituents denotes whether the molecule is R_a (clockwise), or S_a (anti-clockwise), with a subscript a to show the chirality is axial.

A further type of chirality can be seen in helicenes. These are large polycyclic aromatic molecules, which twist around, like an auger. They exhibit axial chirality, but do not follow the *R*/*S* convention. They are labelled **P**, for plus, a right-handed helix, or **M**, for minus, a left-handed helix.

Another naming convention commonly found is the D/L system. This system is based on the configuration of atoms, and their relation to the configuration of glyceraldehyde. Molecules are given the classification D- when their configuration is the same as (*R*)-glyceraldehyde, while those that are the same as (*S*)-glyceraldehyde are given the classification L-. There is no direct correlation between the *R*/*S* and D/L systems. This convention is commonly used with biological systems, where it is useful to be able to compare molecules of a similar structure.

The final naming convention uses the ability of chiral molecules to rotate the plane of plane-polarised light. A rotation clockwise gives a (+), while an anti-clockwise rotation gives (-). Again, this has no direct relationship to the other naming conventions.

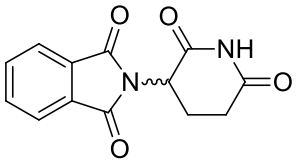
WHY IS CHIRALITY IMPORTANT?

One of the main uses for enantiomerically pure products is for use as medication. The human body, along with all life itself, is an inherently chiral and enantiomerically-pure environment. In the human body, amino acids, used to make proteins, mostly have the same L-configuration, and all sugars have the D-configuration.

While two different enantiomers of the same molecule have the same properties under standard conditions, and therefore will react the same, once they are put into the chiral environment of the body the two may behave in completely different ways. This can range from the unwanted enantiomer being completely inert, to having an alternative, but still beneficial side effect, to producing severe undesired side effects. This is because the target receptors have a defined geometry, so only one enantiomer may have the correct orientation of atoms to interact sufficiently. For this reason, new drug molecules are often synthesised as enantiopure molecules, or more generally, re-patented as enantiopure molecules.

Probably the most well-known example of the extreme differences a single bond geometry change can have on a drug molecule is the use of thalidomide **6** for the treatment of morning sickness in the late 1950s.

6



Structure 6 - Thalidomide

Thalidomide was originally marketed in 1956 by the German company, Chemie Grünenthal, for the treatment of respiratory problems. In 1957 this was extended to include the use as an antiemetic for the treatment of morning sickness. In the following years, there was a marked increase

in the number of miscarriages and babies being born with birth defects. This increase was attributed to the (*S*)-enantiomer of thalidomide being teratogenic, while the (*R*)-enantiomer was the active drug molecule.[2] The drug was found to racemise *in vivo*, so producing an enantiopure version of the (*R*)-thalidomide was not an option.[2] The drug was withdrawn from use in 1961, and drug testing since this disaster has become much more thorough.[3]

The company which marketed the drug in the UK, now a part of Diageo PLC, contribute at least £6.5million per year to The Thalidomide Trust, which helps to support the people affected by this disaster.[4]

Thalidomide has now been approved for use as a treatment for a complication of leprosy,[5] and it is also used as a cancer growth blocker for cases of multiple myeloma.[6]

HOW IS CHIRALITY OBTAINED?

Most reactions at a chemist's disposal are not inherently asymmetric. Therefore, for each reaction step which introduces an asymmetric centre, around 50% of the product is of the unwanted enantiomer. In addition to this, the separation of the two products is not trivial, due to both enantiomers exhibiting the same physical characteristics under standard conditions. Chemists must either separate their desired enantiomer from the mixture, or develop asymmetric reactions to negate the need for extensive separation.

Separation is possible through several methods, such as chiral chromatography, which is prohibitively expensive for large scale synthesis; enzyme resolution, which is only suitable for certain functional groups; or fractional crystallisation, which is only possible where the molecule of interest crystallises.

Alternatively, should separation prove to be too costly, Reactions are available that can either use chiral ligands to impart stereoselectivity on the reaction, or use starting materials which already have a chiral centre, which can be transferred through to the final molecule.

CHIRAL HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

High performance liquid chromatography (HPLC) is a technique used to separate mixtures of analytes. The mixture of analytes is passed through a column packed with a stationary phase, in the flow of a mobile phase, which is a mixture of solvents. The analytes partition between the two phases, and the relative affinity of each analyte to the specific phases used, determines by how far the analyte is delayed on the column. Analytes with a high affinity for the stationary phase will elute after those which have a low affinity, hence separating them.

The analytes eluting from the column are detected using a detector appropriate for the specific molecule. For example, a UV-absorbance detector may be used if the molecule absorbs UV light, a fluorescence detector could be used if the molecule fluoresces.

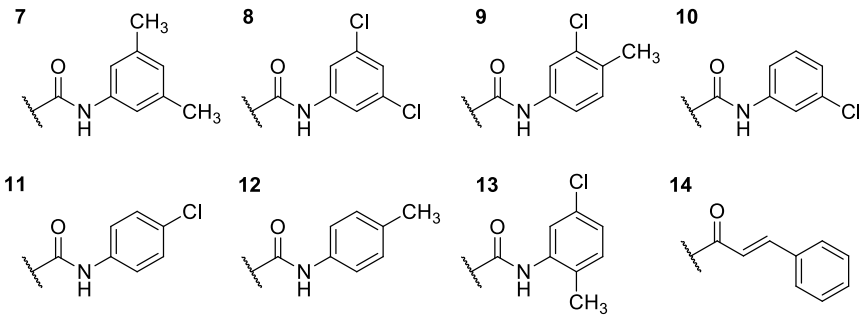
It is also possible to couple more than one detector to the same system. This most common pairing is a UV-absorbance detector with a mass spectrometer. This can help to determine which peak on the chromatogram corresponds to the molecule of interest, by giving accurate mass data. However, this method is unable to determine the difference between two stereoisomers.

Chiral high performance liquid chromatography is similar to standard HPLC, except the stationary phase is altered to form a chiral environment. Several different asymmetric materials can be coated onto the support. They are often derivatives of polysaccharides such as cellulose or amylose, featuring many asymmetric centres. Different derivatives can be coated on to produce many varied environments. Finding the right combination of solvents and columns can often be tiresome, but column manufacturers are often happy to offer a chiral method development service.[7,8]

There is a large range of different coatings available for HPLC columns.[9] One company, Daicel, have many different column materials available, in several different particle sizes and column lengths. They are based on either an amylose or cellulose support, which gives the column its chirality. The three alcohol groups on each sugar unit are then functionalised with a "selector" group, which is often done by formation of an ester or carbamate. Daicel recently introduced an "Immobilised" column series, where the column coating is bonded onto the silica support material, instead of just being coated on. This means the type of solvents that can be used on the column is not restricted. Previously, with the

coated columns, the use of, for example, chlorinated solvents would remove the chiral coating from the silica support.

Most common chiral "selector" groups form carbamates or esters on bonding to the polysaccharide backbone, some of which are given below.



Structures 7-14 - Examples of some selector groups in chiral HPLC columns.

While the "selector" groups above are all fairly similar, they are different enough to favour one molecule over another.

ENZYME RESOLUTION

Enzymes can also be used to separate two enantiomers. Due to the spatially defined pockets in some enzymes, only one enantiomer of a product may fit the pocket, meaning just that one enantiomer reacts, forming a different molecule which is then easier to separate.[10]

One common example is the introduction of an alcohol group at a pro-chiral carbon. This creates two enantiomers at the reaction centre. A lipase enzyme, such as CalB (*Candida Antarctica lipase*) can then be used to acylate just one of the alcohols in a kinetic resolution process. When run to completion, this produces a mixture of 50% of one enantiomer, and 50% of the other enantiomer, but with an acyl group attached, which is usually easier to separate using conventional methods.

Should the original substrate racemise during the reaction, it is termed a dynamic kinetic resolution, and the acylation of the desired product

effectively protects it from racemisation. This means the enzyme reaction is constantly progressing to restore the equilibrium, and this can produce a theoretical yield of 100% of the desired enantiomer.

FRACTIONAL CRYSTALLISATION

Fractional crystallisation is a process whereby molecules are separated from a solution of two or more solutes.[11] However, this process is not always useful on its own when trying to separate two enantiomers, because they often have the same solubility.

On some occasions crystallisation of enantiomeric mixtures will form conglomerates.[12] This is where each enantiomer crystallises out separately. They can either crystallise at the same time, in which case they would appear as two mirror image crystals which can often be separated using a microscope and tweezers; or crystallisation of one enantiomer can be encouraged over the other, by having a saturated solution, and adding a crystal of previously purified, enantiopure compound.

Often though, the two enantiomers co-crystallise. In cases such as this, a chiral derivatizing agent can be used to form diastereoisomers, which can then be crystallised separately. This however introduces further steps to the synthesis, to add and then remove the agent.

CHIRAL POOL COMPOUNDS

A common method used to obtain a chiral product is to use starting materials which come from nature. As mentioned above, nature is asymmetric, so the products it produces are also often asymmetric. Sugars and amino acids are examples of natural compounds which are available on a large scale as enantiomerically pure materials. Such compounds can provide an easy and inexpensive way of inserting asymmetry into a molecule, but there are limitations on the type of

molecules that can be used. Much more value can be obtained by taking a prochiral molecule, and transforming it into a stereodefined enantiomerically pure product.

ASYMMETRIC SYNTHESIS

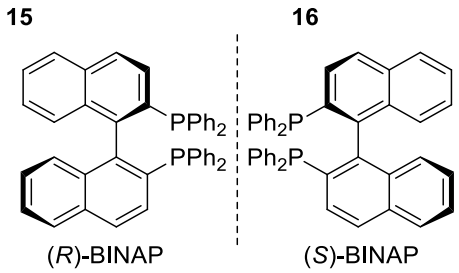
By far the most important way of obtaining chiral molecules is using asymmetric synthesis. Some reactions which use metal co-ordination sites as the reaction centre can be modified with suitable ligands to relay their chirality across to the product. This is the process to be undertaken in this research project.

There are countless different ligand designs used in modern chemistry. Most ligands use bulky structures, with electron rich elements to bind to a metal atom, although not all catalysts require a metal to work. Common heteroatoms used in ligand design are oxygen, nitrogen, phosphorus, and sulphur. They usually work by blocking off certain areas of the ligand-metal complex with large groups, forcing the pro-chiral molecule to attack, or be attacked, from a defined region, presenting only one face of the pro-chiral molecule to the reagent. These systems can be very efficient, often obtaining *ee*s in excess of 95%, from only a few mol% of catalyst.[13,14]

Whilst there are countless different molecules which can be used as a chiral ligand for a specific case, there are only a few specific classes of ligands which are well known and can be used on several mechanistically unrelated reactions. These are known as privileged ligands.[15]

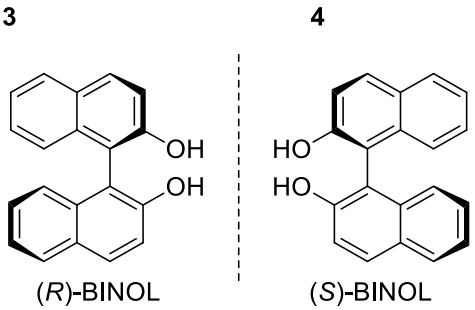
Several of the common ligand systems used are based on the BINAP backbone. BINAP is different from most ligands, because it does not have any chiral centres. All the carbons are sp^2 hybridised which does not at first sight seem a good chiral ligand design. However, due to the bulky nature of the two naphthyl rings, they cannot lie in the same plane, and

one has to rotate to accommodate the other. Therefore, the molecule exhibits axial chirality, and exists in both (*R*)- and (*S*)-enantiomers. The formation of BINAP usually proceeds from BINOL, through the *bis*-triflate derivative.



Structures 15,16 - Both enantiomers of BINAP

BINOL itself can be a ligand system in its own right, where the alcohol groups replace the diphenylphosphine groups of BINAP. This is commonly used with rhodium for asymmetric hydrogenation.[16]

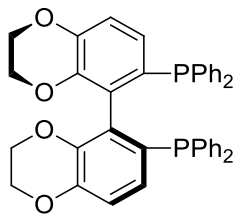


Structure 3,4 - Both enantiomers of BINOL

There is a range of similar ligands where the diphenylphosphine groups on BINAP are replaced with ditolylphosphine, or dixylylphosphine groups. These enable access to more sterically hindered ligands. This variation of groups allows the user to tune the ligand to the specific reaction.

Another avenue for customisation can be obtained through manipulation of the naphthalene rings. One such example used in this thesis is SYNPHOS.

17

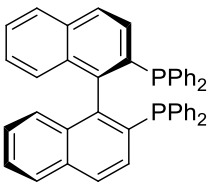


Structure 17 - (*S*)-SYNPHOS

This ligand no longer contains delocalised system in the end rings, as the end benzene rings are replaced with dioxene moieties. This affects the steric bulk of the group, because the end ring is no longer planar; and the electronic properties, because the oxygen is more electronegative than the CH group it replaces. This ligand was originally developed as a ligand for asymmetric hydrogenation using a ruthenium catalyst. [14]

One or both of the naphthalene rings can even be swapped for a phenyl ring, giving even greater flexibility in tuning the ligands.[17] Examples are below

15



(*R*)-BINAP

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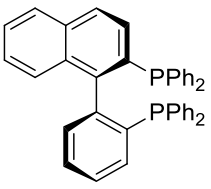
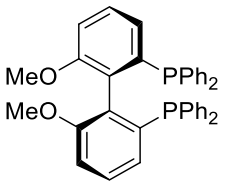


(*R*)-MeO-NAPhePHOS

19

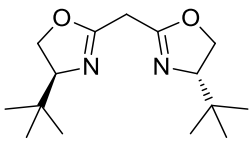


(*R*)-MeO-BIPHEP

Structures 15,18,19 - Examples of swapping naphthalene rings for phenyl rings

Bis-oxazoline ligands were developed in an attempt to mimic the metal binding site of vitamin B_{12}, where a cobalt atom is bound in the centre of a corrin ring.[15] Only half of the ring is formed, but addition of suitable groups to the oxazole can add additional binding sites to complete the tetra-dentate ligand.

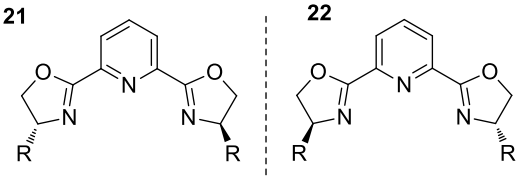
20



Structure 20 - A *bis*-oxazoline ligand

PyBOX ligands are a subset of the larger group of *bis*-oxazoline ligands. The "Py" refers to the pyridine in the centre. The substituent groups can be varied to produce a large number of different ligands with differing steric bulk, which can be used in a variety of different situations. *Bis*-oxazoline ligands have been previously used with both copper(I) salts, and in reactions with alkynes, so are an interesting ligand for this project.[18]

21 **22**

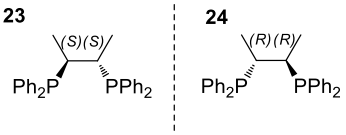


(*R*)-PyBOX (*S*)-PyBOX

Structures 21,22 - Both enantiomers of a generic PyBOX ligand

Whilst there are very complicated ligands such as those above, with several different elements, rings, and substituents, there are some that have a much simpler structure. Chiraphos is one such example.

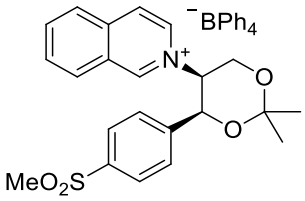
23 **24**



Structures 23,24 - Both enantiomers of Chiraphos

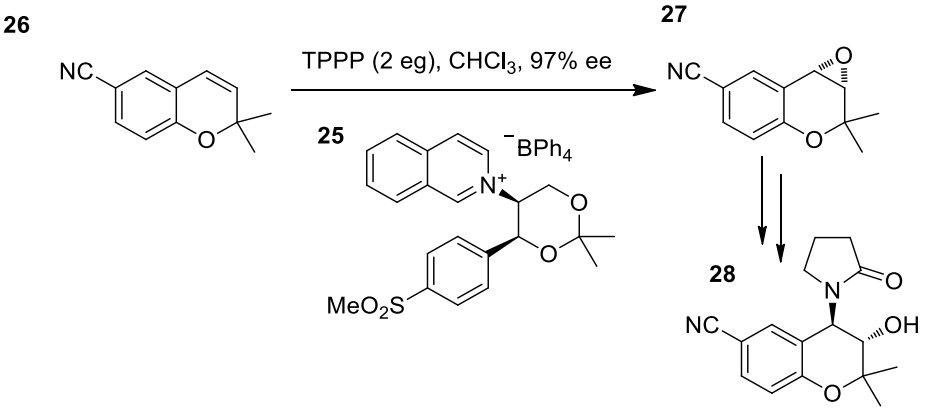
The ligands described above all need a metal atom to make them into a catalyst that is useful in asymmetric synthesis. Recent work within this group has focused on organic, metal-free catalysts, based on an iminium salt.[19]

25



Structure 25 - Metal-free iminium salt catalyst

This catalyst is one of a range produced in the lab, and they have for example been used to epoxidise *cis*-chromene **26** in up to 97% *ee*.[20] Ring-opening of the resultant epoxide **27** gives the correct arrangement for the active isomer of cromakalim, levcromakalim **28**.



Scheme 1 - Page's use of metal-free iminium salt catalyst 25 in key epoxidation step towards levcromakalim 28

CLICK CHEMISTRY PHILOSOPHY

The term "Click Chemistry" was coined by K. Barry Sharpless from The Scripps Research Institute.[21] It refers to a group of reactions which are "modular, wide in scope, give very high yields, generate only inoffensive by-products that can be removed by nonchromatographic methods, and be stereospecific (but not necessarily enantioselective)". They can often occur in aqueous solvents, meaning they can be more environmentally-friendly than other reactions.

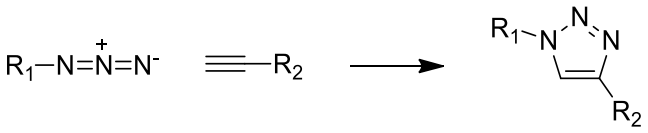
The philosophy behind click chemistry attempts to mimic nature, in the way proteins and sugars are created by joining together smaller subunits. Proteins are formed from repeating amino acid groups, and sugars from monosaccharide units. In the laboratory, if larger molecules can be built in several parts, and then "clicked" together, it would speed up the discovery of new drug candidates, as several different moieties could be clicked together in different orders to produce a vast range of molecules in a short space of time.

Some reactions that can fall into this classification are,

- Nucleophilic opening of small rings, such as epoxides, aziridines, aziridinium ions, and episulphonium ions;
- Cycloaddition reactions, such as 1,3-dipolar cycloaddition, and the Diels-Alder family of cycloadditions;
- "Non-aldol" type carbonyl chemistry, such as formation of ureas, thioureas, aromatic heterocycles, oxime ethers, hydrazones, and amides;
- Additions to C-C multiple bonds, such as epoxidation, dihydroxylation, aziridination, sulphenyl halide addition, and Michael additions.

COPPER(I) CATALYSED HUISGEN 1,3-DIPOLAR CYCLOADDITION

The most popular reaction under the click chemistry umbrella is the copper(I) catalysed Huisgen 1,3-dipolar cycloaddition, in which an alkyne and an azide moiety react together to form a 1,4-disubstituted triazole, as shown in Scheme 2. The reaction is so popular, that when people refer to "click chemistry", this is the reaction they think of. From here on in, the click reaction will refer to this one reaction.



Scheme 2 – General click chemistry reaction

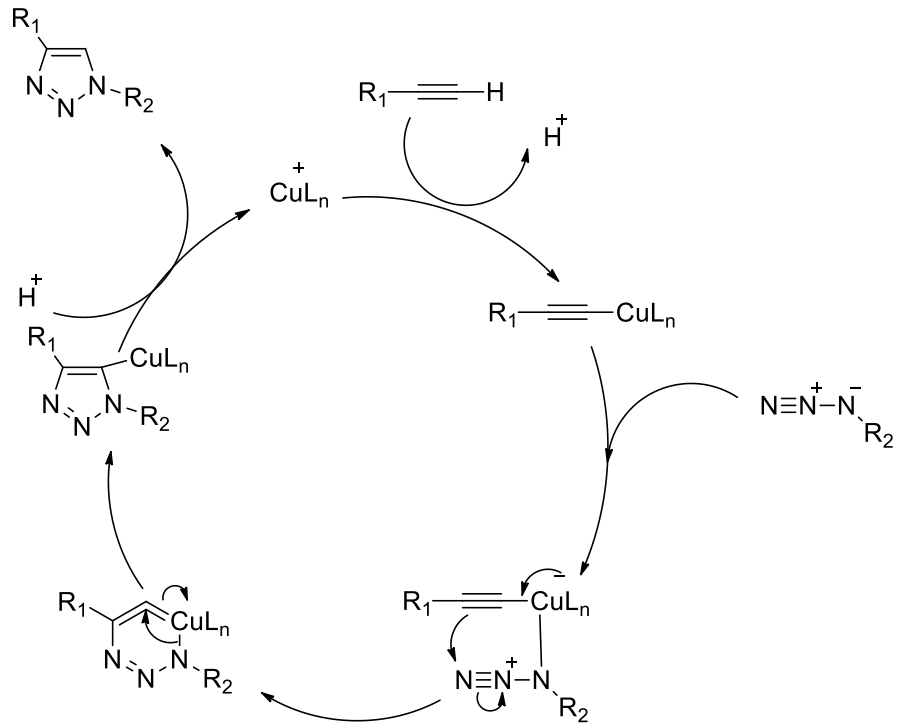
This cyclisation reaction was first discovered by Michael in 1893.[22] Further work by Huisgen in the 1960s brought the 1,3-dipolar cycloaddition into common use, and, as such, it was named after Huisgen himself.[23] The standard reaction does not use a catalyst, requires quite harsh reaction conditions, and gives a mixture of the 1,4- and 1,5-regioisomers. Due to this, the uncatalysed reaction does not fit under the click chemistry terminology.

Surprisingly, it was not until 2002 that Meldal and Tornoe discovered that by using copper(I) salts as catalysts for the reaction in common organic solvents, the rate of reaction was increased, and only the 1,4-regioisomer was produced.[24] At the same time, Sharpless independently developed the same process in aqueous conditions using a copper(II) salt with a reducing agent, such as sodium ascorbate, to generate the active copper(I) species *in situ*.[25] This method avoided the problems associated with the use of just copper(I) salts, such as the purity due to reaction with oxygen to form inactive copper(II) species and reactive oxygen species; disproportionation to form inactive copper(0) and copper(II); and the

formation of diacetylenes through a cross-coupling reaction, such as the Glaser or Strauss coupling reactions.

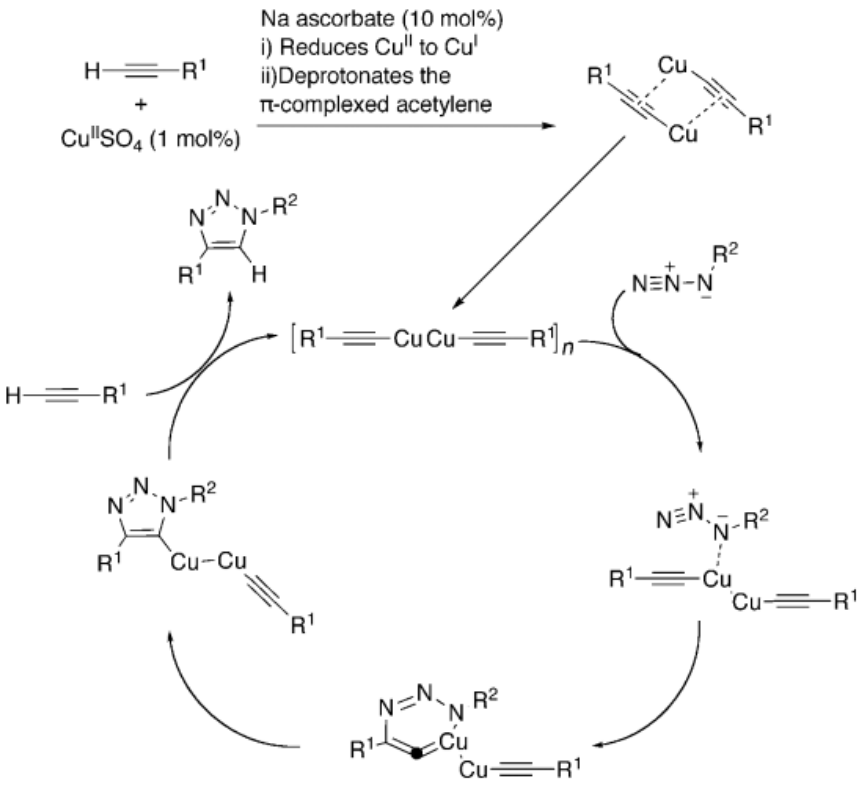
The mechanism of the click reaction is thought to proceed through a copper acetylide and a copper metallacycle. However, there are several proposed mechanisms.

In the first proposed mechanism shown in Scheme 3, the copper is thought to coordinate to the π-bond of the alkyne. The terminal proton is then removed, and the copper acetylide is formed. The azide then binds to the copper. Intermolecular attack then occurs on the azide by the alkyne, facilitated by the charge on the copper. The six-membered copper metallacycle then undergoes ring contraction. A proton then exchanges with the copper to form the triazole product, and regenerates the copper catalyst.[26]



Scheme 3 - Mechanism proposed by Himo

Another study by Buckley suggests that two copper atoms are required, and reports experimental evidence that dinuclear alkynylcopper(I) ladderane complexes are the active species.[27] Their work used copper(II) sulphate as the pre-catalyst. The copper was reduced to the active oxidation state using sodium ascorbate, which then formed a complex with the terminal alkyne. Many of these complexes would join together, forming a ladderane complex. This complex was obtained as a yellow insoluble product after several days of reaction, and X-ray powder diffraction has shown that there are two copper(I) atoms holding the alkyne groups together.

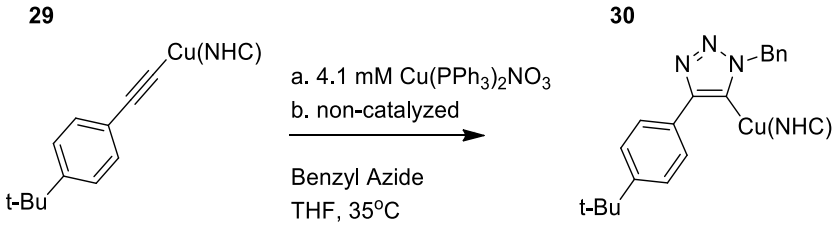


Scheme 4 - Mechanism proposed by Buckley

This pre-formed catalyst was used in a click reaction with the same terminal alkyne and an azide, and gave yields up to 98%. The reaction was also performed using the conditions used originally by Sharpless, and gave results that were comparable to those obtained with the ladderane complex.

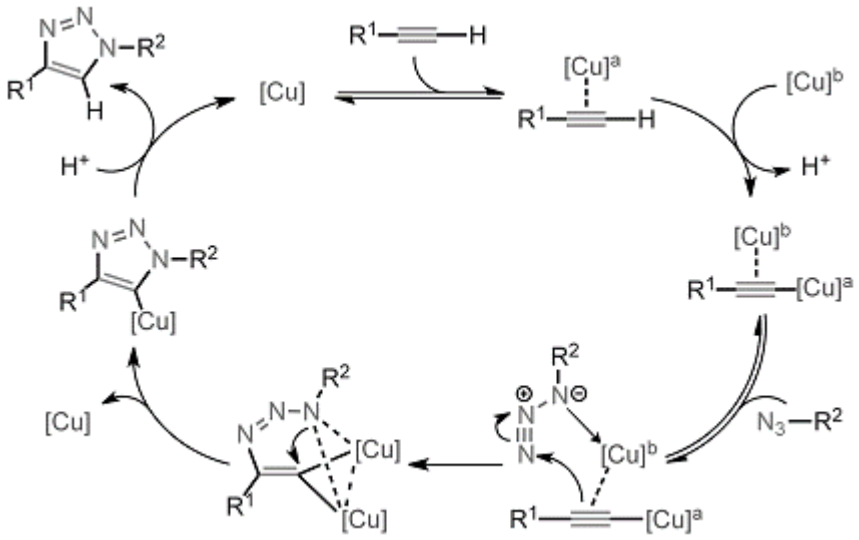
Another study by Worrell used heat-flow reaction calorimetry to show that two copper atoms are required.[28] Recent literature on the click reaction of 1-iodoalkynes shows that the terminal alkyne-iodide bond does not need to be severed for the reaction to occur, hinting at the fact that a copper-acetylide is not required for the click reaction.[29] The copper merely interacts through π-interactions. If the reaction is catalysed through the π-interactions, it suggests that in terminal alkynes the copper(I) acetylide is formed, which activates the alkyne, then a second copper atom is required for the catalysis.

A preformed copper acetylide **29** was synthesized, and was treated with benzyl azide, both with, and without an exogenous copper catalyst. Their results showed the reaction without the exogenous copper catalyst produced no appreciable products, whereas the reaction with the catalyst ran to completion within 20 minutes.



Scheme 5 - Method used by Worrell using preformed copper acetylide

For this mechanism, shown in Scheme 6, the copper is thought to coordinate to the π-bond of the alkyne as before. The terminal proton is removed and a copper acetylide is formed. Now that the triple bond is activated, a second copper atom can coordinate to the π-bond. The azide now enters and attacks the second copper atom, causing the triple bond to break and join onto the terminal end of the azide, leaving both copper atoms at the opposite end of the alkene. Ring contraction then takes place, ejecting a copper atom. A proton then exchanges with the remaining copper atom, to form the triazole product.



Scheme 6 - Mechanism proposed by Worrell

USES OF CLICK CHEMISTRY

Click chemistry has only been around for 15 years, yet it is becoming an increasingly important technique in numerous areas of chemistry. Its popularity could be due to the current push towards "green" chemistry, and chemistries that provide an easy separation of products. One major advantage to click chemistry is the speed of the reaction, and ease of creating a large library of compounds, by merely changing the azide or alkyne used. Often the products can be separated by a simple filtration or crystallisation, and the use of chromatography as a means of separation is regarded as unsatisfactory in click chemistry.

Click chemistry has been used in a wide range of areas, some of which are:

- Dendrimer formation[30,31]
- Peptidomimetic chemistry[32,33]
- Fluorescent tagging[34]
- Polymer formation[35]
- Polymer derivatisation[36]
- Liquid Crystals[37]
- Self-Assembled Monolayers[38]
- Functionalised sugars[39]
- Cyclophane ligand design[40]

One use for click chemistry is in the peptidomimetic area of chemistry. A recent review by Pedersen and Abell discusses the advantages of using triazoles in place of peptide linkers, such as the very similar bond lengths, and polarity. The 1,4-triazole linker gives a good approximation to the *trans*-peptide bond, whereas the 1,5-triazole linker gives an even closer approximation to a *cis*-peptide bond, as shown in Figure 1.[32]

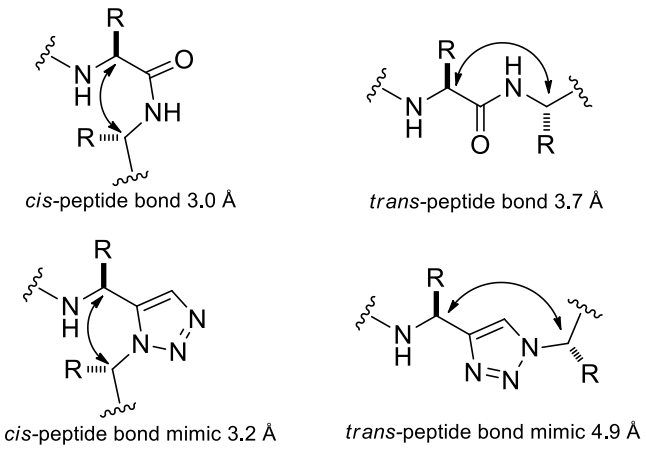
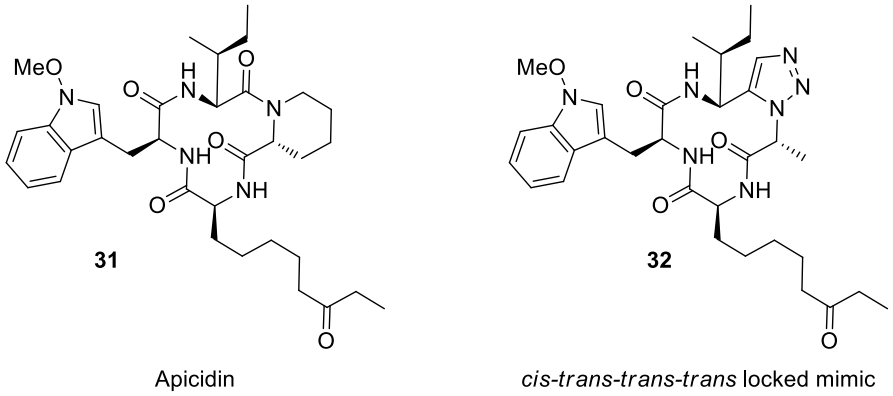


Figure 1 - Comparison of peptide bond lengths with their triazole mimics.

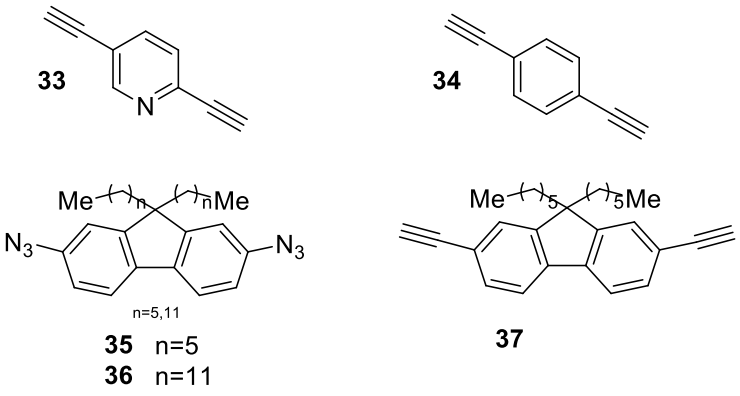
Horne used these properties to lock the conformation of tetrapeptides, and prove that the more potent conformation of apicidin, a histone deacetylase inhibitor (HDAC), is not the all-*trans* structure observed in solution, but a *cis-trans-trans-trans* conformation.[33]



Structure 31,32 - Apicidin, and the *cis-trans-trans-trans*-mimic produced by Horne

The group synthesised the precursor molecule, with the appropriate alkyne and azide end groups. They then performed two cyclisation reactions, the first was heated and used no catalyst. This gave a mixture of the two regioisomers, and they were able to successfully purify out the 1,5-regioisomer, shown above. The other reaction used a copper salt, to give the 1,4-regioisomer. An *in-vitro* fluorescence assay was then used to confirm the active conformation.

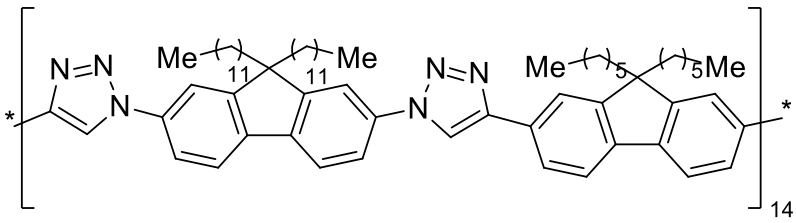
The click reaction can also be used to produce functionalised polymers in several ways. When suitable *bis*-azides and *bis*-alkynes are reacted together, fully conjugated polymers can be created for use as fluorophores.[41] Work by van Maarseveen and Reek subjected *bis*-azides **35** and **36** to click reaction conditions in the presence of *bis*-alkynes **33** and **34**. This formed conjugated polymers with up to 73 repeating units, as detected by size-exclusion chromatography for the reaction of **33** with **36**.



Structure 33-37 – *Bis*-azides and *bis*-alkynes used by van Maarseveen and Reek[41]

A further experiment used *bis*-alkyne **37** with *bis*-azide **36**. This resulted in fully conjugated polymer **38** with 14 repeating units.

38



Structure 38 - Click polymer synthesized by Maarseveen and Reek

Click chemistry has been used to functionalise an azido-polymer, which has azide groups on the side chains. There are many examples in the literature. The one below, by Lecomte, is performed by ring-opening co-polymerisation of caprolactone with an azido-caprolactone.[36] The resultant azido-polymer **39** is subjected to click reaction conditions, in the presence of one of several alkynes, to form functionalised polymer **40**. This functionalisation alters the properties of the polymer, such as its solubility. For example, functionalisation with *N*,*N*,*N*-triethylpropargyl ammonium bromide, would help solubilise the polymer in aqueous environments, such as the human body.

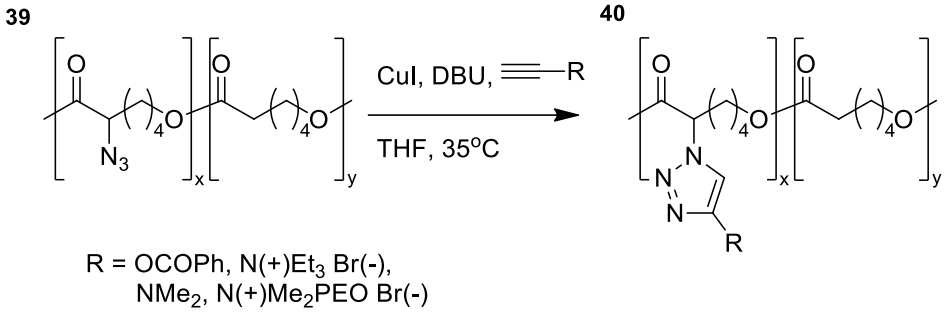


Figure 2 - Functionalising an azido-polymer

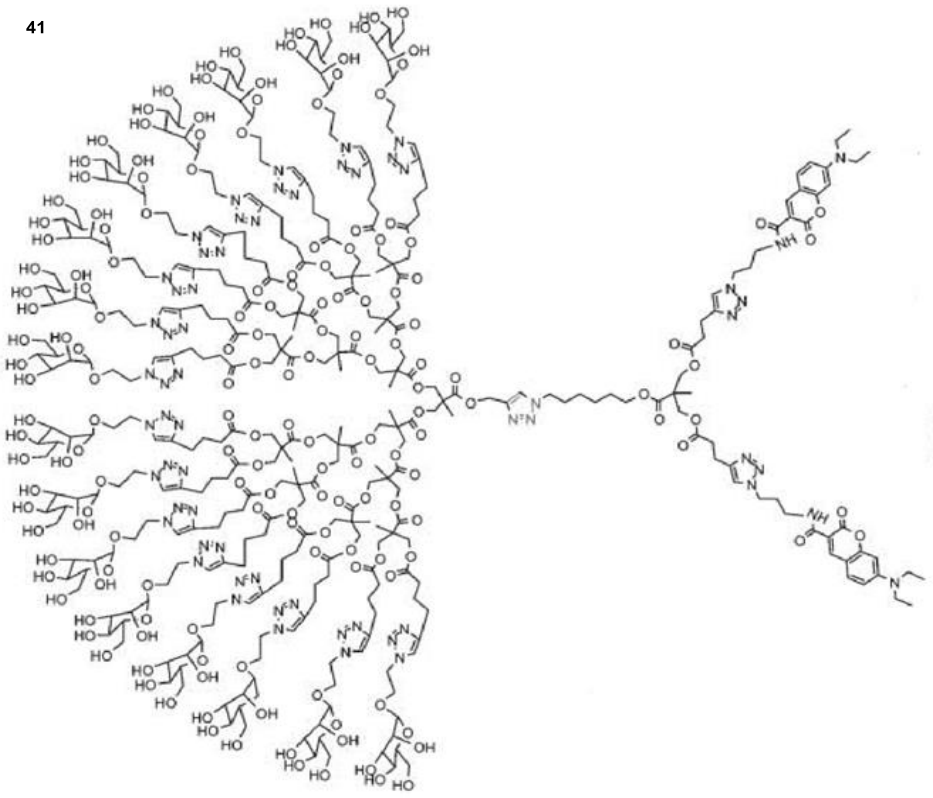
Dendrimers are macromolecules which mimic the branching of a tree. They are made up of a core molecule, linking units, and capping units. The capping units often have a specific protein binding capability, or fluorescent tags. Click chemistry has been used in this area to link the three pieces together.

The simplest use of click chemistry in dendrimer formation is the connection of two pre-built dendrons with different functionalities. For example, one dendron could have sugar molecules for protein recognition on the outer edge, and the other dendron may have fluorescent molecules. Joining these two dendrons together using the click reaction forms a fluorescent protein detector. This modular approach allows a large range of dendrons to be synthesised, each with a different property.

It is then possible to “pick and mix” the properties that are required. For example, several different dendrons can be synthesised, each with a fluorescent molecule which has a different excitation wavelength. Then it is easy to form a new dendrimer with a different excitation profile if required.

A more in depth use of click chemistry is in the building stages of the dendrimer, by linking the units together. Structure **41** is an example of a dendrimer built using both these methods.[30] The left half is a dendron, initially formed by controlled esterification of 2,2-bis(hydroxymethyl)propionic acid. Next, an alkyne containing group is ligated to the final layer. In this case, the sugar group is functionalised with an azide, and is joined on under click reaction conditions. The right half of structure **41** is built in a similar way, but here a fluorescent marker is used. The two halves can then be joined under click reaction conditions, to form the full dendrimer.

41



Structure 41 - Bifunctional dendrimer

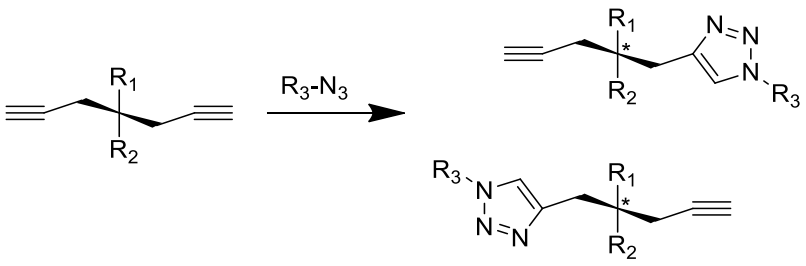
DESYMMETRISATION

Desymmetrisation is the process of removing one or more symmetry elements, such that chiral molecules are obtained from prochiral ones. This could be a change which removes for example a mirror plane, or rotational axis.

Generally, desymmetrisation is often not useful. Without careful control the molecule may react at more than one reaction site, forming a statistical mixture of the products. However, desymmetrisation can be readily promoted by certain enzymes, and, due to the nature of an enzyme, the step is usually enantioselective.[42,43,44,45]

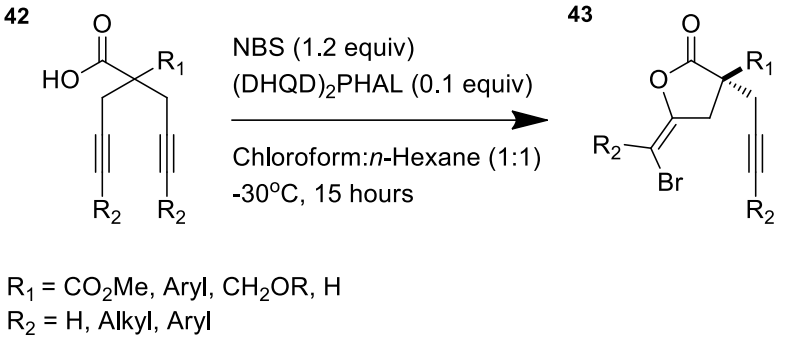
Some achiral reactions can be adapted to form a desymmetrisation version. This can be done by creating a substrate with two reaction sites. One reaction site may be favoured over the other due to steric hindrance or favourable interactions from other groups. Ligands can be introduced to further influence the reaction site choice. Highly effective ligands used in conjunction with crystallisation techniques can desymmetrise some substrates with *ee*s up to 100%.[46]

Scheme 7 outlines the intention of this desymmetrisation project.



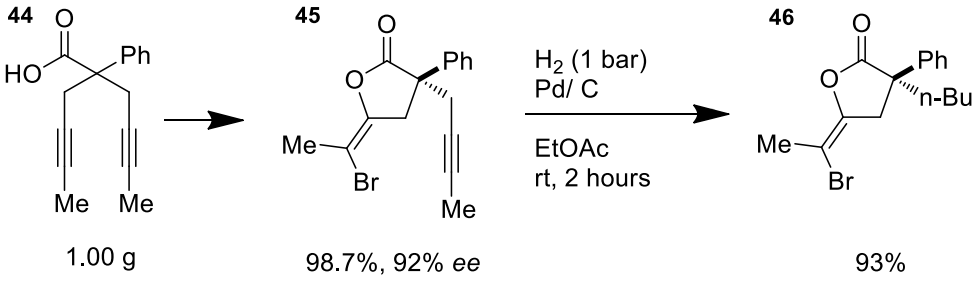
Scheme 7 - Desymmetrisation of a *bis*-alkyne using CuAAC

Previous work with the desymmetrisation of dialkynes has tended towards intramolecular cyclisations of one alkyne, leaving the other available for future functionalisation. Hennecke used a similar substrate to that used in this thesis.[47] The group progressed through a bromolactonisation of diyne **42** as shown in Scheme 8, obtaining results of up to 98% yield, and 96% *ee*.



Scheme 8 - Procedure used by Hennecke

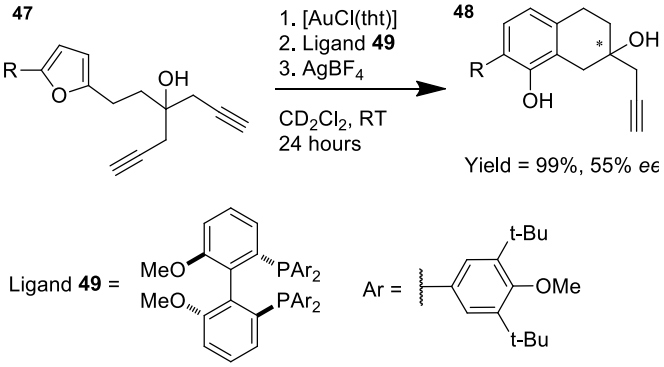
15 examples were synthesised, mostly using NBS for a bromolactonisation, but NCS and NIS were also used, performing a chlorolactonisation, and iodolactonisation, respectively. In addition, the group performed the cyclisation reaction using one gram of *bis*-alkyne **44**, under the same conditions, and then a selective hydrogenation afforded the unsaturated n-butyl derivative **46**, shown in Scheme 9, in a 93% overall yield.



Scheme 9 - Gram-scale synthesis used by Hennecke

The advantage of this process is that internal alkynes can be used. This is not possible using the copper-catalysed azide-alkyne cycloaddition (CuAAC) process, as only terminal alkynes can be catalysed using copper.

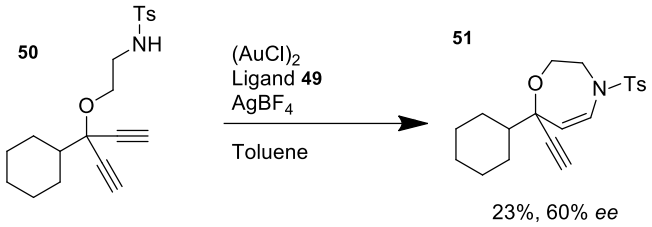
Another desymmetrisation process uses a gold catalyst to cyclise one of the alkynes. Hashmi is well known in the gold catalysis area, and has written several reviews on the topic.[48,49,50,51] His group synthesised a furan-diyne substrate **47** which they cyclised to form phenol **48**, with no interference or side reactions from the other alkyne group.[52]



Scheme 10 - Procedure with best conditions used by Hashmi

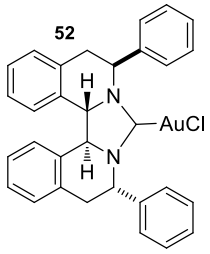
Overall, in excess of 20 chiral ligands were tested, including several chiral ferrocene derivatives, through to BINAP and BINOL based ligands, with the best results coming from BIPHEP ligand **49**, with the conditions shown in Scheme 10.

Another group using gold catalysis on diyne structures is the group of Czekelius.[53] Their work uses 1,4-diynes such as structure **50** instead of the 1,6-diynes in this thesis, and mentioned above. The process, shown in Scheme 11, forms a 7-membered heterocycle **51**, which is an often seen motif in natural products, but there are few methods to synthesise them selectively.



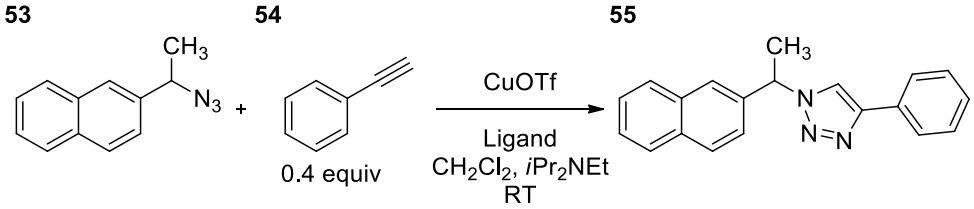
Scheme 11 - Procedure used by Czekelius to form 7-membered heterocycles

The majority of their work is concerned with achiral ligands, so the desymmetrisation is uncontrolled and racemic products are formed. However, they do use two chiral ligands at the end of the paper. The first uses optically pure NHC^{H} as a ligand **52**, which gave a good yield of 60%, but a low *ee* of 17% was obtained. Switching to ligand **49** as used by Hashmi, gave an improved *ee* of 60%, at the cost of a lower yield of 23%.



Structure 52 – [AuCl(NHC^{H})]

The first and, at the start of the project, only mention of a desymmetrisation process using click chemistry was made by Fokin in 2005.[54] However, their work focused on kinetic resolution of compounds, by using the click reaction. They worked with a chiral mono-azide **53**, and a *gem*-diazide, both reacting with phenylacetylene **54**, so the sense of the reaction was reversed compared with our work. The work discussed in this thesis is related to a *bis*-alkyne, reacting with an azide.



Scheme 12 - Procedure used by Fokin

In their research, they evaluated ten ligands, all of which were of the PyBOX category. Reactions were run as per Scheme 12, and conversions, which were capped at 40% due to limiting the alkyne reagent, ranged from 16 – 39%. Selectivity, which is given by the below formula, gave values from -1.8 up to 3.2. The results are shown in Table 1. Enantiomeric excesses were not stated.

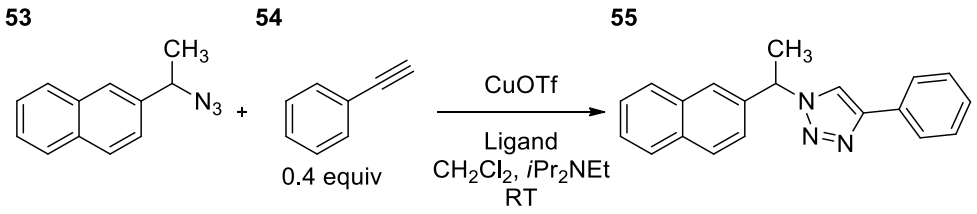
$$s = \frac{\ln[A/A_0]}{\ln[B/B_0]} = \frac{\ln[(A_0\text{-}X)/A_0)]}{\ln[(A_0\text{-}Y)/A_0)]}$$

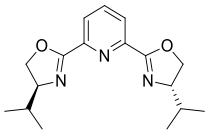
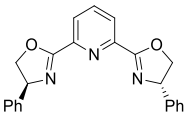
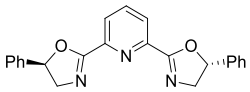
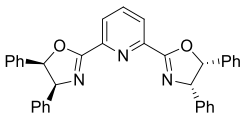
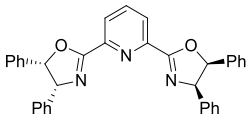
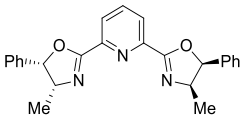
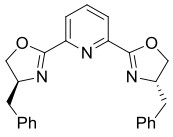
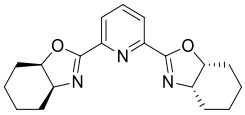
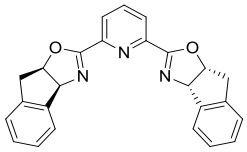
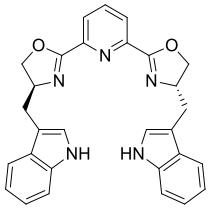
where
$A_0 = B_0$ = the starting concentration of each azide enantiomer
X, Y = measured concentrations of triazole enantiomers

The table shows that the majority of the reactions almost reach completion. Entry 1 uses i*so*-propyl side chains, but it is apparent they do not have enough steric bulk to impart any selectivity on the reaction. However, by introducing a larger group, such as a phenyl (entry 2), the selectivity increases. Entry 3 shows that by moving the phenyl group one carbon further away from the metal binding site the effect on selectivity is negated. However, having the phenyl group on both the sites, as in entries 4 and 5, causes the selectivity to be partially restored, but not to the level obtained with just the one phenyl group. This may be due to the

phenyl groups aligning with each other, causing them to restrict their movement, whereas with the single group it is free to rotate. Interestingly, entry 5 uses the opposite enantiomer of ligand to entry 4, and, as expected, the selectivity is to the same degree, but reversed.

Table 1 - Ligand evaluation by Fokin. Selectivity is given as a ratio of k_{fast}/k_{slow}.



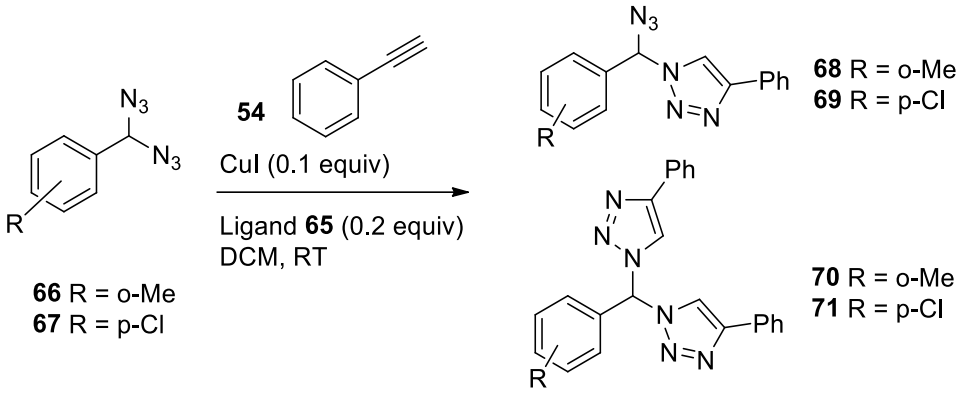
Entry	Ligand	Conversion	Selectivity
1	(*S*,*S*)-**56** 	39%	1.0
2	**57** 	38%	3.2
3	**58** 	37%	1.0
4	**59** 	31%	2.0
5	**60** 	19%	-2.0
6	**61** 	37%	-1.8
7	**62** 	34%	1.6
8	**63** 	16%	1.0
9	**64** 	38%	1.5
10	**65** 	22%	2.8

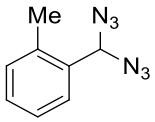
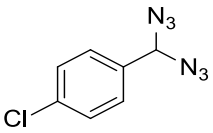
Entry 6 reduces the steric bulk on the first carbon atom, by replacing the phenyl group for a much smaller methyl group. This reduces the selectivity. Entry 7 moves the phenyl group away from the ligand by one carbon unit by using a benzyl side chain. This gives the group more flexibility, but this again lowers the selectivity. Entries 8 and 9 use larger side groups, but their movement is restricted by forming a ring with them. This again reduces the selectivity. In the case of entry 8, no selectivity is obtained. Entry 9 is a direct analogue of entry 2, in that a phenyl group is attached to the oxazole ring at the 5-position, but in this case there is a methylene linking it to the 4-position on the ring, restricting the flexibility. The fact that the selectivity is more than halved, shows that the phenyl group is held in a conformation which is not effective as a stereoselective ligand for this reaction. Finally, entry 10 uses a tryptophan side chain, and this affords good selectivity, but at a lower conversion rate.

Further reactions were performed to investigate three other variables in the reaction. The copper source, complex concentration and ligand copper proportions were individually varied to see how they affected the reaction. They found that copper(I) iodide gave the best selectivity, at 10 mol% copper, to 20 mol% ligand.

The second, smaller, section of the paper used a prochiral *gem*-diazide, with ligand **65** and the best reactions conditions found in the previous step, summarised in Table 2. The authors found that the reaction was progressing on to form the *bis*-triazole product as the major product, instead of the expected mono-triazole. They attributed this behaviour to the high reactivity of a Cu-organometallic intermediate, as described by Rodionov, who had previously performed studies on the reaction.[55]

Table 2 - Fokin's Results from gem-diazide reactions



	Mono-triazole	*Bis*-triazole
66 	23% yield 16% *ee*	60% yield
67 	25% yield 59% *ee*	63% yield

At the end of the paper is a single sentence on work with 1-phenylpropargylic compounds where it is stated that attempts to perform a kinetic resolution on these compounds resulted in no enantiomeric discrimination. There is no mention of any work with prochiral *bis*-alkyne compounds, and we believe that our project was entirely novel at the outset.

Rodionov has previously performed the click reaction on *bis*-alkynes, but they were not prochiral compounds.[55] His work used both a diazide and *bis*-alkyne shown below to investigate the mechanism of the click reaction.

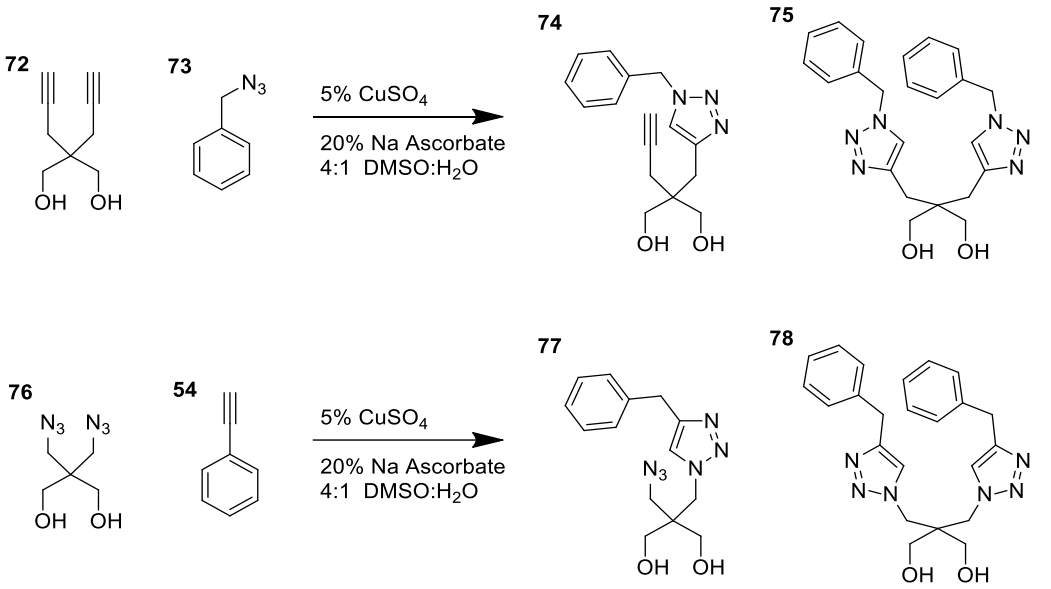


Figure 3 – Reactions performed by Rodionov

His results showed that diazide **76** reacts with phenylacetylene **54** to form mainly the *bis*-triazole product **78**, with only a trace of mono-triazole **77**. However, the reaction performed with *bis*-alkyne **72** and benzyl azide **73** produced a statistical mixture of the mono- and *bis*-products. This work, combined with the work from Fokin, showing that even with a bulky ligand the majority of the product is the *bis*-triazole, shows that there is an additional complication to the diazide reaction.

RESEARCH OBJECTIVES

The overall aim of the project is to develop an enantioselective methodology to create chirally useful molecules, by using a click chemistry intermediate step.

Firstly, prochiral *bis*-alkynes are formed from a range of easily available, and inexpensive prochiral methylene based compounds. These are then subjected to standard click chemistry conditions. A range of different substrates are formed, along with a range of different azide groups.

Because only benzyl azide was commercially available, a range of different azide moieties were synthesised. Synthesis will probably occur *in-situ* with the click reaction, or immediately before. Because azides can be unstable and potentially explosive it is desirable to have them formed this way, to minimise the chance of deterioration, or explosion.

Once a suitable combination between substrate and azide has been found, the reaction conditions are altered to try to increase the yield of the mono-substituted product.

Further into the project a period is spent evaluating chiral ligands with which an enantioselective click step will be performed. Prior to this, a chiral separation is to be undertaken on the racemic samples, to form a chiral analysis procedure. This is necessary to determine how successful the desymmetrisation step is.

RELATED WORK

Shortly after the conclusion of the practical research portion of this thesis, Zhou published a paper on the same topic.[56] Their research focused on the formation of quaternary oxindoles, such as **79** and **80**, and performing an asymmetric click reaction on them, to obtain useful chiral molecules which could be subjected to further functionalisation on the remaining alkyne group.

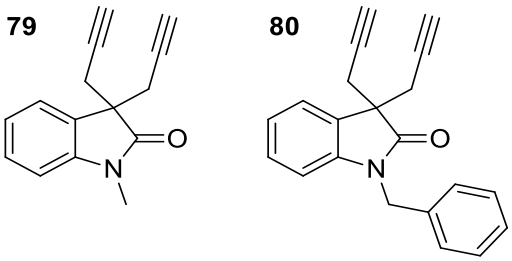
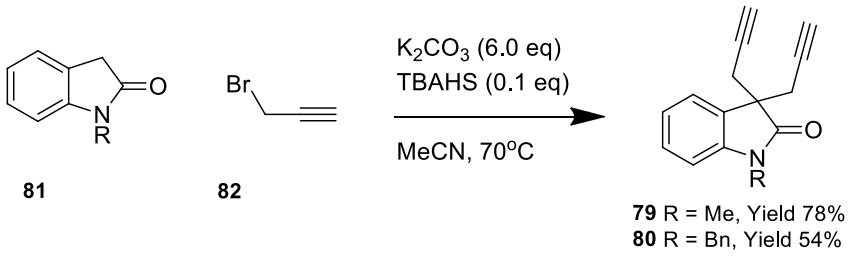


Figure 4 - Oxindoles used by Zhou

The 1,6-heptadiynes used were synthesised from N-protected oxindoles and propargyl bromide, shown in Scheme 13. 11 different 1,6-heptadiynes were synthesised, with yields ranging from 35 to 81%.

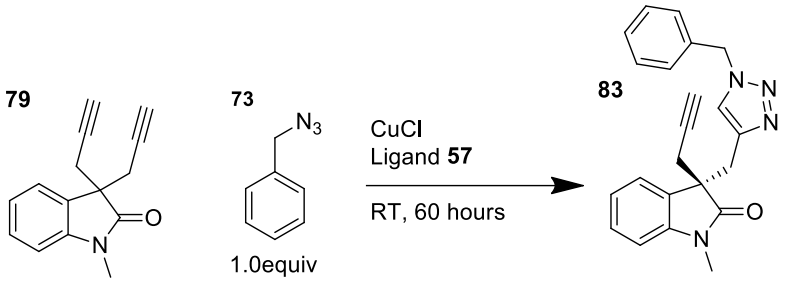


Scheme 13 - Process used by Zhou for synthesis of oxindole based 1,6-heptadiynes

For the majority of the experiments, Zhou achieved results similar to those performed previously by Rodionov, in that more of the *bis*-triazole product was formed than the mono-triazole product. In some cases, results as low as 10% mono-triazole product to 90% *bis*-triazole product were obtained. By changing the solvent to acetone the ratio was reduced to 1:2. This encouraged Zhou to try several different ketone solvents, one of which, 2,5-hexadione, reversed the results, and gave a 7:1 ratio of products, in favour of the mono-product.

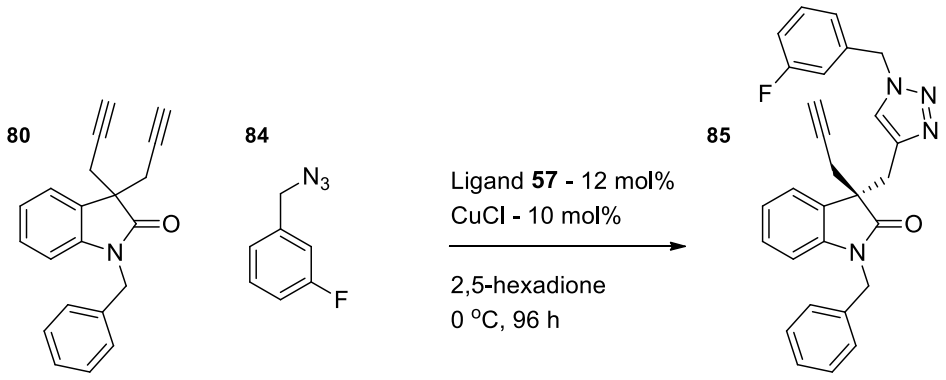
It is interesting to note the differences between entries 1 and 2 in Table 3. On addition of the ligand, the amount of *bis*-product actually increases, with 11% mono-triazole and 44% *bis*-triazole formed with a ligand, compared to 10% mono-triazole and 30% *bis*-triazole with no ligand. This shows that using a ligand may have an adverse effect on the reaction, with the steric bulk causing the mono-triazole product to remain within the reaction sphere long enough for a reaction to take place on the second alkyne. Unfortunately, no further work was performed in the other solvents using no ligand, so no further comparison can be made.

Table 3 - A summary of results by Zhou.



Entry	Solvent	Reagents	Ratio of mono to *bis* product	Isolated yield of mono-product	*ee*
1	CH_2Cl_2	Ligand – 0 mol% CuCl – 10 mol%	1:3	10%	N/A
2	CH_2Cl_2	Ligand – 12 mol% CuCl – 10 mol%	1:4	11%	67%
3	acetone	Ligand – 12 mol% CuCl – 10 mol%	1:2	20%	75%
4	2-butanone	Ligand – 12 mol% CuCl – 10 mol%	1:2	21%	77%
5	2-pentanone	Ligand – 12 mol% CuCl – 10 mol%	1:2	22%	75%
6	3-pentanone	Ligand – 12 mol% CuCl – 10 mol%	1:2	21%	84%
7	cyclopentanone	Ligand – 12 mol% CuCl – 10 mol%	1:2	24%	60%
8	2,5-hexadione	Ligand – 18 mol% CuCl – 15 mol%	7:1	77%	90%

Ratio of products determined by ^1H NMR spectroscopy, using CH_2Br_2 as internal standard.



Scheme 14 - Best reaction conditions from Zhou

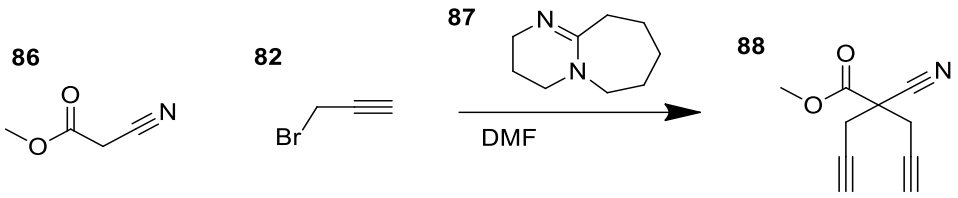
Further modifications to the substrate and azide as shown in Scheme 14 gave results up to a ratio of 12:1 in favour of the mono-product, with 82% isolated yield of the mono-product, obtained with an *ee* of 89%. Changing the azide from 3-fluorobenzyl azide to an *N*-(2-azidoethyl)phthalimide moiety gave a higher *ee* of 98%, but lowered the yield to 56%.

Fortunately, the mono-triazole products could be crystallised out, and the absolute configuration of their products has been established, and shown to be that shown as the product in Scheme 14.

Up until the appearance of this publication, we had hoped that we were the only group working on such a procedure. The fact that another group was working on it too, and with such a large group of researchers, validated our interest in the area. Following this, we announced our results by way of a publication, which is attached as an appendix.

THE ESTER SERIES

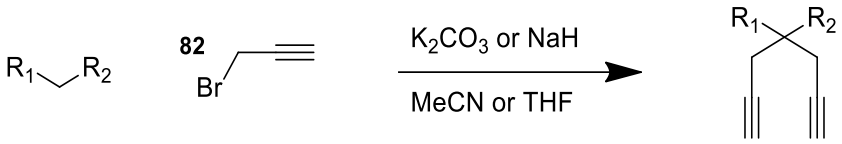
The *bis*-alkyne click substrates of the type shown in Scheme 15 were originally synthesised by Oediger and Möller, but for a different purpose.[57] The group reacted methyl cyanoacetate **86** with 2.2 equivalents of propargyl bromide **82**, using 2.2 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **87** as the base, producing the *bis*-alkyne product **88** in 77% yield, as per Scheme 15. Their procedure then led to forming cyclised products from the two alkyne moieties.



Scheme 15 - Method used by Oediger to form *bis*-alkyne 88

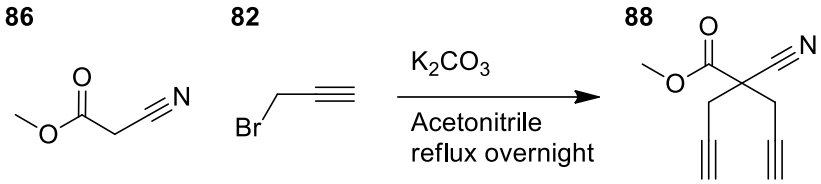
A similar synthesis is used here, but with potassium carbonate as the base instead of DBU due to the much lower cost, and acetonitrile as the solvent instead of DMF, mainly because of the high toxicity of DMF compared to acetonitrile. Several variations have been attempted, and some products synthesised. A selection of results from both the ester and phosphonate series are detailed in Table 4.

Table 4 - *Bis*-alkyne products formed with yields



Compound Number	R_1	R_2	Yield (%)
88	CO_2Me	CN	78-97
89	CO_2Me	Ph	66
90	CO_2Me	*p*-OMe-Ph	0
91	CO_2Et	*p*-Me-Ph	0
92	CO_2Me	C(O)Me	31
93	CO_2Me	*p*-NO_2-Ph	0
94	CO_2Me	Pyridine	30
95	CO_2Et	$CO_2{}^tBu$	19
96	CO_2Bn	CN	38
97	$CO_2{}^tBu$	CN	53
98	CO_2Menthyl	CN	63 (2 steps)
99	$P(O)(OEt)_2$	CN	19
100	$P(O)(OMe)_2$	CO_2Me	Not separated
101	$P(O)(OMe)_2$	C(O)Me	0
102	$P(O)(O$*i*$Pr)_2$	CO_2Et	0

The first substrate was produced from methyl cyanoacetate **86**, as this was relatively inexpensive, and it is easy to follow the reaction by NMR spectroscopy due to the singlet produced by the methyl group.



Scheme 16 - Synthesis of bis-alkyne 88 from methyl cyanoacetate 86

After purification of the product by column chromatography, the proton NMR spectrum showed three signals; the singlet from the methyl, a doublet from the methylene groups, and a triplet from the terminal alkyne protons. The carbon NMR spectrum was assigned through use of a HMQC spectrum. The three signals for the carbon atoms attached to

protons were easily assigned. The ester carbon was easily recognised as having the highest shift, followed by the nitrile carbon. The remaining two signals were provisionally assigned, assuming the peak with a similar shift to the terminal alkyne was the other end of the alkyne, and the remaining quaternary carbon having a lower signal intensity than the others. Infra-red analysis showed the product also had a nitrile group, with a stretch at 2249 cm^{-1}, and an ester group, with a stretch at 1740 cm^{-1}, as expected. Analysis by mass spectrometry showed the high-resolution mass to be within 0.5 ppm of the predicted mass, which is in excellent agreement.

The synthesis was successful, and has given yields up to 97%. Larger scale reactions were attempted, and with the increased quantities, vacuum distillation was a viable option to purify the compound. The recovered yield here was 78%, but the purification step was easier, and gave a much purer compound which solidified into a large white solid. This was ground down to give a colourless powder which was much easier to handle than the thick oils produced previously.

Further into the research project, literature was found which used acetone as the solvent at room temperature overnight.[48] This gave a cleaner, greener method of production, and after extraction from the reaction solvent, addition of ethanol to the impure product generally produced large crystals of the product. This fitted well with the philosophy of click chemistry.

To further confirm the product had been formed, X-ray crystallography was performed on the crystalline product thanks to Jean-Francois Lohier at the University of Caen. The structure obtained is shown below.

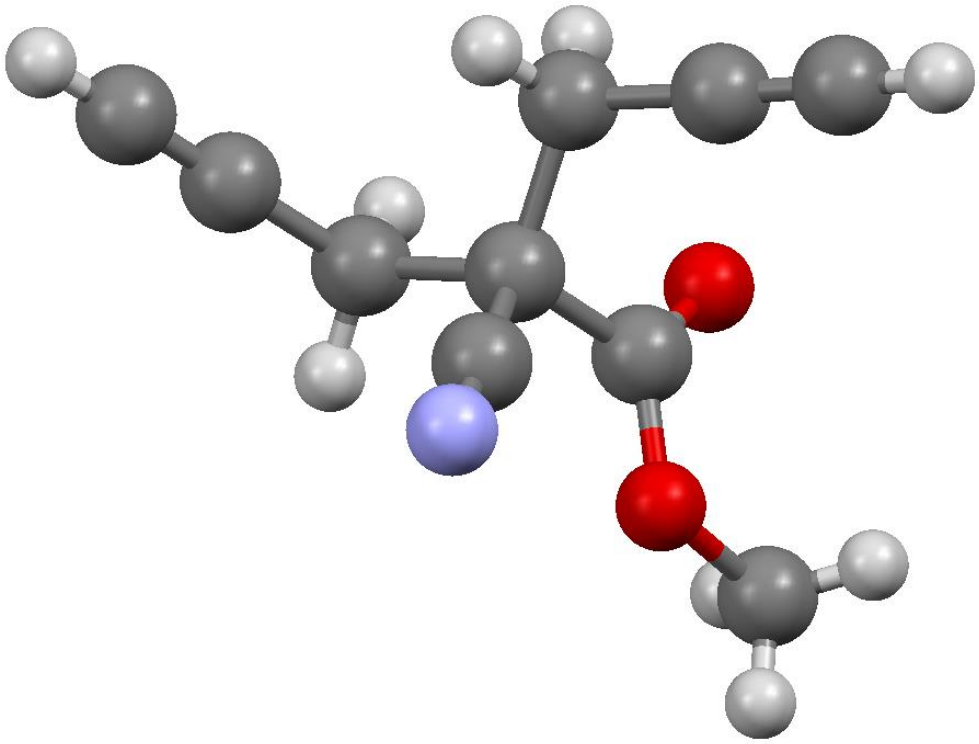
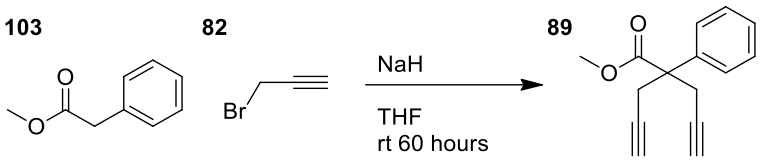


Figure 5 - X-ray crystal structure of *bis*-alkyne 88

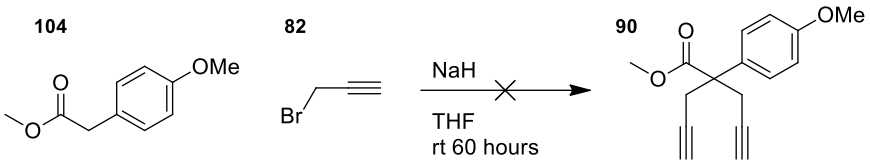
Interestingly, the two alkyne groups are pointing away from each other, rather than aligning together. This projects the two alkynes into two different areas of space, theoretically meaning a suitable ligand could be designed to link to the ester and nitrile groups and present the copper reaction site to just one of the alkynes. This, of course, assumes the molecule adopts this configuration while in solution, and it is not just due to the crystal packing.



Scheme 17 - Synthesis of *bis*-alkyne 89 from methyl phenylacetate 103

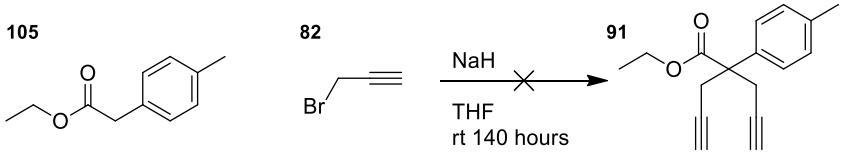
The first change to this process was to use methyl phenylacetate **89** as the substrate of the *bis*-alkyne reaction. This change was adopted because during the racemic click step discussed later, a large amount of *bis*-reaction product was being formed. Due to the high affinity of nitriles to copper salts, we thought that the nitrile was interfering with the reaction, and perhaps holding the copper in close proximity to the molecule, so it could easily react with the second alkyne, something which was not intended.[58]

Unfortunately, forming *bis*-alkyne **89** from methyl phenylacetate **103** required harsher conditions, using sodium hydride as the base. This could be because the p*K*a for the phenyl derivative is much higher.[59] However, a small amount of product was produced, which was subjected to the click procedure. The click reaction was successful, and showed 30% conversion to the mono-product, and a further 9% to the *bis*-product, as calculated from the relative areas of the methyl signals on the proton NMR spectrum. However, due to the phenyl group on the backbone, and the phenyl groups on the benzyl azide coinciding on the NMR spectrum, it was impossible to locate the triazole proton under the aromatic protons. Due to the difficulty of assigning signals in the NMR spectrum, combined with the harsher synthesis, this substrate was set aside.



Scheme 18 – Attempted synthesis of *bis*-alkyne 90 from methyl *p*-methoxyphenylacetate 104

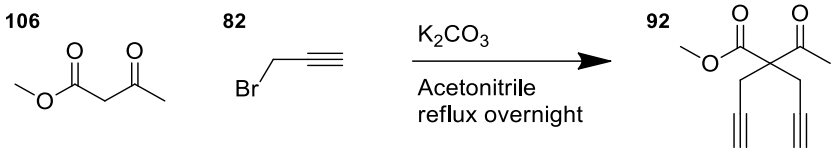
Methyl *p*-methoxyphenylacetate **104** was suggested as the next substrate in an attempt to clear up the aromatic area of the NMR spectrum. The *p*-methoxyphenyl group would exhibit two doublets in the aromatic region of the NMR spectrum, instead of the multiplet in the phenyl version. Unfortunately, attempts to synthesise *bis*-alkyne **90** were unsuccessful. The first method attempted used the sodium hydride reaction that worked for the phenyl variant. This method did not produce the expected peaks in the proton NMR spectrum and showed some starting material remaining. The reaction was reattempted by heating at reflux. Again, the product peaks were not seen in the proton NMR spectrum. Less starting material remained this time, so this showed some reaction was occurring. Next, a weaker base, potassium carbonate, was used. Again, the proton NMR spectrum showed no peaks from the product. Some high multiplicity, low intensity peaks were found around 3 ppm, which were assumed to be from the mono-substituted products.



Scheme 19 - Attempted synthesis of *bis*-alkyne 91 from ethyl p-tolylacetate 105

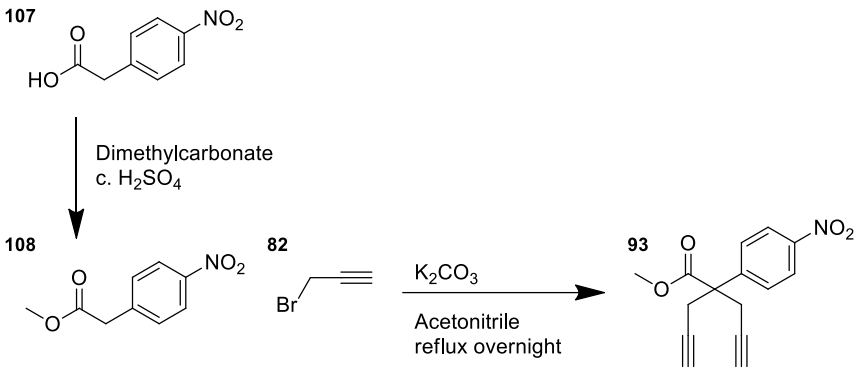
We theorised that the methoxy group deactivated the reaction site. Ethyl *p*-tolylacetate **105** was the next to be attempted, in the hope that by changing the *p*-methoxy for the tolyl moiety, the reaction would proceed. The ester is also different, due to the methyl ester being commercially unavailable, although this should not have a significant effect on the

reaction. Again, potassium carbonate was chosen as the weak base, following the same procedure as before. After heating under reflux over a weekend, the proton NMR spectrum showed that no reaction had occurred. The protocol using sodium hydride was attempted, and the reaction was heated under reflux overnight. Analysis of the proton NMR spectrum showed little reaction, but a series of very low intensity peaks in the expected position for the additional alkyne peaks gave hope that the reaction was in fact working. The reaction was repeated and left for six days, after which no additional product appeared in the proton NMR spectrum. This caused this substrate to be set aside too.



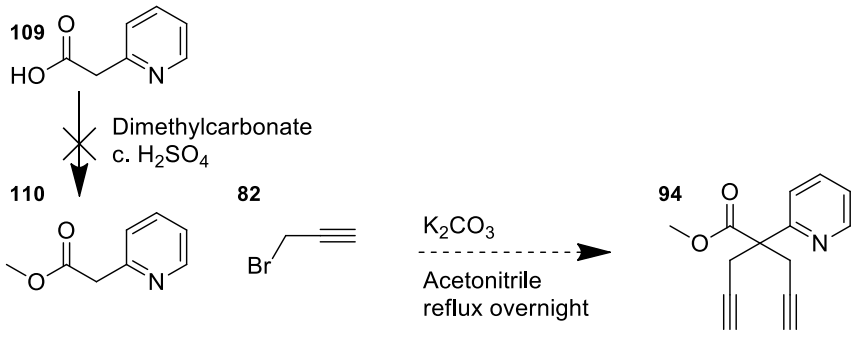
Scheme 20 - Synthesis of *bis*-alkyne 92 from methyl acetoacetate 106

Methyl acetoacetate **106** was the next molecule to be investigated. This has an ester on one side of the molecule, and a methylcarbonyl moiety on the other. This was also chosen to simplify the NMR spectrum. Given the ease of analysing reactions with a methyl ester, putting an methyl group on the other half of the molecule should give another easy to identify singlet. The potassium carbonate procedure was attempted, and formed the product in 31% yield.



Scheme 21- Synthesis of *bis*-alkyne 93 from *p*-nitrophenylacetic acid 107, via methyl ester 108

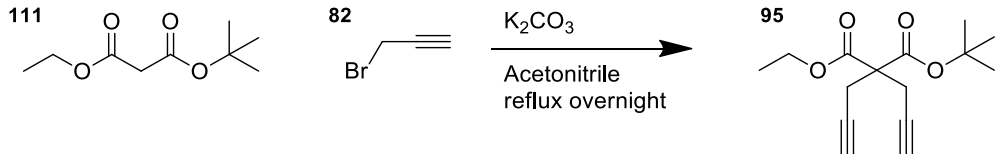
Methyl *p*-nitrophenylacetate **108** was synthesised from the corresponding acid **107**, using dimethyl carbonate, with concentrated sulphuric acid as a catalyst. The formation of *bis*-alkyne **93** from this was achieved using the standard potassium carbonate procedure. Proton NMR analysis showed the product had been formed and no starting material was present, but the product did contain some mono-substituted product as an impurity. Separation by column chromatography could not separate the two products cleanly, and only gave about a 30% recovered yield of the *bis*-alkyne product.



Scheme 22 - Attempted synthesis of *bis*-alkyne 94 from 2-(pyridin-2-yl)acetic acid 109, via methyl ester 110

Methyl 2-(pyridin-2-yl)acetate **110** was chosen because of its close relation to the cyano group, both having the nitrogen two atoms away from the proposed asymmetric centre. Unfortunately the similarity of its

atom positions did not extend to the reactivity. Synthesis of ester **110** was attempted from the corresponding acid **109**, using dimethycarbonate and concentrated sulphuric acid. Whilst no starting material was present in the proton NMR of the crude reaction mixture, there did not appear to be any peaks that could correspond to the product either, specifically the three to two ratio of methyl and methylene protons. The synthesis of *bis*-alkyne **94** was therefore not attempted.



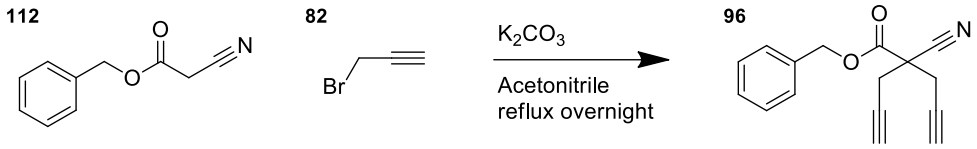
Scheme 23 - Synthesis of *bis*-alkyne 95 from *tert*-butyl ethyl malonate 111

A malonate is a diester derived from malonic acid. They have an active methylene unit, surrounded by two ester groups. Mixed malonates are pro-chiral, in that the two ester groups are different with a pro-chiral centre on the methylene between the esters.

Formation of *bis*-alkynes from these should be easier, because of the two ester groups. Any two alcohols can be used to create a mixed malonate, so this also allows for a wide range of different substrates. The initial mixed malonate chosen was *tert*-butyl ethyl malonate **111**.

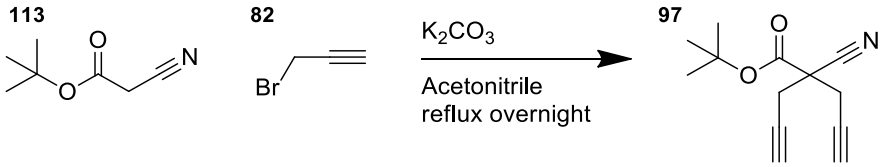
The reaction to form *bis*-alkyne **95** was first attempted with potassium carbonate as the base, but analysis of the proton NMR spectrum showed that no product was formed. A search of the literature uncovered a previous attempt to perform a similar reaction, but with a symmetrical malonate, and hexyl bromide, instead of propargyl bromide.[60] On following the same procedure, which used sodium hydride as the base, the product was formed in just 19% yield.

Realising that changing the nitrile moiety on our original backbone only gave detrimental results, we changed our focus onto changing the other side of the backbone, the ester.



Scheme 24 - Synthesis of *bis*-alkyne 96 from benzyl cyanoacetate 112

Firstly, benzyl cyanoacetate **112** was tried. The reaction proceeded well under the standard potassium carbonate procedure and the crude proton NMR spectrum showed peaks characteristic of the product *bis*-alkyne **96**, with an amount of starting material present. Purification via column chromatography gave a yield of 28%.



Scheme 25 - Synthesis of *bis*-alkyne 97 from *tert*-butyl cyanoacetate 113

Following on from the methyl ester giving a clear singlet in the proton NMR spectrum for easy determination of reaction progress, *tert*-butyl cyanoacetate **113** was chosen next. It also gives the clear singlet, but at a much lower chemical shift. The outcome of the NMR spectroscopy in the presence of a chiral lanthanide shift reagent using the methyl cyanoacetate *bis*-alkyne **88**, detailed later, was instrumental in the choice of this new structure. The reaction proceeded well under the potassium carbonate procedure, and yields up to 58% were obtained. Crystallisation from ethanol produced pale yellow crystals which were suitable for X-ray crystallography. Jean-Francois Lohier at the University of Caen assisted me in the mounting of this crystal, and performed the analysis. The crystal structure is given in Figure 6.

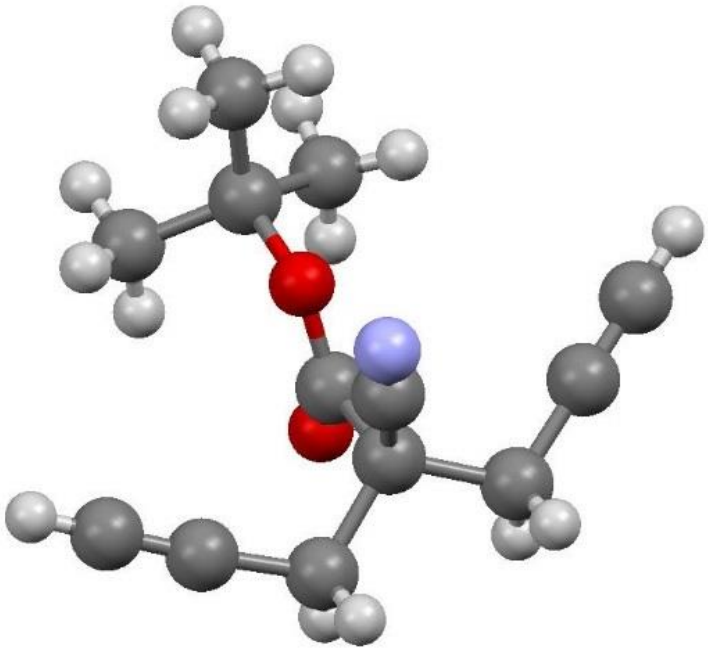
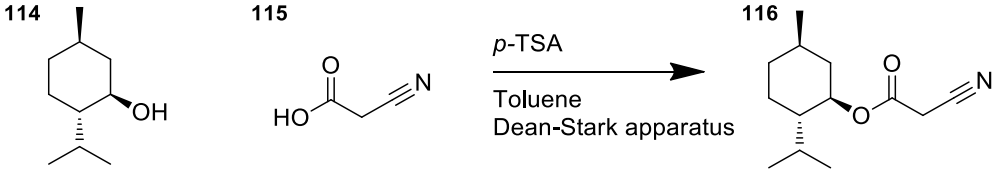


Figure 6 - X-ray crystal structure of *bis*-alkyne 97

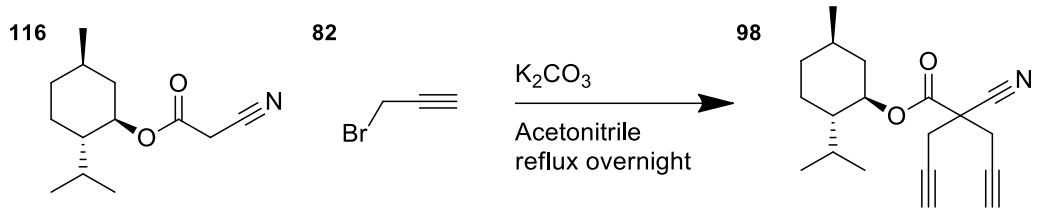
The two alkyne groups are again pointing away from each other, and they form a mirror plane through the molecule. Their position is notable, with the terminal alkyne protons out away from the centre of the molecule, compared to Figure 5, where one is near the molecule and the other is away. This may mean it is harder for the ligand to have an effect while distinguishing the two alkynes. Again, this assumes the molecule adopts this configuration while in solution, and it is not just due to the crystal packing.



Scheme 26 - Synthesis of menthyl 2-cyanoacetate 116 from L-menthol 114 and 2-cyanoacetic acid 115

The final ester change performed was using L-menthol **114** to form an ester. 2-Cyanoacetic acid **115** and L-menthol **114** were added to toluene, and the reaction was catalysed by *p*-TSA using a Dean-Stark apparatus.

This afforded an orange reaction mixture. The product **116** proved not to be miscible with n-pentane, whereas the impurities were. The crude reaction mixture was therefore stirred vigorously in n-pentane, and the mixture was filtered off to give an 81% recovered yield of the desired menthyl cyanoacetate product **116**.



Scheme 27 - Synthesis of *bis*-alkyne 98 from menthyl cyanoacetate 116

This menthyl cyanoacetate was subjected to the standard potassium carbonate reaction to afford *bis*-alkyne **98**, which after purification by vacuum distillation, gave a recovered yield of 78%. Recrystallization from ethanol again gave crystals suitable for X-ray crystallography. Jean-Francois Lohier at the University of Caen performed the experiment, and the structure is shown in Figure 7.

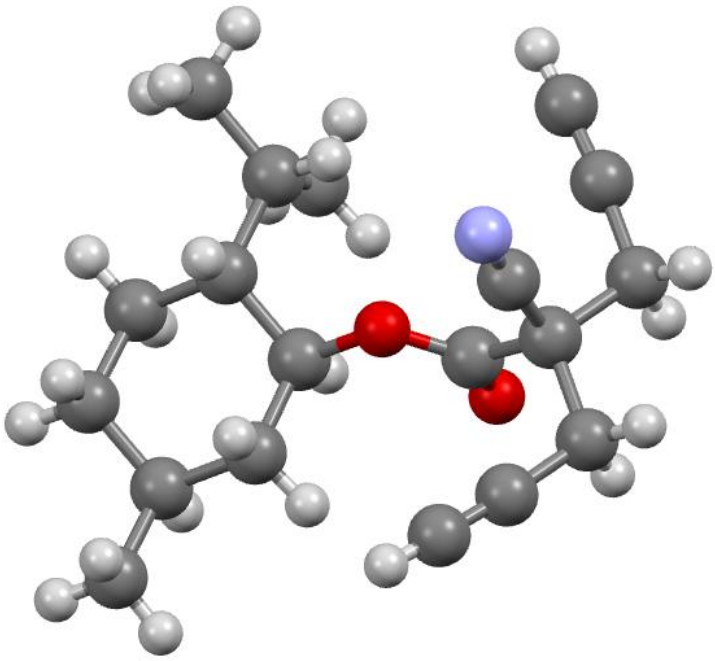
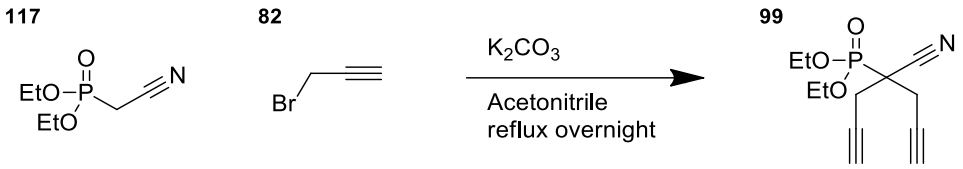


Figure 7 - X-ray crystal structure of *bis*-alkyne 98

Following the above research, we concluded that the most appropriate molecules to investigate further would be the original methyl **88** and *tert*-butyl **97** cyanoacetates because they are easy to make in a good yield and it is easy to follow the reaction by proton NMR spectroscopy. In addition, the L-menthyl cyanoacetate **98** was chosen because it could be produced easily in excellent yield, and might allow the sense of asymmetric induction from the proposed asymmetric 'click' reaction to be determined, if the relative stereochemistry of the mono-triazole could be proven by crystallography. The menthyl ester, however, may act as a chiral auxiliary in the click reaction, perhaps resulting in an improved, or reduced *ee* by double stereodifferentiation.

PHOSPHONATE ESTERS

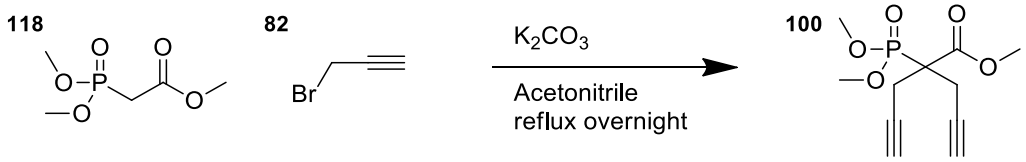
In addition to esters, and a mixed malonate, the synthesis of phosphonate esters was investigated. A phosphonate ester is similar to a standard carbonate ester, in that a double-bonded oxygen, and alkoxy groups are bonded to the phosphorus, the difference being there are two alkoxy groups, instead of one.



Scheme 28 - Synthesis of *bis*-alkyne 99 from diethyl cyanophosphonate 117

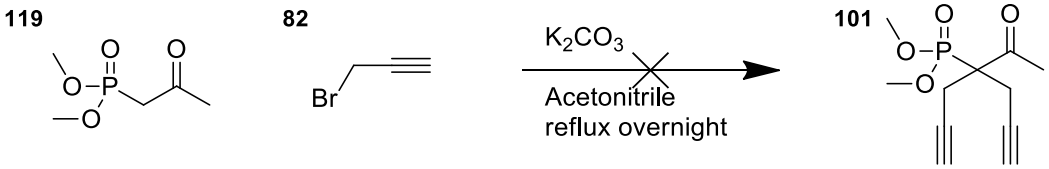
Diethyl cyanophosphonate **117** was the first phosphonate ester used, and is a close analogue of the original methyl cyanoacetate **86** precursor, except with ethyl alcohol groups on the phosphonate ester, in place of the methyl ester. A literature search found only one previous preparation of the compound.[61] This required the use of potassium metal in dry diethyl ether as the first step to form the potassium derivative, before addition of the propargyl bromide. This was deemed extreme reaction conditions which would not fit well with the 'click' chemistry philosophy. We decided to use our standard reaction procedures established with the cyanoacetate ester and should they not work, the phosphonate series would be discarded.

The reaction proceeded using the potassium carbonate protocol, and analysis of the proton NMR spectrum showed very few impurities. Purification by silica gel chromatography using petroleum ether and ethyl acetate as the eluent gave an overall 19% yield of product **99** as a pale yellow oil.



Scheme 29 - Synthesis of *bis*-alkyne 100 from trimethyl phosphonoacetate 118

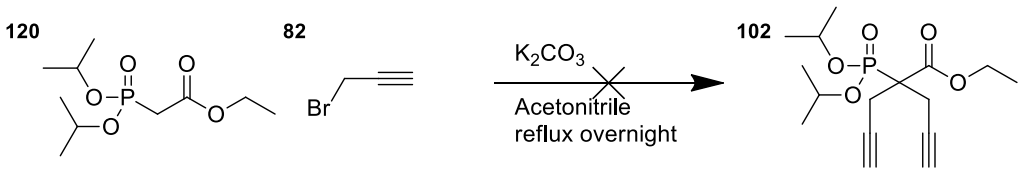
Trimethyl phosphonoacetate **118** was the next phosphonate investigated. This is similar to the mixed malonate backbone of the ester series, with an ester on one side, and the phosphonate ester on the other. There was no literature precedent this reaction. The reaction again proceeded well using the potassium carbonate protocol, and analysis of the proton NMR spectrum showed that the product had formed, but with some impurities. The impurity peaks were close to the product peaks, so we theorised that these could have come from the starting material and mono-substituted product. Purification by silica-gel chromatography using petroleum ether and ethyl acetate as the eluent was unable to separate the mono- and *bis*-substituted products fully. A small amount of impure *bis*-alkyne product **100** was obtained, but further purification was not attempted. The click reaction was performed on this mixture of products.



Scheme 30 – Attempted synthesis of *bis*-alkyne 101 from dimethyl 2-oxopropylphosphonate 119

Another phosphonate ester backbone used was dimethyl 2-oxopropylphosphonate **119**. This is an analogue of the methyl acetoacetate backbone of the ester series **92**, in that it has the phosphonate ester on one side of the methylene, and a methylcarbonyl group on the other. The potassium carbonate procedure was used, but

analysis of the proton NMR spectrum showed numerous signals from products which were not expected, and could not be identified. The *bis*-alkyne product **101** was not found among these signals.



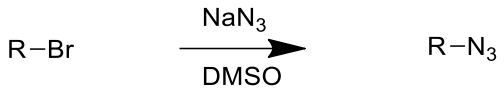
Scheme 31 – Attempted synthesis of *bis*-alkyne 102 from ethyl 2-(di-isopropyl phosphono)acetate 120

The final phosphonate used was ethyl 2-(di-*iso*propoxy phosphoryl) acetate **120**. This is another analogue of the mixed malonate from the ester series, However, analysis of proton NMR spectra resulting from the standard potassium carbonate procedure gave no sign of the product *bis*-alkyne **102.**

Of the phosphonate esters investigated, none appeared to provide the ease of reaction and excellent yield required for a 'click' chemistry protocol, compared to the ester series. This avenue was therefore discontinued. The two phosphonate compounds which had been synthesised successfully and partly purified were subjected to the click reaction procedures.

AZIDE COMPOUNDS

The azide moieties were synthesised using the method proposed by Alvarez and Alvarez where the corresponding bromide was treated at ambient temperature in a 0.5 M solution of sodium azide in dimethyl sulphoxide.[62] These reactions achieved yields of up to 98% in just one hour.



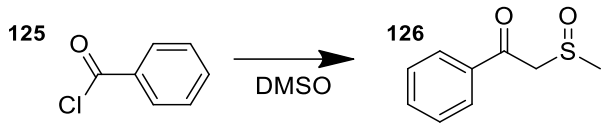
Scheme 32 - Method used by Alvarez to form azide

Following these procedures, the synthesis of benzyl azide was achieved, and has given yields of up to 94%. Several different azide moieties were made as part of this project; these are detailed in Table 5.

Table 5 - Azide moieties formed with yields

Azide	Yield	Compound Number
Benzyl	94%	**73**
Benzhydryl	99%	**121**
Trityl	98%	**122**
Benzoyl	76%	**123**
2-nitrobenzyl	94%	**124**

The reaction with benzoyl chloride was attempted using the standard reaction in DMSO, but on addition of the chloride to the DMSO solution a violent reaction occurred. Later research found that DMSO reacts with benzoyl chloride **125** to form 2-(methylsulphinyl)-1-phenylethanone **126**.[63]



Scheme 33 - Unexpected reaction of benzoyl chloride with DMSO

A literature method for the synthesis was found, which used an acetone water mix as the solvent system.[64] This reaction gave the product in a yield of 76%.

Comparison of click reactions performed using commercial benzyl azide and my freshly prepared benzyl azide showed they both performed equally well. This gave me confidence in using this process to synthesise azides for further reactions.

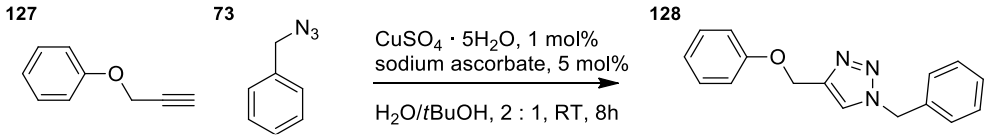
On leaving the benzyl azide in the fridge for some time, the colourless liquid turned pale yellow. This could indicate some deterioration of the compound. However, as all the reactions to produce the azides generally give very pure products, in almost quantitative yield, in a short reaction time, they can be produced as and when needed for the click reaction step, and used without further purification. Generally, they can be produced in the time it takes to charge the reaction vessels with the other reagents.

In addition to the stepwise procedure, there were several reported procedures where the azide is formed *in-situ* during the reaction. This method has several advantages. Firstly, azides are known to be explosive, and are highly volatile. With this method, the azide is not isolated, and there will theoretically be a very small quantity in the reaction at any one time due to the efficiency of the click reaction. Secondly, as mentioned above, the azide may deteriorate after some time. With the formation occurring *in-situ*, and the other reactants being present in a large excess over the formed azide, the click reaction occurs very rapidly, eliminating the time for deterioration.

As a mid-ground between the two procedures, a one-pot, two-step reaction was developed. In the review on copper-catalysed azide-alkyne cycloadditions by Meldal and Tornøe, they summarised numerous click reactions from the seven years preceding the paper.[65] Many of the reactions proceeded in DMSO, which is the same solvent used for formation of the azide. So for the mid-ground, the azide was formed using the same procedure as Alvarez, but no purification was performed. A small sample of the reaction mixture was taken after an hour, and NMR analysis showed the progress of the reaction. The benzyl protons shift slightly between the bromide and azide in the proton NMR spectrum, from 4.50 ppm for benzyl bromide, to 4.35 ppm in benzyl azide. In addition, IR spectroscopy was used to show the stretch corresponding to the C-Br group at around 1600 cm^{-1} had disappeared, and the C-N_3 group had replaced it, with a stretch at around 2100 cm^{-1}. Once at this stage, the reagents for the click reaction, the *bis*-alkyne and the copper source, were added to the existing reaction media and the reaction was allowed to proceed as normal.

CLICK PRODUCTS

The click chemistry step follows a variation to the protocol originally set out by Sharpless where alkyne **127** and benzyl azide **73** are suspended in *tert*-butanol/water and a copper(II) source is added.[25]



Scheme 34 - Procedure used by Sharpless

A 91% yield of the product 1,4-regioisomer **128** was achieved using just 1 mol% of copper(II) sulphate, with 5 mol% of sodium ascorbate to reduce it to the active copper(I) species. There is no contamination by the 1,5-regioisomer. The variation used in this thesis uses copper powder as the catalyst, and relies on air oxidation of the copper to form the active catalyst.[66]

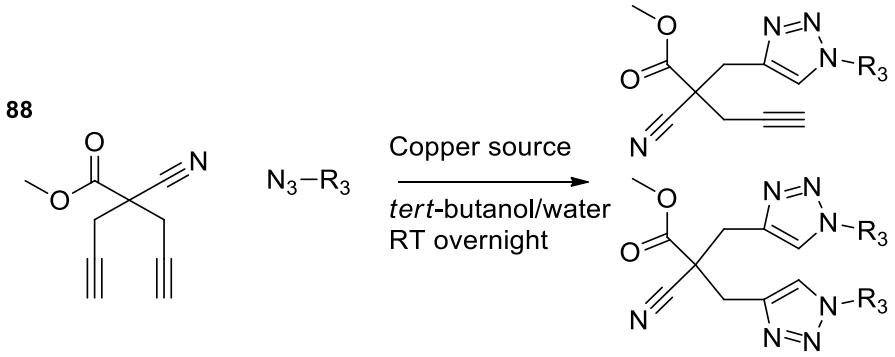
At the start of the project, a series of reactions were performed to gauge the efficacy of several copper sources for the reaction. A literature search showed numerous copper sources and forms that had been used in previous CuAAC research, including a review listing.[65] Several copper(I) and copper (II) salts were selected for testing, along with copper (0) powder, the results are given in Table 6.

Table 6 - Comparison of copper sources

	Copper Source	NMR Results
1	$CuSO_4$	44 / 31 / 25
2	CuI	50 / 25 / 25
3	Cu_2O	57 / 19 / 24
4	CuCl	52 / 27 / 21
5	CuBr	55 / 23 / 22
6	$Cu(OAc)_2$	52 / 27 / 21
7	Cu(0)	58 / 30 / 12

The outcome of the reaction showed that copper(II) sulphate and copper(0) powder produced about the same amount of mono-triazole product, but copper(0) powder gave a lower yield of the unwanted *bis*-triazole product. The four copper(I) sources, copper iodide, oxide, chloride and bromide, and copper (II) acetate, all gave slightly lower yields, with the additional problem of impurities from the DIPEA used, which was still present in some of the NMR spectra. Therefore, copper powder was chosen for our catalyst for the racemic reactions. In addition, this made the reaction easier to purify, as the reaction mixture could be filtered after quenching to remove the copper powder. After this, removal of the solvents under vacuum would give the products and any remaining starting material, which can be separated easily by column chromatography.

However, for the work with ligands, copper(0) powder is not suitable, and copper(I) iodide would be used instead. To ensure the ligand is having an effect on the reaction, all copper atoms need to be interacting with a ligand. The process of having an excess of copper powder and relying on oxidation by air is not compatible with this.



Scheme 35 - Standard click chemistry reaction using *bis*-alkyne 88

Due to the lack of chiral induction in this step, as no ligands are used, both the mono- and *bis*-substituted products are synthesised as a mixture, as shown in Scheme 35. Separation of the two products required column chromatography. The starting material elutes first, followed by the mono-product, then the *bis*-product. Purification in this way is easy and produces the mono-product in a clean state. The mono-product in this reaction is of course racemic.

The NMR spectrum of the crude reaction mixture was particularly useful, as the methyl singlets from the starting material, mono- and *bis*-products are well separated, and an easy comparison can be made to obtain percentage yields. See Figure 8.

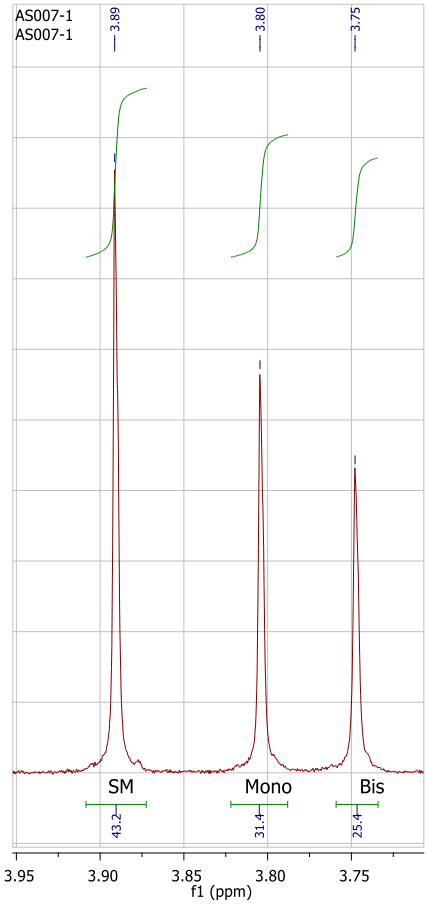
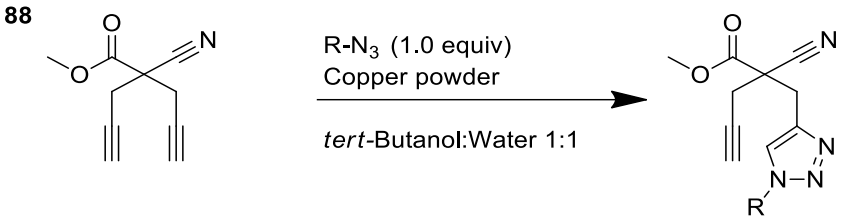
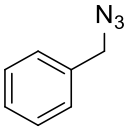
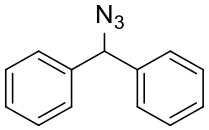
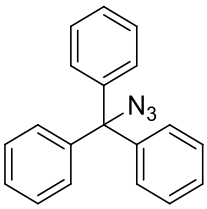
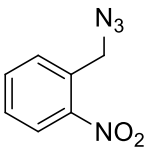


Figure 8 - Section from proton NMR showing the three methyl singlets.

The same *bis*-alkyne **88** was treated with the other azides that had been synthesised and the results are shown in Table 7. Of the results obtained, the benzhydryl product gave the best mono-selectivity at a reasonable rate. This is probably to do with the bulkiness of the group. The trityl group did give better mono-selectivity with only a trace amount of the *bis*-product, but required reaction at reflux for two days to give only 14% yield, whereas the benzhydryl group reacted at room temperature, and gave 26% conversion, with 85% of the mono product.

Table 7 - Summary of results with differing azide group



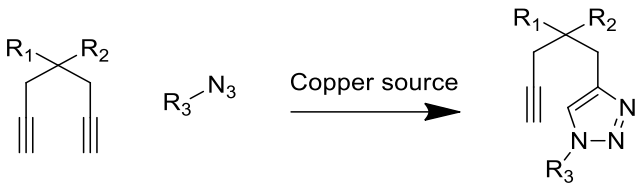
 **73**	 **121**	 **122**	 **124**
Benzyl azide	Benzhydryl azide	Trityl azide	2-nitrobenzyl azide
Reacted at room temperature	Reacted at room temperature	Reacted only under reflux	Reacted at room temperature
SM 53% Mono 25% *Bis* 22%	SM 74% Mono 22% *Bis* 4%	SM 86% Mono 14% *Bis* Trace	SM 28% Mono 46% *Bis* 26%

Despite this, benzyl azide was chosen as the one to take forward into further analysis. Both benzyl bromide and azide are liquids, which can easily be measured out using a syringe on a small scale, whereas benzhydryl bromide is a lumpy solid, which is harder to weigh out, as only a few milligrams is required per ligand assessment. It is also easier to track by NMR analysis, because the benzyl protons are unobstructed, whereas the benzhydryl proton is masked under the phenyl group in the proton NMR spectrum. In addition, should the chiral ligand system be effective enough to produce a good *ee,* very little of the *bis*-product should be produced as it requires reaction on the disfavoured alkyne.

Therefore, the higher reaction rate of benzyl over benzhydryl azide may produce higher conversions in a shorter time.

At first, our research was focused on improving the mono-selectivity. Several different reaction solvents and catalysts were tested, a summary of which are shown in Table 8.

Table 8 - Click reactions performed without a ligand



	Alkyne	Azide	Solvent	Copper Source	Azide Source	NMR Results
1	**88**	**73**	*t*BuOH/H_2O	$Cu(OAc)_2$	Commercial	52 / 27 / 21
2	**88**	**73**	*t*BuOH/H_2O	$CuSO_4$	Commercial	44 / 31 / 25
3	**88**	**73**	*t*BuOH/H_2O	Cu(0)	Commercial	58 / 30 / 12
4	**88**	**73**	Toluene	Cu(0)	Commercial	53 / 32 / 15
5	**88**	**73**	DMSO	Cu(0)	*In-situ*	25 / 75 / 0 25 / 53 / 22
6	**88**	**73**	DMSO	Cu(0)	*In-situ*	70 / 30 / 0
7	**88**	Phenyl	DMSO/H_2O	CuI	*In-situ*	26 / 59 / 15
8	**88**	**123**	*t*BuOH/H_2O	Cu(0)	Premade	100 / 0 / 0
9	**88**	**121** (R)	*t*BuOH/H_2O	Cu(0)	Premade	47 / 22 / 31
10	**88**	**124**	*t*BuOH/H_2O	Cu(0)	Premade	29 / 47 / 24
11	**88**	**122**	*t*BuOH/H_2O	Cu(0)	Premade	100 / 0 / 0
12	**96**	**73** (50)	*t*BuOH/H_2O	Cu(0)	Premade	48 / 29 / 23

	Alkyne	Azide	Solvent	Copper Source	Azide Source	NMR Results
13	**97**	**73** (50)	*t*BuOH/H_2O	Cu(0)	Premade	39 / 37 / 24
14	**92**	**121**	*t*BuOH/H_2O	Cu(0)	Premade	42 / 18 / 40
15	**95**	**121**	*t*BuOH/H_2O	Cu(0)	Premade	56 / 20 / 24
16	**99**	**73** (50)	*t*BuOH/H_2O	Cu(0)	Premade	16 / 21 / 63
17	**100**	**73** (50)	*t*BuOH/H_2O	Cu(0)	Premade	N/A
18	**88**	**122** (R)	*t*BuOH/H_2O	Cu(0)	Premade	86 / 14 / 0
19	**88**	**121**	*t*BuOH/H_2O	Cu(0)	Premade	74 / 22 / 4
20	**97**	**121**	*t*BuOH/H_2O	Cu(0)	Premade	41 / 25 / 34
21	**97**	**121** (50)	Toluene	Cu(0)	Premade	57 / 8 / 35
22	**97**	**73** (-40)	Toluene	CuI	Premade	51 / 17 / 32
23	**88**	**73** (-40)	Toluene	CuI	Premade	52 / 22 / 26
24	**88**	**73** (μ 125)	*t*BuOH/H_2O	$CuSO_4$	Microwave	32 / 30 / 38
25	**88**	**73** (μ 125)	*t*BuOH/H_2O	$CuSO_4$	Microwave	43 / 42 / 15
26	**88**	**73** (μ 125)	*t*BuOH/H_2O	$CuSO_4$	Microwave	36 / 26 / 38
27	**88**	**73** (μ 70)	THF	$CuSO_4$	Microwave	37 / 46 / 17

NMR results are given as ratio of SM/Mono/*Bis* products. All reactions performed at, or just above, RT, excluding those which were performed at the temperature in the brackets, under reflux (R), or in a focussed microwave reactor at the stated temperature (μ X). Azide source: Commercial means used as purchased from Alfa Aesar, with no purification. Premade means synthesised by myself, and purified immediately prior to use. *In situ* means synthesised by myself, and not purified prior to use. Microwave methods used benzyl azide synthesised from sodium azide and benzyl bromide inside the microwave reactor as the reaction progressed.

Entries 1 to 3 compare the use of different copper sources for the reaction, and all give about 30% conversion of the mono-substituted product. Entry 3, using just copper powder as the catalyst, has the lowest amount of impurity from the *bis*-substituted product. This, coupled with the ease of separation of the catalyst at the end, made this the clear choice for further use in the ligand-free synthesis.

Entry 4 changed the solvent to toluene, from a mixture of water and *tert*-butanol. This was in preparation for ligand assisted reactions later, that generally take place in toluene. This did not have much effect on the reaction, with the yields of both products similar to that of entry 3.

Entries 5 and 6 formed the benzyl azide *in-situ*, before the click reagents were added. This means the same reaction solvent is used. The original proton NMR analysis of entry 5, prior to purification, appeared to show an unprecedented yield of 75% mono-triazole, with no *bis*-triazole produced at all. Unfortunately, after separation by column chromatography, proton NMR analysis showed the product fractions to consist of both products, 71% mono to 29% *bis*-product. This phenomenon has not been explained so far. It was thought that the column conditions could have aided the change, but stirring of the purified mono-product in the column eluent with silica produced no *bis*-product. This experiment has been performed several times under the same conditions, and has not had the same outcome. For example, entry 6 uses the same conditions, but the yield of mono-product was just 30%, similar to that of the previous reactions. There was no *bis*-product detected in this reaction either, and none was retrieved after purification.

Entry 7 followed the procedure set out by Liang, for the formation of phenyl azide *in-situ*.[67] This was successful, and gave a large proportion of the mono-product. This method was considered for future use, but it

would be unsuitable for the reactions using ligands as the aqueous solvent conditions are not compatible with most ligands being used.

Entries 8 to 11 used different azide groups. Entry 9 used benzhydryl azide, and the reaction was performed at reflux. This gave a good yield of the mono-triazole, but a larger proportion of the unwanted *bis*-triazole. The reaction was performed again later on for entry 19, this time at room temperature which gave the same yield of mono-triazole, but much less of the *bis*-triazole by-product. Benzoyl and trityl azides did not form any products at room temperature, but entry 18 shows trityl azide does react under reflux conditions. The steric hindrance of the three phenyl groups attached to a single carbon atom is clearly at play here.

Entries 12 and 13 used different substituents on the alkyne backbone. These reactions were performed at 50 ^{O}C in an attempt to produce a larger quantity of mono-products for easier separation and analysis. Changing the methyl ester to benzyl or *tert*-butyl gave results similar to the original methyl ester. The benzyl ester variant was also not easy to follow by proton NMR analysis, as the only singlet from which to obtain ratios does not move sufficiently to form separate signals, especially when combined with the benzyl proton signal from the azide.

Entry 14 used the acetoacetate backbone with benzhydryl azide. The proton NMR analysis showed 40% conversion to the undesired *bis*-product, with just 18% conversion to the mono-product. Entry 15 used the mixed malonate, *tert*-butyl ethyl malonate with benzhydryl azide. This gave similar results to the original cyanoacetate, but with slightly more *bis*-product. These two *bis*-alkynes were originally created to avoid having a nitrile group in the molecule, because it was thought it may be holding the copper reaction centre in the vicinity of the second alkyne group, causing an increase in the *bis*-click product. However, these reactions

both have a higher yield of the *bis*-click product, so this theory has been proved wrong.

Entry 16 was the first phosphonate ester, based on diethyl cyanophosphonate. This reaction gave just 21% conversion to the mono-triazole, but 63% conversion to the undesired *bis*-product. Entry 17 was based on the other successful phosphonate ester, Trimethyl phosphonoacetate. Whilst the reaction did in fact form some products, the multitude of overlapping methyl signals in the proton NMR caused for an impossible task in obtaining any yield data from it.

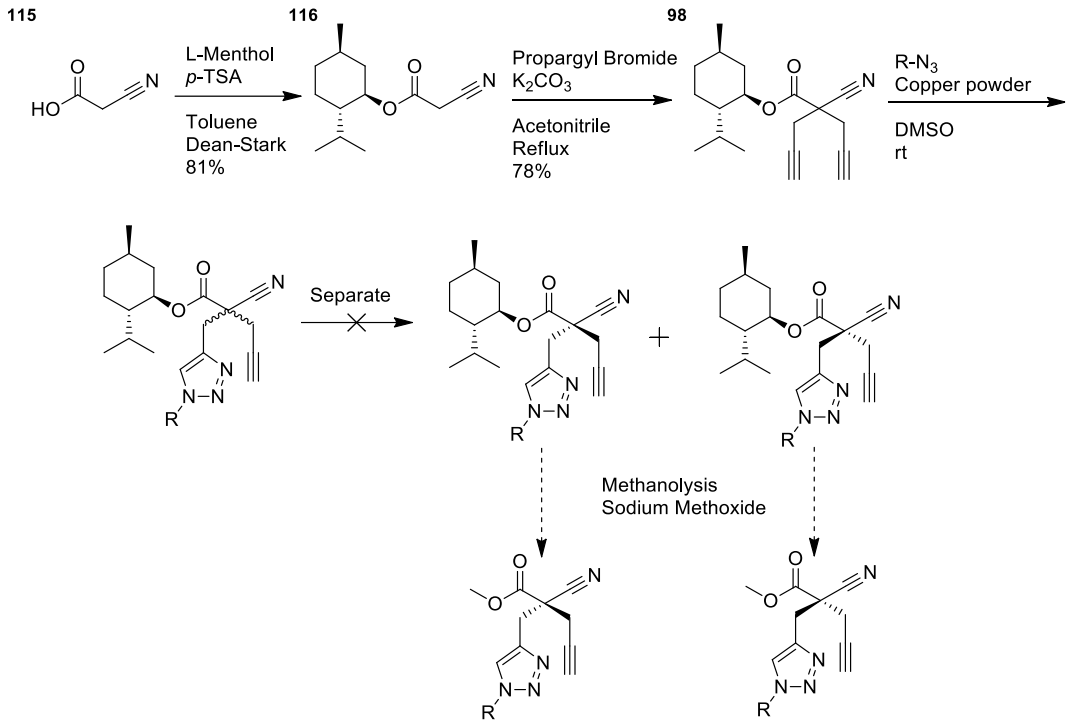
Entries 20 and 21 used the *tert*-butyl cyanoacetate backbone, with benzhydryl azide. The standard reaction at room temperature in a *tert*-butanol and water mixture gave results similar to the methyl cyanoacetate version. The reaction in toluene at the higher temperature of 50 ^{O}C gave a lower overall conversion, and mostly to the *bis*-triazole. In this case it seems the higher reaction temperature favours formation of the *bis*-triazole over the mono-triazole.

Entries 22 and 23 were preliminary reactions performed under the same conditions that would be used when the ligands were used. In this case, copper(I) iodide worked well, compared to previous reactions in *tert*-butanol:water, where it gave a lower yield than using copper(0) powder. In this case, both methyl and *tert*-butyl cyanoacetates were used, and gave very similar results, with a slight advantage to the methyl cyanoacetate.

Entries 24 to 27 were conducted in a focussed microwave reactor. They all used benzyl azide, which was synthesised during the reaction from sodium azide and benzyl bromide. Whilst the reactions proceed much quicker than the standard reactions, all of the azide was consumed in just 15 minutes, they have a tendency to form a large proportion of the *bis*-product, and between the three reactions using aqueous solvent

conditions, there is a large variation in the conversions. Entry 24 and 25 were irradiated for 20 minutes each, with entry 26 being irradiated for just 15 minutes, yet entry 26 gives an overall conversion almost as high as entry 24, and both are higher than entry 25. Looking at the mono-triazole though, entry 25 gave the best proportion of mono-product, with 42%, and 15% of the *bis*-triazole. This is similar to the results from using THF as the solvent in entry 27, and at the lower temperature.

As described above, a menthol ester was introduced, and followed the procedure set out in Scheme 36. The initial plan was to try to perform a fractional crystallisation on the product to separate the stereoisomers. Menthol is a cheap, readily available chiral alcohol, which would easily introduce defined chirality into the molecule. A search of the literature brings up hundreds of results for the more sterically hindered, and more expensive, 8-phenylmenthol, which is well known because it has been used by Corey in the synthesis of prostaglandins.[68] Menthol itself is not as widely used as a chiral auxiliary for the purpose of crystallisation, but it has been used.[69]

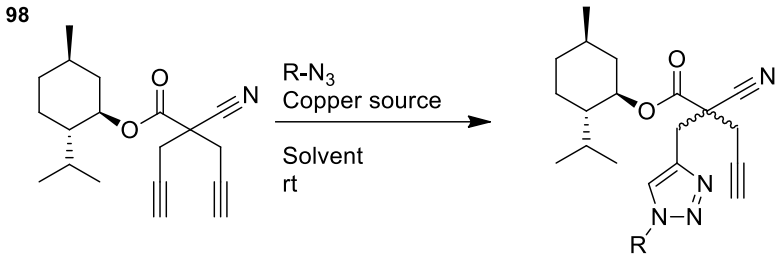


Scheme 36 - Proposed method using L-Menthol as a chiral auxiliary

Methanolysis of the menthol ester of the separated products would then give the original triazole products, which could be analysed to validate the chiral shift NMR and HPLC analytical methods, and also to determine the absolute configuration of the products.[70]

The click reaction was performed on a smaller scale, and proceeded well, even on the hindered *bis*-alkyne. The reaction was performed with benzyl azide, and benzhydryl azide, both pre-made, and *in situ* methods. Analysis by proton NMR spectroscopy showed yields of up to around 50% mono-product, with the remainder being starting material and *bis*-product. The full results are given in Table 9.

Table 9 - Results from reactions using L-Menthol *bis*-alkyne 98



	Azide	Solvent	Copper Source	Azide Source	NMR Results
1	**121**	*t*BuOH/H_2O	$CuSO_4$	Premade	95 / 5 / 0
2	**121**	DMSO	Cu(0)	*In situ*	35 / 51 / 14
3	**121**	*t*BuOH/H_2O	Cu(0)	Premade	73 / 23 / 4
4	**73**	*t*BuOH/H_2O	Cu(0)	Premade	32 / 45 / 23
5	**121**	*t*BuOH/H_2O	Cu(0)	Premade	30 / 54 / 16

NMR results given as ratio of SM/Mono/*Bis* products. All reactions performed at, or just above, RT. Azide source: Premade means synthesised by myself, and purified out immediately prior to use. *In situ* means synthesised by myself, and not purified out prior to the click reaction taking place in the same reaction vessel.

The reaction indicated in Table 9, entry 1 used benzhydryl azide. The reaction was performed at room temperature overnight, and shows very little yield. This could indicate that due to the combined bulkiness of the ester group and azide group, the reaction is slower.

Entry 2 also used benzhydryl azide, and the reaction was again performed at room temperature, over a weekend. This time the reaction was performed in DMSO, as the two equivalents of azide were synthesised *in-situ* beforehand. In addition, this used copper powder as the copper

source, rather than copper (II) sulphate. This gave a much better yield, and this reaction was purified successfully using column chromatography.

Entry 3 formed a brown sludge upon working up, which did not dissolve in any solvents. Extraction with pentane was attempted, and proton NMR analysis of this showed some mono-product had leached into the solvent, along with a small amount of the starting material. Further extraction brought out more of the mono-product, and the combined triturates were purified by column chromatography to give a 5% recovered yield of the mono-product.

Entries 4 and 5 were run concurrently. Entry 4 used benzyl azide, whereas the other reactions with the menthyl ester all used benzhydryl azide. TLC analysis of both reactions after a weekend at room temperature showed minimal reaction, perhaps due to the low temperature in the lab. The reactions were then heated to 50 ^{O}C for a further two days, which gave good yields of the mono-products by proton NMR analysis. Extraction of the benzhydryl azide reaction brought about the mono-product, as before. However, extraction of the benzyl azide reaction was unsuccessful at purifying the product. In addition, the brown oily sludge formed did not dissolve in any solvents tried.

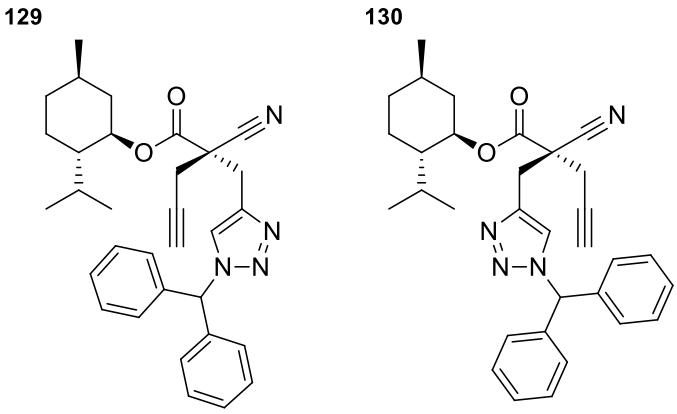
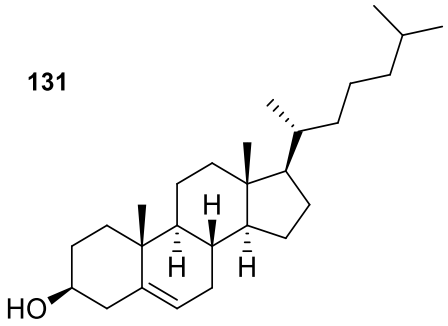


Figure 9 - Two diastereoisomers formed from *bis*-alkyne 98 and azide 121

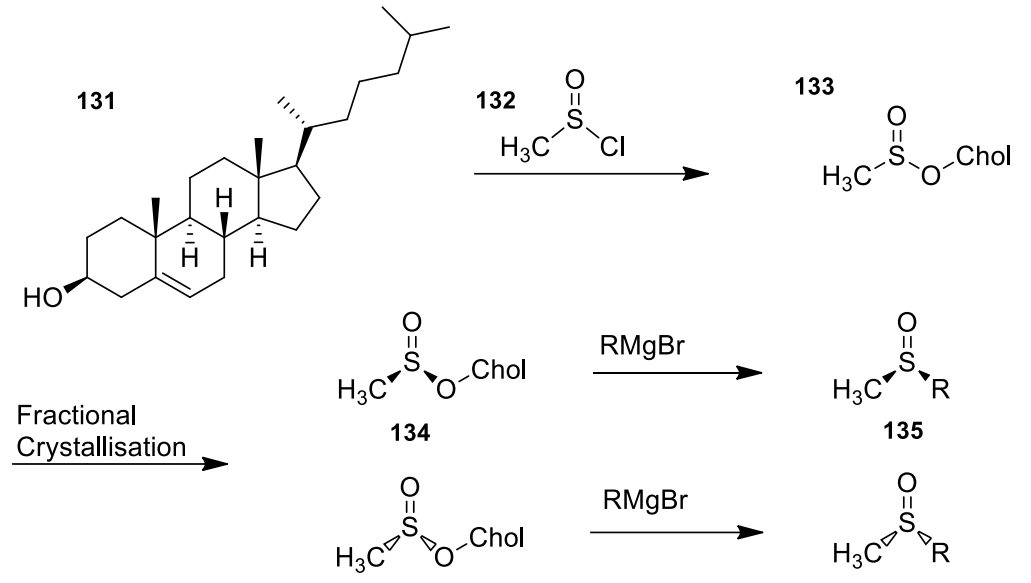
Separation of the two diastereoisomers was attempted. Firstly, column chromatography was investigated. TLC analysis using several different solvent systems was performed, but no separation could be obtained. Fractional crystallisation was attempted next, from both ethanol and pentane, solvents which have favoured crystallisation of the *bis*-alkynes before, but no crystals were formed. Crystallisation was also attempted from bi-layer systems, and several solvent mixtures, but these all failed to produce any crystals.

131



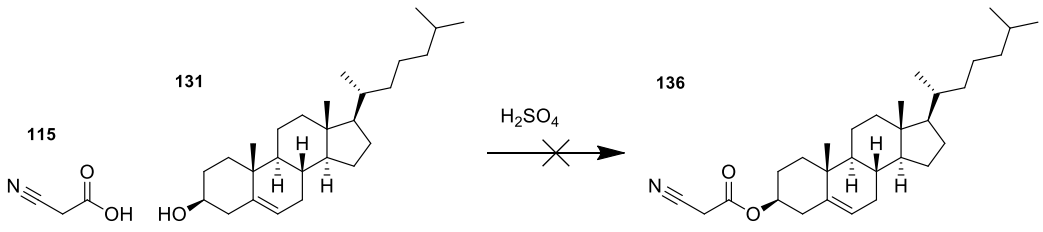
Structure 131 - Cholesterol

Cholesterol **131** is another chiral alcohol which has been used as a chiral auxiliary for a fractional crystallisation, so it was chosen as the next chiral auxiliary.[71] Andersen used a menthyl group as a chiral auxiliary for the formation of dialkyl sulphoxides **135**.[72] Similar to our work, these proved to be problematic, because the menthyl methylsulphinates exist as oils, which are difficult to obtain pure. Therefore, as per Scheme 37, Andersen changed his procedure to use cholesterol in his work, and the addition of the cholesterol group enabled separation of the two diasteroisomers by crystallisation. Cholesterol **131** was combined with methanesulphinyl chloride **132** to form the sulphinate **133** in quantitative yield. Crystallisation at this point managed to separate the two different diastereoisomers of the product **134**. The next step was to introduce the second alkyl group using a Grignard reagent, ejecting the cholesterol group, and leaving the chiral dialkyl sulphoxides **135**.



Scheme 37 - Procedure used by Andersen using cholesterol (Chol) as a chiral auxiliary to form chiral dialkyl sulphoxides.

I attempted a similar procedure given by Guseva, but unfortunately, the acid-catalysed reaction with 2-cyanoacetic acid **115** produced no product.[73] On standing, the reaction mixture congealed together in the bottom of the flask, and could not be removed.



Scheme 38 - Procedure used in attempted synthesis of cholesteryl cyanoacetate 136

While there is a literature precedent for formation of the acid chloride of 2-cyanoacetic acid, there is none for the formation of the cholesteryl ester this way.[73,74] The only method in the literature for formation of cholesteryl cyanoacetate uses the transesterification of ethyl cyanoacetate in refluxing toluene with the boiling off of ethanol as the driving force.[75] Neither of these methods were attempted however, as the project had moved on to the ligand evaluation.

CHIRAL ANALYSIS PROCEDURE

Very early into the project, once a pure mono-triazole sample had been formed, we began to develop a procedure to analyse the *ee* of the products. Chiral HPLC analysis is the standard procedure here, and was the first to be attempted.

Samples of a racemic mono-triazole made from methyl cyanoacetate **88** and benzhydryl azide **121** were formed, and run through a Chiralcel OD-H column. Initial trials of the chiral HPLC analysis failed due to the peaks appearing as a negative absorption on the HPLC trace. This appeared to give results from racemic, through to a 34% *ee* on the same sample. This was clearly not a viable way of performing the analysis. To try to determine why negative peaks were experienced, the sample was transferred to a fluorescence spectrophotometer. However, it exhibited no fluorescence under the same conditions as in the HPLC detector. An additional sample was made using fresh solvents and this still exhibited the same negative peak problem. As HPLC analysis worked well for other samples, but appeared to not work for my compounds, this method of analysis was disregarded.

The next procedure attempted was gas chromatography. This is similar to HPLC, but instead of a liquid mobile phase, a gaseous mobile phase is used, at elevated temperatures. The column length is also increased dramatically from a few centimetres to several metres. The compounds are made up in a solvent which evaporates quickly under the high temperatures of the apparatus, to allow the analyte to be taken up in the gas flow. Detection of any analytes was done using a flame ionisation detector. This uses a hydrogen flame to ionise the gas stream as it comes out of the chromatography column, which doubles as the positive electrode. The ions are then attracted to a negative electrode. This process creates a current through the device, which is measurable. If

there is a larger amount of analyte being ionised, then the current increases. This variation forms the chromatogram.

A sample of the mono-triazole used for HPLC was created, and analysed on the gas chromatograph. Unfortunately, no products could be found in the GC trace. A more concentrated sample was made up, and this too showed no products on the chromatogram. There are several explanations for this, the products may have not interacted at all with the column, and gone straight through, either with, or close to the injection solvent peak. Another possibility is that they interacted strongly with the column, so had a very high retention time. This means the peak would appear very broad which would be harder to spot on the chromatogram. In addition it may appear outside the normal run time so would not be seen.

After the initial failed HPLC and GC analyses, we turned to chiral shift NMR spectroscopy. This involved the portion-wise addition of a europium-based camphorate chiral derivatizing agent (CDA) to the NMR sample and obtaining a new spectrum after each addition. As more of the CDA is added some peaks from the two enantiomers may separate.

The two enantiomers would exhibit the same NMR spectrum under normal conditions, but on addition of the CDA to the sample, interactions between the analyte and CDA form diastereoisomers, which have different NMR spectra.

There are several CDAs which can be used. The three ligands in Figure 10 are commonly found in CDAs, complexed with either europium, lutetium, lanthanum, ytterbium or praseodymium.[76]

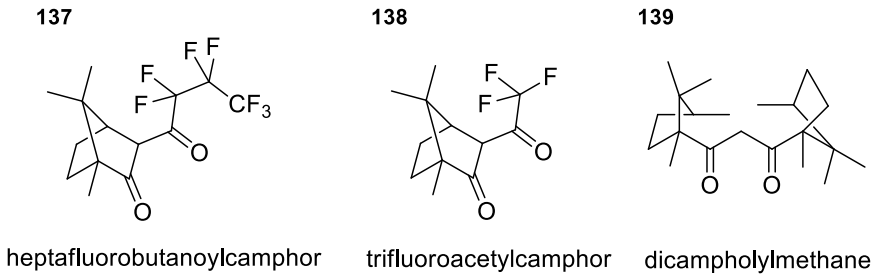
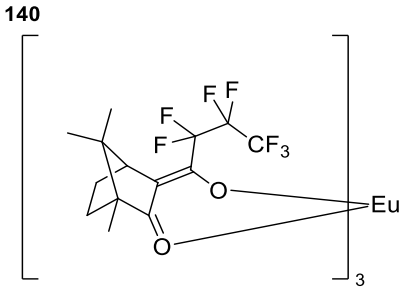
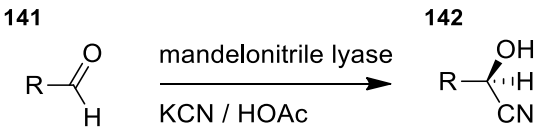


Figure 10 - β-diketone ligands commonly found in Chiral Derivatizing Agents[77]



Structure 140 - $Eu(hfc)_3$, the chosen Chiral Derivatizing Agent

The CDA chosen, shown above, was europium(III) tris[3-(heptafluoropropylhydroxymethylene)-d-camphorate] ($Eu(hfc)_3$) **140**. This particular molecule has a literature precedent for being used as a CDA for nitrile-containing molecules, so was expected to work well.[78] In this work, the authors formed optically active cyanohydrins **142** from aldehydes **141**, using an enzyme, mandelonitrile lyase, as in Scheme 39, which is found in a crude extract of almond flour. The CDA was then used to determine the enantiomeric excess of the samples.



Scheme 39 - Procedure used by Brussee *et al.*, for formation of cyanohydrins

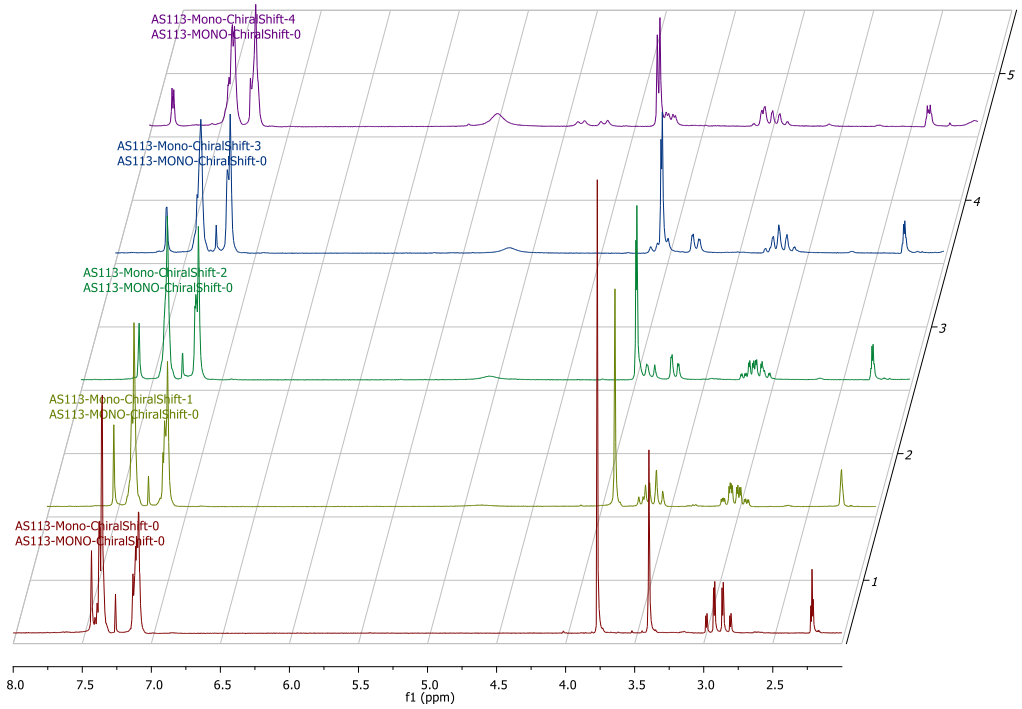


Figure 11 - Effect of addition of CDA on mono-triazole product of *bis*-alkyne 88 with benzhydryl azide 121. The front spectrum is prior to any additions.

As can be seen in Figure 11, each addition of the CDA causes the peaks to separate further. The peak with the most pronounced effect starts at just under 3.5 ppm, from the methylene adjacent to the triazole. Unfortunately, the methyl singlet just above it blocks the higher shifted signal at the key point after the third addition when the peaks have been separated. A further addition causes the least shifted peak to move underneath the methyl singlet, in addition to the methyl signal starting to split.

For this reason, the *tert*-butyl ester *bis*-alkyne **97** was developed because it does not contain any signals in the methyl group area that could interfere with the separation. The chiral shift procedure was repeated, shown in Figure 12.

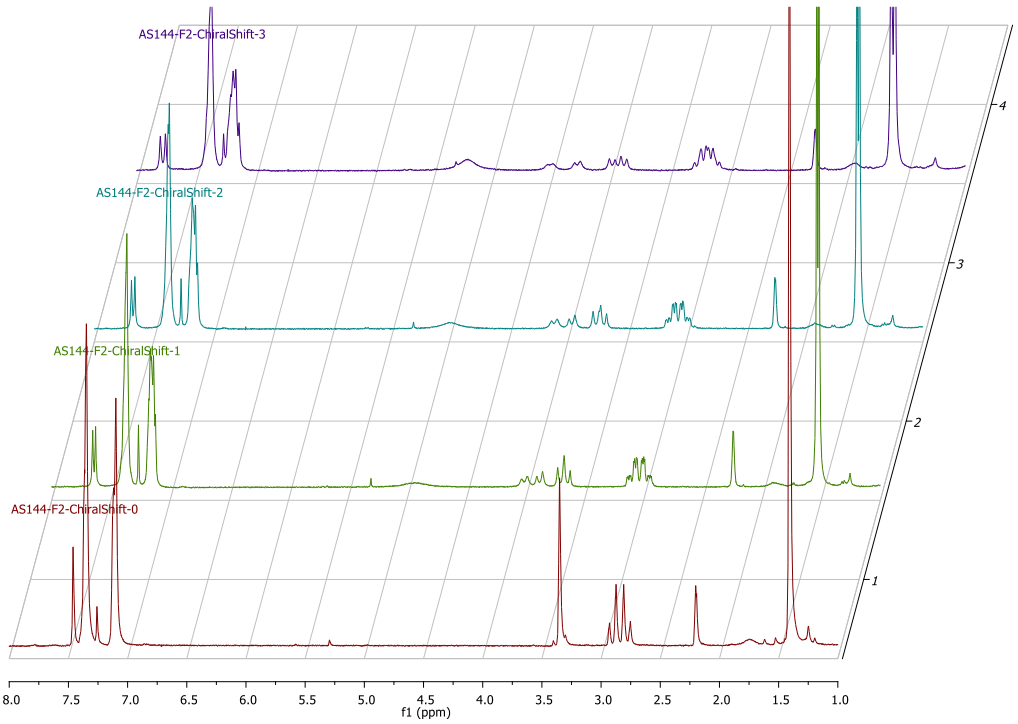


Figure 12 - Effect of addition of CDA on mono-triazole product of *bis*-alkyne 97 with benzhydryl azide 121. The front spectrum is prior to any additions.

As can be seen, with just one addition the signal that starts just below 3.5 ppm separates into two doublets, and what appears at first to be a triplet. The two doublets were assumed to be the signal from one proton, and the "triplet" was assumed to be two overlapping doublets the same as the other signal, from the other proton. Further additions show the doublets separating further, and the "triplet" splits further, into two doublets as expected.

The original singlet corresponds to two protons on the methylene adjacent to the triazole. On reaction with the CDA, each proton on each enantiomer is in a different environment, causing four signals. In addition, the signal is now split by the other methylene proton, because it is in a different environment. This causes the four doublet signals obtained.

The triazole and *tert*-butyl signals are also beginning to separate, giving potentially three signal ratios from which to obtain an *ee*. In this case the product was racemic, as expected.

During my period of study in France, one racemic sample was given to their HPLC technician for analysis. After a period of testing on several different columns and conditions, he returned with separation conditions for my molecule, using their HPLC system. Throughout the rest of my period of study in France he performed my HPLC analysis.

The conditions he found used a Daicel Chiralpak IC column, instead of the OD-H column attempted before. The main difference is the selector used on the chiral cellulose backbone. The new OD-H column uses 3,5-dimethylphenylcarbamate **7**, whereas the IC column uses 3,5-dichlorocarbamate **8**, which would give a very different electronic environment, with two mildly electron donating groups per phenyl group, rather than two highly electron withdrawing groups. In addition, the OD-H column material is coated onto the polysaccharide support material, which means it can be removed by putting the wrong solvents through it, whereas the IC column coating is immobilised onto the support, allowing for a much wider range of solvents. In fact, the manufacturer has stated that no known organic solvent will deteriorate the column coating.[79]

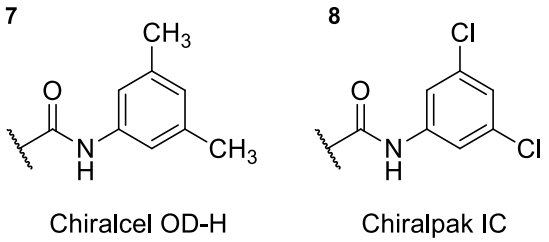


Figure 13 -Selectors used in the chiral columns

Later in the project, the chiral shift procedure was verified by using samples that had been shown to have an *ee*, once the chiral HPLC procedure had been established. Two samples were chosen, one was from the reaction using (*R*)-Tol-BINAP as the ligand, which exhibited an *ee* of 33% by HPLC analysis, and the other used (*S*)-Tol-BINAP, and exhibited an *ee* of 33% in favour of the opposite enantiomer.

The same CDA was used as above, and gave similar shift patterns. The ester which had been used was the methyl cyanoacetate *bis*-alkyne **88**, so extra shift reagent was required to shift the signals clear of the other peaks. This had an undesirable effect, in that the preferred signal previously identified at just under 3.5 ppm was split so far that it was impossible to distinguish the peaks. Fortunately, the methyl signal starting at just under 4 ppm could be split, and an *ee* was calculated for both samples.

Table 10 - Comparison of results from NMR in the presence of a chiral lanthanide shift reagent to chiral HPLC

	Least Shifted Peak Area	Most Shifted Peak Area	*ee* from NMR	*ee* from HPLC
(*R*)-Tol-BINAP	35.8	64.2	28 %	33 %
(*S*)-Tol-BINAP	64.4	35.6	29 %	33 %

The results show very good agreement between the two analysis methods, but both exhibit a slightly lower *ee* using the NMR method. The two enantiomers of ligand used have the opposite influence on the *ee* as was expected.

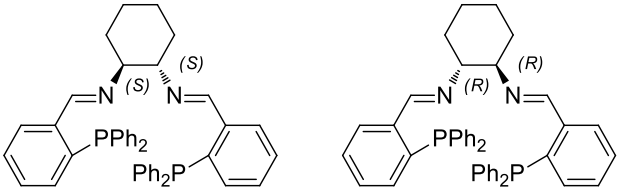
On my return to England we purchased a matching column for chiral analysis, and by using another HPLC machine the results were replicated, with no negative peaks. I improved upon the method by increasing the temperature of the column oven, which increases the rate of exchange between the phases, and changing the polarity of the solvent to shorten the retention time as much as possible, whilst keeping the two peaks of interest separated. This is important because at longer retention times the peaks tend to be broader, with longer tails, due to diffusion inside the column, which makes measurement less accurate. In addition, shorter retention times mean less solvent is used in the process, and the results can be obtained much more quickly, further reinforcing the green credentials of the click chemistry procedure.

To validate the method, a purified sample that had been analysed in France was re-run using the new method, and the results were in good agreement, as can be seen in Table 11, but with markedly shorter retention times.

Table 11 - Comparison of HPLC conditions and results for sample in Caen, France and Norwich.

Variable	Caen, France	Norwich, UK
Column Type	Chiralpak-IC	Chiralpak-IC
Mobile Phase	Heptane – *i*-PrOH	Hexane – *i*-PrOH
Solvent Ratio	80 – 20	70 – 30
Flow rate	1 mL min^{-1}	1 mL min^{-1}
Column Temperature	20 ^{O}C	40 ^{O}C
Peak 1 Retention	68.80 min	30.02 min
Peak 1 Area (%)	41.24	40.41
Peak 2 Retention	76.83 min	33.00 min
Peak 2 Area (%)	58.76	59.59
ee	18%	19%

As part of the Interreg exchange program, Damien Deschamps spent a period of study in our laboratory. His research included the development of phosphine ligands, and he brought some ligand samples with him. These included both the (*S,S*) and (*R,R*) enantiomers of *N*,*N*'-*bis*[o-(diphenylphosphino)benzylidene]-1,2-diiminocyclohexane **143**.

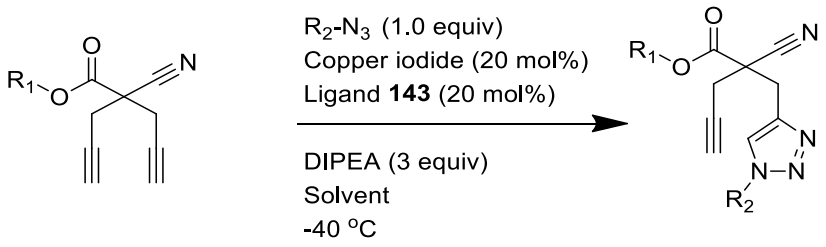


(*S,S*)-**143** (*R,R*)-**143**

Figure 14 - Both enantiomers of *N*,*N*'-*bis*[o-(diphenylphosphino)benzylidene]-1,2-diiminocyclohexane synthesised by Damien Deschamps

The first reactions performed with the above ligand showed mixed results. Entry 2 in Table 12 was the first reaction performed using a chiral ligand. The azide was being formed in the reaction before using the same reaction media, so the reaction solvent was kept as DMSO for the click step too. Proton NMR analysis of the reaction the next day showed no reaction using the ligand and copper(I) iodide. On addition of copper powder to the reaction vessel, proton NMR analysis the following day showed the reaction had proceeded as expected and gave a good yield of the mono-product. This shows that the combination of copper(I) iodide and ligand may not be suitable for reactions in this solvent. To combat this inconvenience, for all further reactions with a ligand the azide will either be purchased commercially, or made in a separate reaction and purified out immediately prior to being used in the reaction, and DMSO will be avoided as a reaction solvent for the click step when using a ligand.

Table 12 - Table of results for reactions with ligand 143.



Entry	Ester/ Azide	Ligand / Copper source	Solvent	Azide Source	NMR Results SM/Mono/*Bis*	*ee* (%)
1	**88 / 73**	(±)-**143** / CuI	THF	Commercial	58 / 29 / 13	N/A
2	**88 / 73**	(*R,R*)-**143** / CuI then Cu(O)	DMSO	*in-situ*	100 / 0 / 0 20 / 56 / 24	N/A
3	**97 / 121**	(*S,S*)-**143** / CuI	Toluene 50 °C	Premade	22 / 59 / 19	3 CS
4	**97 / 121**	(*S,S*)-**143** / CuI	Toluene 0 °C	Premade	87 / 11 / 2	5 CS
5	**97 / 73**	(*S,S*)-**143** / CuI 40 / 20 mol%	Toluene	Premade	65 / 30 / 5	3 1st
6	**97 / 73**	(*S,S*)-**143** / CuI	DCM	Premade	37 / 46 / 17	0
7	**97 / 73**	(*S,S*)-**143** / CuI	Toluene	Premade	75 / 23 / 2	0
8	**97 / 73**	(*S,S*)-**143** / CuI	Toluene	Premade	63 / 30 / 7	2 2nd
9	**88 / 73**	(*S,S*)-**143** / CuI	Toluene	Premade	43 / 43 / 14	0
10	**88 / 73**	(*S,S*)-**143** / CuI 40 / 20 mol%	Toluene	Premade	66 / 31 / 3	0
11	**98 / 73**	(*S,S*)-**143** / CuI	Toluene	Premade	100 / 0 / 0	N/A

NMR results obtained by comparison of proton NMR peaks, and are percentages. Equivalents used are as per the scheme, unless stated otherwise. *ee* results obtained by proton NMR spectroscopy in the presence of a chiral lanthanide shift reagent (CS) or chiral-HPLC. HPLC results show which peak was the larger.

Entries 3 to 8 used the *tert*-butyl cyanoacetate as the basis for the *bis*-alkyne **97** instead of the methyl ester **88**. This slight increase in size of the ester did not appear to influence the reaction much, with broadly similar results.

Entries 3 and 4 used benzhydryl azide **121**, at two different temperatures. As would be expected, the reaction at 50 °C produced more products than the reaction at 0 °C. In addition there was a very slight improvement in the *ee* at the lower temperature.

The remaining entries in the table were run at -40 °C and used benzyl azide, but show no discernible *ee*'s. Changing the solvent to DCM in entry 6 increases the yield of the mono-product, but chiral-HPLC analysis showed the product to be racemic.

Entries 5, 7 and 8 all had one variable changed. Entry 5 increased the quantity of ligand, while keeping everything else the same, including the amount of copper (I) iodide. This was to ensure the copper catalyst was completely bound to a ligand, and there was no excess of copper giving adverse results. The yields were similar to the standard reactions though, and no *ee* was found.

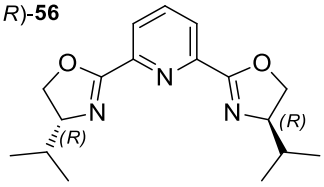
Entry 7 doubled the quantity of *bis*-alkyne in the reaction, while entry 8 doubled the azide. Doubling the azide was expected to produce more of both products, while doubling the alkyne, in effect, halving the azide, was expected to produce a lower overall yield, but with it, less of the *bis*-product. This is exactly what was found, but again, no *ee* was exhibited in the reactions.

Entries 9 and 10 went back to the methyl *bis*-alkyne **88**, with entry 9 at standard quantities of reagents, and entry 10 with double ligand. In this case, doubling the quantity of ligand did in fact decrease the quantity of *bis*-triazole product formed, and reduced the quantity of mono-product.

This may show that the ligand and copper do not fully form a complex at a 1:1 ratio, and it requires a slight excess of ligand to ensure full association. For further reactions this will be the case.

Entry 11 was an attempt to use a menthol ester as a chiral auxiliary, by using *bis*-alkyne **98**. However, no reaction was observed. This could be due to the reaction being run at –40 ^{O}C. At this temperature the other reactions proceed well, but being a bulkier ester a higher temperature may have given better results, but at this point the ligand was set aside, because it was exhibiting no selectivity on the reaction. In addition, as stated in the previous section, reactions without chiral induction were able to product the mono-product, but efforts to separate the menthyl ester diasteroisomers were unsuccessful, so the menthyl ester *bis*-alkyne **98,** was also set aside.

(*R*,*R*)-**56**

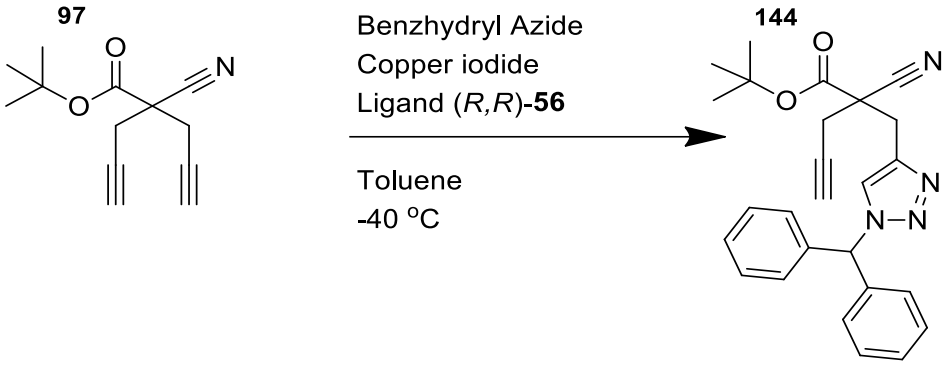


Structure 56 - (*R*,*R*)-*i*Pr-PyBOX ligand

Due to the literature precedent for PyBOX ligands being used with copper(I) salts, a simple PyBOX ligand, (*R*,*R*)-**56** was chosen for the next reactions.[80] The results are shown in Table 13.

With this new ligand the first reaction was very promising, with no detected *bis*-product, and a yield of mono-product of 16%. However, analysis by proton NMR spectroscopy in the presence of a chiral lanthanide shift reagent showed an *ee* of just 4%. A second attempt under the same conditions gave less mono-product, but a large amount of *bis*-product was produced, which was not expected.

Table 13 - Table of results for reactions with (*R,R*)-*i*Pr-PyBox 56.



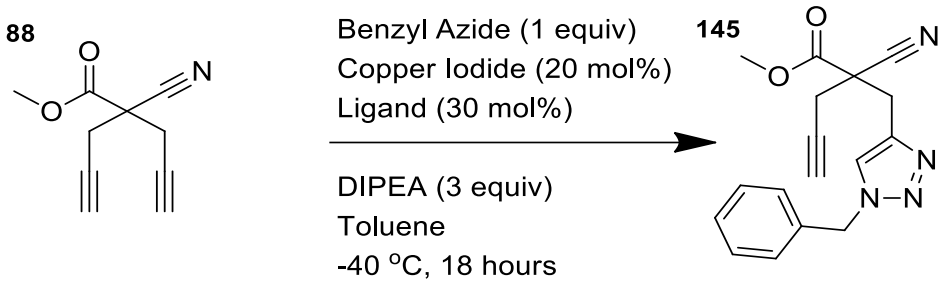
Entry	Azide Source	NMR Results SM/Mono/*Bis*	*ee* (%)
1	Premade	84 / 16 / 0	4 CS
2	Premade	51 / 11 / 38	0 CS

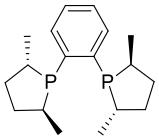
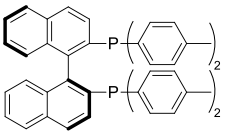
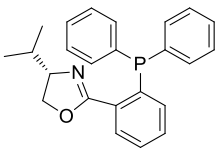
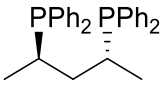
NMR results obtained by comparison of NMR peaks, and are percentages. *ee* result obtained by proton NMR spectroscopy in the presence of a chiral lanthanide shift reagent (CS).

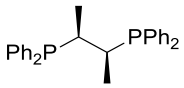
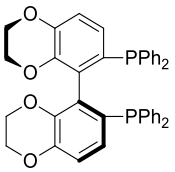
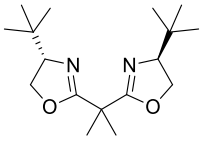
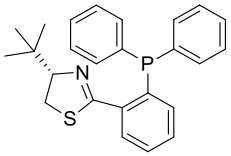
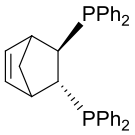
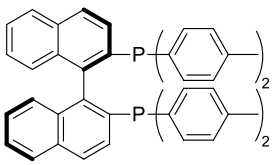
We thought that even though the ligand had been used carefully, and resealed thoroughly, it had still deteriorated and was no longer effective as a ligand. However, the deterioration products may have helped catalyse the reaction because the yields were so much higher than any other reaction. This ligand was then set aside, primarily because of the low *ee* obtained, but also the unexpected rapid deterioration of the ligand.

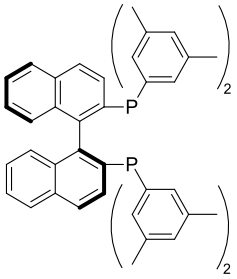
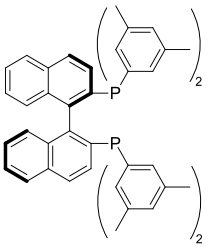
The laboratory in Caen had a much larger range of ligands available, so several new ones were tried. The results from the click reactions using these are detailed in Table 14.

Table 14 - Ligand assessment using methyl cyanoacetate *bis*-alkyne 88



Entry	Ligand	NMR Results SM/Mono/*Bis*	1st Eluting Peak	2nd Eluting Peak	*ee* (%)
1	(*S,S*)-Me-DUPHOS (*S,S*)-**146** 	67 / 33 / 0	50.36	49.64	1 1st
2	(*S*)-Tol-BINAP (*S*)-**147** 	96 / 4 / 0	41.24	58.76	18 2nd
3	(*S*)-*i*Pr-Oxazoline-TPP (*S*)-**148** 	65 / 32 / 3	50.64	49.36	1 1st
4	(*R,R*)-BDPP (*R,R*)-**149** 	86 / 14 / 0	50.17	49.83	0

Entry	Ligand	NMR Results SM/Mono/*Bis*	1st Eluting Peak	2nd Eluting Peak	*ee* (%)
5	(*S*,*S*)-Chiraphos (*S*,*S*)-**150** 	59 / 37 / 4	49.85	50.15	0
6	(*S*)-SYNPHOS (*S*)-**17** 	100 / 0 / 0	N/A	N/A	N/A
7	(*S*)-*t*Bu-*Bis*Oxazoline (*S*)-**151** 	53 / 32 / 15	48.66	51.34	3 2nd
8	(*S*)-*t*Bu-Thiazoline-TPP (*S*)-**152** 	60 / 35 / 5	49.09	50.91	2 2nd
9	(*R*,*R*)-NORPHOS (*R*,*R*)-**153** 	66 / 34 / 0	42.17	57.83	16 2nd
10	(*R*)-Tol-BINAP (*R*)-**147** 	75 / 19 / 6	52.21	47.79	4 1st

Entry	Ligand	NMR Results SM/Mono/*Bis*	1st Eluting Peak	2nd Eluting Peak	*ee* (%)
11	(*S*)-Xyl-BINAP (*S*)-**154** 	53 / 41 / 6	47.16	52.84	6 2nd
12	(*R*)-Xyl-BINAP (*R*)-**154** 	62 / 35 / 3	52.60	47.40	5 1st

NMR results given as ratio of SM/Mono/*Bis* products obtained from crude proton NMR spectrum. Benzyl azide was synthesised and purified out immediately before use in the reaction using the standard procedure. *ee* obtained from chiral HPLC analysis, and shows which peak was larger.

Entry 1 shows the use of (*S,S*)-Me-DUPHOS, **146** which at first gave a reassuring yield of mono product, with no trace of the *bis*-product present. Unfortunately, after separating the product by column chromatography, the product proved to exhibit no discernible *ee* by chiral HPLC analysis.

Entry 2, however, was the first sign that our methodology could work. The reaction with (*S*)-Tol-BINAP (*S*)-**147** gave a disappointing yield of just 4%, but there was again no trace of any *bis*-products. Chiral HPLC analysis of the purified product showed an *ee* of 18%, in favour of the slower eluting enantiomer. This initial result prompted further research on this ligand, and related ligands.

Entry 3 used (*S*)-*i*Pr-Oxazoline-TPP **148**, which has both oxazoline and phosphine binding sites, which gave a good yield of the mono product, but also 3% of the *bis*-product was detected. An *ee* of just 1% was obtained in favour of the faster eluting enantiomer.

Entries 4 and 5 both use smaller, simpler ligands, with two diphenylphosphine groups separated by a three or two carbon unit, respectively. However, neither (R,R)-*Bis*-Diphenylphosphino pentane **149** or (S,S)-Chiraphos **150** gave a detectable *ee*, but the additional methylene unit in **149** appears to give better mono-selectivity, but a slower reaction, with just the 14% yield of mono-product, compared to entry 5 with 37% reaction to mono-product, and a further 4% to *bis*-product.

Entry 6 used (*S*)-SYNPHOS **17**, which was chosen because of the similarity to (*S*)-Tol-BINAP **147**, but it exhibits different electronic and steric properties due to the change of the peripheral rings from a phenyl rings to fully unsaturated dioxins. This change did not have the desired effect on the reaction, because no reaction products could be detected in the proton NMR spectrum. This could be because the electronegative oxygen atoms pulled the electron density from the catalytic copper atom. With a lower electron density on the copper atom, it would become a weaker nucleophile, and may be unable to attack the alkyne. Without an attack on an alkyne the click reaction cannot take place.

After previous results with a PyBOX ligand proved unsuccessful, a BOX ligand, (S)-tBu-BisOxazoline **151** was tried for entry 7, due to the similar properties to the PyBOX. Unfortunately, the properties were too similar, and an *ee* of just 3% was achieved, with a yield of 32% mono-product, and 15% *bis*-product.

Entry 8 used a ligand developed and synthesised by a lab member in Caen. Their ligand, **152**, is similar to oxazoline **148** used in entry 3. This used a thiazoline group, instead of an oxazoline. The electronic and steric properties of this ligand are somewhat different, because sulphur is larger, and less electrophilic. The larger size of the sulphur would distort the five-membered ring, forcing the nitrogen closer to the phosphorus leaving a smaller chiral pocket for the copper catalytic centre.[81] In addition, the bulkiness of the thiazoline group is larger because the *iso*-propyl group is exchanged for a *tert*-butyl group. The click reaction using this ligand gave very similar results to the oxazoline of entry 3, with a yield of 35% mono-product, and 5% *bis*-product. The ee was also of a similar magnitude, but favoured the opposite, slower eluting enantiomer.

Entry 9 used a norbornene based *bis*(diphenylphosphine), (*R,R*)-NORPHOS **153** as the ligand. Proton NMR analysis of the reaction mixture showed a yield of 34% of the mono-product, with no *bis*-product detected. Chiral HPLC analysis of the purified product showed a reasonable 16% *ee* in favour of the slower eluting enantiomer. This result prompted this ligand to be investigated further too.

In entry 2, the bulkiness of the BINAP backbone could have helped improve the *ee*, by restricting the angle of attack of one of the alkynes. To prove this theory, entry 10 using the opposite enantiomer, (*R*)-Tol-BINAP (*R*)-**147**, was performed. The initial reaction used an existing ligand sample, and gave an unexpected yield of 19% mono-product, with 6% *bis*-product. The *ee* was also a lot lower at 4%, but was in favour of the opposite, faster eluting enantiomer, as expected. This was further indication that the methodology was working, but the lower mono-selectivity and *ee* suggested that this ligand sample had deteriorated.

In addition to swapping enantiomers, there is another series of ligands which vary the phosphine groups. Entries 11 and 12 use di(3,5-

xylyl)phosphine groups in place of the di-*p*-tolylphosphine groups, but retained the bis-napthalene structure **154**. Both enantiomers of the ligand were used. The (*S*)-enantiomer produced 41% of the mono-product, with 6% of the *bis*-product impurity, which exhibits an *ee* of 6% in favour of the slower eluting enantiomer. The (*R*)-enantiomer produced 35% of the mono-product, with 3% of the *bis*-product impurity, which exhibited an *ee* of 5% in favour of the faster eluting enantiomer.

As expected, using the opposite enantiomer of the ligand favours the opposite enantiomer of the product. This shows that the reaction is in fact being influenced by the chirality of the ligand.

(*S*)-Tol-BINAP and (*S*)-Xyl-BINAP both favour the slower eluting enantiomer, whereas (*R*)-Tol-BINAP and (*R*)-Xyl-BINAP both favour the faster eluting enantiomer. However, the Xyl-BINAP ligands both exhibit higher yields, but at a lower *ee* than the Tol-BINAP ligands. This could show that the BINAP backbone is a good starter backbone for further ligand design that is outside the scope of this thesis. Xyl-BINAP is bulkier than Tol-BINAP, and gave a lower selectivity. Perhaps reducing the steric bulk further by using diphenylphosphine groups, or rearranging the di-*p*-tolylphosphine groups to the *ortho*- or *meta*-positions could affect the selectivity of the reaction.

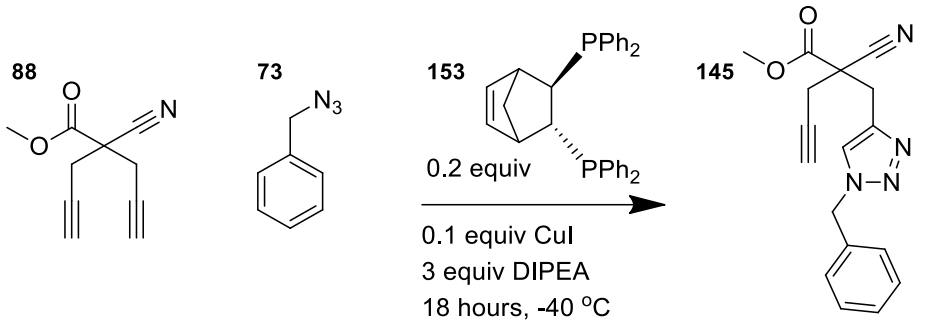
Good results were only obtained with ligands containing *bis*(diaryl) phosphine groups, but not all ligands containing this moiety were successful. (*S,S*)-Chiraphos and (*R,R*)-NORPHOS both contain the same P-C-C-P arrangement of atoms, but the rigidity and strained structure of the latter ligand backbone makes it much better at selecting one alkyne over the other.

Further work was performed on improving the selectivity of the Tol-BINAP and Xyl-BINAP series, as well as (*R*,*R*)-NORPHOS.

(*R,R*)-NORPHOS

(*R,R*)-NORPHOS **153** was one of the ligands chosen to be taken through to try to improve the selectivity. The first process chosen was to vary the solvent used in the reaction. Results are given in Table 15.

Table 15 - Reactions with (*R,R*)-NORPHOS 153 varying the solvent conditions



Entry	Solvent	NMR Results SM/Mono/*Bis*	1st Eluting Peak	2nd Eluting Peak	*ee* (%)	
1	Toluene	72 / 25 / 3	45.48	54.52	9	2nd
2	Acetone	55 / 39 / 6	46.47	53.53	7	2nd
3	Ethanol	81 / 17 / 2	55.34	44.66	11	1st
4	DMF	61 / 29 / 10	46.93	53.07	6	2nd
5	THF	58 / 34 / 8	46.97	53.03	6	2nd
6	EtOAc	61 / 35 / 4	46.78	53.22	6	2nd
7	Et_2O	70 / 27 / 3	46.33	53.67	7	2nd
8	Methanol	68 / 28 / 4	46.41	53.59	7	2nd

NMR results given as ratio of SM/Mono/*Bis* products obtained from crude proton NMR spectrum. Benzyl azide was synthesised and purified out immediately before use in the reaction using the standard procedure. *ee* obtained from chiral HPLC analysis, and shows which peak was larger.

The stand-out result is for entry 3. Using ethanol appears to reverse the selectivity of the reaction, however, on closer inspection of the HPLC trace, the tail of the peak eluting just before the first enantiomer is masked under the first peak. Therefore, this result should be disregarded.

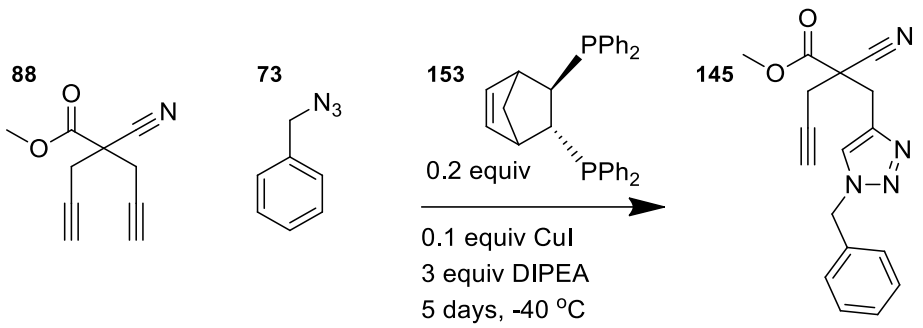
This series of reactions were performed on a reduced catalyst loading of 10 mol% of copper(I) iodide, with 20 mol% of ligand, mainly to reduce the amount of ligand used per reaction. Because of this, another control reaction was performed in toluene. This gave a reduced yield of 25% of the mono-product, compared to 34% previously, which can be attributed to the lower catalyst loading. In addition, the *ee* dropped from 16% to 9%, with a slight increase in the *bis*-product produced. The other results all give yields of the mono-product similar to that of the original reaction in toluene, or slightly higher, often with a small amount of the *bis*-product too. But, the *ee*s are all lower than the control toluene run.

The reactions were all repeated for 5 days, with the aim of increasing the yield. Results for this are given in Table 16.

Entry 3, using ethanol as the solvent is again the stand out result, this time for positive reasons. This gave an *ee* slightly higher than the toluene control reaction, with a comparable yield.

All the yields from this series of reactions were marginally higher than for the previous overnight reactions, except for entry 4, with DMF. This is not what was expected, and can only be put down to the effect of impurities from dimethylamine in the DMF in the previous reaction acting as an additional base, whereas a fresh bottle must have been used for the longer period reactions.

Table 16 - Reactions with (*R,R*)-NORPHOS 153 varying the solvent conditions and allowing a longer reaction period



Entry	Solvent	NMR Results SM/Mono/*Bis*	1st Eluting Peak	2nd Eluting Peak	*ee* (%)	
1	Toluene	68 / 29 / 3	46.72	53.28	7	2nd
2	Acetone	56 / 40 / 4	47.94	52.06	4	2nd
3	Ethanol	71 / 25 / 4	44.85	55.15	10	2nd
4	DMF	93 / 6 / 1	46.64	53.36	7	2nd
5	Hexane	97 / 2 / 1	48.58	51.42	3	2nd
6	THF	53 / 38 / 9	47.17	52.83	6	2nd
7	EtOAc	49 / 43 / 8	48.36	51.64	3	2nd
8	Et_2O	45 / 48 / 7	47.89	52.11	4	2nd

NMR results given as ratio of SM/Mono/*Bis* products obtained from crude proton NMR spectrum. Benzyl azide was synthesised and purified out immediately before use in the reaction using the standard procedure. *ee* obtained from chiral HPLC analysis, and shows which peak was larger.

The DMF reaction has a slightly higher *ee* in this series of reactions, possibly due to the dimethylamine impurities artificially decreasing the *ee* and increasing the yield in the original reaction, whereas the remainder have either the same, or lower. This result matches well with a previous reaction, where (*S,S*)-Me-DuPHOS gave a negligible *ee* with a yield of 33% after 18 hour reaction (Table 14, Entry 1) but with a reaction for just 4 hours an improved *ee* of 5% with a yield of 8% was exhibited. In both cases no *bis*-product was detected.

This suggests that the reaction proceeds in good *ee* at first, but after some time the complex somehow loses its ability to transfer its chirality to the reaction meaning the *ee* drops as both enantiomers are produced in equal proportions.

This could show the ligand in question does not bind tightly enough to the copper atom, so when a competing achiral ligand, such as the alkyne or nitrile groups on the *bis*-alkyne, becomes involved, the chiral ligand may be displaced, leaving the catalytic centre devoid of chiral induction. Although, should the chiral ligand leave or decompose, you would expect some *bis*-product to be formed. In addition, there is generally an excess of chiral ligand over the copper catalyst to allow for any disassociations, but, by being used in catalytic quantities, there is always a greater excess of other competing molecules in the reaction.

The reaction conditions were also optimised for the BINAP based ligands, results of which are given in Table 17.

The reaction with (*S*)-Tol-BINAP, (*S*)-**147**, entry 1, benefitted from the slight increase in temperature, and gave a marginal improvement in yield, up from 4 to 5%, and there was also 1% of the *bis*-product detected too. In addition, the *ee* improved dramatically to 33%, still in favour of the slower eluting peak. Entry 2 had the same changes but for the opposite enantiomer, (*R*)-Tol-BINAP, (*R*)-**147**. The yields obtained here are much lower than the previous reaction, but mirror the results for (*S*)-Tol-BINAP, (*S*)-**147** almost perfectly, giving a yield of 6%, and an *ee* of 33% in favour of the faster eluting enantiomer.

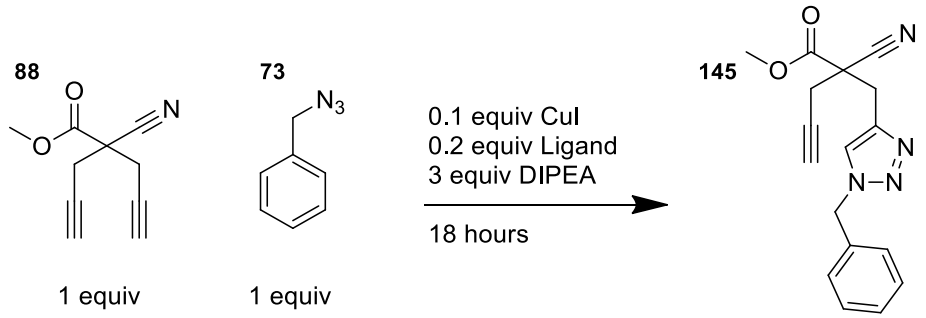
Entry 3 changes the solvent to chloroform. For (*S*)-Tol-BINAP, (*S*)-**147**, this dramatically increases the yield of the mono-product from 4% to 46% with 5% *bis*-product impurity, but at the expense of the *ee*, which is reduced down to 17%.

Changing the solvent to acetonitrile, entry 4, produces no products. This could be because the acetonitrile can form ligands with the copper catalyst. This would prevent any reaction from occurring.

Entries 5 to 8 were performed at the slightly lower temperature of –50^{O}C. As expected, all four gave lower yields at the lower temperatures.

The best result was obtained with (*S*)-Tol-BINAP (*S*)-**147,** and (*R*)-Tol-BINAP (*R*)-**147**, consisting of a 33% *ee* in opposing directions, but this was only a 5-6% yield, and was unable to be replicated.

Table 17 – Reactions with various BINAP based ligands, varying the solvent and temperature conditions.



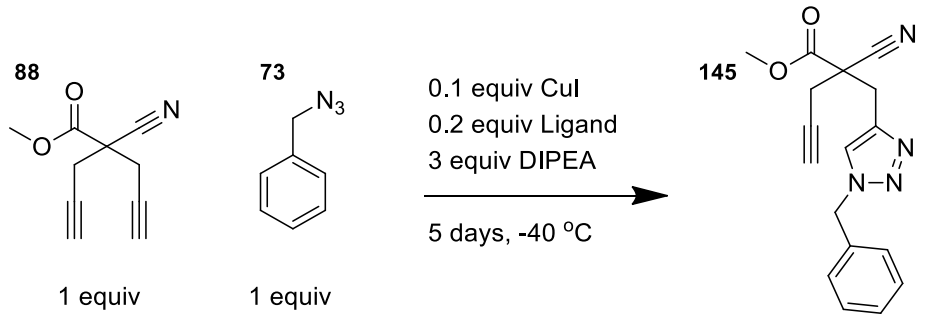
Entry	Ligand	Solvent Temp	NMR Results SM/Mono/*Bis*	1st Peak	2nd Peak	*ee* (%)
1	(*S*)-**147**	Toluene -30 °C	94 / 5 / 1	33.64	66.36	33 2nd
2	(*R*)-**147**	Toluene -30 °C	94 / 6 / 0	66.54	33.46	33 1st
3	(*S*)-**147**	Chloroform -30 °C	49 / 46 / 5	41.63	58.37	17 2nd
4	(*S*)-**147**	Acetonitrile -30 °C	100 / 0 / 0	N/A	N/A	N/A
5	(*S*)-**147**	Chloroform -50 °C	98 / 2 / 0	43.13	56.87	14 2nd
6	(*S*)-**154**	Chloroform -50 °C	97 / 3 / 0	47.87	52.13	4 2nd
7	(*S*)-**147**	Toluene -50 °C	95 / 5 / 0	41.23	58.77	18 2nd
8	(*R*)-**147**	Toluene -50 °C	99 / 1 / 0	59.25	40.75	19 1st

NMR results given as ratio of SM/Mono/*Bis* products obtained from crude proton NMR spectrum. Benzyl azide was synthesised and purified out immediately before use in the reaction using the standard procedure. *ee* obtained from chiral HPLC analysis, and shows which peak was larger.

The reaction time was another variable that was investigated, and the results are shown in Table 18. Entries 1 and 2 were using the tolyl containing ligand, **147**, and show an increase in the yield of the mono-product as hoped, from 4% up to 13% for (*S*)-**147**, and up to 9% for (*R*)-**147**. However, they do both exhibit a lower *ee* than before of 13-14%. Entries 3 and 4 used the xylyl containing ligands, **154**, and exhibit a similar yield as before, and identical *ee*s are obtained.

For entries 1 and 2, leaving the reaction for longer increased the yield, but lowered the *ee*, again indicating the chiral ligand is somehow deteriorating during the reaction and allowing the *ee* to reduce.

Table 18 – Reactions with various BINAP based ligands, varying the reaction time

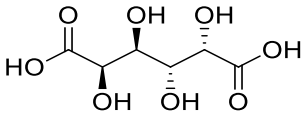


Entry	Ligand	Solvent Temp	NMR Results SM/Mono/*Bis*	1st Peak	2nd Peak	*ee* (%)
1	(*S*)-**147**	Toluene	86 / 13 / 1	43.08	56.92	14 2nd
2	(*R*)-**147**	Toluene	90 / 9 / 1	56.62	43.38	13 1st
3	(*S*)-**154**	Chloroform	61 / 35 / 4	46.81	53.19	6 2nd
4	(*R*)-**154**	Acetonitrile	74 / 24 / 2	52.49	47.51	5 1st

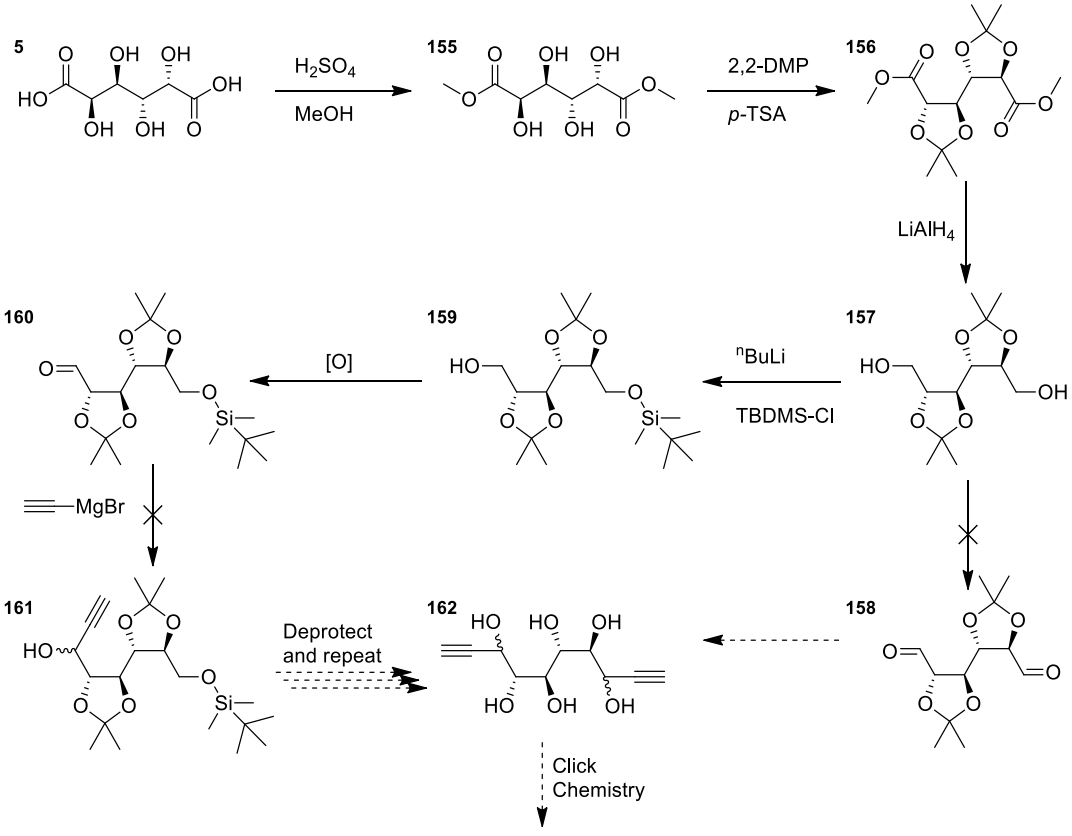
NMR results given as ratio of SM/Mono/*Bis* products obtained from crude proton NMR spectrum. Benzyl azide was synthesised and purified out immediately before use in the reaction using the standard procedure. *ee* obtained from chiral HPLC analysis, and shows which peak was larger.

ADDITIONAL WORK IN THE AREA

Another visiting student, Ali Moawia, from Caen, was tasked with performing click reactions as a desymmetrisation step on *meso*-compounds. We chose to focus our research on the mucic acid backbone **5**. The intention of the project was to create a *bis*-alkyne out of the molecule, from which to perform a novel click desymmetrisation step.



Structure 5 - Mucic acid backbone



Scheme 40 - First procedure for formation of *meso-bis*-alkyne from mucic acid

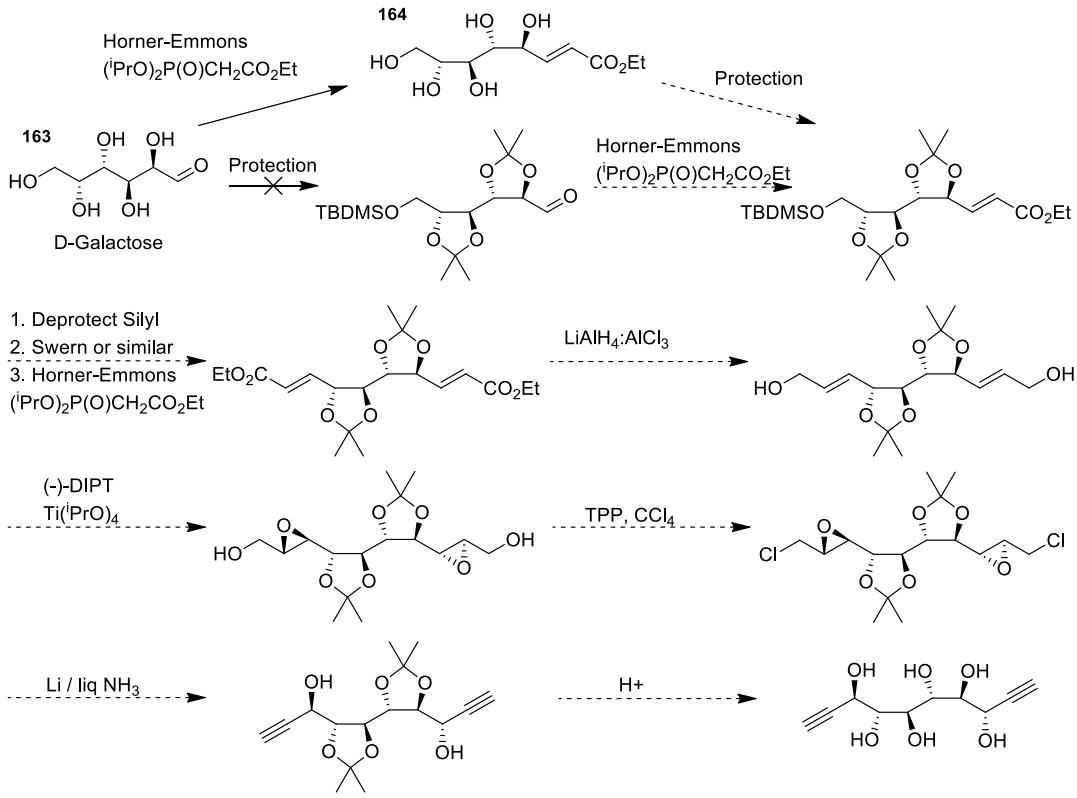
This was to be done by protecting the acid groups by acid catalysed esterification using methanol, to form the diester **155**. Next, the diols were protected by *bis*-acetonides **156**. Reaction with lithium aluminium hydride then resulted in reduction of the ester groups to free alcohol groups **157**, with the original intention of reoxidising back to an aldehyde **158**. Several different methods were attempted, either part-reduction directly from the ester to the aldehyde, or oxidation back from the alcohol to the aldehyde.

- DIBAL (reduction)
- Pyridinium chlorochromate[82]
- IBX[83]
- Dess-Martin Periodinane[84]
- TPPP with IBA to form IBX in situ[85]
- Parikh-Doering oxidation[86]

None of these methods afforded the *bis*-aldehyde **158**, as hoped. However, reaction with IBX gave the mono-aldehyde. Further work consisted of protecting just one of the alcohols from the reduced product using a silane protecting group **159**. The remaining alcohol could then be oxidised to the mono-aldehyde **160**. Reaction with ethynylmagnesium bromide would then afford an alkyne moiety at one end, and the silane at the other **161**. Deprotection, followed by oxidation and a further addition of the Grignard reagent should give the *bis*-alkyne **162**. Reactions were completed up to, and including the first addition of ethynylmagnesium bromide.

During this time, I assisted Ali by making each product on a larger scale, while he proceeded with new reactions.

I also independently researched a second route to the same molecule shown in Scheme 41, starting with D-galactose **163**, which already has an aldehyde at the end of its open chain form. My procedure stemmed from a similar methodology found in the literature, where a prochiral allylic alcohol is converted into an alkynol.[87]



Scheme 41 - Second procedure for formation of *meso-bis*-alkyne from D-galactose

The initial procedure was to protect the terminal alcohol, followed by *bis*-acetonide protection of the remaining alcohol groups. The first protection was attempted with TBDMS-Cl, trityl chloride, and acetal formation with benzaldehyde, but these protections either produced no products, or very low yields, unsuitable for isolation and further reactions.

Out of frustration, the Horner-Emmons reaction was tried directly on the sugar itself. A small trace of the product **164** was seen in an NMR, identified by the alkene proton signal, but it could not be isolated. At this point in the research, the visiting student returned to France, and this area of research was taken on by another student in our research group.

This thesis has shown that it is possible to form a chiral compound using click chemistry, on a pro-chiral *bis*-alkyne. The best result was the 33% *ee* obtained in both directions from (*S*)- and (*R*)-Tol-BINAP, albeit at a low yield.

The paper from Zhou, released shortly after the practical project had finished was met with mixed opinions within the group. On the one hand they had published work in this area of chemistry first, and had achieved much higher *ee*s than our work, but it proves that our work is of importance to the scientific community.

Their success came about from a chance use of acetone as a solvent, which increased the proportion of mono-triazole product, whilst still being the minor product. Further research into solvents with the same carbonyl moiety gave them a very successful procedure using 2,5-hexadione. In my research, the use of acetone as the reaction solvent also increased the proportion of mono-product produced, but this was not picked up on as all of my standard reactions have always produced more mono-triazole product than *bis*-triazole, therefore the increase was not as pronounced. Overall, their best result was a 12:1 mix of products, whereas I had several reactions which produced no *bis*-product at all, including my first reaction with (*R,R*)-NORPHOS **153**, which had 34% mono-product, with no *bis*-product.

Comparing the *ee* results obtained, they achieved a much higher *ee* in their research. This may be because the oxindole backbone of their molecule is more rigid than the ester and nitrile used in this thesis, so it always presents the same shape. The two separate groups used in this thesis can rotate and move around in space, reducing the efficiency of the catalyst.

Possible further research would be attempting to recreate the work of Zhou to confirm their results. In addition, using their best solvent, 2,5-hexadione, for reactions with my compounds would show whether the solvent choice is universal, or only applicable with oxindoles. The ligand they chose was a PyBox ligand, with phenyl side chains, **57**. In this thesis I used an *iso*-propyl PyBOX ligand **56**, which was unsuccessful in getting an *ee*, so the entire PyBOX ligand class was ignored. Therefore, it would be wise to go back and investigate several different PyBOX ligands.

In addition, other substrates could be investigated. Possibilities include sulphones, or forming a link between the ester and nitrile, introducing rigidity into the backbone.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES

^{1}H and ^{13}C NMR spectra were obtained on a Varian Unity+ at 400 and 100 MHz respectively, or on a Varian Gemini 2000 at 300 and 75 MHz respectively, or on a Bruker Ascend at 500 and 125 MHz respectively. Chemical shifts are referenced to the residual solvent peak, or by using TMS as an internal standard. All spectra were recorded in $CDCl_3$ unless specified otherwise.

Infrared spectra were recorded using a Perkin-Elmer Paragon 1000 FT-IR. Either neat, using an ATR attachment, mixed in a nujol mull, or in the case of thick oils, applied directly to a KBr disc.

Microwave-assisted reactions were conducted using a Biotage Initiator, within sealed vials. Microwave irradiation power was typically a maximum of 100 W.

Samples requiring purification were purified by column chromatography using silica gel as the adsorbent. Reactions were monitored using TLC Silica Gel 60, embedded with a fluorescent indicator, and were visualised with either UV irradiation at 254 nm, or by using a potassium permanganate TLC stain, developed by heating.

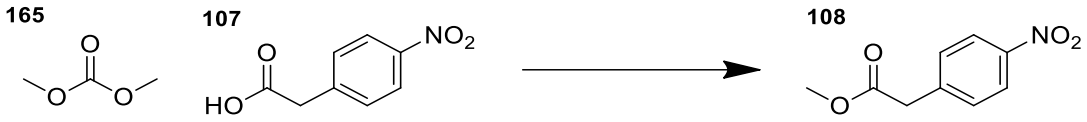
Anhydrous reactions were carried out in flame dried glassware, under an inert atmosphere of either dry nitrogen or dry argon.

Most reagents were obtained from commercial sources and used without any further purification. Anhydrous THF and diethyl ether were dried using the sodium / benzophenone ketyl radical, prior to distillation. Light petroleum used for column chromatography was distilled prior to use.

Optical rotation measurements were obtained using a Bellingham and Stanley ADP-440 polarimeter operating at the sodium (D) line emission of λ=589 nm at the temperatures specified.

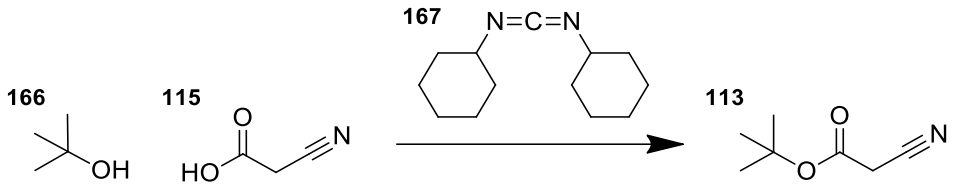
REACTIONS TO FORM *BIS*-ALKYNE PRECURSORS

108 METHYL *P*-NITROPHENYLACETATE[88]



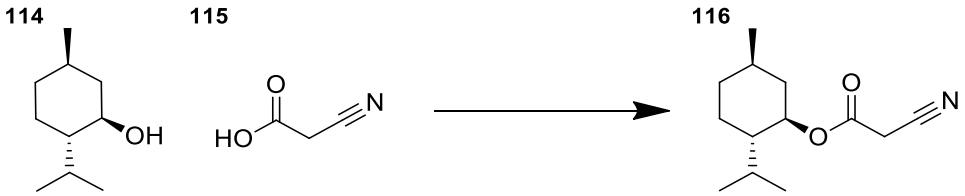
4-nitrophenylacetic acid **107** (2.00 g, 11 mmol) was added to a clean carousel tube. Dimethyl carbonate **165** (3 mL, 3.21 g, 35.6 mmol) was added, and the reaction was heated at reflux overnight. The brown solution was allowed to cool, and poured in to aqueous sodium bicarbonate (10%, 10 mL) while stirring. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water and brine (10 mL each), and dried over anhydrous magnesium sulphate. After filtration and evaporation of the solvents, proton NMR analysis showed the product had formed, and none of the precursor acid remained. No further purification was performed. This gave methyl *p*-nitrophenylacetate **108** as a pale orange oil (1.929 g, 9.89 mmol, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H, 3.74 (s, 2H), 3.73 (s, 3H).

Literature values: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 3.76 (s, 2H), 3.73 (s, 3H).



2-Cyanoacetic acid **115** (1.701 g, 20 mmol) was suspended in acetonitrile (20 ml) and *tert*-butanol **166** (2.391 ml, 25.00 mmol). To this, a solution of N,N'-Dicyclohexylcarbodiimide **167** (4.54 g, 22.00 mmol) in DCM (22 ml) was added under stirring at RT. The reaction mixture was stirred for 30 minutes, then filtered through Celite, and the solvents were evaporated. Proton NMR analysis of the residue showed complete conversion to the product. The product, *tert*-butyl cyanoacetate **113** was not purified, but was taken straight through to the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (s, 2H), 1.50 (s, 9H).

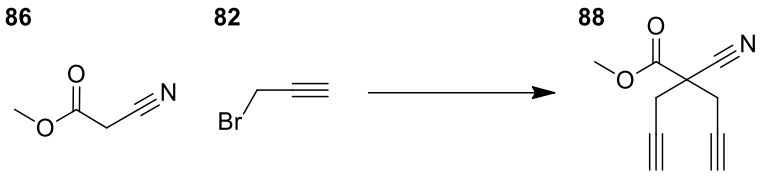
Literature values: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (s, 2H), 1.51 (s, 9H).



2-Cyanoacetic acid **115** (10.12 g, 119 mmol) and L-menthol **114** (36.219 g, 232 mmol) were dissolved in toluene (300 mL). p-TSA (2.263 g, 11.90 mmol) was added and the reaction heated at reflux overnight, with azeotropic removal of water using a Dean-Stark apparatus. The orange reaction mixture was allowed to cool, and the solvents were evaporated. The residue solidified once cool. The solid was broken up, and n-pentane was added. The mixture was stirred vigorously for 4 hours, allowing the solid to completely break up and turning the pentane orange. The solid was collected by filtration, and analysed by proton NMR spectroscopy. No further purification was necessary. This gave L-menthyl-cyanoacetate **116** as a white powder (21.626 g, 97 mmol, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (td, *J* = 10.9, 4.5 Hz, 1H), 3.42 (s, 2H), 2.05 – 1.96 (m, 1H), 1.89 – 1.79 (m, 1H), 1.74 – 1.64 (m, 2H), 1.55 – 1.38 (m, 2H), 1.13 – 0.98 (m, 2H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.87 – 0.82 (m, 1H), 0.76 (d, *J* = 7.0 Hz, 3H).

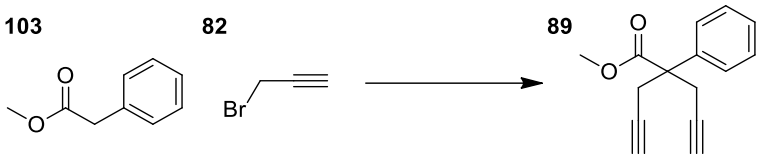
Literature values: ^{1}H NMR ($CDCl_3$) δ 5.0 (1H, dt), 3.75 (2H, s), 2.2-0.95 (18H, m); IR (KBr pellet): 3000-2850, 2223, 1730, 1450, 1230, 1130.

88 METHYL 2-CYANO-2-(PROP-2-YN-1-YL)PENT-4-YNOATE[57]



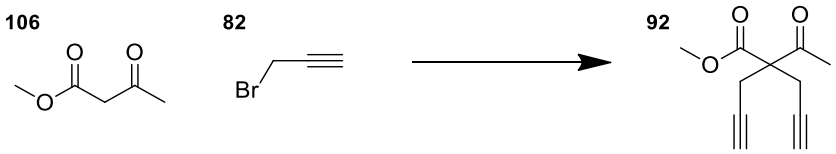
Methyl cyanoacetate **85** (20 g, 202 mmol) was suspended in acetonitrile (600 mL). Potassium carbonate (69.7 g, 505 mmol) was added, and the reaction was cooled in an ice bath. Propargyl bromide in toluene **82** (80%, 49.5 mL, 444 mmol) was added and the orange suspension was heated at reflux overnight. The deep yellow suspension was allowed to cool, and worked up with water (400 mL). The deep brown organic layer was separated, and the brown aqueous layer was extracted with ethyl acetate (3 x 250 mL). The combined organic layers were washed with water and brine (250 mL each), and dried over anhydrous magnesium sulphate. After filtration and evaporation of the solvents, the resulting brown oil was purified by vacuum distillation at 115 – 125 ^{O}C. Methyl-2-cyano-2-(prop-2-yn-1-yl)pent-4-ynoate **88** was isolated as a colourless oil, which solidified to a white solid (25.1 g, 143 mmol, 71%): m.p. 46-48 °C; IR (neat) ν_{max} / cm^{-1} 3275, 2957, 1740, 1437, 1322, 1287, 1263, 1226, 1078, 963, 789, 694, 653, 465; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 2.94 (d, *J* = 2.6 Hz, 4H), 2.24 (t, *J* = 2.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 117.0, 76.0, 73.7, 54.1, 47.1, 25.6; HRMS (NSI) Calcd. for $C_{10}H_{13}O_2N_2$ ($[M+NH_4]^+$) 193.0972. Found 193.0971.

Literature values: m.p. 43-45 °C; IR (KBr) ν_{max} / cm^{-1} 3277, 2957, 1743, 1438, 1325, 1288, 1266, 1227, 1079, 964, 790, 695, 655, 465; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.87 (s, 3 H), 2.92 (d, *J* = 2.6 Hz, 4 H), 2.23 (t, *J* = 2.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 116.9, 76.0, 73.7, 54.1, 47.2, 25.7; HRMS (EI (+), 70 eV): $C_{10}H_9NO_2$ (175.18), $[C_{10}H_8NO_2]$+: calcd 174.0555, found 174.0568.

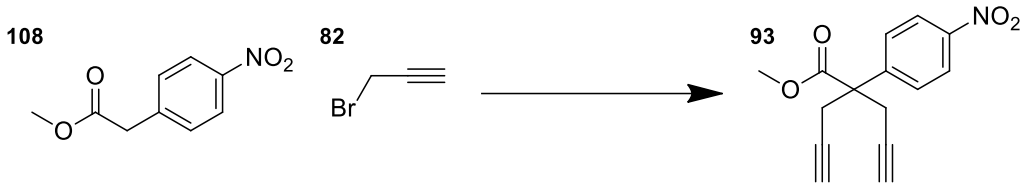


Sodium hydride (1.2 g, 30 mmol) was added to a flame dried flask, under an atmosphere of nitrogen. Dry THF (50 mL) was added, and the mixture was cooled to 0 ^{O}C in an ice bath. Methyl phenylacetate **103** (1.89 mL, 13.3 mmol) was added, followed by propargyl bromide in toluene **82** (80%, 5.6 mL, 40.3 mmol). The reaction was stirred at room temperature for 60 hours, under the nitrogen atmosphere. The reaction was worked up cautiously with water, and extracted into ethyl acetate. The combined organics were washed with water and brine (50 mL each), and dried over anhydrous magnesium sulphate. After filtration, the solvents were evaporated, and no further purification was performed to separate the product from remaining starting materials. The product **89** was obtained as an impure pale oil (2.00 g, 8.8 mmol, 66%): IR (neat): 3298, 3287, 1730, 1291, 1217. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.21 (m, 5H), 3.70 (s, 3H), 3.19 (dd, *J* = 16.7, 2.6 Hz, 2H), 3.09 (dd, *J* = 16.5, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 2H).

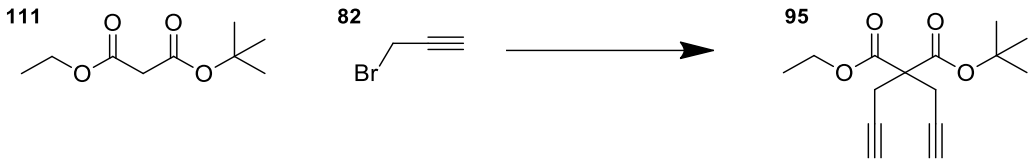
Literature values: ^{1}H NMR: δ 7.37-7.24 (m, 5 H), 3.69 (s, 3 H), 3.12 (dq, J = 2.6, 7.0 Hz, 4 H), 1.97 (d, J = 2.6 Hz, 2 H). ^{13}C NMR: δ 172.8, 138.5, 127.8, 127.0, 125.3, 79.2, 70.7, 52.4, 52.0, 24.8. IR (neat): 3296, 3286, 1729, 1290, 1218.



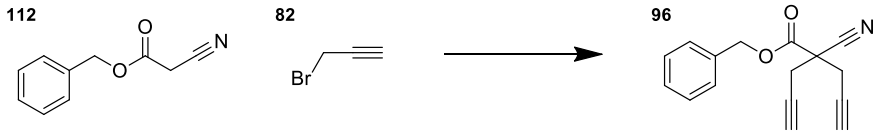
Methyl acetoacetate **106** (1 mL, 1.076 g, 9.27 mmol), propargyl bromide in toluene **82** (80%, 2.1 mL, 18.85 mmol) and potassium carbonate (2.82 g, 20.39 mmol) were combined in acetonitrile (20 mL). The yellow suspension was heated at reflux overnight. The cooled reaction mixture was worked up with water (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with water and brine (20 mL each), dried over anhydrous magnesium sulphate and after filtration, the solvents were evaporated. Crystallisation from ethanol gave crystals of the pure product **92** (550 mg, 2.9 mmol, 31%): IR (neat) ν_{max} / cm^{-1} 3277, 2967, 2159, 2029, 1977, 1747, 1712, 1428, 1288, 1210, 1166, 840; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.00 (dd, *J* = 17.4, 2.7 Hz, 2H), 2.93 (dd, *J* = 17.5, 2.7 Hz, 2H), 2.21 (s, *J* = 7.7 Hz, 3H), 2.03 (t, *J* = 2.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.88, 169.89, 78.62, 72.21, 62.55, 53.41, 26.34, 21.99; HRMS (NSI) Calcd. for $C_{11}H_{13}O_3$ ($[M+H]^+$) 193.0859. Found 193.0859.



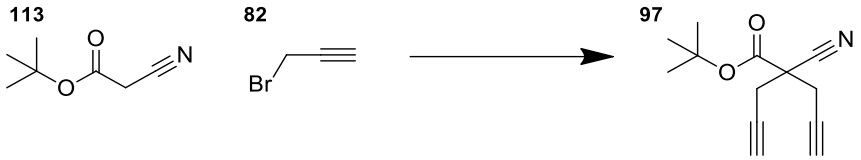
Methyl 4-nitrophenyl acetate **108** (1.93 g, 9.89 mmol) was suspended in acetonitrile (50 mL). Potassium carbonate (3.41 g, 24.73 mmol) was added and the colour changed from pale orange to deep purple. Propargyl bromide in toluene **82** (80%, 2.4 mL, 21.76 mmol) was added, and the reaction was heated at reflux overnight. The cooled reaction mixture was worked up with water (50 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with water and brine (20 mL each), dried over anhydrous magnesium sulphate and after filtration, the solvents were evaporated. Purification by column chromatography, eluting with petroleum ether:EtOAc 9:1 gave the product **93** as a yellow oil (0.99 g, 3.63 mmol, 37% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 3.68 (s, 3H), 3.15 (dd, *J* = 16.7, 2.6 Hz, 2H), 3.04 (dd, *J* = 16.7, 2.6 Hz, 2H), 1.99 (d, *J* = 2.6 Hz, 2H).



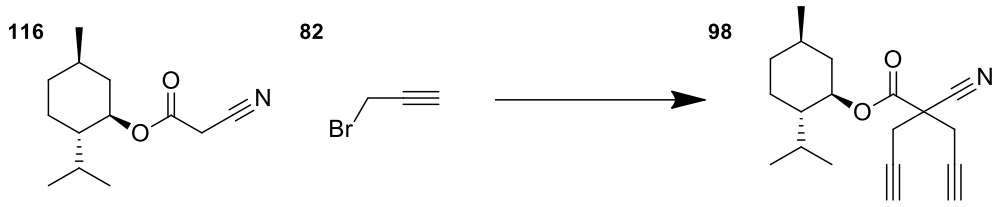
Tert-butyl ethyl malonate **111** (1 mL, 0.994 g, 5.28 mmol), propargyl bromide in toluene **82** (80%, 1.2 mL, 10.77 mmol) and potassium carbonate (1.61 g, 11.62 mmol) were combined in acetonitrile (20 mL). The yellow suspension was heated at reflux overnight. The cooled reaction mixture was worked up with water (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with water and brine (20 mL each), dried over anhydrous magnesium sulphate and after filtration, the solvents were evaporated to give the pure product **95** (262 mg, 0.99 mmol, 19%): IR (neat) ν_{max} / cm^{-1} 3284, 3262, 2983, 2938, 2159, 2028, 1728, 1475, 1450, 1369, 1305, 1198, 1148, 1095, 890 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H), 2.90 (d, *J* = 2.7 Hz, 4H), 1.99 (t, *J* = 2.6 Hz, 2H), 1.41 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.11, 167.69, 82.86, 78.87, 71.73, 62.04, 56.81, 27.91, 22.60, 14.29; HRMS (NSI) Calcd. for $C_{15}H_{20}O_4Na$ ($[M+Na]^+$) 287.1254. Found 287.1259.



Benzyl cyanoacetate **112** (1 mL, 6.53 mmol), propargyl bromide in toluene **82** (80%, 1.6 mL, 14.37 mmol) and potassium carbonate (2.26 g, 16.33 mmol) were combined in acetonitrile (50 mL) to give a yellow suspension. The reaction was heated at reflux overnight. The reaction was allowed to cool, then worked up with water (30 mL), and the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with water and brine (30 mL each) and dried over anhydrous magnesium sulphate. After filtration, the solvents were evaporated, to give benzyl-2-cyano-2-(prop-2-yn-1-yl)pent-4-ynoate **96** as a brown oil. (0.453 g, 1.8 mmol, 28%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.32 (m, 5H), 5.30 (s, 2H), 2.95 (d, *J* = 2.6 Hz, 4H), 2.18 (t, *J* = 2.6 Hz, 2H).



Tert-butyl cyanoacetate **113** (5 mL, 35.0 mmol), propargyl bromide in toluene **82** (80%, 8.57 mL, 77 mmol) and potassium carbonate (12.08 g, 87 mmol) were combined in acetonitrile (100 mL) to give a yellow suspension. The reaction was heated at reflux over the weekend. The reaction was cooled, and worked up with water (75 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with water and brine (50 mL each), and dried over anhydrous magnesium sulphate. After filtration, the solvents were evaporated, and the product **97** was obtained as pale crystals by crystallisation from ethanol, (4.00 g, 18.4 mmol, 52.7%): m.p. 59.5-61.3 °C; IR (neat) ν_{max} / cm^{-1} 3289, 2989, 2979, 2941, 2249, 2159, 2029, 1977, 1728, 1468, 1398, 1370, 1346, 1319, 1262, 1149, 832; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (d, *J* = 2.7 Hz, 4H), 2.19 (t, *J* = 2.7 Hz, 2H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 117.7, 85.5, 76.6, 73.6, 47.8, 27.9, 25.8; HRMS (NSI) Calcd. for $C_{13}H_{19}O_2N_2$ ($[M+NH_4]^+$) 235.1441. Found 235.1444.



L-Menthyl cyanoacetate **116** (21.4 g, 96 mmol) was dissolved in acetonitrile (600 mL). Potassium carbonate (33.1 g, 240 mmol) and propargyl bromide in toluene **82** (80%, 23.5 mL, 211 mmol) were added, and the reaction was heated at reflux overnight. The reaction was cooled to room temperature, and worked up with water until any remaining potassium carbonate had dissolved and a deep brown reaction mixture was obtained. The aqueous layer was then extracted with EtOAc (3 x 100 mL). The combined organics were then washed with water, and then brine (100 mL each), and dried over anhydrous magnesium sulphate. After filtration, the solvents were evaporated. Vacuum distillation of the residue (140-144 °C at 0.4 mbar) gave the product as a pale yellow oil. On standing and cooling with dry ice, the oil solidified, and was ground into a fine powder. Proton NMR analysis showed the product was pure and no further purification was necessary (22.24 g, 74.3 mmol, 78%): m.p. 47-49 ^{o}C; $[\alpha]^{22}_{D}$ -46^{o} (c = 1.02, ethanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (td, *J* = 11.0, 4.4 Hz, 1H), 2.93 (t, *J* = 2.7 Hz, 4H), 2.21 (dt, *J* = 6.3, 2.6 Hz, 2H), 2.07 – 1.91 (m, 2H), 1.77 – 1.64 (m, 2H), 1.58 – 1.42 (m, 2H), 1.15 – 0.99 (m, 2H), 0.97 – 0.83 (m, 7H), 0.76 (d, *J* = 6.9 Hz, 3H).

Diethyl cyanomethylphosphonate **117** (1 mL, 6.18 mmol), propargyl bromide in toluene **82** (80%, 1.4 mL, 12.57 mmol) and potassium carbonate (1.88 g, 13.59 mmol) were combined in acetonitrile (20 mL). The yellow suspension was heated at reflux over the weekend. The cooled reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with water and brine (20 mL each), dried over anhydrous magnesium sulphate and after filtration, the solvents were evaporated. Purification of the product was attempted by column chromatography, eluting with petroleum ether:EtOAc 1:1 to give the product **99** (295 mg, 1.17 mmol, 18.9%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 – 4.26 (m, 4H), 3.02 – 2.93 (m, 4H), 2.30 – 2.24 (m, 2H), 1.44 – 1.36 (m, 6H).

Literature values: b.p.: 136-137 °C. Elemental Analysis: C, 56.92; H, 6.37; P, 12.23. Found C, 55.4; H, 6.5; P, 12.2.

Trimethyl phosphonoacetate **118** (1 mL, 6.94 mmol), propargyl bromide in toluene **82** (80%, 1.6 mL, 14.36 mmol) and potassium carbonate (2.11 g, 15.2 mmol) were combined in acetonitrile (20 mL). The yellow suspension was heated at reflux over the weekend. The cooled reaction mixture was worked up with water (50 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with water and brine (20 mL each), dried over anhydrous magnesium sulphate and after filtration, the solvents were evaporated. Purification by column chromatography, eluting with petroleum ether:EtOAc 9:1 was attempted, but the mono- and *bis*-substituted products could not be completely separated. No further purification was performed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.81 (s, 6H), 3.02 (t, *J* = 2.7 Hz, 2H), 2.98 (d, *J* = 2.6 Hz, 2H), 2.07 (t, *J* = 2.6 Hz, 2H); IR (neat) ν_{max} / cm^{-1} 3289, 2985, 2242, 1431, 1392, 1251, 1162, 1012, 980, 794, 652, 555.

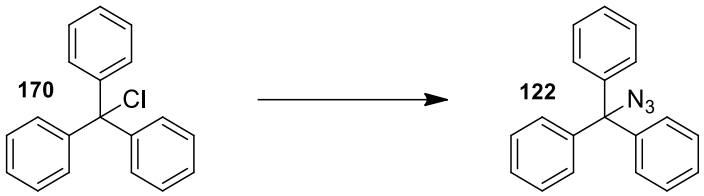
73 BENZYL AZIDE[62]

Sodium azide (3.58 g, 55.0 mmol) was added to DMSO (120 mL) and stirred vigorously until fully dissolved. Benzyl bromide **168** (6.54 mL, 55 mmol) was added. The reaction mixture was stirred at RT overnight. The colourless liquid was worked up with water (100 mL), and extracted with diethyl ether (3 x 100 mL). The extractions were washed with water (2 x 80 mL) and brine (80 mL). The ether layer was dried over $MgSO_4$ and after filtration, it was evaporated to dryness, giving benzyl azide **73** as a colourless oil (6.9 g, 51.8 mmol, 94%): IR (neat) ν_{max} / cm^{-1} 3455, 3028, 2970, 2946, 2093, 1605, 1586, 1496, 1454, 1349, 1252; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H), 4.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.55, 129.05, 128.52, 128.44, 55.00.

Literature values: IR (neat) ν_{max} / cm^{-1} 2094 (C-N_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.26 (m, 5H), 4.35 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.42, 128.90, 128.37, 128.29, 54.84.

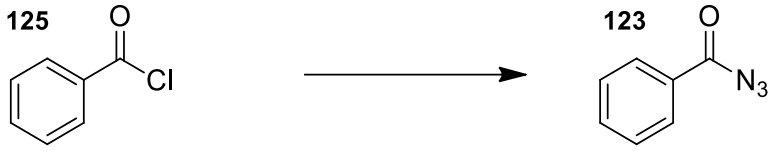
Sodium azide (1.973 g, 30.3 mmol) was added to DMSO (50 mL) and stirred until it dissolved fully. Benzhydryl bromide **169** (5 g, 20.23 mmol) was then added, to give an orange solution. The reaction mixture was stirred at RT overnight. The orange solution was worked up with water (50 mL). The mixture was then stirred until it had cooled back to RT. The mixture was then extracted with diethyl ether (3 x 50 mL). The extractions were combined, washed with water (2 x 50 mL) and brine (50 mL) and dried over $MgSO_4$. After filtration, the solvents were removed under vacuum to give benzhydryl azide **121** (4.155 g, 19.86 mmol, 98%): IR (neat) ν_{max} / cm^{-1} 3028, 2970, 2095, 1659, 1610, 1493, 1450, 1365, 1230, 1217, 1079, 1030, 960, 743, 599; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 10H), 5.71 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.77, 128.90, 128.25, 127.58, 68.72.

Literature values: IR (neat): ν_{max} / cm^{-1} 2097. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.23 (m, 10H), 5.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 139.5, 128.7, 128.0, 127.4, 68.5.



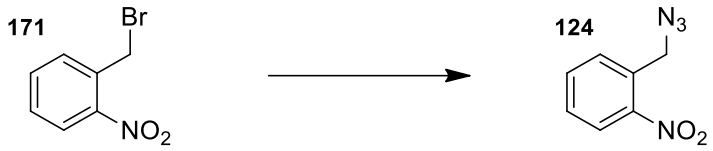
Sodium azide (520 mg, 8.0 mmol) was added to DMSO (20 mL) and stirred until it had dissolved fully. Chlorotriphenylmethane **170** (2.230 g, 8.00 mmol) was added, and the reaction was allowed to stir overnight. The reaction mixture was diluted with water (20 mL) and then extracted with diethyl ether (3 x 30 mL). The combined organics were washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulphate, and after filtration, evaporated to dryness under reduced pressure. Trityl azide **122** was obtained as a colourless oil, which crystallised into pale purple crystals (2.239 g, 98%): Mp 64-65 °C lit. 64 °C, IR (neat) ν_{max} / cm^{-1} 3455, 3025, 2970, 2097, 1596, 1489, 1446, 1365, 1216; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 15H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.35, 128.70, 128.44, 127.94, 77.37.

Literature values: ^{1}H NMR (25°C, CD_2Cl_2, 300 MHz): δ 7.66 – 7.01 (m, Ph). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 143.7, 129.0, 128.8, 128.3, 77.8; IR (neat) ν_{max} / cm^{-1} 3332 (w), 3060 (w), 3019 (w), 2107 (s), 2093 (s), 1591 (w), 1487 (m), 1445 (s), 1254 (s), 1200 (m), 1184 (w), 1166 (w), 1152 (w), 1082 (w), 1032 (w), 1001 (w), 940 (w), 896 (m), 843 (w), 770 (m), 761 (m), 752 (s), 717 (m), 696 (s), 667 (m), 629 (m), 557 (m)



Sodium azide (616 mg, 9.5 mmol) was dissolved in water (5 mL). Benzoyl chloride **125** (1 mL, 8.62 mmol) was added to acetone (6 mL) in a separate flask. Both solutions were cooled to 0 °C, then mixed together and stirred vigorously for 30 minutes. The reaction mixture was allowed to settle into 2 layers. The top acetone layer was removed and poured over ice. White crystals formed, which were filtered off, washed with cold water, and allowed to dry. This gave the product benzoyl azide **123** as colourless crystals (968 mg, 6.58 mmol, 76%): Mp 30-31 °C lit 29-31 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H), 7.64 – 7.56 (m, 1H), 7.48 – 7.40 (m, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.7, 134.4, 130.8, 129.4, 128.8.

Literature values: ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.03 (d, *J* = 7.6 Hz, 2 H), 7.62 (t, *J* = 7.4 Hz, 2 H), 7.46 (t, *J* = 7.8 Hz, 1 H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.5, 134.3, 130.6, 129.4, 128.6.

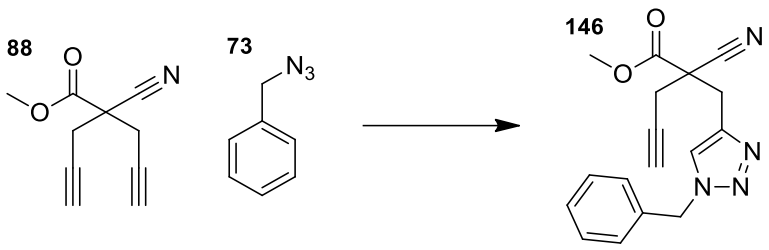


Sodium azide (520 mg, 8.0 mmol) was added to DMSO (20 mL) and stirred vigorously until it had dissolved fully. 2-Nitrobenzyl bromide **171** (1.728 g, 8.00 mmol) was added, and the reaction was allowed to stir overnight. The reaction mixture was diluted with water (20 mL) and then extracted with diethyl ether (3 x 30 mL). The combined organics were washed with water (30 mL) and brine (30 mL), dried over sodium sulphate, and after filtration, evaporated to dryness under reduced pressure. 2-Nitrobenzyl azide **124** was obtained as an orange oil (1.341 g, 7.53 mmol, 94%): IR (neat) ν_{max} / cm^{-1} 3455, 3016, 2970, 2946, 2101, 1738, 1611, 1578, 1523, 1445, 1353, 1293, 1228, 1217, 857, 788, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.9 Hz, 1H), 7.73 – 7.64 (m, 2H), 7.55 – 7.48 (m, 1H), 4.85 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.23, 134.22, 131.78, 130.31, 129.23, 125.49, 52.18.

Literature values: IR (neat) ν_{max} / cm^{-1} 2105 (C-N_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 1H), 7.71 – 7.66 (m, 2H), 7.54 – 7.50 (m, 1H), 4.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 133.9, 131.5, 130.1, 128.9, 125.2, 51.9.

CLICK REACTION STEP

CONVENTIONAL METHOD



Methyl 2-cyano-2-(prop-2-yn-1-yl)pent-4-ynoate **88** was suspended in the solvent (typically *tert*-butanol/water (1:1)). The copper catalyst was added (typically 2 equivalents copper powder), followed by the azide (typically 1.1 equivalents). The reaction was stirred vigorously overnight. The reaction was quenched with water and then extracted with ethyl acetate. The combined organics were then washed with water and brine, dried over anhydrous magnesium sulphate, and after filtration, the solvents were removed under reduced pressure.

IN-SITU METHOD

Sodium azide (0.412 g, 6.34 mmol) was dissolved in DMSO (25 mL) with vigorous stirring. Benzyl bromide **168** (0.830 mL, 6.98 mmol) was added, and the reaction stirred for another 2 hours. Analysis by proton NMR of the crude reaction mixture checked for the disappearance of the benzyl protons at 4.50 ppm relating to benzyl bromide, and the appearance of the benzyl protons from benzyl azide at 4.35 ppm. Methyl 2-cyano-2-(prop-2-yn-1-yl)pent-4-ynoate **88** (1 g, 5.71 mmol) and copper powder (0.605 g, 9.51 mmol) were added, and the reaction was stirred at RT overnight. The reaction was diluted with water. The copper powder was removed by filtration through Celite, and the resulting liquid was extracted with ethyl acetate several times. The combined organics were washed with water and brine, and then dried over anhydrous magnesium

sulphate. After filtration, the solvents were removed under reduced pressure.

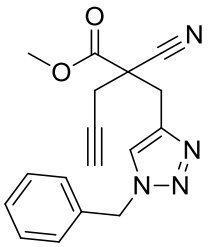
MICROWAVE METHOD

Methyl 2-cyano-2-(prop-2-yn-1-yl)pent-4-ynoate **88** (100 mg, 0.57 mmol), copper(II) sulphate (14 mg, 0.057 mmol), sodium ascorbate (113 mg, 0.57 mmol) and sodium azide (41 mg, 0.63 mmol) were combined in a 5 mL microwave reactor vial. The solvent, (*tert*-butanol/water, 1:1, 4 mL) was added, and the vial sealed. Benzyl bromide **168** (0.068 mL, 0.57 mmol) was added through the septum, and the vessel was heated in the microwave reactor at 125 ^{O}C, 100 W, for 20 minutes. The cooled reaction was worked up with water, and extracted with ethyl acetate. The combined organics were washed with water and brine, and then dried over anhydrous magnesium sulphate. After filtration, the solvents were then removed under reduced pressure.

LIGAND ASSISTED METHOD

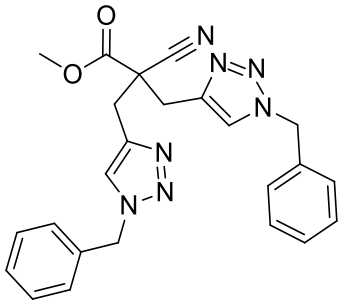
(*R,R*)-NORPHOS (*R,R*)-**153** (0.017 g, 0.038 mmol) and copper(I) iodide (4.76 mg, 0.025 mmol) were combined in toluene (5 mL). DIPEA (0.131 mL, 0.750 mmol) was added, and the reaction was allowed to stir at RT to allow the complex to form. The reaction was then cooled to –40 °C and methyl 2-cyano-2-(prop-2-yn-1-yl)pent-4-ynoate **88** (0.044 g, 0.250 mmol) and benzyl azide **73** (0.031 mL, 0.25 mmol) were added, and the reaction was stirred at –40 °C for 18 hours. The reaction was filtered through silica while still cold, to avoid allowing any further reaction to occur, and the silica pad was washed with DCM (5 mL). The solvents were evaporated, and the residue analysed by proton NMR spectroscopy. Further dilution was performed to create a sample for chiral HPLC analysis.

146 METHYL 2-((1-BENZYL-1*H*-1,2,3-TRIAZOL-4-YL)METHYL)-2-CYANOPENT-4-YNOATE



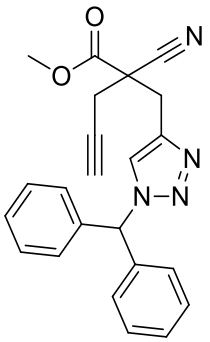
The product was purified by column chromatography, eluting with petroleum ether:EtOAc (2:1). This gave the mono product as a pale yellow oil (0.737 g, 2.39 mmol, 41.9%): IR (neat) ν_{max} / cm^{-1} 3280, 3141, 2256, 1739; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.41 – 7.32 (m, 3H), 7.26 – 7.21 (m, 2H), 5.52 (s, 2H), 3.80 (s, 3H), 3.39 (s, 2H), 2.93 (dd, *J* = 16.9, 2.6 Hz, 1H), 2.81 (dd, *J* = 16.9, 2.6 Hz, 1H), 2.22 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.22, 134.61, 129.10, 128.73, 128.20, 127.91, 123.32, 117.71, 76.74, 73.58, 54.13, 53.96, 49.07, 32.17, 26.28; HRMS (NSI) Calcd. for $C_{17}H_{17}N_4O_2$ ($[M+H]^+$) 309.1346. Found 309.1345.

METHYL 3-(1-BENZYL-1*H*-1,2,3-TRIAZOL-4-YL)-2-((1-BENZYL-1H-1,2,3-TRIAZOL-4-YL)METHYL)-2-CYANOPROPANOATE



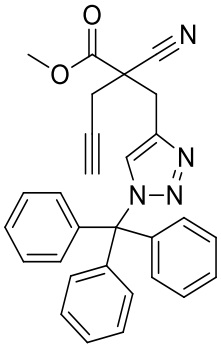
The product was purified by column chromatography as described above. *Bis*-triazole product eluted after mono-triazole product as pale yellow oil: IR (neat) ν_{max} / cm^{-1} 3132, 3065, 3035, 2997, 2962, 2246, 1740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, 2H), 7.33 – 7.23 (m, 6H), 7.20 – 7.12 (m, 4H), 5.42 (s, 4H), 3.61 (s, 3H), 3.48 – 3.14 (m, 4H); HRMS (NSI) Calcd. For $C_{24}H_{24}N_7O_2$ ($[M+H]^+$) 442.1986. Found 442.1984.

METHYL 2-((1-BENZHYDRYL-1*H*-1,2,3-TRIAZOL-4-YL)METHYL)-2-CYANOPENT-4-YNOATE



The product was purified by column chromatography, eluting with petroleum ether:EtOAc (2:1). Recrystallisation from ethanol gave the product as a white powder (0.967 g, 2.52 mmol, 21%): m.p. 107.8-108.8 ^{o}C; IR (neat) ν_{max} / cm^{-1} 3246, 3148, 2946, 2250, 1752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.42 – 7.36 (m, 6H), 7.19 – 7.09 (m, 5H), 3.78 (s, 3H), 3.41 (s, 2H), 2.96 (dd, *J* = 16.9, 2.6 Hz, 1H), 2.85 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.22 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.42, 138.08, 129.21, 129.17, 128.89, 128.82, 128.29, 128.11, 123.37, 117.82, 76.91, 73.67, 68.39, 54.13, 49.38, 32.52, 26.49; HRMS (NSI) Calcd. For $C_{23}H_{21}N_4O_2$ ($[M+H]^+$) 385.1659. Found 385.1664.

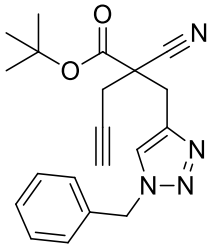
METHYL 2-CYANO-2-((1-TRITYL-1*H*-1,2,3-TRIAZOL-4-YL)METHYL)PENT-4-YNOATE



The reaction was performed at reflux. Proton NMR analysis showed 14% yield of the product. Product was not purified. NMR in appendix contains the starting material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.39 – 7.27

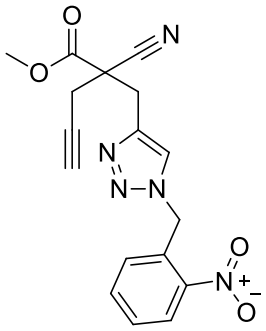
(m, 15H), 3.85 (s, 3H), 3.48 (s, 2H), 2.92 (dd, *J* = 15.5, 2.8 Hz, 2H), 2.84 (dd, *J* = 11.2, 2.6 Hz, 1H), 2.29 (t, *J* = 2.7 Hz, 1H).

TERT-BUTYL 2-((1-BENZYL-1*H*-1,2,3-TRIAZOL-4-YL)METHYL)-2-CYANOPENT-4-YNOATE



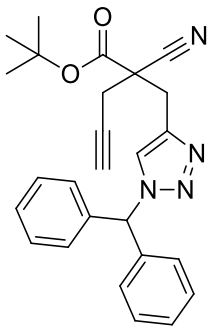
The product was purified by column chromatography, eluting with pentane:EtOAc (1:2). This gave the mono product as a pale oil (43 mg, 0.123 mmol, 24.5%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.41 – 7.34 (m, 3H), 7.30 – 7.24 (m, 2H), 5.54 (s, 2H), 3.36 (s, 2H), 2.90 (dd, *J* = 16.8, 2.6 Hz, 1H), 2.78 (dd, *J* = 16.8, 2.6 Hz, 1H), 2.22 (t, *J* = 2.6 Hz, 1H), 1.44 (s, 9H).

METHYL 2-((1-(2-NITROBENZYL)-1*H*-1,2,3-TRIAZOL-4-YL)METHYL)-2-CYANOPENT-4-YNOATE



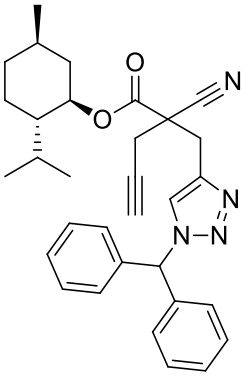
The product was synthesised using the standard procedure, but separation of the products was not attempted. Proton NMR analysis showed the yield to be 47% mono-triazole, with a further 24% as the *bis*-triazole, and the remaining 29% was remaining starting material. The combined NMR is given in the appendix.

144 *TERT*-BUTYL 2-((1-BENZHYDRYL-1*H*-1,2,3-TRIAZOL-4-YL)METHYL)-2-CYANOPENT-4-YNOATE



The product was purified by column chromatography, eluting with pentane:EtOAcc (1:2). This gave the mono product as a colourless oil (51 mg, 0.120 mmol, 16.8%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.41 - 7.33 (m, 6H), 7.16 - 7.09 (m, 5H), 3.36 (d, J = 3.0 Hz, 2H), 2.91 (dd, J = 16.8, 2.6 Hz, 1H), 2.79 (dd, J = 16.8, 2.7 Hz, 1H), 2.21 (t, J = 2.6 Hz, 1H), 1.41 (s, 9H).

L-MENTHYL 2-((1-BENZHYDRYL-1*H*-1,2,3-TRIAZOL-4-YL)METHYL)-2-CYANOPENT-4-YNOATE

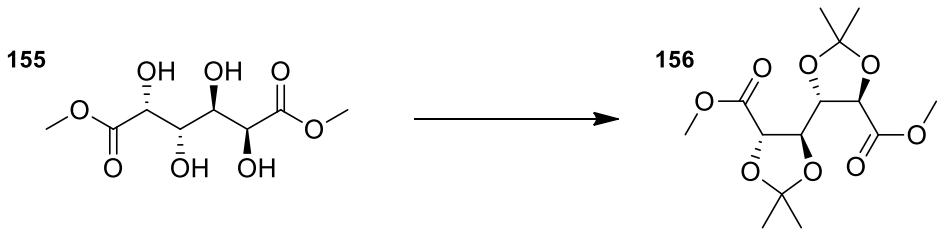


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.42 – 7.30 (m, 6H), 7.19 – 7.05 (m, 5H), 4.75 (ddd, *J* = 20.4, 10.8, 4.3 Hz, 1H), 3.38 (s, 2H), 2.96 (d, *J* = 16.8 Hz, 1H), 2.83 (d, *J* = 16.6 Hz, 1H), 2.21 – 2.12 (m, 1H), 2.02 – 1.81 (m, 2H), 1.68 (d, *J* = 10.8 Hz, 2H), 1.51 – 1.38 (m, 2H), 1.11 – 0.96 (m, 2H), 0.92 – 0.64 (m, 11H); IR (neat) ν_{max} / cm^{-1} 3289, 2922, 2099, 1738, 1454, 1244, 1215, 1038, 950.

155 D-GALACTARIC ACID DIMETHYL ESTER[95]

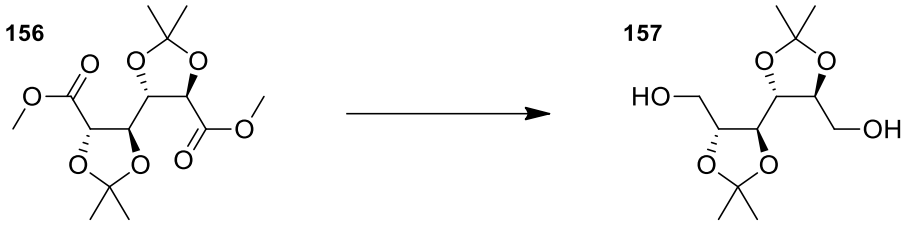
D-Galactaric Acid **5** (100 g, 476 mmol) was suspended in Methanol (500 mL). Sulphuric acid (7.5 mL, 141 mmol) was added, and the reaction stirred at reflux overnight. The reaction was allowed to cool to RT, and then placed in an ice bath for 30 mins. The white precipitate was filtered off, washed with water, and dried in a vacuum oven overnight. This gave D-galactaric acid dimethyl ester **155** (103.573 g, 435 mmol, 91%) as a white powder: Mp 185 °C; ^{1}H NMR (400 MHz, DMSO) δ 4.94 - 4.87 (d, J = 7.9 Hz, 2H), 4.84 - 4.74 (dd, J = 5.9, 2.6 Hz, 2H), 4.31 (d, J = 8.0, 2H), 3.79 - 3.68 (m, 2H), 3.62 (s, 6H) ; IR (neat) vmax / cm–1 3246, 3148, 2946, 1752

Literature values: Mp 189 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.63 (s, 6H, OMe), 3.77 (m, 2H, O*H*), 4.30 (d, *J*=8.1 Hz, 2H, C*H*–OH), 4.80 (m, 2H, O*H*), 4.91 (d, 2H, *J*=8.1 Hz, C*H*–OH); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 51.43, 70.27, 71.20, 174.11; IR (KBr) 3345, 3265, 3120, 2966, 2923, 1726, 1384, 1288, 1119, 1052 cm^{-1}; EI-MS *m*/*z* 239 (M^++H), 221 (M^++H−H_2O). Anal. Calcd for $C_8H_{14}O_8$: C 40.34, H 5.92. Found: C 40.15, H 5.91.



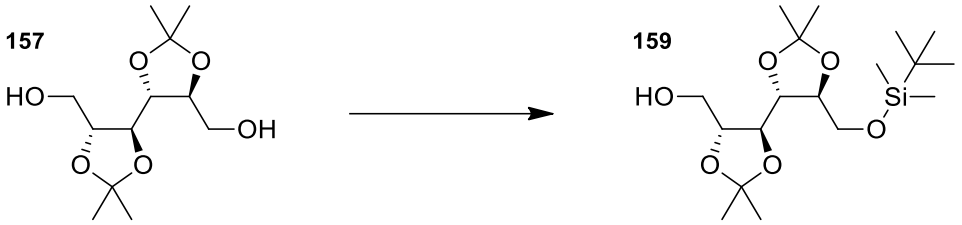
(2*R*,3*S*,4*R*,5*S*)-dimethyl 2,3,4,5-tetrahydroxyhexanedioate **155** (23.79 g, 100 mmol) was suspended in acetone (1.2 l). 2,2-Dimethoxypropane (184 mL, 1498 mmol) and *p*-TSA (5.68 g, 33.0 mmol) were added, and the reaction was stirred at RT over the weekend. The deep red/brown liquid was evaporated to dryness to give a brown solid. The solid was taken up in ethyl acetate, and washed with Na_2CO_3 to remove the *p*-TSA. The organic layer was then washed with water and brine, dried over $MgSO_4$ and after filtration, evaporated to dryness again. The brown oil soon solidified. The solid was recrystallised from ethanol to give a 3.5 g of a cream solid. A second recrystallisation was performed on the filtrate. NMR analysis of the first 3.5 g batch showed it to be pure product **156**. Mp 100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 - 4.58 (m, 2H), 4.52 - 4.46 (m, 2H), 3.82 - 3.80 (s, 6H), 1.51 - 1.46 (s, 6H), 1.45 - 1.40 (s, 6H).

Literature values: Mp 98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 1.38 (s, 6H, Me), 1.44 (s, 6H, Me), 3.76 (s, 6H, OMe), 4.44 (m, 2H, C*H*–O), 4.56 (m, 2H, C*H*–O); ^{13}C NMR ($CDCl_3$, 101 MHz) *δ* 25.84, 26.89, 52.52, 75.69, 78.90, 112.22, 171.36; IR (KBr) 3498 (w), 3029, 2988, 2959, 2941, 1759, 1375, 1219, 1126, 854 cm^{-1}; FAB-MS (NBA) *m/z* 319 (M^++H), 261 (M^++H−acetone). Anal. Calcd for $C_{14}H_{22}O_8$: C 52.82, H 6.97. Found: C 52.46, H 6.94.



Lithium aluminium hydride (1.897 g, 50.0 mmol) was suspended in dry ether (75 mL) at 0 °C. Di-*iso*propylidene D-galactaric acid dimethyl ester **156** (7.23 g, 22.71 mmol) was suspended in dry ether (175 mL) in a separate flask. The contents of the second flask were transferred dropwise via cannula to the $LiAlH_4$ flask, and allowed to stir overnight. Sodium sulphate (3 g) was added to the mixture, and stirred for 30 mins. Water (5 mL) was then cautiously added. The mixture was then allowed to stir for a further 30 mins. The mixture was filtered through Celite and sodium sulphate. The solvents were then evaporated, leaving an orange aqueous "sludge". This was taken up in DCM, and diluted slightly with water. The DCM layer was removed and the solvents evaporated. This gave di-*iso*propylidene galactitol **157** (3.652 g, 13.9 mmol, 61%) as a white powder: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 - 4.02 (m, 2H), 3.90 - 3.67 (m, 6H), 2.51 - 2.43 (dd, *J* = 8.6, 4.3 Hz, 2H), 1.42 (s, 6H), 1.40 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.10, 81.48, 78.80, 62.58, 27.14, 27.01.

Literature values: Mp 111 °C (diethyl ether–hexane); $[\alpha]_D^{23}$ 0.0 (c, 0.75 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40, 1.42 (12H, 2 × s, 2 × C(CH3)2), 2.28–2.30 (2H, dd, J 4.1 Hz, J 8.7 Hz, 2 × OH), 3.74–3.87 (6H, m), 4.04–4.10 (2H, m); ^{13}C NMR (50.3 MHz, $CDCl_3$): 26.8, 26.9 (2 × q, 2 × C(CH3)2), 62.3 (t, C-1, C-6), 78.4, 81.3 (2 × d, C-2, C-3, C-4, C-5) and 109.8 (s, 2 × C(CH3)2).



Di-*iso*propylidene D-galactitol **157** (0.950 g, 3.62 mmol) was suspended in dry THF (50 mL) at –78 °C. Butyllithium (1.45 mL, 3.62 mmol, 2.5 M) was added slowly, and the reaction was stirred for an hour. TBDMS-Cl (0.546 g, 3.62 mmol) was then added portionwise, and the reaction was allowed to complete for 4 hours. The reaction was allowed to warm to RT and worked up with the addition of water. The aqueous layer was extracted with DCM. The combined organics were washed with water, brine, and then dried over $MgSO_4$. After filtration, the solvents were then removed under reduced pressure. This afforded a small amount of the mono-silyl protected di-*iso*propylidene D-galactitol **159**, which was not purified, but was detected in the NMR by the appearance of the low shift signals, characteristic of a silyl protecting group.

Literature values: ^{1}H NMR ($CDCl_3$): δ 0.07–0.08 (m, 6 H; $Si(CH_3)_2$), 0.87–0.94 (m, 9 H; *t*Bu), 1.35, 1.36, 1.37, 1.38 (each s, 12 H; *i*Pr), 3.59 (dd, $J_{5,6}$=12.0 Hz, $J_{6\alpha,6\beta}$=5.6 Hz, 1 H; H6α), 3.72 (dd, $J_{1,2}$=11.3 Hz, $J_{1\alpha,1\beta}$=4.6 Hz, 1 H; H1α), 3.79 (dd, $J_{5,6\beta}$=2.2 Hz, 1 H; H6β), 3.80 (dd, $J_{4,5}$=5.3 Hz, $J_{3,4}$=2.4 Hz, 1 H; H4), 3.88 (t, $J_{1\beta,2}$=2.6 Hz, 1 H; H1β), 3.90 (t, $J_{2,3}$=1.3 Hz, 1 H; H3), 3.99–4.03 ppm (m, 2 H; H2, H5); ^{13}C NMR ($CDCl_3$): δ=0.10, 0.19 ($Si(CH_3)_2$), 24.57 (*t*Bu), 31.73, 32.70, 32.73, 32.75 (*i*Pr), 68.73 (C6), 69.69 (C1), 88.19 (C4), 84.73 (C3), 88.19 (C5), 88.27 ppm (C2); HR-MS (FAB): *m*/*z* calcd for $C_{18}H_{36}O_6Si$: 377.2359; found: 377.2364 $[M+H]^+$.

REFERENCES

[1] R. S. Cahn, C. Ingold and V. Prelog, "Specification of Molecular Chirality," *Angewandte Chemie International Edition,* vol. 5, no. 4, pp. 385-415, 1966.

[2] S. K. Teo, W. A. Colburn, W. G. Tracewell, K. A. Kook, D. I. Stirling, M. S. Jaworsky, M. A. Scheffler, S. D. Thomas and O. L. Laskin, "Clinical Pharmacokinetics of Thalidomide," *Clinical Pharmacokinetics,* vol. 43, no. 5, pp. 311-327, April 2004.

[3] The FDA, "50 Years after Thalidomide: Why Regulation Matters," 7 February 2012. [Online]. Available: http://blogs.fda.gov/fdavoice/index.php/2012/02/50-years-after-thalidomide-why-regulation-matters/. [Accessed 12 6 2014].

[4] "Joint Press Release issued by: Diageo plc; Thalidomide UK and the Thalidomide Trust, National Advisory Council;," Thalidomide UK, 8 December 2005. [Online]. Available: http://www.thalidomideuk.com/diageoagreement.htm. [Accessed 12 June 2014].

[5] Center for Drug Evaluation and Research, "FDA Approval Letter for Thalidomide," 16 July 1998. [Online]. Available: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/20785ltr.pdf. [Accessed 29 November 2015].

[6] V. Eleutherakis-Papaiakovou, A. Bamias and M. A. Dimopoulos, "Thalidomide in cancer medicine," *Annals of Oncology,* vol. 15, no. 8, pp. 1151-1160, 2004.

[7] Chiral Technologies, “Free Method Development,” 2015. [Online]. Available: http://chiraltech.com/free-method-development/. [Accessed 29 November 2015].

[8] Phenomenex, “Application Development,” 2015. [Online]. Available: http://www.phenomenex.com/Home/Phenologix. [Accessed 29 November 2015].

[9] Daicel Corporation, “Chiral Selectors poster,” 22 February 2013. [Online]. Available: http://chiraltech.com/wp-content/uploads/2014/03/Chiral_Selectors_Poster_34x22_FINAL-2-22-13.pdf. [Accessed 21 August 2014].

[10] A. Ghanem and H. Y. Aboul-Enein, “Lipase-mediated chiral resolution of racemates in organic solvents,” *Tetrahedron: Asymmetry,* vol. 15, p. 3331–3351, 2004.

[11] A. Collet, M. J. Brienne and J. Jacques, “Optical resolution by direct crystallization of enantiomer mixtures,” *Chemical Reviews,* vol. 80, no. 3, pp. 215-230, 1980.

[12] J. Jacques, A. Collet and S. H. Wilen, Enantiomers, racemates, and resolutions, Wiley, 1981.

[13] P. C. B. Page, L. F. Appleby, D. Day, Y. Chan, B. R. Buckley, S. M. Allin and M. J. McKenzie, “Highly Enantioselective Total Synthesis of (−)-(3’S)-Lomatin and (+)-(3’S,4’R)-trans-Khellactone,” *Organic Letters,* vol. 11, no. 9, pp. 1991-1993, 2009.

[14] S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genet, N. Champion and P. Dellis, "Synthesis and Molecular Modeling Studies of SYNPHOS, a New, Efficient Diphosphane Ligand for Ruthenium-Catalyzed Asymmetric Hydrogenation," *European Journal of Organic Chemistry,* vol. 2003, no. 10, pp. 1931-1941, 2003.

[15] T. P. Yoon and E. N. Jacobsen, "Privileged chiral catalysts," *Science,* vol. 299, no. 5613, pp. 1691-1693, 2003.

[16] A. Preetz, H.-J. Drexler, S. Schulz and D. Heller, "BINAP: rhodium-diolefibn complexes in asymmetric hydrogenation," *Tetrahedron: Asymmetry,* vol. 21, no. 9-10, pp. 1226-1231, 2010.

[17] S. D. d. Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion and P. Dellis, "SYNPHOS®, a new chiral diphosphine ligand: synthesis, molecular modeling and application in asymmetric hydrogenation," *Tetrahedron Letters,* vol. 44, no. 4, pp. 823-826, 2003.

[18] C. Wei and C.-J. Li, "Enantioselective Direct-Addition of Terminal Alkynes to Imines Catalyzed by Copper(I)pybox Complex in Water and in Toluene," *Journal of the American Chemical Society,* vol. 124, no. 20, pp. 5638-5639, 2002.

[19] P. C. B. Page, L. F. Appleby, Y. Chan, D. P. Day, B. R. Buckley, A. M. Z. Slawin, S. M. Allin and M. J. McKenzie, "Kinetic Resolution in Asymmetric Epoxidation using Iminium Salt," *The Journal of Organic Chemistry,* vol. 78, pp. 8074-8082, 2013.

[20] P. C. B. Page, B. R. Buckley, H. Heaney and A. J. Blacker, "Asymmetric Epoxidation of cis-Alkenes Mediated by Iminium Salts: Highly Enantioselective Synthesis of Levcromakalim," *Organic Letters,* vol. 7, no. 3, pp. 375-377, 2005.

[21] H. C. Kolb, M. G. Finn and K. B. Sharpless, "Click Chemistry: Diverse Chemical Function from a Few Good Reactions," *Angewandte Chemie,* pp. 2004-2021, 2001.

[22] A. Michael, "Ueber die Einwirkung von Diazobenzolimid auf Acetylendicarbonsäuremethylester," *Journal für Praktische Chemie,* vol. 48, no. 1, pp. 94-95, 1893.

[23] R. Huisgen, "Kinetics and Mechanism of 1,3-Dipolar Cycloadditions," *Angewandte Chemie International Edition,* vol. 2, no. 11, pp. 633-645, 1963.

[24] C. W. Tornøe, C. Christensen and M. Meldal, "Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides," *Journal of Organic Chemistry,* vol. 67, no. 9, pp. 3057-3064, 2002.

[25] V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, "A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes," *Angewandte Chemie International Edition,* vol. 41, no. 14, pp. 2596-2599, 2002.

[26] F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, "Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates," *Journal of the American Chemical Society,* vol. 127, no. 1, pp. 210-216, 2005.

[27] B. R. Buckley, S. E. Dann and H. Heaney, "Experimental Evidence for the Involvement of Dinuclear Alkynylcopper(I) Complexes in Alkyne–Azide Chemistry," *Chemistry - A European Journal,* vol. 16, no. 21, pp. 6278-6284, 2010.

[28] B. T. Worrell, J. A. Malik and V. V. Fokin, "Direct Evidence of a Dinuclear Copper Intermediate in Cu(I)-Catalyzed Azide-Alkyne Cycloadditions," *Science,* vol. 340, no. 6131, pp. 457-460, 2013.

[29] J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless and V. V. Fokin, "Copper(I)-Catalyzed Cycloaddition of Organic Azides and 1-Iodoalkynes," *Angewandte Chemie International Edition,* vol. 48, no. 43, pp. 8018-8021, 2009.

[30] P. Wu, M. Malkoch, J. N. Hunt, R. Vestberg, E. Kaltgrad, M. G. Finn, V. V. Fokin, K. B. Sharpless and C. J. Hawker, "Multivalent, bifunctional dendrimers prepared by click chemistry.," *Chemical Communications,* no. 46, pp. 5775-5777, 2005.

[31] B. Volt, "The potential of cycloaddition reactions in the synthesis of dendritic polymers," *New Journal of Chemistry,* vol. 31, no. 7, p. 1139, 2007.

[32] D. S. Pedersen and A. Abell, "1,2,3-Triazoles in Peptidomimetic Chemistry," *European Journal of Organic Chemistry,* no. 13, pp. 2399-2411, 2011.

[33] W. S. Horne, C. A. Olsen, J. M. Beierle, A. Montero and M. R. Ghadiri, “Probing the Bioactive Conformation of an Archetypal Natural Product HDAC Inhibitor with Conformationally Homogeneous Triazole-Modified Cyclic Tetrapeptides,” *Angewandte Chemie International Edition,* vol. 48, no. 26, pp. 4718-4724, 2009.

[34] K. E. Beatty, F. Xie, Q. Wang and D. A. Tirrell, “Selective Dye-Labeling of Newly Synthesized Proteins in Bacterial Cells,” *Journal of the American Chemical Society,* vol. 127, no. 41, pp. 14150-14151, 2005.

[35] J.-F. Lutx, H. G. Borner and K. Weichenhan, “Combining Atom Transfer Radical Polymerization and Click Chemistry: A Versatile Method for the Preparation of End-Functional Polymers,” *Macromolecular Rapid Communications,* vol. 26, no. 7, pp. 514-518, 2005.

[36] R. Riva, S. Schmeits, F. Stoffelbach, C. Jérome, R. Jérome and P. Lecomte, “Combination of ring-opening polymerization and "click" chemistry towards functionalization of aliphatic polyesters,” *Chemical Communications,* no. 42, pp. 5334-5336, 2005.

[37] F. Yang, Y. Zhang and H. Guo, “Novel supramolecular liquid crystals: cyclodextrin-triphenylene column liquid crystals based on click chemistry,” *New Journal of Chemistry,* vol. 37, no. 8, pp. 2275-2279, 2013.

[38] D. Samanta, P. Murugan, S. J. Ananthakrishnan, N. Somanathan, S. K. Das, S. N. Jaisankar and A. B. Mandal, “"Click" polymerization on a self-assembled monolayer: a convenient approach to functionalize various surfaces with poytriazoles,” *Chemical Communications,* vol. 48, no. 99, pp. 12068-12070, 2012.

[39] P.-H. Elchinger, P.-A. Faugeras, B. Boens, F. Brouillette, D. Montplaisir, R. Zerrouki and R. Lucas, “Polysaccharides: The "Click" Chemistry Impact,” *Polymers,* vol. 3, pp. 1607-1651, 2011.

[40] J.-T. Hou, Q.-F. Zhang, B.-Y. Xu, Q.-S. Lu, Q. Liu, J. Zhang and X.-Q. Yu, “A novel BINOL-based cyclophane via click chemistry: synthesis and its applications for sensing silver ions,” *Tetrahedron Letters,* vol. 52, no. 38, pp. 4927-4930, 2011.

[41] D. J. V. van Steenis, O. R. David, G. P. van Strijdonck, J. H. van Maarseveen and J. N. Reek, “Click-chemistry as an efficient synthetic tool for the preparation of novel conjugated polymers,” *Chemical Communications,* no. 34, pp. 4333-4335, 2005.

[42] D. Oves-Costales, L. Song and G. L. Challis, “Enantioselective desymmetrisation of citric acid catalysed by the substrate-tolerant petrobactin biosynthetic enzyme AsbA,” *Chemical Communications,* no. 11, pp. 1389-1391, 2009.

[43] G. Allan, A. J. Carnell, M. L. Escudero Hernandez and A. Pettman, “Desymmetrisation of 4,4-disubstituted cyclohexanones by enzyme-catalysed resolution of their enol acetates,” *Journal of the Chemical Society, Perkin Transactions 1,* no. 20, pp. 3382-3388, 2000.

[44] C. Bonini, R. Racioppi and L. Viggiani, “Enzyme-catalyzed desymmetrization of meso-skipped polyols to useful chiral building blocks,” *Tetrahedron: Asymmetry,* vol. 4, no. 5, pp. 793-805, 1993.

[45] D. R. Deardorff, R. B. Amador, J. W. Morton, H. Y. Kim, C. M. Taniguchi, A. A. Balbuena, S. A. Warren, V. Fanous and S. T. Choe, “Chiral induction in cyclopentyl-derived 1,3-meso-diesters: enantioselective hydrolyses with electric eel acetylcholinesterase,” *Tetrahedron: Asymmetry,* vol. 10, no. 11, pp. 2139-2152, 1999.

[46] T. Ikariya, S. Hashiguchi, K. Murata and R. Noyori, “PREPARATION OF OPTICALLY ACTIVE (R,R)-HYDROBENZOIN FROM BENZOIN OR BENZIL,” *Organic Syntheses,* vol. 82, pp. 10-17, 2005.

[47] M. Wilking, C. Mück-Lichtenfeld, C. G. Daniliuc and U. Hennecke, “Enantioselective, Desymmetrizing Bromolactonization of Alkynes,” *Journal of the American Chemical Society,* vol. 135, no. 22, pp. 8133-8136, 2013.

[48] A. S. K. Hashmi, T. Häffner, M. Rudolph and F. Rominger, “Gold catalysis: domino reaction of en-diynes to highly substituted phenols,” *Chemistry,* vol. 17, no. 29, pp. 8195-8201, 2011.

[49] P. D. A. Stephen K. Hashmi and P. D. Graham J. Hutchings, “Gold Catalysis,” *Angewandte Chemie International Edition,* vol. 45, no. 47, pp. 7896-7936, 2006.

[50] A. S. K. Hashmi and M. Rudolph, “Gold catalysis in total synthesis,” *Chem. Soc. Rev.,* no. 37, pp. 1766-1775, 2008.

[51] A. H. Prof., “Homogeneous Gold Catalysis Beyond Assumptions and Proposals—Characterized Intermediates,” *Angewandte Chemie International Edition,* vol. 49, no. 31, p. 5232–5241, 2010.

[52] A. S. K. H. Prof. Dr., M. H. Dr., F. R. Dr. and J. W. B. Dr., “Gold Catalysis: Enantiotopos Selection,” *Chemistry - A European Journal,* vol. 15, no. 48, p. 13318–13322, 2009.

[53] K. Wilckens, M. Uhlemann and C. Czekelius, “Gold-Catalyzed endo-Cyclizations of 1,4-Diynes to Seven-Membered Ring Heterocycles,” *Chemistry - A European Journal,* no. 15, pp. 13323-13326, 2009.

[54] J.-c. Meng, V. V. Fokin and M. G. Finn, “Kinetic resolution by copper-catalyzed azide–alkyne cycloaddition,” *Tetrahedron Letters,* vol. 46, no. 27, pp. 4543-4546, 2005.

[55] V. O. Rodionov, V. V. Fokin and M. G. Finn, “Mechanism of the Ligand-Free CuI-Catalyzed Azide–Alkyne Cycloaddition Reaction,” *Angewandte Chemie International Edition,* vol. 44, no. 15, pp. 2210-2215, 2005.

[56] F. Zhou, C. Tan, J. Tang, Y.-Y. Zhang, W.-M. Gao, H.-W. Wu, Y.-H. Yu and J. Zhou, “Asymmetric Copper(I)-Catalyzed Azide–Alkyne Cycloaddition to Quaternary Oxindoles,” *Journal of the American Chemical Society,* vol. 135, no. 30, pp. 10994-10997, 2013.

[57] H. Oediger and F. Möller, “Dialkylation in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene,” *Justus Liebigs Annalen der Chemie,* vol. 2, pp. 348-351, 1976.

[58] F. A. Cotton, G. WIlkinson, C. A. Murillo and M. Bochmann, Advanced Inorganic Chemistry, 6 ed., New York: Wiley, 1999.

[59] F. G. Bordwell and H. E. Fried, "Acidities of the hydrogen-carbon protons in carboxylic esters, amides, and nitriles," *The Journal of Organic Chemistry,* vol. 46, no. 22, pp. 4327-4331, 1981.

[60] Y. Ueda, W. Muramatsu, K. Mishiro, T. Furuta and T. Kawabata, "Functional Group Tolerance in Organocatalytic Regioselective Acylation of Carbohydrates," *The Journal of Organic Chemistry,* vol. 74, no. 22, pp. 8802-8805, 2009.

[61] A. N. Pudovik and N. G. Khusainova, "Esters and Nitriles of Propynylphosphonoacetic Acid," *Russian Journal of General Chemistry English Translation,* vol. 39, pp. 2366 - 2368, 1969.

[62] S. G. Alvarez and M. T. Alvarez, "A Practical Procedure for the Synthesis of Alkyl Azides at Ambient Temperature in Dimethyl Sulfoxide in High Purity and Yield," *Synthesis,* no. 4, p. 413, 1997.

[63] S. Thea and G. Cevasco, "A novel reaction of benzoyl chlorides in dimethyl sulfoxide," *Journal of Organic Chemistry,* vol. 53, no. 17, pp. 4121-4122, 1988.

[64] E. W. Barrett and C. W. Porter, "Further Studies on a Molecular Rearrangement Induced by Ultrasonic Waves," *Journal of the American Chemical Society,* vol. 63, no. 12, pp. 3434-3435, 1941.

[65] C. W. Tornøe and M. Meldal, "Cu-Catalyzed Azide-Alkyne Cycloaddition," *Chemistry Reviews,* vol. 108, pp. 2952-3015, 2008.

[66] O. David, S. Maisonneuve and J. Xie, “Generation of new fluorophore by Click chemistry: synthesis and properties of β-cyclodextrin substituted by 2-pyridyl triazole,” *Tetrahedron Letters,* vol. 48, no. 37, p. 6527–6530, 2007.

[67] J. Andersen, S. Bolvig and X. Liang, “Efficient One-Pot Synthesis of 1-Aryl 1,2,3-Triazoles from Aryl Halides and Terminal Alkynes in the Presence of Sodium Azide,” *Synlett,* vol. 2005, no. 19, pp. 2941-2947, 2005.

[68] E. J. Corey and H. E. Ensley, “Preparation of an optically active prostaglandin intermediate via asymmetric induction,” *Journal of the American Chemical Society,* vol. 97, no. 23, pp. 6908-6909, 1975.

[69] G. Solladié, J. Hutt and A. Girardin, “Improved Preparation of Optically Active Methyl p-Tolyl Sulfoxide,” *Synthesis,* vol. 1987, no. 2, p. 173, 1987.

[70] W. Pavelich and R. Taft Jr, “The Evaluation of Inductive and Steric Effects on Reactivity. The Methoxide Ioncatalyzed Rates of Methanolysis of l-Menthyl Esters in Methanol,” *Journal of the American Chemical Society,* vol. 79, no. 18, pp. 4935-4940, 1957.

[71] K. K. Andersen, B. Bujnicki, J. Drabowicz, M. Mikolajczyk and J. B. O'Brien, “Synthesis of enantiomerically pure alkyl and aryl methyl sulfoxides from cholesteryl methanesulfinates,” *The Journal of Organic Chemistry,* vol. 49, no. 21, pp. 4070-4072, 1984.

[72] J. Drabowicz, B. Bujnicki and M. Mikolajczyk, “Organosulfur compounds. 30. Improved procedure for synthesis of chiral sulfoxides,” *The Journal of Organic Chemistry,* vol. 47, no. 17, pp. 3325-3327, 1982.

[73] T. I. Guseva, N. G. Senchenya, I. P. Gol'ding, K. A. Mager and Y. G. Gololobov, “Synthesis of functionally substituted cyanoacetates,” *Russian Chemical Bulletin,* vol. 42, no. 3, pp. 478-480, 1993.

[74] H. A. Albrecht, G. Beskid, N. H. Georgopapadakou, D. D. Keith, F. M. Konzelmann, D. L. Pruess, P. L. Rossman, C. C. Wei and J. G. Christenson, “Dual-action cephalosporins: cephalosporin 3'-quinolone carbamates,” *Journal of Medicinal Chemistry,* vol. 34, no. 9, pp. 2857-2864, 1991.

[75] P. P. G. Co., “Process for preparing cyanoacetic acid esters of sterols”. United States of America Patent 2,693,477, 2 November 1954.

[76] R. Gawley and J. Aubé, Principles of Asymmetric Synthesis, Oxford: Elsevier, 1996.

[77] R. L. Clark, B. T. Wenzel and T. J. Wenzel, “Diamagnetic lanthanide tris β-diketonate complexes with aryl-containing ligands as chiral NMR discriminating agents,” *Tetrahedron: Asymmetry,* vol. 24, no. 5-6, pp. 297-304, 2013.

[78] J. Brussee, W. Loos, C. Kruse and A. Van Der Gen, “J. Brussee, W.T. Loos, C.G. Kruse, A. Van Der Gen,” *Tetrahedron,* vol. 46, no. 3, pp. 979-986, 1990.

[79] Daicel, “Chiralpak Immobilized Columns,” [Online]. Available: http://www.hplc.sk/pdf/Daicel/ImmobilizedChiralpaksFAQs.pdf. [Accessed 21 August 2014].

[80] J. Díez, M. P. Gamasa and M. Panera, “Tetra-, di-, and mononuclear copper(I) complexes containing (S,S)-iPr-pybox and (R,R)-Ph-pybox ligands.,” *Inorganic chemistry,* vol. 45, no. 25, pp. 10043-10045, 2006.

[81] J. Mazuela, O. Pàmies and M. Diéguez, “Phosphite-Thiazoline versus Phosphite-Oxazoline for Pd-Catalyzed Allylic Substitution Reactions: A Case for Comparison,” *ChemCatChem,* vol. 5, no. 6, pp. 1504-1516, 2013.

[82] E. Corey and J. W. Suggs, “Pyridinium chlorochromate. An efficient reagent for oxidation of primary and secondary alcohols to carbonyl compounds,” *Tetrahedron Letters,* vol. 16, no. 31, pp. 2647-2650, 1975.

[83] A. Duschek and S. F. Kirsch, “2-Iodoxybenzoic Acid—A Simple Oxidant with a Dazzling Array of Potential Applications,” *Angewandte Chemie International Edition,* vol. 50, no. 7, p. 1524–1552, 2011.

[84] D. B. Dess and J. C. Martin, “Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones,” *The Journal of Organic Chemistry,* vol. 48, no. 22, pp. 4155-4156, 1983.

[85] P. C. B. Page, L. F. Appleby, B. R. Buckley, S. M. Allin and M. J. McKenzie, "In-situ generation of 2-Iodoxybenzoic Acid (IBX) in the presence of Tetraphenylphosphonium monoperoxysulfate (TPPP) for the conversion of primary alcohols into the corresponding aldehydes," *Synlett,* vol. 2007, no. 10, pp. 1565-1568, 2007.

[86] J. Parish and W. Doering, "Sulfur trioxide in the oxidation of alcohols by dimethyl sulfoxide," *Journal of the American Chemical Society,* vol. 89, no. 21, pp. 5505-5507, 1967.

[87] J. S. Yadav, A. S. Reddy, C. S. Reddy, B. V. S. Reddy, V. Saddanapu and A. Addlagatta, "First Stereoselective Total Synthesis and Biological Evaluation of Amphidinin B and Its Analogues," *European Journal of Organic Chemistry,* vol. 2011, no. 4, pp. 696-706, 2011.

[88] M. Figlus, A. C. Tarruella, A. Messer, S. L. Sollisb and R. C. Hartley, "Low molecular weight MPEG-assisted organic synthesis," *Chemical Communications,* no. 46, pp. 4405-4407, 2010.

[89] M. Nahmany and A. Melman, "Facile Acylation of Sterically Hindered Alcohols through Ketene Intermediates," *Organic Letters,* vol. 3, no. 23, pp. 3733-3735, 2001.

[90] D. N. Tirelli, A. Altomare, R. Solaro, F. Ciardelli, U. Meier, C. Bosshard and P. Günter, "Structure-Activity Relationship of New Organic NLO Materials Based on Push-Pull Azodyes. Synthesis and molecular properties of the dyes," *Journal fur Praktische Chemie/Chemiker-Zeitung,* vol. 340, no. 2, pp. 122-128, 1998.

[91] X. Wang, H. Chakrapani, J. W. Madine, M. A. Keyerleber and R. A. Widenhoefer, "Cyclization/Hydrosilylation of Functionalized 1,6-Diynes Catalyzed by Cationic Platinum Complexes Containing Bidentate Nitrogen Ligands," *The Journal of Organic Chemistry,* vol. 67, no. 9, p. 2778–2788, 2002.

[92] M. Kitamura, S. Kato, M. Yano, N. Tashiro, Y. Shiratake, M. Sando and T. Okauchi, "A reagent for safe and efficient diazo-transfer to primary amines: 2-azido-1,3-dimethylimidazolinium hexafluorophosphate," *Organic & Biomolecular Chemistry,* no. 12, pp. 4397-4406, 2014.

[93] P. Froeyen, "A Particularly Convenient One-Pot Synthesis of N-Alkoxycarbonyl, N- Acyl and N-Aroyl Substituted Iminophosphoranes. Improved Preparation of Azidoformates, Aroyl and Alkanoyl Azides. An Alternative Route to Complex Amides.," *Phosphorus, Sulfur, and Silicon and the Related Elements,* vol. 78, no. 1-4, pp. 161-172, 1993.

[94] B. M. Cunha, I. N. Trindade, N. A. Couto, P. Costa, P. Rodrigues, M. Barros, M. Costa, M. Duarte, M. Fernandez and P. J. A. Madeira, "Gas-phase interaction between nickel (II) and nitrobenzyl azides: An ESI-MSn study," *International Journal of Mass Spectrometry,* vol. 351, pp. 27-36, 2013.

[95] S. Amslinger, A. Hirsch and F. Hampel, "Synthesis of a biotinated amphiphile," *Tetrahedron,* vol. 60, no. 50, pp. 11565-11569, 2004.

[96] D. D. Long, R. J. E. Stetz, R. J. Nash, D. G. Marquess, J. D. Lloyd, A. L. Winters, N. Asano and G. W. J. Fleet, "Open-chain acetonides of D-galactono-1,4-lactone as starting materials for pyrrolidines, azepanes and 5-azidomethyltetrahydrofuran-2-carboxylates: monomers for polyhydroxylated nylon and for tetrahydrofuran carbopeptoids," *Journal of the Chemical Society, Perkin Transactions 1,* vol. 1999, no. 8, pp. 901-908, 1999.

[97] T. Maeda and S.-I. N. Dr., "FRET-Based Direct and Continuous Monitoring of Human Fucosyltransferases Activity: An Efficient synthesis of Versatile GDP-L-Fucose Derivatives from Abundant d-Galactose," *Chemistry: A European Journal,* vol. 14, no. 2, pp. 478-487, 2007.

LETTER 2723

An Investigation of the Asymmetric Huisgen 'Click' Reaction[1]

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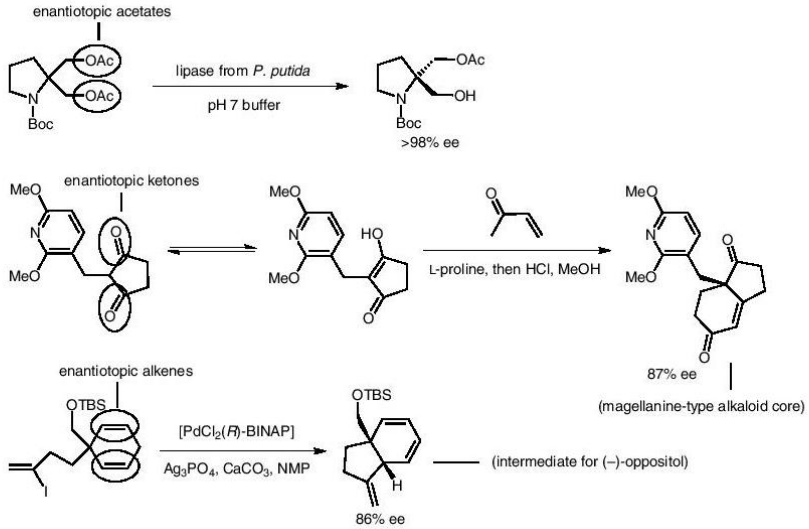
Abstract: The preparation of a series of new prochiral bis-alkynes is reported. A selection of chiral ligands is examined to gain additional information about the scope of the new asymmetric Huisgen 'click' reaction [the desymmetrisation of bis-alkynes using chiral ligands in conjunction with the widely applied copper-catalysed azide–alkyne cycloaddition (CuAAC) triazole synthesis]. The development of a new chiral assay for (±)-methyl 2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-2-cyanopent-4-ynoate, and the production of this mono-triazole in up to 18% enantiomeric excess is described.

Key words: chiral ligands, copper, CuAAC reaction, asymmetric synthesis

Desymmetrisation reactions[2] are a powerful tool in enantioselective synthesis since they allow access to chiral non-racemic products from bond-formation chemistry that does not directly introduce chirality at the reaction centre (Scheme 1). Classic examples are the use of lipases[3] with prochiral diesters, or the Hajos–Parrish reaction,[4] which distinguishes the two enantiotopic ketones of a 2,2-disubstituted cyclohexane-1,3-dione. More recently, the development of asymmetric Heck coupling reactions[5] has transformed the synthetic application of the palladium-catalysed arylation of α,β-unsaturated esters and related substrates. This reaction was originally prized in synthesis because, in contrast to conjugate addition[6] with diarylcuprates, Heck coupling achieves a comparable C–C bond formation, but retains the alkene functionality in the product. The valuable reactivity of the alkene is thus still available to be employed again (for example in epoxidation[7] or cycloaddition[8] processes). Although valuable, however, this conventional use of Heck coupling does not produce a new stereogenic centre, and it was 17 years from its first description[9] in the literature until the first reports[10] of its use with a chiral ligand.



Scheme 1 Desymmetrisation reactions in synthesis[3,4b,5e]

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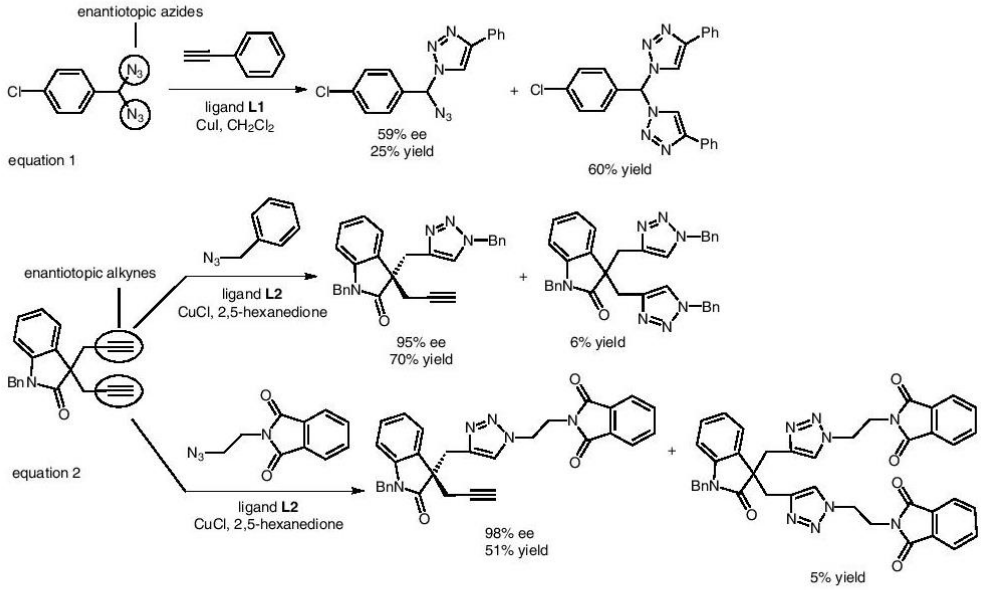


Scheme 2 Examples of asymmetric 'click' reactions[27,28]

There are many powerful, generally applicable, high-yielding C–C bond-forming reactions that have similarly been overlooked for investigation with chiral ligands for the same reason (that they do not typically form stereogenic centres). Some years ago,[11] it occurred to us that the popular copper-catalysed 'click' reaction between an alkyne and an azide [the copper-catalysed azide–alkyne cycloaddition (CuAAC)],[12] which forms a flat achiral triazole functional group, was just such a case. Sharpless introduced the concept of 'click' chemistry in 2001,[13] emphasising the strategic power of bond-forming chemistry that can be applied in almost any situation. By definition, 'click' reactions are easy to carry out, fast, and high-yielding, so the concept of an asymmetric 'click' reaction is highly attractive, promising enantiopure products in almost quantitative yield. Indeed, during the last decade, the CuAAC reaction has been applied in almost every conceivable situation (recent examples are in fields as diverse as electrochemistry,[14] polymer science,[15] bioimaging,[16] drug delivery,[17] metabolic glycoengineering,[18] supramolecular organogels,[19] neoglycoproteins,[20] magnetic[21] and electronic[22] materials, dendrimers,[23] immobilised cyclodextrin derivates,[24] fluorescence sensors,[25] and semiconductors[26]), but, at the start of our work, compared to these many thousands of CuAAC papers, there was only one report[27] of its use with a chiral ligand (for an example, see Figure 1, **L1**). This study from Fokin and Finn's group at the Scripps Institute employed a prochiral bis-azide reacting with alkynes to form chiral mono-azide derivatives containing triazole functionality (Scheme 2, eq 1). For our own investigations, we felt that the synthetic value of alkynes in organic chemistry afforded the desymmetrisation of prochiral bis-alkynes much greater potential, and we therefore focused our attention in that direction. Our initial work has concentrated on simple, readily available prochiral bis-alkynes that can easily be obtained from β-keto esters or cyanoacetate esters by alkylation with two equivalents of propargyl bromide. Very recently, an extremely elegant demonstration of this type of asymmetric 'click' chemistry was reported by Zhou,[28] with enantiomeric excesses as high as 98%, working with a different, but structurally related class of prochiral bis-alkynes obtained from an N-protected oxindole (Scheme 2, eq 2 and Figure 1, **L2**). The publication of this highly important paper by Zhou et al. prompts us to disclose our own results in this area. We describe here the synthesis and characterisation of new examples of cyanoacetate-derived prochiral bis-alkynes, their mono- and bis-triazole products from the CuAAC reaction, and preliminary results with a representative series of chiral ligands.

Our prochiral starting materials are easily obtained by heating methyl or *tert*-butyl cyanoacetate with propargyl bromide and potassium carbonate at reflux temperature in acetonitrile for 15–70 hours.[29] Methyl acetoacetate gave the prochiral methyl 2-acetyl-2-(prop-2-yn-1-yl)pent-4-ynoate ester by the same procedure. Unsymmetrical malonate diesters (e.g., the ethyl, *tert*-butyl diester **4**) can also be used (Scheme 3).[30]

The CuAAC reaction with benzyl azide was examined first using copper powder[31] for ease of work-up[32] (simple filtration), and also with copper iodide under microwave conditions[33] (using a combination of the 'one pot' benzyl bromide, sodium azide, alkyne method,[34] and the homo-

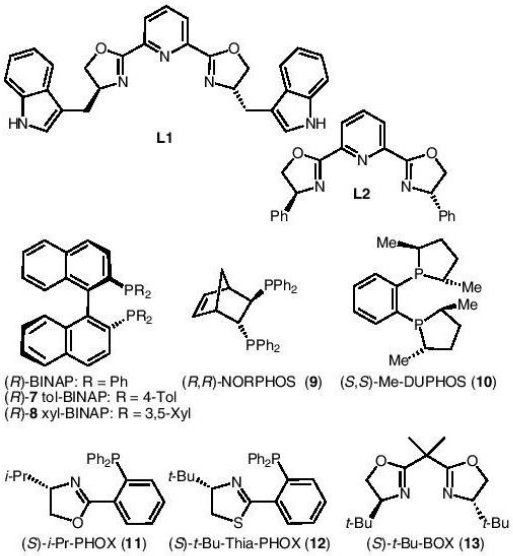
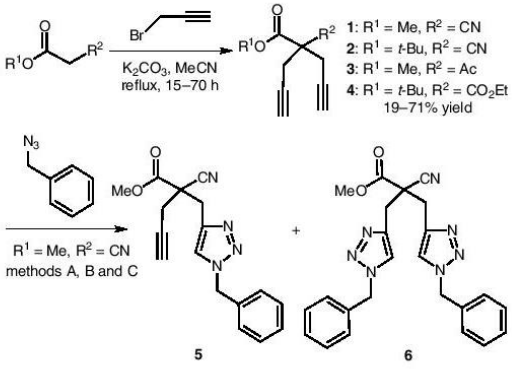


Figure 1 Structures of **L1** and **L2** and chiral ligands tested in our work (**7**–**13**)



Scheme 3 Preparation and CuAAC reactions of prochiral 2,2-diynes [method A: copper powder; method B: microwave irradiation with copper powder; method C: chiral ligand with copper iodide and diisopropylethylamine (DIPEA)]; see Tables 1–3

geneous *tert*-butanol–water procedure[35]). The bis-alkyne **1** was reactive under both of these conditions, and, depending upon the concentration of reagents and the excess of the azide, mixtures of the starting material **1** and the mono- and bis-triazoles[36,37] (**5**[38] and **6**[39]) were produced (Table 1). An authentic racemic sample of **5** obtained in this way was separated by analytical HPLC using a Chiralpak IC column with heptane–isopropyl alcohol (80:20 v/v) as the mobile phase (1 mL·min^{-1}). The two enantiomers were eluted separately with retention times of 67 and 75 minutes. Shorter elution times are possible using hexane–isopropyl alcohol (70:30 v/v at 1 mL·min^{-1}; retention times of 31 and 34 minutes), establishing a convenient high-throughput chiral analysis for the investigation of the asymmetric 'click' reaction, using the ratios of peak areas observed at 229 nm.

The reaction was examined next in the presence of (*R*)- and (*S*)-tol-BINAP (**7**), in toluene, employing a 1:1 ratio of the bis-alkyne **1** and benzyl azide and 10 mol% of copper(I) iodide. The reaction was stopped after 18 hours (21% conversion) and analysed by chiral HPLC. With (*R*)-**7**, the faster eluting peak was larger than the second peak, showing a modest enantiomeric excess of about 13% (calculated from the areas of the two peaks). The reaction employing (*S*)-**7**, was again stopped before completion (38% conversion). In this experiment, the second (slower eluting) peak was the larger. A similar enantiomeric excess (15%), favouring the opposite enantiomer, was observed (Table 2).

Based on this protocol, we next performed a preliminary survey of a range of chiral ligands, but obtained the mono-

Table 1 CuAAC Reactions of the Bis-Alkyne **1** with Benzyl Azide[a]

Method	Time (h)	BnN_3 (equiv)	Concn (M)	Recovered **1** (%)	Mono-triazole **5** (%)	Bis-triazole **6** (%)
A	40	1[b]	0.06	57	30	13
A	16	1[b]	0.05	59	37	4
A	16	2.5[b]	0.04	16	28	56
B	16	1[c]	0.24	71	28	1
B	16	1[c]	0.4	19	54	27
C	0.17	1[d]	0.14	94	5	1
C	0.25	1[d]	0.14	38	26	36
C	0.33	1[d]	0.14	32	30	38

[a] Reactions in *t*-BuOH–H_2O for method A, in DMSO for method B, and in toluene for method C; see Scheme 3 and citations in the text.
[b] Added as benzyl azide.
[c] Generated in situ[40] before the 'click' reaction, using benzyl bromide and sodium azide.
[d] Generated in situ during the 'click' reaction, using benzyl bromide and sodium azide.

Table 2 Asymmetric 'Click' Reactions at –40 °C with 10 mol% Catalyst Loading (2:3 Ratio of Copper Iodide and Chiral Ligand)

Ligand[a]	Solvent	Time	SM/ mono/bis[b]	ee (%)	er[c]
(*R*)-tol-BINAP	toluene	18 h	79:19:2	13	56:44
(*S*)-tol-BINAP	toluene	18 h	62:35:3	15	42:58
(*R*)-xyl-BINAP	toluene	5 d	74:24:2	5	53:47
(*S*)-xyl-BINAP	toluene	5 d	61:35:4	6	47:53
(*R*,*R*)-NORPHOS	toluene	18 h	72:25:3	9	46:54
(*R*,*R*)-NORPHOS	Et_2O	18 h	70:27:3	7	46:54
(*R*,*R*)-NORPHOS	EtOH	5 d	71:25:4	10	45:55
(*R*,*R*)-NORPHOS	MeOH	18 h	68:28:4	7	46:54
(*R*,*R*)-NORPHOS	EtOAc	18 h	61:35:4	6	47:53
(*R*,*R*)-NORPHOS	EtOAc	5 d	49:43:8	3	48:52
(*R*,*R*)-NORPHOS	Et_2O	5 d	45:48:7	4	48:52

[a] tol-BINAP = 1,1′-binaphthalene-2,2′-diylbis[bis(4-methylphenyl)phosphine]; xyl-BINAP = 1,1′-Binaphthalene-2,2′-diyl-bis[bis(3,5-dimethylphenyl)phosphine]; (*R*,*R*)-NORPHOS = (2*R*,3*R*)-(–)-2,3-Bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene.
[b] Ratio of starting material to mono- and bis-triazoles.
[c] HPLC ratios of peak areas eluting at 31 min and 34 min using a 4.6 mm × 250 mm, 5 μm Daicel Chiralpak IC column with hexane–*i*-PrOH (70:30 v/v) at 1 mL·min^{-1} [or at 67 and 75 min eluting at 1 mL·min^{-1} with heptane–*i*-PrOH (80:20 v/v)].

triazole product in lower enantiomeric excesses. Using (*R*)-xyl-BINAP (**8**) gave the same sense of asymmetric induction as (*R*)-tol-BINAP, but only 5% enantiomeric excess. Because of the very low enantiomeric excess, S order of large/small peaks was reversed, which proved to be the case (6% ee). Perhaps because of the more bulky ligand, the xyl-BINAP reaction was much slower than the tol-BINAP alternative, and these reactions required five days to reach comparable levels of consumption of the azide (26–39% conversions). (*R*,*R*)-NORPHOS (**9**) has also been examined, and after 18 hours gave only 9% enantiomeric excess. In all of these reactions (see Table 2), small amounts of the achiral bis-triazole **6** were also observed. Using (*R*,*R*)-NORPHOS, a selection of reaction solvents (methanol, ethanol, ethyl acetate and diethyl ether) were tested, but gave similar results (3–10% ee). The reaction in ethanol required five days to achieve 29% conversion. The enantiomeric excess obtained in ethanol at 29% conversion (10%) was very similar to the enantiomeric excess obtained after 18 hours in our initial NORPHOS experiment (28% conversion, 9% ee). The lowest enantiomeric excesses in the NORPHOS experiments were encountered in ethyl acetate and diethyl ether when the reactions were allowed to proceed to about 50–55% conversion. In these examples, because of the longer reaction times, noticeably more of the bis-triazole product **6** was present.

Table 3 Asymmetric 'Click' Reactions at –40 °C with 20 mol% Catalyst Loading (2:3 Ratio of Copper Iodide and Chiral Ligand) in Toluene

Ligand[a]	Time	SM/mono/bis[b]	ee (%)	er[c]
(*R*,*R*)-NORPHOS (**9**)	18 h	66:34:0	16	42:58
(*S*,*S*)-Me-DUPHOS (**10**)	4 h	92:8:0	5	53:47
(*S*)-*i*-Pr-PHOX (**11**)	18 h	60:35:5	3	48:52
(*S*)-*t*-Bu-Thia-PHOX (**12**)	18 h	60:35:5	2	49:51
(*S*)-*t*-Bu-BOX (**13**)	18 h	53:31:15	3	48:52
(*S*)-tol-BINAP (**7**)	18 h	94:6:0	18	41:59

[a] (*R*,*R*)-NORPHOS = (2*R*,3*R*)-(–)-2,3-bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene; (*S*,*S*)-Me-DUPHOS = 1,2-bis[(2*S*,5*S*)-2,5-dimethylphospholano]benzene; (*S*)-*i*-Pr-PHOX = (*S*)-2-(2-diphenylphosphinophenyl)-4-*iso*-propyl-4,5-dihydrooxazole; (*S*)-*t*-Bu-Thia-PHOX = (*S*)-2-(2-diphenylphosphinophenyl)-4-*tert*-butyl-4,5-dihydrothiazole; (*S*)-*t*-Bu-BOX = 2,2′-*iso*-propylidene-bis(4-*tert*-butyloxazoline); (*S*)-tol-BINAP = 1,1′-binaphthalene-2,2′-diylbis[bis-(4-methylphenyl)phosphine].
[b] Ratio of starting material to mono- and bis-triazoles.
[c] HPLC ratios of peak areas eluting at 31 min and 34 min using a 4.6 mm × 250 mm, 5 μm Daicel Chiralpak IC column with hexane–*i*-PrOH (70:30 v/v) at 1 mL·min^{-1} [or at 67 and 75 min eluting at 1 mL·min^{-1} with heptane–*i*-PrOH (80:20 v/v)].

The best result with (*R*,*R*)-NORPHOS (**9**) was obtained in toluene by increasing the quantities of copper(I) iodide and ligand **9** and keeping the reaction time as 18 hours (Table 3). Under these conditions, at 34% conversion, none of the bis-triazole was observed and the chiral discrimination was improved to give the mono-triazole **5** in 16% enantiomeric excess.[41] With this higher catalyst loading (20 mol% CuI and 30 mol% chiral ligand), the range of chiral auxiliaries tested in this study was expanded to include (*S*,*S*)-Me-DUPHOS (**10**), (*S*)-*i*-Pr-PHOX ligand (**11**)[42] and the (*S*)-*t*-Bu-Thia-PHOX ligand (**12**)[43] (Figure 1), as well as an example of a non-phosphorus bidentate ligand [(*S*)-*t*-Bu-BOX (**13**)], but all four gave low enantiomeric excesses in the range 2–5%. (*S*)-Tol-BINAP was also studied with the higher catalyst loading, giving the mono-triazole product in 18% enantiomeric excess at a low conversion.

In conclusion, the development of asymmetric 'click' chemistry is still at a very early stage, but it is clear from our results and those of Zhou et al.[28] that the efficiency of asymmetric induction is sensitive to the structure of the prochiral bis-alkyne and the choice of solvent, as well as the nature of the ligand class itself. The examples reported here include chelating diphosphines, chelating 'P–N' monophosphine ligands, and a BOX-type non-phosphine chelating ligand, but with our cyanoacetate series of prochiral bis-alkynes, all significantly underperform the PYBOX ligand employed initially by Meng, Fokin and Finn,[27] and now optimised by Zhou et al.[28]

Acknowledgment

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References and Notes

(1) Asymmetric click chemistry, Part 1.
(2) Rovis, T. *Recent Advances in Catalytic Asymmetric Desymmetrization Reactions*, In *New Frontiers in Asymmetric Catalysis*; Mikami, K.; Lautens, M., Eds.; John Wiley & Sons: Hoboken, **2007**, 275–311.
(3) Donohoe, T. J.; Rigby, C. L.; Thomas, R. E.; Nieuwenhuys, W. F.; Bhatti, F. L.; Cowley, A. R.; Bhalay, G.; Linney, I. D. *J. Org. Chem.* **2006**, *71*, 6298.
(4) (a) Bradshaw, B.; Bonjoch, J. *Synlett* **2012**, *23*, 337. (b) Murphy, R. A.; Sarpong, R. *Org. Lett.* **2012**, *14*, 632.
(5) (a) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533. (b) Guiry, P. J.; Kiely, D. *Curr. Org. Chem.* **2004**, *8*, 781. (c) Dounay, A. M.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2495. (d) Stephenson, G. R. *Asymmetric Palladium-Catalysed Coupling Reactions*, In *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Kluwer Academic Publishers: London, **1996**, 275–298. (e) Sato, Y.; Mori, M.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 757.
(6) (a) Posner, G. H. *Org. React.* **1972**, *19*, 1. (b) See also: Perlmutter, P. *Asymmetric Conjugate Addition Reactions*, In *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Kluwer Academic Publishers: London, **1996**, 222–230.
(7) Kotoku, N.; Kato, T.; Narumi, F.; Ohtani, E.; Kamada, S.; Aoki, S.; Okada, N.; Nakagawa, S.; Kobayashi, M. *Bioorg. Med. Chem.* **2006**, *14*, 7446.
(8) von Zezschwitz, P.; de Meijere, A. *Top. Organomet. Chem.* **2006**, *19*, 49.
(9) For the first examples using aryl and alkenyl halides, see: (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P. Jr. *J. Org. Chem.* **1972**, *37*, 2320. (c) See also: Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.
(10) (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738. (b) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.
(11) Sheldon, A.; Deschamps, D.; Buttress, J. M.; Alayrac, C.; Gaumont, A.-C.; Stephenson, G. R.; Page, P. C. B. Poster Abstract, Eleventh Anglo-Norman Organic Chemistry Colloquium (ANORCQ XI), Caen, France, 15–17 April, **2012**, P24.
(12) (a) Liang, L.; Astruc, D. *Coord. Chem. Rev.* **2011**, *255*, 2933. (b) Tornoe, C. W.; Christensen, C.; Medal, M. *J. Org. Chem.* **2002**, *67*, 3057. (c) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (d) Huisgen, R. *Proc. Chem. Soc.* **1961**, 357. (e) See also: Huisgen, R.; Knorr, R. *Naturwissenschaften* **1961**, *48*, 716. (f) For the cycloaddition reaction between phenyl azide and an acetylenic ester, see: Michael, A. *J. Prakt. Chem.* **1893**, *48*, 94.
(13) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
(14) (a) Cernat, A.; Griveau, S.; Richard, C.; Bedioui, F.; Sandulescu, R. *Electroanal.* **2013**, *25*, 1369. (b) Ripert, M.; Farre, C.; Chaix, C. *Electrochim. Acta* **2013**, *91*, 82.
(15) (a) Tian, Y.; Shi, W.; Luo, J.; Ma, F.; Mi, H.; Lei, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 3636. (b) Li, J.; Benicewicz, B. C. *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 3572.
(16) (a) Zhou, M.; Zhang, X.; Bai, M.; Shen, D.; Xu, B.; Kao, J.; Ge, X.; Achilefu, S. *RSC Adv.* **2013**, *3*, 6756. (b) Neves, A. A.; Stockmann, H.; Wainman, Y. A.; Kuo, J. C.-H.; Fawcett, S.; Leeper, F. J.; Brindle, K. M. *Bioconjugate Chem.* **2013**, *24*, 934. (c) Pérez-Ojeda, M. E.; Trastoy, B.; Rol, Á.; Chiara, M. D.; García-Moreno, I.; Chiara, J. L. *Chem. Eur. J.* **2013**, *19*, 6630.
(17) Ding, J.; Zhao, L.; Li, D.; Xiao, C.; Zhuang, X.; Chen, X. *Polym. Chem.* **2013**, *4*, 3345.
(18) Memmel, E.; Homann, A.; Oelschlaeger, T. A.; Seibel, J. *Chem. Commun.* **2013**, *49*, 7301.
(19) Liu, D.; Wang, D.; Wang, M.; Zheng, Y.; Koynov, K.; Auernhammer, G. K.; Butt, H.-J.; Ikeda, T. *Macromolecules* **2013**, *46*, 4617.
(20) Wojnar, J. M.; Lee, D. J.; Evans, C. W.; Mandal, K.; Kent, S. B. H.; Brimble, M. A.; Witczak, Z. J.; Bielski, R. *In Click Chemistry in Glycoscience* **2013**, 253.
(21) Xu, C.; Shen, X.; Ye, L. *J. Mater. Chem.* **2012**, *22*, 7427.
(22) Hardy, C. G.; Islam, Md. S.; Gonzalez-Delozier, D.; Morgan, J. E.; Cash, B.; Benicewicz, B. C.; Ploehn, H. J.; Tang, C. *Chem. Mater.* **2013**, *25*, 799.
(23) Rapakousiou, A.; Wang, Y.; Belin, C.; Pinaud, N.; Ruiz, J.; Astruc, D. *Inorg. Chem.* **2013**, *52*, 6685.
(24) Chen, Y.; Ye, Y.; Li, R.; Guo, Y.; Tan, H. *Fibers Polym.* **2013**, *14*, 1058.
(25) Takei, Y.; Murata, A.; Yamagishi, K.; Arai, S.; Nakamura, H.; Inoue, T.; Takeoka, S. *Chem. Commun.* **2013**, *49*, 7313.
(26) Jung, J.; Pang, X.; Feng, C.; Lin, Z. *Langmuir* **2013**, *29*, 8086.
(27) Meng, J.; Fokin, V. V.; Finn, M. G. *Tetrahedron Lett.* **2005**, *46*, 4543.
(28) Zhou, F.; Tan, C.; Tang, J.; Zhang, Y.-Y.; Gao, W.-M.; Wu, H.-H.; Yu, Y.-H.; Zhou, J. *J. Am. Chem. Soc.* **2013**, *135*, 10994.
(29) **Methyl 2-Cyano-2-(prop-2-yn-1-yl)pent-4-ynoate (1); Typical Procedure**
Methyl cyanoacetate (20 g, 202 mmol) was suspended in MeCN (600 mL). K_2CO_3 (69.7 g, 505 mmol) was added and the mixture was cooled in an ice bath. Propargyl bromide (49.5 mL, 444 mmol) was added, and the resulting orange suspension was heated at reflux temperature overnight. The deep yellow suspension was allowed to cool and worked up with H_2O (400 mL). The deep brown organic layer was separated, and the brown aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with H_2O (250 mL) and brine (250 mL), and dried over anhydrous $MgSO_4$. After evaporating the solvents, the resulting brown oil was purified by vacuum distillation at 115–125 °C to give methyl 2-cyano-2-(prop-2-yn-1-yl)pent-4-ynoate (**1**) as a colourless oil, which solidified to a white solid (25.1 g, 143 mmol, 71%). IR (neat): 3275, 2249 (nitrile), 1740 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3 H), 2.94 (d, *J* = 2.6 Hz, 4 H), 2.24 (t, *J* = 2.6 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 117.0, 76.0, 73.7, 54.1, 47.1, 25.6. HRMS (NSI): *m/z* $[M + NH_4]^+$ calcd for $C_{10}H_{13}O_2N_2$: 193.0972; found: 193.0971.
***tert*-Butyl 2-Cyano-2-(prop-2-yn-1-yl)pent-4-ynoate (2)**
Yield: 4.0 g (53%); pale solid. IR (neat): 3289, 2989, 2979, 1728 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.86 (d, *J* = 2.7 Hz, 4 H), 2.19 (t, *J* = 2.7 Hz, 2 H), 1.50 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 117.7, 85.5, 76.6, 73.6, 47.8, 27.9, 25.8. HRMS (NSI): *m/z* $[M + NH_4]^+$ calcd for $C_{13}H_{19}O_2N_2$: 235.1441; found: 235.1444.

Methyl 2-Acetyl-2-(prop-2-yn-1-yl)pent-4-ynoate (3)
Yield: 550 mg (31%); white solid. IR (neat): 3277, 2967, 1747 (C=O), 1712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.75 (s, 3 H), 2.90–2.95 (m, 4 H), 2.18 (s, 3 H), 2.00 (t, *J* = 2.7 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.9, 169.9, 78.6, 72.2, 62.6, 53.4, 26.3, 22.0. HRMS (NSI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{13}O_3$: 193.0859; found: 193.0859.

(30) *tert*-Butyl ethyl malonate (1 mL, 0.994 g, 5.28 mmol), propargyl bromide (2.1 mL, 18.85 mmol) and K_2CO_3 (2.82 g, 20.39 mmol) were combined in MeCN (20 mL). The yellow suspension was heated at reflux temperature overnight. The cooled reaction mixture was worked up with H_2O (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$ and the solvents evaporated. Crystallisation of the residue from EtOH gave crystals of the pure product, 1-*tert*-butyl 4-ethyl 2,2-di(prop-2-yn-1-yl)malonate (**4**) (262 mg, 0.99 mmol, 19%). IR (neat): 3284, 3262, 2983, 1728 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.19 (q, *J* = 7.1 Hz, 2 H), 2.90 (d, *J* = 2.6 Hz, 4 H), 1.99 (t, *J* = 2.6 Hz, 2 H), 1.41 (s, 9 H), 1.23 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.1, 167.7, 82.9, 78.9, 71.7, 62.0, 56.8, 27.9, 22.6, 14.3. HRMS (NSI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{20}O_4Na$: 287.1254; found: 287.1259.

(31) (a) Gommermann, N.; Gehrig, A.; Knochel, P. *Synlett* **2005**, 2796. (b) For an example with copper nanoparticles, see: Orgueira, H. A.; Fokas, D.; Isome, Y.; Chan, P. C.-M.; Baldino, C. M. *Tetrahedron Lett.* **2005**, *46*, 2911. (c) For an example with copper turnings, see: David, O.; Maisonneuve, S.; Xie, J. *Tetrahedron Lett.* **2007**, *48*, 6527.

(32) General procedure for method A: benzyl azide (1–2.5 equiv) and methyl 2-cyano-2-(prop-2-yn-1-yl)pent-4-ynoate (**1**) (1 g, 5.71 mmol) were dissolved in *t*-BuOH–H_2O (2:1 v/v) (for concentrations, see Table 1) and Cu powder (2 equiv) was added. The mixture was stirred at r.t. overnight and then diluted with H_2O. After filtration through Celite to remove the Cu powder, the resulting liquid was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O and brine and then dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure. Representative procedure for method B with in situ generation of the benzyl azide: NaN_3 (0.412 g, 6.34 mmol) was dissolved in DMSO (25 mL) with vigorous stirring. Benzyl bromide (0.830 mL, 6.98 mmol) was added, and the mixture stirred for 2 h. Methyl 2-cyano-2-(prop-2-yn-1-yl)pent-4-ynoate (**1**) (1 g, 5.71 mmol) and Cu powder (0.605 g, 9.51 mmol) were added, and the mixture stirred at r.t. overnight. The mixture was diluted with H_2O. After filtration through Celite to remove the Cu powder, the resulting liquid was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O and brine, and then dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure.

(33) Representative procedure for method C: methyl 2-cyano-2-(prop-2-yn-1-yl)pent-4-ynoate (**1**) (100 mg, 0.57 mmol), copper(I) iodide (16 mg, 0.064 mmol) and NaN_3 (46 mg, 0.705 mmol) were combined in a 5 mL microwave reactor vial. The solvent (*t*-BuOH–H_2O, 1:1, 4 mL) was added and the vial sealed. Benzyl bromide (0.076 mL, 0.64 mmol) was added through the septum, and the vessel was heated in a microwave reactor at 125 °C, 100 W, for 20 min. The cooled mixture was worked up with H_2O, and extracted with EtOAc. The combined organic layers were washed with H_2O and brine, and then dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure. The products were isolated by column chromatography, eluting with hexane–EtOAc (2:1), see references 38 and 39. .

(34) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223.

(35) Cravotto, G.; Mendicuti, F.; Martina, K.; Tagliapietra, S.; Robaldo, B.; Barge, A. *Synlett* **2008**, 2642.

(36) Simple diynes are known to form bis-triazoles by double CuAAC reactions, see: (a) Park, I. S.; Kwon, M. S.; Kim, Y.; Lee, J. S.; Park, J. *Org. Lett.* **2008**, *10*, 497. (b) Monkowius, U.; Ritter, S.; König, B.; Zabel, M.; Yersin, H. *Eur. J. Inorg. Chem.* **2007**, 4597. (c) Lee, B.-H.; Wu, C.-C.; Fang, X.; Liu, C. W.; Zhu, J.-L. *Catal. Lett.* **2013**, *143*, 572. (d) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853. (e) The control of mono- and bis-products from 1,3-butadiene has been studied: Aizpurua, J. M.; Azcune, I.; Fratila, R. M.; Balentova, E.; Sagartzazu-Aizpurua, M.; Miranda, J. I. *Org. Lett.* **2010**, *12*, 1584. Similar bis-triazole formation is possible in the CuAAC reactions of mono-alkynes though competing Glaser-type alkyne coupling processes: (f) Angell, Y.; Burgess, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 3649. (g) González, J.; Pérez, V. M.; Jiménez, D. O.; Lopez-Valdez, G.; Corona, D.; Cuevas-Yañez, E. *Tetrahedron Lett.* **2011**, *52*, 3514.

(37) (a) For an example of the formation of a bis-triazole from a glycine-derived *meso* bis-alkyne, see: Struthers, H.; Mindt, T. L.; Schibli, R. *Dalton Trans.* **2010**, *39*, 675. (b) Statistical mixtures of mono- and bis-triazoles have been reported previously for a 'click' reaction of a *meso*-diyne performed in the absence of a chiral ligand, see: Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 2210.

(38) **Methyl 2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-2-cyanopent-4-ynoate (5)**
For yields, see Table 1; mp 71–72 °C. IR (neat): 2249 (nitrile), 1748 (C=O), 1497 (C=C aromatic), 1455 (N=N), 1436 (C-H alkyne) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.49 (s, 1 H), 7.41–7.32 (m, 3 H), 7.26–7.21 (m, 2 H), 5.52 (s, 2 H), 3.80 (s, 3 H), 3.39 (s, 2 H), 2.93 (dd, *J* = 16.9, 2.6 Hz, 1 H), 2.81 (dd, *J* = 16.9, 2.6 Hz, 1 H), 2.22 (t, *J* = 2.6 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.2, 134.6, 129.1, 128.7, 128.2, 127.9, 123.3, 117.7, 76.7, 73.6, 54.1, 49.1, 32.2, 26.3. HRMS (NSI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{17}N_4O_2$: 309.1346; found: 309.1345.

(39) **Methyl 3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-2-cyanopropanoate (6)**
For yields, see Table 1. IR (neat): 3132, 3065, 3035, 2997, 2962, 2246 (nitrile), 1740 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53 (s, 2 H), 7.28–7.20 (m, 6 H), 7.09–7.15 (m, 4 H), 5.39 (s, 4 H), 3.58 (s, 3 H), 3.24–3.20 (m, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.1, 134.9, 129.2, 128.8, 128.4, 128.1, 123.6, 118.5, 54.2, 53.9, 50.4, 32.4. HRMS (NSI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{24}N_7O_2$: 442.1986; found: 442.1984.

(40) Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413.

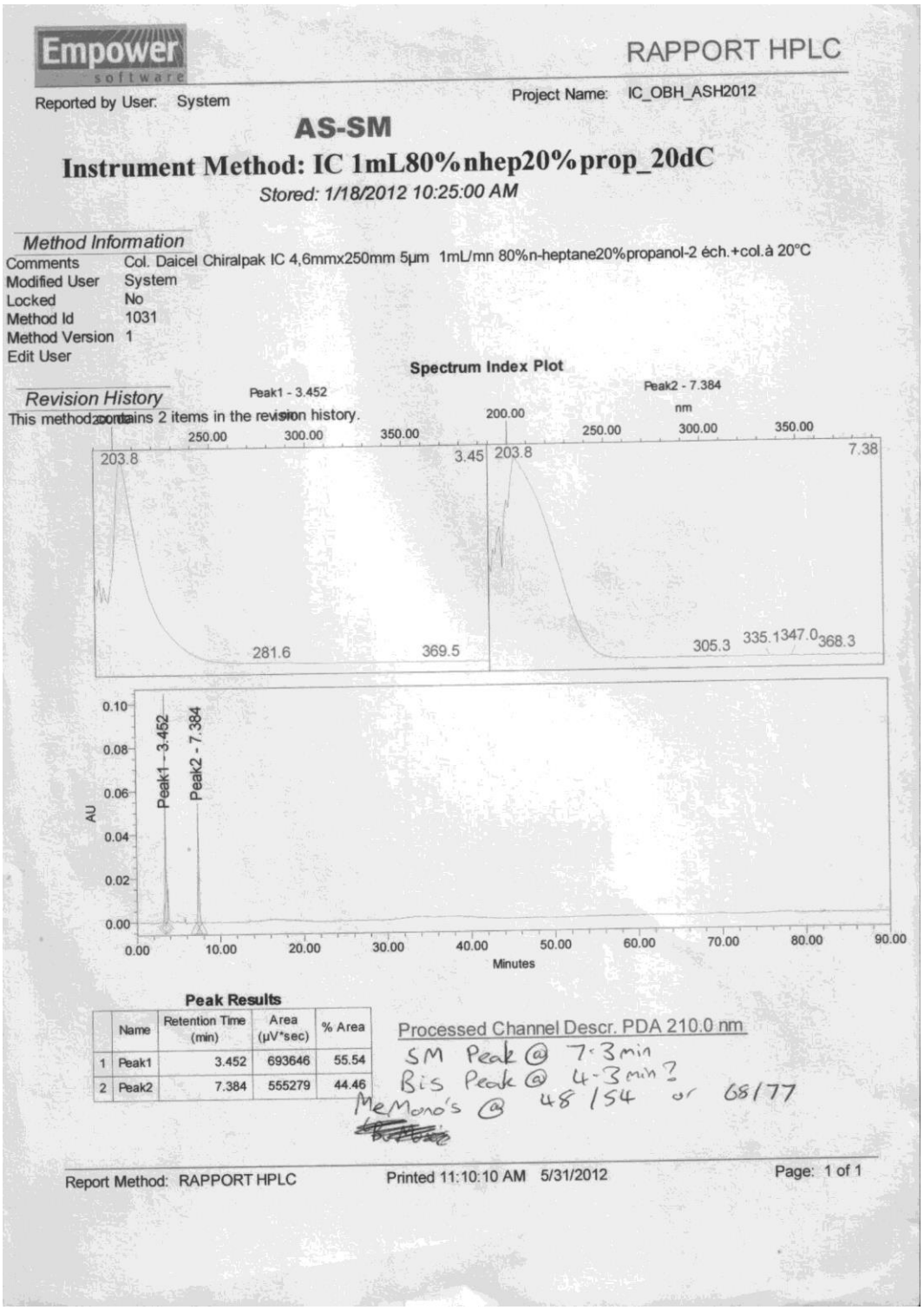
(41) (*R*,*R*)-NORPHOS (0.017 g, 0.038 mmol) and copper(I) iodide (4.76 mg, 0.025 mmol) were combined in toluene (5 mL). DIPEA (0.13 mL, 0.750 mmol) was added, and the mixture was allowed to stir at r.t. to allow the complex to form. The mixture was then cooled to –40 °C and methyl 2-cyano-2-(prop-2-yn-1-yl)pent-4-ynoate (**1**) (0.044 g, 0.250 mmol) and benzyl azide (0.031 mL, 0.25 mmol) were added, and the mixture stirred at –40 °C for 18 h. The mixture was filtered through silica while still cold, to prevent any further reaction occurring, and the silica pad was washed through with CH_2Cl_2 (5 mL). The solvents were evaporated, and the residue was analysed by NMR spectroscopy.

(42) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.

(43) (a) Gaumont, A.-C.; Gulea, M.; Masson, S. unpublished results. (b) For the isopropyl example of this ligand series, see: Abrunhosa, I.; Delain-Bioton, L.; Gaumont, A.-C.; Gulea, M.; Masson, S. *Tetrahedron* **2004**, *60*, 9263. (c) See also: Gaumont, A.-C.; Gulea, M.; Levillain, J. *Chem. Rev.* **2009**, *109*, 1371.

REACTIONS UNDER RACEMIC CONDITIONS

TERT-BUTYL CYANOACETATE *BIS*-ALKYNE



Empower software

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS-SM

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

Method Information

Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot

Peak1 - 3.452 Peak2 - 7.384

nm

200.00 250.00 300.00 350.00 200.00 250.00 300.00 350.00

203.8 3.45 203.8 7.38

281.6 369.5 305.3 335.1 347.0 368.3

AU

0.10 0.08 0.06 0.04 0.02 0.00

Peak1 - 3.452 Peak2 - 7.384

0.00 10.00 20.00 30.00 40.00 50.00 60.00 70.00 80.00 90.00

Minutes

Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	3.452	693646	55.54
2	Peak2	7.384	555279	44.46

Processed Channel Descr. PDA 210.0 nm

SM Peak @ 7.3 min

Bis Peak @ 4.3 min ?

MeMono's @ 48/54 or 68/77

Report Method: RAPPORT HPLC

Printed 11:10:10 AM 5/31/2012

Page: 1 of 1

Empower software

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS-BIS

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

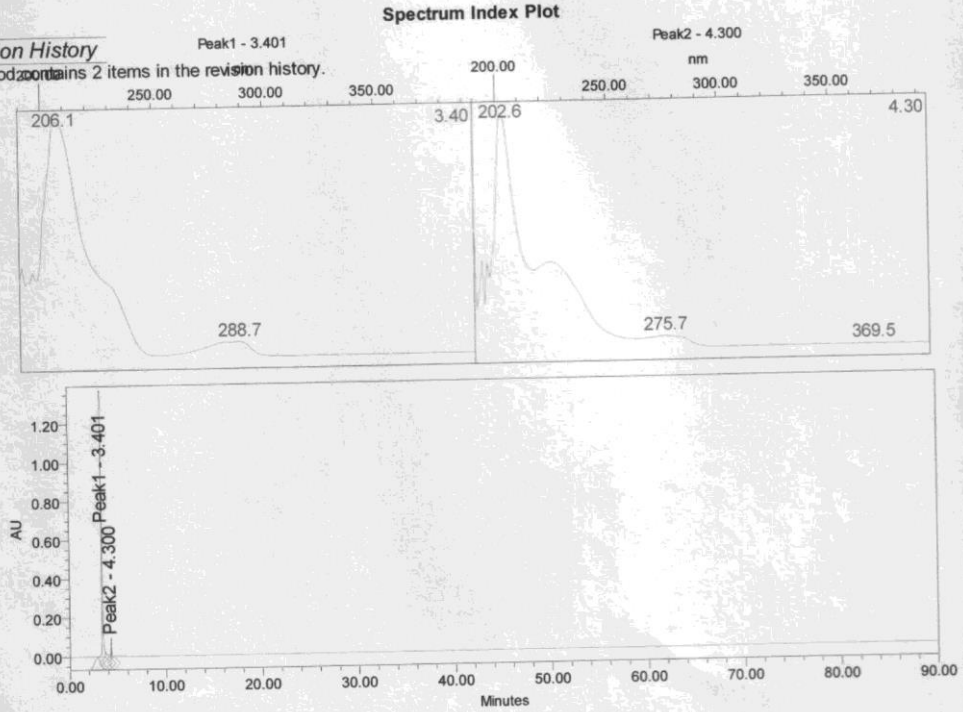
Method Information

Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot



Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	3.401	8999397	95.68
2	Peak2	4.300	406574	4.32

Processed Channel Descr. PDA 210.0 nm

Report Method: RAPPORT HPLC

Printed 11:10:10 AM 5/31/2012

Page: 1 of 1

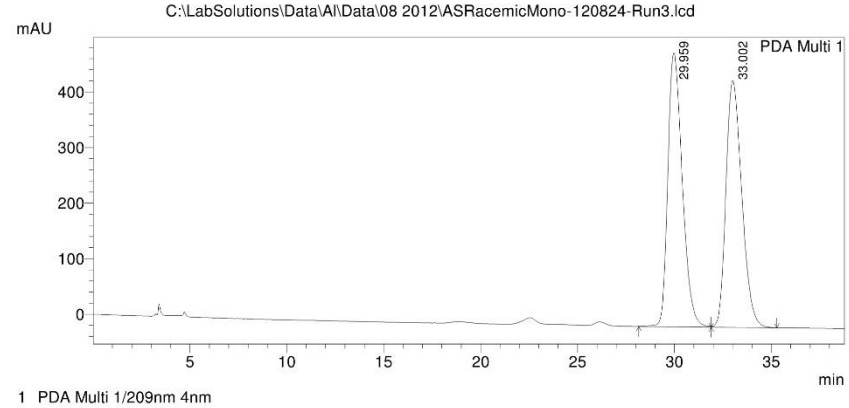
==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\AI\Data\08 2012\ASRacemicMono-120824-Run3.lcd

Acquired by	: Admin
Sample Name	: AS-RacemicMono
Sample ID	: INJ3
Tray#	: 1
Vail #	: 2
Injection Volume	: 10 uL
Data File Name	: ASRacemicMono-120824-Run3.lcd
Method File Name	: 70 Hexane, 30 IPA, 1ml-min 60min.lcm
Batch File Name	: 180812 Batch 1.lcb
Report File Name	: Default.lcr
Data Acquired	: 8/24/2012 9:31:31 AM
Data Processed	: 8/30/2012 11:05:49 AM

<Chromatogram>

C:\LabSolutions\Data\AI\Data\08 2012\ASRacemicMono-120824-Run3.lcd



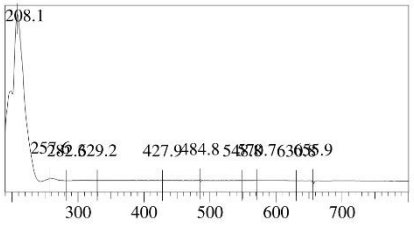
1 PDA Multi 1/209nm 4nm

Quantitative Results

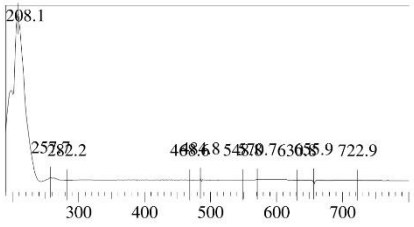
PDA

ID#	Name	Ret. Time	Area	Height	Conc.
1	RT29.959	29.959	25620964	493071	50.334
2	RT33.002	33.002	25280536	444489	49.666

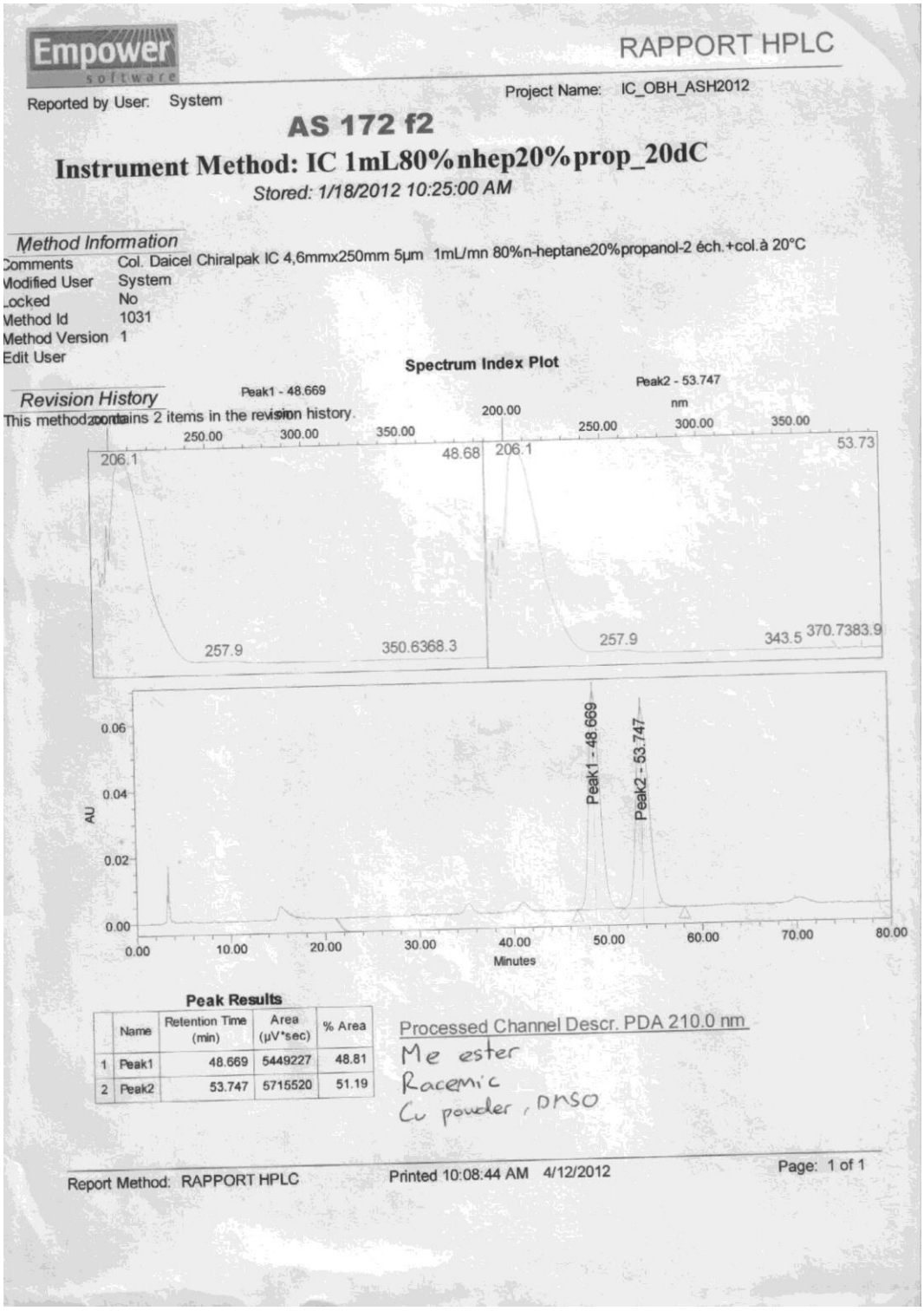
Peak 1



Peak 2



C:\LabSolutions\Data\AI\Data\08 2012\ASRacemicMono-120824-Run3.lcd



Empower software

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS 172 f2

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

Method Information

Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot

Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	48.669	5449227	48.81
2	Peak2	53.747	5715520	51.19

Processed Channel Descr. PDA 210.0 nm

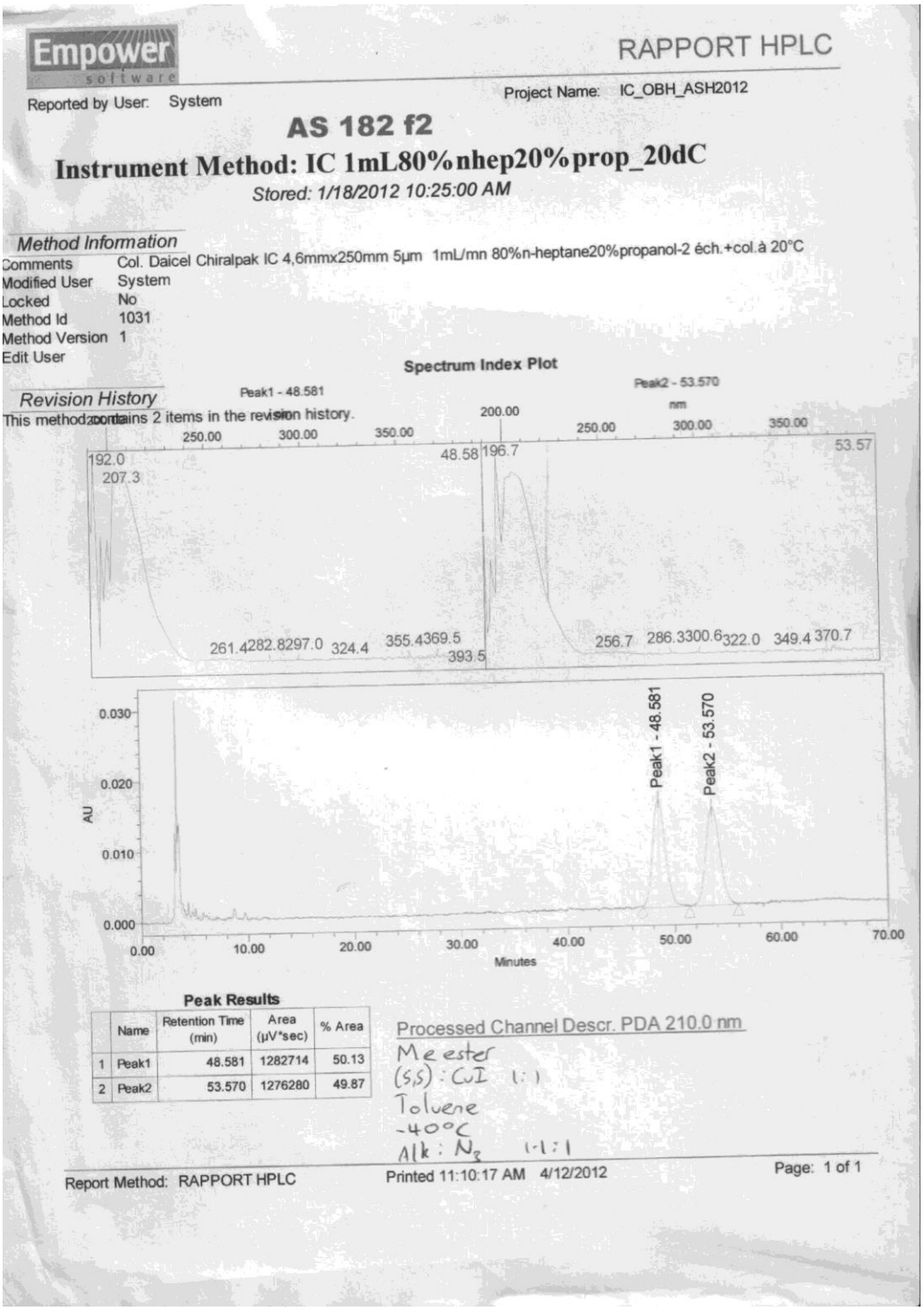
Me ester
Racemic
Cu powder, DMSO

Report Method: RAPPORT HPLC

Printed 10:08:44 AM 4/12/2012

Page: 1 of 1

METHYL ALKYNE WITH BENZYL AZIDE USING (*S,S*)-LIGAND



Empower software

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS 182 f2

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

Method Information

Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot

Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	48.581	1282714	50.13
2	Peak2	53.570	1276280	49.87

Processed Channel Descr. PDA 210.0 nm

Me ester
(S,S) : CuI 1:1
Toluene
-40°C
Alk : N_3 1-1:1

Report Method: RAPPORT HPLC

Printed 11:10:17 AM 4/12/2012

Page: 1 of 1

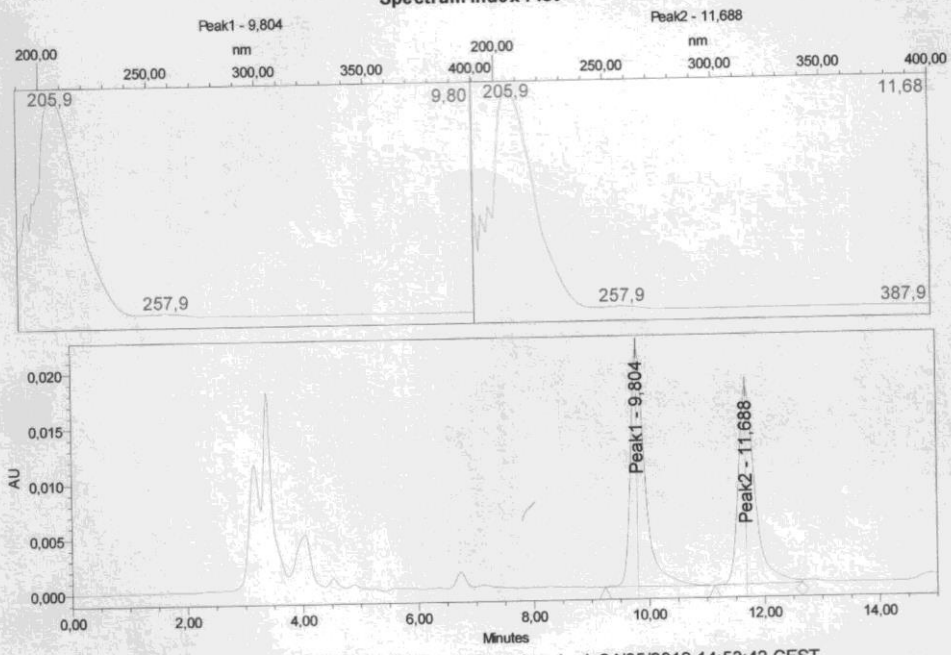
Empower2 software

rapport

SAMPLE INFORMATION

Sample Name:	AS190	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	UI
Vial:	1	Acq. Method Set:	PM IA 1ml 8020 hept_Prop2 20dc
Injection #:	1	Processing Method:	3
Injection Volume:	10,00 ul	Channel Name:	210,0nm
Run Time:	15,0 Minutes	Proc. Chnl. Descr.:	PDA 210,0 nm
Date Acquired:	24/05/2012 14:53:42 CEST		
Date Processed:	24/05/2012 15:16:33 CEST		

Spectrum Index Plot



SampleName: AS190; Vial: 1; Injection: 1; Date Acquired: 24/05/2012 14:53:42 CEST

tBu ester
(S,S) :CuI 2:1
Toluene
-40°C
Alk:N_3 1·1·1

Peak Results

	Name	RT	Area	% Area
1	Peak1	9,804	381709	51,34
2	Peak2	11,688	361790	48,66

2·7% ee

Reported by User: System
Report Method: rapport
Report Method ID 1032
Page: 1 of 1

Project Name: IA-ODH-OJH 2012
Date Printed:
24/05/2012
15:50:05 Europe/Paris

Empower software

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS199

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

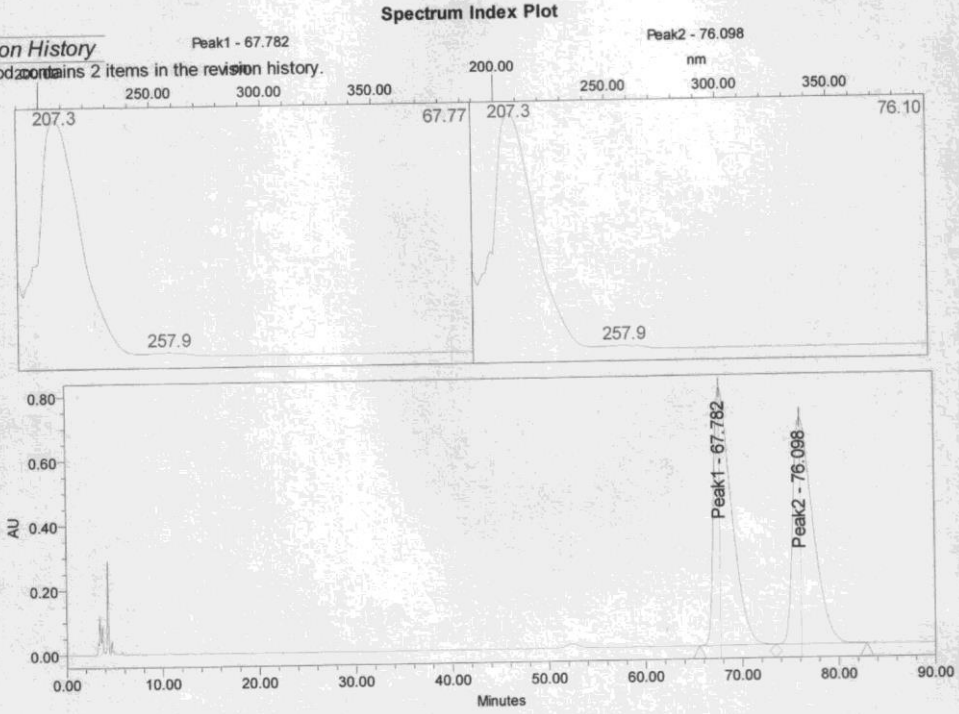
Method Information

Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot

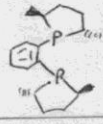


Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	67.782	103498183	50.36
2	Peak2	76.098	102022604	49.64

Processed Channel Descr. PDA 210.0 nm

Me ester

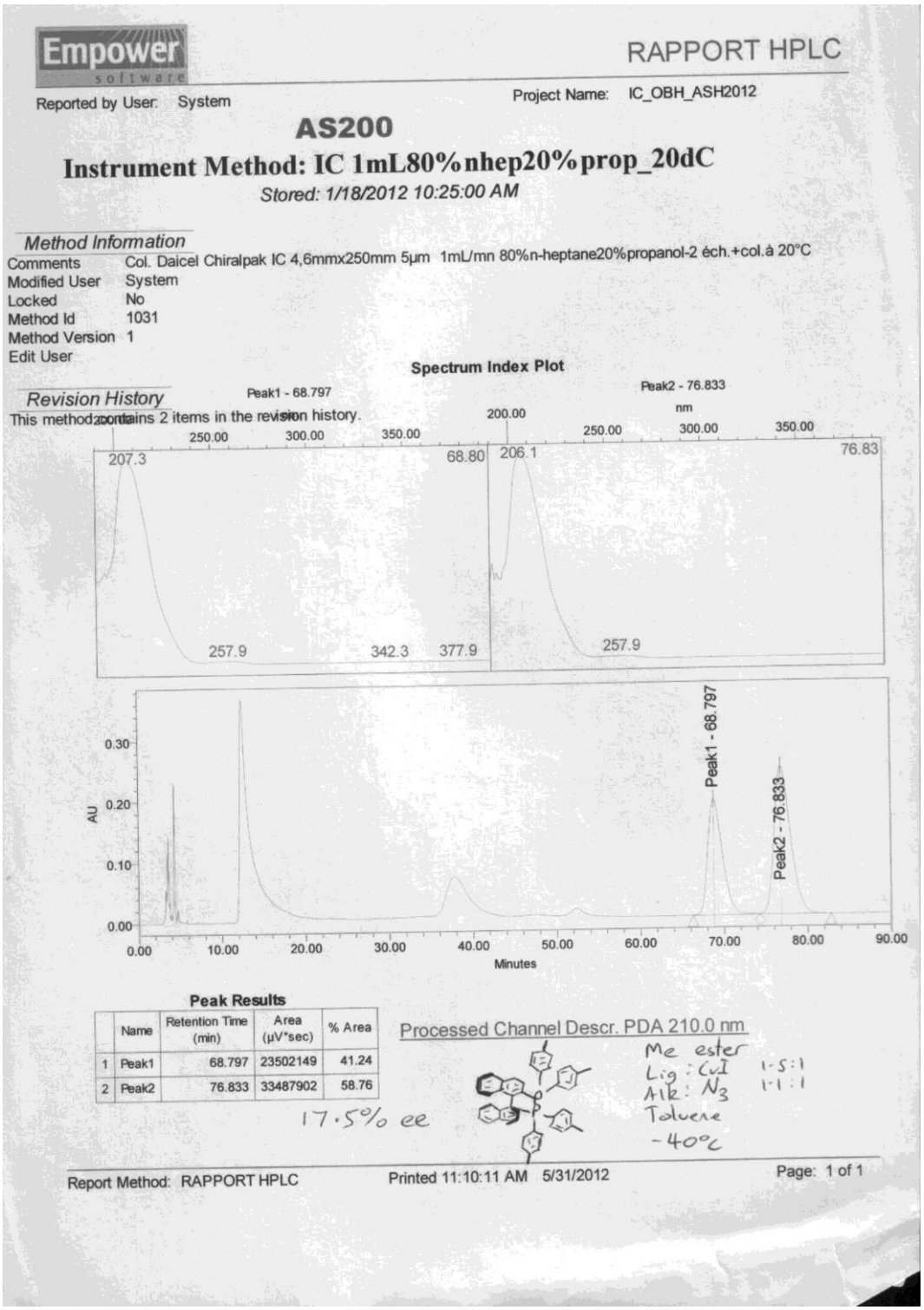


(S,S) 1·5:1 Ligand CuI Toluene

Report Method: RAPPORT HPLC

Printed 11:10:11 AM 5/31/2012 -40°C

Page: 1 of 1



Empower software

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS200

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

Method Information

Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot

Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	68.797	23502149	41.24
2	Peak2	76.833	33487902	58.76

17.5% ee

Processed Channel Descr. PDA 210.0 nm

Me ester
Lig : CuI 1-5:1
Alk : N_3 1-1:1
Toluene
-40°C

Report Method: RAPPORT HPLC

Printed 11:10:11 AM 5/31/2012

Page: 1 of 1

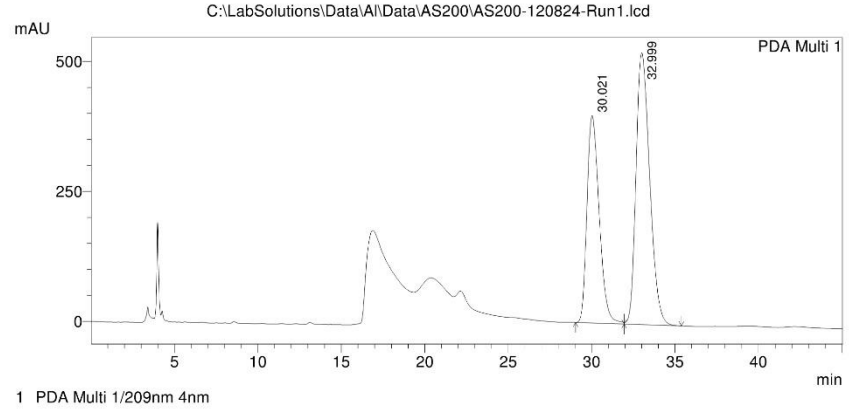
==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\AI\Data\AS200\AS200-120824-Run1.lcd

Acquired by	: Admin
Sample Name	: AS200
Sample ID	: INJ1
Tray#	: 1
Vail #	: 3
Injection Volume	: 10 uL
Data File Name	: AS200-120824-Run1.lcd
Method File Name	: 70 Hexane, 30 IPA, 1ml-min 45 min.lcm
Batch File Name	:
Report File Name	: REPORT-FORMAT.lcr
Data Acquired	: 8/24/2012 10:15:21 AM
Data Processed	: 8/30/2012 10:32:10 AM

<Chromatogram>

C:\LabSolutions\Data\AI\Data\AS200\AS200-120824-Run1.lcd



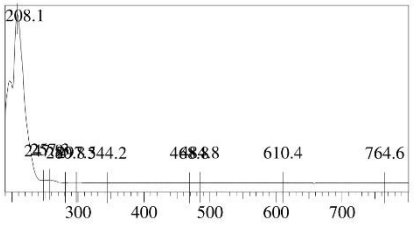
1 PDA Multi 1/209nm 4nm

Quantitative Results

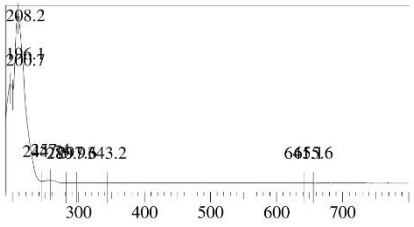
PDA

ID#	Name	Ret. Time	Area	Height	Conc.
1	RT30.021	30.021	20275053	398747	40.412
2	RT32.999	32.999	29896272	522529	59.588

Peak 1



Peak 2



C:\LabSolutions\Data\AI\Data\AS200\AS200-120824-Run1.lcd

Empower software

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS201

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

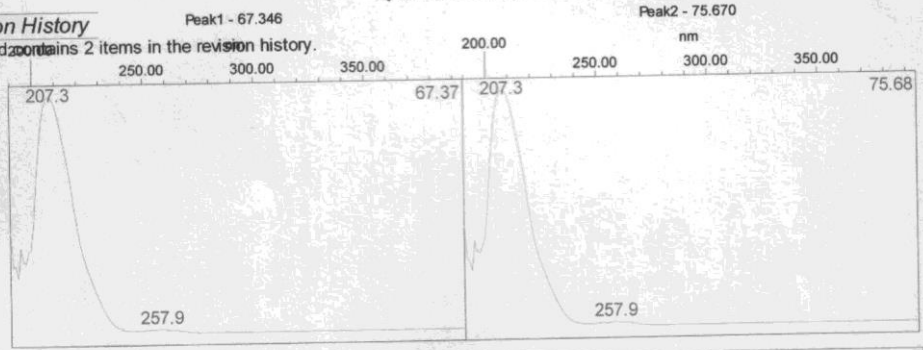
Method Information

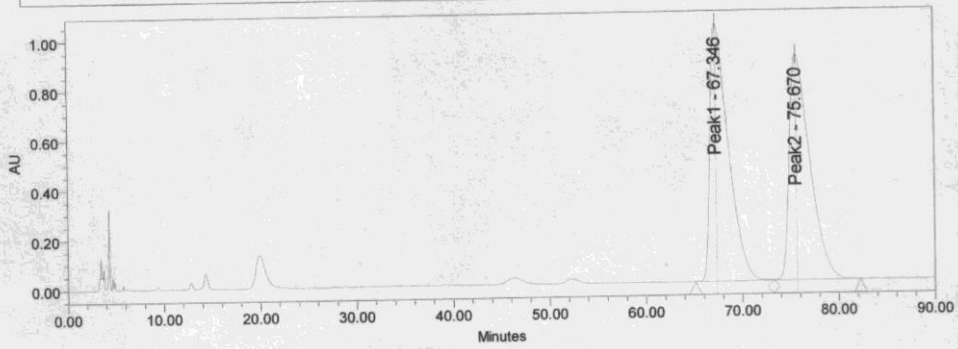
Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot

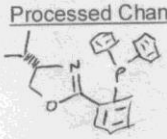




Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	67.346	138318825	50.64
2	Peak2	75.670	134811213	49.36

Processed Channel Descr. PDA 210.0 nm



Me ester 1·5:1
Ligand: CuI 1·1:1
Alk: N_3
Toluene
-40°C

Report Method: RAPPORT HPLC Printed 11:10:11 AM 5/31/2012 Page: 1 of 1

Empower software

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS202

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

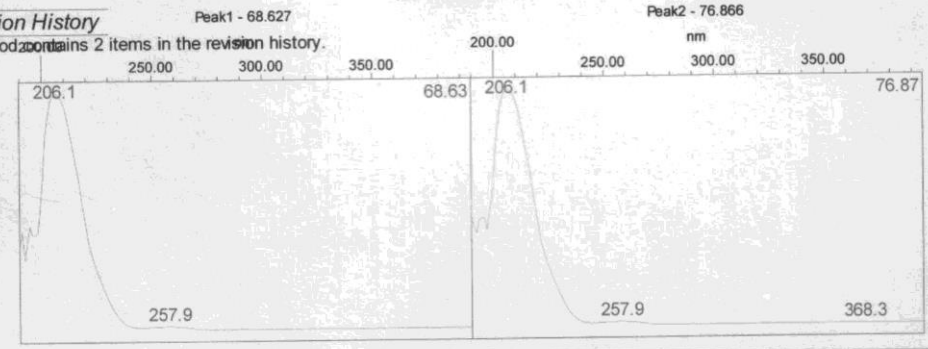
Method Information

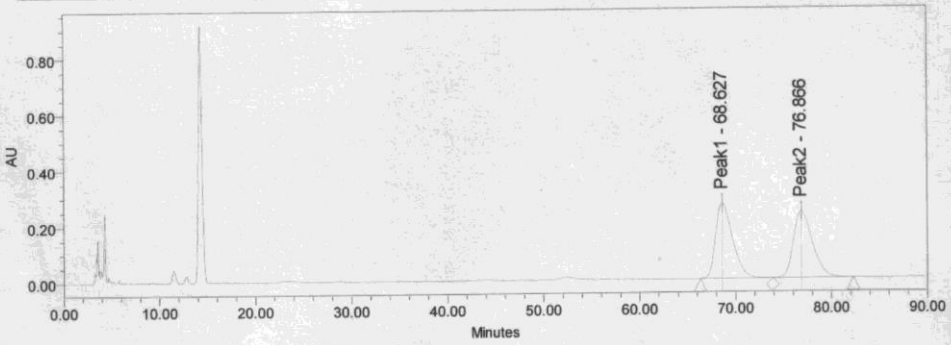
Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot

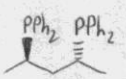




Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	68.627	33124967	50.17
2	Peak2	76.866	32905387	49.83

Processed Channel Descr. PDA 210.0 nm



Me ester
Lig: CuI 1·5:1
Alk: N_3 1·1:1
Toluene
-40°C

Report Method: RAPPORT HPLC

Printed 11:10:10 AM 5/31/2012

Page: 1 of 1

Empower software

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS203

Instrument Method: IC 1mL80%nhep20%prop_20dC

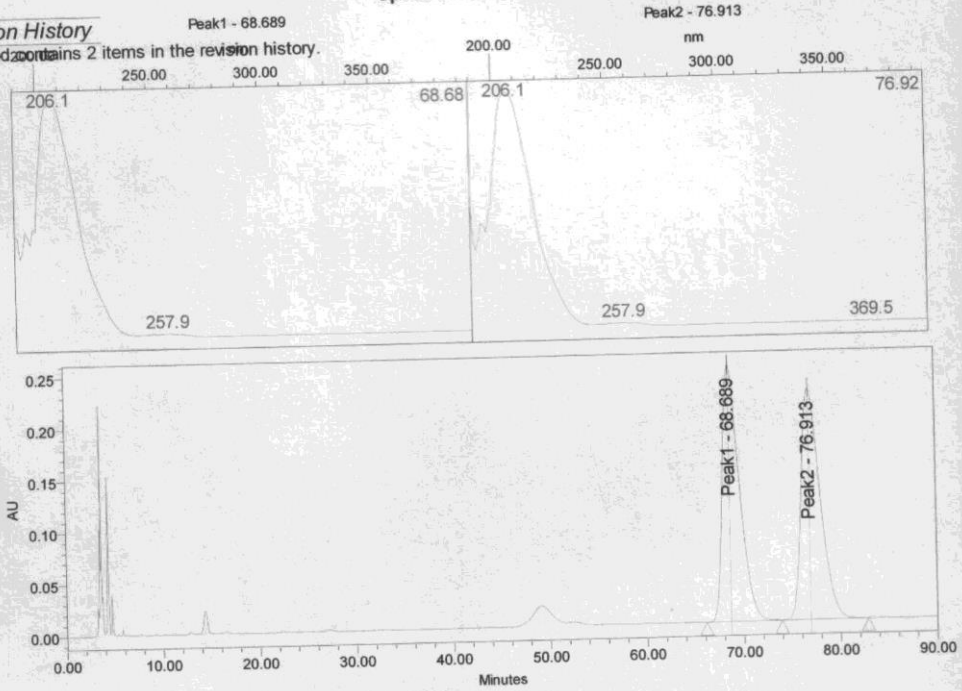
Stored: 1/18/2012 10:25:00 AM

Method Information

Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.



Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	68.689	30578986	49.85
2	Peak2	76.913	30760392	50.15

Processed Channel Descr. PDA 210.0 nm

Report Method: RAPPORT HPLC Printed 3:11:36 PM 6/11/2012 Page: 1 of 1

Empower software L3

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS205

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

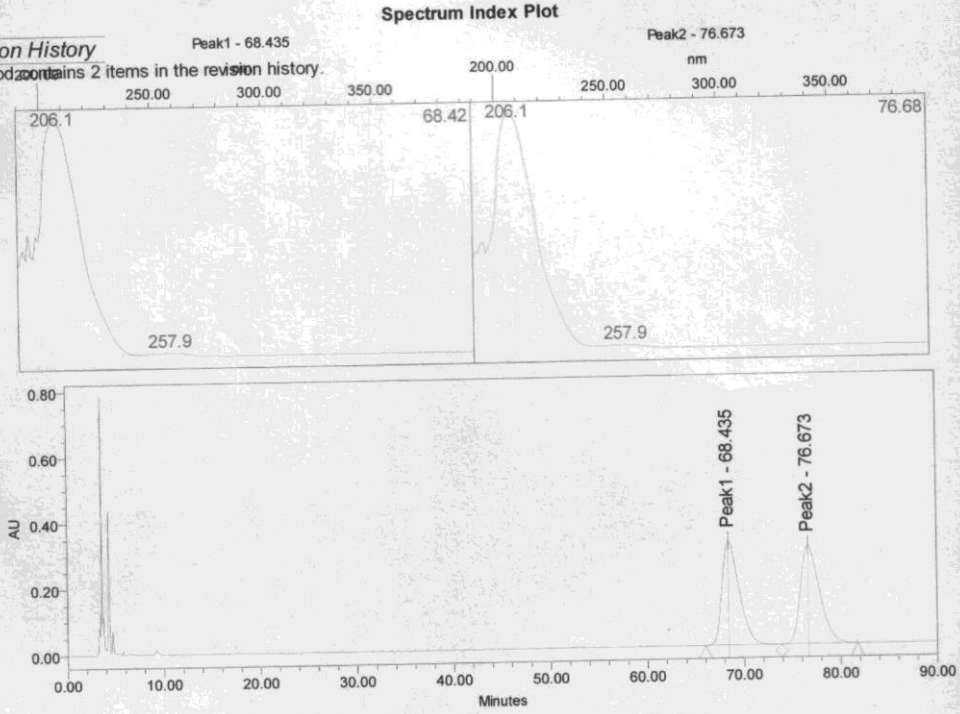
Method Information

Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot



Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	68.435	38916995	48.66
2	Peak2	76.673	41062927	51.34

Processed Channel Descr. PDA 210.0 nm

Report Method: RAPPORT HPLC Printed 3:11:36 PM 6/11/2012 Page: 1 of 1

Empower software

L4 Thiazoline.

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS206

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

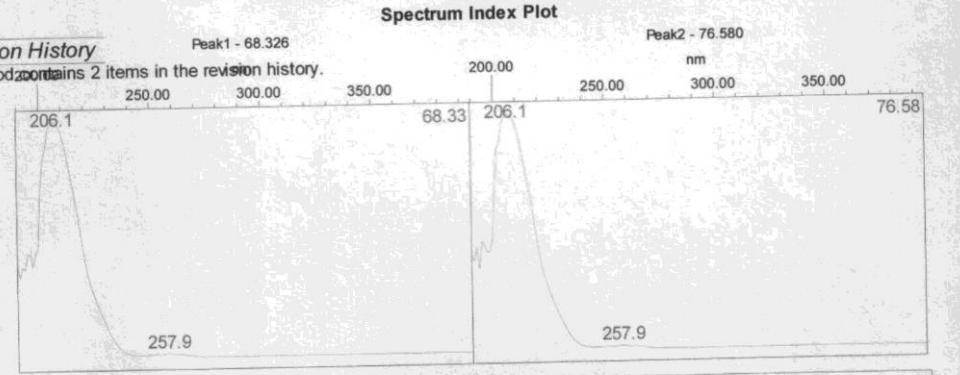
Method Information

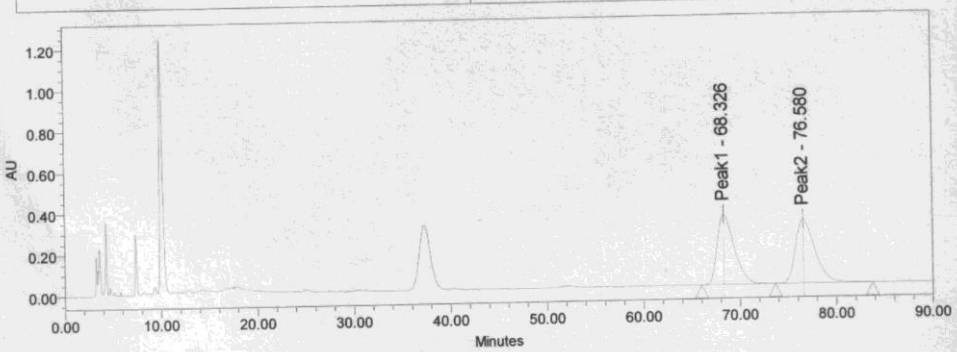
Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot





Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	68.326	41931521	49.09
2	Peak2	76.580	43479485	50.91

Processed Channel Descr. PDA 210.0 nm

Report Method: RAPPORT HPLC Printed 3:12:06 PM 6/11/2012 Page: 1 of 1

Empower software

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS211

Instrument Method: IC 1mL80%nhep20%prop_20dC

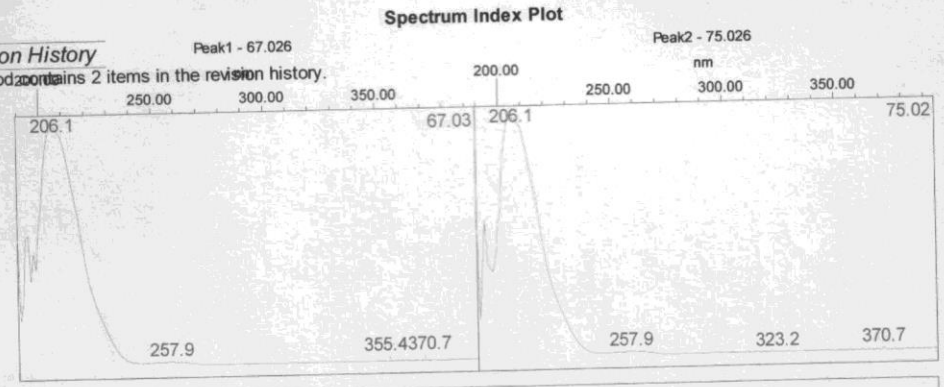
Stored: 1/18/2012 10:25:00 AM

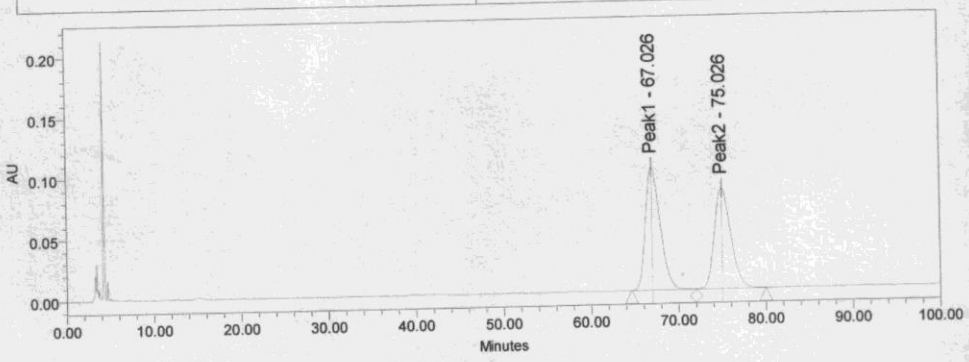
Method Information

Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.



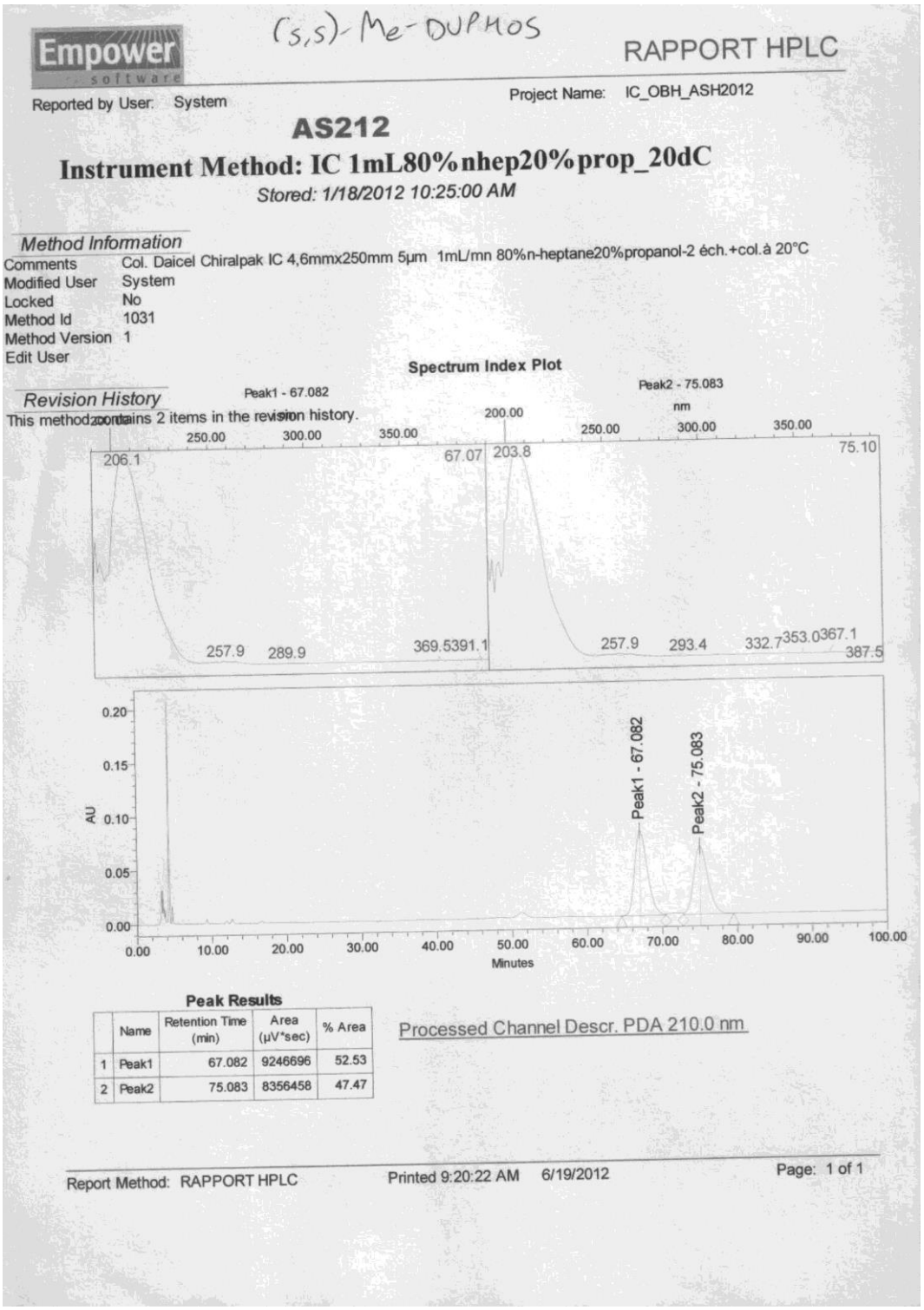


Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	67.026	11901799	52.21
2	Peak2	75.026	10892947	47.79

Processed Channel Descr. PDA 210.0 nm

Report Method: RAPPORT HPLC Printed 9:20:55 AM 6/19/2012 Page: 1 of 1



(S,S)-Me-DUPHOS

Empower software

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS212

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

Method Information

Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot

Peak1 - 67.082

Peak2 - 75.083

nm

206.1 67.07 203.8 75.10

257.9 289.9 369.5391.1 257.9 293.4 332.7353.0367.1 387.5

AU

Peak1 - 67.082

Peak2 - 75.083

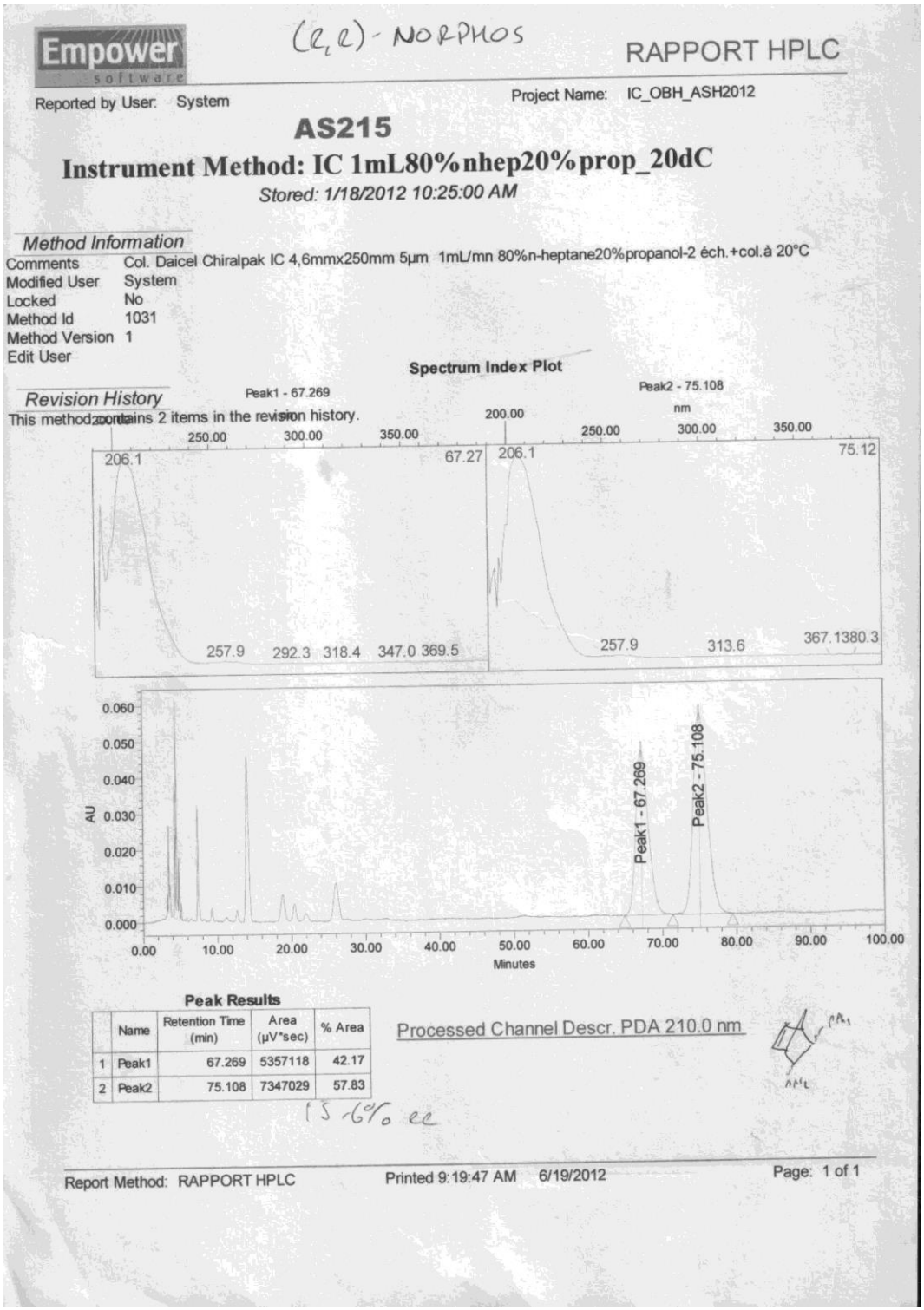
Minutes

Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	67.082	9246696	52.53
2	Peak2	75.083	8356458	47.47

Processed Channel Descr. PDA 210.0 nm

Report Method: RAPPORT HPLC Printed 9:20:22 AM 6/19/2012 Page: 1 of 1



Empower software

(R,R)-NORPHOS

RAPPORT HPLC

Reported by User: System

Project Name: IC_OBH_ASH2012

AS215

Instrument Method: IC 1mL80%nhep20%prop_20dC

Stored: 1/18/2012 10:25:00 AM

Method Information

Comments	Col. Daicel Chiralpak IC 4,6mmx250mm 5µm 1mL/mn 80%n-heptane20%propanol-2 éch.+col.à 20°C
Modified User	System
Locked	No
Method Id	1031
Method Version	1
Edit User	

Revision History

This method contains 2 items in the revision history.

Spectrum Index Plot

Peak1 - 67.269 | Peak2 - 75.108

nm

206.1 67.27 257.9 292.3 318.4 347.0 369.5

206.1 75.12 257.9 313.6 367.1380.3

AU

Peak1 - 67.269

Peak2 - 75.108

Minutes

Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Peak1	67.269	5357118	42.17
2	Peak2	75.108	7347029	57.83

Processed Channel Descr. PDA 210.0 nm

15 -6% ee

Report Method: RAPPORT HPLC

Printed 9:19:47 AM 6/19/2012

Page: 1 of 1

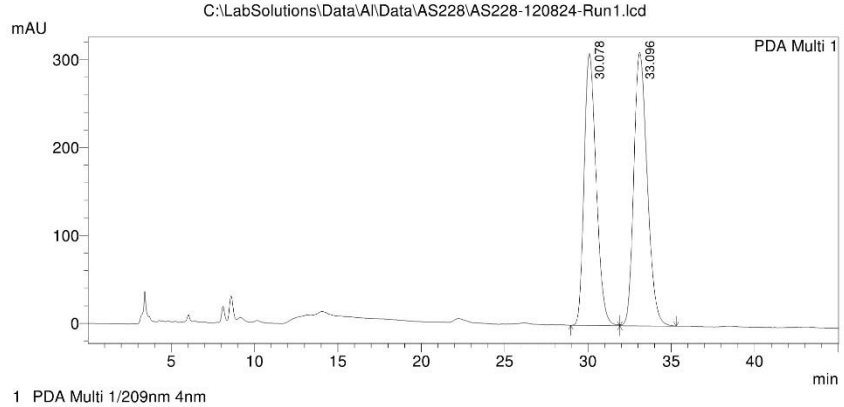
==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\AI\Data\AS228\AS228-120824-Run1.lcd

Acquired by	: Admin
Sample Name	: AS228
Sample ID	: INJ1
Tray#	: 1
Vail #	: 7
Injection Volume	: 10 uL
Data File Name	: AS228-120824-Run1.lcd
Method File Name	: 70 Hexane, 30 IPA, 1ml-min 45 min.lcm
Batch File Name	: 180812 Batch 1.lcb
Report File Name	: Default.lcr
Data Acquired	: 8/24/2012 1:35:16 PM
Data Processed	: 8/24/2012 2:23:39 PM

<Chromatogram>

C:\LabSolutions\Data\AI\Data\AS228\AS228-120824-Run1.lcd



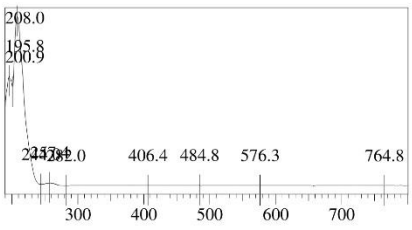
1 PDA Multi 1/209nm 4nm

Quantitative Results

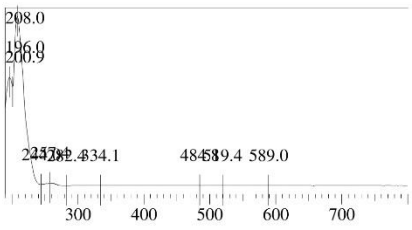
PDA

ID#	Name	Ret. Time	Area	Height	Conc.
1	RT30.078	30.078	15544743	309282	47.159
2	RT33.096	33.096	17417440	310831	52.841

Peak 1



Peak 2



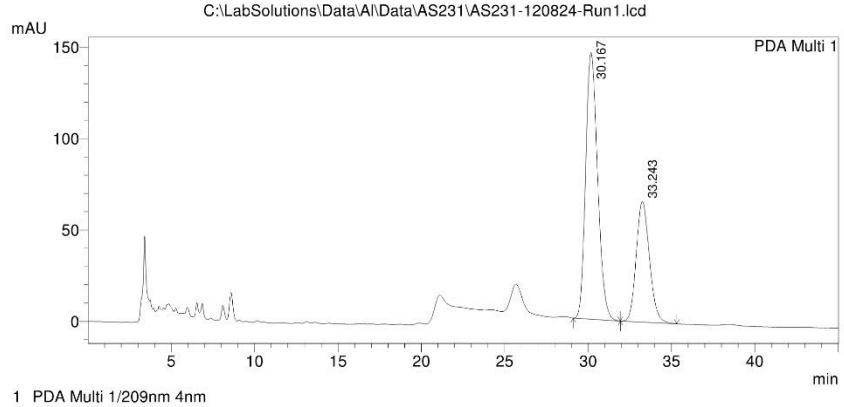
==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\AI\Data\AS231\AS231-120824-Run1.lcd

Acquired by	: Admin
Sample Name	: AS231
Sample ID	: INJ1
Tray#	: 1
Vail #	: 9
Injection Volume	: 10 uL
Data File Name	: AS231-120824-Run1.lcd
Method File Name	: 70 Hexane, 30 IPA, 1ml-min 45 min.lcm
Batch File Name	: 180812 Batch 1.lcb
Report File Name	: Default.lcr
Data Acquired	: 8/24/2012 3:06:25 PM
Data Processed	: 8/24/2012 4:46:09 PM

<Chromatogram>

C:\LabSolutions\Data\AI\Data\AS231\AS231-120824-Run1.lcd



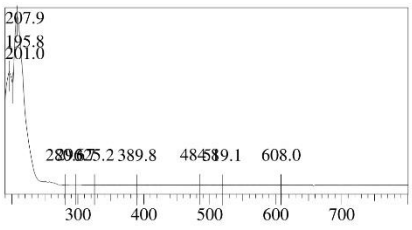
1 PDA Multi 1/209nm 4nm

Quantitative Results

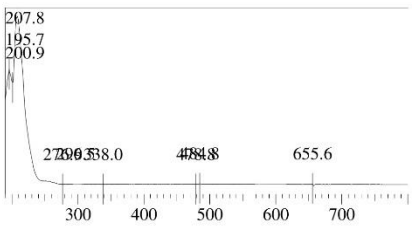
PDA

ID#	Name	Ret. Time	Area	Height	Conc.
1	RT30.167	30.167	7258255	145850	66.536
2	RT33.243	33.243	3650576	65966	33.464

Peak 1



Peak 2



C:\LabSolutions\Data\AI\Data\AS231\AS231-120824-Run1.lcd

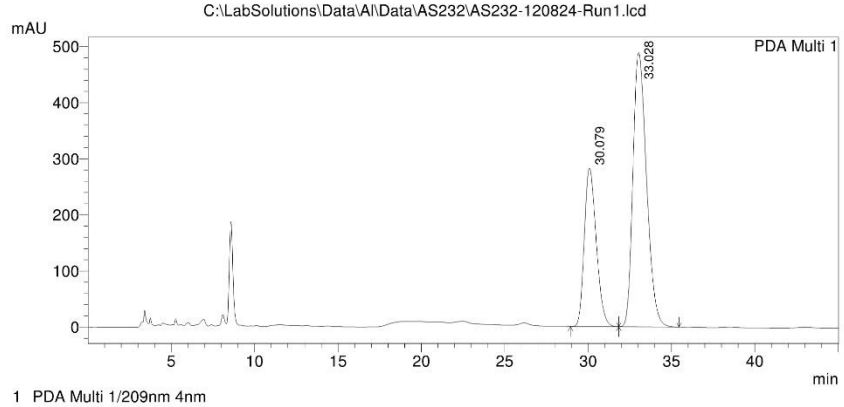
==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\AI\Data\AS232\AS232-120824-Run1.lcd

Acquired by	: Admin
Sample Name	: AS232
Sample ID	: INJ1
Tray#	: 1
Vail #	: 10
Injection Volume	: 10 uL
Data File Name	: AS232-120824-Run1.lcd
Method File Name	: 70 Hexane, 30 IPA, 1ml-min 45 min.lcm
Batch File Name	: 180812 Batch 1.lcb
Report File Name	: Default.lcr
Data Acquired	: 8/24/2012 3:51:58 PM
Data Processed	: 8/24/2012 5:13:36 PM

<Chromatogram>

C:\LabSolutions\Data\AI\Data\AS232\AS232-120824-Run1.lcd



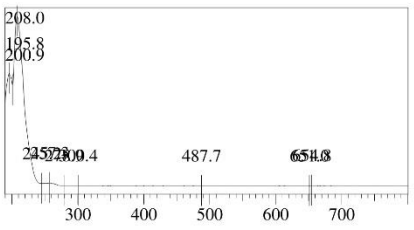
1 PDA Multi 1/209nm 4nm

Quantitative Results

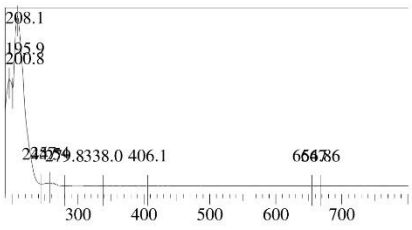
PDA

ID#	Name	Ret. Time	Area	Height	Conc.
1	RT30.079	30.079	14075357	282226	33.642
2	RT33.028	33.028	27763534	488727	66.358

Peak 1



Peak 2



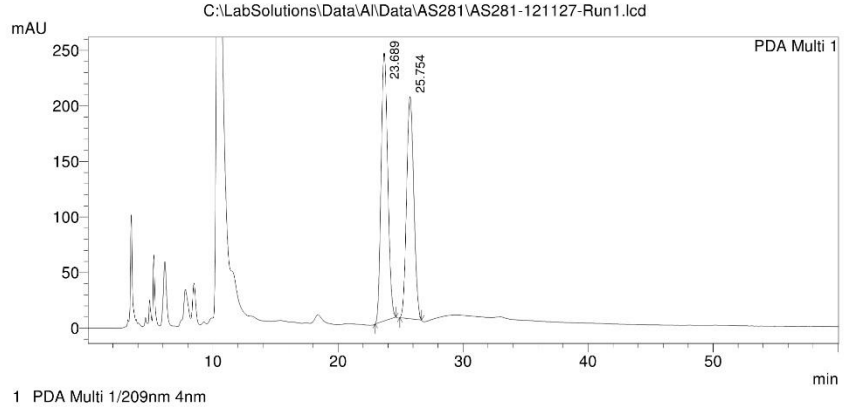
==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\AI\Data\AS281\AS281-121127-Run1.lcd

Acquired by	: Admin
Sample Name	: AS281
Sample ID	: INJ1
Tray#	: 1
Vail #	: 5
Injection Volume	: 10 uL
Data File Name	: AS281-121127-Run1.lcd
Method File Name	: 70 Hexane, 30 IPA, 1ml-min 60min.lcm
Batch File Name	: 240912 Batch 1.lcb
Report File Name	: REPORT-FORMAT.lcr
Data Acquired	: 11/27/2012 8:56:41 PM
Data Processed	: 11/27/2012 9:56:48 PM

<Chromatogram>

C:\LabSolutions\Data\AI\Data\AS281\AS281-121127-Run1.lcd



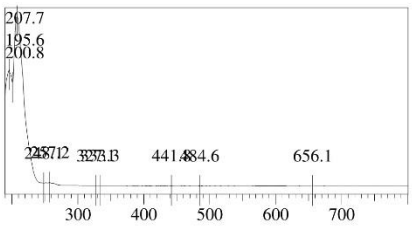
1 PDA Multi 1/209nm 4nm

Quantitative Results

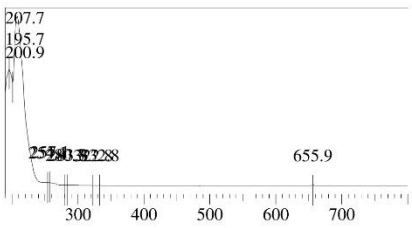
PDA

ID#	Name	Ret. Time	Area	Height	Conc.
1	RT23.689	23.689	8912538	241531	52.599
2	RT25.754	25.754	8031909	200164	47.401

Peak 1



Peak 2

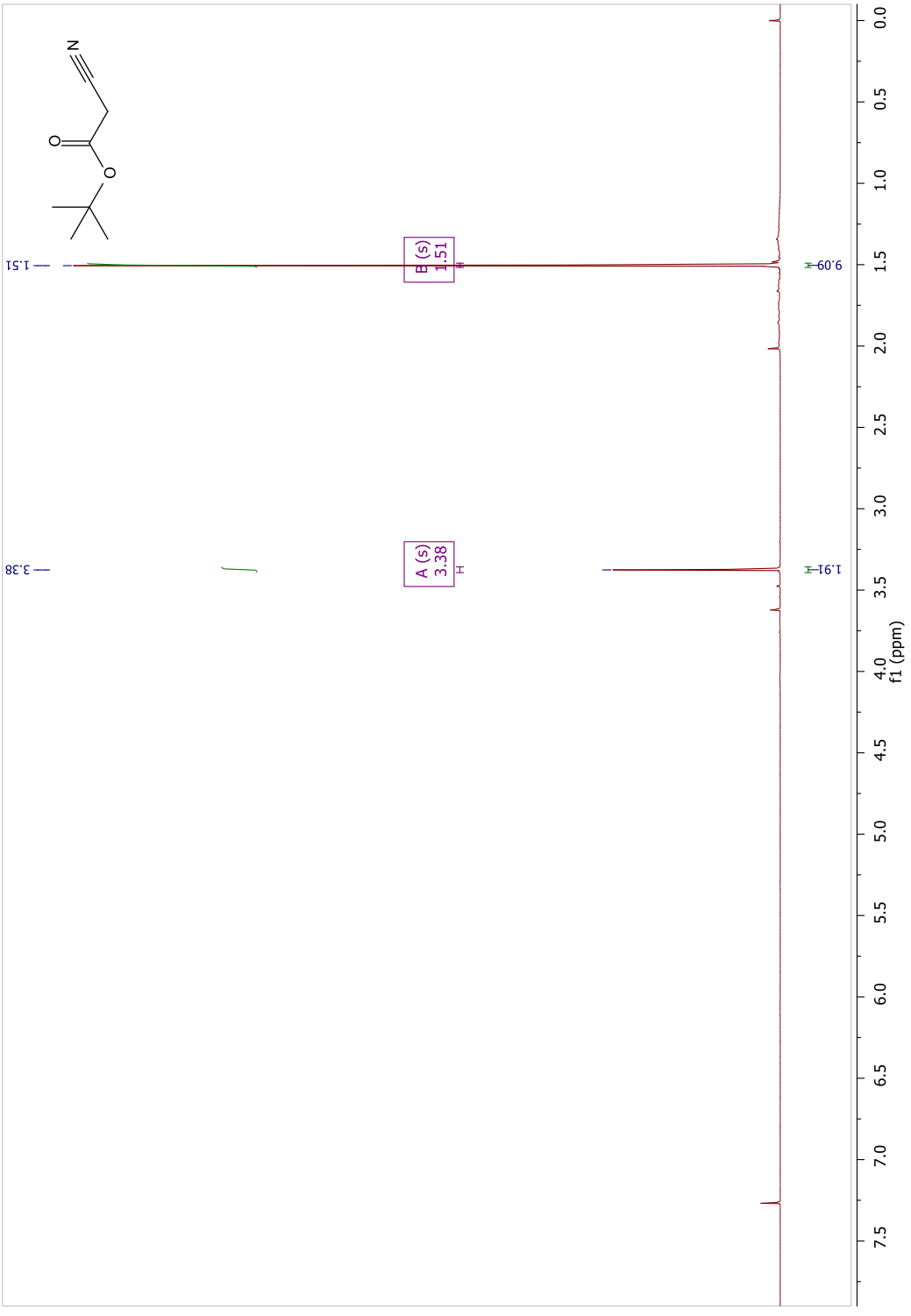


C:\LabSolutions\Data\AI\Data\AS281\AS281-121127-Run1.lcd

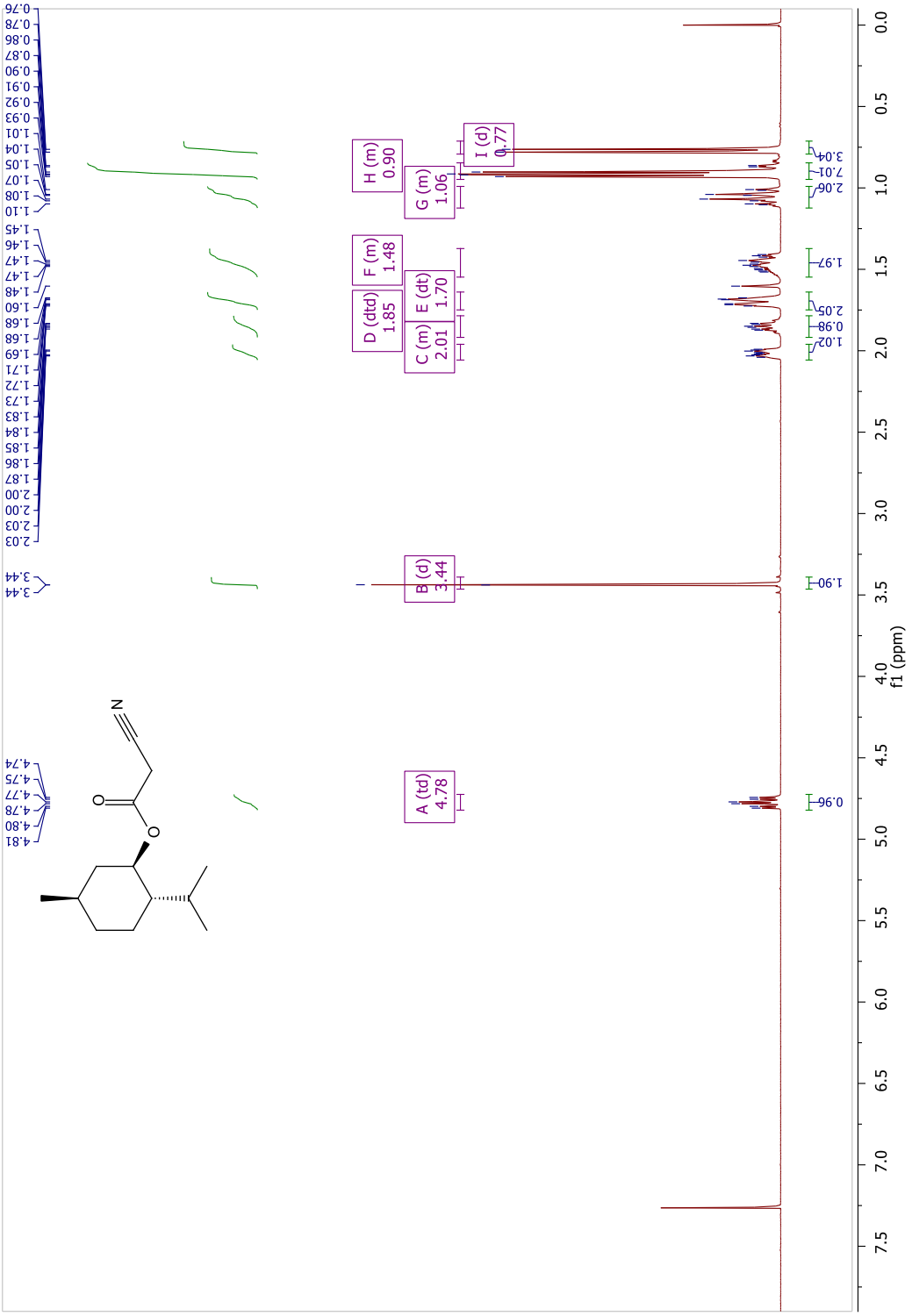
BIS-ALKYNE PRECURSORS

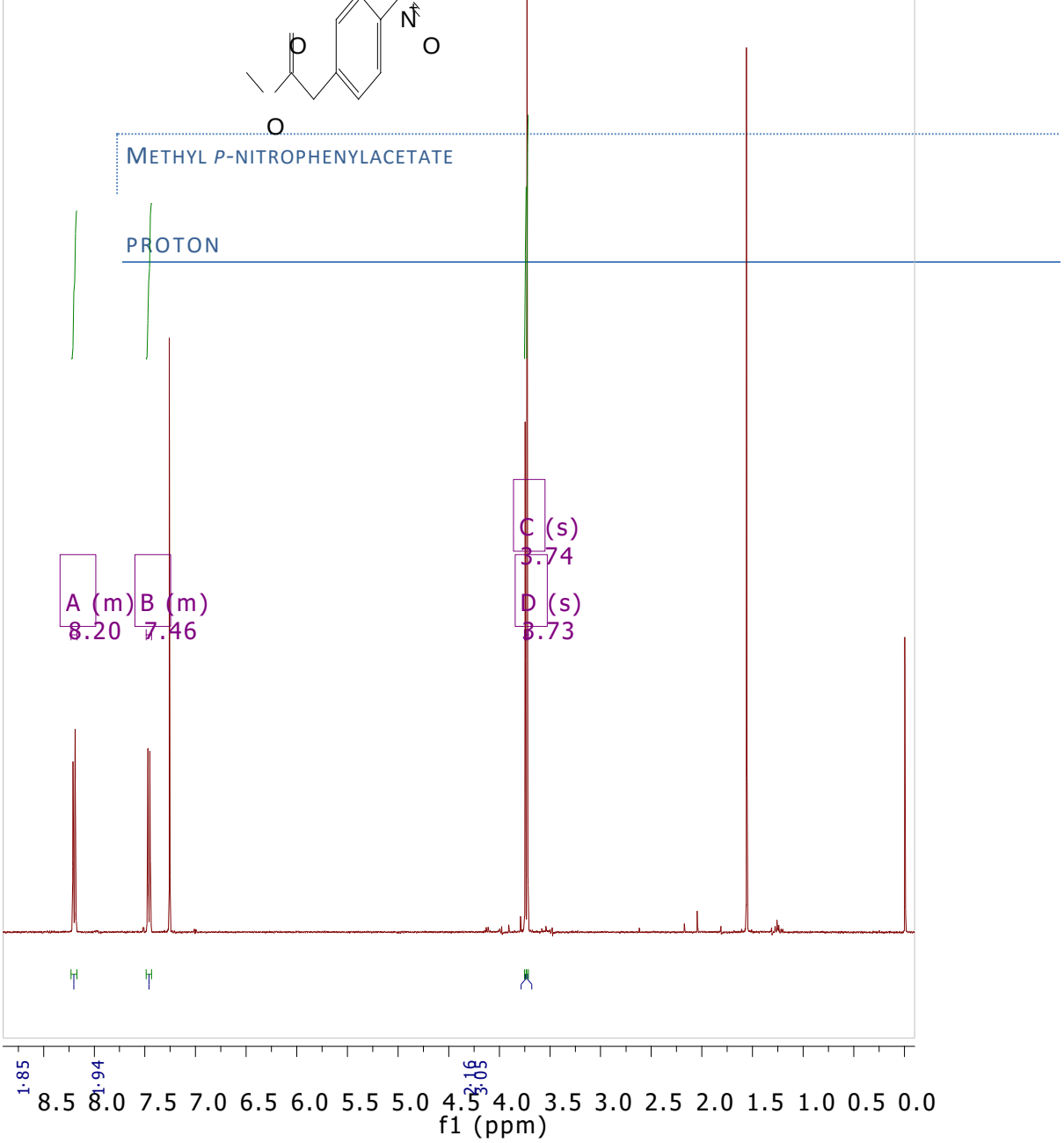
TERT-BUTYL 2-CYANOACETATE

PROTON



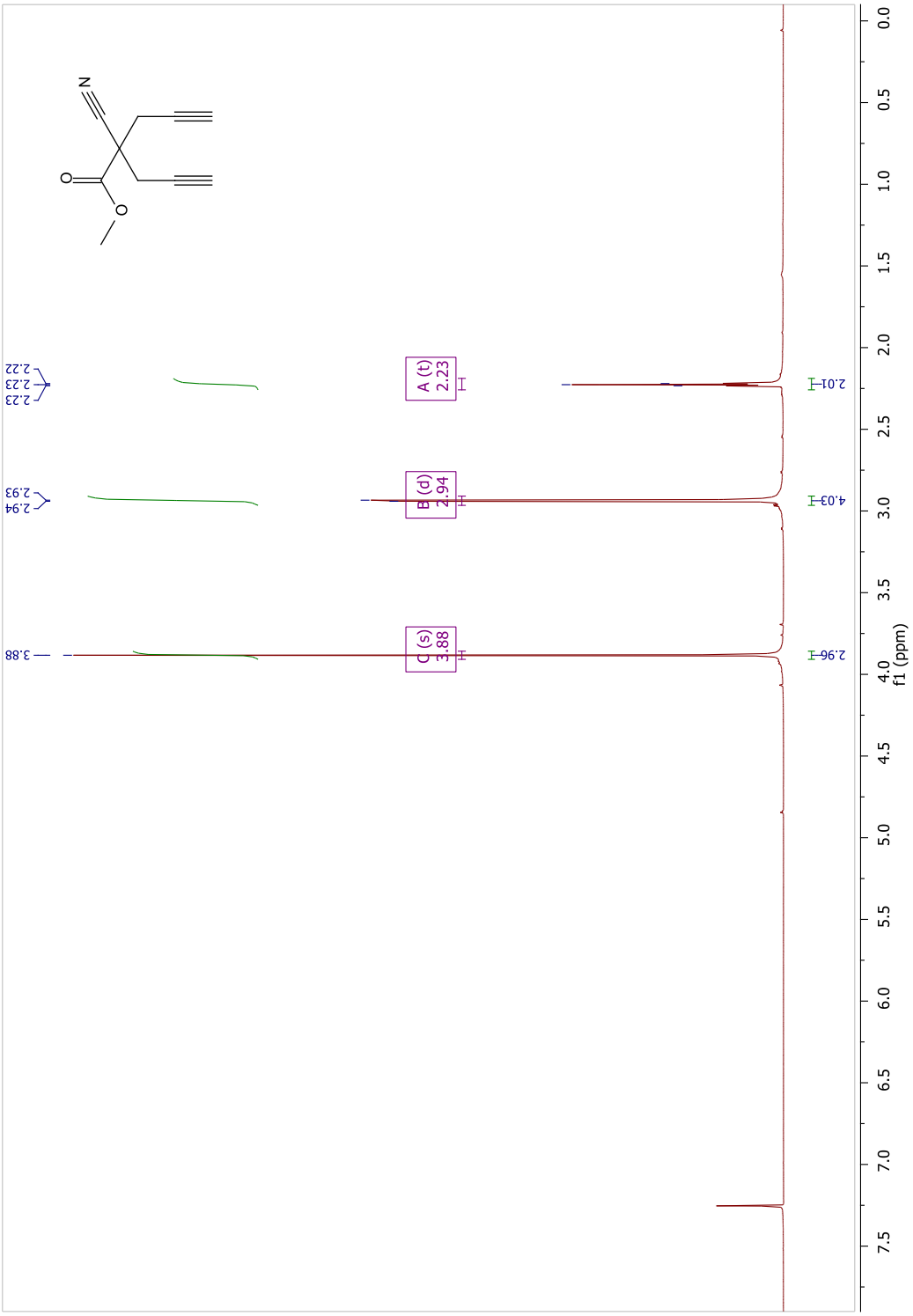
PROTON

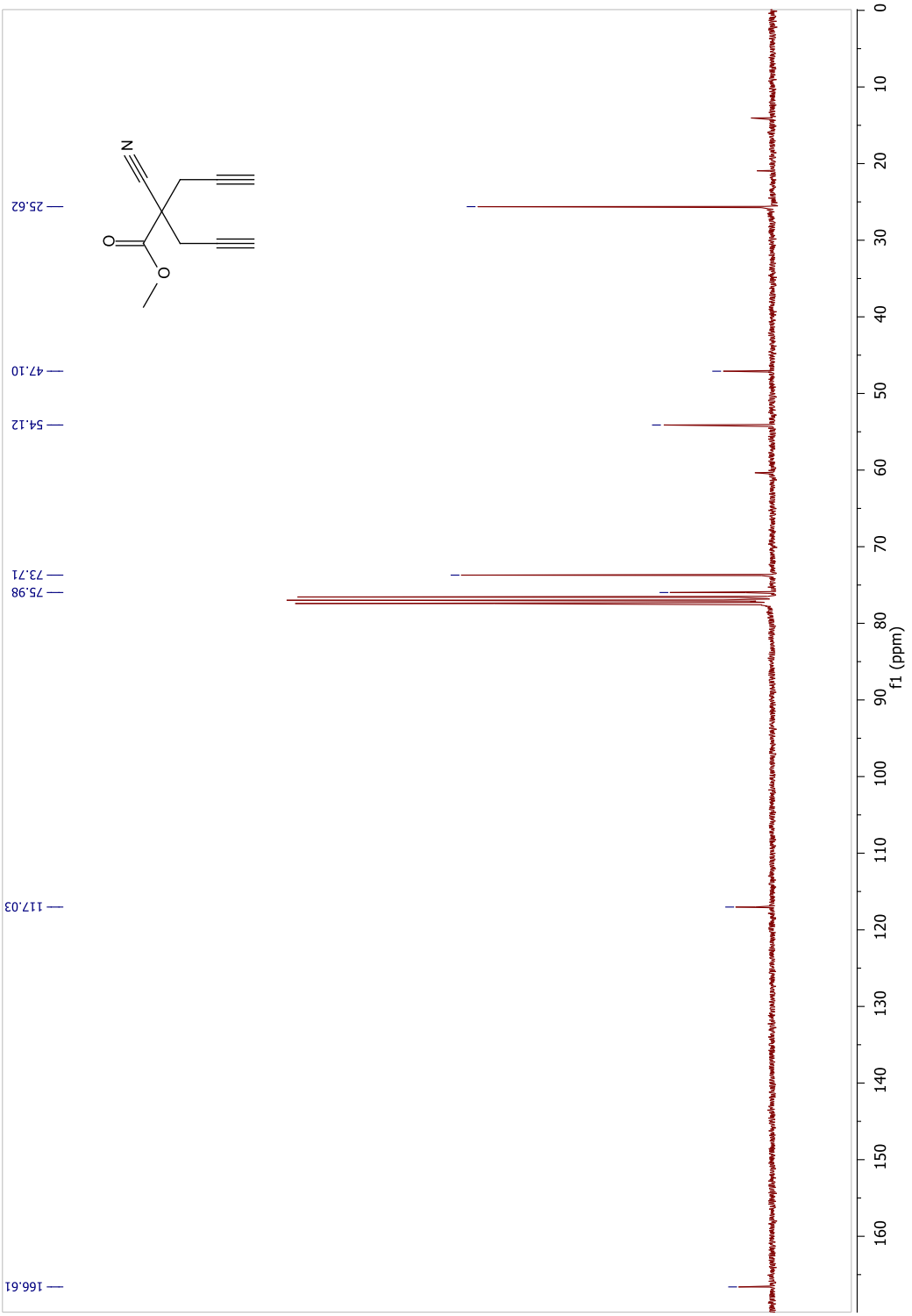

I (d) 0.77
H (m) 0.90
G (m) 1.06
F (m) 1.48
E (dt) 1.70
D (dtd) 1.85
C (m) 2.01
B (d) 3.44
A (td) 4.78
3.04
7.01
2.06
1.97
2.05
0.98
1.02
1.90
0.96
f1 (ppm)


O
N
O
O
METHYL P-NITROPHENYLACETATE
PROTON
A (m)
8.20
B (m)
7.46
C (s)
3.74
D (s)
3.73
1.85
1.94
2.16
3.05
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

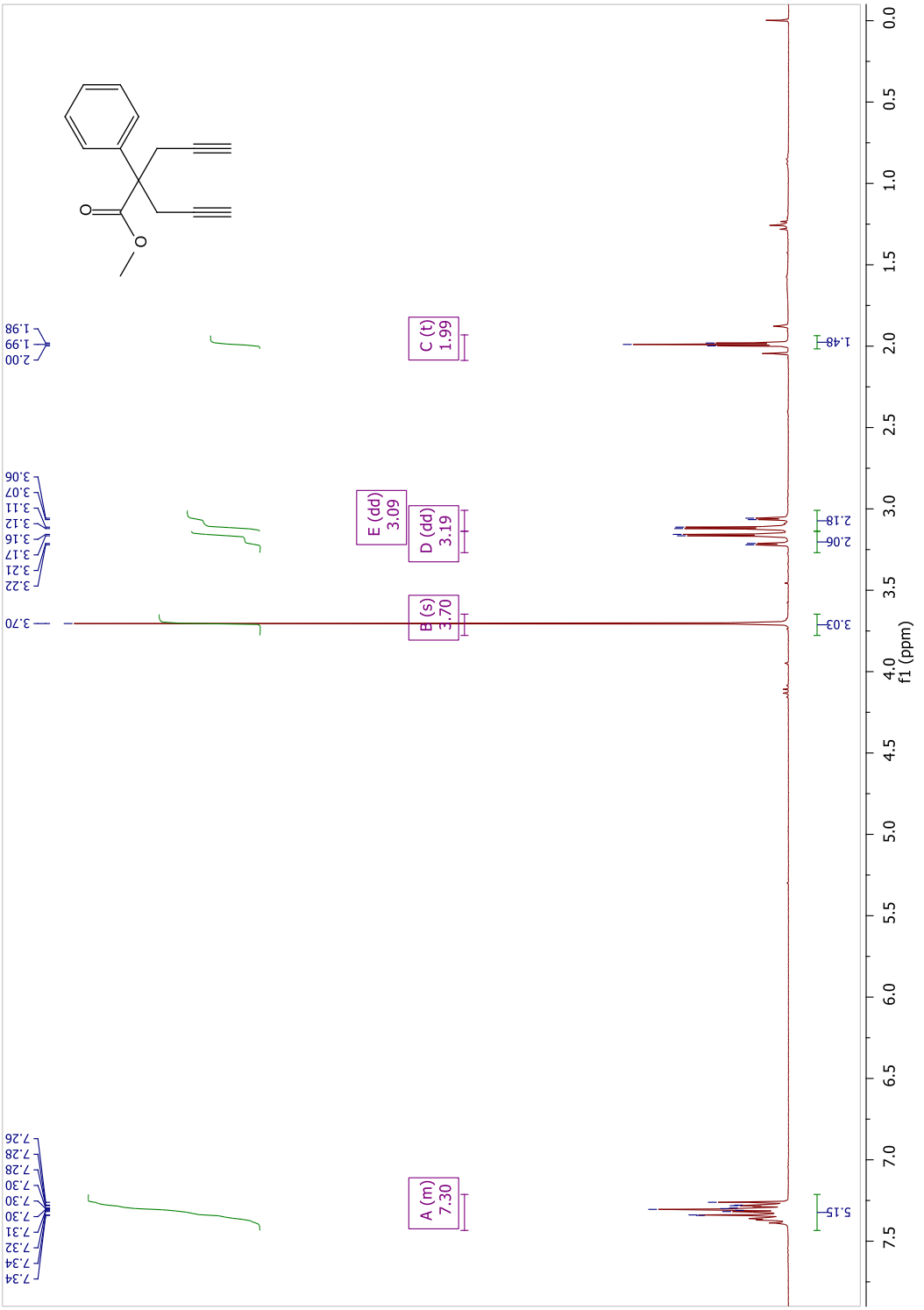
METHYL 2-CYANO-2-(PROP-2-YN-1-YL)PENT-4-YNOATE

PROTON

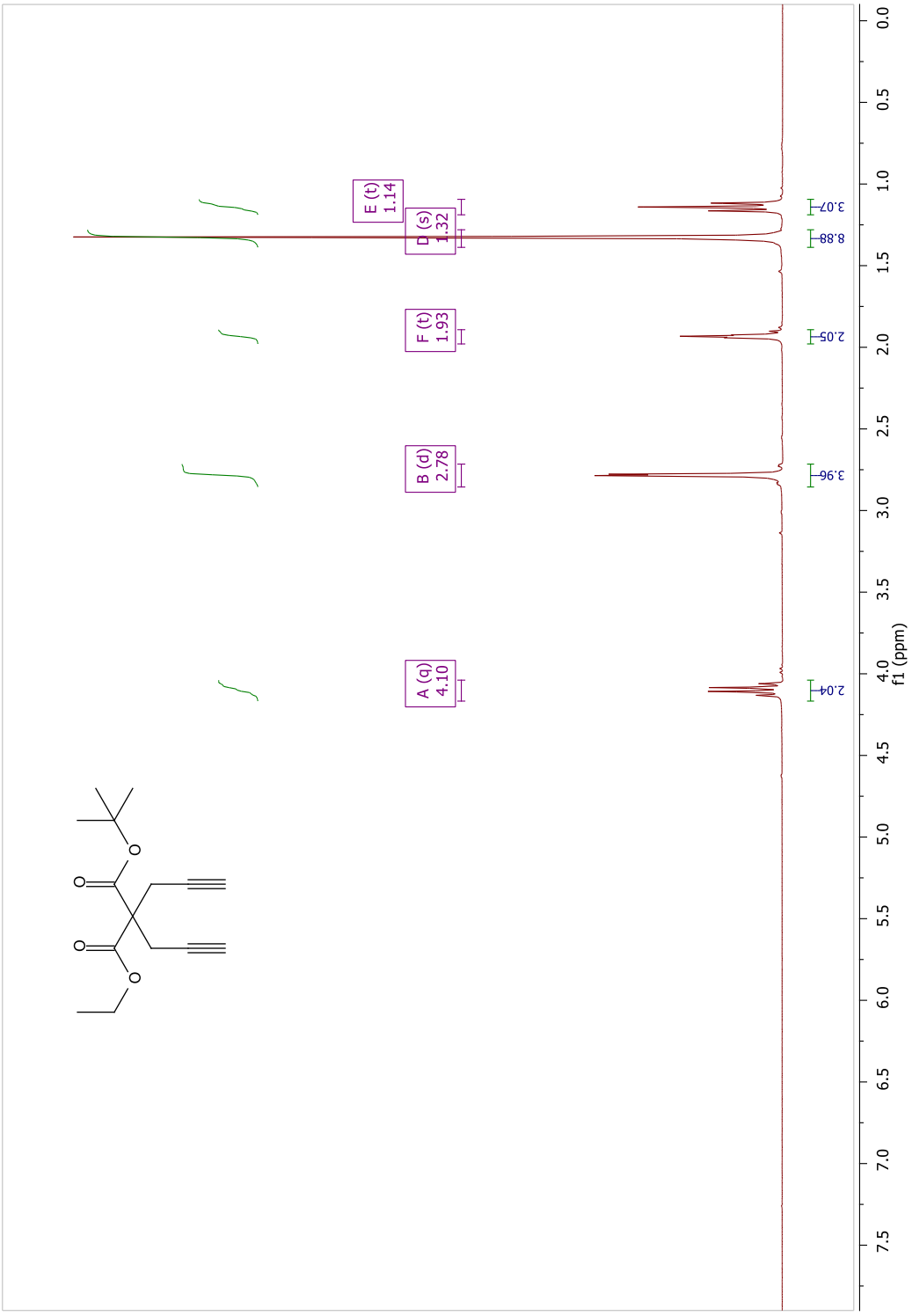


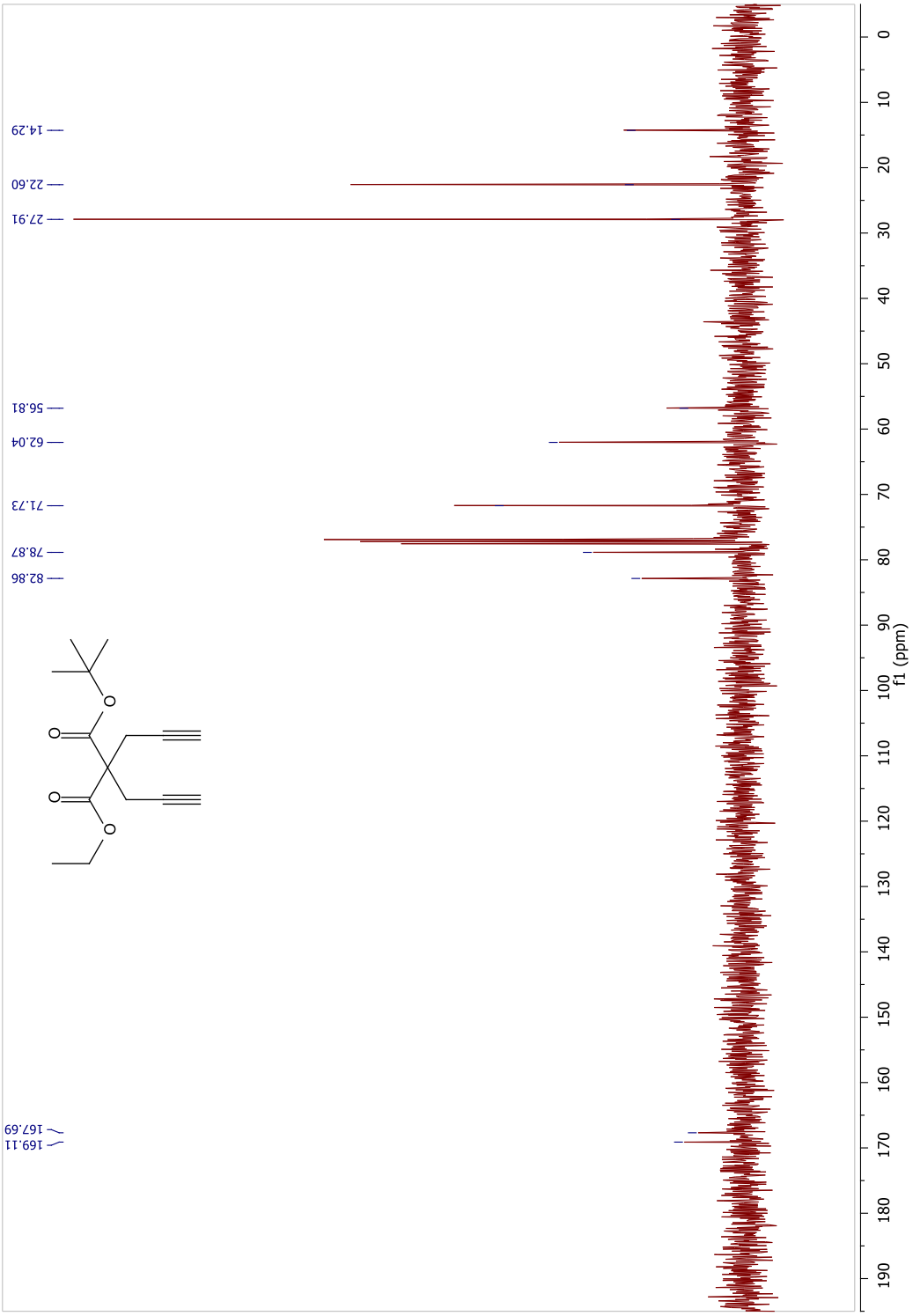

166.61
117.03
75.98
73.71
54.12
47.10
25.62
f1 (ppm)

PROTON

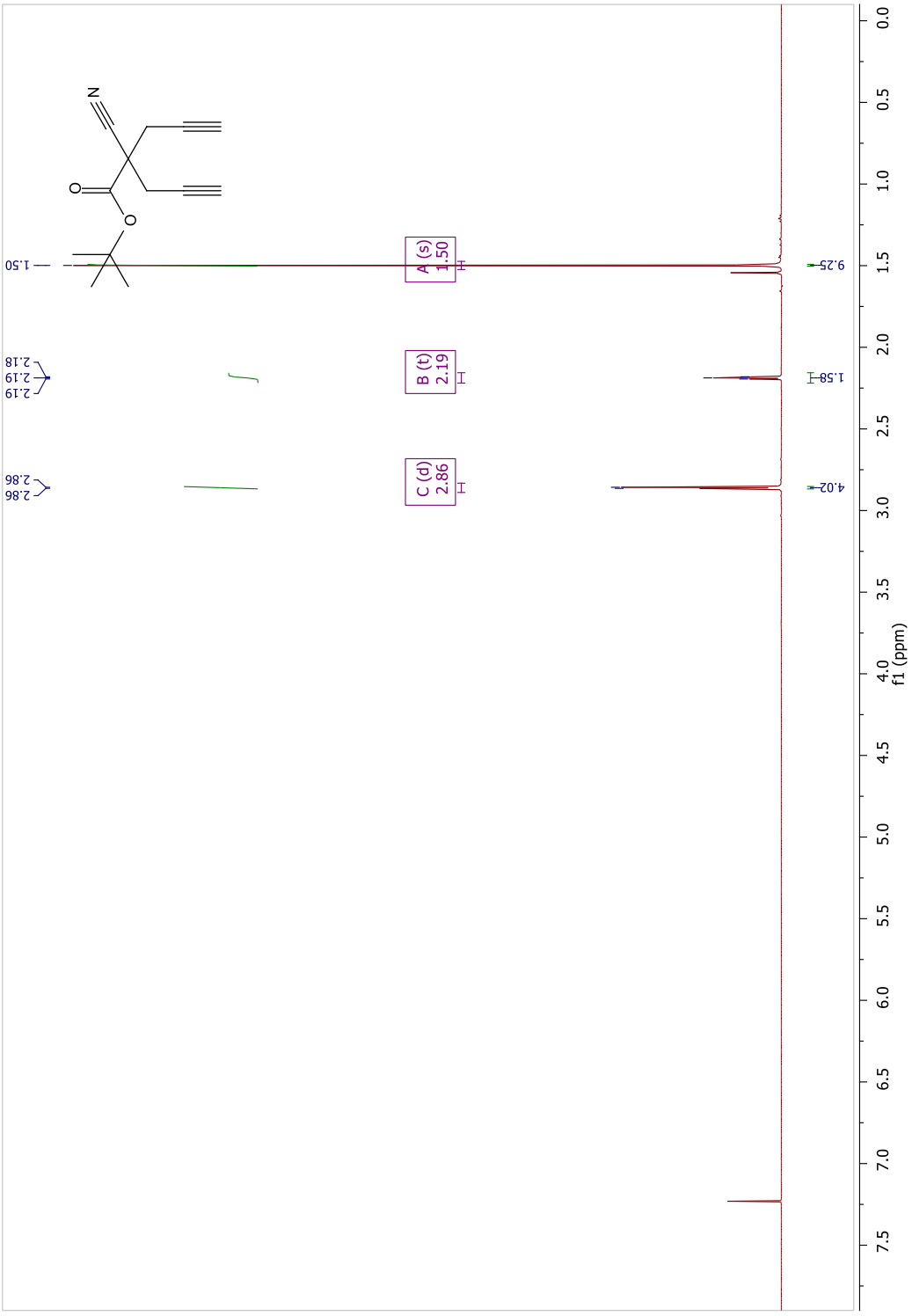


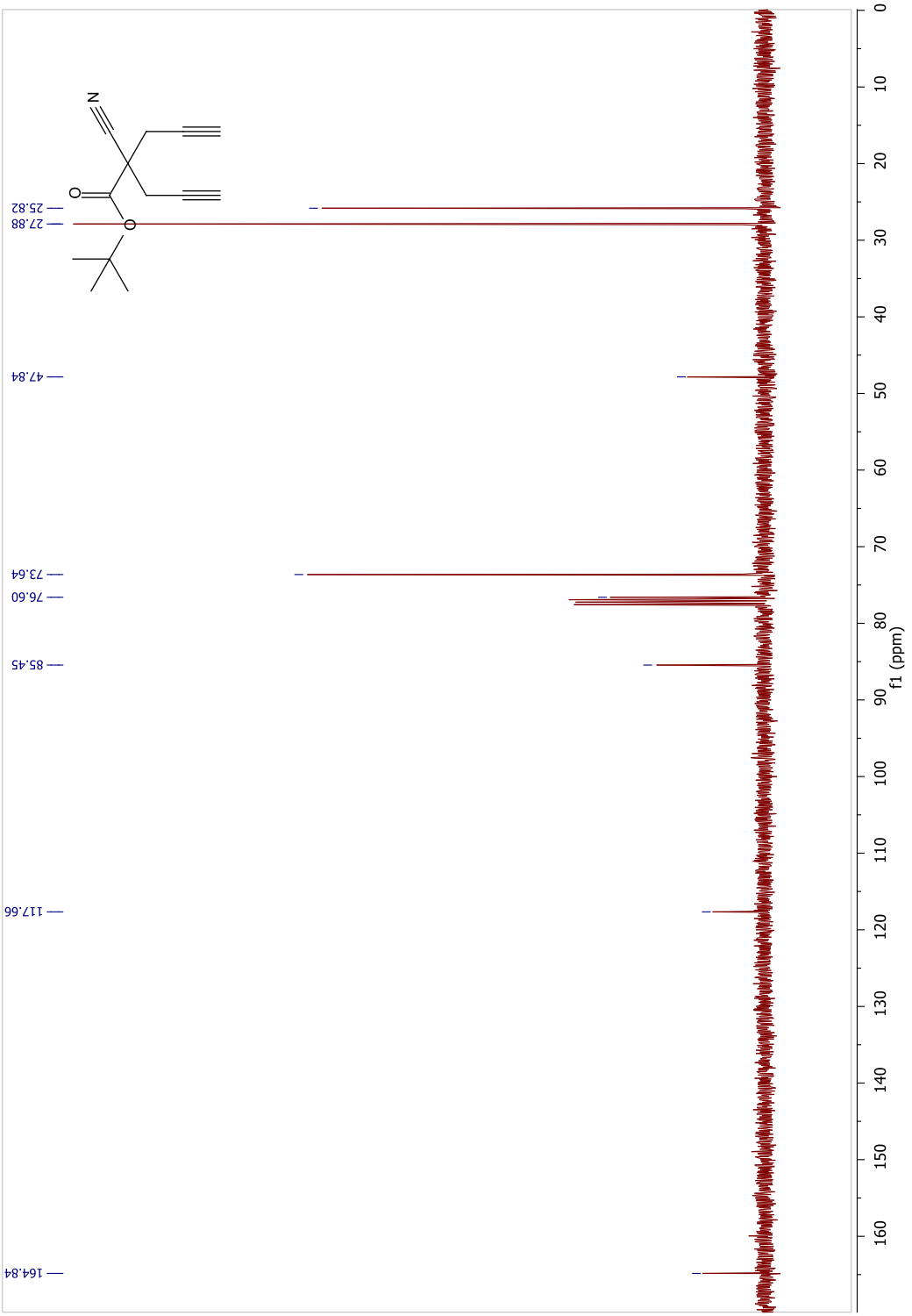
PROTON


E (t)
1.14
D (s)
1.32
F (t)
1.93
B (d)
2.78
A (q)
4.10
3.07
8.88
2.05
3.96
2.04
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

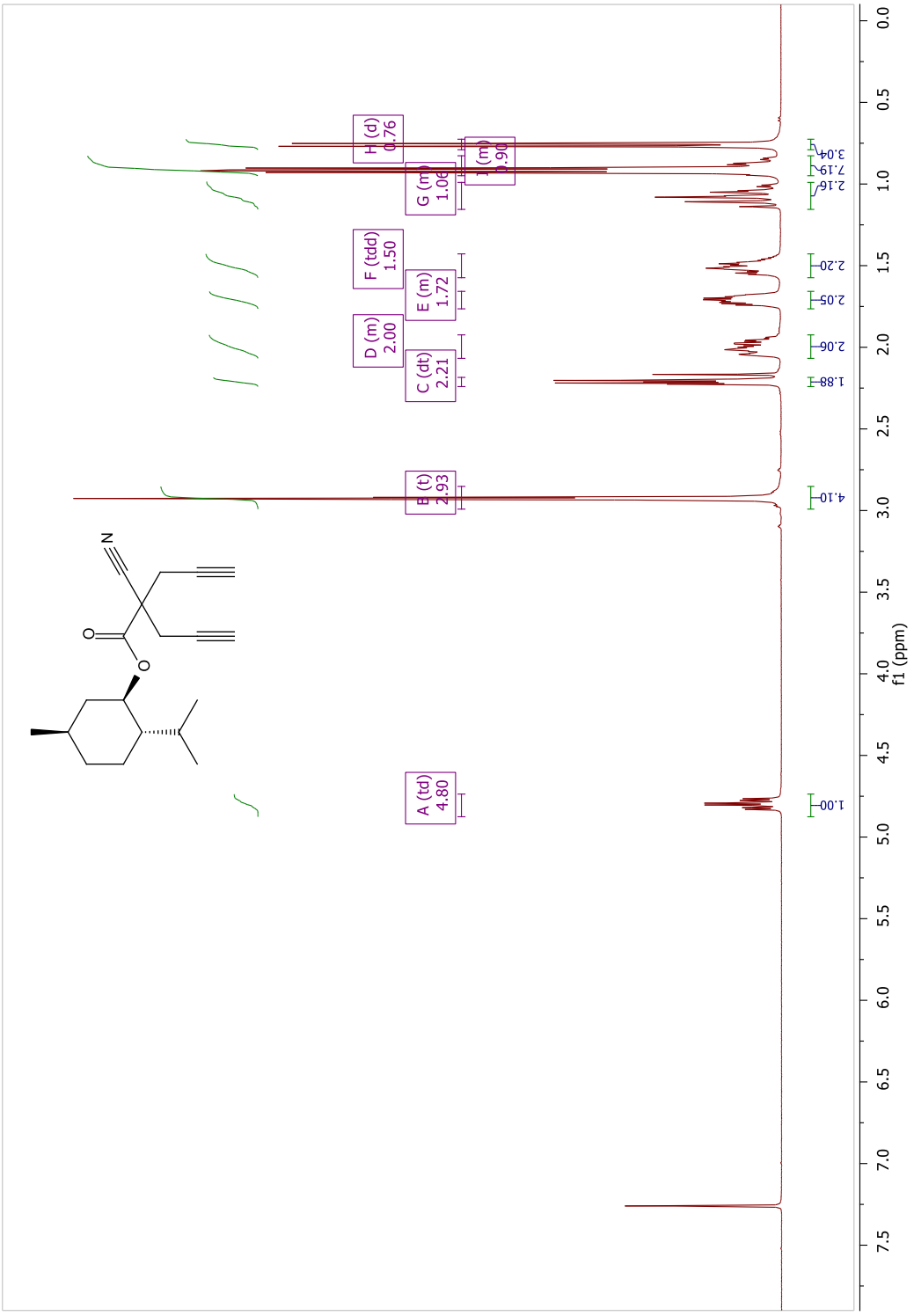

14.29
22.60
27.91
56.81
62.04
71.73
78.87
82.86
167.69
169.11
f1 (ppm)

PROTON

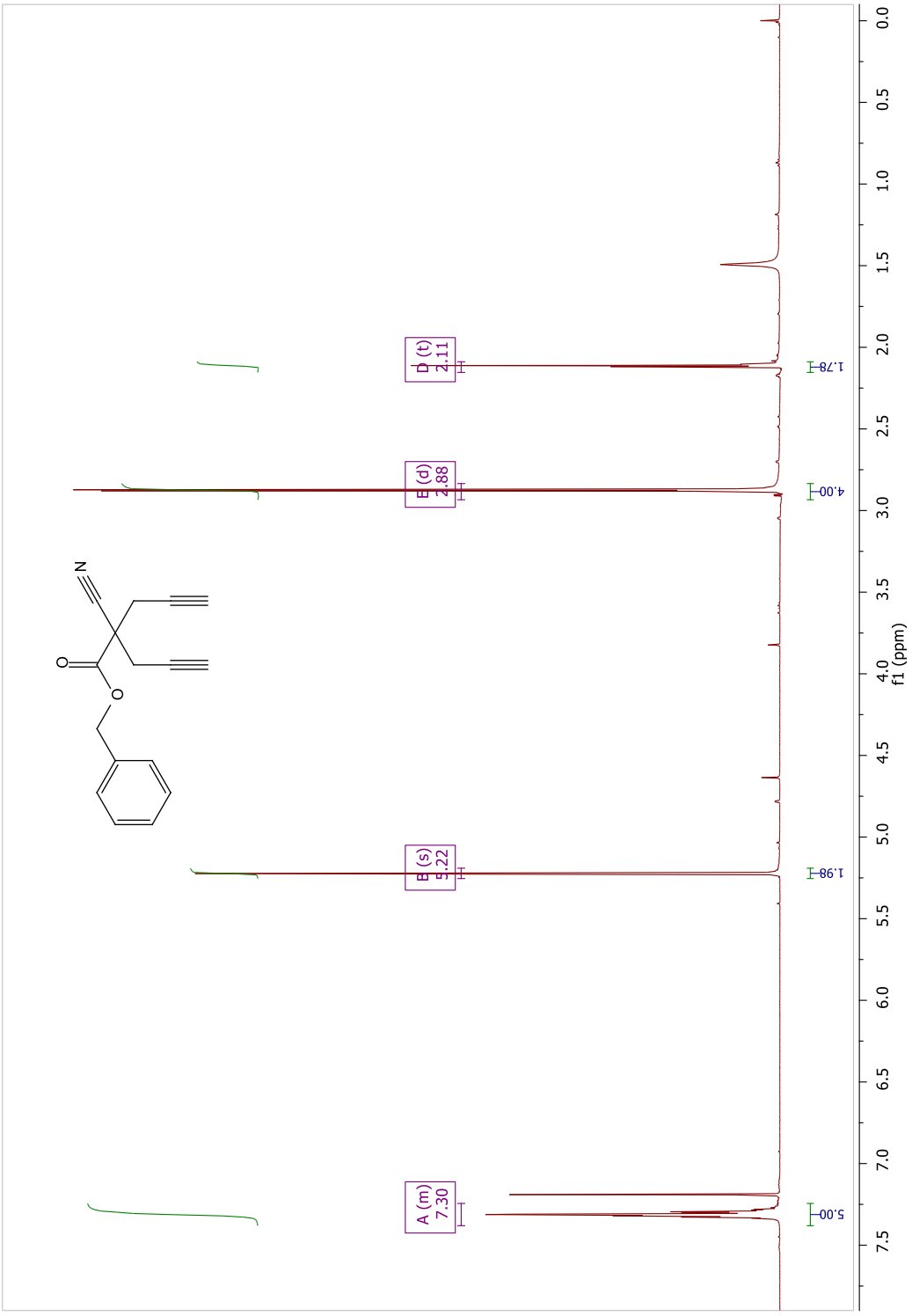

N
O
O
1.50
2.18
2.19
2.19
2.86
2.86
A (s)
1.50
B (t)
2.19
C (d)
2.86
9.25
1.58
4.02
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)


N
O
O
25.82
27.88
47.84
73.64
76.60
85.45
117.66
164.84
f1 (ppm)

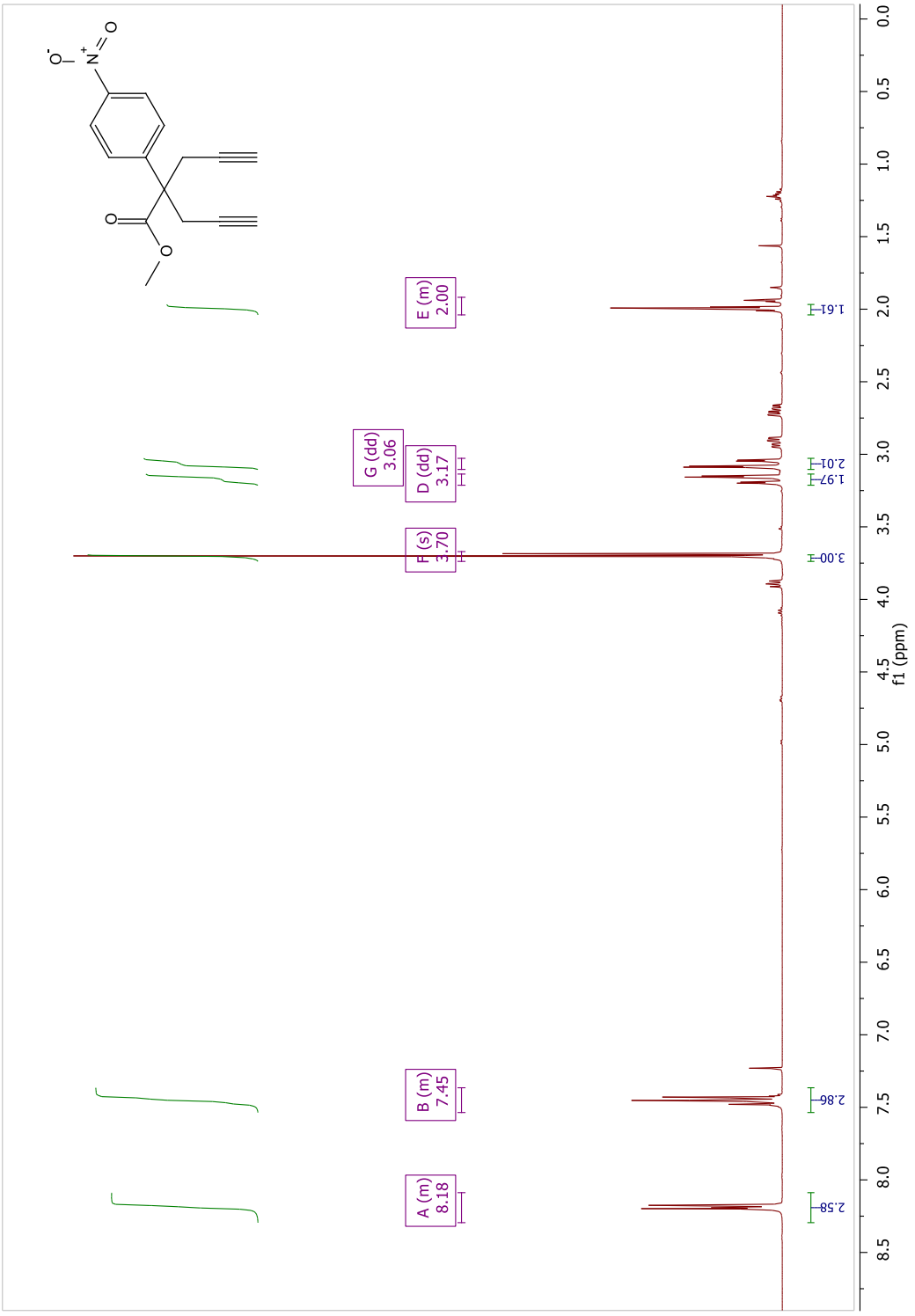
PROTON


H (d) 0.76
G (m) 1.06
I (m) 0.90
F (tdd) 1.50
E (m) 1.72
D (m) 2.00
C (dt) 2.21
B (t) 2.93
A (td) 4.80
3.04
7.19
2.16
2.20
2.05
2.06
1.88
4.10
1.00
N
O
O
f1 (ppm)

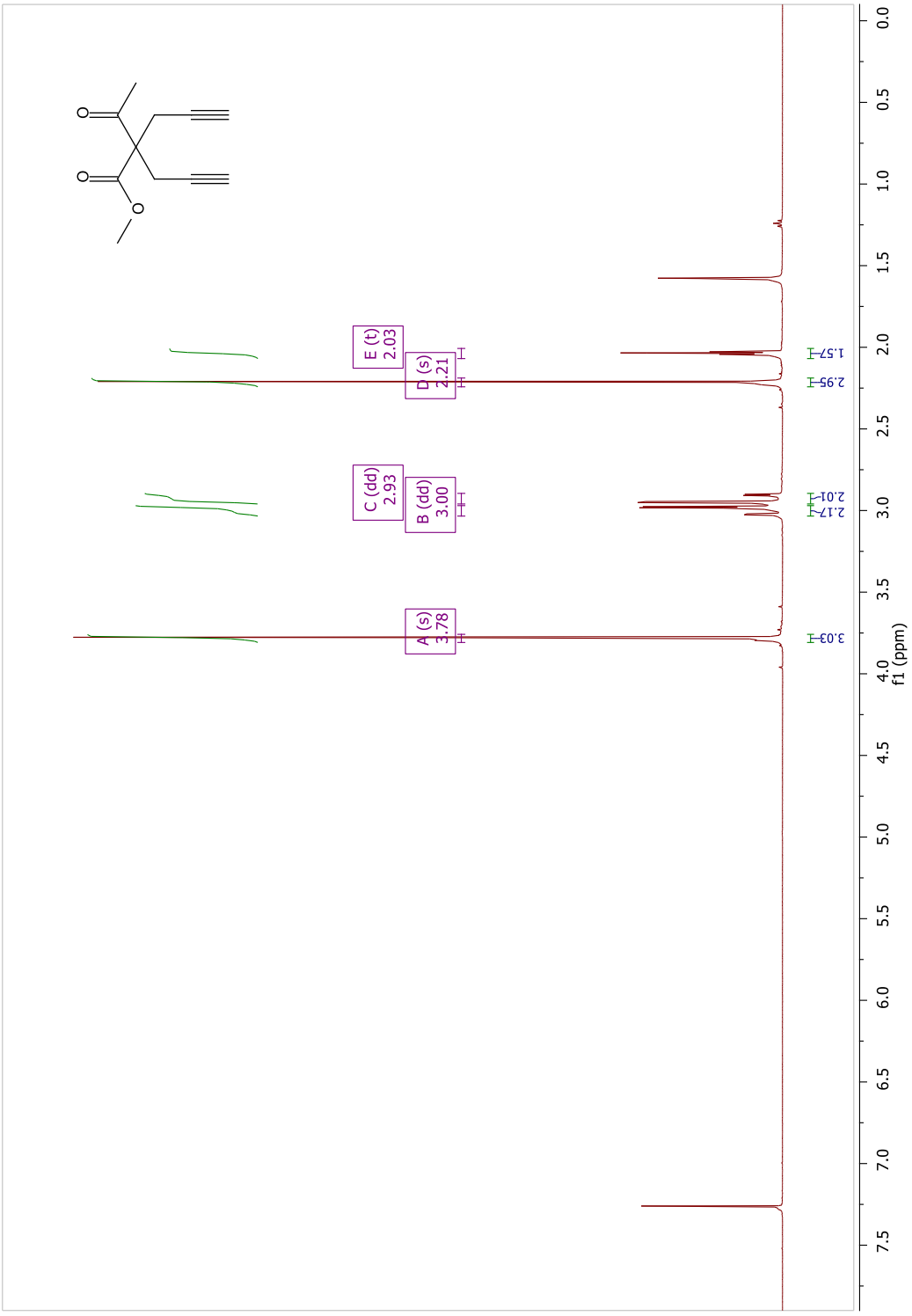
PROTON


D (t)
2.11
1.78
B (d)
2.88
4.00
B (s)
5.22
1.98
A (m)
7.30
5.00
N
O
O
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

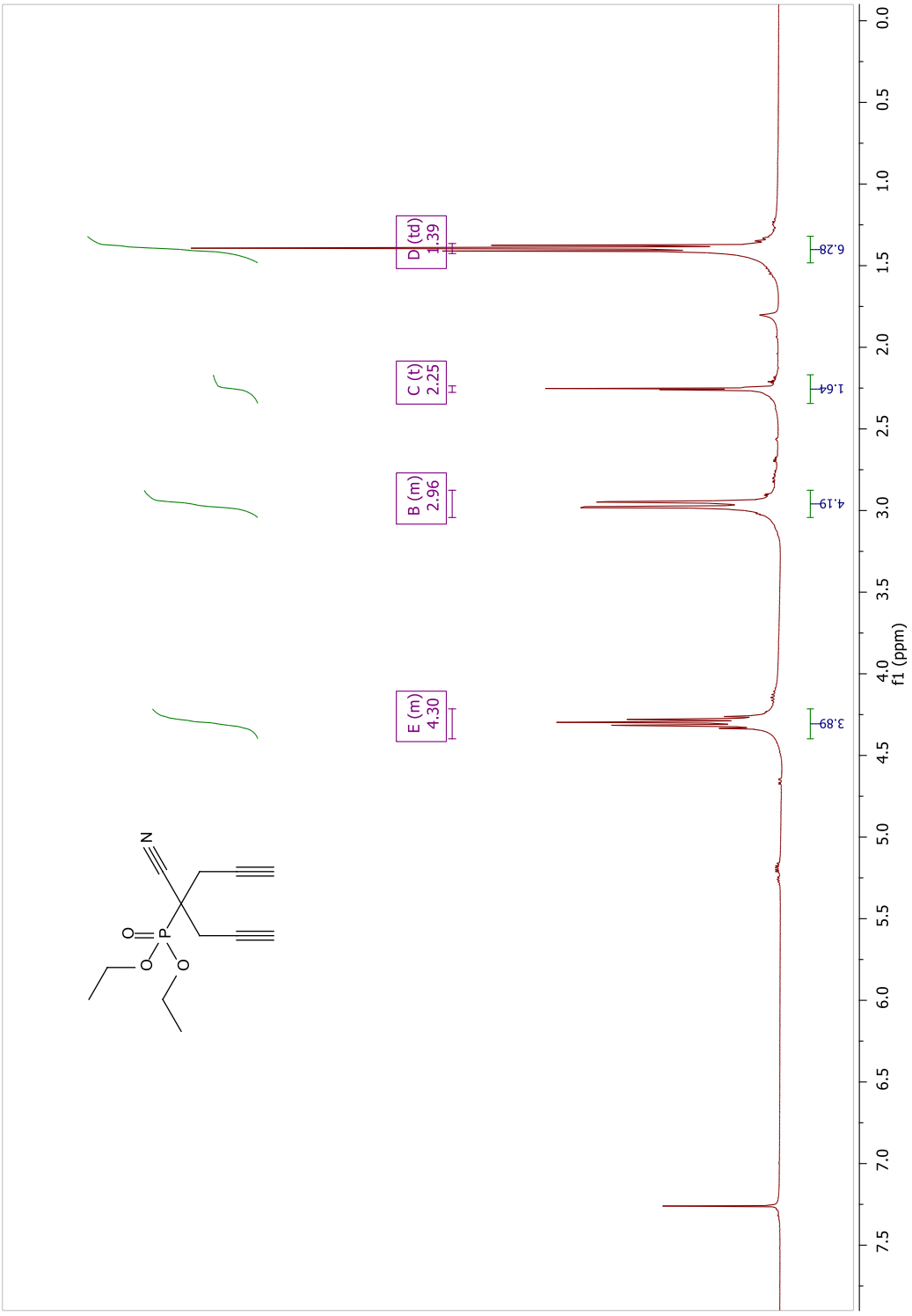
PROTON


A (m)
8.18
B (m)
7.45
D (dd)
3.17
E (m)
2.00
F (s)
3.70
G (dd)
3.06
1.61
2.01
1.97
3.00
2.86
2.58
f1 (ppm)

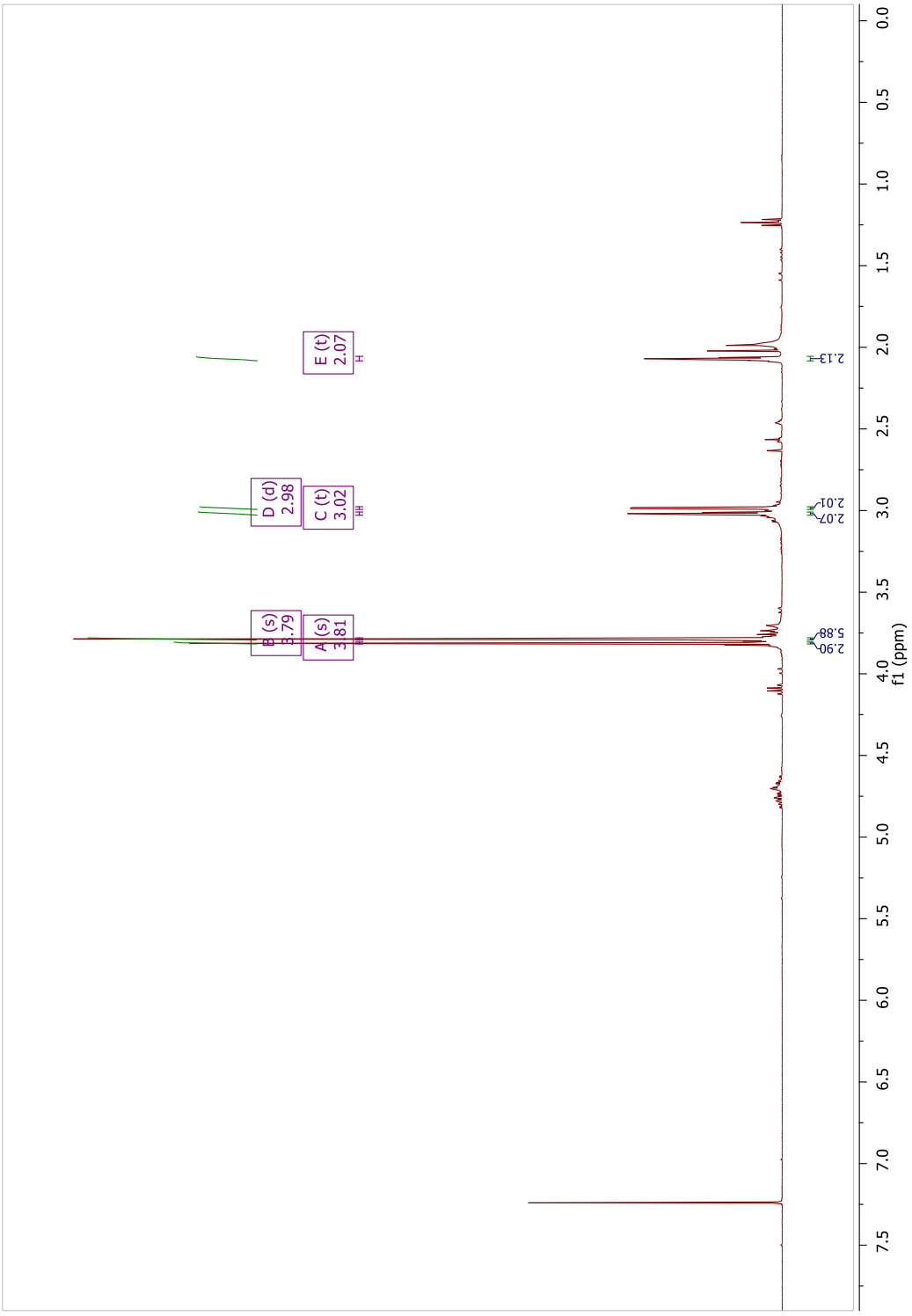
PROTON



PROTON

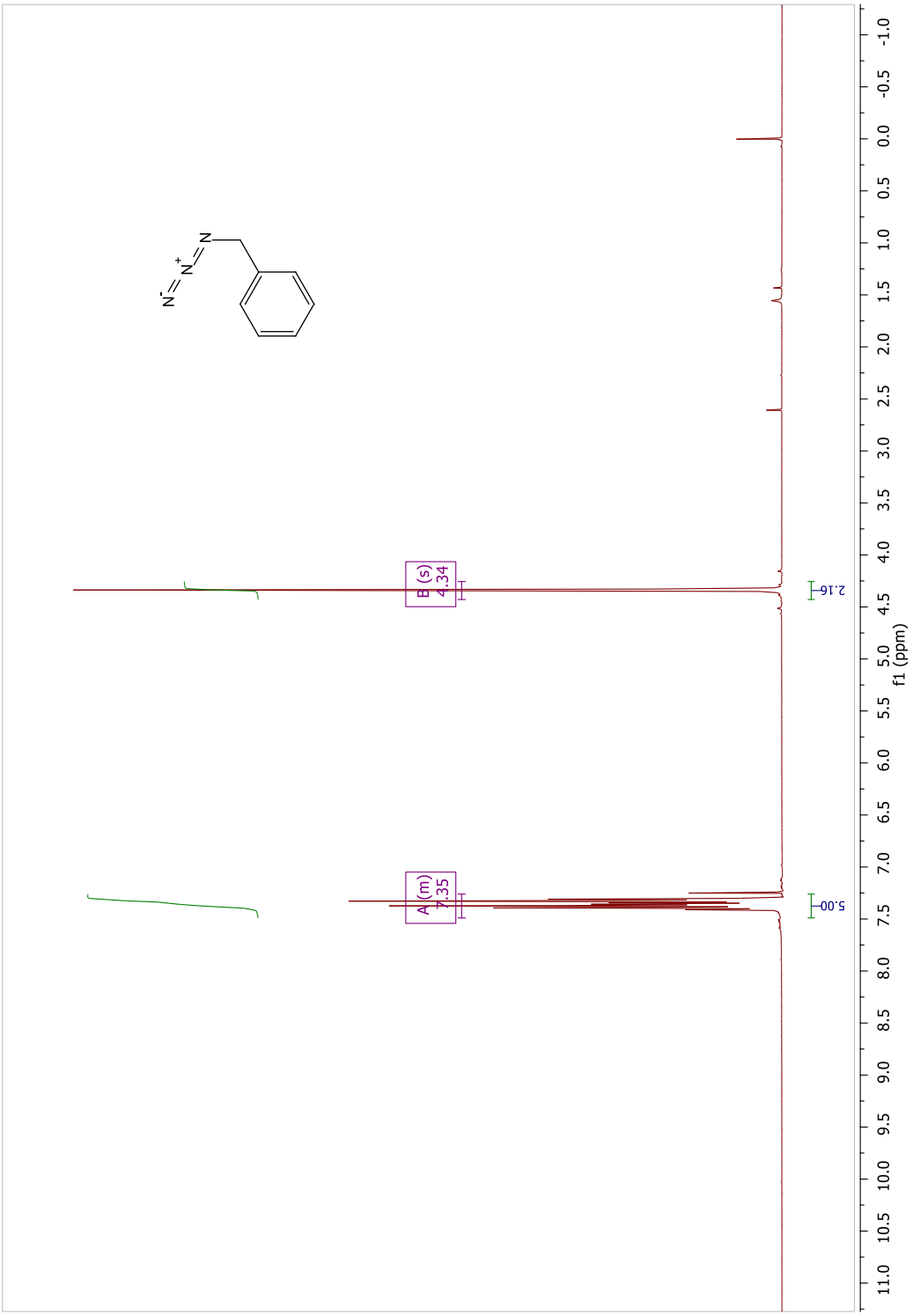


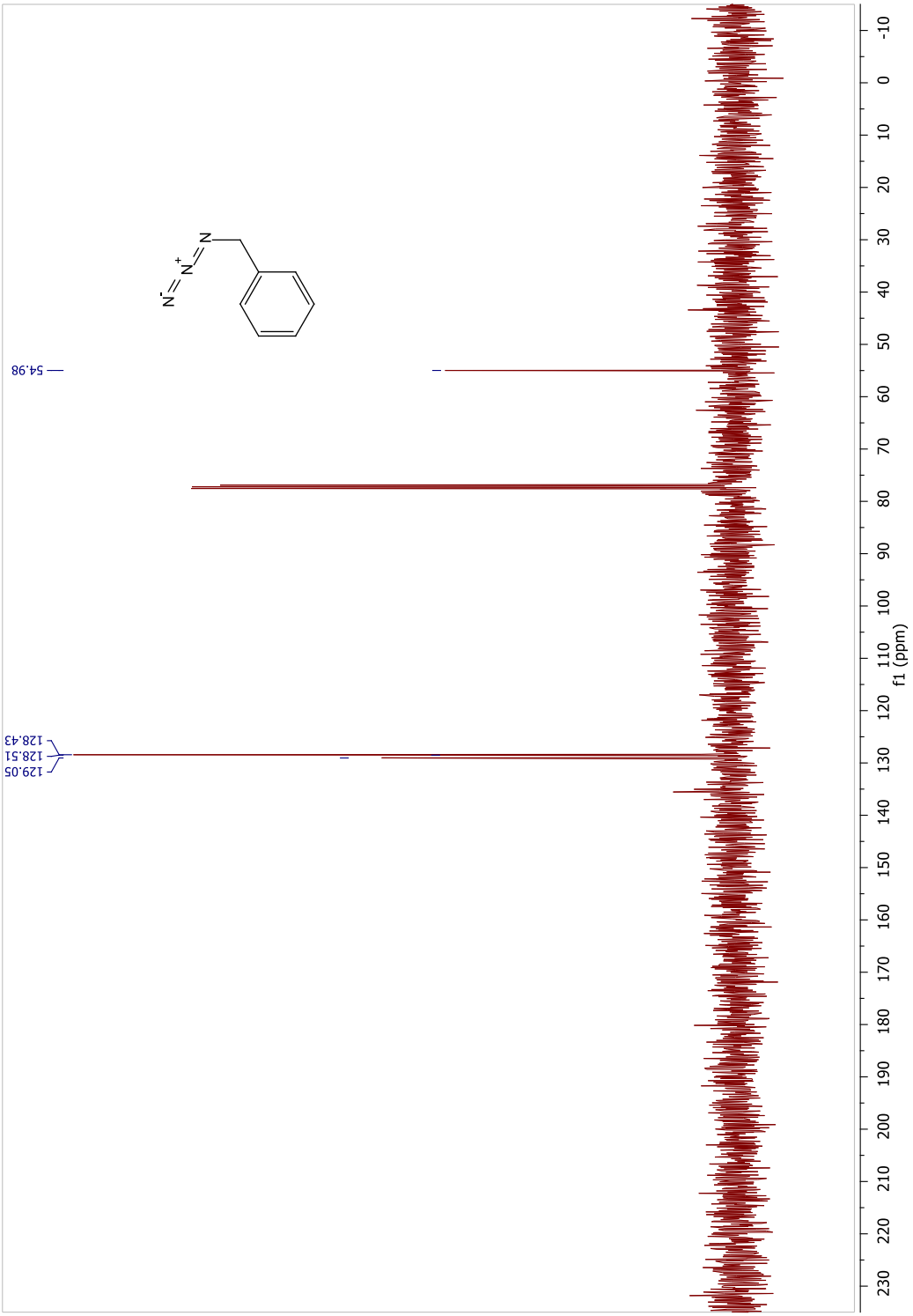
PROTON


E (t)
2.07
D (d)
2.98
C (t)
3.02
B (s)
3.79
A (s)
3.81
2.13
2.07
2.01
5.88
2.90
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

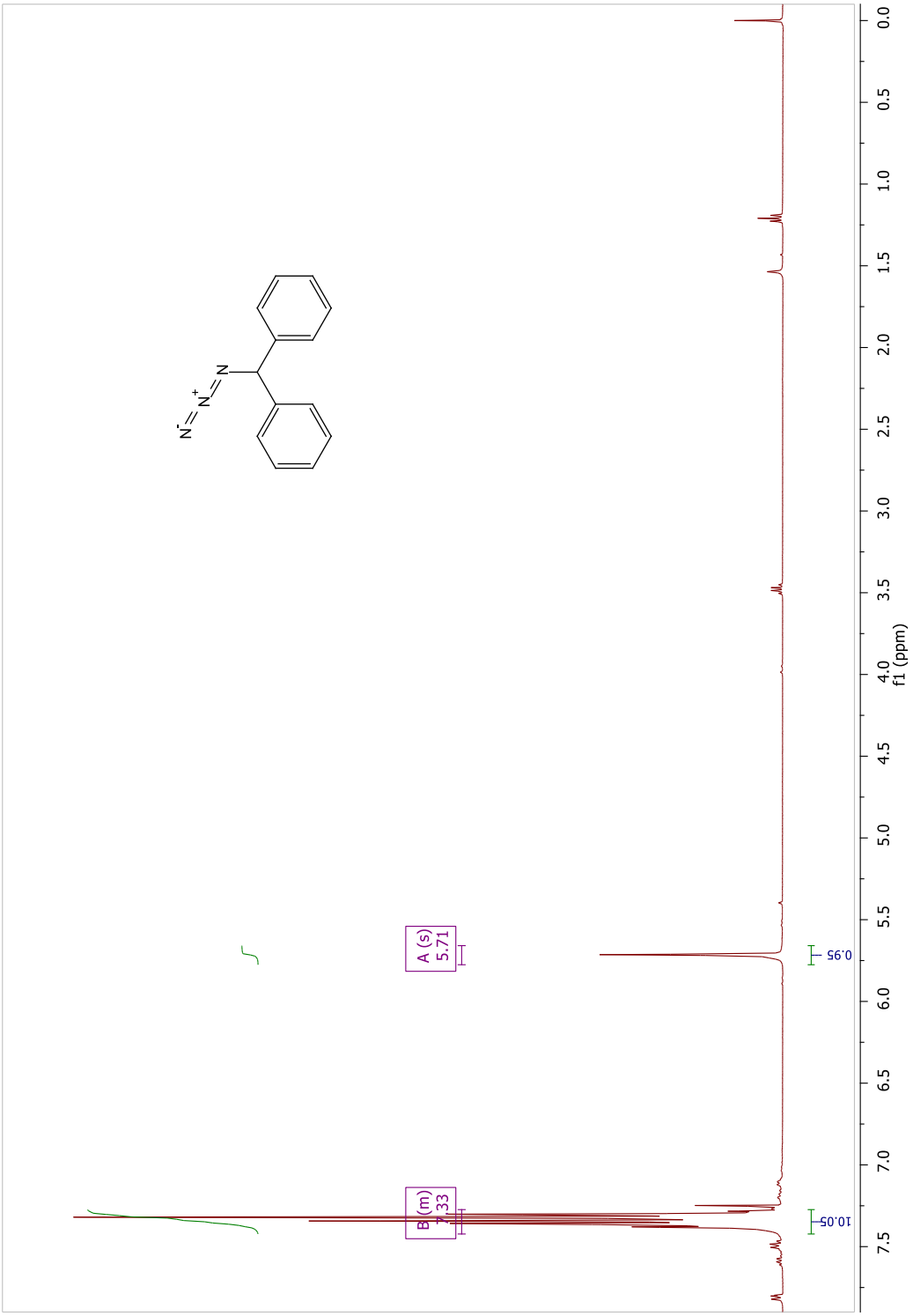
BENZYL AZIDE

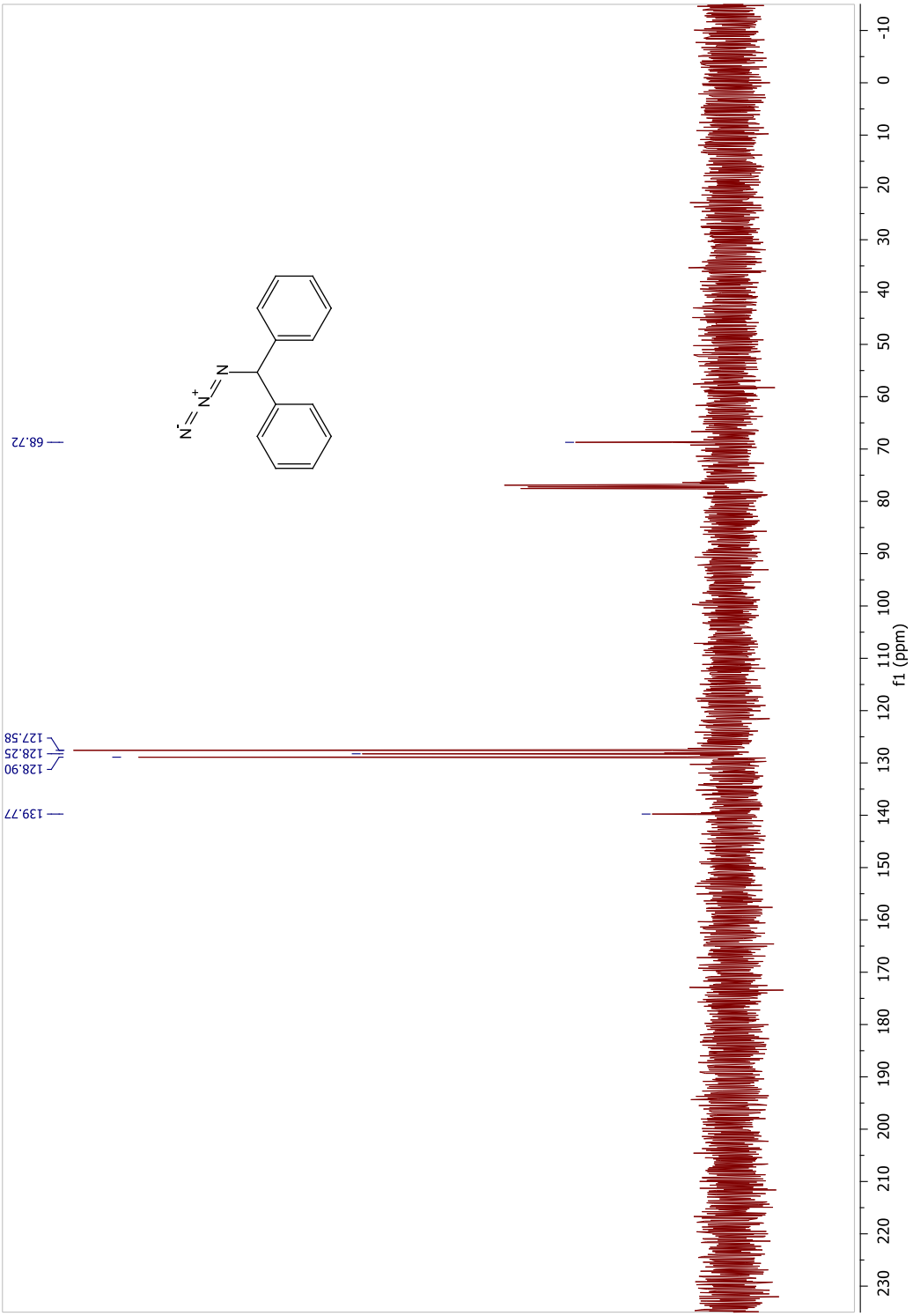
PROTON



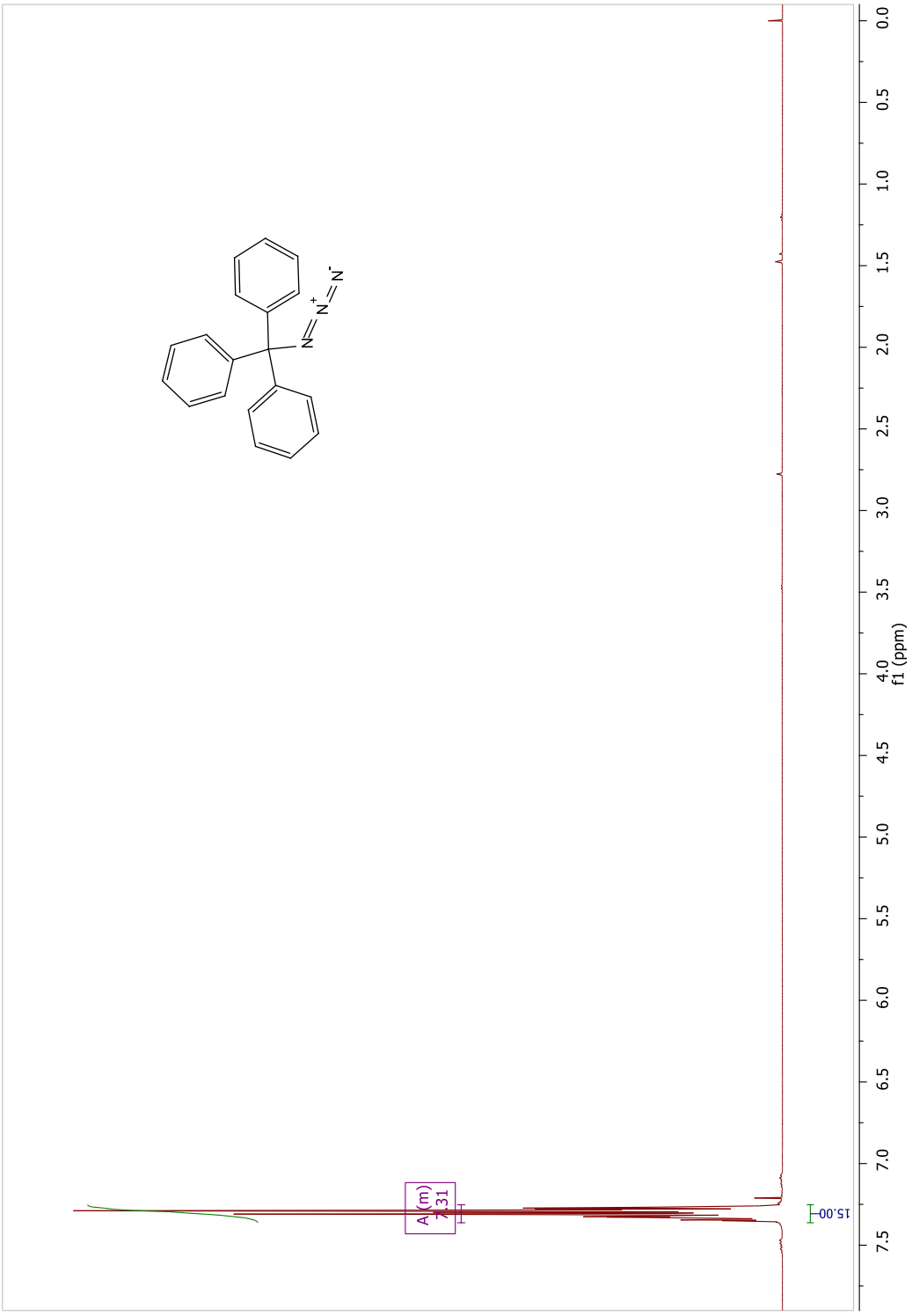

54.98
129.05
128.51
128.43
f1 (ppm)

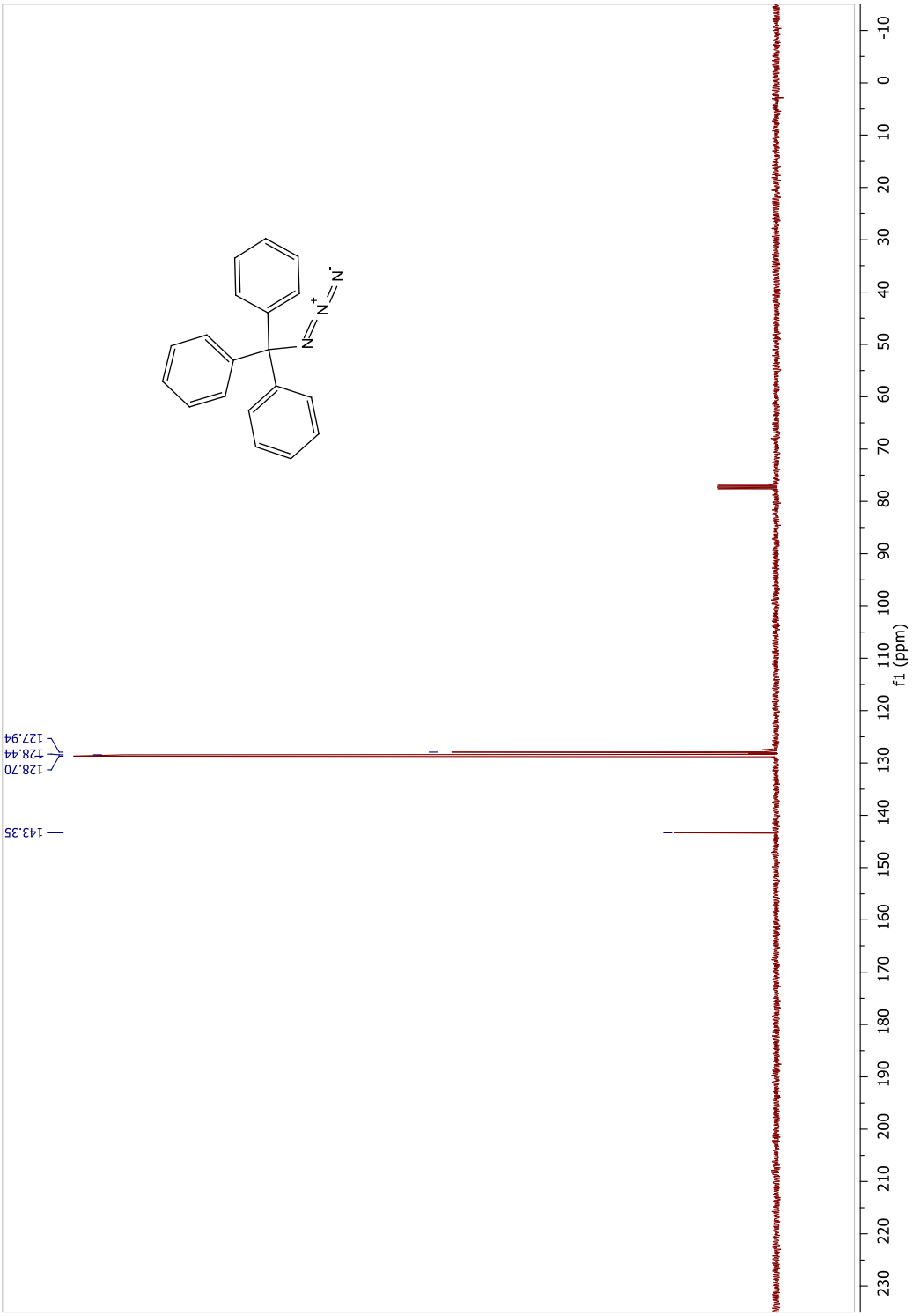
PROTON


A (s)
5.71
B (m)
7.33
0.95
10.05
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

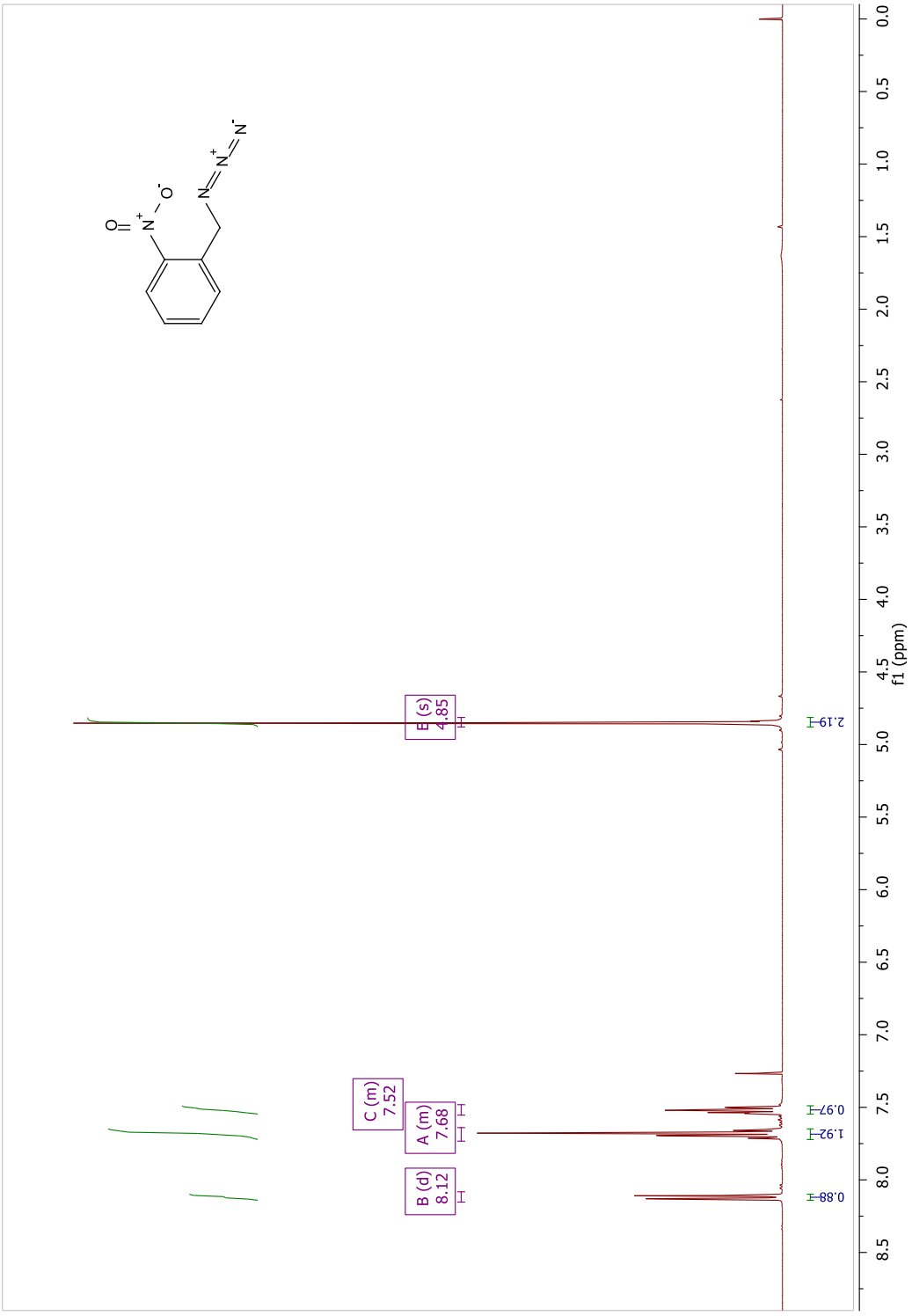

68.72
127.58
128.25
128.90
139.77
f1 (ppm)

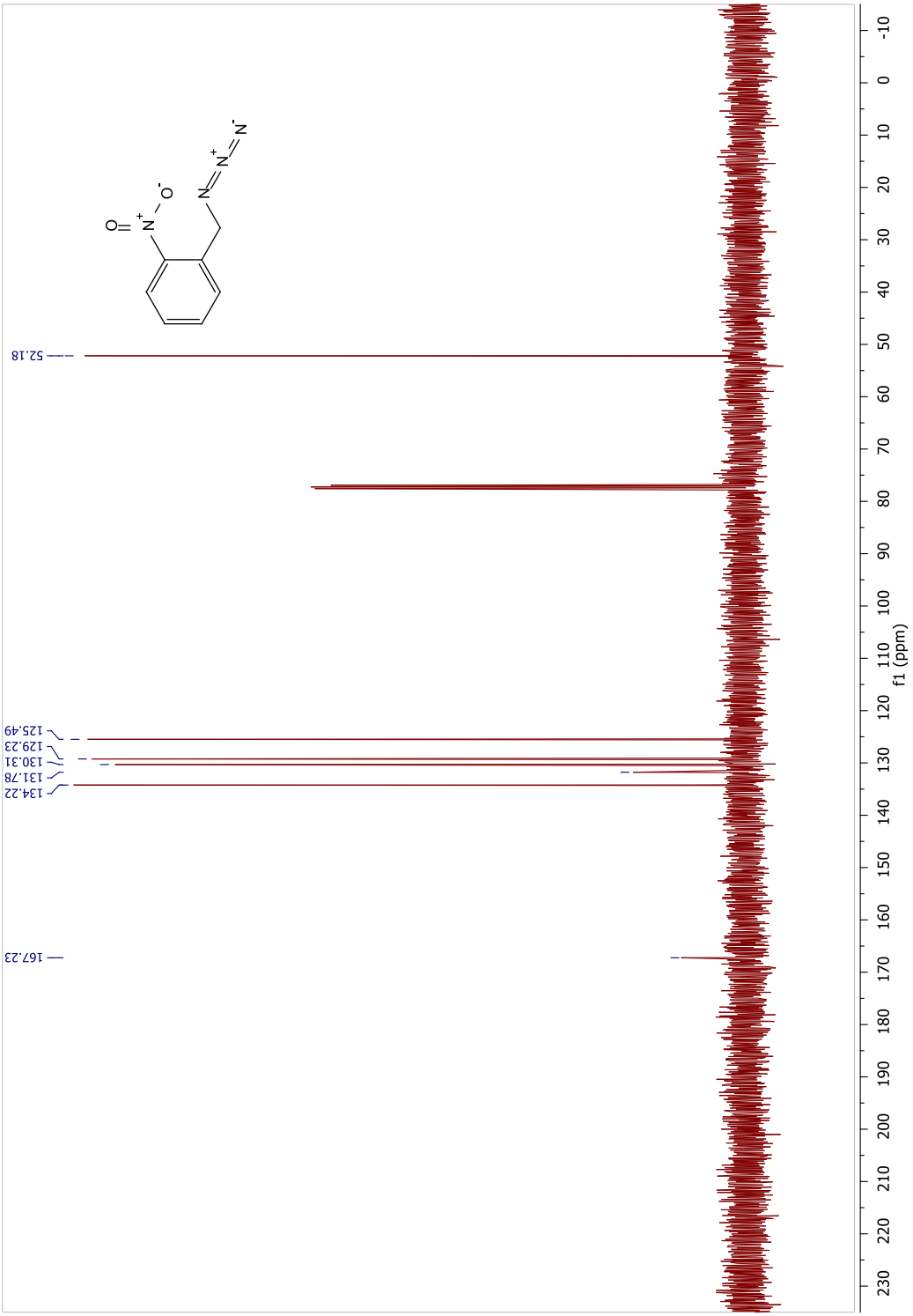
PROTON




143.35
128.70
128.44
127.94
f1 (ppm)

PROTON

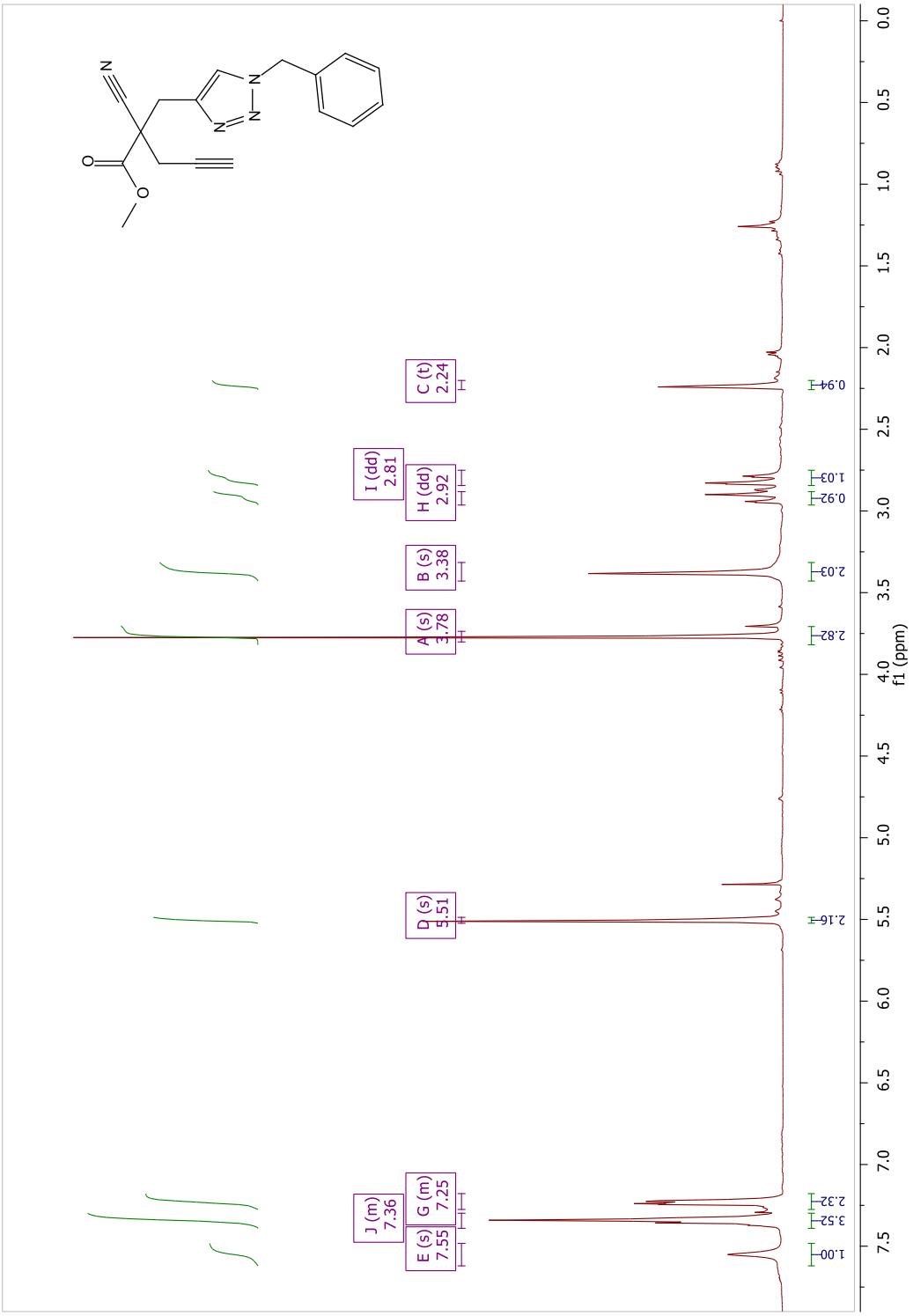



52.18
125.49
129.23
130.31
131.78
134.22
167.23
f1 (ppm)

CLICK REACTION STEP

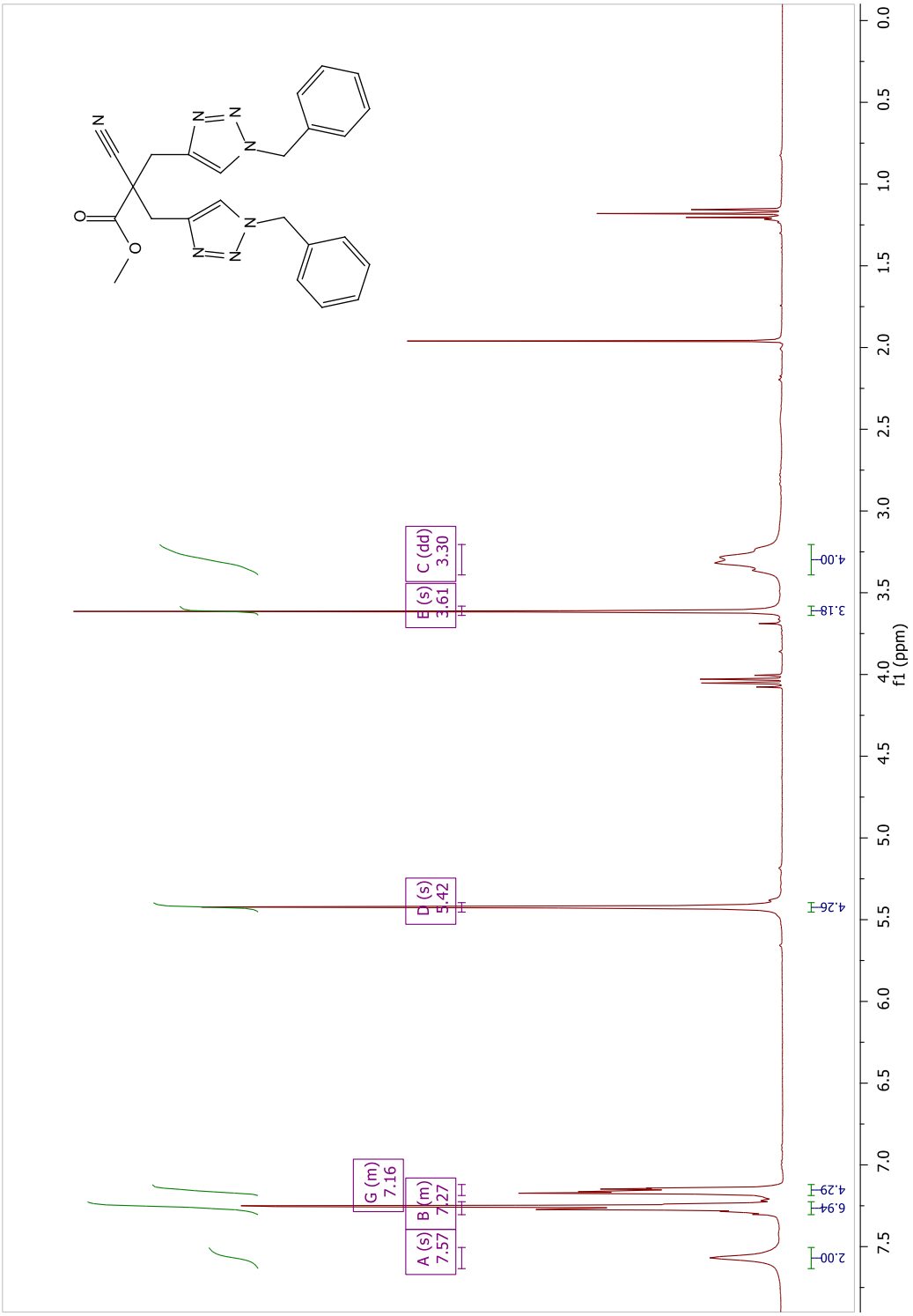
METHYL 2-((1-BENZYL-1*H*-1,2,3-TRIAZOL-4-YL)METHYL)-2-CYANOPENT-4-YNOATE

PROTON

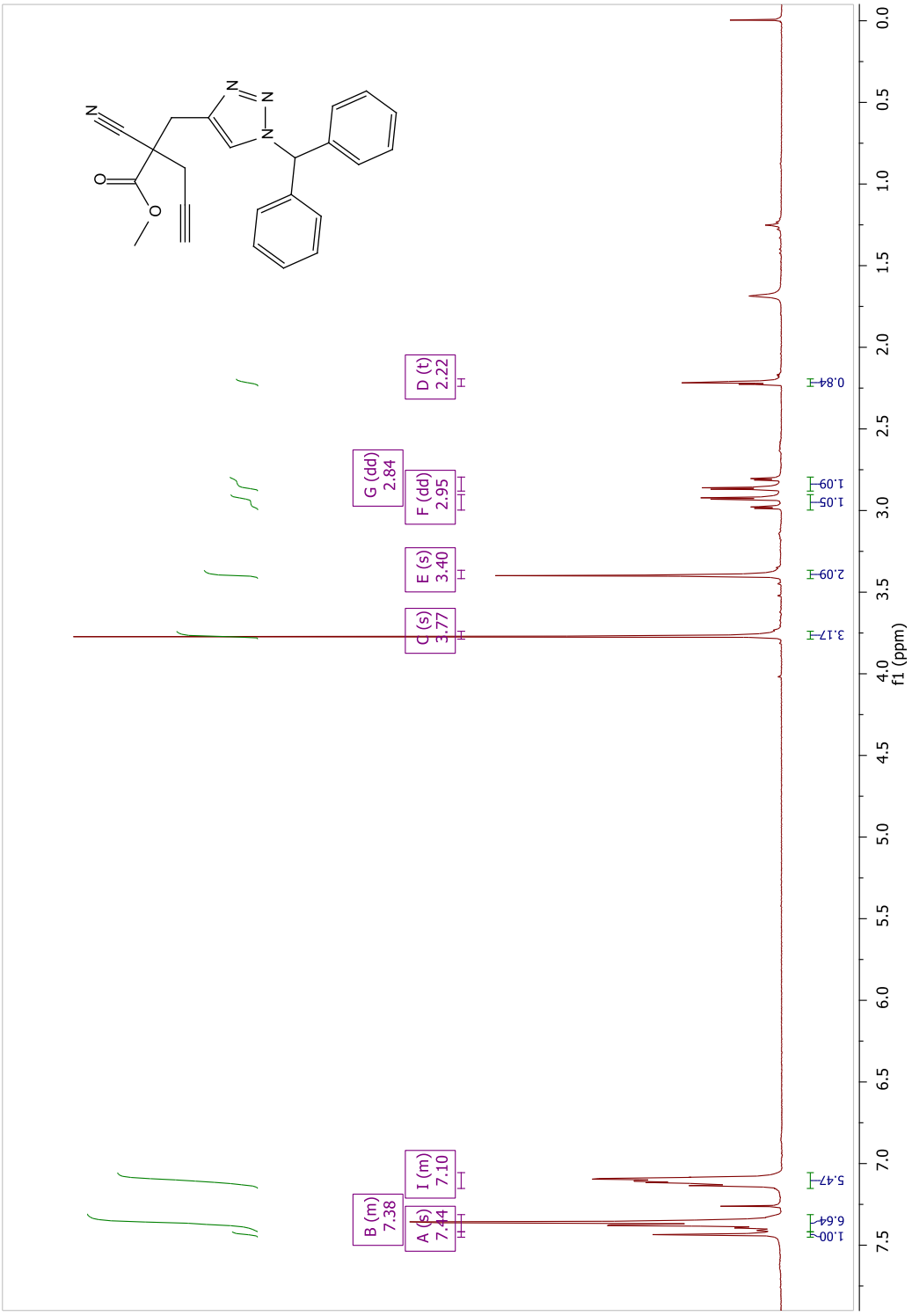


METHYL 3-(1-BENZYL-1*H*-1,2,3-TRIAZOL-4-YL)-2-((1-BENZYL-1H-1,2,3-TRIAZOL-4-YL)METHYL)-2-CYANOPROPANOATE

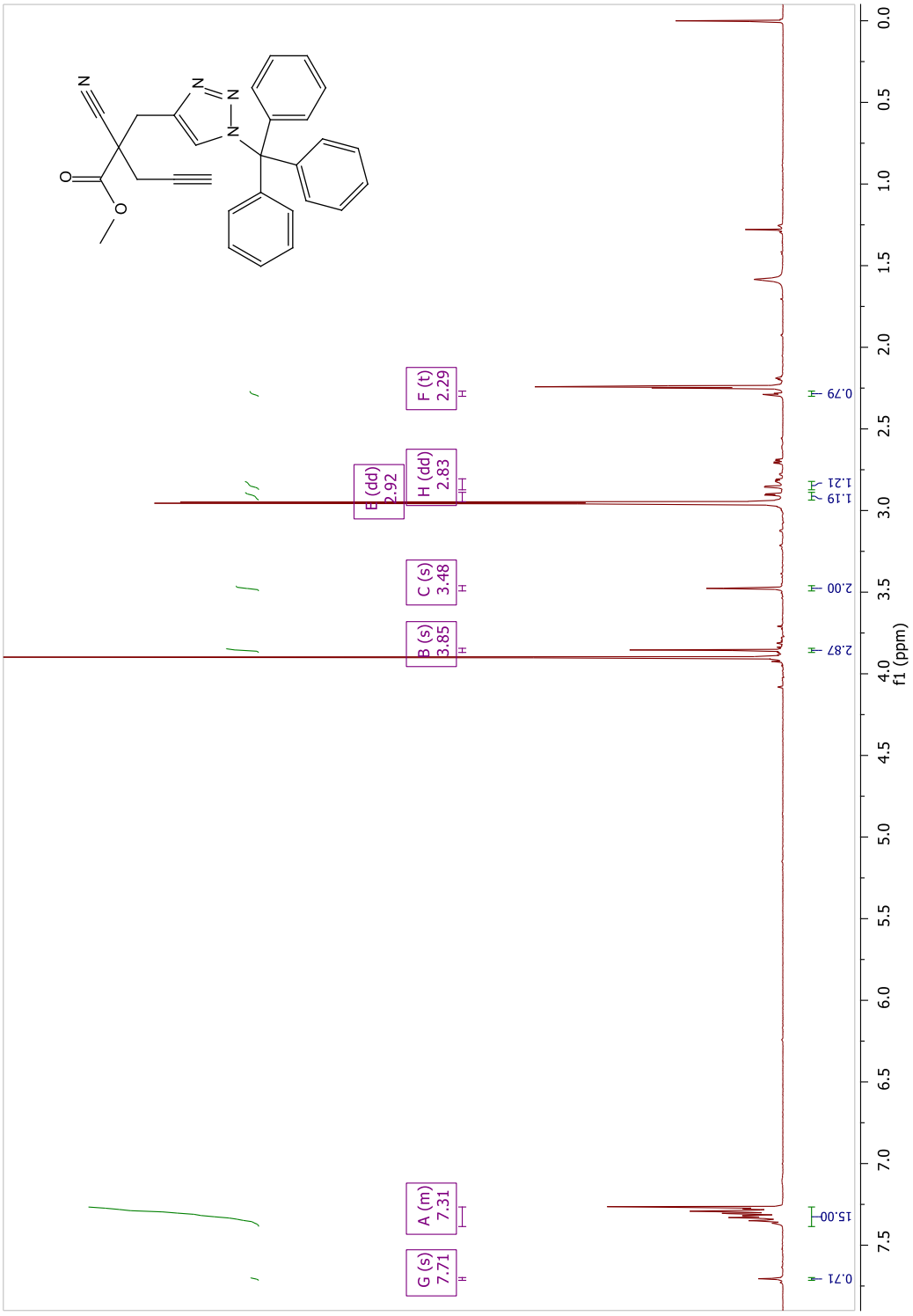
PROTON



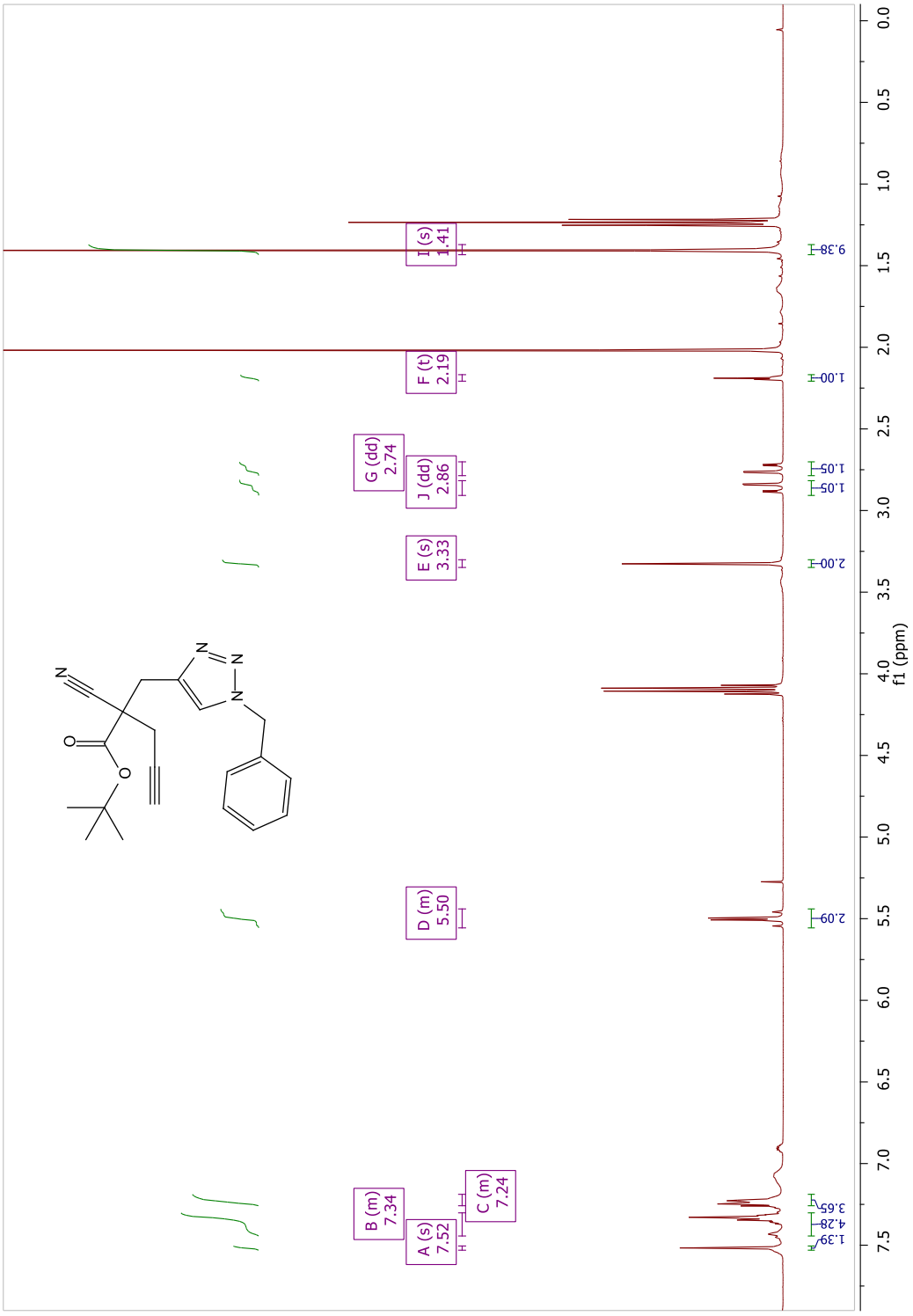
PROTON


D (t) 2.22
G (dd) 2.84
F (dd) 2.95
E (s) 3.40
C (s) 3.77
B (m) 7.38
A (s) 7.44
I (m) 7.10
0.84
1.09
1.05
2.09
3.17
5.47
6.64
1.00
f1 (ppm)

PROTON

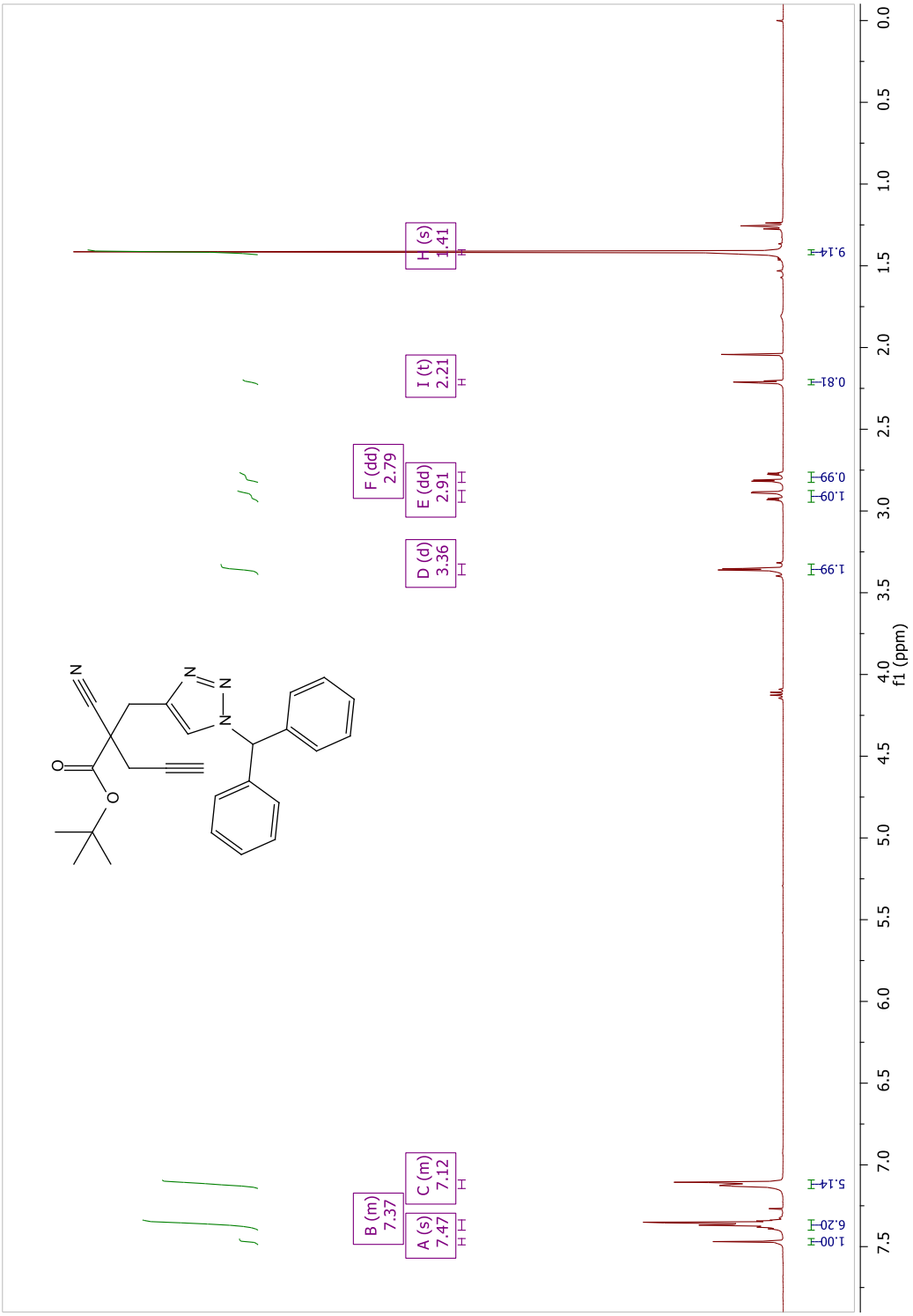

F (t) 2.29
E (dd) 2.92
H (dd) 2.83
C (s) 3.48
B (s) 3.85
A (m) 7.31
G (s) 7.71
0.79
1.19
1.21
2.00
2.87
15.00
0.71
f1 (ppm)

PROTON


I (s)
1.41
F (t)
2.19
G (dd)
2.74
J (dd)
2.86
E (s)
3.33
D (m)
5.50
B (m)
7.34
A (s)
7.52
C (m)
7.24
9.38
1.00
1.05
1.05
2.00
2.09
3.65
4.28
1.39
f1 (ppm)

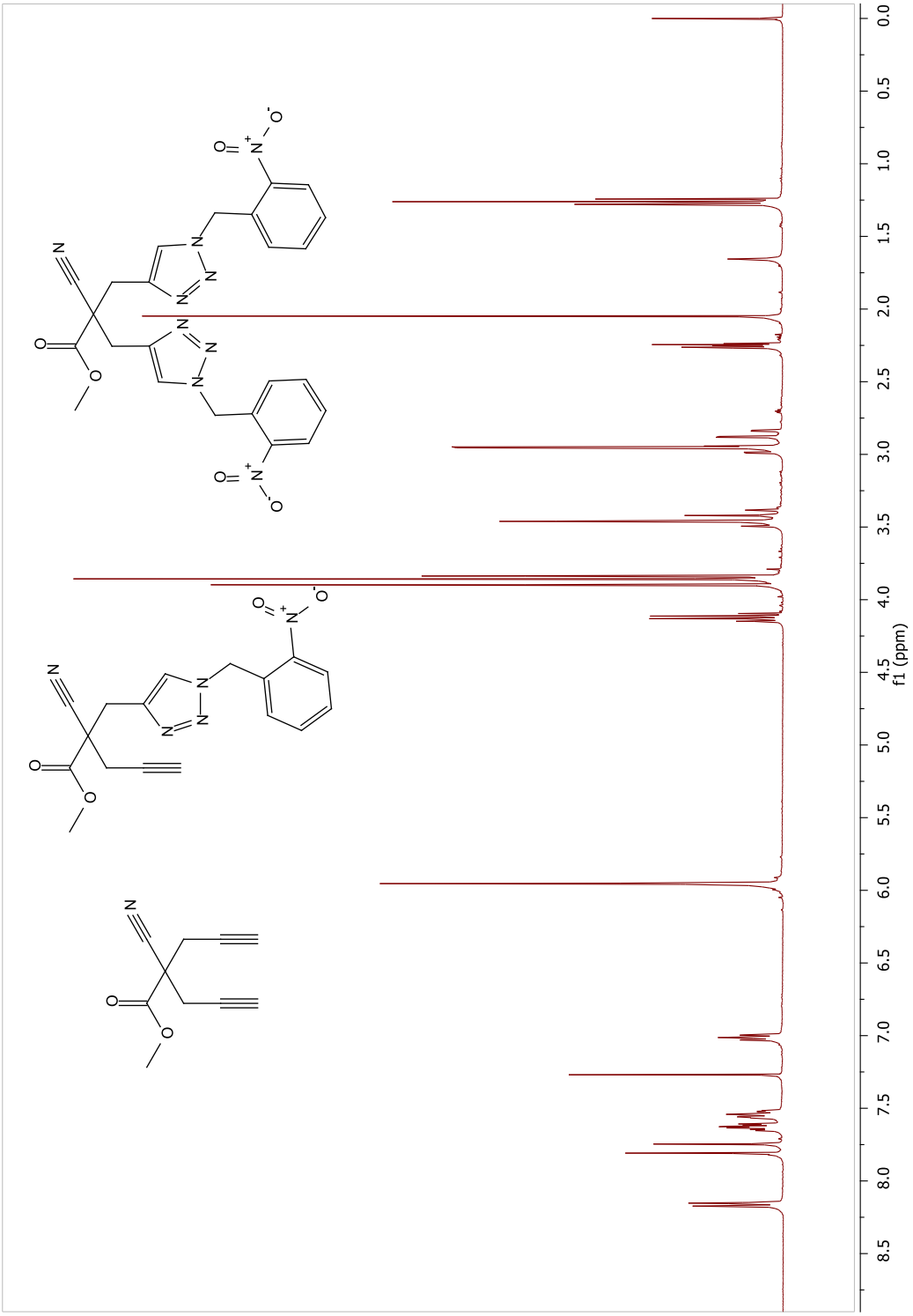
TERT-BUTYL 2-((1-BENZHYDRYL-1*H*-1,2,3-TRIAZOL-4-YL)METHYL)-2-CYANOPENT-4-YNOATE

PROTON

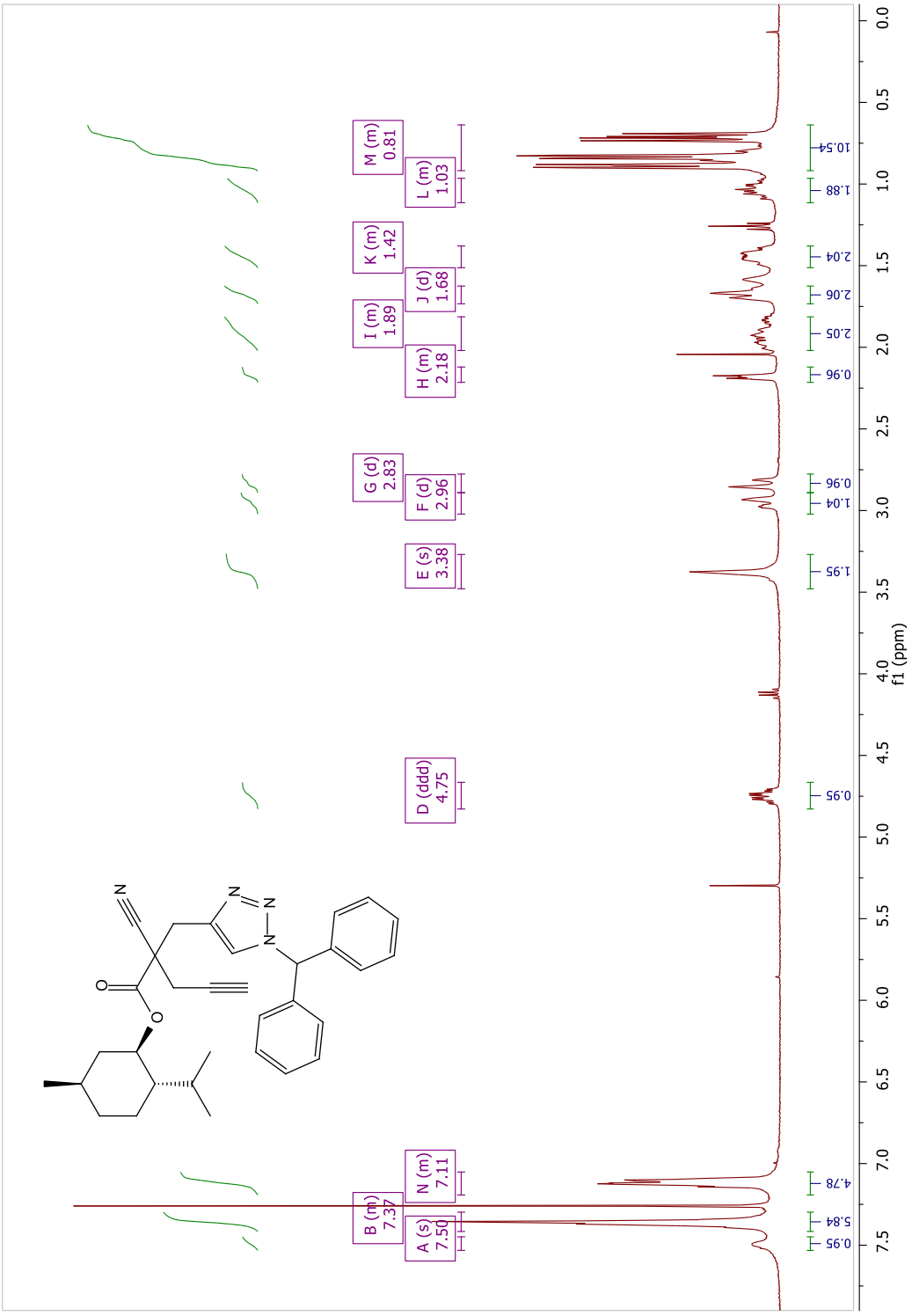


Methyl 2-((1-(2-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-cyanopent-4-ynoate

Proton showing starting material, with mono- and *bis*-triazole products.

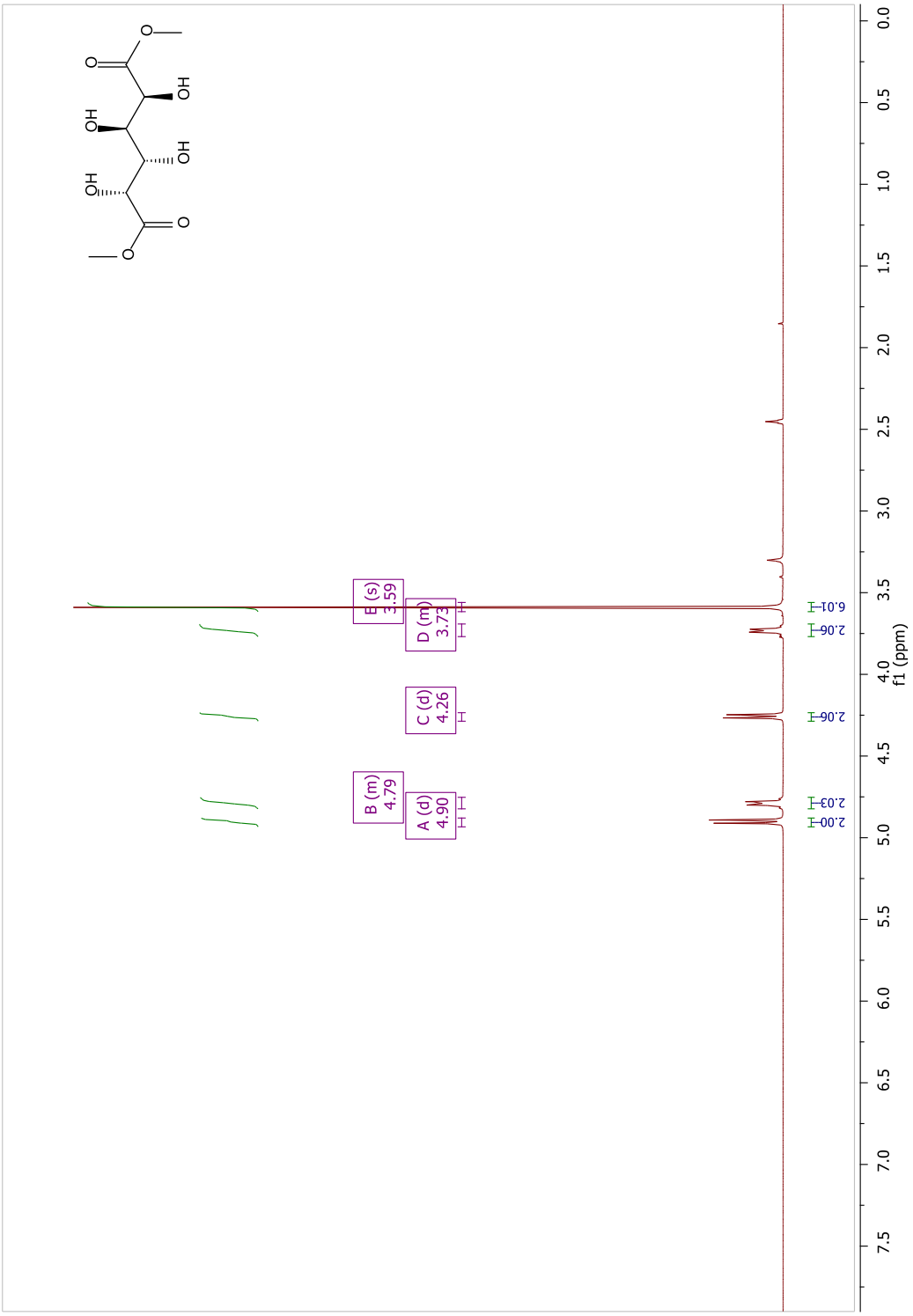


PROTON

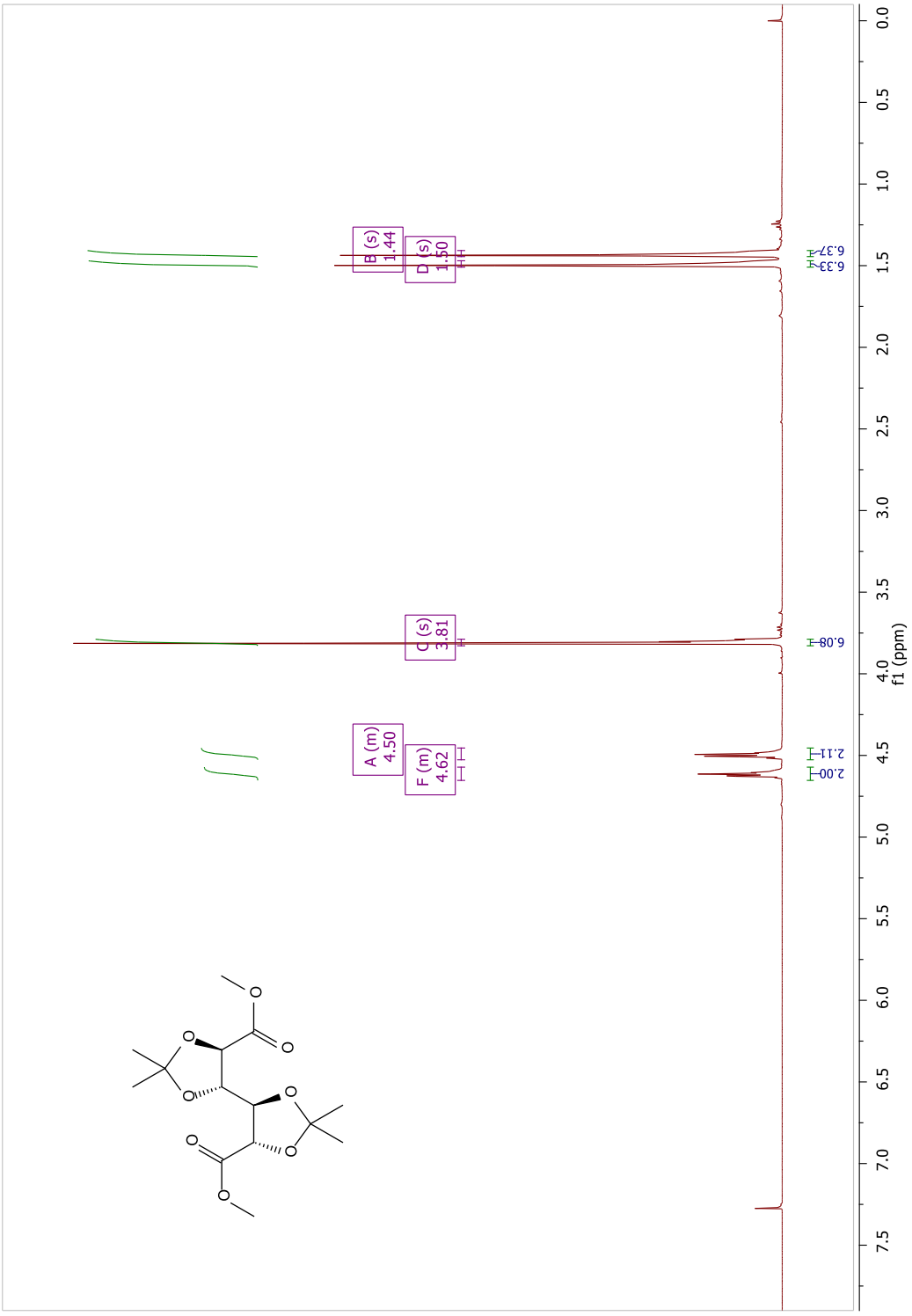

M (m) 0.81
L (m) 1.03
K (m) 1.42
J (d) 1.68
I (m) 1.89
H (m) 2.18
G (d) 2.83
F (d) 2.96
E (s) 3.38
D (ddd) 4.75
N (m) 7.11
B (m) 7.37
A (s) 7.50
10.54
1.88
2.04
2.06
2.05
0.96
0.96
1.04
1.95
0.95
4.78
5.84
0.95
f1 (ppm)

D-GALACTARIC ACID DIMETHYL ESTER

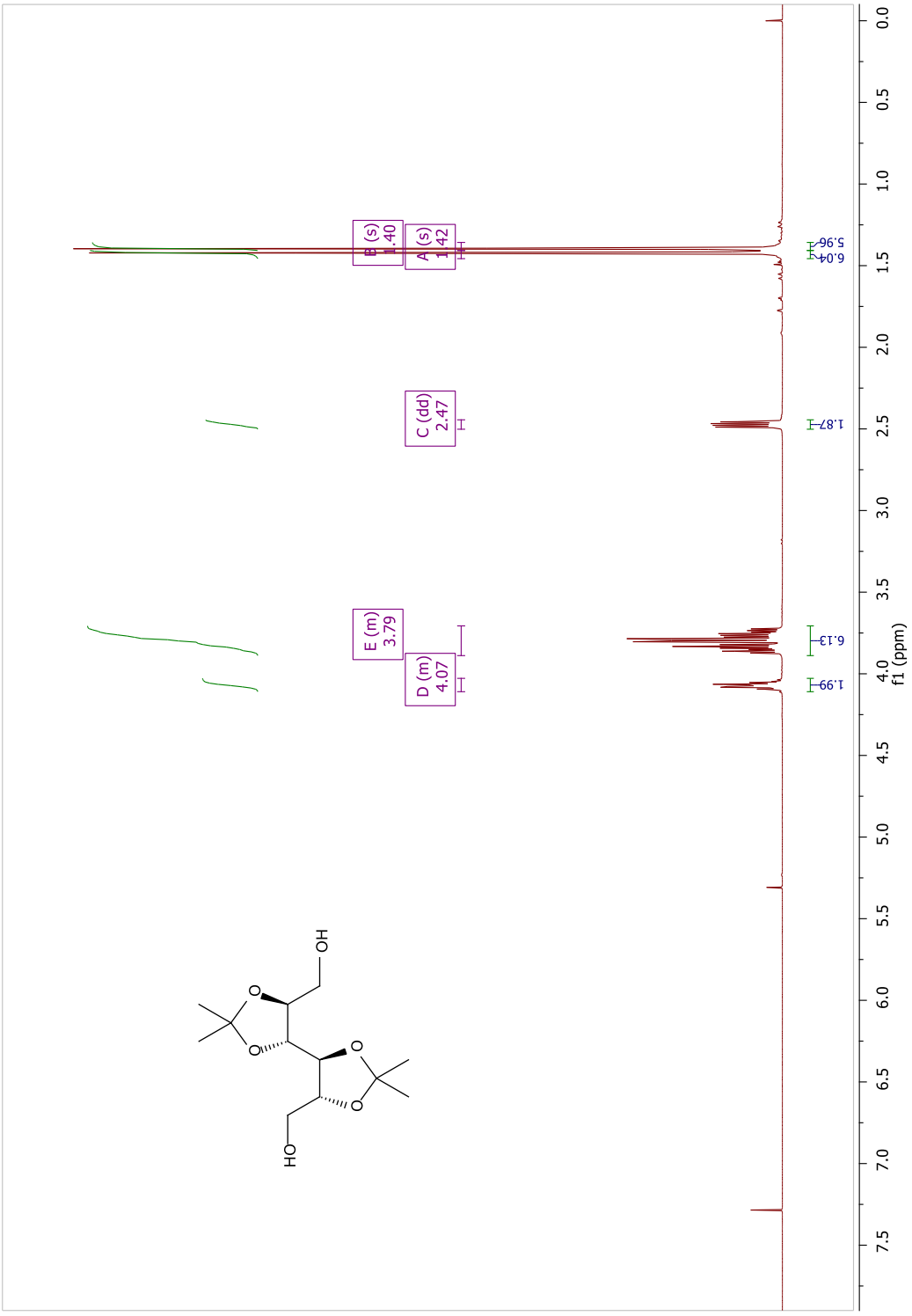
PROTON

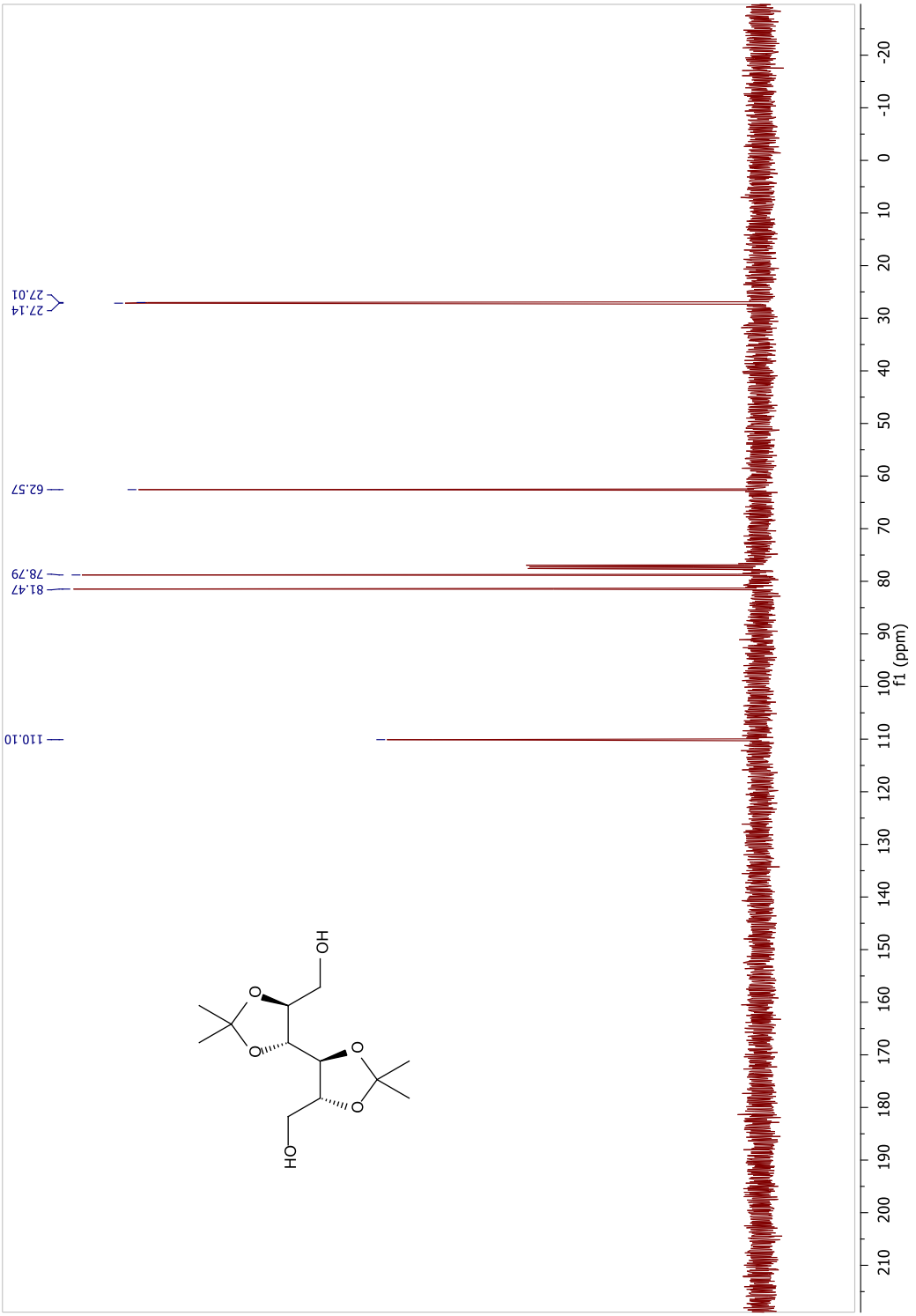


PROTON

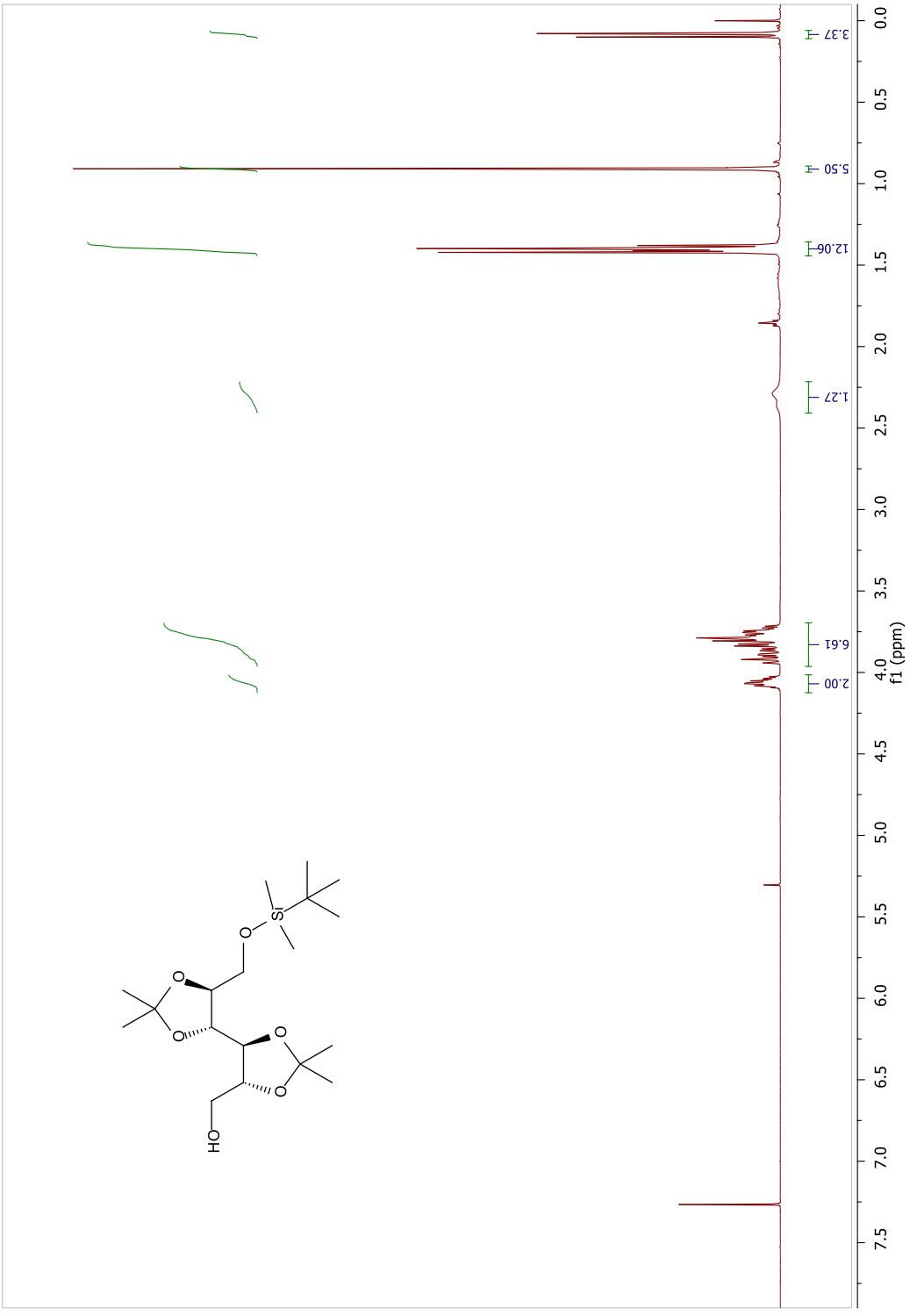


PROTON


B (s)
1.40
A (s)
1.42
C (dd)
2.47
E (m)
3.79
D (m)
4.07
5.96
6.04
1.87
6.13
1.99
f1 (ppm)
OH
HO


27.01
27.14
62.57
78.79
81.47
110.10
f1 (ppm)
OH
HO
O
O
O
O

PROTON SHOWING PARTIAL REACTION



METHYL 2-CYANO-2-(PROP-2-YN-1-YL)PENT-4-YNOATE

Computing details

Data collection: Bruker *APEX2*; cell refinement: Bruker *SAINT*; data reduction: Bruker *SAINT*; program(s) used to solve structure:*SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

Crystal data

$C_{10}H_9NO_2$	$F(000) = 368$
$M_r = 175.18$	$D_x = 1.210$ Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Hall symbol: -P 2yn	Cell parameters from 9826 reflections
$a = 8.6196$ (19) Å	$\theta = 2.4$–$30.4°$
$b = 6.748$ (2) Å	$\mu = 0.09$ mm^{-1}
$c = 17.057$ (4) Å	$T = 291$ K
$\beta = 104.204$ (13)°	Block, colorless
$V = 961.7$ (4) Å^3	0.59 × 0.32 × 0.26 mm
$Z = 4$	

Data collection

Bruker APEX-II CCD diffractometer	2700 independent reflections
Radiation source: fine-focus sealed tube	2209 reflections with $I > 2\sigma(I)$
Graphite monochromator	$R_{int} = 0.022$
φ and ω scans	$\theta_{max} = 29.6°$, $\theta_{min} = 2.5°$
Absorption correction: numerical (Saint)	$h = -11 \rightarrow 11$
$T_{min} = 0.906$, $T_{max} = 0.974$	$k = -9 \rightarrow 9$
23983 measured reflections	$l = -22 \rightarrow 23$

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.040$	Hydrogen site location: inferred from neighbouring sites
$wR(F^2) = 0.116$	All H-atom parameters refined

	$w = 1/[\sigma^2(F_o^2) + (0.056P)^2 +$
$S = 1.03$	$0.1536P]$
	where $P = (F_o^2 + 2F_c^2)/3$
2700 reflections	$(\Delta/\sigma)_{max} = 0.001$
154 parameters	$\Delta\rho_{max} = 0.23$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -0.17$ e Å^{-3}

Special details

Refinement

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

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.30160 (11)	0.22487 (14)	0.05468 (6)	0.0354 (2)
C9	0.46032 (11)	0.27406 (15)	0.11505 (6)	0.0371 (2)
C8	0.27806 (12)	0.00906 (16)	0.04457 (7)	0.0434 (2)
C5	0.31241 (13)	0.31883 (17)	−0.02712 (6)	0.0419 (2)
C2	0.16101 (12)	0.31983 (17)	0.08270 (6)	0.0406 (2)
C6	0.16604 (13)	0.29365 (17)	−0.09059 (6)	0.0458 (3)
C3	0.15046 (12)	0.25436 (16)	0.16288 (7)	0.0438 (2)
C4	0.13952 (15)	0.2035 (2)	0.22712 (9)	0.0600 (3)
C10	0.72146 (16)	0.1686 (3)	0.17699 (11)	0.0697 (4)
C7	0.04686 (17)	0.2717 (2)	−0.14089 (8)	0.0634 (4)
N1	0.25638 (14)	−0.15604 (16)	0.03437 (8)	0.0649 (3)
O2	0.56181 (9)	0.12547 (13)	0.12687 (5)	0.0552 (2)
O1	0.48822 (10)	0.43505 (13)	0.14420 (6)	0.0571 (2)
H1	0.1744 (15)	0.463 (2)	0.0825 (7)	0.047 (3)*
H5	0.4047 (16)	0.2597 (19)	−0.0437 (8)	0.053 (4)*
H2	0.0633 (17)	0.2874 (19)	0.0438 (8)	0.052 (3)*
H4	0.3330 (16)	0.455 (2)	−0.0173 (8)	0.054 (4)*
H3	0.126 (2)	0.156 (3)	0.2787 (12)	0.097 (6)*
H6	−0.048 (3)	0.252 (3)	−0.1821 (12)	0.093 (6)*
H7	0.781 (3)	0.051 (4)	0.1754 (14)	0.122 (7)*
H8	0.718 (3)	0.185 (4)	0.2307 (16)	0.125 (8)*
H9	0.772 (4)	0.279 (4)	0.1512 (19)	0.158 (11)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}

C1	0.0333 (4)	0.0320 (4)	0.0414 (5)	0.0013 (3)	0.0103 (4)	0.0011 (4)
C9	0.0351 (4)	0.0387 (5)	0.0391 (5)	0.0025 (4)	0.0121 (4)	0.0005 (4)
C8	0.0398 (5)	0.0381 (5)	0.0521 (6)	0.0006 (4)	0.0108 (4)	0.0007 (4)
C5	0.0424 (5)	0.0430 (6)	0.0418 (5)	−0.0019 (4)	0.0130 (4)	0.0022 (4)
C2	0.0350 (5)	0.0423 (6)	0.0456 (5)	0.0062 (4)	0.0123 (4)	0.0040 (4)
C6	0.0495 (6)	0.0462 (6)	0.0426 (5)	0.0059 (5)	0.0128 (4)	−0.0001 (4)
C3	0.0343 (5)	0.0472 (6)	0.0515 (6)	0.0005 (4)	0.0136 (4)	0.0017 (4)
C4	0.0502 (6)	0.0754 (9)	0.0559 (7)	−0.0030 (6)	0.0157 (5)	0.0132 (6)
C10	0.0430 (6)	0.0790 (10)	0.0753 (10)	0.0174 (7)	−0.0083 (6)	−0.0173 (8)
C7	0.0545 (7)	0.0789 (10)	0.0521 (7)	0.0119 (6)	0.0038 (6)	−0.0076 (6)
N1	0.0691 (7)	0.0384 (5)	0.0858 (8)	−0.0046 (5)	0.0162 (6)	−0.0034 (5)
O2	0.0406 (4)	0.0506 (5)	0.0670 (5)	0.0128 (3)	−0.0009 (4)	−0.0106 (4)
O1	0.0482 (4)	0.0462 (5)	0.0711 (6)	0.0013 (3)	0.0034 (4)	−0.0153 (4)

Geometric parameters (Å, º)

C1—C8	1.4746 (15)	C2—H1	0.972 (14)
C1—C9	1.5333 (14)	C2—H2	0.961 (14)
C1—C2	1.5466 (13)	C6—C7	1.1752 (18)
C1—C5	1.5559 (14)	C3—C4	1.1741 (18)
C9—O1	1.1943 (13)	C4—H3	0.970 (19)
C9—O2	1.3133 (12)	C10—O2	1.4601 (16)
C8—N1	1.1359 (15)	C10—H7	0.95 (2)
C5—C6	1.4568 (16)	C10—H8	0.93 (3)
C5—H5	0.991 (13)	C10—H9	1.01 (3)
C5—H4	0.942 (15)	C7—H6	0.95 (2)
C2—C3	1.4610 (15)		
C8—C1—C9	111.52 (8)	C3—C2—H1	109.8 (7)
C8—C1—C2	110.46 (8)	C1—C2—H1	107.9 (7)
C9—C1—C2	109.90 (8)	C3—C2—H2	109.4 (8)
C8—C1—C5	109.54 (9)	C1—C2—H2	108.2 (8)
C9—C1—C5	105.91 (8)	H1—C2—H2	108.0 (10)
C2—C1—C5	109.40 (8)	C7—C6—C5	178.88 (13)

O1—C9—O2	124.89 (10)	C4—C3—C2	178.84 (12)
O1—C9—C1	122.13 (9)	C3—C4—H3	176.7 (12)
O2—C9—C1	112.88 (9)	O2—C10—H7	104.6 (14)
N1—C8—C1	177.70 (13)	O2—C10—H8	110.4 (15)
C6—C5—C1	112.78 (9)	H7—C10—H8	106 (2)
C6—C5—H5	110.5 (8)	O2—C10—H9	109.6 (17)
C1—C5—H5	108.7 (7)	H7—C10—H9	108 (2)
C6—C5—H4	109.7 (8)	H8—C10—H9	117 (2)
C1—C5—H4	106.7 (8)	C6—C7—H6	178.6 (12)
H5—C5—H4	108.3 (11)	C9—O2—C10	115.74 (10)
C3—C2—C1	113.42 (8)		

Computing details

Program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008).

Crystal data

$C_{13}H_{15}NO_2$	V = 2759.5 (6) Å^3
M_r = 217.26	Z = 8
?, ?	F(000) = 928
a = 18.921 (2) Å	D_x = 1.046 Mg m^{-3}
b = 9.2761 (11) Å	Mo $K\alpha$ radiation, λ = 0.71073 Å
c = 17.744 (2) Å	μ = 0.07 mm^{-1}
α = 90°	T = 291 K
β = 117.614 (4)°	× × mm
γ = 90°	

Data collection

Radiation source: fine-focus sealed tube	R_{int} = 0.026
Graphite monochromator	θ_{max} = 25.4°, θ_{min} = 2.5°
14693 measured reflections	h = −21→22
4689 independent reflections	k = −11→8
3494 reflections with $I > 2\sigma(I)$	l = −21→21

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)]$ = 0.053	Hydrogen site location: inferred from neighbouring sites
$wR(F^2)$ = 0.193	H atoms treated by a mixture of independent and constrained refinement
S = 1.07	$w = 1/[\sigma^2(F_o^2) + (0.1308P)^2 + 0.1072P]$ where $P = (F_o^2 + 2F_c^2)/3$
4689 reflections	$(\Delta/\sigma)_{max} < 0.001$
295 parameters	$\Delta\rho_{max}$ = 0.17 e Å^{-3}
0 restraints	$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Special details

Refinement

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

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C9	0.41320 (11)	0.26397 (18)	0.29103 (11)	0.0521 (5)
C1	0.45465 (11)	0.39252 (17)	0.27408 (10)	0.0488 (4)
C8	0.42527 (11)	0.53004 (19)	0.29019 (11)	0.0533 (5)
C2	0.43880 (13)	0.3872 (2)	0.18031 (12)	0.0594 (5)
H2A	0.4658	0.4675	0.1697	0.071*
H2B	0.4609	0.2988	0.1709	0.071*
C5	0.54529 (12)	0.3793 (2)	0.33313 (12)	0.0640 (5)
H5A	0.5649	0.2922	0.3190	0.077*
H5B	0.5723	0.4607	0.3235	0.077*
C10	0.32159 (13)	0.1957 (2)	0.34818 (13)	0.0662 (6)
C3	0.35483 (17)	0.3938 (2)	0.12118 (14)	0.0676 (6)
C6	0.56448 (14)	0.3751 (3)	0.42222 (14)	0.0799 (6)
C12	0.27899 (19)	0.2931 (3)	0.3824 (2)	0.0974 (9)
H12A	0.3175	0.3425	0.4320	0.146*
H12B	0.2448	0.2364	0.3971	0.146*
H12C	0.2476	0.3624	0.3397	0.146*
C4	0.2862 (2)	0.3973 (3)	0.07436 (19)	0.1028 (9)
H4	0.2318	0.4002	0.0373	0.123*
C13	0.26224 (19)	0.1217 (3)	0.2684 (2)	0.1051 (9)
H13A	0.2322	0.1927	0.2263	0.158*
H13B	0.2266	0.0645	0.2809	0.158*
H13C	0.2900	0.0606	0.2472	0.158*
C11	0.3793 (2)	0.0952 (3)	0.4150 (2)	0.1147 (11)
H11A	0.4035	0.0336	0.3900	0.172*
H11B	0.3512	0.0375	0.4374	0.172*
H11C	0.4198	0.1504	0.4600	0.172*
C7	0.5761 (2)	0.3717 (4)	0.49276 (18)	0.1263 (12)
H7	0.5854	0.3691	0.5490	0.152*
C22	0.07206 (12)	0.80723 (18)	0.88462 (11)	0.0539 (5)
C14	0.04357 (11)	0.68081 (18)	0.82168 (10)	0.0532 (5)
C21	0.08446 (12)	0.54547 (19)	0.86167 (11)	0.0561 (5)
C23	0.16896 (13)	0.8739 (2)	1.03081 (11)	0.0605 (5)
C18	0.06077 (14)	0.7173 (2)	0.74647 (12)	0.0650 (6)
H18A	0.0456	0.6358	0.7079	0.078*

H18B	0.0280	0.7987	0.7155	0.078*
C19	0.14408 (16)	0.7519 (2)	0.77332 (14)	0.0713 (6)
C15	−0.04736 (13)	0.6611 (2)	0.78842 (13)	0.0673 (5)
H15A	−0.0746	0.7492	0.7606	0.081*
H15B	−0.0662	0.5844	0.7465	0.081*
C16	−0.06727 (15)	0.6265 (3)	0.85587 (17)	0.0858 (7)
C25	0.23218 (16)	0.7814 (3)	1.09774 (15)	0.0882 (7)
H25A	0.2075	0.7021	1.1113	0.132*
H25B	0.2622	0.8379	1.1479	0.132*
H25C	0.2672	0.7451	1.0767	0.132*
C20	0.2099 (2)	0.7815 (3)	0.79445 (19)	0.0999 (9)
H20	0.2629	0.8054	0.8115	0.120*
C24	0.20600 (19)	0.9949 (3)	1.00444 (18)	0.1012 (8)
H24A	0.2374	0.9555	0.9797	0.152*
H24B	0.2395	1.0515	1.0534	0.152*
H24C	0.1647	1.0548	0.9635	0.152*
C26	0.10762 (16)	0.9209 (3)	1.05738 (15)	0.0961 (8)
H26A	0.0679	0.9791	1.0133	0.144*
H26B	0.1331	0.9762	1.1089	0.144*
H26C	0.0827	0.8376	1.0669	0.144*
C17	−0.0790 (2)	0.5975 (4)	0.9128 (2)	0.1342 (13)
H17	−0.0883	0.5742	0.9584	0.161*
O2	0.36727 (8)	0.30322 (11)	0.32470 (7)	0.0534 (4)
O4	0.13010 (8)	0.76968 (12)	0.95851 (7)	0.0541 (4)
O1	0.42465 (10)	0.14398 (14)	0.27454 (10)	0.0800 (5)
O3	0.04207 (10)	0.92369 (14)	0.86343 (8)	0.0790 (5)
N1	0.40393 (12)	0.63920 (17)	0.30183 (11)	0.0720 (5)
N2	0.11262 (12)	0.43739 (19)	0.88952 (11)	0.0770 (5)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C9	0.0554 (12)	0.0541 (9)	0.0539 (10)	0.0037 (8)	0.0313 (10)	0.0001 (7)
C1	0.0458 (11)	0.0551 (9)	0.0501 (10)	0.0013 (7)	0.0262 (10)	0.0002 (7)
C8	0.0543 (12)	0.0555 (10)	0.0553 (10)	−0.0046 (8)	0.0299 (10)	−0.0008 (7)
C2	0.0647 (15)	0.0691 (11)	0.0558 (11)	0.0005 (9)	0.0377 (12)	−0.0002 (8)
C5	0.0545 (14)	0.0768 (12)	0.0673 (12)	0.0017 (9)	0.0338 (12)	0.0017 (9)
C10	0.0781 (15)	0.0607 (10)	0.0804 (13)	−0.0133 (10)	0.0541 (13)	−0.0038 (9)
C3	0.0717 (19)	0.0810 (13)	0.0527 (13)	0.0090 (11)	0.0310 (15)	−0.0007 (9)

C6	0.0497 (14)	0.1204 (18)	0.0616 (14)	−0.0008 (12)	0.0189 (12)	−0.0017 (11)
C12	0.116 (2)	0.0892 (15)	0.138 (2)	−0.0177 (14)	0.102 (2)	−0.0161 (14)
C4	0.081 (2)	0.144 (3)	0.0706 (17)	0.0194 (18)	0.0244 (18)	−0.0085 (15)
C13	0.108 (2)	0.0990 (18)	0.124 (2)	−0.0508 (16)	0.067 (2)	−0.0369 (15)
C11	0.143 (3)	0.113 (2)	0.120 (2)	0.0221 (18)	0.087 (2)	0.0495 (17)
C7	0.082 (2)	0.225 (4)	0.0630 (16)	−0.001 (2)	0.0261 (17)	−0.0040 (18)
C22	0.0576 (13)	0.0546 (10)	0.0497 (11)	0.0062 (9)	0.0251 (11)	0.0026 (7)
C14	0.0506 (12)	0.0546 (9)	0.0470 (10)	0.0065 (8)	0.0163 (10)	0.0024 (7)
C21	0.0479 (12)	0.0573 (10)	0.0513 (10)	−0.0007 (9)	0.0130 (10)	−0.0059 (8)
C23	0.0605 (13)	0.0676 (11)	0.0526 (11)	−0.0065 (9)	0.0255 (11)	−0.0150 (8)
C18	0.0779 (16)	0.0666 (11)	0.0514 (11)	0.0003 (10)	0.0308 (12)	−0.0030 (8)
C19	0.0844 (19)	0.0732 (13)	0.0697 (13)	−0.0081 (12)	0.0471 (14)	−0.0106 (9)
C15	0.0530 (13)	0.0725 (12)	0.0650 (12)	0.0050 (9)	0.0176 (11)	0.0039 (9)
C16	0.0580 (16)	0.1047 (17)	0.0946 (17)	0.0035 (12)	0.0352 (15)	0.0153 (13)
C25	0.0784 (19)	0.0975 (16)	0.0628 (14)	0.0080 (13)	0.0108 (14)	−0.0140 (11)
C20	0.094 (2)	0.119 (2)	0.106 (2)	−0.0273 (17)	0.063 (2)	−0.0228 (15)
C24	0.114 (2)	0.0870 (16)	0.0989 (17)	−0.0399 (15)	0.0461 (17)	−0.0182 (13)
C26	0.0819 (18)	0.135 (2)	0.0775 (15)	0.0095 (15)	0.0421 (15)	−0.0309 (14)
C17	0.097 (3)	0.198 (4)	0.131 (3)	0.013 (2)	0.073 (2)	0.040 (2)
O2	0.0591 (9)	0.0527 (6)	0.0622 (8)	−0.0068 (5)	0.0398 (7)	−0.0064 (5)
O4	0.0556 (9)	0.0549 (7)	0.0476 (7)	0.0014 (6)	0.0205 (7)	−0.0038 (5)
O1	0.1078 (13)	0.0522 (8)	0.1142 (12)	0.0069 (7)	0.0804 (11)	−0.0024 (7)
O3	0.0958 (13)	0.0591 (8)	0.0639 (9)	0.0217 (8)	0.0216 (9)	0.0039 (6)
N1	0.0855 (14)	0.0585 (9)	0.0861 (12)	0.0007 (8)	0.0517 (12)	−0.0027 (8)
N2	0.0724 (13)	0.0614 (10)	0.0762 (12)	0.0102 (9)	0.0167 (11)	−0.0002 (8)

Geometric parameters (Å, º)

C9—O1	1.1960 (19)	C22—O3	1.197 (2)
C9—O2	1.314 (2)	C22—O4	1.308 (2)
C9—C1	1.532 (2)	C22—C14	1.535 (2)
C1—C8	1.472 (2)	C14—C21	1.473 (3)
C1—C5	1.545 (3)	C14—C15	1.549 (3)
C1—C2	1.549 (2)	C14—C18	1.551 (2)
C8—N1	1.144 (2)	C21—N2	1.135 (2)
C2—C3	1.443 (4)	C23—O4	1.499 (2)
C2—H2A	0.9700	C23—C25	1.503 (3)
C2—H2B	0.9700	C23—C26	1.506 (3)
C5—C6	1.449 (3)	C23—C24	1.508 (3)
C5—H5A	0.9700	C18—C19	1.455 (3)
C5—H5B	0.9700	C18—H18A	0.9700
C10—O2	1.500 (2)	C18—H18B	0.9700
C10—C13	1.504 (3)	C19—C20	1.156 (4)
C10—C11	1.505 (4)	C15—C16	1.447 (3)
C10—C12	1.512 (3)	C15—H15A	0.9700
C3—C4	1.173 (4)	C15—H15B	0.9700
C6—C7	1.166 (3)	C16—C17	1.161 (4)
C12—H12A	0.9600	C25—H25A	0.9600
C12—H12B	0.9600	C25—H25B	0.9600
C12—H12C	0.9600	C25—H25C	0.9600
C4—H4	0.9300	C20—H20	0.9300
C13—H13A	0.9600	C24—H24A	0.9600
C13—H13B	0.9600	C24—H24B	0.9600
C13—H13C	0.9600	C24—H24C	0.9600
C11—H11A	0.9600	C26—H26A	0.9600
C11—H11B	0.9600	C26—H26B	0.9600
C11—H11C	0.9600	C26—H26C	0.9600
C7—H7	0.9300	C17—H17	0.9300
O1—C9—O2	127.03 (16)	O3—C22—C14	120.37 (17)
O1—C9—C1	120.60 (15)	O4—C22—C14	111.99 (14)
O2—C9—C1	112.36 (13)	C21—C14—C22	111.83 (15)
C8—C1—C9	111.27 (13)	C21—C14—C15	108.99 (15)
C8—C1—C5	109.72 (15)	C22—C14—C15	108.72 (15)
C9—C1—C5	108.27 (14)	C21—C14—C18	109.15 (15)
C8—C1—C2	109.49 (14)	C22—C14—C18	108.43 (14)
C9—C1—C2	108.95 (14)	C15—C14—C18	109.70 (15)
C5—C1—C2	109.10 (15)	N2—C21—C14	176.5 (2)
N1—C8—C1	177.82 (18)	O4—C23—C25	101.72 (15)
C3—C2—C1	112.29 (15)	O4—C23—C26	108.15 (17)
C3—C2—H2A	109.1	C25—C23—C26	111.39 (19)

C1—C2—H2A	109.1	O4—C23—C24	109.18 (15)
C3—C2—H2B	109.1	C25—C23—C24	110.8 (2)
C1—C2—H2B	109.1	C26—C23—C24	114.7 (2)
H2A—C2—H2B	107.9	C19—C18—C14	113.20 (17)
C6—C5—C1	112.33 (16)	C19—C18—H18A	108.9
C6—C5—H5A	109.1	C14—C18—H18A	108.9
C1—C5—H5A	109.1	C19—C18—H18B	108.9
C6—C5—H5B	109.1	C14—C18—H18B	108.9
C1—C5—H5B	109.1	H18A—C18—H18B	107.8
H5A—C5—H5B	107.9	C20—C19—C18	179.0 (3)
O2—C10—C13	108.51 (16)	C16—C15—C14	112.33 (17)
O2—C10—C11	109.25 (19)	C16—C15—H15A	109.1
C13—C10—C11	114.2 (2)	C14—C15—H15A	109.1
O2—C10—C12	101.37 (15)	C16—C15—H15B	109.1
C13—C10—C12	110.2 (2)	C14—C15—H15B	109.1
C11—C10—C12	112.4 (2)	H15A—C15—H15B	107.9
C4—C3—C2	178.5 (2)	C17—C16—C15	176.3 (3)
C7—C6—C5	176.8 (3)	C23—C25—H25A	109.5
C10—C12—H12A	109.5	C23—C25—H25B	109.5
C10—C12—H12B	109.5	H25A—C25—H25B	109.5
H12A—C12—H12B	109.5	C23—C25—H25C	109.5
C10—C12—H12C	109.5	H25A—C25—H25C	109.5
H12A—C12—H12C	109.5	H25B—C25—H25C	109.5
H12B—C12—H12C	109.5	C19—C20—H20	180.0
C3—C4—H4	180.0	C23—C24—H24A	109.5
C10—C13—H13A	109.5	C23—C24—H24B	109.5
C10—C13—H13B	109.5	H24A—C24—H24B	109.5
H13A—C13—H13B	109.5	C23—C24—H24C	109.5
C10—C13—H13C	109.5	H24A—C24—H24C	109.5
H13A—C13—H13C	109.5	H24B—C24—H24C	109.5
H13B—C13—H13C	109.5	C23—C26—H26A	109.5
C10—C11—H11A	109.5	C23—C26—H26B	109.5
C10—C11—H11B	109.5	H26A—C26—H26B	109.5
H11A—C11—H11B	109.5	C23—C26—H26C	109.5
C10—C11—H11C	109.5	H26A—C26—H26C	109.5
H11A—C11—H11C	109.5	H26B—C26—H26C	109.5
H11B—C11—H11C	109.5	C16—C17—H17	180.0
C6—C7—H7	180.0	C9—O2—C10	122.00 (13)
O3—C22—O4	127.64 (17)	C22—O4—C23	122.48 (14)

Computing details

Data collection: Bruker *APEX2*; cell refinement: Bruker *SAINT*; data reduction: Bruker *SAINT*; program(s) used to solve structure:*SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

Crystal data

$C_{19}H_{25}NO_2$	D_x = 1.120 Mg m^{-3}
M_r = 299.40	Mo $K\alpha$ radiation, λ = 0.71073 Å
Hexagonal, $P6_5$	Cell parameters from 9000 reflections
Hall symbol: P 65	θ = 2.4–30.8°
a = 10.4912 (2) Å	μ = 0.07 mm^{-1}
c = 27.9324 (6) Å	T = 150 K
V = 2662.50 (9) Å^3	Block, colorless
Z = 6	0.41 × 0.40 × 0.33 mm
F(000) = 972	

Data collection

Bruker APEX-II CCD diffractometer	5099 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	R_{int} = 0.030
Graphite monochromator	θ_{max} = 30.5°, θ_{min} = 2.2°
φ and ω scans	h = −14→14
70214 measured reflections	k = −14→14
5401 independent reflections	l = −39→39

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)]$ = 0.031	All H-atom parameters refined
$wR(F^2)$ = 0.080	$w = 1/[\sigma^2(F_o^2) + (0.0481P)^2 + 0.1856P]$ where $P = (F_o^2 + 2F_c^2)/3$
S = 1.04	$(\Delta/\sigma)_{max}$ = 0.001
5401 reflections	$\Delta\rho_{max}$ = 0.23 e Å^{-3}
299 parameters	$\Delta\rho_{min}$ = −0.12 e Å^{-3}
1 restraint	Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881

Primary atom site location: structure-invariant direct methods

Absolute structure parameter: 1.2 (6)

Special details

Refinement

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

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
N1	0.31634 (10)	1.09908 (10)	0.19531 (3)	0.02988 (18)
O2	0.53700 (7)	1.02433 (8)	0.12887 (2)	0.02323 (13)
O1	0.51696 (10)	1.05475 (12)	0.04998 (3)	0.0433 (2)
C11	0.62402 (10)	0.85951 (10)	0.15330 (3)	0.02178 (16)
C15	0.79823 (10)	1.12790 (10)	0.13222 (4)	0.02521 (17)
C1	0.38526 (9)	1.12169 (10)	0.10463 (3)	0.02147 (16)
C14	0.93050 (10)	1.10411 (10)	0.13012 (3)	0.02394 (17)
C10	0.65438 (9)	0.98843 (10)	0.12095 (3)	0.02173 (16)
C3	0.35030 (10)	1.10659 (10)	0.15615 (3)	0.02164 (16)
C12	0.75586 (11)	0.83419 (11)	0.14787 (4)	0.02689 (18)
C2	0.48785 (10)	1.06181 (11)	0.09105 (3)	0.02384 (17)
C7	0.46477 (11)	1.28769 (11)	0.09112 (4)	0.02740 (18)
C16	0.47255 (10)	0.72217 (10)	0.14417 (3)	0.02655 (18)
C13	0.90067 (10)	0.97161 (12)	0.16089 (4)	0.02830 (19)
C4	0.24030 (11)	1.03349 (12)	0.07593 (3)	0.02756 (18)
C18	0.43998 (13)	0.60084 (12)	0.18049 (4)	0.0352 (2)
C5	0.16661 (12)	0.87762 (13)	0.08899 (4)	0.0347 (2)
C19	1.06959 (11)	1.24416 (12)	0.14546 (4)	0.0315 (2)
C9	0.70321 (14)	1.43727 (13)	0.14442 (5)	0.0404 (2)
C8	0.59783 (11)	1.37317 (11)	0.11974 (4)	0.02993 (19)
C17	0.45205 (14)	0.66160 (14)	0.09321 (4)	0.0384 (2)
C6	0.11516 (17)	0.75370 (16)	0.10150 (6)	0.0523 (3)
H4	0.1769 (14)	1.0748 (14)	0.0821 (5)	0.024 (3)*
H2	0.3920 (16)	1.3222 (15)	0.0957 (5)	0.034 (3)*
H3	0.784 (3)	1.486 (3)	0.1643 (9)	0.080 (6)*
H1	0.4867 (15)	1.2921 (15)	0.0573 (5)	0.028 (3)*
H6	0.080 (3)	0.663 (3)	0.1122 (8)	0.079 (7)*
H7	0.6494 (15)	0.9593 (15)	0.0882 (5)	0.028 (3)*
H14	0.7938 (14)	1.1606 (14)	0.1657 (5)	0.025 (3)*

H15	0.8095 (17)	1.2059 (17)	0.1099 (6)	0.040 (4)*
H13	0.9437 (13)	1.0814 (13)	0.0958 (4)	0.020 (3)*
H9	0.7608 (15)	0.8089 (14)	0.1175 (5)	0.026 (3)*
H12	0.8941 (15)	0.9941 (16)	0.1962 (5)	0.031 (3)*
H8	0.6224 (13)	0.8880 (14)	0.1854 (4)	0.019 (3)*
H10	0.7409 (17)	0.7517 (17)	0.1676 (5)	0.040 (4)*
H11	0.9862 (16)	0.9511 (15)	0.1582 (6)	0.035 (3)*
H16	0.3987 (14)	0.7508 (14)	0.1487 (5)	0.028 (3)*
H25	1.1535 (17)	1.2334 (17)	0.1462 (6)	0.040 (4)*
H18	0.3542 (19)	0.5720 (18)	0.0902 (6)	0.049 (4)*
H23	1.0923 (16)	1.3229 (17)	0.1237 (5)	0.037 (3)*
H21	0.4592 (17)	0.6392 (18)	0.2125 (5)	0.037 (4)*
H19	0.4636 (18)	0.735 (2)	0.0702 (7)	0.049 (4)*
H20	0.3369 (19)	0.5251 (18)	0.1765 (6)	0.043 (4)*
H24	1.057 (2)	1.273 (2)	0.1772 (7)	0.051 (5)*
H17	0.5218 (19)	0.6310 (18)	0.0849 (6)	0.049 (4)*
H22	0.4959 (19)	0.5549 (19)	0.1751 (6)	0.046 (4)*
H5	0.2667 (16)	1.0480 (16)	0.0427 (5)	0.034 (3)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0310 (4)	0.0338 (4)	0.0266 (4)	0.0176 (4)	0.0041 (3)	0.0051 (3)
O2	0.0235 (3)	0.0309 (3)	0.0226 (3)	0.0191 (3)	0.0002 (2)	0.0004 (2)
O1	0.0550 (5)	0.0799 (7)	0.0221 (3)	0.0540 (5)	0.0040 (3)	0.0036 (4)
C11	0.0239 (4)	0.0240 (4)	0.0214 (4)	0.0150 (3)	−0.0009 (3)	−0.0018 (3)
C15	0.0233 (4)	0.0244 (4)	0.0321 (5)	0.0150 (3)	0.0010 (3)	0.0002 (3)
C1	0.0201 (4)	0.0270 (4)	0.0219 (4)	0.0152 (3)	0.0001 (3)	0.0027 (3)
C14	0.0215 (4)	0.0284 (4)	0.0249 (4)	0.0148 (3)	−0.0005 (3)	−0.0030 (3)
C10	0.0215 (4)	0.0279 (4)	0.0226 (4)	0.0175 (3)	0.0004 (3)	−0.0003 (3)
C3	0.0199 (4)	0.0228 (4)	0.0253 (4)	0.0130 (3)	−0.0005 (3)	0.0026 (3)
C12	0.0283 (4)	0.0266 (4)	0.0324 (5)	0.0187 (4)	−0.0017 (4)	−0.0001 (4)
C2	0.0226 (4)	0.0299 (4)	0.0241 (4)	0.0170 (3)	0.0004 (3)	0.0008 (3)
C7	0.0278 (4)	0.0285 (4)	0.0295 (4)	0.0167 (4)	0.0033 (3)	0.0088 (3)
C16	0.0242 (4)	0.0257 (4)	0.0290 (4)	0.0119 (4)	−0.0005 (3)	−0.0031 (3)
C13	0.0239 (4)	0.0333 (5)	0.0326 (5)	0.0180 (4)	−0.0044 (3)	0.0000 (4)
C4	0.0252 (4)	0.0364 (5)	0.0258 (4)	0.0189 (4)	−0.0057 (3)	−0.0027 (4)
C18	0.0351 (5)	0.0286 (5)	0.0363 (5)	0.0118 (4)	0.0062 (4)	0.0025 (4)
C5	0.0287 (5)	0.0374 (5)	0.0361 (5)	0.0151 (4)	−0.0081 (4)	−0.0101 (4)
C19	0.0238 (4)	0.0326 (5)	0.0361 (5)	0.0125 (4)	0.0004 (4)	−0.0057 (4)
C9	0.0374 (6)	0.0316 (5)	0.0452 (6)	0.0120 (5)	−0.0007 (5)	−0.0041 (5)
C8	0.0314 (5)	0.0253 (4)	0.0339 (5)	0.0147 (4)	0.0077 (4)	0.0059 (4)
C17	0.0389 (6)	0.0350 (6)	0.0315 (5)	0.0111 (5)	−0.0055 (4)	−0.0086 (4)
C6	0.0484 (7)	0.0340 (6)	0.0641 (9)	0.0129 (5)	−0.0059 (6)	−0.0079 (6)

Geometric parameters (Å, º)

N1—C3	1.1409 (12)	C7—H2	1.004 (15)
O2—C2	1.3187 (11)	C7—H1	0.969 (13)
O2—C10	1.4734 (10)	C16—C18	1.5267 (15)
O1—C2	1.1990 (12)	C16—C17	1.5296 (15)
C11—C10	1.5220 (12)	C16—H16	0.970 (14)
C11—C12	1.5407 (13)	C13—H12	1.025 (15)
C11—C16	1.5416 (13)	C13—H11	1.025 (15)
C11—H8	0.949 (12)	C4—C5	1.4630 (16)
C15—C10	1.5196 (13)	C4—H4	0.974 (14)
C15—C14	1.5289 (12)	C4—H5	0.959 (15)
C15—H14	1.005 (13)	C18—H21	0.959 (15)
C15—H15	0.988 (16)	C18—H20	0.977 (17)
C1—C3	1.4740 (12)	C18—H22	0.939 (18)
C1—C2	1.5405 (12)	C5—C6	1.184 (2)
C1—C4	1.5506 (13)	C19—H25	0.942 (16)
C1—C7	1.5551 (13)	C19—H23	0.955 (16)
C14—C19	1.5257 (14)	C19—H24	0.969 (18)
C14—C13	1.5278 (14)	C9—C8	1.1859 (17)
C14—H13	1.013 (12)	C9—H3	0.93 (2)
C10—H7	0.958 (14)	C17—H18	0.990 (17)
C12—C13	1.5260 (14)	C17—H19	0.960 (18)
C12—H9	0.898 (14)	C17—H17	0.964 (18)
C12—H10	0.971 (16)	C6—H6	0.88 (2)
C7—C8	1.4629 (15)		
C2—O2—C10	117.22 (7)	C8—C7—H1	111.9 (8)
C10—C11—C12	106.72 (7)	C1—C7—H1	105.8 (8)
C10—C11—C16	113.09 (7)	H2—C7—H1	108.2 (12)
C12—C11—C16	114.67 (7)	C18—C16—C17	110.21 (9)
C10—C11—H8	108.0 (8)	C18—C16—C11	111.46 (8)
C12—C11—H8	107.9 (7)	C17—C16—C11	114.03 (8)
C16—C11—H8	106.2 (8)	C18—C16—H16	106.9 (8)
C10—C15—C14	112.36 (7)	C17—C16—H16	106.4 (8)
C10—C15—H14	109.1 (8)	C11—C16—H16	107.4 (8)
C14—C15—H14	107.0 (8)	C12—C13—C14	112.32 (8)
C10—C15—H15	108.5 (9)	C12—C13—H12	107.3 (8)
C14—C15—H15	111.6 (10)	C14—C13—H12	109.8 (8)
H14—C15—H15	108.1 (12)	C12—C13—H11	110.3 (8)
C3—C1—C2	112.56 (7)	C14—C13—H11	110.3 (8)
C3—C1—C4	108.88 (7)	H12—C13—H11	106.6 (11)
C2—C1—C4	107.82 (7)	C5—C4—C1	110.52 (8)
C3—C1—C7	108.82 (8)	C5—C4—H4	110.9 (7)
C2—C1—C7	107.70 (7)	C1—C4—H4	109.1 (8)

C4—C1—C7	111.09 (7)	C5—C4—H5	111.6 (9)
C19—C14—C13	112.35 (8)	C1—C4—H5	106.6 (9)
C19—C14—C15	109.95 (8)	H4—C4—H5	107.9 (12)
C13—C14—C15	109.70 (8)	C16—C18—H21	110.9 (9)
C19—C14—H13	108.3 (7)	C16—C18—H20	107.3 (10)
C13—C14—H13	107.9 (7)	H21—C18—H20	111.3 (14)
C15—C14—H13	108.5 (7)	C16—C18—H22	112.6 (10)
O2—C10—C15	106.10 (7)	H21—C18—H22	108.0 (13)
O2—C10—C11	107.93 (7)	H20—C18—H22	106.6 (14)
C15—C10—C11	113.48 (7)	C6—C5—C4	175.44 (13)
O2—C10—H7	107.8 (8)	C14—C19—H25	113.1 (9)
C15—C10—H7	112.0 (8)	C14—C19—H23	111.0 (9)
C11—C10—H7	109.2 (8)	H25—C19—H23	105.9 (14)
N1—C3—C1	174.79 (9)	C14—C19—H24	110.1 (11)
C13—C12—C11	111.66 (8)	H25—C19—H24	107.7 (15)
C13—C12—H9	109.1 (9)	H23—C19—H24	108.9 (14)
C11—C12—H9	109.5 (9)	C8—C9—H3	178.5 (16)
C13—C12—H10	110.3 (9)	C9—C8—C7	176.97 (11)
C11—C12—H10	109.8 (9)	C16—C17—H18	109.7 (10)
H9—C12—H10	106.3 (12)	C16—C17—H19	110.9 (11)
O1—C2—O2	126.75 (9)	H18—C17—H19	111.0 (14)
O1—C2—C1	120.82 (8)	C16—C17—H17	113.0 (11)
O2—C2—C1	112.43 (7)	H18—C17—H17	105.3 (14)
C8—C7—C1	111.54 (8)	H19—C17—H17	106.8 (14)
C8—C7—H2	112.0 (8)	C5—C6—H6	176.8 (16)
C1—C7—H2	107.1 (8)		