The Regioselective Synthesis of Deuterated 4-Alkyl-γ-Lactones.

A thesis presented in partial fulfilment of the requirements
for the degree of

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At Massey University.

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Corrections

p. 3, para 1, line 7	predominantly (not predominately)
p. 14, para 2, line 3	radical cations should read radical anions
p. 18, para 2, line 5	propargylic (not propagylic)
p. 22, para 1, line 1	propargylic (not propagylic)
p. 20, ref 24	Nevada (not Nervada)
p. 61, ref 1	Nevada (not Nervada)
p. 21, ref 47	The second author's surname is Tramontano
p. 26, para 2, line 6	rationale (not rational)
p. 29, line 6	integration (not intergration)
p. 37, para 2, line 1	replacing water with benzene (not replacing water for benzene)
p. 42, para 2, line 4	stoichiometric (not stiochiometric)
p. 44, para 3, line 6	reaction's (not reactions)
p. 47, para 2, line 1	1-^{2}H-decyne is compound (**3.20**) – not (**3.19**)
p. 48, line 7	^{1}H (superscript 1)
p. 50, para 2, line 14	confirmation (not conformation)
p. 51, para 2, line 3	from the BuLi solution (not for)
p. 56, para 1, line 9	from (not form)
p. 56, para 2, line 3	affected (not effected)
p. 58, para 2, line 1	from should be deleted from this sentence
p. 58, para 4, line 3	unfavourably with (not unfavourable to)
p. 62, title	Comparative (not Comparitive)
p. 69, line 5	equilibria (not equilibra)
p. 70, para 2, line 1	be should be deleted from this sentence
p. 83, para 2, line 6	hexane (not hesane)
p. 87	the footnote belongs on page 86

Abstract.

γ-Lactones are important flavour compounds that occur naturally in foodstuffs such as fruit and dairy products. Their presence, or absence, has a considerable influence on the perceived quality of these products. It is therefore important to be able to accurately measure the concentrations of certain γ-lactones. Deuterium labelled compounds offer the possibility of achieving this through stable isotope dilution assays (SIDA). To achieve maximum sensitivity in SIDA of γ-lactones requires two to four deuterium atoms to be placed regioselectively within the lactone ring, where they are retained in the base peak of the labelled analogue upon electron ionisation mass spectroscopy. To this end, two syntheses of regioselectively deuterium ring labelled γ-lactones have been developed.

Initially, three tetradeuterated 2,2,3,3-$^{2}H_4$-γ-lactones were prepared. The key step in these syntheses involved the reduction of a doubly protected hydroxy acetylenic acid with deuterium gas in the presence of Wilkinson's catalyst. 2,2,3,3-$^{2}H_4$-γ-Dodecalactone was prepared in 25% overall yield with 95% deuterium incorporation, 2,2,3,3-$^{2}H_4$-γ-decalactone in 46% yield with 89% deuterium incorporation and 2,2,3,3-$^{2}H_4$-γ-octalactone in 36% yield with 90% deuterium incorporation. While higher catalyst loadings (10 mol%) resulted in shorter reduction times, a higher degree of deuterium incorporation was achieved at lower catalyst loadings (5 mol%).

A second, one-pot radical synthesis of ring-labelled γ-lactones was also developed which involved the addition of a two-carbon acetoxy radical to an appropriate 1,1,2-deuterated 1-alkene. This synthesis produced trideuterated γ-lactones without deuterium in the potentially exchangeable position α to the carbonyl moiety. Extensive GC optimisation for this process was undertaken using unlabelled precursors. A combination of 1-alkene (1.5 mmol), 2-iodoacetamide (0.5 mmol), 1,1'-azo-*bis*-cyclohexanecarbonitrile (radical initiator) (1.0 mmol) and water (50 mmol) in benzene (10 mL) was found to be optimal. The synthesis of 1,1,2-$^{2}H_3$-1-decene, 1,1,2-$^{2}H_3$-1-octene and 1,1,2-$^{2}H_3$-1-hexene was pursued via the reduction of appropriate 1-^{2}H-1-alkynes with deuterium gas over Lindlar's

catalyst. This apparently simple transformation, proved difficult due to the volatility of the target 1,1,2-$^2H_3$-1-alkenes. Nonetheless, under the optimised radical conditions, 3,3,4-$^2H_3$-γ-dodecalactone was prepared in a 69% isolated yield from 1,1,2-$^2H_3$-1-decene with 96% deuterium incorporation. 3,3,4-$^2H_3$-γ-Octalactone was prepared in 17% yield from 1,1,2-$^2H_3$-1-hexene with 92% deuterium incorporation. It is suggested the efficiency of the radical lactonisation process was dependant upon the purity of the 1,1,2-$^2H_3$-1-alkene as under the optimised conditions, unlabelled γ-decalactone and γ-octalactone were prepared in 91% and 94% isolated yields respectively.

Application of the radical strategy for the synthesis of 3,3,4-$^2H_3$-*(Z)*-6-dodecen-γ-lactone was envisaged but the required deuterated precursor was not accessible. The alternative dideuterated 6,7-$^2H_2$-*(Z)*-6-dodecen-γ-lactone was, however, prepared in 75% yield with 96% deuterium incorporation via the partial reduction of 6-dodecyn-γ-lactone with deuterium gas over Lindlar's catalyst.

The deuterated lactones prepared in this thesis have since proved of value as internal standards for SIDA.

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Finally my family; Mum, Dad, Mark, Nathan and my Grandparents. Your unconditional support (both financially and emotionally), enthusiasm and encouragement for my studies, has without a doubt been the most significant contribution of all. Thank you.

Simon and Dave.

Simon and Dave are not what they seem,
Their dull appearance is part of their scheme.
I know of their plans. I know their techniques.
My supervisors are outer space alien freaks!

They landed on earth in spaceships humongous.
Posing as chemists they now walk among us.
My supervisors deny this, but I know the truth.
They're here to enslave me and spoil my youth.

Early each morning as the sun rises,
Simon and Dave put on their earthling disguises.
I knew right away their masks weren't legit.
Their faces are lined – they sag and don't fit.

The earth's gravity makes them sluggish and slow.
They say not to run wherever I go.
They live by the clock. They're slaves to routines.
They work the year 'round. They're almost machines.

They deny that coffee breaks have much worth.
They cannot be human. They're not of this earth.
I cannot escape their alien gaze,
And they're warping my mind with their alien ways.
For sinister plots, this ones a gem.
They're trying to turn me into on of them!

Poem modified from William B. Watterson II.

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Abbreviations.

ACCN	1,1'-azo-bis-cyclohexanecarbonitrile
ACPA	4,4'-azo-*bis*-4-cyanopentanoic acid
AIBN	2,2'-azo-*bis*-isobutyronitrile
b.p.	boiling point
br.	broad
BuLi	*n*-butyl lithium
cat.	catalytic
CI	chemical ionisation
cm^{-1}	wave number
^{o}C	degrees Celsius
d	doublet
DMF	dimethylformamide
δ	chemical shift
EI	electron impact
eq.	molar equivalent(s)
eV	electron volts
GC	gas chromatography
GCMS	gas chromatography-mass spectrometry
hr(s)	hour(s)
Hz	Hertz
i.d.	internal diameter
IDA	isotope dilution assay
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
m	multiplet
min(s)	minute(s)
mmHg	millimetres of mercury

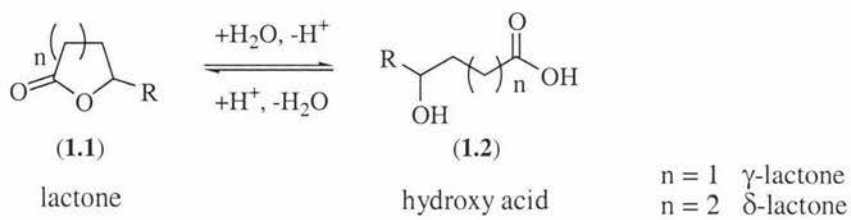
mmol	millimole
mol	mole
MS	mass spectrometry
NMR	nuclear magnetic resonance
ν_{max}	absorption maxima (IR)
PhH	benzene
ppm	parts per million
p.s.i.	pounds per square inch
q	quartet
quint	quintet
r.p.m.	revolutions per minute
rt	room temperature
SIDA	stable isotope dilution assay
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBDMSCl	*tert*-butyldimethylsilyl chloride
THF	tetrahydrofuran
tlc	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine

Chapter 1

Introduction.

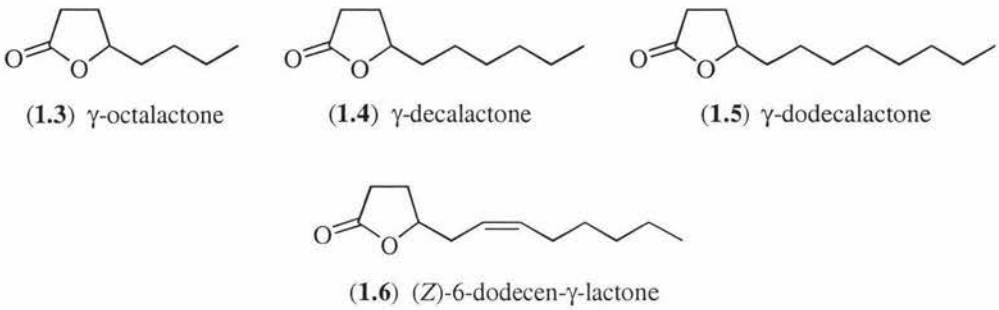
1.1 General Introduction.

4-Alkyl-γ- (**1.1**, n=1) and 5-alkyl-δ-lactones (**1.1**, n=2) are important flavour and aroma compounds, which occur widely in nature. They are formed by the acid-catalysed intramolecular cyclisation of the corresponding γ- or δ-hydroxycarboxylic acids (**1.2**) (n = 1 and 2 respectively) with concomitant loss of water.[1] The process is pH dependent. (**Scheme 1.1**) In an aqueous environment, equilibrium is established between the open-chain hydroxycarboxylate (**1.2**) and the cyclised form (**1.1**).[1]



Scheme 1.1

The structural possibilities for lactones are great, ranging from highly substituted polycyclic systems to simple mono-substituted compounds. Laduwahetty[2] and Collins[3-6] have written comprehensive reviews on the general synthesis of saturated and unsaturated lactones. The work presented here, however, focuses specifically on 4-alkyl-γ-lactones, of general structure (**1.1**, n = 1), which represent a very important class of this compound type. 4-Alkyl-γ-lactones derived from aliphatic hydroxycarboxylic acids of carbon chain length C8 to C12, account for greater than 94% of the annual volume of lactones used in the flavour industry.[1] The odour potency of both γ- and δ-lactones strongly depends on the nature of the aliphatic side chain (R).[7] It has been shown generally that lactones with even-numbered carbon chains are quantitatively predominant in foodstuffs.[8,9] The γ-lactones in **Figure 1.1** were therefore selected as synthetic targets.



(**1.3**) γ-octalactone (**1.4**) γ-decalactone (**1.5**) γ-dodecalactone

(**1.6**) (Z)-6-dodecen-γ-lactone

Figure 1.1

These lactones (**Figure 1.1**) occur in a wide range of foodstuffs, particularly in natural fruit extracts[10] and dairy products.[11] An homologous series of 4-alkyl (and alkenyl) -γ-lactones (γ-penta to γ-dodeca) have been identified as volatiles in peach aroma,[9] with γ-dodecalactone (**1.5**) recognised as the major contributor.[12] Similar distributions of these lactones have been found in the volatiles of nectarines.[8] (Z)-6-Dodecen-γ-lactone (**1.6**) has been identified in butter,[13,14] Cheddar cheese,[15] in the flowers of the tuberose plant (*Polianthes tuberosa L.*)[16] and as a pheromone of the black-tailed deer.[17]

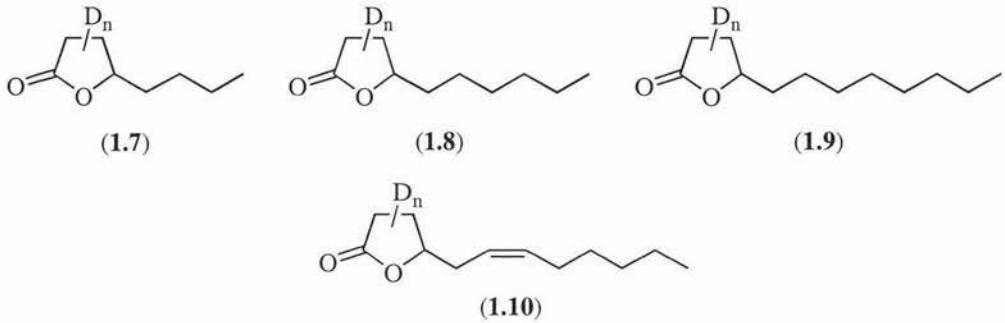
Intense and characteristic odours are attributed to these compounds (**Figure 1.1**) due to their low odour detection threshold values. The odourous notes of the lactones are in general described as being of 'tropical fruit' and in some cases 'coconut', 'liquor-like' or 'peach-like'.[12] Not surprisingly, flavour differences between γ- and δ-lactones are observed. For example, γ-decalactone (**1.4**) has a peach odour, whereas the corresponding δ-decalactone has a coconut odour.[12] Generally γ-lactones have much more potent odours than δ-lactones. γ-Octalactone (**1.3**), for example, has an odour detection threshold (ODT) of 7 ppb in water, while δ-octalactone has an ODT of 400 ppb in water.[8] γ-Decalactone (**1.4**) has an ODT (in water) of 11 ppb and γ-dodecalactone (**1.5**) an ODT (in water) of 7 ppb. The ODT for (Z)-6-dodecen-γ-lactone (**1.6**) has not yet been determined, but is likely to be less than 1.0 ppm.[11] This compound is described as having a sweet[18] or soapy aroma.[15]

4-Alkyl-γ- and 5-alkyl-δ-lactones (**1.1**) contain a single stereocenter at the ring fusion and two enantiomeric forms of these compounds are therefore possible. While many enantioselective syntheses of these lactones have been reported[2-6] it was not the aim of the work presented to prepare optically active or enantio-enriched lactone samples. It is, nonetheless, of interest to note that the R configuration of these materials is naturally preferred, especially with increasing chain length of the 4 or 5 alkyl substituent.[1] The biological activity of certain lactones has also been associated predominately with a specific optical isomer.[19] For example, black-tailed deer show a preference for the predominant (R)-(-) enantiomer of the pheromone (**1.6**), whose composition is (89%(R)-(-)/11%(S)-(+)).[20]

The ratio of flavour components within a food is vital for its acceptance as a product by the consumer. If this ratio is not appropriate, a product can be deemed undesirable. To enhance flavour and aroma, 4-alkyl-γ-lactones can be intentionally added to foodstuffs at concentrations often comparable to those occurring naturally within food.[10] Usually they are added at levels of less then 20 ppm, but typically within a range of 0.05 to 80 ppm.[1]

1.2 Measurement Techniques.

Due to the potent sensory impact of many lactones, it is often necessary to monitor their concentrations within certain foods. Deuterium labelling offers the possibility of achieving this through isotope dilution methods as discussed in section **1.2.1**. The need to measure small quantities (sub ppm levels) of specific 4-alkyl-γ-lactones in foodstuffs led to the selection of four deuterated compounds as synthetic targets (**Figure 1.2**): $^{2}H_{n}$-γ-octalactone (**1.7**), $^{2}H_{n}$-γ-decalactone (**1.8**), $^{2}H_{n}$-γ-dodecalactone (**1.9**) and $^{2}H_{n}$-(*Z*)-6-dodecen-γ-lactone (**1.10**). The positioning of the deuterium label will be discussed in section **1.2.2**.



(**1.7**) (**1.8**) (**1.9**)

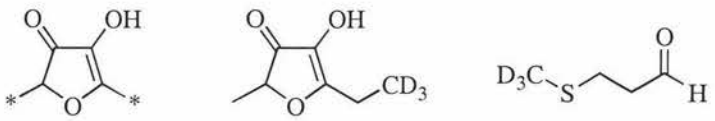
(**1.10**)

Figure 1.2

1.2.1 Isotope Dilution Assays (IDAs).

Isotope incorporation into organic molecules has proved of immense value for structure determination, mechanistic studies and investigations into reaction kinetics.[21] It is also of great value as a tool for accurately measuring low levels of organic materials in complex mixtures. The accurate quantitation of samples through this technique is referred to as a stable isotope dilution assay (SIDA) and utilises mass spectrometry (MS) for isotope detection and differentiation. Deuterium (^2H) is the isotope used most frequently. It is relatively cheap compared to other isotopes and is non-radioactive. Significant work in the development of ^{13}C SIDA, however, has also been undertaken.[13,15]

The concept of an isotope dilution assay (IDA) was introduced in 1966 for the determination of glucose in plant tissues.[22] It is the most accurate method currently available for the quantification of aroma compounds, particularly if they are labile and in low concentrations.[23] The technique has also proven useful in research related to off-flavours that are caused by an imbalance of odorants. For example, the meaty-brothy odor defect in low fat Cheddar cheese was attributed primarily to an increase in the concentrations of furaneol (**1.11**), homofuraneol (**1.12**) and methional (**1.13**). (**Figure 1.3**) In this study both deuterium and ^{13}C labels were used, as indicated.[15]



(**1.11**) (**1.12**) (**1.13**)

* indicates ^{13}C labelling

Figure 1.3

The principle of SIDA involves the quantification of a specific analyte within a sample matrix through the addition of a known quantity of a stable isotope labelled analogue as an internal standard. Due to the near identical physical and chemical properties of the labelled internal standard and the analyte, losses of the analyte during the isolation procedure are compensated for. The labelled and unlabelled materials are recovered (or lost) with equal efficiency[23] and hence errors in subsequent analytical measurements (MS) are reduced to a minimum.

The concentration of the analyte is usually determined by GC-MS, which not only allows specific detection of the target compound and its labelled analogue, by virtue of their respective molecular masses, but also enables precise quantitation on the basis of the relative intensities of the observed signals.[24] In principle, the addition of an isotopically labelled compound to a sample results in an absolute quantitative measurement of the compound, providing a homogeneous distribution of the standard and analyte within the sample has been achieved.

1.2.2 Mass Spectral Requirements.

Isotopes of elements differ in the number of neutrons in their nuclei and therefore give rise to ions of different mass in a mass spectrometer. Because of this MS is the most commonly used method for the determination of stable isotopes.[25]

To minimise interferences with masses originating from the analyte, deuterium labelling should increase the molecular weight of a standard by at least two mass units.[24] An increase of three to four mass units is ideal, as this even further differentiates the species under investigation from its naturally occurring unlabelled analogues.

The possibility of cleavage at a particular bond under mass spectrometric conditions is related to bond strength and the stability of fragments formed upon ionisation. In the case of γ-lactones, under standard electron impact (EI) conditions (70 eV), cleavage is favoured at the alkyl substituted carbon, C4. (**Figure 1.4**)

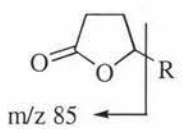


Figure 1.4

To achieve maximum sensitivity in the MS the deuterium label should ideally be placed in the portion of the molecule which gives rise to the most intense ion or base peak of the mass spectrum. After a consideration of the fragmentation pattern of lactones, where the base peak is derived from the ring fragment m/z = 85 (**Figure 1.4**), it was envisaged that placement of a deuterium label within the ring would give maximum sensitivity in the EI mass spectrum. The target compound should therefore have a minimum of three deuterium atoms placed regioselectively in the ring of the lactone. While incorporating deuterium into the side chain R is likely to be an easier synthetic process, maximising sensitivity in isotope dilution assays remains an important issue and requires a regioselective synthesis placing deuterium in the lactone ring.

1.2.3 Effect of Deuterium on the NMR Spectra.

1.2.3.1 ^{1}H NMR.

Deuterium has a spin number of 1 and a small quadrapole moment. Furthermore, deuterium exhibits only a small coupling with protons; the H-D coupling constant (J_{HD}) is approximately 15% of the corresponding J_{HH} coupling constant.[26] Overall, the introduction of deuterium results in a simplification of the ^{1}H NMR spectrum.

The effect of deuterium introduction on the ^{1}H NMR spectrum can be considered for a γ-lactone (**Figure 1.5**). For simplicity the diamagnetic non-equivalence of the α, β and δ protons will be ignored.

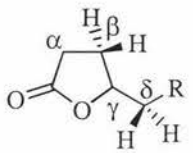
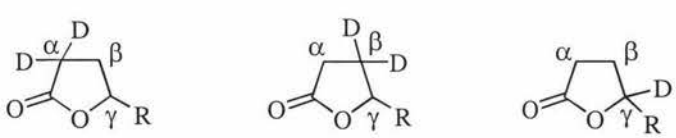


Figure 1.5

In the ^{1}H NMR spectrum of the unlabelled material the α methylene protons (**Figure 1.5**) would consist of a first order triplet. The β methylene protons would appear as a triplet ($J_{(\alpha\text{-}\beta)}$) split further by coupling to Hγ giving rise to a triplet of triplets.† The γ methine would appear as a triplet ($J_{(\gamma\text{-}\beta)}$), split further by any δ protons on the R substituent ($J_{(\gamma\text{-}R)}$). Deuterium can in principle, be substituted at any of these three sites in the lactone ring, i.e. α (**1.14**), β (**1.15**) or γ (**1.16**) positions. (**Figure 1.6**)



(1.14) **(1.15)** **(1.16)**

Figure 1.6

† Assuming $J_{\alpha\beta}=J_{\beta\gamma}$ this triplet of triplets collapses to a simple quintet.

Deuterium introduced at the α position of the lactone (**1.14**) will result in the following changes in the ^{1}H NMR spectrum. The signal for the α protons would be absent, the β protons would appear as a simple doublet and the γ protons will be unaffected. Deuterium in the β position (**1.15**) would result in the disappearance of the signal for the protons at this position, while the α protons would appear as a singlet and the γ proton would be observed as a singlet split further by the presence of δ protons on the R substituent. Substitution of the γ proton would result in a loss of signal at the γ position (**1.16**) while the α protons would be unaffected and the β protons would appear as a triplet. However, it is noted that the actual spectra for such compounds (**Figure 1.6**) would appear more complex due to the diamagnetic non-equivalence of the α, β and δ protons. Nonetheless, this simple treatment serves as a valuable predictive tool for the analysis of regioselective deuterium incorporation in γ-lactones. Furthermore, integration of residual proton signals after deuteration allows for a simple estimate of deuterium incorporation.

1.2.3.2 ^{13}C NMR.

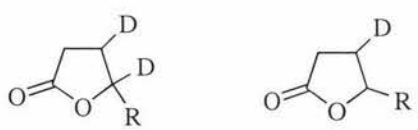
The effect of deuterium introduction on the ^{13}C NMR spectrum can also be considered. (**Figure 1.6**) Substitution of the single hydrogen at the γ position for a deuterium atom (**1.16**) would result, in a dramatic decrease in the intensity of that carbon signal. The spin number of deuterium is one resulting in splitting of the reduced ^{13}C signal into a triplet (ratio 1:1:1) having a coupling (J) value equal to ~0.15 x J_{CH}.[26]

The ^{13}C resonance of a $^{13}CD_2$ signal (such as that for α in (**1.14**) and β in (**1.15**)) would be significantly reduced and may be undetectable. This is due not only to the effective quaternary nature of the carbon atom but also due to further splitting of the ^{13}C signal into a low intensity quintet. As only deuterated-labelled carbons will be affected by these phenomena, their assignments can be attributed to the peak (or peaks) which effectively disappear upon comparison with unlabelled spectra.

1.3 Synthetic Routes to γ-Lactones.

Many γ-lactone syntheses have been developed.[2-6] Some of the more common approaches used involve multi-component synthesis in both solution and solid phase, ring-closing metathesis[27] and metal-mediated synthesis. While many of these approaches are efficient and grant access to a diverse range of γ-lactones, few are suitable for modification to include deuterium regioselectively in the ring of the final product. Hence, many of these syntheses are not relevant to the aims of this thesis and will not be considered further.

There are few examples of the targeted formation of deuterated γ-lactones and those which are known,[28,29] make no specific mention of deuterium incorporation as a tool for SIDA. Specific reference to the synthesis of γ-dodecalactone and γ-decalactone with ring deuterium incorporation have, however, been reported by Haffner and Tressl.[10] (**Figure 1.7**) The ^{2}H-labelled γ-lactones (**1.17**) and (**1.18**) were isolated as the metabolic products of the lactone producing yeast *Soridiobolus salmonicolor*.



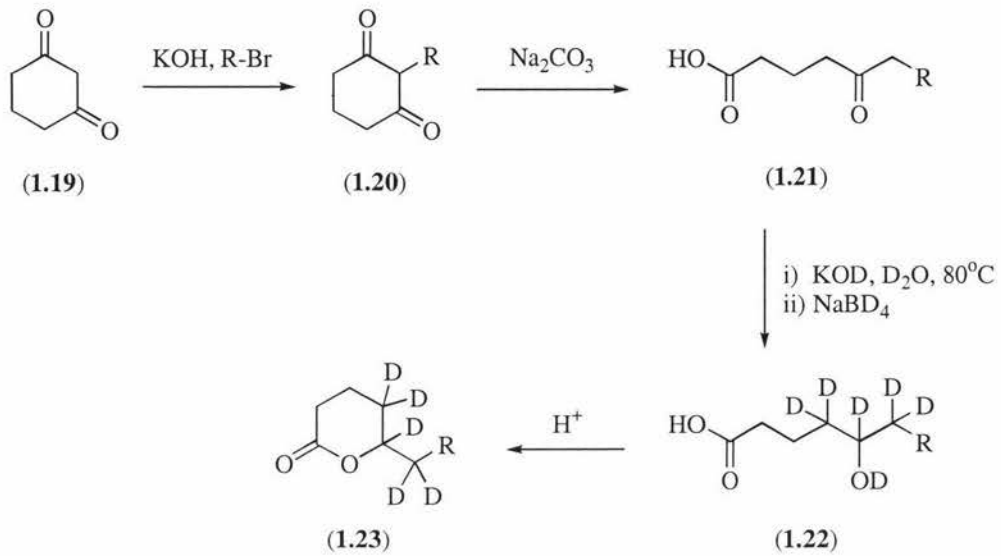
(**1.17**) (**1.18**)

γ-Decalactone R = C_6H_{13}
γ-Dodecalactone R = C_8H_{17}

Figure 1.7

This study gained a detailed insight into the oxidative fate of ^{2}H-labelled epoxy fatty acids with respect to the biosynthesis of these lactones.

The synthesis of labelled δ-lactones for use in SIDA has received some attention and is worth mentioning in this context. The synthetic procedure for δ-lactones (**Scheme 1.2**), described below by Schieberle *et al.*, was modified specifically to introduce deuterium not only into the side chain of the molecule but also into the ring of the δ-lactone.[13,24]



(**1.19**) (**1.20**) (**1.21**)

(**1.23**) (**1.22**)

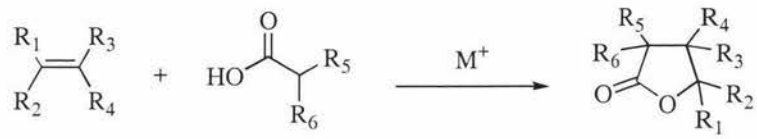
Scheme 1.2

Cyclohexane-1,3-dione (**1.19**) was mono-alkylated in the presence of potassium hydroxide and an appropriate alkyl or allyl bromide in refluxing dioxane/water (1:1) to give the corresponding 1-substituted 2,6-cyclohexanedione (**1.20**). Ring cleavage in an excess of refluxing aqueous sodium bicarbonate solution gave the 5-oxo acid (**1.21**) after acidification to pH 3.0. Subsequent base catalysed deuterium exchange at 80°C and sodium borodeuteride reduction gave the 5-hydroxy acid (**1.22**), which cyclised to the δ-lactone to afford the $^2H_5$-δ-lactone (**1.23**) at low pH.

While no specific examples of deuterated 4-alkyl-γ-lactones satisfying the labelling requirements for SIDA have been reported, there are several synthetic approaches that do offer this potential. Two general strategies were identified, a radical coupling strategy and a reductive strategy and these are considered below.

1.3.1 Incorporation of Deuterium via a Radical Strategy.

The application of free-radical reactions in modern synthetic organic chemistry is increasing and this approach to γ-lactones has been utilised successfully by several groups.[30-34] Heiba *et al.*[30] reported the synthesis of a range of γ-lactones via the addition of substituted carboxylate salts to alkenes at elevated temperatures. (**Scheme 1.3**)

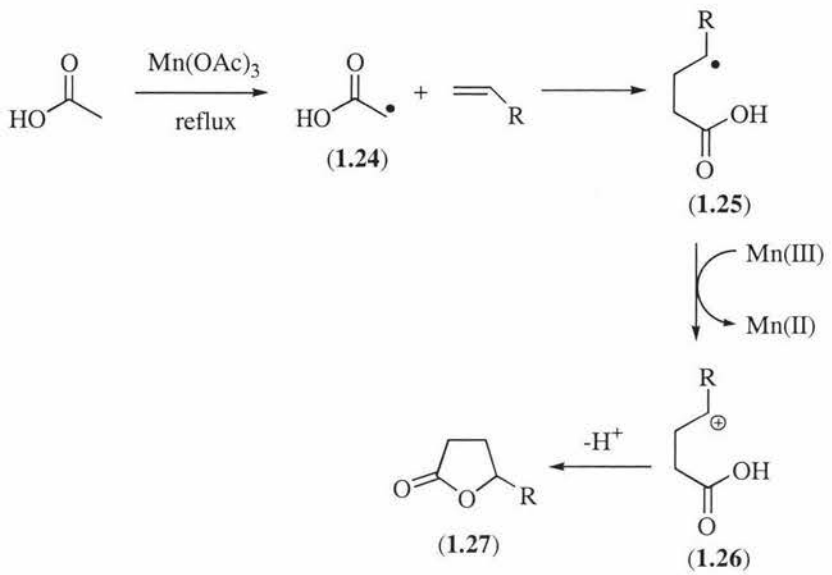


M^+ = Mn(III), Ce(IV), V(V)

Scheme 1.3

This synthesis, a simple one-step process, was developed from readily available olefins and carboxylic acid precursors. The reaction consists of the formal addition of a suitable carboxylic acid (with an α-hydrogen atom) across the double bond of an olefin in the presence of two stoichiometric equivalents of certain metal carboxylate salts.

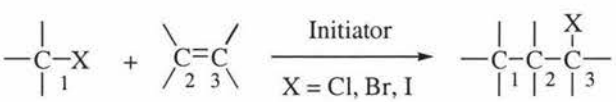
The thermal decomposition of metal carboxylates proceeds via the selective and direct generation of carboxymethyl radicals (**1.24**). (**Scheme 1.4**)[32] Manganic (III) salts have been used most extensively due to their ready availability and high solubility, although other transition metals, notably cerium and vanadium, have proved equally effective.[30]



Scheme 1.4

In refluxing acetic acid (118°C), $Mn(OAc)_3$ decomposes to generate the carboxymethyl radical (**1.24**) that adds regioselectively to 1-alkenes giving the second radical species (**1.25**). Radical (**1.25**) is oxidised, by a second equivalent of $Mn(OAc)_3$, to give an intermediate carbocation (**1.26**), which, under the reaction conditions, cyclises spontaneously, with loss of a proton, to produce the γ-lactone (**1.27**). This is a very general process and a range of γ-lactones have been prepared where R may contain allyl or alkynyl functionality.[30]

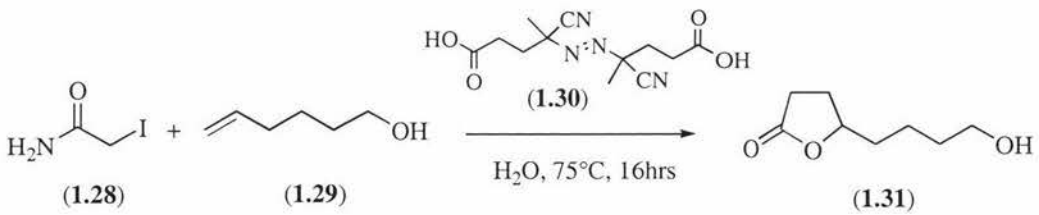
Other free-radical strategies have also been reported. One method, in particular, has emerged as a powerful tool for γ-lactone synthesis and as a C-C bond forming reaction in general. This strategy is referred to as the "halogen atom transfer process" (**Scheme 1.5**) and has been studied extensively by Curran and co-workers.[33,35-39]



Scheme 1.5

The reaction is a convenient way to generate new C-C bonds via the addition of an alkyl halide, as a radical precursor, to a C-C multiple bond.[33] This process can accommodate concomitant cyclisation processes, a necessity for lactone formation.

Yorimitsu *et al.*[34] have utilised Curran's atom transfer process and reported the isolation of γ-lactones in good yields from the addition of a 2-iodocarbonyl compound to an 1-alken-ω-ol in water in the presence of a radical initiator. (**Scheme 1.6**)

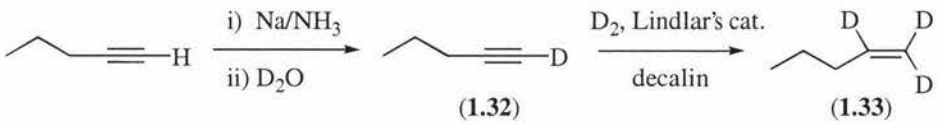


Scheme 1.6

2-iodoacetamide (**1.28**) and 5-hexen-1-ol (**1.29**) reacted in the presence of the radical initiator 4,4'-azo-bis-4-cyanopentanoic acid (**1.30**) at 75°C for a period of 16 hrs. Isolation of γ-(4-hydroxybutyl)-γ-lactone (**1.31**) in 95% yield was reported for this reaction. A 93% yield was obtained under otherwise identical conditions with 2-iodoacetic acid as the 2-iodocarbonyl component.

The reaction is a useful single step process that proceeds in high yield. It is, however, limited as the reaction is conducted under aqueous conditions to ensure solubility of the alkenol and other reactants. Nonetheless, this process has potential as a route to deuterated 4-alkyl-γ-lactones as either the 1-alkene component or the iodo-carbonyl moiety could readily be exchanged for a simple deuterated variant. Furthermore, the possibility also exists of carrying out a comparable reaction in an organic solvent.

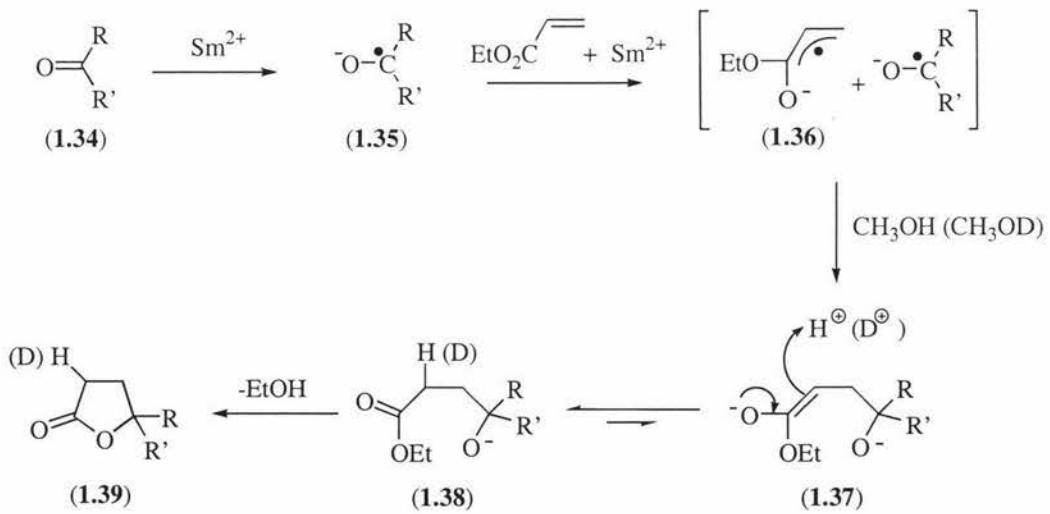
Potentially, the introduction of deuterium into the ring of the γ-lactone could be achieved in both **Scheme 1.4** and **Scheme 1.6** through the use of a labelled 1,1,2-$^2H_3$-alkene. Sirokman *et al.*[21] has reported the synthesis of 1,1,2-$^2H_3$-alkenes with high isotopic purity (92% for 1,1,2-$^2H_3$-pentene) by the method outlined below. (**Scheme 1.7**)



Scheme 1.7

Deprotonation of the terminal alkyne was achieved using sodium in liquid ammonia and the resultant sodium acetylide was quenched with deuterium oxide to yield the deuterated acetylene (**1.32**). Reduction of (**1.32**) with gaseous deuterium in the presence of Lindlar's catalyst in pure decalin proceeded without difficulty and afforded the 1,1,2-$^{2}H_3$-alkene (**1.33**).

Other radical strategies have also been employed in the synthesis of 2-^{2}H-γ-lactones (**1.39**). A range of ketones and aldehydes were reduced in the presence of SmI_2 to give intermediate radical cations (**1.35**), which coupled smoothly with ethyl acrylate to afford γ-lactones in an efficient one pot process.[40] The overall transformation is shown in **Scheme 1.8**.



Scheme 1.8

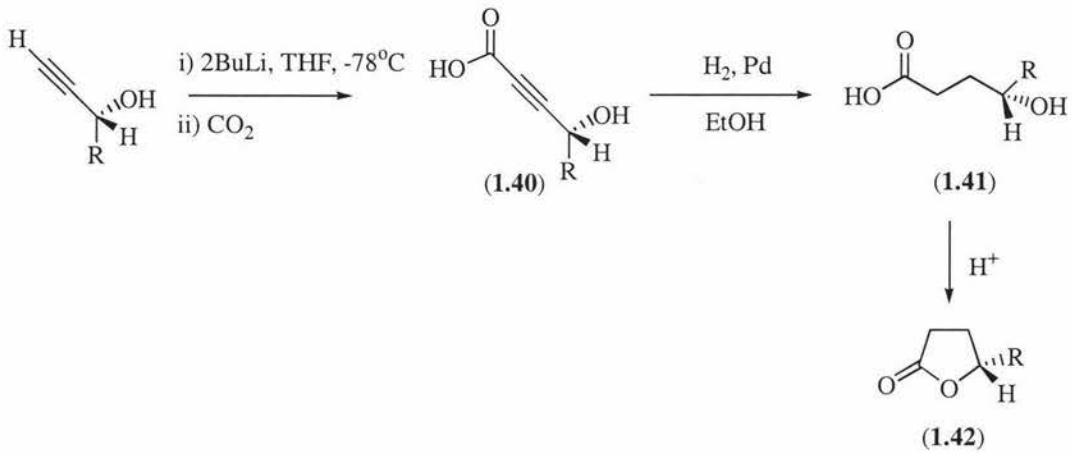
The likely pathway for this process, suggested by the authors,[40] involves the reduction of the carbonyl compound to a radical ketyl species (**1.35**). Subsequent coupling to an allylic radical (**1.36**), generated under the reaction conditions by a further samarium mediated one-electron transfer, gives an intermediate ester enolate (**1.37**). In the presence of a suitable proton source (the solvent), the enolate (**1.37**) is converted to the α-hydroxy ester (**1.37**), which spontaneously cyclises to afford the γ-lactone (**1.39**). This process is tolerant of a range of allyl, alkyl and aryl substituents and numerous γ-lactones have been prepared in good yield.

Using deuterated methanol as the solvent, deuterium was incorporated regioselectively at C2 of the lactone.[40] To incorporate further deuterium into the lactone ring and thereby satisfy the labelling requirements of SIDA, a $^{2}H_{1}$-aldehyde, i.e. R' = D (**1.34**) could be employed. Alternately, a suitable deuterated acrylate would offer another route to deuterated γ-lactones.

1.3.2 Incorporation of Deuterium via a Reductive Strategy.

Reducing unsaturated bonds with deuterium gas is potentially one of the easiest and most efficient methods of introducing deuterium into a molecule. In general, it is preferential that a deuterium label be introduced as late as possible in the synthesis. This has two major advantages: to retain the integrity of the label without unwanted exchange phenomena and to ensure the most efficient use of expensive ^{2}H-labelled reagents (this is also an argument for keeping the number of steps in a labelled synthesis to a minimum). Several approaches to saturated and unsaturated lactones have been presented using reductive strategies. Modification of these processes using deuterium gas could lead to ^{2}H-ring labelled lactones. Some relevant examples are reviewed below.

The dianions of optically active propargylic alcohols (obtained by the asymmetric reduction of α-acetylenic ketones),[41-44] have been added to carbon dioxide to generate α-hydroxy propargylic acid derivatives of high optical purity.[42] (**Scheme 1.9**)

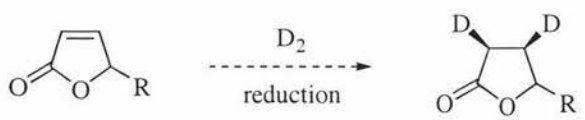


(1.40) (1.41) (1.42)

Scheme 1.9

Reduction of the alkyne (**1.40**) with hydrogen gas over palladium on charcoal and subsequent acid catalysed lactonisation of the intermediate hydroxy acid (**1.41**) afforded the enantio-enriched 4-alkyl-γ-lactone (**1.42**) in good yield. This approach to γ-lactones has obvious potential as a route to deuterated analogues. Complete reduction of the acetylene (**1.40**) with deuterium gas would incorporate four deuterium atoms directly into the ring of the lactone.

In general the reduction of butenolides (of general structure **1.43**) with deuterium, offers a potentially short and therefore valuable route to di-deuterated-4-alkyl-γ-lactones (**1.44**). (**Scheme 1.10**)

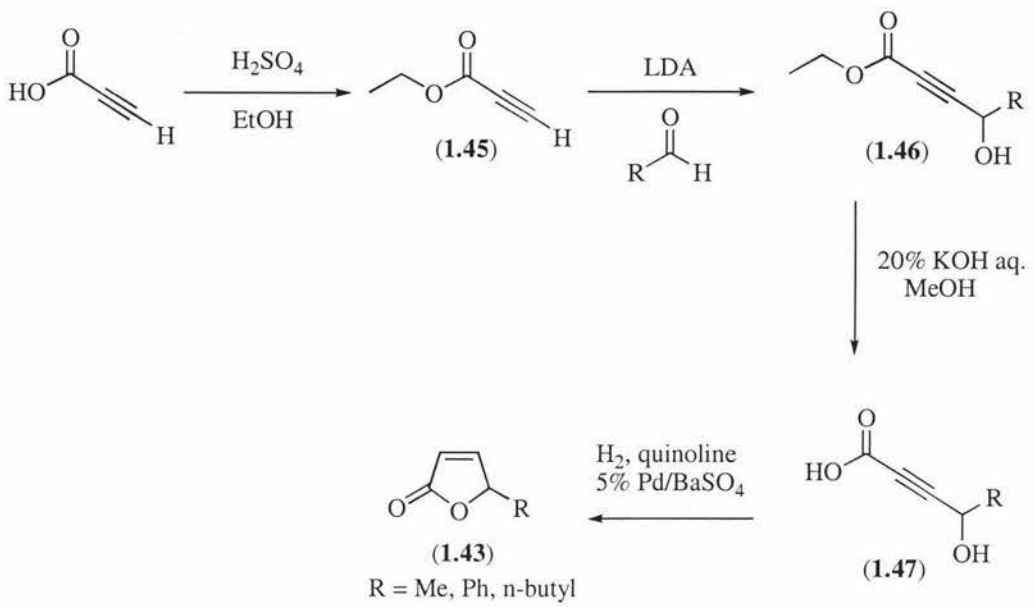


(1.43) (1.44)

Scheme 1.10

Examples involving the incomplete reduction of a propargylic alcohol derivative prior to ring closure have been reported in the synthesis of butenolides.[45-47] While not generally used to prepare deuterium labelled compounds directly these methods have obvious potential for a synthesis of labelled γ-lactones. Indeed, butenolides from any source can be regarded as precursors to $^{2}H_2$-γ-lactones.

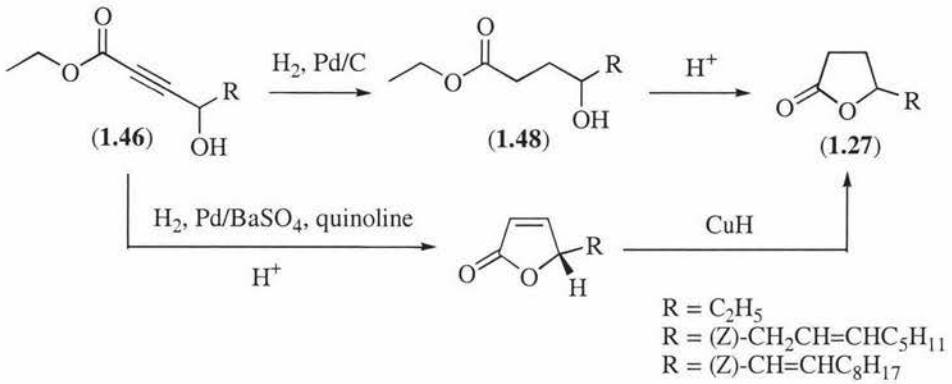
A versatile and high yielding approach to butenolides has been reported by Herrmann *et al.*.[46] (**Scheme 1.11**)



Scheme 1.11

Propiolic acid was esterified (**1.45**) and the lithium salt of ethyl propiolate reacted with an aldehyde to yield the corresponding hydroxy ester (**1.46**). Base catalysed hydrolysis of the ester gave the acid (**1.47**) and partial hydrogenation (with H_2) in methanol over 5% palladium-on-barium sulfate in the presence of quinoline gave the butenolide (**1.43**) after acidification of the hydrogenation solution.[46]

Complete catalytic reduction of the propargylic alcohol of general type (**1.47**) (**Scheme 1.11**) with deuterium gas over a suitable catalyst prior to ring closure has the potential to generate ring deuterated-$^2H_4$-γ-lactones. The unlabelled variant of this idea has been reported by Midland and Tramontano.[47] (**Scheme 1.12**)



Scheme 1.12

4-Alkyl-γ-lactones were prepared directly from 4-hydroxy-2-alkynoates (**1.46**) by complete reduction (H_2, Pd/C, MeOH) to the γ-hydroxy ester (**1.48**) followed by acid-catalysed lactonisation. Alternatively, the stepwise partial reduction of (**1.46**) (H_2, $Pd/BaSO_4$ with quinoline in MeOH) to afford an intermediate butenolide was also reported. The saturated lactone (**1.27**) was obtained from the butenolide by conjugate reduction with copper hydride. This strategy accommodates an unsaturated side chain R. A deuterated sequence is equally viable.

1.4 Conclusions.

Syntheses of γ-lactones, which may allow regioselective incorporation of deuterium, have been reviewed. Two general approaches have been identified. Application of a radical strategy for the synthesis of 4-alkyl-γ-lactones offers the convenience of a single step process. It does, however, require access to suitable deuterated precursors. An alternative reductive strategy, where a suitable hydroxy propagylic acid is reduced in the presence of deuterium gas and a metal catalyst, does however offer more ready access to regioselectively ring deuterated γ-lactones. A reductive approach was therefore undertaken initially and is discussed in **Chapter 2**.

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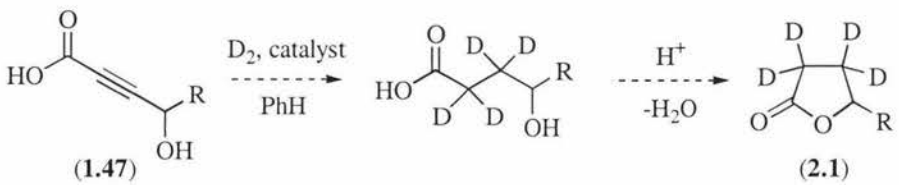
Chapter 2

Synthesis of 2,2,3,3-$^2H_4$-4-Alkyl-γ-Lactones

2.1 Introduction.

In **Chapter 1** it was suggested that γ-hydroxy propagylic acid derivatives of general structure (**1.47**) could be considered as 4-alkyl-γ-lactone precursors, being transformed to the lactone via a simple reduction step (section **1.3.2**). Replacing deuterium for hydrogen in the catalytic reduction of such alkynes (**1.47**) offers the potential of incorporating four deuterium atoms regioselectively into the lactone ring (**2.1**). (**Scheme 2.1**)



Scheme 2.1

Deuterated lactones of general structure (**2.1**) satisfy the general requirements for SIDA necessary to obtain maximum sensitivity (Section **1.2.2**). These lactones have four deuterium atoms to clearly differentiate them from the unlabelled compound in the mass spectrum under EI conditions. The deuterium atoms are incorporated regioselectively in the ring of the lactone contributing to the most intense, or base peak, in the mass spectrum. A series of three 2,2,3,3-$^2H_4$-4-alkyl-γ-lactones were identified as target compounds. (**Figure 2.1**)

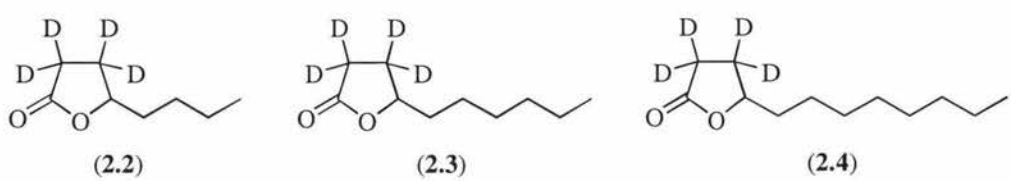
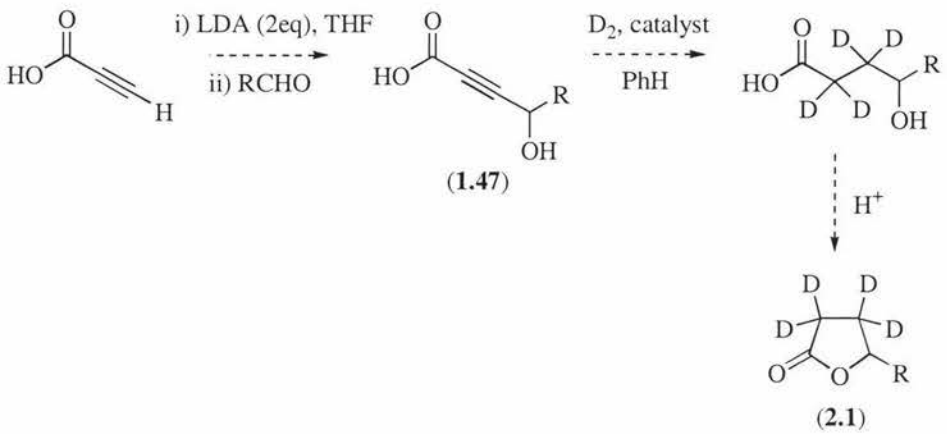


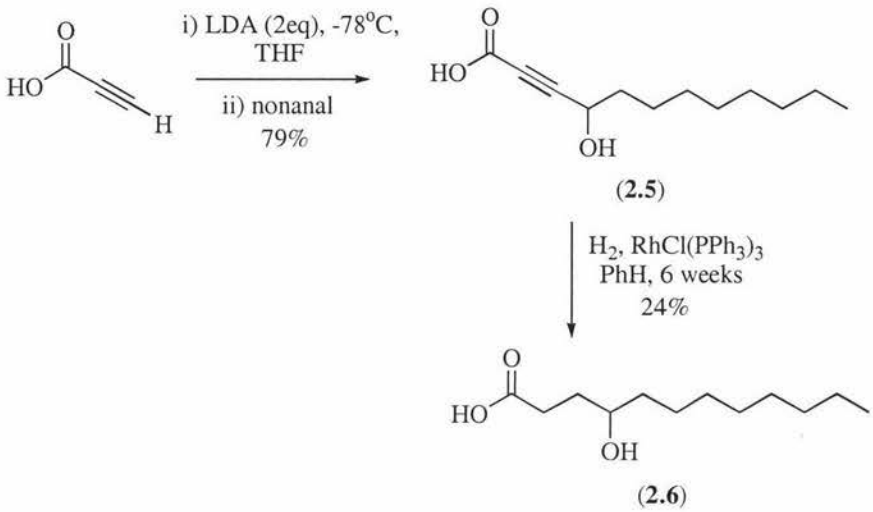
Figure 2.1

It was originally suggested that the synthesis of these lactones (**Figure 2.1**) be conducted according to the scheme outlined below. (**Scheme 2.2**) It was anticipated that formation of the dianion of propionic acid and addition to a suitable aldehyde would generate an intermediate hydroxy acid (**1.47**), which under conventional catalytic conditions could be reduced and cyclised to the deuterated γ-lactone (**2.1**). A homogeneous catalyst, Wilkinson's catalyst ($(Ph_3P)_3RhCl$), was chosen to prevent scrambling of the deuterium label, a recognised problem associated with heterogeneous catalysts.[1,2]



Scheme 2.2

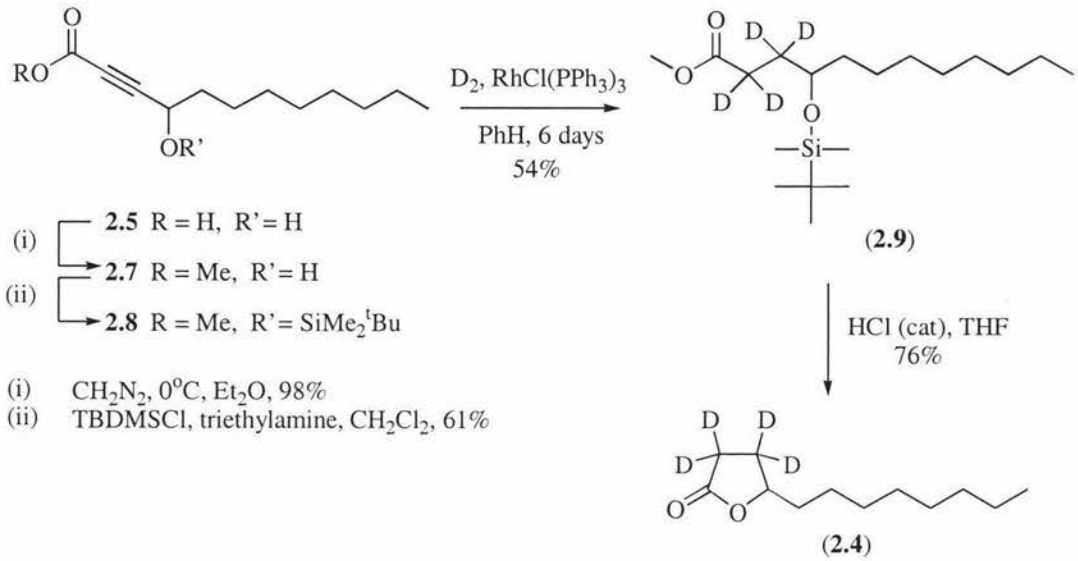
2.2 Synthesis of 4-Hydroxydodecanoic Acid.[3]



Scheme 2.3

The dianion of propionic acid, generated with 2 equivalents of LDA at –78°C in THF, was reacted with nonanal to give 4-hydroxydodec-2-ynoic acid (**2.5**) in 79% yield after recrystallisation. The attempted reduction of (**2.5**) with hydrogen gas and Wilkinson's catalyst in benzene was found to proceed extremely slowly (6 weeks) and in only poor yield (24% (**2.6**) isolated).[3] It is believed the sluggish nature of this reduction is due to complexation of the hydroxy acid (**2.5**), or a partially reduced intermediate thereof, to the rhodium catalyst. While complexation of the alkyne (oxidative addition) is a necessary requirement of the catalytic cycle of Wilkinson's catalyst, the process also calls for loss or de-complexation of the substrate (reductive elimination) after the reduction step.[4] Strong chelation of the acid and alcohol functional groups is believed to significantly retard this important step. It was therefore expected that protection of the polar acid and alcohol groups would reduce this problem and accelerate the reduction of the acetylene.

2.3 Synthesis of 2,2,3,3-$^2H_4$-γ-Dodecalactone.



Scheme 2.4

4-Hydroxydodec-2-ynoic acid (**2.5**)[3] was protected as the methyl ester by methylation with diazomethane in ether. This gave 4-hydroxydodec-2-ynoic acid methyl ester (**2.7**) in a 98% isolated yield. ^{1}H NMR analysis of the methyl ester (**2.7**) showed a broad exchangeable singlet at 3.41 ppm, and a three-proton singlet at 3.75 ppm, corresponding to the alcohol and methyl ester groups respectively. GCMS gave a molecular ion of m/z = 226 (2%), and fragmentation consistent with the presence of a methyl ester.

Further protection of the secondary alcohol moiety in (**2.7**) as the *tert*-butyldimethylsilyl ether (TBDMS) was achieved under standard silylation conditions.[5] Treatment of (**2.7**) with *tert*-butyldimethylsilyl chloride (TBDMSCl) and triethylamine in dichloromethane afforded 4-*tert*-butyldimethylsiloxydodec-2-ynoic acid methyl ester (**2.8**) in 61% yield after chromatography on silica gel. The ^{1}H NMR spectrum of the silyl ether (**2.8**) showed no exchangeable alcohol signal and exhibited two, three-proton singlets at 0.11 and 0.14 ppm. An increase in intensity of the existing three-proton signal centered at 0.90 ppm to twelve protons was also observed, due to a coincidental resonance of the ^{t}Bu group with the terminal methyl group of the alkyl chain. These observations, together with new signals at –5.1 (Si*C*H$_3$), -4.5 (Si*C*H$_3$), 18.2 (SiC(*C*H$_3$)$_3$) and 25.7 (Si*C*(CH$_3$)$_3$) in the ^{13}C NMR

spectrum, were fully consistent with the formation of the TBDMS silyl ether. Further conformation was given by GCMS. A single homogeneous peak exhibiting a molecular ion of m/z = 340 (1%) was observed.

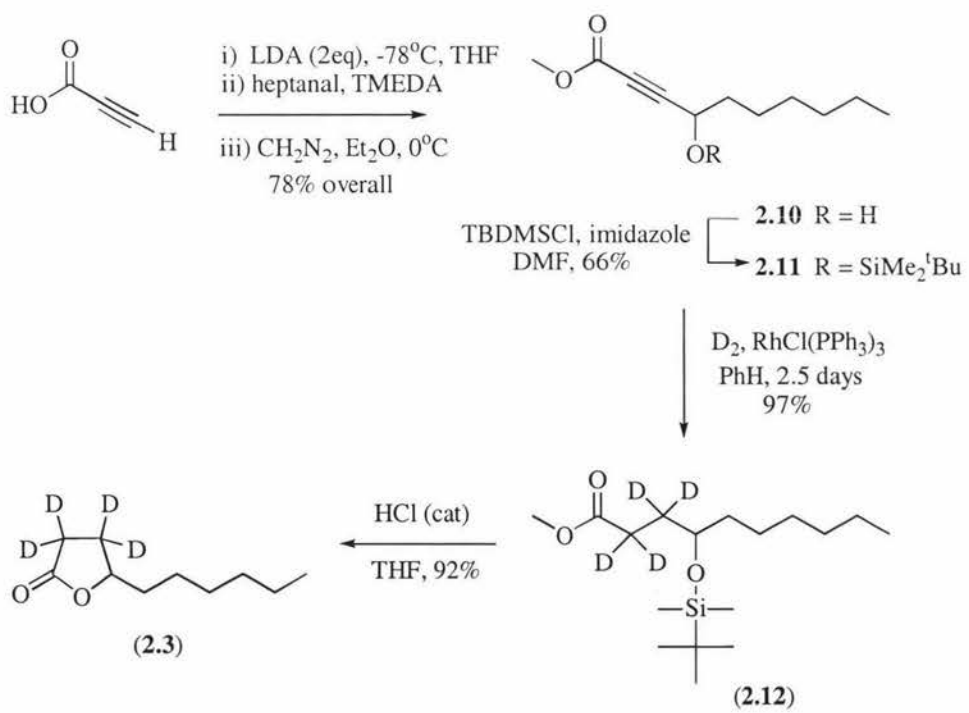
The complete reduction of acetylene (**2.8**) was performed using Wilkinson's catalyst (5 mol%) in benzene and deuterium gas to afford a 54% yield of (**2.9**) after 6 days. The rate of reduction of 4-*tert*-butyldimethylsiloxydodec-2-ynoic acid methyl ester (**2.8**) in comparison to that observed for 4-hydroxydodec-2-ynoic acid (**2.5**), under otherwise identical conditions, did increase as anticipated from 6 weeks to 6 days. This observation supported our earlier rational in relation to the chelation to the metal catalyst by the unprotected species (**2.5**). 2,2,3,3-$^{2}H_4$-4-*tert*-Butyldimethylsiloxydodecanoic acid methyl ester (**2.9**) showed little change in the ^{1}H NMR spectra from the alkyne (**2.8**), although the two three-proton singlets at 0.11 and 0.14 ppm ($Si(CH_3)_2$) had collapsed into one six-proton singlet at 0.04 ppm. Intriguingly no signal for the –C*H*(OTDBMS) methine proton was detected, believed perhaps to be obscured under the methyl ester peak. Disappearance of the alkynic carbons in the ^{13}C NMR spectrum was observed, although the new CD_2 signals were obscured in the noise and could not be seen. Formation of 2,2,3,3-$^{2}H_4$-4-*tert*-butyldimethylsiloxydodecanoic acid methyl ester (**2.9**) was confirmed by GCMS with a molecular ion of m/z = 348 (1%) being observed. This represents an increase of 8 mass units, from the alkyne (**2.8**) corresponding to the incorporation of four deuterium atoms.

Having successfully reduced the acetylenic ester to (**2.9**), it remained to deprotect both the acid and ester groups and effect cyclisation to give the target lactone. This was achieved by acid catalysed ring closure with a catalytic quantity of HCl in THF. 3,3,4,4-$^{2}H_4$-γ-dodecalactone (**2.4**), having the intense peach odour characteristic of γ-dodecalactone noted during purification, was obtained in a 76% yield after distillation. ^{1}H NMR comparison of (**2.4**) with unlabelled γ-dodecalactone (**1.5**) showed the absence of the ring proton signals: i.e. a two proton doublet of triplets at 2.34 ppm, and a two proton multiplet at 2.18 ppm. Collapse of the one-proton multiplet at 4.36 ppm into a triplet was also observed for the γ ring proton of (**2.4**). Diastereotopicity of the δ protons (in the alkyl substituent) was also observed and resulted in the appearance of two, one-proton multiplets at 1.60 and 1.71 ppm. Analysis of ^{1}H NMR data and intergration of residual peaks indicated that deuterium

incorporation of 97% had been achieved. ^{13}C NMR showed the absence of two carbon signals at 27.5 and 28.7 ppm. These signals were obscured by noise and the expected multiplicity of the signals could not be confirmed. GCMS gave a single homogeneous peak, showing a molecular ion of m/z = 202 (<1%) for 3,3,4,4-$^2H_4$-γ-dodecalactone (**2.4**), corresponding to a difference of 4 mass units from unlabelled γ-dodecalactone (**1.5**) (m/z = 198). This is fully consistent with the substitution of 4 protons for deuterium atoms. The fragmentation pattern indicated that the deuterium label was indeed positioned in the ring of the lactone, with the anticipated base peak of m/z = 89 (100%) corresponding to ring fragmentation containing all four deuterium atoms.

2.4 Synthesis of 2,2,3,3-$^2H_4$-γ-Decalactone.

The general strategy successfully used for the synthesis of 3,3,4,4-$^2H_4$-γ-dodecalactone (**2.4**) was applied to the synthesis of 3,3,4,4-$^2H_4$-γ-decalactone (**2.3**). Several minor changes, however, were made in an attempt to increase the yields of each step. (**Scheme 2.5**)



Scheme 2.5

The dianion of propionic acid, generated with 2 equivalents of LDA at –78°C in THF, was reacted with heptanal in the presence of TMEDA to afford a 4-hydroxydec-2-ynoic acid intermediate. Without characterisation the crude acid was treated directly with an etheral solution of diazomethane to give 4-hydroxydec-2-ynoic acid methyl ester (**2.10**) in 78% overall yield. The ^{1}H NMR spectrum for (**2.10**) showed a broad exchangeable singlet at 3.21 ppm and a singlet at 3.75 ppm, corresponding to an alcohol and methyl ester group respectively. A molecular ion of M^{+}-H of m/z = 197 (52%) was obtained by GCMS.

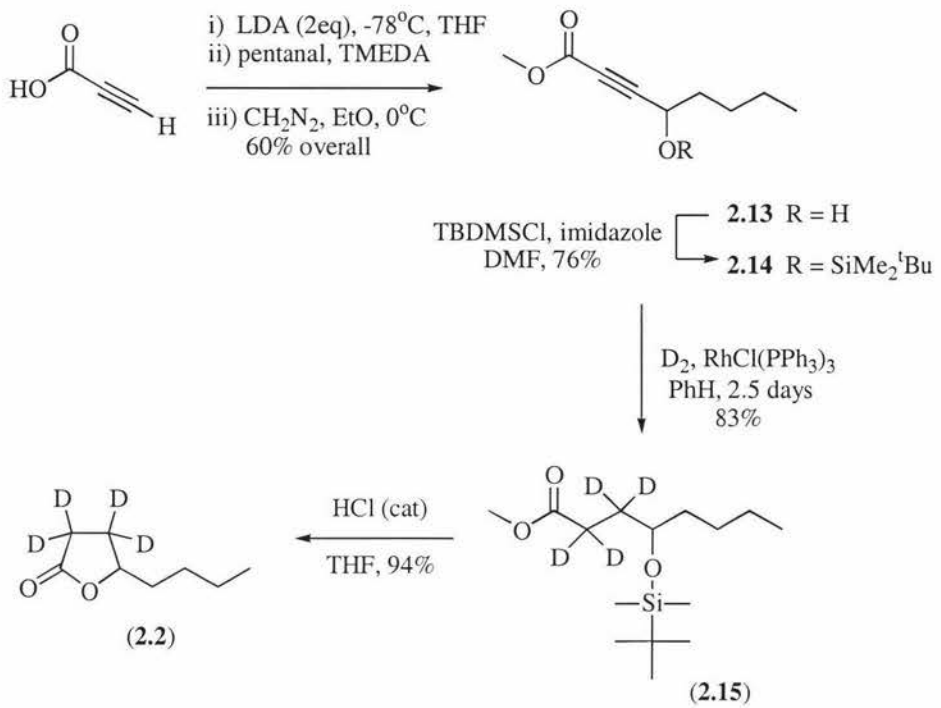
Protection of the secondary alcohol (**2.10**) as the silyl ether was achieved by treatment with TBDMSCl and imidazole in DMF at 0°C[5] and afforded 4-*tert*-butyldimethylsiloxydec-2-ynoic acid methyl ester (**2.11**) in 66% yield after chromatography on silica gel. Formation of the TBDMS ether (**2.11**) was evidenced in the ^{1}H NMR spectra with no exchangeable alcohol signal observed and by the appearance of two, three-proton singlets at 0.11 and 0.14 ppm. An increase in intensity of the existing three-proton signal centered at 0.89 ppm to twelve protons was also observed again due to a coincidental resonance of the *tert*-butyl group with the terminal alkyl methyl group. These observations together with new signals at –5.1 ($SiCH_3$), -4.5 ($SiCH_3$), 18.2 ($SiC(CH_3)_3$) and 25.7 ($SiC(CH_3)_3$) in the ^{13}C NMR spectrum, were fully consistent with the formation of the TBDMS silyl ether. Further conformation was given by GCMS showing an M^{+}-H ion of m/z = 311 (2%), as a single, homogeneous peak.

The complete reduction of acetylene (**2.11**) was performed using deuterium gas and Wilkinson's catalyst at 10 mol% loading, where before 5 mol% was used, and afforded a 97% yield of (**2.12**) after 2.5 days. 2,2,3,3-$^{2}H_4$-4-*tert*-Butyldimethylsiloxydecanoic acid methyl ester (**2.12**) again showed little change in the ^{1}H NMR spectra in comparison with the alkyne (**2.11**). Most significant was the collapse of the two, three-proton singlets at 0.11 and 0.14 ppm into one six-proton singlet at 0.04 ppm. Disappearance of the alkynic carbons in the ^{13}C NMR spectrum was seen, although the new CD_2 signals were not observed above the noise. Formation of 2,2,3,3-$^{2}H_4$-4-*tert*-butyldimethylsiloxydecanoic acid methyl ester (**2.12**) was confirmed by GCMS with a molecular ion of m/z = 320 (<1%) obtained, an increase of 8 mass units from (**2.11**), corresponding to the incorporation of four deuterium atoms.

Deprotection and cyclisation of the reduced acetylenic ester (**2.12**) was achieved with catalytic HCl in THF, and afforded 3,3,4,4-$^{2}H_4$-γ-decalactone (**2.3**) in 92% yield after distillation. An intense peachy odour, characteristic of γ-decalactone, was noticed upon isolation of 3,3,4,4-$^{2}H_4$-γ-decalactone (**2.3**). ^{1}H NMR comparison of (**2.3**) with unlabelled γ-decalactone (**1.4**) showed the near complete disappearance of the ring proton signals, and intergration of these residual peaks indicated that deuterium incorporation of 89% had been achieved. Collapse of the one-proton multiplet at 4.40 ppm into a triplet was also observed for the γ ring proton of (**2.3**). Diastereotopicity of the δ methylene protons (in the alkyl substituent) was observed and resulted in two, one-proton multiplets at 1.60 and 1.71 ppm. ^{13}C NMR showed the loss of two carbon signals at 27.6 and 28.6 ppm (C2 and C3). As before, these signals were partially obscured by noise and the expected multiplicity could not be confirmed. GCMS gave a homogeneous peak showing a weak molecular ion of m/z = 174 (<1%) for 3,3,4,4-$^{2}H_4$-γ-decalactone (**2.3**), a difference of 4 mass units from γ-decalactone (**1.4**) (m/z = 170). This is consistent with the substitution of 4 protons for deuterium atoms. The fragmentation pattern indicated that the deuterium label was indeed positioned in the ring of the lactone, with the anticipated base peak of m/z = 89 (100%) corresponding to the ring fragment containing four deuterium atoms.

2.5 Synthesis of 2,2,3,3-$^{2}H_4$-γ-Octalactone

The general strategy successfully used in the synthesis of 3,3,4,4-$^{2}H_4$-γ-decalactone (**2.3**) was applied to the synthesis of 3,3,4,4-$^{2}H_4$-γ-octalactone (**2.2**). (**Scheme 2.6**)



Scheme 2.6

The dianion of propionic acid, generated with 2 equivalents of LDA at –78°C in THF, was reacted with pentanal in the presence of TMEDA to afford a 4-hydroxyoct-2-ynoic acid intermediate. Without characterisation the crude acid was treated directly with an etheral solution of diazomethane to give 4-hydroxyoct-2-ynoic acid methyl ester (**2.13**) in 60% overall yield. The ^{1}H NMR spectrum for (**2.13**) showed a singlet at 3.77 ppm, corresponding to the methyl ether group.

Protection of the secondary alcohol (**2.13**) as the silyl ether was achieved by treatment with TBDMSCl and imidazole in DMF at 0°C, and afforded 4-*tert*-butyldimethylsiloxyoct-2-ynoic acid methyl ester (**2.14**) in 76% yield after chromatography on silica gel. Formation of (**2.14**) was evidenced in the ^{1}H NMR spectra by the appearance of features consistent with earlier observations. Together with new peaks at –5.1 (Si*C*H$_3$), -4.5 (Si*C*H$_3$), 18.2 (SiC(*C*H$_3$)$_3$) and 25.7 (Si*C*(CH$_3$)$_3$) in the ^{13}C NMR spectrum, these observations were fully consistent with the formation of the TBDMS silyl ether. Further conformation was given by GCMS showing an M$^+$-H ion of m/z = 284 (<1%), as a single homogeneous peak.

The complete reduction of acetylene (**2.14**) was again performed using deuterium gas and Wilkinson's catalyst at 10 mol% loading, and afforded an 83% yield of (**2.15**) after 2.5 days. In comparison with alkyne (**2.14**) 2,2,3,3-$^{2}H_4$-4-*tert*-butyldimethylsiloxyoctanoic acid methyl ester (**2.15**) again showed the collapse of the two, three-proton singlets at 0.11 and 0.14 ppm into a six-proton singlet at 0.04 ppm. Disappearance of the alkynic carbons in the ^{13}C NMR spectrum was seen, although again the new CD_2 signals were obscured by the noise and could not be observed. Formation of 2,2,3,3-$^{2}H_4$-4-*tert*-butyldimethylsiloxyoctanoic acid methyl ester (**2.15**) was confirmed by GCMS with a molecular ion of m/z = 292 (1%) obtained, an increase of 8 mass units, corresponding to the incorporation of four deuterium atoms.

Deprotection and cyclisation of the reduced acetylenic ester (**2.15**) was achieved with catalytic HCl in THF, and afforded 3,3,4,4-$^{2}H_4$-γ-octalactone (**2.2**) in 94% yield after distillation. An intense coconut odour, characteristic of γ-octalactone, was noticed upon isolation of 3,3,4,4-$^{2}H_4$-γ-octalactone (**2.2**). ^{1}H NMR comparison of (**2.2**) with unlabelled γ-octalactone (**1.3**) showed the near complete disappearance of the ring proton signals, and integration of these residual peaks indicated that deuterium incorportion of 90% had been achieved. Collapse of the one-proton multiplet at 4.40 ppm into a triplet was also observed for the γ ring proton of (**2.2**). Diastereotopicity of the δ protons (in the alkyl substituent) was also observed, and resulted in two one-proton multiplets at 1.60 and 1.71 ppm. ^{13}C NMR showed the loss of two carbon signals, at 28.0 and 28.8 ppm (C2 and C3). These features were again partially obscured by noise and the expected multiplicity could not be confirmed. GCMS gave an homogeneous peak showing a molecular ion of m/z = 146 (<1%) for 3,3,4,4-$^{2}H_4$-γ-octalactone (**2.2**), a difference of 4 mass units from γ-octalactone (**1.3**) (m/z = 142), equivalent to the substitution of 4 protons for 4 deuterium atoms. The fragmentation pattern indicated that the deuterium label was positioned in the ring of the lactone, with the anticipated base peak of m/z = 89 (100%) corresponding to the ring fragment containing four deuterium atoms.

2.6 Conclusions.

The introduction of four deuterium atoms regioselectively into the ring of a γ-lactone by reduction of a doubly protected hydroxy acetylenic acid has proved successful for the synthesis of the three target lactones: 3,3,4,4-$^2H_4$-γ-dodecalactone (**2.4**), 3,3,4,4-$^2H_4$-γ-decalactone (**2.3**) and 3,3,4,4-$^2H_4$-γ-octalactone (**2.2**). Consistent spectral changes were observed for each intermediate in the syntheses and comparison of the labelled lactones with their unlabelled analogues indicated regioselective deuteration had been achieved to a high degree (89-97%). It is suggested that with further refinement the efficiency of this strategy for the synthesis of 2,2,3,3-$^2H_4$-γ-lactones could be improved and would be amenable to the synthesis of other lactones of this class. A summary of yields is given in **Table 2.1**.

Table 2.1

Step	$^2H_4$-γ-dodecalactone (**2.4**)	$^2H_4$-γ-decalactone (**2.3**)	$^2H_4$-γ-octalactone (**2.2**)
1 addition/ methylation	98%[†]	78%	60%
2 silylation	61%	66%	76%
3 reduction (time)	54% (6 days)	97% (2.5 days)	83% (2.5 days)
4 deprotection/ lactonisation	76%	92%	94%
Overall Yield	25%	46%	36%
% deuteration	97%	89%	90%

[†]Methylation only

An increase in the overall yields of (**2.3**) and (**2.2**) with respect to (**2.4**) reflects an improvement in the silylation and reduction protocols used. Nonetheless, improved handling skills must also be taken into account. The dramatic increase in reduction yields, and decreased reduction time can be attributed to an increase in catalyst loading from 5 mol% (**2.4**) to 10 mol% (**2.3** and **2.2**). The formation of $^2H_4$-γ-dodecalactone with 97% deuterium incorporation suggests that the homogeneous reduction of hydroxyalkynoic acid

derivatives with Wilkinson's catalyst is best performed with low catalyst loadings i.e. 5 mol%. At 10 mol%, as used for (**2.3**) and (**2.2**), a reduced deuterium incorporation was observed albeit, with shorter reduction times. A high degree of regioselective deuterium incorporation is arguably more important than this saving in time.

References.

(1) Mohrig, J. R., Dabora, S. L., Foster, T. F., Schultz, S. C., *J. Org. Chem.* **1984**, *49*, 5179-5182.

(2) Birch, A. J., Walker, K. A. M., *J. Chem. Soc. (C)* **1966**, 1894-1896.

(3) Fielder, S., unpublished results, HortResearch.

(4) March, J. *Advanced Organic Chemistry*; 4th ed.; John Wiley & Sons: New York, 1992.

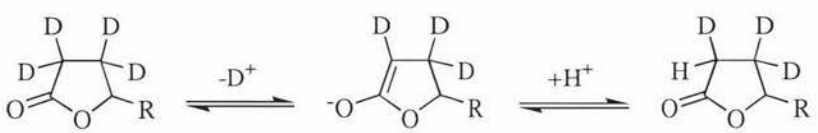
(5) Lilly, M., J., Ph.D. Thesis, Massey University, 1998.

Chapter 3

Free Radical Synthesis of 3,3,4-$^2H_3$-4-Alkyl-γ-Lactones.

3.1 Introduction.

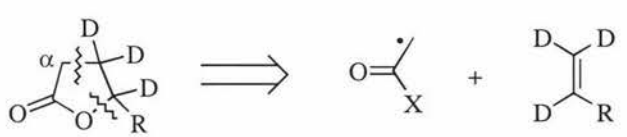
The reductive strategy utilised to synthesis 2,2,3,3-$^2H_4$-γ-lactones (Chapter 2, **Schemes 2.3-2.5**), while successful, has some disadvantages. Firstly, as with many multi-stepped procedures, the synthesis is time consuming and relatively low yielding overall (**Table 2.1**). Secondly, in order to be considered robust, an isotope label must be introduced at a non-exchangeable position within the molecule. This presents a potential problem when dealing with the deuterated lactones generated in **Chapter 2** (**Figure 2.1**), as protons (and deutrons) α to carbonyl functionality are known to enolise in the presence of acid or base and may therefore exchange with protons from the sample matrix.[1] (**Scheme 3.1**)



γ-lactone enolate ion

Scheme 3.1

This phenomenon can jeopardise the integrity of the labelled standard and the potential for D/H exchange such as this must therefore be removed. The tri-deuterated structural varients (**3.1**) alleviate this problem yet still comply with the broader requirements of SIDA where three deuterium atoms are retained in the lactone ring for maximum sensitivity in the mass spectrum.



(3.1) **(3.2)** **(3.3)**

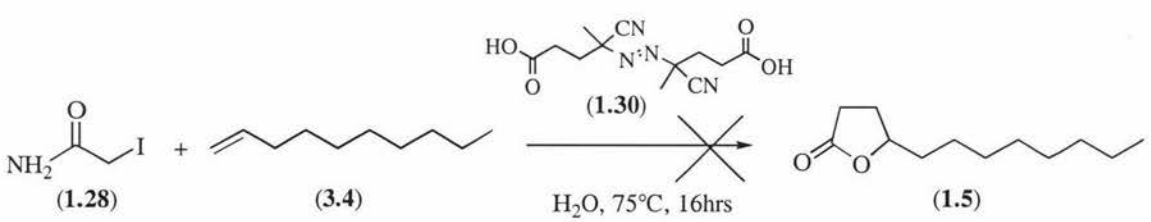
X = OR, NR_2 R = alkyl

Figure 3.1

The possibility of incorporating deuterated substrates into known reactions using free-radical chemistry has been discussed in section **1.3.1**. In these examples the target lactone was generated through coupling of a two-carbon acetoxy radical equivalent (**3.2**) (X = OH, NH_2) with an appropriate alkene, the origin of the R substituent (**Figure 3.1**). Therefore, as a general requirement for all the syntheses reviewed (section **1.3**), introduction of deuterium regioselectively into the non-exchangeable β and γ positions of 4-alkyl-γ-lactones (**3.1**) requires access to 1,1,2-$^2H_3$-alkenes (**3.3**). One of the main objectives of this work was to develop a synthesis of deuterium labelled γ-lactones from readily available starting materials with the minimum number of steps. To this end the elegant method of Yorimitsu *et al.*[2] was adapted as a potentially short synthesis to 3,3,4-$^2H_3$-γ-lactones. (**Scheme 1.6**)

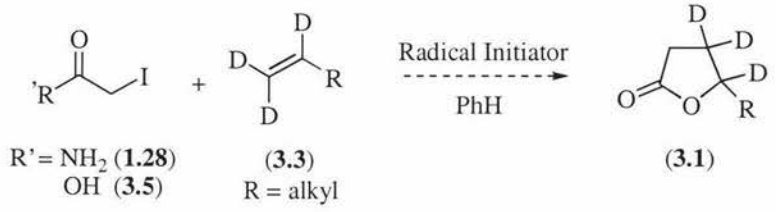
3.2 The Halogen Transfer Reaction as a Route to 3,3,4-$^2H_3$-4-Alkyl-γ-lactones.

The halogen atom transfer reaction is a powerful method for the generation of new C-C bonds via the addition of an alkyl halide to a C-C multiple bond.[3] (**Scheme 1.5**) The importance of this reaction in the formation of γ-lactones has been discussed in section **1.3.1**, and a variety of ω-hydroxyalkyl lactones were prepared in good yield by Yorimitsu and co-workers by this method[2]. However, in an attempted synthesis of γ-dodecalactone (**Scheme 3.2**), where the radical addition of a 2-iodocarbonyl moiety to a simple alkene not bearing a terminal hydroxy group (i.e. 1-decene (**3.4**)) was described, the complete recovery of 1-decene was reported without the formation of any lactone products. It was suggested, by the authors, that this was due to the insolubility of 1-decene in water.[2]



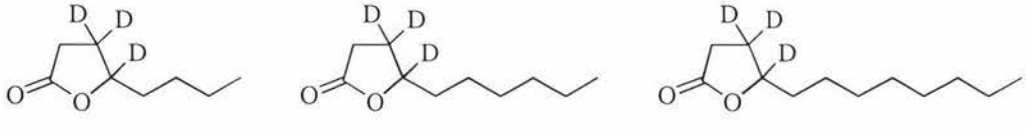
Scheme 3.2

This observation suggested to us that the substitution of an aprotic non-polar solvent for water would provide a simple and convenient one-step synthesis of 3,3,4-$^2H_3$-4-alkyl-γ-lactones of general structure (**3.1**) from simple 1,1,2-$^2H_3$-1-alkenes not bearing a terminal hydroxy group (**3.3**). (**Scheme 3.3**)



Scheme 3.3

It was anticipated that replacing water for benzene, and utilising a more conventional radical initiator[†] would constitute a one step synthesis of γ-lactones suitable for incorporation of 3-deuterium atoms regioselectively within the lactone ring. A series of 3 γ-lactones were initially identified as synthetic targets via this route (**Figure 3.2**): 3,3,4-$^2H_3$-γ-octalactone (**3.6**), 3,3,4-$^2H_3$-γ-decalactone (**3.7**) and 3,3,4-$^2H_3$-γ-dodecalacone (**3.8**).

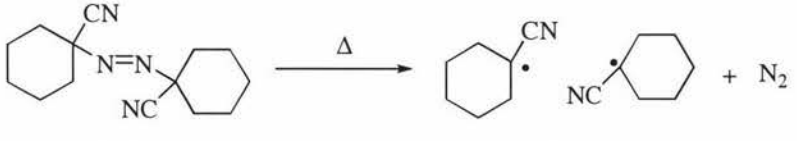


(**3.6**) (**3.7**) (**3.8**)

Figure 3.2

Following a mechanism analogous to that postulated by Yorimitsu *et al.*[2] (**Scheme 1.6**), it was anticipated that this process would proceed as outlined in **Scheme 3.4**.

Step 1

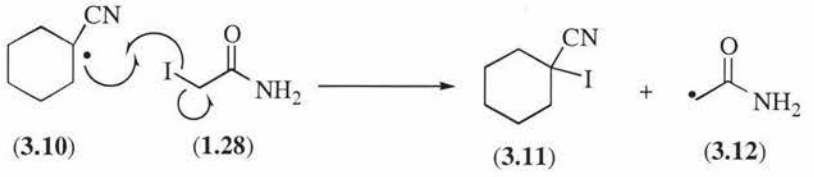


(**3.9**) (**3.10**)

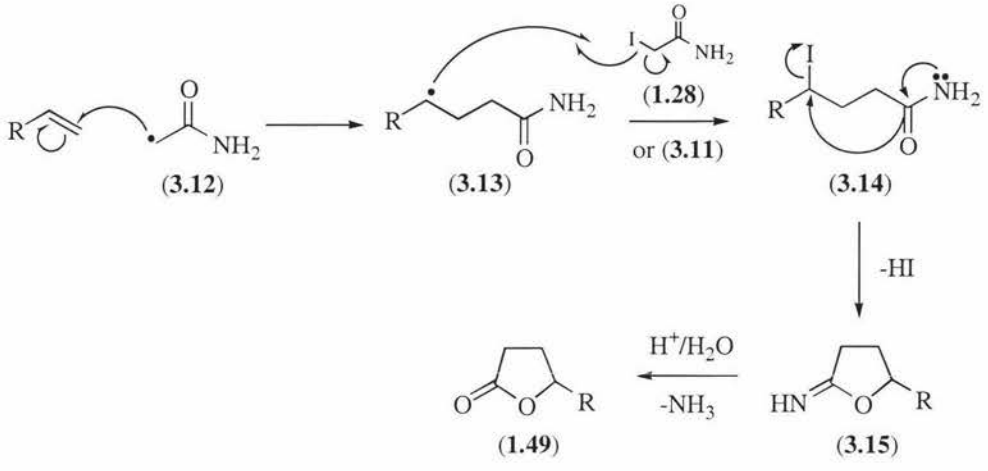
Scheme 3.4

[†] The choice of radical initiator is discussed in section 3.3.1.

Step 2



Step 3



Scheme 3.4 (continued)

The process is initiated by the thermal decomposition of the radical initiator (1,1'-azo-*bis*-cyclohexanecarbonitrile (**3.9**)) to generate two equivalent radicals (**3.10**) and nitrogen gas, (Step 1). In a second step (Step 2), cyclohexyl radicals (**3.10**) abstract an iodine atom from an α-iodocarbonyl species, (2-iodoacetmaide (**1.28**)) to give the acetamide radical (**3.12**) in the initial stages of an atom transfer process. The acetamide radical (**3.12**) adds to the 1-alkene (Step 3) to produce the secondary carbon-centered radical (**3.13**), to which iodine is transferred from either a second molecule of 2-iodoacetamide (**1.28**), or from the iodocyclohexylnitrile (**3.11**) formed initially in the iodine abstraction reaction. Cyclisation of (**3.14**), under the reaction conditions, with loss of HI, gives the imine intermediate (**3.15**), which is hydrolysed to give the γ-lactone (**1.49**) in the final step of the process.

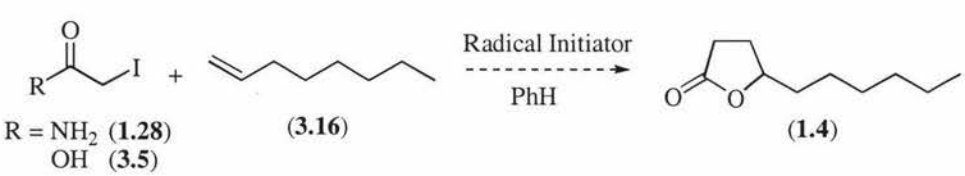
3.3 Optimisation Reactions.

The radical cascade outlined in (**Scheme 3.4**) represents a complex series of events with a number of potential variables. To establish the feasibility of this process in benzene and to optimise the reaction required a systematic approach. Under the reaction conditions described by Yorimitsu *et al.* (**Scheme 1.6**) an ω-hydroxy-1-alkene, α-iodocarbonyl and radical initiator in a 1.5:1.0:0.5 mole ratio gave lactones in good yield (93-95%).[2] This stoichiometry was chosen as the starting point in the optimisation of the reaction of simple alkenes under conventional conditions.

3.3.1 Reaction Conditions.

In an effort to achieve maximum lactone yields, each variable in the reaction (**Scheme 3.5**) was examined independently. To accomplish this, an experimental technique was devised in which a number of small-scale reactions could be carried out simultaneously. Scintillation vials, employed as reaction vessels, were placed in a vibrating water bath (200 r.p.m.), and variables were altered independently. (**Tables 3.1-3.4**) Reactions were analysed by gas chromatography (GC) and an estimation of lactone yield was calculated. (**Appendix 3.1**) The best results of each set of experimental parameters were repeated for validity and further optimisations conducted from there.

Although $^{2}H_3$-γ-lactones were identified as synthetic targets (**Figure 3.2**), optimisation reactions were carried out with unlabelled 1-octene (**3.16**) as the alkene source. (**Scheme 3.5**)



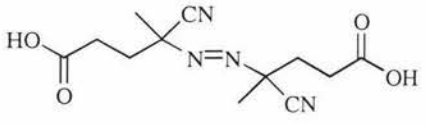
R = NH_2 (**1.28**)
OH (**3.5**)

(**3.16**)

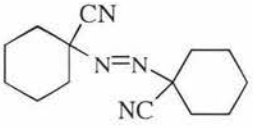
(**1.4**)

Scheme 3.5

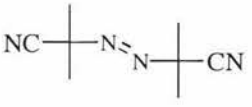
2-Iodoacetamide (R = NH_2, **1.28**) and 2-iodoacetic acid (R = OH, **3.5**) were employed as α-iodocarbonyl moieties. Three radical initiators were evaluated (**Figure 3.3**): 4,4'-azo-*bis*-4-cyanopentanoic acid (ACPA) (**1.30**), 1,1'-azo-*bis*-cyclohexanecarbonitrile (ACCN) (**3.9**), 2,2'-azo-*bis*-isobutyronitrile (AIBN) (**3.17**).



(**1.30**)



(**3.9**)



(**3.17**)

Figure 3.3

ACPA (**1.30**) is a water-soluble free radical initiator (used by Yorimitsu *et al.*[2]), while ACCN (**3.9**) is reported to be a more efficient radical initiator than AIBN (**3.17**).[4] All reactions were conducted at 75°C over 18 hrs in 10mL of benzene unless otherwise stated (i.e. 0.1 M).[†]

3.3.2 First Optimisation Series.

The aim of the first series of optimisations was to identify which combination of radical initiator and α-iodocarbonyl compound (using literature mole ratios[2]) resulted in the highest yield of γ-decalactone (**1.4**) as determined by GC.

Table 3.1

entry	1-Octene (mmol)	2-Iodoacetic acid (mmol)	2-Iodoacetamide (mmol)	AIBN (mmol)	ACPA (mmol)	ACCN (mmol)	% Lactone (GC Yield)
1	1.5	-	1.0	0.5	-	-	8%
2	1.5	1.0	-	0.5	-	-	6%
3	1.5	-	1.0	-	0.5	-	0%
4	1.5	1.0	-	-	0.5	-	7%
5	1.5	-	1.0	-	-	0.5	10%
6	1.5	1.0	-	-	-	0.5	9%

[†] No further optimization of concentration was made.

With the exception of ACPA and 2-iodoacetamide (**Table 3.1**, entry 3) all the combinations investigated saw the formation of γ-decalactone. However, results from this first series indicated ACCN (**3.9**) generally gave marginally higher yields than the other two initiators (**Table 3.1**, entries 5-6) and further testing concentrated only on the use of this initiator. With only a modest increase in yields noticed for 2-iodoacetamide (**Table 3.1**, entries 1, 5) over 2-iodoacetic acid (**Table 3.1**, entries 2, 4, 6), testing was continued for both α-iodocarbonyls.

3.3.3 Second Optimisation Series.

The second optimisation series investigated the effect of the mole ratios of reactants on product yield. (**Table 3.2**) The mole ratio for each reactant (1-octene, 2-iodoacetamide/2-iodoacetic acid and ACCN) was sequentially doubled with respect to that of the literature ratios. The ratio for ACCN was also halved (**Table 3.2**, entries 7-8).

Table 3.2

entry	1-Octene (mmol)	2-Iodoacetic acid (mmol)	2-Iodoacetamide (mmol)	ACCN (mmol)	% Lactone (GC Yield)
1	1.5	-	2.0	0.5	5%
2	1.5	2.0	-	0.5	3%
3	3.0	-	1.0	0.5	9%
4	3.0	1.0	-	0.5	7%
5	1.5	-	1.0	1.0	23%
6	1.5	1.0	-	1.0	9%
7	1.5	-	1.0	0.25	5%
8	1.5	1.0	-	0.25	4%

Results from this series clearly showed the combination of 1-octene, 2-iodoacetamide, and ACCN (1.5:1.0:1.0) (**Table 3.2**, entry 5) to be the highest yielding (23%). With 2-iodoacetamide again generating higher yields of lactone than 2-iodoacetic acid the next series of optimisations examined the use of 2-iodoacetamide only.

3.3.4 Third Optimisation Series.

With an optimal reactant combination established, mole ratios were again varied in an effort to increase yields further, focusing on the best result obtained from the previous series (**Table 3.2**, entry 5). Ratios were alternatively halved and doubled but as the highest previous result was obtained with twice the initiator concentration (**Table 3.2**, entry 5), the mole ratio of ACCN was also tripled (**Table 3.3**, entry 6) in an attempt to explore the significance of this parameter. In view of the anticipated value and scarcity of labelled compounds (i.e. $^{2}H_3$-alkenes), alternative mole ratios for the alkene were also examined and variations in concentration of this component were also investigated (**Table 3.3**, entries 7-8).

Table 3.3

entry	1-Octene (mmol)	2-Iodoacetamide (mmol)	ACCN (mmol)	% Lactone (GC Yield)
1	1.5	0.5	1.0	72%
2	1.5	2.0	1.0	36%
3	0.75	1.0	1.0	14%
4	3.0	1.0	1.0	48%
5	1.5	1.0	2.0	47%
6	1.5	1.0	3.0	51%
7	0.75	0.5	1.0	36%
8	0.75	2.0	1.0	2%
9	1.5	0.5	-	0%

The best results for this series were obtained from a combination of 1-octene (1.5 mmol), 2-iodoacetamide (0.5 mmol) and ACCN (1.0 mmol) (**Table 3.3**, entry 1) giving a 72% GC yield of γ-decalactone (**1.4**). Although theoretically only 0.5 mmol of ACCN should be required to generate a stiochiometric concentration of free radicals (1.0 mmol) (**Scheme 3.4**), it was found experimentally that vials containing 1.0 mmol of initiator gave higher yields of lactone (c.f. **Table 3.2**). This raised concern as to the efficiency of the radical initiator. A reaction with 1-octene (1.5 mmol) and 2-iodoacetamide (0.5 mmol) in benzene (10 mL) with no radical initiator was performed and resulted in the complete recovery of

starting materials only (**Table 3.3**, entry 9). This confirmed the importance of the radical initiator, although did not explain the significance of its apparent excess. It is suggested that 1.0 mmol of initiator is required to maintain an appropriate flux of radical intermediates (**3.10**, **Scheme 3.4**) necessary for the reaction to proceed.

Over the course of these experiments, benzene loss was observed from a number of the vials. In such cases the reaction mixtures were reconstituted to the initial concentration with additional benzene before GC analysis. Where necessary the affected reaction was repeated (>2 mL loss). While encouraging GC results were obtained, it was realised that solvent loss from the vials could mean other factors might also be affecting the observed results. Water from the water bath, or atmospheric oxygen could have entered the vials and consequently facilitated or impeded lactone formation. Indeed, the mechanism proposed by Yorimitsu *et al.*[2] necessitates the presence of water to hydrolyse the intermediate imine (**3.15**, **Scheme 3.4**) and it is suggested that the presence of advantageous water entering the reaction vessels was, with hindsight, vital to the formation of the γ-decalactone.

The significance of these external influences was realised when a 64% isolated yield of γ-decalactone was obtained from a scintillation vial using the optimised reactant ratios (72% GC yield) (**Table 3.3**, entry 1), but a duplicate reaction conducted in a round-bottomed flask under anhydrous conditions in an oil bath produced no lactone as judged by tlc. To achieve a reproducible reaction the consideration of water, air and also aluminium (from the scintillation vial lids) as possible catalysts/suppressors had to be accounted for. The presence of water, required in the final step (**Scheme 3.4**), is expected to aid lactone production, while atmospheric oxygen has the potential to promote peroxide formation and therefore inhibit lactone production. The presence of aluminium, only considered after considerable corrosion was noted on some vial caps, may potentially assist in the removal of HI from the reaction and thus catalyse ring closure but slow hydrolysis of (**3.15**). Duplicate vials of the optimised reaction (**Table 3.3**, entry 1) conducted with and without aluminium foil in the caps were tested to survey the affect of aluminium foil on the

reaction. It was found, however, to have an insignificant effect on lactone yields, with both vials giving similar GC results (64% with, 69% without) under optimised conditions.

To test the importance of other external variables, reproducible reaction conditions using standard experimental equipment had to first be established. It was considered that while valuable initially for obtaining GC yields leaky scintillation vials were perhaps not a good choice of reaction vessel. A controlled procedure was achieved using a conventional round-bottom flask (20 mL) fitted with a condenser. Four reactions were run in parallel with two of the flasks flushed continuously with nitrogen (flasks 1 and 2) to eliminate both oxygen and atmospheric water, and two fitted with calcium chloride drying tubes to eliminate atmospheric water but otherwise maintain an atmosphere of dry air (flasks 3 and 4). Water (1 mol eq.) was added to one flask of each atmosphere type (nitrogen or air, flasks 1 and 3), and the contents refluxed for 18 hrs. (**Table 3.4**)

Table 3.4

flask	1-Octene (mmol)	2-Iodoacetamide (mmol)	ACCN (mmol)	Water (mmol)	Atmosphere		% Lactone (GC Yield)
					Air	N_2	
1	1.5	0.5	1.0	-	-	✓	9%
2	1.5	0.5	1.0	1.0	-	✓	26%
3	1.5	0.5	1.0	-	✓	-	1%
4	1.5	0.5	1.0	1.0	✓	-	1%

Both reactions conducted under an atmosphere of air (flasks 3 and 4), irrespective of water content, produced only 1% γ-decalactone by GC analysis (**Table 3.4**, flasks 3 and 4). The reaction performed under an atmosphere of nitrogen, in the absence of water gave a 9% yield (flask 1), while in the presence of 1 equivalent of water (flask 2) a yield of 26% was obtained (**Table 3.4**, flasks 1 and 2). Although this result is still much less than that obtained from the scintillation vial (**Table 3.3**, flask 1 (72%)), it established the reactions success under controlled conditions and demonstrated the necessary presence of water in the reaction.

The formation of peroxides in the presence of an oxygen rich atmosphere (flasks 3, 4), was tested for the crude reaction mixtures with the tlc dip *p*-amino-N:N-dimethyl-aniline sulphate.[5] A negative test for both reactions established the absence of any peroxides in these mixtures. The lower yields of lactone obtained under an air atmosphere cannot therefore be adequately explained.

3.3.5 Final Optimisations.

The final optimisation iteration involved determining the optimum concentration of water required for the reaction. 5, 10, 50 and 100 molar equivalents of water were tested under both atmospheres (nitrogen and air). (**Table 3.5**)

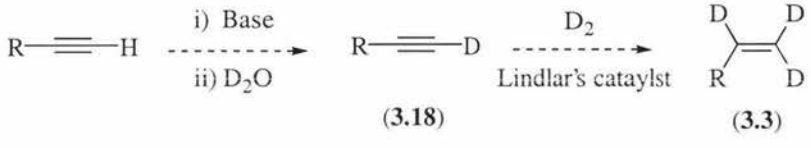
Table 3.5

entry	1-Octene (mmol)	2-Iodoacetamide (mmol)	ACCN (mmol)	Water (mmol)	Atmosphere		% Lactone (GC Yield)
					Air	N_2	
1	1.5	0.5	1.0	5.0	-	✓	8%
2	1.5	0.5	1.0	10.0	-	✓	35%
3	1.5	0.5	1.0	5.0	✓	-	1%
4	1.5	0.5	1.0	10.0	✓	-	2%
5	1.5	0.5	1.0	50.0	-	✓	82%
6	1.5	0.5	1.0	100.0	-	✓	42%
7	1.5	0.5	1.0	50.0	✓	-	3%
8	1.5	0.5	1.0	100.0	✓	-	1%

An estimated GC result of 82% was obtained with 50 equivalents of water under a nitrogen atmosphere (**Table 3.5**, entry 5). When repeated preparatively this was improved even further and resulted in the isolation of γ-decalactone in 91% yield after distillation. This demonstrates the value of this optimisation protocol, where an initial yield of 10 % (**Table 3.1**, entry 5) eventually lead to a 91% yield of the γ-decalactone over a series of four optimisation steps. With a high yielding synthesis of unlabelled γ-decalactone established, the synthesis of $^{2}H_3$-alkenes and their utilisation in the regioselective synthesis of $^{2}H_3$-γ-lactones was investigated.

3.4 Deuterium Incorporation.

Arguably one of the most convenient methods of generating $^2H_3$-alkenes (**3.3**) is the reduction of the corresponding ^2H-alkyne (**3.18**), using deuterium gas in the presence of Lindlar's catalyst (**Scheme 3.6**). Lindlar's catalyst is a partially deactivated palladium catalyst. Deactivation controls activity and enables the partial reduction of acetylenes.[6] It was anticipated that the synthesis of ^2H-alkynes could be achieved by deprotonation of the acetylenic hydrogen of a 1-alkyne and deuteration of the resulting acetylide with deuterium oxide in a manner analogous to the method of Sirokman *et al.*[7] (**Chapter 1**). It was surprising to find that few other literature procedures for this simple process have been reported. This may reflect the difficulties encountered with this apparently simple yet non-trivial transformation.†



(**3.18**) (**3.3**)

R = C_4H_9, C_6H_{13}, C_8H_{17}

Scheme 3.6

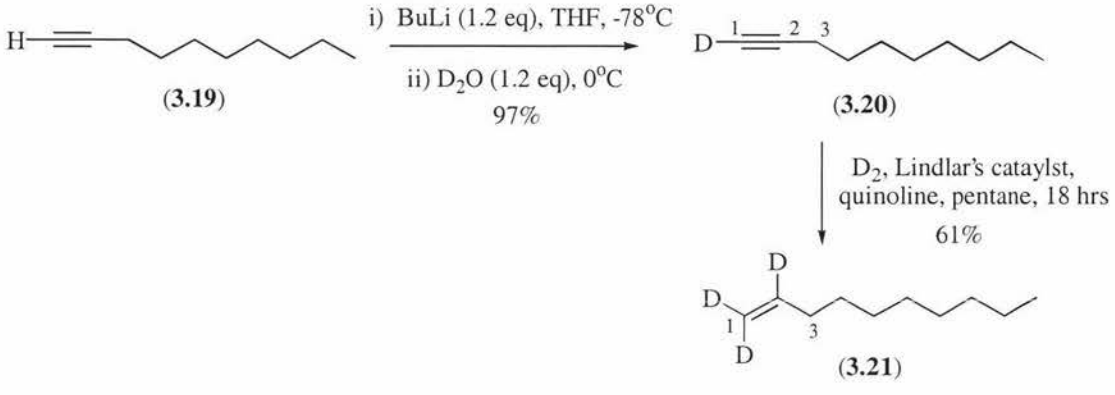
The alkene component is responsible for introducing the alkyl substituent (R) into the γ-lactone (Section **3.1**). Hence, to generate the target lactones (**Figure 3.2**): 3,3,4-$^2H_3$-γ-octalactone (**3.6**), 3,3,4-$^2H_3$-γ-decalactone (**3.7**) and 3,3,4-$^2H_3$-γ-dodecalacone (**3.8**), access to 1,1,2-$^2H_3$-hexene (R = C_4H_9), 1,1,2-$^2H_3$-octene (R = C_6H_{13}) and 1,1,2-$^2H_3$-decene (R = C_8H_{17}) respectively, was required.

† This procedure (**Scheme 3.6**) has however been used.[8]

3.4.1 Synthesis of 1,1,2-$^2H_3$-Alkenes.

3.4.1.1 1,1,2-$^2H_3$-Decene.

Synthesis of 1-^{2}H-decyne (**3.20**) was achieved by the deprotonation of 1-decyne (**3.19**) with BuLi (1.2 eq.) in THF at –78°C and quenching the reaction mixture with deuterium oxide (1.2 eq.). (**Scheme 3.7**) Acetylene (**3.20**) was isolated in 97% yield after distillation as a mobile colourless oil.



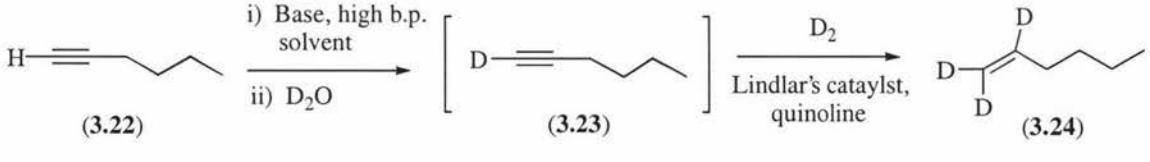
Scheme 3.7

The formation of 1-^{2}H-decyne (**3.19**) was confirmed by comparison of the NMR spectra with the unlabelled compound. 1-Decyne (**3.19**) exhibits a single proton triplet at 1.94 ppm (alkynic proton) and integration of the ^{1}H NMR spectra for 1-^{2}H-decyne (**3.20**) showed a residual signal of 0.02H at 1.92 ppm, indicating 98% deuterium incorporation had been achieved. Further comparison showed the two-proton triplet of doublets for C3 (**3.19**) had collapsed to a simple triplet at 2.18 ppm in the deuterated analogue (**3.20**). Comparison of ^{13}C NMR spectra showed the terminal alkynic signals (C1 and C2) had lost intensity significantly and been replaced by a pair of 1:1:1 triplets. GCMS confirmed the transformation to 1-^{2}H-decyne (**3.20**) with a molecular ion of m/z = 139, one mass unit higher than 1-decyne being observed.

Hydrogenation of 1-^{2}H-decyne (**3.20**) in pentane with deuterium gas in the presence of Lindlar's catalyst poisoned with quinoline afforded 1,1,2-$^2H_3$-decene (**3.21**) in 61% yield after distillation. ^{1}H NMR of $^2H_3$-decene (**3.21**) on comparison with unlabelled decene showed the near complete absence of the alkenic protons, specifically the one-proton multiplet (C2) at 5.42 ppm and the two one-proton multiplets (C1) at 4.90-4.95 ppm. The two-proton multiplet (C3) of decene had collapsed into a triplet at 2.07 ppm for $^2H_3$-decene (**3.21**). This material showed 93% deuterium incorporation as determined by 1H NMR. ^{13}C NMR data showed a dramatic decrease in intensity of the deuterated carbon signals with splitting of the two alkenic signals into a multiplet at 113.6 ppm (C1) and a 1:1:1 triplet at 138.9 ppm (C2). Mass spectral analysis gave additional conformation of the presence of 1,1,2-$^2H_3$-decene, showing a molecular ion of m/z = 143 (15%), a difference from unlabelled 1-decene of 3 mass units, corresponding to the substitution of three hydrogen atoms for three deuterium atoms.

3.4.1.2 1,1,2-$^2H_3$-Hexene via 1-^{2}H-Hexyne.

The synthesis of 1-$^2H_3$-hexene via 1-^{2}H-hexyne required a different approach due to the volatility of 1-hexyne (b.p. ≈ 64°C). Where previously, 1-decene was isolated from a lower b.p. solvent (pentane), under reduced pressure, this was not feasible for 1-hexyne. Attempts at transforming 1-hexyne (**3.22**) into 1,1,2-$^2H_3$-hexene (**3.24**) in a high boiling solvent and distilling the product from it were therefore investigated. (**Scheme 3.8**)



Scheme 3.8

3.4.1.2.1 Tetraethyleneglycol Dimethyl Ether as Solvent.

Using tetraethyleneglycol dimethyl ether (tetraglyme) as solvent, 1-hexyne (**3.22**) was treated with BuLi (1.2 eq.) and quenched with deuterium oxide (1.2 eq.). Total conversion to 1-^{2}H-hexyne (**3.23**) was assumed (but not verified) and Lindlar's catalyst and quinoline were added without isolation of the intermediate 1-^{2}H-alkyne. The mixture was reduced using deuterium gas but uptake was slow, with only half (55%) the anticipated gas uptake occurring in 4 weeks. The addition of extra catalyst did not increase this rate and the reduction was consequently stopped, the mixture distilled and the fraction boiling between 61-72°C collected. ^{13}C NMR analysis showed the collected faction to contain a mixture of 1,1,2-$^{2}H_3$-hexene, 1-^{2}H-hexyne and unlabelled hexane (originating from the BuLi solution) in an estimated ratio of (1:2:12). Attempts to separate this mixture proved unsuccessful.

The sluggish nature of the reduction was thought to be a consequence of the polarity of the tetraglyme where solvation of the palladium catalyst slowed exchange with the substrate and therefore prevented reduction occurring at a practical rate. Consequently a less polar solvent was employed and to ensure the absence of hexanes an alternative base to BuLi (as a solution in hexanes) was sought. To this end the preparation of $^{2}H_3$-hexene was attempted in undecane (b.p. 193-196°C).

3.4.1.2.2 Undecane as Solvent.

In this approach to 1,1,2-$^{2}H_3$-hexene, sodium hydride was used as the base (**Scheme 3.7**) for the deprotonation of 1-hexyne in undecane as an involatile solvent. The use of undecane has the additional advantage that the parafin oil, in which the sodium hydride is dispersed, need not be removed, as is usually the case with this material.

Hexyne (**3.22**) was treated with NaH (1.05 eq.) and quenched with deuterium oxide (1.05 eq.). Total conversion to 1-^{2}H-hexyne (**3.23**) was assumed but again not confirmed and Lindlar's catalyst and quinoline were added to the undecane solution. The mixture was

reduced using deuterium gas. After 2.5 days, the reaction mixture had over-reduced and water had been drawn inadvertantly into the reaction flask from the gas reservoir. The water was decanted from the reaction mixture and the undecane solution passed through a short plug of $MgSO_4$, before distillation. A colourless fraction was collected at a somewhat higher boiling point than expected (89-97°C) and was found by NMR to be largely undecane in composition. This was initially puzzling, yet on further investigation it was discovered that undecane (b.p. 193-196°C) azeotropes with water (4.0% wt.) at 98-99°C.[9] 1,1,2-$^2H_3$-Hexene was not observed and this approach was abandoned.

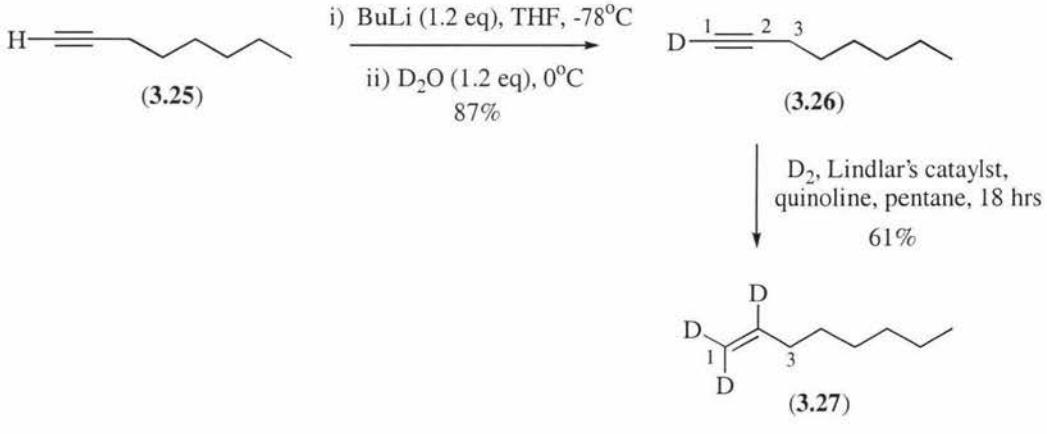
3.4.1.2.3 Tetradecane as Solvent.

The synthesis of 1,1,2-$^2H_3$-hexene was also attempted with tetradecane (b.p. 252-254°C) as an involatile solvent. 1-Hexyne (**3.22**) was treated with NaH (1.05 eq.) and quenched with deuterium oxide (1.05 eq.). Lindlar's catalyst and quinoline were added (assuming complete conversion) and the mixture reduced using deuterium gas. (**Scheme 3.7**) Reduction under these conditions was, however, again very slow with the required volume of gas consumed after 2 weeks. Distillation from the solvent proved difficult and volatiles were removed under reduced pressure and trapped at low temperatures (liquid N_2). This approach gave a mixture of $^2H_3$-hexene (**3.24**) (with 94% deuterium incorporation) and 1-^{2}H-hexyne in a yield of 42% (by mass balance) in a ratio of 1:0.8 (as estimated by ^{1}H NMR). Comparison of the ^{1}H NMR spectra with unlabelled 1-hexene showed the near complete absence of the alkenic protons, while ^{13}C NMR comparison showed a dramatic decrease in intensity and splitting of the deuterated alkenic carbon signals into a multiplet at 113.5 ppm (C1), and a 1:1:1 triplet at 131.2 ppm (C2). GCMS gave additional conformation as to the presence of 1,1,2-$^2H_3$-hexene (**3.24**), with a molecular ion of m/z = 87 (27%) obtained. This represents a difference of 3 mass units in comparison to unlabelled hexene, corresponding to the substitution of three hydrogen atoms for three deuterium atoms. Attempts to purify $^2H_3$-hexene prepared by this method by short path distillation were unsuccessful and the crude material containing the alkyne was used in subsequent reactions.

3.4.1.3 1,1,2-$^2H_3$-Octene.

3.4.1.3.1 Method A: n-Butyl lithium as Base.

A procedure similar to that used to prepare 1-decyne (**Scheme 3.6**) was attempted initially. 1-Octene (**3.25**) was treated with BuLi (1.2 eq.) followed by deuteration with deuterium oxide (1.2 eq.). (**Scheme 3.9**)



Scheme 3.9

Difficulty was experienced in the isolation of 1-^{2}H-octyne (**3.26**) by this method, due to its volatility (b.p. 122-123°C). Nonetheless, a crude yield of 87% (containing some hexanes for the BuLi) was obtained with 92% deuterium incorporation. NMR analysis showed changes in the ^{1}H and ^{13}C spectra fully consistent with the formation of 1-^{2}H-octyne (**3.26**). These included the absence of an alkynic proton at 1.93 ppm and the collapse of the alkynic carbon signals (C1 and C2) in the ^{13}C NMR spectra to 1:1:1 triplets. Attempts to remove residual hexanes from 1-^{2}H-octyne by distillation resulted in significant losses (80-90%). 1-^{2}H-Octyne was therefore used in subsequent synthesis without purification.

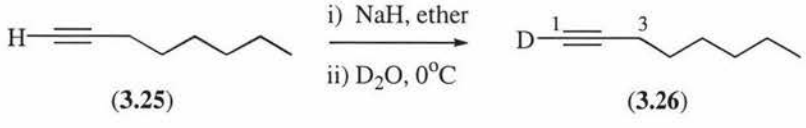
Lindlar's catalyst and quinoline were added to a solution of 1-^{2}H-octyne (**3.26**) in pentane and reduction to 1,1,2-$^2H_3$-octene proceeded without apparent difficulty over 18 hrs. Indeed a 61% yield after distillation of 1,1,2-$^2H_3$-octene (**3.27**) was obtained (by mass balance) with 88% deuterium incorporation. However, on closer inspection of the ^{1}H NMR

of 1,1,2-$^2H_3$-octene (**3.27**) prepared in this way, it was discovered that the sample contained significant quantities of 1-butanol (40%) (b.p. ≈ 118°C) as a contaminant. 1-Butanol had co-distilled with the octene (b.p. ≈ 122°C) during the attempted purification by short path distillation. It is likely that this material originated from the BuLi solution, formed by the reaction with oxygen to generate an intermediate peroxide, which was later reduced in the presence of Lindlar's catalyst. The presence of butanol was later found to act as an inhibitor of the radical lactonisation process. In an attempt to remove the butanol, the solution of 1,1,2-$^2H_3$-octene (**3.27**) in pentane was passed through a short plug of silica, but difficulty was again experienced in the recovery of this relatively volatile alkene on such a small scale.

The additional difficulty of removing traces of quinoline (b.p. ≈ 113°C), despite extensive acid washing of the reaction mixture, led to an evaluation of the reduction without quinoline present. Two attempts were made, differing only in the choice of solvent. Ethyl acetate and hexane were employed. Both methods, however, resulted in over reduction and analysis of the reaction mixtures revealed 1,1,2-$^2H_3$-octene (**3.27**) to be present together with 1,1,1,2,2-$^2H_5$-octane and butanol. An alternative, more straightforward synthesis of 1,1,2-$^2H_3$-octene was therefore investigated.

3.4.1.3.2 Method B: Sodium hydride as Base.

The use of sodium hydride as a base was explored to avoid the introduction of butanol and hexanes (**Scheme 3.10**). Four attempts were made at the conversion of 1-octyne into 1-^{2}H-octyne and these are outlined in. (**Table 3.6**)



(**3.25**) (**3.26**)

Scheme 3.10

Table 3.6

Entry	NaH (eq.)	D_2O (eq.)	$^2H_5$-acetic acid (eq.)	Sonication (min)	% conversion
1	1.3	1.3	–	–	60%
2	2.0	2.0	–	–	75%
3	3.0	5.0	–	30 min	86%
4	3.0	5.0	1.0	30 min	87%

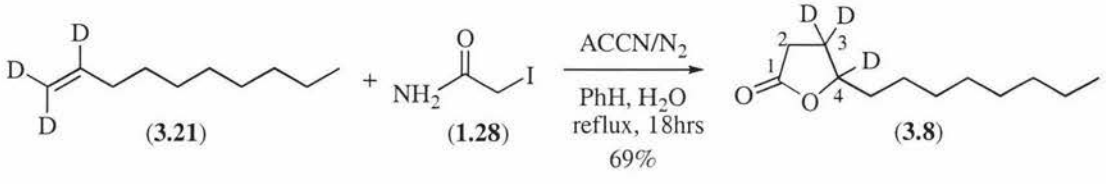
Initial attempts to prepare 1,1,2-$^2H_3$-octene with a slight excess of both NaH and D_2O (**Table 3.6**, entry 1), resulted in only a 60% conversion of the unlabelled octyne as judged by ^1H NMR analysis (through loss of the terminal alkynic proton at 1.92 ppm). While the addition of a two-fold excess of reagents (**Table 3.6**, entry 2) saw an increase in the percent conversion, the degree of deuterium incorporation remained surprisingly low (75%). In an attempt to effect complete conversion the reaction mixture was sonicated in the presence of excess NaH (**Table 3.6**, entry 3). However, even in the presence of $^2H_5$-acetic acid (**Table 3.6**, entry 4), conversion remained surprisingly incomplete. These observations remain difficult to explain and no further attempts to optimise the preparation of 1-^2H-octyne by this method were made and this material (entry 4) was used in subsequent experiments.

3.5 3,3,4-$^2H_3$-4-Alkyl-γ-Lactone Synthesis via the Radical Method.

With access to 1,1,2-$^2H_3$-decene (**3.21**) of high chemical and isotopic purity, small quantities of 1,1,2-$^2H_3$-hexene (**3.24**) and 1,1,2-$^2H_3$-octene (**3.27**) (albeit containing butanol) the synthesis of deuterated γ-lactones under the optimized free radical conditions was attempted.

3.5.1 3,3,4-$^2H_3$-γ-Dodecalactone.

Under the optimised conditions described earlier (Section **3.3**), 1,1,2-$^2H_3$-decene (**3.21**) (3.5 mmol), 2-iodoacetamide (1.2 mmol), ACCN (2.3 mmol) and water (0.1 mol) in benzene (23 mL, i.e. 0.1 M) were refluxed for 18 hrs under an atmosphere of nitrogen. (**Scheme 3.11**)

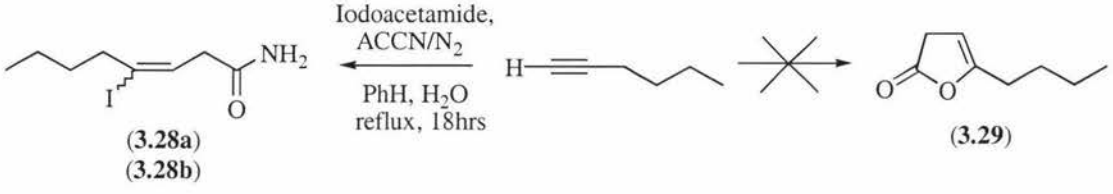


Scheme 3.11

Tlc analysis of the reaction indicated the lactone was present and this was confirmed by the characteristic peachy smell of the crude reaction mixture during workup. A yield of 69% was obtained for 4,4,5-$^2H_3$-γ-dodecalactone (**3.8**) after chromatography and distillation with 96% deuterium incorporation as judged by ^1H NMR. Comparison of ^1H NMR spectra for (**3.8**) with unlabelled γ-dodecalactone (**1.5**) showed the expected simplification of splitting patterns (Section **1.2.3**) and, more significantly, the disappearance of the one-proton quintet at 4.31 ppm (C4) and two methylene multiplets at 1.82 and 2.26 ppm (C3). The two-proton multiplet (C2) at 2.52 ppm had collapsed into a broadened singlet of comparable chemical shift (δ = 2.52 ppm). ^{13}C NMR signals for the deuterated carbons were easily distinguishable, with C4 appearing as a 1:1:1 triplet at 80.8 ppm, and C3 as a multiplet centered around 27.4 ppm. A molecular ion of m/z = 201 (<1%) was obtained by GCMS analysis of the distilled material, a difference corresponding to three deuterium atoms from the unlabelled γ-dodecalactone. A base peak of m/z = 88 (100%) was observed. This result demonstrated the regioselective synthesis of 3,3,4-$^2H_3$-γ-lactones in good yield by a simple one-pot procedure.

3.5.2 3,3,4-$^2H_3$-γ-Octalactone.

The 1,1,2-$^2H_3$-hexene (**3.24**) isolated from the involatile solvent tetradecane contained unreduced 1-^{2}H-hexyne (**3.23**). To ensure the residual 1-hexyne would not interfere with the radical lactonisation process it was tested in place of the alkene under otherwise identical, optimised radical conditions. (**Scheme 3.12**)

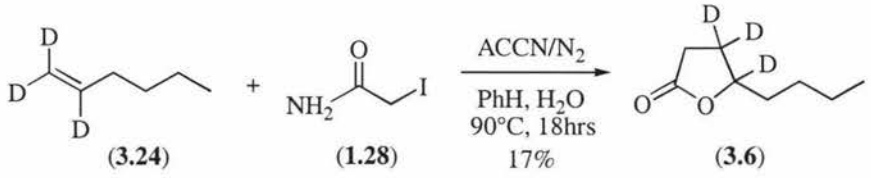


(**3.28a**)
(**3.28b**)

(**3.29**)

Scheme 3.12

As expected the butenolide (**3.29**) was not observed, however, a mixture of two minor products were detected by tlc. ^{1}H NMR analysis suggested these products to be the 4-iodooct-3-eneamides (**3.28a**) and (**3.28b**), as a mixture of cis/trans isomers (6:1). Significant in this assignment was the appearance of two doublets centered at 3.00 and 3.12 ppm (C2) in a ratio of 6:1. A single proton triplet at 5.79 ppm (C3) and a broad exchangeable –NH_2 signal were also observed at 5.95 ppm. ^{13}C NMR showed the amide (C1) at 172.3 and 174.5 ppm and alkenic carbons at 94.6 and 98.7 (C4) and 114.6 and 116.4 (C3) ppm. This result suggests that any residual 1-hexyne present should be transformed to the iodoalkene and not interfere with the 1,1,2-$^2H_3$-hexene lactonisation process. The 1,1,2-$^2H_3$-hexene/1-^{2}H-hexyne sample obtained from tetradecane was therefore used in an effort to generate 3,3,4-$^2H_3$-γ-octalactone. (**Scheme 3.13**)



(**3.24**) (**1.28**) (**3.6**)

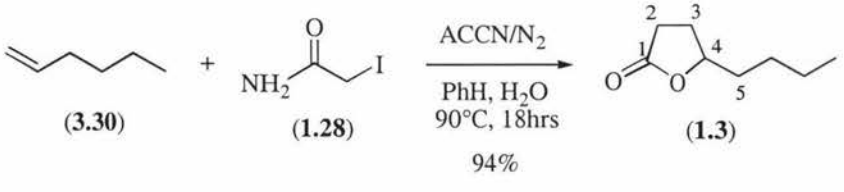
Scheme 3.13

Isolation of 4,4,5-$^2H_3$-γ-octalactone (**3.6**) was achieved after purification by flash chromatography in a 17% yield with 92% deuterium incorporation. The presence of iodoacetamides (**3.28**) (presumably as a deuterated analogue) were detected but not isolated from the reaction mixture. Comparison of ^1H NMR spectra of (**3.6**) with unlabelled γ-octalactone showed the disappearance of the one-proton multiplet at 4.46 ppm (C4) and the two methylene multiplets at 1.88 and 2.31 ppm (C3). ^{13}C NMR showed splitting of the deuterated carbons with C4 appearing as a 1:1:1 triplet at 80.5 ppm and C3 as a multiplet centered at 27.3 ppm. A molecular ion of m/z = 145 (<1%) was obtained by GCMS, a difference form unlabelled γ-octalactone of three mass units, corresponding to the substitution of three hydrogen atoms for three deuterium atoms. Similarly a base peak of m/z = 88 (100%), shifted three mass units from the corresponding base peak of the non-deuterated γ-octalactone, was also observed.

The disappointingly low yield of (**3.6**) obtained under the optimised conditions but in the presence of hexyne is in stark contrast to the optimal yields obtained earlier and suggest the presence of hexyne significantly effected the efficiency of the radical lactonisation process.

3.5.3 Unlabelled γ-Octalactone.

To demonstrate the effectiveness of the free-radical lactonisation reaction the synthesis of γ-octalactone was performed with freshly distilled, unlabelled 1-hexene (**3.30**). (**Scheme 3.14**)



(**3.30**) (**1.28**) (**1.3**)

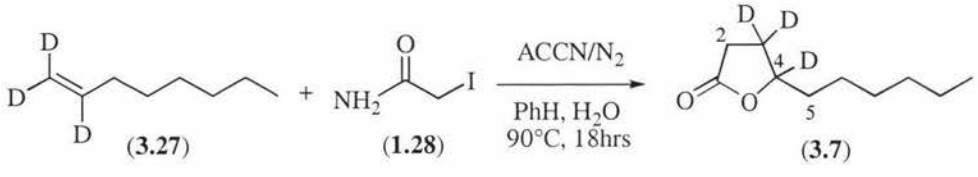
Scheme 3.14

This reaction resulted in the successful isolation of 94% γ-octalactone after distillation and suggests that with access to sufficient quantities of pure 1,1,2-$^2H_3$-hexene (not a trivial

synthesis), the corresponding 3,3,4-$^2H_3$-γ-octalactone is likely to be equally accessible in yields comparable to that obtained for the unlabelled analogue above.

3.5.4 Attempted Synthesis of 3,3,4-$^2H_3$-γ-Decalactone.

The optimised radical reaction was performed on a sample of 1,1,2-$^2H_3$-octene containing butanol (50%). 1,1,2-$^2H_3$-Octene/butanol (nominally 12.6 mmol in octene), 2-iodoacetamide (**1.28**) (4.2 mmol), ACCN (8.4 mmol) and water (0.4 mol) in benzene (84 mL) were refluxed for 18 hrs under an atmosphere of nitrogen. (**Scheme 3.15**)



Scheme 3.15

The reaction mixture was worked up following the standard procedures, however, no product was observed by tlc or could be detected by ^1H NMR.

The reaction was repeated for 1,1,2-$^2H_3$-octene containing $^2H_5$-octane and butanol (1:1:0.6). 1,1,2-$^2H_3$-Octene/butanol/$^2H_5$-octane (nominally 1.5 mmol in octene), 2-iodoacetamide (**1.28**) (0.5mmol), ACCN (1.0 mmol) and water (50 mmol) in benzene were refluxed for 18 hrs under an atmosphere of nitrogen. (**Scheme 3.15**) Again no 3,3,4-$^2H_3$-γ-decalactone (**3.7**) was generated. Further attempts to prepare 3,3,4-$^2H_3$-γ-decalactone (**3.7**) with $^2H_3$-octene contaminated with butanol and $^2H_5$-octane were also unsuccessful. While this result proved disappointing it should be remembered that the unlabelled γ-decalactone was isolated in 91% yield as part of the optimization protocol and suggests (as with $^2H_3$-hexene) the presence of contaminants in the alkene component is very significant. With access to supplies of pure $^2H_3$-octene it is suggested 3,3,4-$^2H_3$-γ-decalactone will be accessible by this procedure.

3.6 Comparative Procedure: Mn(III) Chemistry.

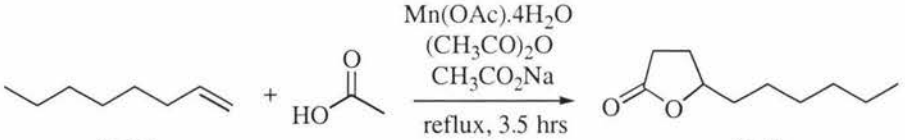
To establish the relative efficiency of the optimised radical reaction, described in detail in section **3.3**, a comparative reaction was conducted using the simple one-step Mn(III) approach developed by Heiba *et al.*[10,11] (section **1.3.1**). The work of Heiba *et al.* has received attention from a number of authors and has also been extensively reviewed.[12,13]

The most convenient laboratory preparation of γ-lactones from as stated by Heiba *et al.*,[10] involves the *in situ* formation of manganic acetate by the reaction of potassium permanganate and manganous acetate. This method permits the one-step synthesis from readily available reagents as $KMnO_4$, $Mn(OAc)_2$, an olefin and a carboxylic acid. (**Scheme 3.16**)[11]

$$KMnO_4 + 4Mn(OAc)_2.4H_2O + 8HOAc \longrightarrow 5Mn(OAc)_3 + 20H_2O + KOAc$$

Scheme 3.16

To directly compare the optimised free-radical reaction process with Heiba's approach, the following reaction was conducted. (**Scheme 3.17**)

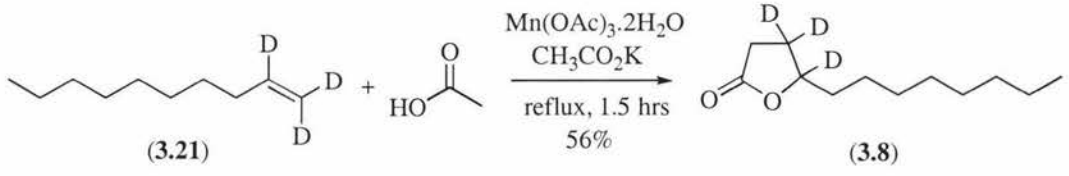


(**3.16**) (**1.4**)

Scheme 3.17

Removal of acetic acid from the reaction mixture proved difficult, nonetheless, γ-decalactone (**1.4**) was obtained in 38% yield after distillation. This result compares unfavourable to the radical reaction, in which a 91% yield for γ-decalactone (**1.4**) was obtained after distillation.

The harsh experimental conditions required for the manganic reaction (i.e. refluxing in acetic acid b.p. 118°C), raised concern as to how the integrity of a deuterium label would withstand such conditions. 1,1,2-$^2H_3$-Decene, with 93% deuterium incorporation, was trialed under Hebia's conditions with manganic acetate in refluxing acetic acid to assess this. (**Scheme 3.18**)



Scheme 3.18

3,3,4-$^2H_3$-γ-Dodecalactone was obtained in a 56% yield after distillation with 90% deuterium incorporation as judged by NMR. The radical approach again compares favourably, (**Scheme 3.11**) with a yield of 69% obtained for (**3.8**) with 90% deuterium incorporation. The deuterium label is not greatly affected by the harsh manganic acetate conditions.

3.7 Conclusions.

The regioselective synthesis of 3,3,4-$^2H_3$-γ-dodecalactone (**3.8**) and 3,3,4-$^2H_3$-γ-octalactone (**3.6**) have been accomplished successfully by a newly developed free radical process. The reaction utilises cheap and readily available 2-iodoacetamide together with deuterated alkenes in an operationally simple, one-pot procedure. This approach to deuterated γ-lactones, which do not bear deuterium in exchangeable positions within the lactone ring, is likely to prove of value in the synthesis of γ-lactones as standards for SIDA analysis of sensory impact compounds. However, due to the difficulty in preparation and handling of small quantities of volatile alkenes (hexene and octene, typically <100 mg), only 2,2,3-$^2H_3$-γ-dodecalactone was synthesised efficiently (in 69% yield with 96% deuterium incorporation). Nonetheless, 2,2,3-$^2H_3$-γ-octalactone (17% yield with 92% deuterium incorporation) was also prepared. An alternative synthesis of deuterium labelled alkenes is needed to fully realise the potential of the radical chemistry.

The optimised radical conditions were shown to produce near quantitative yields of γ-decalactone (91%) and γ-octalactone (94%) from freshly distilled samples of the appropriate unlabelled alkenes. These results demonstrate the efficiency of the optimised radical process for the preparation of 4-alkyl-γ-lactones and also suggest that the efficiency of the reaction is critically dependant upon the purity of the 1,1,2-$^2H_3$-alkene.

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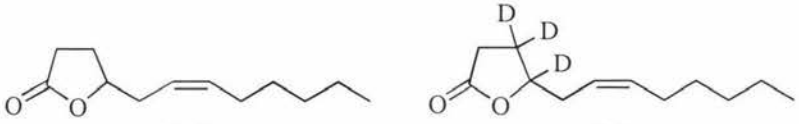
Chapter 4

Approaches to 3,3,4-$^2H_3$-(Z)-6-Dodecen-γ-lactone and a Comparitive γ-Lactone Synthesis

4.1 Introduction.

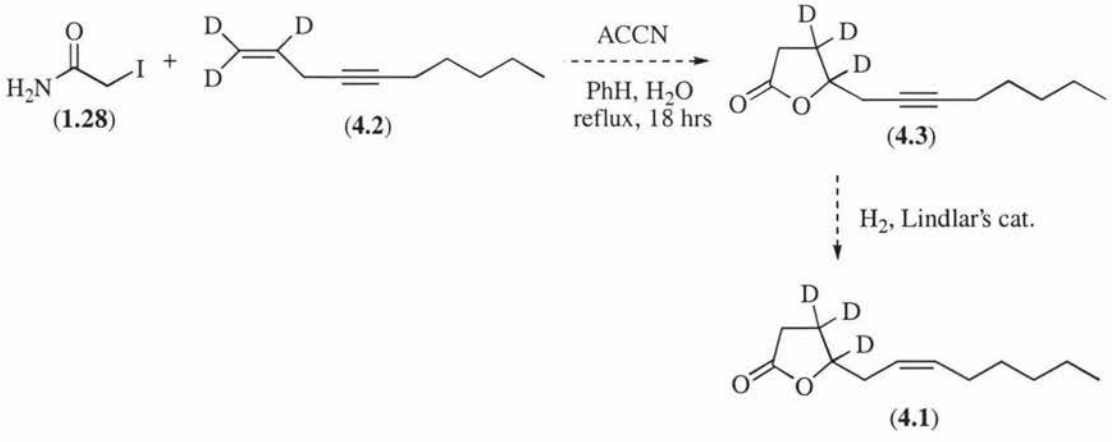
The importance of *(Z)*-6-dodecen-γ-lactone (**1.6**, **Figure 4.1**) as a flavour and aroma compound has been discussed in **Chapter 1** (Section **1.1**). It has been identified in a variety of natural products[1] including butter[2,3] and cheese.[4] Access to 3,3,4-$^2H_3$-*(Z)*-6-dodecen-γ-lactone (**4.1**, **Figure 4.1**) would allow for the quantitation of unlabelled *(Z)*-6-dodecen-γ-lactone (**1.6**) at sub ppm levels. This can be achieved through the use of SIDA and electron impact (EI) mass spectroscopic techniques (Section **1.2**). This ideally requires three deuterium atoms positioned regioselectively in the ring of the lactone (and hence the base peak upon fragmentation) to clearly differentiate it from the unlabelled analogue.



(**1.6**) (**4.1**)

Figure 4.1

Initially it was envisiged that the simple one pot, radical process developed in **Chapter 3**, would grant access to 3,3,4-$^2H_3$-*(Z)*-6-dodecen-γ-lactone (**4.1**). (**Scheme 4.1**)



(**1.28**) (**4.2**) (**4.3**)

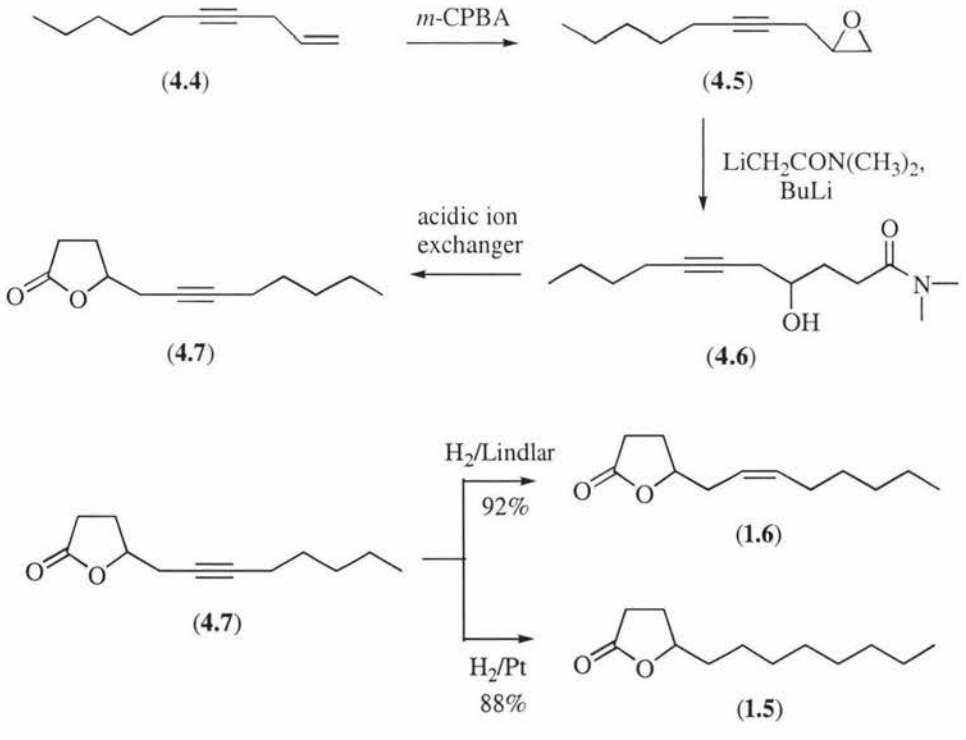
(**4.1**)

Scheme 4.1

This approach required access to 1,1,2-$^2H_3$-1-dec-4-yne (**4.2**). Partial reduction of 3,3,4-$^2H_3$-6-dodecyne-γ-lactone (**4.3**), formed as an intermediate, in the presence of Lindlar's catalyst would yield the desired tri-deuterated γ-lactone (**4.1**) in the final step of a short and very direct synthesis of this important flavour compound. Synthesis of *(Z)*-6-dodecen-γ-lactone (**1.6**, **Figure 4.1**) by this method is discussed in section **4.3**.

4.2 Synthetic Approaches to *(Z)*-6-Dodecen-γ-lactone.

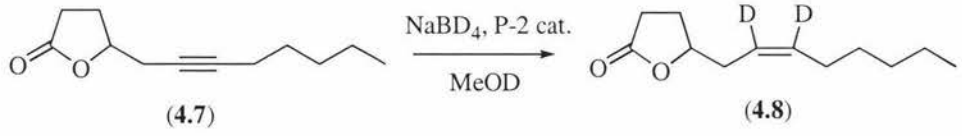
Literature syntheses of *(Z)*-6-dodecen-γ-lactone (**1.6**) were found to involve the preparation of the alkyne 6-dodecyne-γ-lactone (**4.7**) and its subsequent catalytic hydrogenation to the cis-alkene.[2,5-7] A typical example is shown with the method of Sucrow and Klein[7] in which the selective reduction of 6-dodecyne-γ-lactone to either *(Z)*-6-dodecen-γ-lactone (**1.6**) or γ-dodecalactone (**1.5**) was accomplished with the appropriate choice of catalyst in the final step. (**Scheme 4.2**)



Scheme 4.2

1-Decen-4-yne (**4.4**) was epoxidised with *m*-chloroperbenzoic acid to give the epoxyalkyne (**4.5**). The regioselective reaction of (**4.5**) with lithium dimethylacetamide yielded the homopropargylic alcohol (**4.6**), which in the presence of an acidic ion exchange resin, cyclised to afford 6-dodecyne-γ-lactone (**4.7**). Subsequent hydrogenation of 6-dodecyne-γ-lactone (**4.7**) with Lindlar's catalyst gave *(Z)*-6-dodecen-γ-lactone (**1.6**) in 92% yield after distillation, while in the presence of a platinum catalyst complete reduction gave the saturated γ-dodecalactone (**1.5**) in 88% yield.

Sucrow and Klein's approach to *(Z)*-6-dodecen-γ-lactone (**1.6**) has obvious potential as a synthesis of 6,7-$^2H_2$-*(Z)*-6-dodecen-γ-lactone where the deuterium atoms are positioned regioselectively in the alkyl substituent of the lactone, i.e. via reduction of the alkyne (**4.7**) with deuterium gas over Lindlar's catalyst to selectively incorporate two deuterium atoms into the side chain. Indeed, 6,7-$^2H_2$-*(Z)*-6-dodecen-γ-lactone (**4.8**) has been prepared by a variation of this method by Schieberle *et al.*[2] using the alternative reduction catalyst. 6-Dodecyne-γ-lactone (**4.7**), prepared by the method of Widder *et al.*,[6] was reduced using sodium borodeuteride in the presence of a P-2 nickel catalyst[8] in ^{2}H-methanol. (**Scheme 4.3**)

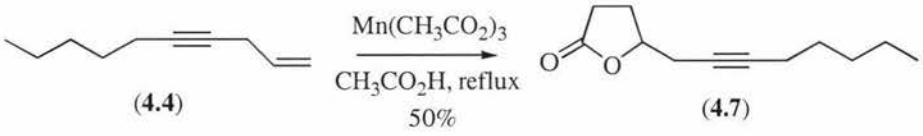


(**4.7**) (**4.8**)

Scheme 4.3

This generated 6,7-$^2H_2$-*(Z)*-6-dodecen-γ-lactone (**4.8**), characterised by mass spectral analysis (EI and CI) in an unreported yield. While this represents a synthesis of deuterium labelled *(Z)*-6-dodecen-γ-lactone, the label is not in the optimum position for maximum sensitivity required by SIDA.

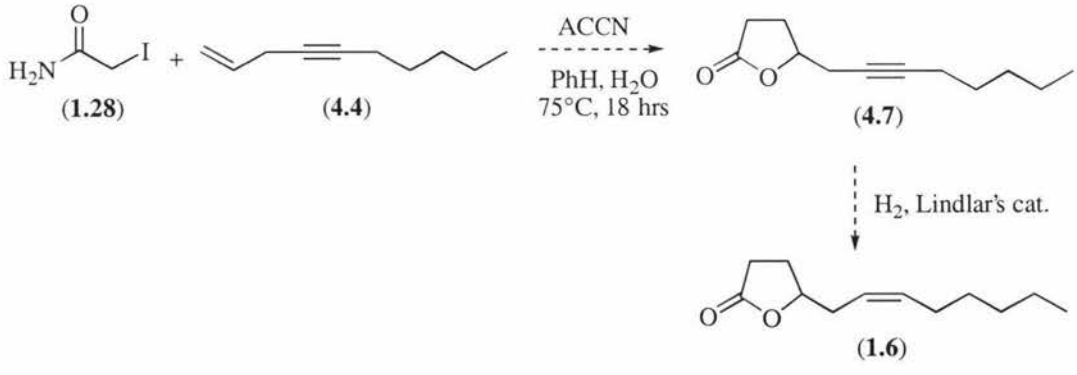
Radical strategies have also been utilised for the synthesis of 6-dodecyn-γ-lactone (**4.7**), and hence represent another possible approach to 6,7-$^2H_2$-*(Z)*-6-dodecen-γ-lactone (**4.8**). Heiba *et al.*[9] reported the synthesis of (**4.7**) in 50% yield via the reaction of manganic acetate with 1-decen-4-yne (**4.4**) in refluxing acetic acid.[†] (**Scheme 4.4**)



Scheme 4.4

4.3 Synthesis of *(Z)*-6-Dodecen-γ-lactone.

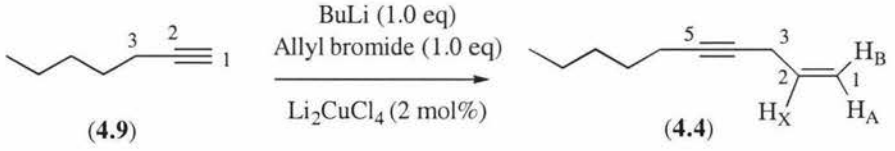
It was decided to trial the optimised radical reaction, envisaged for 3,3,4-$^2H_3$-*(Z)*-6-dodecen-γ-lactone (**4.1**) (**Scheme 4.1**), with the unlabelled precursor 1-decen-4-yne (**4.4**). Subsequent reduction of the alkyne (**4.7**) with hydrogen gas and Lindlar's catalyst would generate *(Z)*-6-dodecen-γ-lactone (**1.6**) (**Scheme 4.5**) in a model synthesis to assess the feasibility of this approach to the labelled compound.



Scheme 4.5

[†] Compare the manganic acetate route to other γ-lactones by Heiba *et al.*[9] described in section **3.6**.

4.3.1 Synthesis of 1-Decen-4-yne.

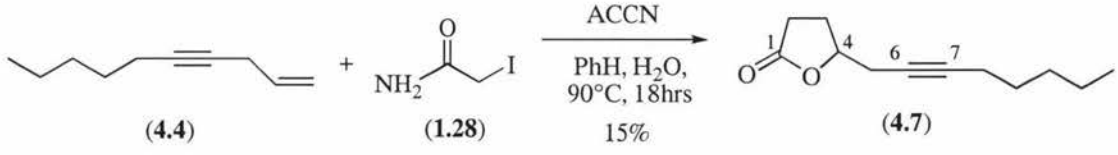


Scheme 4.6

1-Heptyne (**4.9**) was treated with BuLi (1.0 eq.) and the acetylide reacted with allyl bromide (1.0 eq.) and the catalyst dilithium copper tetrachloride (Li_2CuCl_4, 2 mol%), prepared according to the method of Burns *et al.*,[10] at -30°C. Li_2CuCl_4 is believed to catalyse the alkylation of lithium acetylides by the *in situ* formation of the cuprate via a transmetallation step.[10] The reaction afforded 1-decen-4-yne in an 80% yield after distillation. ^1H NMR analysis indicated the characteristic ABX spin system of a terminal vinyl group, i.e. a one-proton multiplet at 5.82 ppm (H_X) and two single-proton doublet pairs at 5.32 ppm (*J* 17 Hz, H_A) and 5.10 ppm (*J* 10 Hz, H_B). ^{13}C NMR showed the presence of two alkenic carbons at 133.3 (C2) and 115.4 (C1) ppm and two alkynic carbons at 82.8 (C4) and 76.4 (C5) ppm. A single homogeneous peak was obtained by GCMS which showed a molecular ion of m/z = 136.

4.3.2 Synthesis of 6-Dodecyn-γ-lactone via the Optimised Radical Method.

The optimised free-radical reaction was performed using 1-decen-4-yne (1.2 mmol) in the presence of 2-iodoacetamide (0.4 mmol), ACCN (0.8 mmol) and H_2O (40 mmol) in benzene (8 mL) and resulted in a 15% yield of (**4.7**) after distillation. (**Scheme 4.7**)



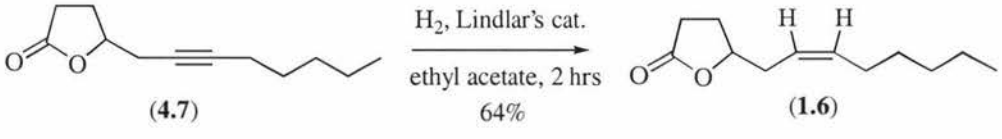
Scheme 4.7

^{1}H NMR spectra for (**4.7**) was complex as signals were overlapped and obscured. Nonetheless, a single proton multiplet, characteristic of the C4 methine proton, was clearly distinguished at 4.61 ppm. ^{13}C NMR showed two alkynic carbons, (C6 and C7), at 83.6 (s) and 73.5 (s) ppm respectively while the carbonyl carbon (C1) appeared at 176.7 (s) ppm. A molecular ion of m/z = 194 (<1%) was obtained by GCMS, and fragmentation consistent with that of a γ-lactone was observed. A base peak of m/z = 85 (100%) corresponding to the expected ring fragment was observed.

Although the low yield was disappointing, it was concluded that H atom abstraction from the interrupted methylene, (C5) of (**4.7**), had significantly disrupted the efficiency of the atom transfer-cyclisation cascade involved in lactone formation. No attempts to improve upon this low yield were made.

4.3.3 Synthesis of *(Z)*-6-Dodecen-γ-lactone.

Having successfully prepared 6-dodecyn-γ-lactone (**4.7**), albeit in low yield, its reduction with hydrogen over Lindlar's catalyst was investigated. Reductions of this type are generally carried out in ethyl acetate without the presence of quinoline as a catalytic inhibitor.[7] Reduction of (**4.7**) with hydrogen gas was therefore attempted under these conditions. (**Scheme 4.8**)



(**4.7**) (**1.6**)

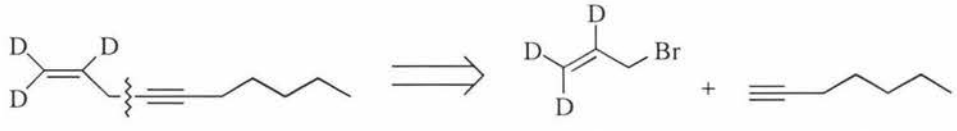
Scheme 4.8

(Z)-6-Dodecen-γ-lactone (**1.6**) was obtained after 2 hrs in an isolated 64% yield after distillation. The ^{1}H NMR spectra was again complex yet clear confirmation of the reduction was granted by the appearance of two single-proton alkenic doublet of multiplets centered at 5.37 and 5.60 ppm exhibiting a coupling constant of 10.9 Hz consistent with the

Z-geometry of the newly formed alkene. ^{13}C NMR spectra of (**1.6**) showed two alkenic carbons at 122.1 and 134.1 ppm. A molecular ion of m/z = 196 (1%) was obtained by GCMS and fragmentation consistent with that of a γ-lactone was observed, in particular a base peak of m/z = 85 (100%).

4.3.4 "Formal Synthesis" of 3,3,4-$^2H_3$-(*Z*)-6-Dodecen-γ-lactone.

Having successfully prepared unlabelled *(Z)*-6-dodecen-γ-lactone (**1.6**) via a radical/reduction strategy, our attention focused on the formation of the ring deuterated $^2H_3$ analogue. To incorporate three deuterium atoms into the lactone ring required access to 1,1,2-$^2H_3$-1-dec-4-yne (**4.2**). Potentially this material (**4.2**) could be prepared from the tri-deuterated allyl bromide (**4.10**) (**Scheme 4.9**) in a manner analogous to the formation of 1-decen-4-yne (**4.4**) (**Scheme 4.6**).



(**4.2**) (**4.10**) (**4.9**)

Scheme 4.9

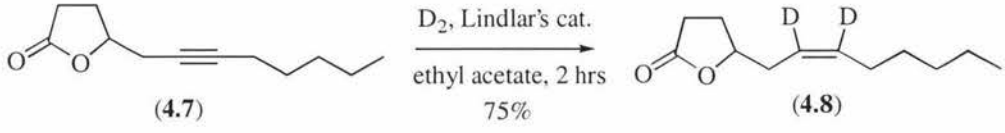
However, access to (**4.2**) was not practical as $^2H_3$-allyl bromide proved very expensive.[†] While a synthesis of this material could be attempted[11] it was decided, due to time constraints, to pursue an alternative approach to deuterated *(Z)*-6-dodecen-γ-lactone (**4.8**).

[†] $^2H_5$-Allyl bromide (98% D) was available at a cost of US$380.00 for 0.25 g from Cambridge Isotopes.

A number of hydrogenation catalysts are available for the reduction of alkynes to alkenes although the stereochemical ambiguities and isomerisations that can accompany heterogeneous catalysts have been well documented.[12,13] It is not uncommon for deuterium scrambling to accompany the addition of deuterium to alkynes, reflecting adsorption-desorption equilibra on the catalyst surface[12]. These difficulties can be overcome however, by employing a selective Lindlar's catalyst (palladium (5%) on calcium carbonate, partially poisoned with lead). [14] Addition of deuterium with Lindlar's catalyst is widely used for the specific deuteration of various unsaturated compounds and has been shown to proceed consistently with highly stereospecific syn addition for an internal alkyne.[14] For this reason Lindlar's catalyst was employed for the reduction of 6-dodecyn-γ-lactone (**4.7**) to 6,7-$^2H_2$-*(Z)*-6-dodecen-γ-lactone (**4.8**).

4.3.5 Synthesis of 6,7-$^2H_2$-*(Z)*-6-Dodecen-γ-lactone.

Reduction of 6-dodecyn-γ-lactone (**4.7**) with deuterium gas, under the reaction conditions employed to prepare *(Z)*-6-dodecen-γ-lactone (**1.6**) (**Scheme 4.8**) was performed (**Scheme 4.10**).



(**4.7**) (**4.8**)

Scheme 4.10

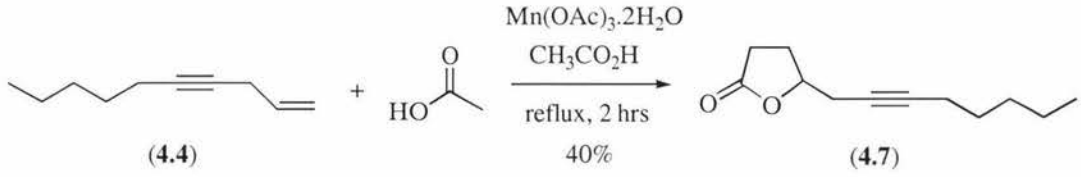
The target compound, 6,7-$^2H_2$-*(Z)*-6-dodecen-γ-lactone (**4.8**) was isolated in 75% yield after distillation with 98% deuterium incorporation as judged by ^1H NMR. Little change other than a slight loss in signal complexity was observed in the ^1H NMR spectra upon comparison of (**4.8**) with unlabelled (**1.6**). ^{13}C NMR spectra of (**4.8**) showed splitting of the alkenic carbon signals, appearing as 1:1:1 triplets at 121.6 and 133.7 ppm. A single homogeneous peak was obtained by GCMS with a molecular ion of m/z = 198 (4%)

corresponding to the incorporation of two deuterium atoms. Fragmentation was also consistent with that of a γ-lactone, with an unlabelled base peak consistent with the expected ring fragmentation of m/z = 85 (100%) being observed.

While 3,3,4-$^2H_3$-*(Z)*-6-dodecen-γ-lactone (**4.1**) was not be prepared via our optimised radical strategy this alternative synthesis provided adequately labelled material for quantification by SIDA techniques.

4.4 Comparative procedure: Mn(III) chemistry.

To establish the relative efficiency of the optimised radical reaction for the preparation of 6-dodecyn-γ-lactone (**4.7**) a comparative reaction was conducted using the one-step synthesis developed by Heiba *et al.*[9,15] discussed in section **1.3.1**, i.e. the manganic acetate approach. In our hands, Heiba's method gave a 40% yield of lactone after distillation. (**Scheme 4.11**) This compares favourably with a 50% yield reported by Heiba[9,15] and is more efficient than our radical process.



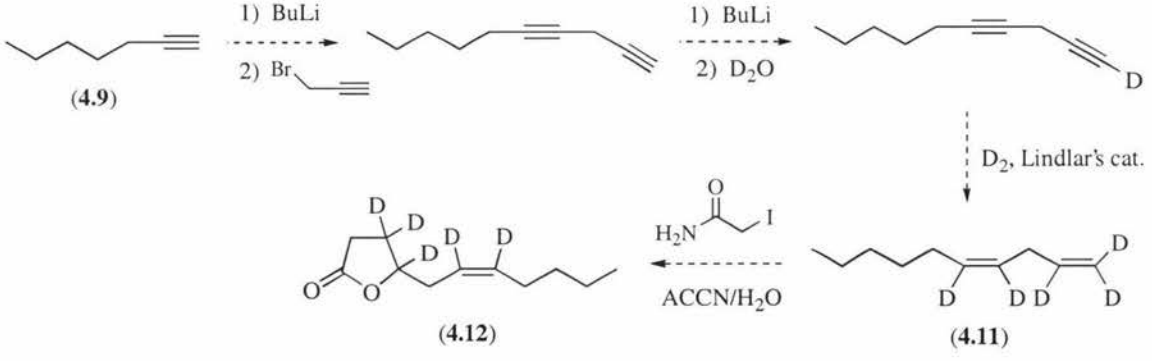
(**4.4**) (**4.7**)

Scheme 4.11

4.5 Conclusions.

A radical strategy towards 3,3,4-$^2H_3$-*(Z)*-6-dodecene-γ-lactone (**4.1**) was originally envisaged (**Scheme 4.1**) but access to the required deuterated precursor (**4.2**) was denied due to cost and time constraints. An alternative deuterated analogue, 6,7-$^2H_2$-*(Z)*-6-dodecen-γ-lactone (**4.8**) was, however, readily accessible and was prepared in 75% yield via the reduction of 6-dodecyn-γ-lactone (**4.7**), itself prepared in modest yield via the novel radical protocol.

The reason for the low yield of 6-dodecyn-γ-lactone (**4.7**) in the radical reaction is unclear although we believe it is due to the proximity of the alkyne to the reaction centre, i.e. the terminal alkene. A potentially useful approach to ring deuterated *(Z)*-6-dodecene-γ-lactones i.e. (**4.12**), might involve addition of an acetoxy radical equivalent to an intermediate diene (**4.11**). Diene (**4.11**) could be prepared by alkylation of heptyne (**4.9**) with propargylic bromide, subsequent deuterium exchange and partial reduction with deuterium. (**Scheme 4.12**)



Scheme 4.12

The addition of acetoxy radical species to methylene interrupted dienes (**4.11**) has yet to be investigated and this may prove to be an alternative route to compounds such as *(Z)*-6-dodecene-γ-lactone isotomers (**4.12**).

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Chapter 5

Experimental.

5.1 General Experimental.

Reactions were performed under an atmosphere of dry nitrogen in oven dried glassware (150°C) unless otherwise stated. Where necessary, solvents and reagents were dried according to the methods of Perrin and Amarego.[1] Reagents (Aldrich Chemical Company, unless otherwise stated) were used as received. Benzene, THF and diethyl ether (BDH) were purified by distillation from sodium benzophenone ketyl.[1] Dichloromethane (BDH) was distilled from calcium hydride and DMF ws distilled from calcium hydride under reduced pressure. Diazomethane was prepared according to the method of Vogel.[2] Reactions were normally monitored by thin layer chromatography (tlc) on aluminum backed Kieselgel 60 F_{254} silica gel plates (Merck) with the specified solvents. Compounds were detected by visualisation under an ultraviolet lamp (365 and 254 nm) followed by treatment with alkaline potassium permanganate dip[3] and strong heating, unless otherwise stated.

Organic solvents partitioned against water as part of an aqueous work up were washed with saturated sodium chloride (brine), dried with anhydrous magnesium sulfate prior to filtration and evaporation of the solvent *in vacuo*. Celite (Serva 545, 0.020-0.044 mm) was used occasionally as a filtration aid.

Flash column chromatography and rapid vacuum filtration were carried out using silica gel (40-62 μm, Merck). Hexane and ethyl acetate (freshly distilled from laboratory grade solvents) were used as the eluents in the specified ratios. Short path distillation was carried out using a GKR-51 Kugelrohr (Büchi) and boiling points in °C at mmHg are given. Unless otherwise indicated, yields were determined from actual masses of material isolated in pure form.

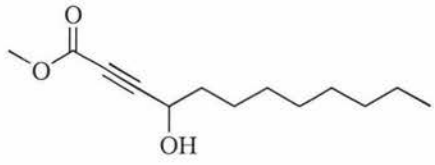
^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on either a Jeol JNM-GX270W or a Bruker Advance 400 NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to chloroform at 7.27 ppm for ^{1}H (270 and 400 MHz) spectra and 77.00 ppm for ^{13}C (68 and 100 MHz) spectra. Coupling constants (J) are given in hertz (Hz). The following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br., broad.

Mass spectra were obtained with a VG70-250S double focusing magnetic sector mass spectrometer (VG Instruments) operating at either 40eV or 70eV. GC-MS was carried out using a Hewlett-Packard 5890 Series II gas chromatograph fitted with a 30 m x 0.25 mm i.d. DB1 column (Alltech) with a film thickness of 0.25 μm; temperature programmed for 5 min at 40°C, 5°C/min, 20 min at 280°C, with a helium head pressure of 2 p.s.i. coupled directly to the mass spectrometer.

Infrared measurements were carried out on a Paragon 1000 FT-IR spectrometer (Perkin-Elmer), with samples as thin films between NaCl plates. Data is reported in wavenumbers (cm^{-1}). Capillary Gas Chromatography (GC) analysis was carried out on a Hewlett-Packard Model 5890 Series II gas chromatography equipped with a flame ionization detector (FID). Separations were achieved using a 30 m x 0.25 mm i.d. SE-30 Econo-Cap capillary column (Alltech) with a film thickness of 0.25 μm; temperature programmed from 50°C (1 min) to 240°C (5 min) at 10°C/min; injector temperature was 200°C and detector temperature was 250°C. The column head pressure was 10 p.s.i. of hydrogen.

5.2 Experimental for Chapter 2.

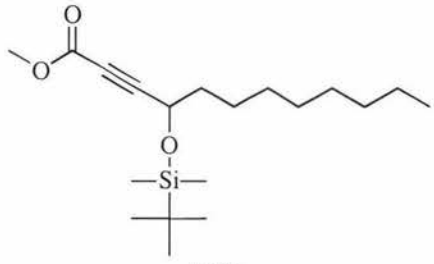
4-Hydroxydodec-2-ynoic acid methyl ester (2.7). (Scheme 2.4)



(**2.7**)

Diazomethane, as a solution in ether (0.8 M), was prepared from diazogen (N-methyl-N-nitrosotoulene-*p*-sulphonamide) and potassium hydroxide according to the method of Vogel.[2] 4-Hydroxydodec-2-ynoic acid (**2.5**)[4] (0.581 g, 2.7 mmol) was dissolved in ether (20 mL) and cooled to 0°C under an atmosphere of dry nitrogen. Diazomethane (2.7 mmol) was added as a single aliquot and the solution was stirred for 5 min. Excess diazomethane was destroyed by the addition of 1% acetic acid in ether (2 mL). Removal of solvents *in vacuo* gave the title compound (**2.7**) (0.607 g, 98%) as a pale yellow oil, which was not purified further. R_f = 0.77 (hexane-ethyl acetate (2:1)); Found: M^+ 226.1578, $C_{13}H_{22}O_3$ requires 226.1569; ν_{max} (film) 3418, 2927, 2857, 1721, 1458, 1436, 1254, 1062 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.85 (3H, t, *J* 6.2 Hz, -CH_3), 1.24 (10H, br. s, -$(CH_2)_5CH_3$), 1.40 (2H, m, -$CH_2(CH_2)_5CH_3$), 1.73 (2H, m, -CH(OH)CH_2-), 3.75 (3H, s, -OCH_3), 4.46 (1H, t, *J* 6.6 Hz -C(OH)*H*-) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1(q), 22.6(t), 24.9(t), 29.2(t), 29.2(t), 29.4(t), 31.8(t), 36.8(t), 52.8(q), 61.9(d), 75.9(s), 88.6(s), 153.8(s) ppm; MS *m/z* (rel. int. %) 226(2), 137(8), 128(7), 123(13), 114(100), 96(18), 81(16), 71(21), 57(45), 43(74).

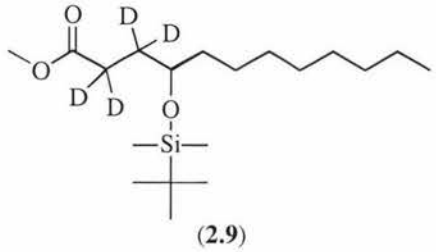
4-*tert*-Butyldimethylsiloxydodec-2-ynoic acid methyl ester (2.8). (Scheme 2.4)



(2.8)

This silylation procedure is a modification of the method used by Lilly.[5] Triethylamine (0.44 mL, 3.1 mmol) and *tert*-butyldimethylsilyl chloride (0.278 g, 2.6 mmol) were added to a solution of the methyl ester (**2.7**) (0.322 g, 1.4 mmol) in dichloromethane (5 mL) at 0°C under an atmosphere of dry N_2. The solution was brought to rt over 1 hr. Tlc at this time showed an incomplete conversion to the silyl ether (**2.8**). Additional equivalents of *tert*-butyldimethylsilyl chloride (0.322 g, 1.4 mmol) and triethylamine (0.44 mL, 3.1 mmol) plus additional dichloromethane (1 mL) were then added. After 48 hrs the reaction mixture was washed with water (2 x 2 mL) and sat. brine (2 mL). The aqueous fractions were back-extracted with ether (2 x 2 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by flash chromatography on silica gel, eluting with hexane through to hexane-ethyl acetate (5:1), gave the title compound (**2.8**) as a pale yellow oil (0.294 g, 61%). R_f = 0.77 (hexane-ethyl acetate (4:1)); Found: M^+ 340.2450, $C_{19}H_{36}O_3Si$ requires 340.2434; ν_{max} (film) 2955, 2929, 2858, 1723, 1464, 1435, 1362, 1341, 1252, 1098 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.11 (3H, s, Si(CH_3)), 0.14 (3H, s, Si(CH_3)) 0.90 (12H, s, -CH_3 and -C(CH_3)$_3$), 1.27 (10H, s, -(CH_2)$_5$$CH_3$), 1.42 (2H, m, -$CH_2$($CH_2$)$_5$$CH_3$), 1.69 (2H, m, -CH(OTBDMS)CH_2-), 3.76 (3H, s, -OCH_3), 4.44 (1H, t, *J* 6.6 Hz, -C*H*(OTBDMS)-) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -5.1, -4.5, 14.1, 18.2, 22.7, 25.0, 25.7, 29.2, 29.3, 29.5, 31.9, 37.8, 52.6, 62.6, 75.6, 89.1, 153.8 ppm; MS *m/z* (rel. int. %) 340(<1), 309(5), 283(65), 265(7), 251(7), 231(30), 171(42), 141(5), 89(100), 73(40), 55(12), 41(15). Further elution gave recovered starting material (**2.6**) (96 mg, 30%) as a pale yellow oil.

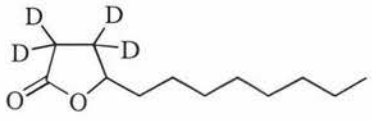
2,2,3,3-$^2H_4$-4-*tert*-Butyldimethylsiloxydodecanoic acid methyl ester (2.9). (Scheme 2.4)



(2.9)

4-*tert*-Butyldimethylsiloxydodec-2-ynoic acid methyl ester (**2.8**) (0.294 g, 0.9 mmol) was dissolved in freshly distilled benzene (10 mL) and Wilkinson's catalyst (5 mol%, 41 mg, 0.04 mmol) was added. The flask was fitted to a hydrogenation apparatus (similar to that described by Vogel)[2] and a freeze/thaw degassing process was repeated three times before the solution was stirred vigorously while the uptake of D_2 gas was monitored. The reaction mixture consumed 2.0 equivalents of D_2 (1.8 mmol) in 6 days, whereupon the flask was isolated from the reservior of deuterium gas. Benzene was removed under reduced pressure and the crude oil was filtered through a short plug of celite with hexane-ethyl acetate (20:1). The product was further purified by flash chromatography on silica gel eluting with hexane through to hexane-ethyl acetate (20:1) to give the title compound (**2.9**) (0.162 g, 54%) as a colourless oil. R_f = 0.34 (hexane-ethyl acetate (20:1)); Found: M^+ 348.2965, $C_{19}H_{36}D_4O_3Si$ requires 348.2997; ν_{max} (film) 2955, 2929, 2857, 1743, 1463, 1435, 1361, 1256, 1196, 1087 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (6H, s, $Si(CH_3)_2$), 0.89 (12H, s, $-CH_3$ and $-C(CH_3)_3$), 1.27 (12H, br. s, $-(CH_2)_6CH_3$), 1.43 (2H, m, $-CH_2(CH_2)_6CH_3$), 3.66 (3H, s, $-OCH_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -4.6, -4.4, 14.1, 18.1, 22.7, 25.2, 25.9, 29.3, 29.6, 29.8, 31.9, 36.9, 51.3, 70.9, 174.1 ppm; MS *m/z* (rel. int. %) 348(1), 291(100), 259(13), 235(14), 89(16), 73(26), 59(6).

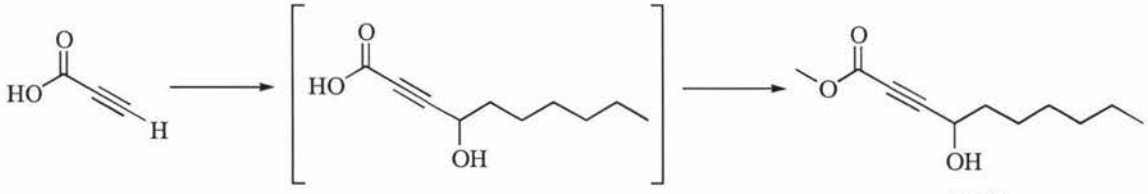
3,3,4,4-$^2H_4$-γ-Dodecalactone (2.4). (Scheme 2.4)



(2.4)

To a stirred solution of 2,2,3,3-$^2H_4$-4-*tert*-butyldimethylsiloxydodecanoic acid methyl ester (**2.9**) (78 mg, 0.2 mmol) in THF (3 mL) was added conc. HCl (0.3 mL). Stirring was continued for 2 hrs whereupon the reaction mixture was diluted with ether (2 mL) and partitioned against sat. sodium bicarbonate (2 x 3 mL), water (2 x 3 mL) and sat. brine (3 mL). The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil. Flash chromatography on silica gel eluting with hexane-ethyl acetate (4:1) gave am oil that was further purified by distillation (140°C at 0.2 mmHg) to give the title compound (**2.4**) (52 mg, 76%) as a colourless oil. R_f = 0.49 (hexane-ethyl acetate (4:1)); Found: M^+ 202.1868, $C_{12}H_{18}D_4O_2$ requires 202.1871; ν_{max} (film) 3519, 2927, 2856, 1770, 1467, 1378, 1348, 1203, 1161, 1113, 1060 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* 6.4 Hz, -C*H*$_3$), 1.27 (12H, br. s, -(C*H*$_2$)$_6$CH$_3$), 1.60 (1H, m, -C(H)*H*- (C5)), 1.71 (1H, m, -C(*H*)H- (C5)), 4.47 (1H, t, *J* 6.4 Hz, -C*H*O- (C4)) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.2(q), 22.7(t), 25.3(t), 27.5 (m, *C*D$_2$), 28.7 (m, *C*D$_2$), 29.2(t), 29.4(t), 29.5(t), 31.9(t), 35.6(t), 80.9(d), 177.1(s) ppm; MS *m/z* (rel. int. %) 202(<1), 184(1), 141(4), 132(9), 104(6), 89(100), 70(8), 60(5), 33(10), 55(11), 41(15), 33(10).

4-Hydroxydeca-2-ynoic acid methyl ester (2.10). (Scheme 2.5)



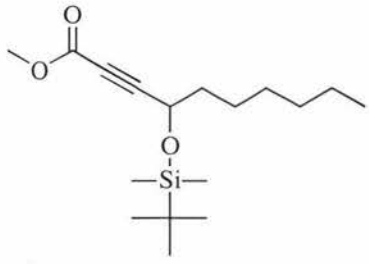
(2.10)

A solution of lithium diisopropylamide (LDA) was prepared by stirring BuLi (1.45 M [hexanes], 21.7 mL, 31.4 mmol) and diisopropylamine (4.12 mL, 31.4 mmol) in THF (20

mL), under argon, at 0°C. This solution was added to a solution of propionic acid (1.0 g, 14.3 mmol) in THF (10 mL) at -78°C. TMEDA (5 mL) and heptanal (1.630 g, 14.3 mmol) were added and the mixture was warmed to rt and stirred. After 1 hr water (10 mL), sat. NH_4Cl (20 mL) and aqueous HCl (10%, 10 mL) were added and the aqueous layer was washed with ether (3 x 10 mL). The organic phase was evaporated and the crude oil was dissolved in ether (40 mL) and extracted with 2% NaOH (2 x 10 mL). The aqueous phase was acidified (pH1) with conc. HCl (2 x 10 mL) and re-extracted with ether (3 x 10 mL). The combined organic phases were washed with water (2 x 10 mL) and sat. brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 4-hydroxydeca-2-ynoic acid a white powder that was treated directly with diazomethane.

Crude 4-hydroxydeca-2-ynoic acid (1.149 g, 6.2 mmol) was dissolved in ether (35 mL) and cooled to 0°C under an atmosphere of dry nitrogen. Diazomethane (6.2 mmol) was added as a single aliquot and the solution was stirred for 5 min. Excess diazomethane was removed by the addition of 1% acetic acid in ether (1.5 mL). Removal of volatiles *in vacuo* and purification by flash chromatography on silica gel eluting with hexane through to hexane-ethyl acetate (4:1) gave the title compound (**2.10**) (0.803 g, 78%) as a pale yellow oil. R_f = 0.59 (hexane-ethyl acetate (1:1)); Found: M^+-H 197.1172, $C_{11}H_{17}O_3$ requires 197.1178; ν_{max} (film) 3422, 2956, 2931, 2860, 1720, 1458, 1437, 1254, 1049 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.86 (3H, t, *J* 6.2 Hz, -C*H*$_3$), 1.26 (6H, s, -(C*H*$_2$)$_3$CH$_3$), 1.43 (2H, m, -C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.73 (2H, m, -CH(OH)C*H*$_2$-), 3.75 (3H, s, -OC*H*$_3$), 4.46 (1H, t, *J* 6.6 Hz, -C(OH)*H*-) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.0, 22.5, 24.9, 28.8, 31.6, 36.8, 52.8, 61.9, 75.9, 88.6, 153.8 ppm; MS *m/z* (rel. int. %) 197(52), 181(45), 113(28), 69(37), 55(72), 43(100).

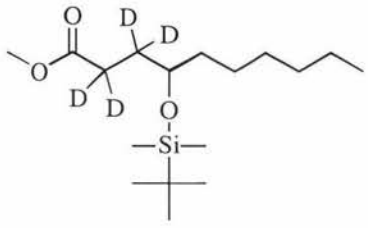
4-*tert*-Butyldimethylsiloxydec-2-ynoic acid methyl ester (2.11). (Scheme 2.5)



(2.11)

To a stirred solution of 4-hydroxydec-2-ynoic acid methyl ester (**2.10**) (0.803 g, 4.1 mmol) in DMF (2 mL) at 0°C was added imidazole (0.331 g, 4.9 mmol) and *tert*-butyldimethylsilyl chloride (0.536 g, 5.0 mmol). The solution was brought to rt and stirred for 18 hrs (until reaction completion as judged by tlc). Water (2 ml) was added to the reaction and the solution was partitioned against ether (3 x 25 mL). The combined etheral extracts were washed with water (2 x 20 mL) and sat. brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude oil that was purified by flash chromatography on silica gel eluting with hexane through to hexane-ethyl acetate (5:1). This gave the title compound (**2.11**) (0.836 g, 66%) as a colourless oil. R_f = 0.59 (hexane-ethyl acetate (4:1)); Found: M^+-H 311.2043, $C_{17}H_{31}O_3Si$ requires 311.2042; ν_{max} (film) 2957, 2859, 1720, 1464, 1436, 1362, 1341, 1249, 1096 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.11 (3H, s, Si(CH_3)), 0.14 (3H, s, Si(CH_3)), 0.89 (12H, s, -CH_3 and -C(CH_3)$_3$), 1.28 (6H, s, -(CH_2)$_3$$CH_3$), 1.41 (2H, m, -$CH_2$($CH_2$)$_3$$CH_3$), 1.71 (2H, m, -CH(OTBDMS)CH_2-), 3.76 (3H, s, -OCH_3), 4.44 (1H, t, *J* 6.4 Hz, -CH(OTBDMS)-) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -5.1, -4.5, 14.1, 18.2, 22.6, 25.0, 25.7, 28.9, 31.7, 37.8, 52.6, 62.6, 75.6, 89.1, 153.8 ppm; MS *m/z* (rel. int. %) 311(2), 281(7), 255(52), 229(24), 203(34), 171(33), 149(7), 89(100), 73(49), 55(21), 41(19).

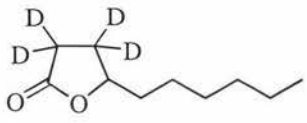
2,2,3,3-$^2H_4$-4-*tert*-Butyldimethylsiloxydecanoic acid methyl ester (2.12). (Scheme 2.5)



(2.12)

4-*tert*-Butyldimethylsiloxydec-2-ynoic acid methyl ester (**2.11**) (0.832 g, 2.1 mmol) was dissolved in freshly distilled benzene (25 mL), and Wilkinson's catalyst (10 mol%, 0.125 g, 0.2 mmol) was added. The flask was fitted to an hydrogenation apparatus[2] and a freeze/thaw degassing process was repeated three times before the solution was stirred vigorously while the uptake of D_2 gas was monitored. The reaction mixture consumed 2.0 equivalents of D_2 (4.2 mmol) in 2.5 days, whereupon the flask was isolated from the reservior of deuterium gas. Benzene was removed under reduced pressure and the crude oil filtered through a small plug of celite with hexane-ethyl acetate (20:1). The product was purified further by flash chromatography on silica gel eluting with hexane through to hexane-ethyl acetate (20:1) to give the title compound (**2.12**) (0.828 g, 97%) as a colourless oil. R_f = 0.56 (hexane-ethyl acetate (4:1)); Found: M^+ 320.2688, $C_{17}H_{32}D_4O_3Si$ requires 320.2688; ν_{max} (film) 2956, 2931, 2858, 1743, 1463, 1435, 1361, 1256, 1198, 1091 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (6H, s, $Si(CH_3)_2$) 0.88 (12H, s, $-CH_3$ and $-C(CH_3)_3$), 1.27 (8H, br. s, $-(CH_2)_4CH_3$), 1.43 (2H, m, $-CH_2(CH_2)_4CH_3$), 3.66 (3H, s, $-OCH_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -4.6, -4.4, 14.1, 18.1, 22.6, 25.2, 25.9, 29.5, 31.9, 37.0, 51.4, 71.0, 174.4 ppm; MS *m/z* (rel. int. %) 320(<1), 289(10), 263(100), 230(76), 174(13), 161(7), 132(7), 115(15), 101(9), 89(76), 73(89), 59(44), 41(27).

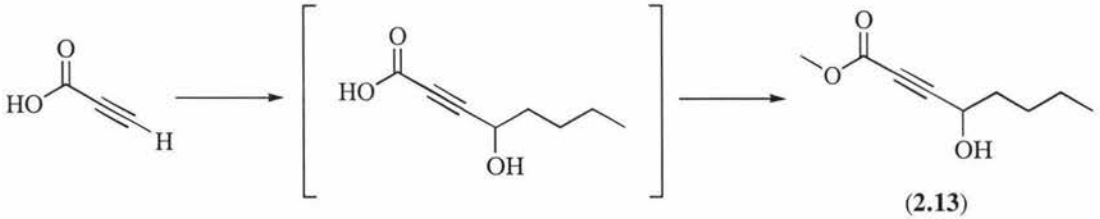
3,3,4,4-$^2H_4$-γ-Decalactone (2.3). (Scheme 2.5)



(**2.3**)

To a stirred solution of 2,2,3,3-$^2H_4$-4-*tert*-Butyldimethylsiloxydecanoic acid methyl ester (**2.12**) (0.729 g, 2.3 mmol) in THF (40 mL) was added conc. HCl (1 mL). Stirring was continued for 2 hrs whereupon the reaction mixture was diluted with ether (10 mL) and partitioned against sat. sodium bicarbonate (2 x 20 mL), water (2 x 20 mL) and sat. brine (20 mL). The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil. Flash chromatography on silica gel eluting with hexane-ethyl acetate (4:1) gave an oil that was further purified by distillation (120°C at 0.2 mmHg) to give the title compound (**2.3**) (0.365 g, 92%) as a colourless oil. R_f = 0.29 (hexane-ethyl acetate (4:1)); Found: M^+ 174.1559, $C_{10}H_{14}D_4O_2$ requires 174.1557; ν_{max} (film) 3524, 2931, 2859, 2361, 1770, 1467, 1379, 1348, 1202, 1112, 1062, 1012 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* 6.4 Hz, -C*H*$_3$), 1.27 (8H, br. s, -(C*H*$_2$)$_4$CH$_3$), 1.60 (1H, m, -C(*H*)H- (C5)), 1.71 (1H, m, -C(H)*H*- (C5)), 4.47 (1H, t, *J* 6.4 Hz, -C*H*O- (C4)) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1(q), 22.6(t), 27.9 (m, *C*D$_2$), 28.6 (m, *C*D$_2$), 25.2(t), 29.0(t), 31.7(t), 35.6(t), 80.9(d), 177.2(s) ppm; MS *m/z* (rel. int. %) 174(<1), 156(1), 141(4), 132(12), 104(5), 89(100), 70(7), 60(6), 41(14), 33(10).

4-Hydroxyoct-2-ynoic acid methyl ester (2.13). (Scheme 2.6)



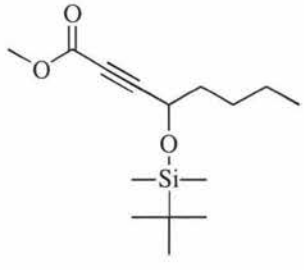
(**2.13**)

A solution of lithium diisopropylamide (LDA) was prepared by stirring BuLi (1.54 M [hexanes], 20.4 mL, 31.4 mmol) and diisopropylamine (4.12 mL, 31.4 mmol) in THF (20 mL), under argon, at 0°C. This solution was added to a solution of propionic acid (1.0 g, 14.3 mmol) in THF (10 mL) at -78°C. TMEDA (5 mL) and pentanal (1.230 g, 14.3 mmol)

were added and the mixture was warmed to rt and stirred. After 1 hr, water (10 mL), sat. NH_4Cl (20 mL) and aqueous HCl (10%, 15 mL) were added and the aqueous layer was washed with ether (3 x 10 mL). The organic phase was evaporated and the crude oil was dissolved in ether (40 mL) and extracted with 2% NaOH (2 x 10 mL). The aqueous phase was acidified (pH 1) with conc. HCl (2 x 10 mL) and re-extracted with ether (3 x 10 mL). The combined organic phases were washed with water (2 x 10 mL) and sat. brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude 4-hydroxyoct-2-ynoic acid as a white powder that was not purified further but treated directly with diazomethane.

Crude 4-hydroxyoct-2-ynoic acid (2.258 g, 14.3 mmol) was dissolved in ether (40 mL) and cooled to 0°C under an atmosphere of dry nitrogen. Diazomethane (14.3 mmol) was added as a single aliquot and the solution was stirred for 5 min. Excess diazomethane was consumed by the addition of 1% acetic acid in ether (2 mL). Removal of volatiles *in vacuo* and purification by flash chromatography on silica gel eluting with hexane through to hesane-ethyl acetate (5:1) gave the title compound (**2.13**) (1.458 g, 60%) as a pale yellow oil. R_f = 0.80 (hexane-ethyl acetate (1:1)); ν_{max} (film) 3414, 2959, 2865, 1720, 1437, 1380, 1256, 1044, 1012 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* 6.2 Hz, -C*H*$_3$), 1.37 (4H, m, -(C*H*$_2$)$_2$CH$_3$), 1.76 (2H, m, -C*H*$_2$(CH$_2$)$_2$CH$_3$), 3.77 (3H, s, -OC*H*$_3$), 4.47 (1H, t, *J* 6.6 Hz, -C*H*(OH)-) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.9, 22.3, 27.0, 36.5, 52.8, 61.9, 76.0, 88.5, 153.8 ppm.

4-*tert*-Butyldimethylsiloxyoct-2-ynoic acid (2.14). (Scheme 2.6)

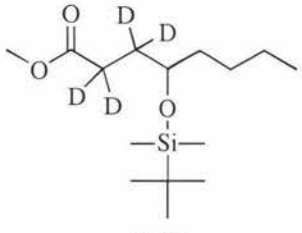


(2.14)

To a stirred solution of 4-hydroxyoct-2-ynoic acid methyl ester (**2.13**) (1.458 g 8.6 mmol) in DMF (4 mL) at 0°C was added imidazole (0.727 g, 10.7 mmol) and *tert*-butyldimethylsilyl chloride (1.309 g, 12.1 mmol). The solution was brought to rt and

stirred for 18 hrs (until reaction completion as judged by tlc). Water (2 mL) was added to the reaction and the solution partitioned against ether (3 x 25 mL). The combined etheral extracts were washed with water (2 x 20 mL) and sat. brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude oil that was purified by flash chromatography on silica gel eluting with hexane through to hexane-ethyl acetate (5:1). This gave the title compound (**2.14**) (1.861 g, 76%) as a pale yellow oil. $R_f = 0.79$ (hexane-ethyl acetate (4:1)); Found: M^+ 284.1817, $C_{15}H_{28}O_3Si$ requires 284.1808; ν_{max} (film) 2958, 2932, 2860, 1723, 1464, 1435, 1362, 1342, 1118, 1253, 1092 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.11 (3H, s, Si(CH_3)), 0.14 (3H, s, Si(CH_3)), 0.90 (12H, s, -CH_3 and -C(CH_3)$_3$), 1.39 (4H, m, -(CH_2)$_2$$CH_3$), 1.70 (2H, m, -$CH_2$($CH_2$)$_2$$CH_3$), 3.77 (3H, s, -O$CH_3$), 4.45 (1H, t, *J* 6.6 Hz, -C*H*(OTBDMS)-) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -5.1, -4.5, 14.0, 18.2, 22.3, 25.7, 27.2, 37.5, 52.7, 62.6, 75.6, 89.1, 153.8 ppm; MS *m/z* (rel. int. %) 284(<1), 227(67), 199(8), 175(45), 141(7), 89(100).

2,2,3,3-$^2H_4$-4-*tert*-Butyldimethylsiloxyoctanoic acid methyl ester (2.15). (Scheme 2.6)

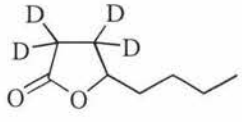


(**2.15**)

4-*tert*-Butyldimethylsiloxyoct-2-ynoic acid (**2.14**) (1.284 g, 4.5 mmol) was dissolved in freshly distilled benzene (25 mL) and Wilkinson's catalyst (10 mol%, 0.215 g, 0.25 mmol) was added. The flask was fitted to an hydrogenation apparatus[2] and a freeze/thaw degassing process was repeated three times before the solution was stirred vigorously while the uptake of D_2 gas was monitored. The reaction mixture consumed 2.0 equivalents of D_2 (9.0 mmol) in 2.5 days, whereupon the flask was isolated from the reservior of deuterium gas. Benzene was removed under reduced pressure and the crude oil was filtered through a small plug of celite with hexane-ethyl acetate (20:1). The product was further purified by flash chromatography on silica gel eluting with hexane through to hexane-ethyl acetate

(20:1) to give the title compound (**2.15**) (1.101 g, 83%) as a colourless oil. R_f = 0.48 (hexane-ethyl acetate (20:1)); Found: M^+ 292.2390, $C_{15}H_{28}D_4O_3Si$ requires 292.2318; ν_{max} (film) 2957, 2932, 2859, 1742, 1472, 1463, 1435, 1361, 1257, 1197, 1089 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (6H, s, $Si(CH_3)_2$), 0.89 (12H, br. s, $-CH_3$ and $-C(CH_3)_3$), 1.30 (4H, m, $-(CH_2)_2CH_3$), 1.42 (2H, m, $-CH_2(CH_2)_2CH_3$), 3.67 (3H, s, $-OCH_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -4.5, -4.3, 14.2, 18.1, 22.9, 25.9, 27.4, 36.7, 51.5, 71.0, 174.3 ppm; MS *m/z* (rel. int. %) 292(1), 261(17), 234(61), 203(99), 174(8), 119(7), 89(56), 73(100), 59(26).

3,3,4,4-$^2H_4$-γ-Octalactone (2.2). (Scheme 2.6)



(**2.2**)

To a stirred solution of 2,2,3,3-$^2H_4$-4-*tert*-butyldimethylsiloxyoctanoic acid methyl ester (**2.15**) (1.005 g, 3.4 mmol) in THF (50 mL) was added conc. HCl (1 mL). Stirring was continued for 3 hrs whereupon the reaction mixture was diluted with ether (20 mL) and partitioned against sat. sodium bicarbonate (2 x 30 mL), water (2 x 30 mL) and sat. brine (30 mL). The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil. Flash chromatography on silica gel eluting with hexane-ethyl acetate (4:1) gave an oil that was further purified by distillation (110°C at 2 mmHg) to give the title compound (**2.2**) (0.355 g, 94%) as a colourless oil. R_f = 0.29 (hexane-ethyl acetate (4:1)); Found: M^+ 146.1246, $C_8H_{10}D_4O_2$ requires 146.1245; ν_{max} (film) 3520, 2958, 2934, 2863, 1772, 1467, 1380, 1348, 1202, 1108, 1061, 1009 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* 6.4 Hz, $-CH_3$), 1.27 (4H, br. s, $-(CH_2)_2CH_3$), 1.60 (1H, m, -C(H)*H*- (C5)), 1.71 (1H, m, -C(*H*)H- (C5)), 4.47 (1H, t, *J* 6.4 Hz, -C*H*O- (C4)) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.8(q), 22.3(t), 27.2(t), 28.0 (m, CD_2), 28.8 (m, CD_2), 35.1(t), 80.7(d), 177.0(s) ppm; MS *m/z* (rel. int. %) 146(<1), 125(1), 104(4), 89(100), 70(2), 60(5), 41(7), 33(9).

5.3 Experimental for Chapter 3.

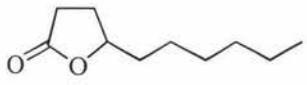
5.3.1 General Procedure for the Optimisation Reactions. Synthesis of γ-Decalactone (1.4).

This is an adaptation of the procedure reported by Yorimitsu *et al.*[6] for the generation of 4-alkylhydroxy-γ-lactones. 1-Octene (X mol) was added to a scintillation vial containing a solution of 2-iodoacetamide or iodoacetic acid (Y mol) and radical initiator[†] (Z mol) in benzene (10 mL). The vial was flushed with argon, sealed (screw cap lid and parafilm) and marked to indicate the initial volume. A blank of benzene (10 mL) was also prepared for each run. Mole ratios (X, Y and Z) were varied in accordance with Tables 3.1 through 3.3.

The vial(s) was placed in a water bath and the bath set vibrating (200 r.p.m.) with the water temperature at 75°C. After 18 hrs aqueous HCl (10%, 1 mL) and water (1 mL) were added to each vial. [‡] Preparation of the sample for GC analysis, involved 1 mL of the crude reaction mixture being diluted to 10 mL with ether. The blank (benzene only) was also diluted this way and γ-decalactone (1 μL) was spiked into this diluted sample prior to analysis. GC analyses were run for each sample and the percentage lactone calculated from the peak area of the standard sample using the method outlined in **Appendix 3.1**. Replicates for the optimum yields of each iteration were performed.

[†] Radical initiators tested include AIBN (**3.17**), ACCN (**3.9**) and ACPA (**1.30**).

γ-Decalactone (1.4); Standard Reproducible Reaction Conditions. Table 3.5 (entry 5)



(1.4)

This is an example of a typical procedure. 1-Octene (0.168 g, 1.5 mmol) and water (0.900 mL, 50 mmol) were added to a stirred solution of 2-iodoacetamide (0.093 g, 0.5 mmol) and ACCN (0.242 g, 1.0 mmol) in benzene (10 mL). This mixture was refluxed under an atmosphere of argon for 18 hrs, whereupon water (1 mL) and aqueous HCl (10%, 1 mL) were added. The reaction mixture was extracted with ether (3 x 5 mL), and the combined organic extracts washed with water (2 x 5 mL) and sat. brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vauco*. Flash chromatography on silica gel, eluting with hexane through to hexane-ethyl acetate (4:1), gave the title compound (**1.4**) as an oil, which was further purified by short path distillation (112-116°C at 0.2 mmHg) (0.083 g, 91%). R_f = 0.31 (hexane-ethyl acetate (4:1)); Found: M^+ 170.1300, $C_{10}H_{18}O_2$ requires 170.1307; ν_{max} (film) 2955, 2931, 2870, 1775, 1467, 1420, 1363, 1282, 1182, 1063, 1012 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (3H, t, *J* 6.4 Hz, -C*H*$_3$), 1.23 (7H, br. s, -C(*H*)H- (C5) and -(C*H*$_2$)$_3$CH$_3$), 1.37 (1H, m, -C(*H*)H- (C6)), 1.58 (1H, m, -C(H)*H*- (C6)), 1.68 (1H, m, -C(H)*H*- (C5)), 1.82 (1H, m, -C(*H*)H- (C3)), 2.27 (1H, m, -C(H)*H*- (C3)), 2.47 (2H, m, -C*H*$_2$C(O)- (C2)), 4.42 (1H, m, -C(O)*H*- (C4)) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1, 22.6, 25.2, 28.0, 28.9, 29.0, 31.7, 35.6, 81.0, 177.1 ppm; MS *m/z* (rel. int. %) 170 (<1), 128(9), 100(5), 85(100), 70(4), 55(10), 43(9), 41(13), 39(4).

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‡ Additional benzene was added to vials in which solvent loss had occurred to compensate for concentration differences before further analysis.

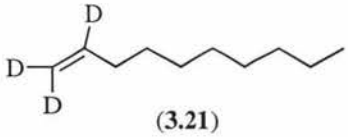
5.3.2 Synthesis of $^2H_3$-Alkenes.

5.3.2.1 1-^{2}H-1-Decyne (3.20). (Scheme 3.7)

(3.20)

To a stirred solution of 1-decyne (1.534 g, 11.1 mmol) in THF (40 mL) at -78°C, was added BuLi (1.2 M [hexanes], 10.8 mL, 13.3 mmol). The mixture was stirred at this temperature for 10 mins before the addition of deuterium oxide (0.24 mL, 13.3 mmol, 99.9% atom D). The reaction mixture was warmed to rt, stirred 2 hrs and washed with ether (3 x 20 mL) and aqueous HCl (10%, 10 mL). The organic phase was washed with water (3 x 10 mL) and sat. brine (10 mL) and the aqueous fractions back-extracted with ether (2 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound (**3.20**) (1.504 g, 97%) with 98% deuterium incorporation as a pale yellow oil. $R_f = 0.94$ (hexane-ethyl acetate (4:1)); Found: M^+ 139.1475, $C_{10}H_{17}D$ requires 139.1471; ν_{max} (film) 2927, 2857, 2598, 1467, 1378, 1327, 1116 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* 6.2 Hz, -C*H*$_3$), 1.28 (8H, br. s, -(C*H*$_2$)$_4$CH$_3$), 1.40 (2H, m, -C*H*$_2$- (C5)), 1.51 (2H, quint., *J* 6.8 Hz -C*H*$_2$- (C4)), 1.92 (0.02H, t, residual *H*C≡C-), 2.18 (2H, t, *J* 6.8 Hz -C*H*$_2$- (C3)) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.2, 18.4, 22.7, 28.6, 28.8, 29.1, 29.2, 31.9, 67.9 (t, C1), 84.2 (t, C2) ppm; MS *m/z* (rel. int. %) 139(<1), 110(6), 96(31), 82(90), 68(51), 57(49), 55(100), 43(66), 41(99), 39(27), 32(10).

1,1,2-$^2H_3$-1-Decene (3.21). (Scheme 3.7)



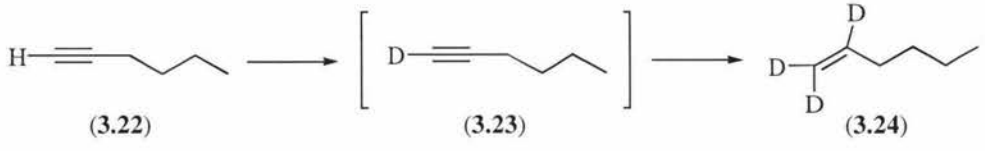
(3.21)

Lindlar's catalyst (0.330 g) and quinoline (0.25 mL) were added to a stirred solution of 1-^{2}H-1-decyne (**3.20**) (1.504 g, 0.01 mol) in pentane (40 mL). The reaction flask was flushed three times with deuterium gas (~10 mL, 99.8% atom D) and attached to a reduction

apparatus[2] where the solution was stirred vigorously while D_2 uptake was monitored. After 18 hrs deuterium uptake was complete (0.01 mol) and the mixture was filtered through a short plug of celite and rinsed with ether (2 x 20 mL), then washed with aqueous HCl (10%, 20 mL), sat. sodium bicarbonate (2 x 10 mL), water (2 x 10 mL) and sat. brine (10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by short path distillation (76-80°C at 15 mmHg) gave the title compound (**3.21**) (0.944 g, 61%) as a colourless oil with 93% deuterium incorporation. R_f = 0.92 (hexane-ethyl acetate (4:1)); Found: M^+ 143.1753, $C_{10}H_{17}D_3$ requires 143.1753; ν_{max} (film) 2958, 2926, 2855, 1584, 1467, 1378, 1118cm^{-1}; ^{1}H NMR (207MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.2 Hz, -C*H*$_3$), 1.31 (12H, br s, -(C*H*$_2$)$_6$CH$_3$), 2.07 (2H, t, *J* 6.2 Hz -C*H*$_2$- (C3)), 4.90-4.95 (0.07H, m, residual *H*$_2$C=CH- (C1)), 5.42 (0.035H, m, residual H$_2$C=C*H*- (C2)) ppm; ^{13}C NMR (68.1MHz, $CDCl_3$) 14.2, 22.8, 29.0, 29.3, 29.4, 29.6, 32.0, 33.7, 113.6 (m, C1), 138.9 (t, C2); MS *m/z* (rel. int. %) 143(15), 114(7), 100(14), 98(12), 86(22), 83(20), 76(75), 56(100), 43(91), 41(59), 39(14).

5.3.2.2 1,1,2-$^2H_3$-Hexene (3.24). (Scheme 3.8)

Attempted synthesis of 1,1,2-$^2H_3$-Hexene.



(**3.22**) (**3.23**) (**3.24**)

Scheme 3.8

Method A (General Procedure): Tetraethyleneglycol Dimethyl Ether as Solvent.

BuLi (1.4 M [hexanes], 38.4 mL, 0.05 mol) was added to a stirred solution of 1-hexyne (3.600 g, 0.04 mol) in tetraethyleneglycol dimethyl ether (tetraglyme) (20 mL) at 0°C. The mixture was quenched with the addition of deuterium oxide (1.052 g, 0.05 mol, 99.9% atom D) warmed to rt and stirred for 2 hrs. The reaction mixture was washed with aqueous

HCl (10%, 20 mL), water (2 x 20 mL) and sat. brine (10 mL), dried over $MgSO_4$ and filtered using additional tetraglyme for rinsing (50 mL). Lindlar's catalyst (1.336 g) and quinoline (1.0 mL) were added to the reaction mixture, and the flask was swept with deuterium gas (2 x ~15 mL, 99.8% atom D). The flask was attached to a reduction apparatus,[2] and it's contents stirred vigorously while D_2 uptake was monitored. Additional catalyst (0.200 g) was added after 1 week, but after 4 weeks with only half the expected gas (0.02 mol) had been consumed the reduction was stopped. Volatiles were removed by heating the reaction mixture at atmospheric pressure and a colourless liquid fraction (64-72°C) was collected. This was shown by NMR analysis to contain a mixture of the target compound (**3.24**), unreduced hexyne (**3.22**) and unlabelled hexane in an estimated ratio of (1:2:12).

Method B: Undecane as Solvent.

Following a procedure similar to that used in method A, a slurry of 1-hexyne (1.430 g, 0.02 mol) and NaH (80% in paraffin oil, 1.081 g, 0.04 mol) in undecane (50 mL) was stirred at 0°C. The mixture was quenched after 2 hrs by the addition of deuterium oxide (0.95 mL, 0.05 mol, 99.9% atom D) and worked up as before. Lindlar's catalyst (0.155 g) and quinoline (0.13 mL) were added to the reaction mixture and the flask was swept with deuterium gas (~15 mL, 99.8% atom D) and placed on a reduction apparatus. The reduction ceased after 72 hrs when water entered the reaction flask due to over reduction (1.0 mmol). The mixture was passed through a short column of $MgSO_4$ and volatiles removed as before. A colourless fraction was collected (88-95°C), which was shown by NMR analysis to consist of undecane-water azeotrope.[7]

Method C: Tetradecane as Solvent.

Following a procedure similar to method A, a slurry of 1-hexyne (3.600 g, 0.04 mol) and pre-washed NaH (80% in paraffin oil, 1.101 g, 0.05 mol) was stirred in tetradecane (50 mL). The mixture was quenched at 0°C with the addition of deuterium oxide (0.95 mL, 0.05 mol, 99.9% atom D), stirred for 2 hrs and worked up following the procedure

described before. Lindlar's catalyst (1.324 g) and quinoline (1.0 mL) were added to the reaction mixture and the flask was swept with deuterium gas (2 x ~15 mL, 99.8% atom D) prior to reduction. Additional catalyst (0.150 g) was added after 1 week, and gas consumption ceased after 2 weeks when the required volume was eventually consumed (0.04 mol). Volatiles were extracted as before and a colourless fraction (72-80°C) was collected. This was shown by NMR analysis to contain a mixture of $^{2}H_3$-1-hexene (94% deuterium incorporation) and 1-^{2}H-hexyne in a yield of 42% (by mass balance) in an estimated ratio of (1:0.8). Data for 1,1,2-$^{2}H_3$-1-hexene: Found: M^+ 87.1127, $C_6H_9D_3$ requires 87.1127; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* 7.2 Hz, -C*H*$_3$), 1.36 (4H, m, -(C*H*$_2$)$_2$CH$_3$), 2.03 (2H, m, -C*H*$_2$- (C3)) 4.92-4.96 (0.06H, m, residual *H*$_2$C=CH- (C1)), 5.42 (0.03H, m, residual H$_2$C=C*H*- (C2)) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.9, 22.2, 31.1, 33.3, 113.5 (m, C1) and 131.2 (t, C2) ppm; MS *m/z* (rel. int. %) 87(27), 74(13), 70(14), 57(88), 43(91), 41(100), 39(25). Data for 1-^{2}H-1-hexyne: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.56 (1.6H, m, DC≡CC*H*$_2$- (C3)) ppm, other signals obscured; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.8, 19.0, 22.3, 31.3, 68.2 (m, C2), 84.3 (m, C1) ppm.

5.3.2.3 Attempted synthesis of 1,1,2-$^{2}H_3$-1-Octene (3.27). (Scheme 3.9)

1-^{2}H-1-Octyne (3.26). (Scheme 3.9)

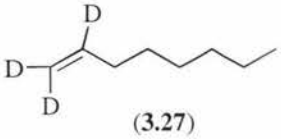
(3.26)

Method A: General procedure using BuLi.

To a stirred solution of 1-octyne (3.750 g, 34.0 mmol) in THF (100 mL) at -78°C, was added BuLi (2.0 M [hexanes], 20 mL, 40 mmol). The solution was stirred at this temperature for 10 min prior to the addition of deuterium oxide (0.830 g, 40.1 mmol. 99.9% atom D). The reaction mixture was brought to rt, stirred for 2 hrs and washed with ether (2 x 20 mL) and aqueous HCl (10%, 20 mL). The organic phase was washed with water (3 x 20 mL) and sat. brine (20 mL) and the aqueous fractions back-extracted with

ether (2 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil (3.276 g, 87%). Attempted purification by short path distillation (81-86°C at 15.5 mmHg) gave a mixture of ^{2}H-octyne (92% deuterium incorporation) and butanol (1:1). Data for 1-^{2}H-1-octyne: Found: M^+ 111.1147, $C_8H_{13}D$ requires 111.1158; ν_{max} (film) 2959, 2933, 2861, 1467, 1379, 1327, 1113, 1071 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* 6.4 Hz, -C*H*$_3$), 1.29 (6H, m, -(C*H*$_2$)$_3$CH$_3$), 1.51 (2H, quint., *J* 6.8, 7.2, Hz -C*H*$_2$- (C4)), 1.93 (0.08H, t, *J* 6.8 Hz, residual HC≡C-), 2.16 (2H, t, *J* 7.0 Hz -C*H*$_2$- (C3)) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.0, 18.4, 22.6, 28.5, 28.5, 31.3, 67.8, 84.2 (t, C1) ppm; MS *m/z* (rel. int. %) 110(2), 96(16), 82(99), 68(41), 55(60), 43(100), 41(77), 39(24). Butanol: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.63 (1H, br. s, -CH_2O*H*) ppm, other signals obscured, ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.8, 18.9, 34.9, 62.6 ppm.

Attempted synthesis of 1,1,2-$^2H_3$-1-Octene (3.27). (Scheme 3.9)



(**3.27**)

First Attempt.

Lindlar's catalyst (0.446 g) and quinoline (0.35 mL) were added to a solution of ^{2}H-octyne/butanol prepared as above (1.620 g, 14.5 mmol) in pentane (55 mL). The flask was flushed three times with deuterium gas (~10 mL, 99.8% atom D) and attached to a reduction apparatus[2] where the solution was stirred vigorously while the uptake of D_2 was monitored. After 18 hrs the calculated volume of gas (14.5 mmol) had been consumed and the reduction ceased. The mixture was filtered through a short plug of celite and rinsed with ether (2 x 20 mL). Then washed with aqueous HCl (10%, 3 x 20 mL), sat. sodium bicarbonate (2 x 10 mL), water (2 x 10 mL) and sat. brine (10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by short path Kugelrohr distillation (78-82°C at 15 mmHg) gave a mixture

of the title compound (**3.27**) and butanol (1:0.85) as an inseparable, colourless oil (0.944 g, 61%). ^{1}H NMR indicated the title compound was present with 88% deuterium incorporation. Data for 1,1,2-$^{2}H_3$-1-octene: ν_{max} (film) 2958, 2926, 2855, 1584, 1467, 1378, 1118 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* 6.2 Hz, -C*H*$_3$), 1.31 (8H, br. s, -(C*H*$_2$)$_4$CH$_3$), 2.07 (2H, t, *J* 6.2 Hz -C*H*$_2$- (C3)) 4.93-4.98 (0.6H, m, residual *H*$_2$C=CH-(C1)), 5.43 (0.12H, m, residual H$_2$C=C*H*- (C2)) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1, 22.7, 28.9, 29.0, 31.8, 33.6, 113.3 (p, *J* 24 Hz, C1), 138.5 (t, *J* 24 Hz, C2) ppm. Butanol: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.62 (0.85H, br. s, -CH$_2$O*H*) ppm, other signals obscured, ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.7, 18.9, 34.9, 62.3 ppm.

Second Attempt.

Lindlar's catalyst (0.142 g) was added to a solution of the ^{2}H-octyne prepared as above (1.369 g, 12.3 mmol) in ethyl acetate (30 mL). The flask was flushed three times with deuterium gas (2 x 20 mL, 99.8% atom D) and attached to a reduction apparatus[2] where the solution was stirred vigorously and the uptake of deuterium monitored. After 18 hrs the reaction mixture had over-reduced (by 0.4 mmol) and the reaction was stopped. The mixture was worked up following the general method described above, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil. NMR analysis on the crude material indicated a mixture of 1,1,2-$^{2}H_3$-1-octene (**3.27**), $^{2}H_5$-octane and butanol to be present in an estimated ratio of (1:1:0.6).

Third Attempt.

Following a similar procedure to that described above Lindlar's catalyst (0.032 g) was added to a solution of ^{2}H-octyne (0.309 g, 2.8 mmol) in hexane (5 mL). After 18 hrs the reaction mixture had over-reduced (1.3 mmol) and the reaction was stopped. The mixture was worked up following the general method described above, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil. NMR analysis on the crude material indicated a mixture of 1,1,2-$^{2}H_3$-1-octene (**3.27**), $^{2}H_5$-octane and butanol to be present in an estimated ratio of (1:1:0.4).

5.3.2.3.1 Attempted synthesis of 1-^{2}H-1-Octyne (3.26). (Scheme 3.10)

Method B: General procedure using NaH. Table 3.6

(3.26)

Entry 1.

1-Octyne (3.750 g, 34.0 mmol) was added to a stirred slurry of ether washed NaH (1.090 g, 45.5 mmol) in ether (100 mL) under argon. Stirring was continued for 30 mins before the mixture was cooled to 0°C and the reaction mixture was quenched with D_2O (0.818 g, 45.5 mmol). The mixture was stirred for a further 10 mins, brought to rt and stirred for 1 hr. The reaction mixture was washed with aqueous HCl (10%, 20 mL), water (2 x 20 mL), sat. brine (20 mL). The aqueous fractions were back-extracted with ether (2 x 20 mL) and the combined organic phase dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude colourless oil. ^{1}H NMR analysis indicated 60% conversion to 1-^{2}H-1-octyne (**3.26**).

Entry 2.

Under the conditions described above 1-octyne (3.750 g, 34.0 mmol) was treated with NaH (2.090 g, 68.1 mmol) and quenched with D_2O (1.363 g, 68.1 mmol). Upon work up (as above) this gave 1-^{2}H-1-octyne (**3.26**) at 75% conversion.

Entry 3.

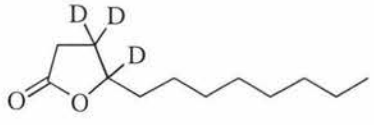
Under the conditions described above 1-octyne (3.750 g, 34.0 mmol) was treated with NaH (3.100 g, 0.103 mol) and placed in a sonicator of 30 mins. The mixture was quenched with D_2O (3.408 g, 0.170 mol) and upon work up (as above) this gave 1-^{2}H-1-octyne (**3.26**) in 86% conversion.

Entry 4.

Under the conditions described above 1-octyne (3.750 g, 34.0 mmol) was treated with NaH (3.280 g, 0.109 mol) and placed in a sonicator of 30 mins. The mixture was quenched with D_2O (3.408 g, 0.170 mol) in the presence of d_4-acetic acid (1.95 mL, 34.0 mmol). Upon work up (as above) this gave 1-^{2}H-1-octyne (**3.26**) in 87% conversion.

5.3.2 Synthesis of $^2H_3$-γ-Lactones.

5.3.3.1 4,4,5-$^2H_3$-γ-Dodecalactone (3.8). (Scheme 3.11)



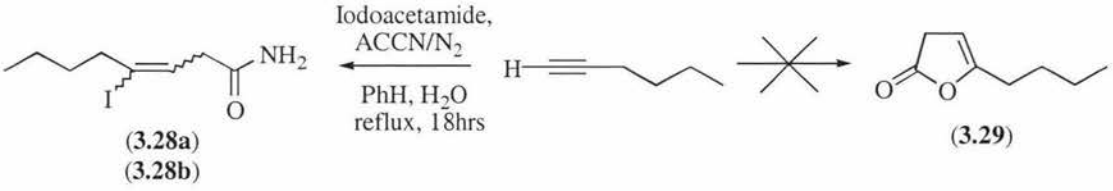
(**3.8**)

2-Iodoacetamide (0.215 g, 1.2 mmol) and ACCN (0.557 g, 2.3 mmol) were added to a stirred solution of 1,1,2-$^2H_3$-decene (0.498 g, 3.5 mmol) in benzene (23 mL). Water (2.15 mL, 0.1 mol) was added and the mixture refluxed under nitrogen for 18 hrs. Aqueous HCl (10%, 2.5 mL) and water (2.5 mL) were added and the mixture extracted with ether (3 x 20 mL). The combined etheral extracts were washed with water (2 x 20 mL) and sat. brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography on silica gel, eluting with hexane through to hexane-ethyl acetate (4:1), to give recovered 1,1,2-$^2H_3$-1-decene (**3.21**) (0.086 g, 17%), ACCN (0.459 g, 79%). Further elution gave a colourless oil which was further purified by short path distillation (135-140°C at 0.2 mmHg) to give the title compound (**3.8**) (0.163 g, 69%) at 96% deuterium incorporation. R_f = 0.45 (hexane-ethyl acetate (4:1)); Found: M^+ 201.1804, $C_{12}H_{19}D_3O_2$ requires 201.1808; ν_{max} (film) 3525, 2927, 2856, 1778, 1467, 1424, 1378, 1259, 1228, 1187, 1124, 1010 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* 6.2 Hz, -C*H*$_3$), 1.27 (11H, br. s, -C(*H*)H- (C5) and -(C*H*$_2$)$_5$CH$_3$), 1.46 (1H, m, -C(*H*)H- (C6)), 1.58 (1H, m, -C(H)*H*- (C6)), 1.73 (1H, m, -C(H)*H*- (C5)), 2.50 (2H, s, -C*H*$_2$(CO)- (C2)), 4.47

(0.04H, m, residual -C*H*-, C4) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1, 22.6, 25.2, 27.4 (m, C3), 28.7, 29.2, 29.3, 29.4, 31.8, 35.4, 80.4 (t, C4), 177.1 ppm; MS *m/z* (rel. int. %) 201(<1), 183(1), 141(3), 131(7), 103(5), 88(100), 84(4), 70(10), 60(4), 56(13), 43(16), 41(20), 32(13).

5.3.3.3 4,4,5-$^2H_3$-γ-Octalactone (3.6).

Attempted lactonisation with 1-hexyne. (Scheme 3.12)



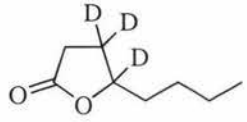
(**3.28a**)
(**3.28b**)

(**3.29**)

Scheme 3.12

2-Iodoacetamide (0.280 g, 1.5 mmol) and ACCN (0.713 g, 2.9 mmol) were added to a stirred solution of 1-hexyne (3.600 g, 4.4 mmol) in benzene (29 mL). Water (2.63 mL, 0.15 mol) was added and the reaction mixture refluxed under nitrogen for 18 hrs. Aqueous HCl (10%, 2.5 mL) and water (2.5 mL) were added and the mixture extracted with ether (2 x 10 mL). The combined etheral extracts were washed with water (2 x 10 mL) and sat. brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting material was purified by flash chromatography on silica gel, eluting with hexane through to hexane-ethyl acetate (4:1) to give a mixture of two products identified as the isomeric acetamides (**3.28a**) and (**3.28b**) in a 6:1 ratio (0.054 g, 13.4%). ^1H NMR (270 MHz, $CDCl_3$) (both isomers) δ 0.91 (3H, t, *J* 7.3 Hz, -C*H*$_3$), 1.29 (4H, m, -(C*H*$_2$)$_2$CH$_3$), 1.50 (2H, m, -CH$_2$- (C5)), 3.00 minor isomer (0.33H, d, *J* 7.7 Hz, -CH$_2$- (C2)), 3.12 major isomer (2H, d, *J* 6.8 Hz, -C*H*$_2$- (C2)), 5.79 (1H, t, *J* 10.1 Hz, -C=C*H*- (C3)), 5.95 (2H, br. s, -NH$_2$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.9, 14.2, 21.4, 22.1, 24.8, 25.6, 28.9, 29.5, 43.7, 45.0, 94.6 (C4), 98.7 (C4), 114.6 (C3), 116.4 (C3), 172.3 (C1), 174.5 (C1) ppm.

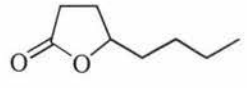
4,4,5-$^2H_3$-γ-Octalactone (3.6). (Scheme 3.13)



(**3.6**)

2-Iodoacetamide (0.131 g, 0.7 mmol) and ACCN (0.339 g, 1.4 mmol) were added to a stirred solution of 1,1,2-$^2H_3$-hexene, containing 1-^2H-hexyne, (0.183 g, 2.1 mmol) in benzene (14 mL). Water (1.26 g, 0.07 mol) was added and the mixture was refluxed under nitrogen for 18 hrs. Aqueous HCl (10%, 2.5 mL) and water (2.5 mL) were added and the mixture extracted with ether (3 x 10 mL). The combined etheral extracts were washed with water (2 x 10 mL) and sat. brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting material was purified by flash chromatography on silica gel, eluting with hexane through to hexane-ethyl acetate (4:1) to give the title compound (**3.6**) (0.017 g, 17%) as a pale yellow oil with 92% deuterium incorporation. R_f = 0.21 (hexane-ethyl acetate (6:1)); Found: M^+ 145.1178, $C_8H_{11}D_3O_2$ requires 145.1167; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* 6.6 Hz, -C*H*$_3$), 1.39 (3H, m, -C*H*$_2$- (C7) and -C(*H*)H- C5)), 1.43 (1H, m, -C(*H*)H- (C6)), 1.61 (1H, m, -C(H)*H*- (C6)), 1.74 (1H, m, -C(H)*H*- (C5)), 2.52 (2H, s, -C*H*$_2$C(O)- (C2)), 4.46 (0.08H, m, residual -C*H*- (C4)) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.9, 22.5, 27.3 (m, C3), 28.7, 28.8, 35.1, 80.5 (t, C4) and 177.0 ppm; MS *m/z* (rel. int. %) 145(<1), 126(1), 102(4), 88(100), 71(5), 57(7), 41(11), 39(6).

4,4,5-$^2H_3$-γ-Octalactone (1.3). (Scheme 3.14)



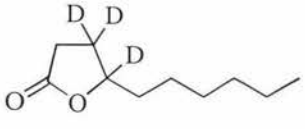
(**1.3**)

2-Iodoacetamide (0.513 g, 2.7 mmol) and ACCN (1.369 g, 5.6 mmol) were added to a stirred solution of freshly distilled 1-hexene (0.678 g, 8.1 mmol) in benzene (50 mL). Water (5.04 mL, 0.28 mol) was added and the mixture refluxed under nitrogen for 18 hrs. Aqueous HCl (10%, 5 mL) and water (5 mL) were added and the mixture extracted with

ether (3 x 40 mL). The combined etheral extracts were washed with water (2 x 40 mL) and sat. brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography on silica gel, eluting with hexane through to hexane-ethyl acetate (4:1), gave a pale yellow oil that was purified further by short path distillation (147-152°C at 11 mmHg) to give the title compound (**1.3**). (0.370 g, 94%) as a colourless oil. R_f = 0.32 (hexane-ethyl acetate (4:1)); Found: M^+ 142.0991, $C_8H_{14}O_2$ requires 142.0994; ν_{max} (film) 3525, 2958, 2935, 2863, 1775, 1461, 1422, 1352, 1289, 1185, 1127, 1021 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* 6.6 Hz, -C*H*$_3$), 1.35 (3H, m, -C*H*$_2$- (C7) and -C(*H*)H- (C5)), 1.41 (1H, m, -C(*H*)H- (C6)), 1.61 (1H, m, -C(H)*H*- (C6)), 1.72 (1H, m, -C(H)*H*- (C5)), 1.88 (1H, m, -C(*H*)H- (C3)), 2.31 (1H, m, -C(H)*H*- (C3)), 2.52 (2H, m, -C*H*$_2$C(O)- (C2)), 4.47 (1H, m, -C*H*- (C4)) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.9, 22.4, 27.3, 28.0, 28.8, 35.3, 81.0 and 177.0 ppm; MS *m/z* (rel. int. %) 142(2), 100(10), 70(5), 85(100), 56(12), 41(23), 39(12).

5.3.2.2 Attempted synthesis of 4,4,5-$^2H_3$-γ-Decalactone (3.7). (Scheme 3.15)

First Attempt.



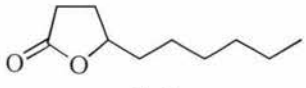
(**3.7**)

2-Iodoacetamide (0.779 g, 4.2 mmol) and ACCN (2.060 g, 8.4 mmol) were added to a stirred solution of $^2H_3$-octene/butanol (1:1) (1.411 g) in benzene (84 mL). Water (7.56 mL, 0.4 mol) was added and the mixture refluxed under nitrogen for 18 hrs. Aqueous HCl (10%, 6 mL) and water (6 mL) were added and the mixture extracted with ether (3 x 50 mL). The combined etheral extracts were washed with water (2 x 50 mL) and sat. brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting material was purified by flash chromatography silica gel, eluting with hexane through to hexane-ethyl acetate (4:1) but yielded no lactone.

Second Attempt.

2-Iodoacetamide (0.100 g, 0.5 mmol) and ACCN (0.242 g, 1.0 mmol) were added to a stirred solution of 1,1,2-$^{2}H_3$-octene/$^{2}H_5$-octane/butanol (1:1:0.6) (0.170 g) in benzene (10 mL). Water (0.90 mL, 50 mmol) was added and the mixture refluxed under nitrogen for 18 hrs. The mixture was worked up following the procedure described above, but NMR analysis indicated no lactone had been produced.

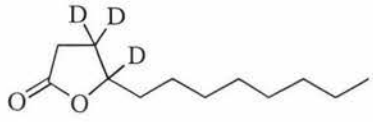
γ-Decalactone (*in Situ* preparation of Manganic Acetate) (1.4). (Scheme 3.14)



(1.4)

This is a modification of the procedure by Heiba *et al.*[8] Potassium permanganate (8.066 g, 0.05 mol) was added to a stirred solution of manganous acetate tetrahydrate (53.27 g, 0.22 mol) in acetic acid (300 mL) at 90°C. Acetic anhydride (75 mL), sodium acetate (126.59 g, 1.52 mol) and 1-octene (16.83 g, 0.15 mol) were added and the mixture refluxed in air for 3.5 hrs. The reaction mixture was diluted with water (250 mL) and extracted with ether (2 x 120 mL). The organic washes were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil, which was purified by short path distillation (110-114°C at 0.2 mmHg) to yield the title compound (**1.4**) (9.768 g, 38%) as a pale yellow oil.

3,3,4-$^2H_3$-γ-Dodecalactone (3.8). (Scheme 3.15)



(**3.8**)

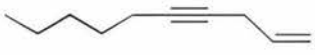
This is a modification of the procedure used by Heiba *et al.*[8] To a stirred solution of $^2H_3$-1-decene (0.113 g, 9.8 mmol, 93% ^2H) and acetic acid (10 mL), was added manganic acetate dihydrate (0.572 g, 2.1 mmol) and potassium acetate (3.562 g, 3 g/10 mL). The solution was refluxed for 1.5 hrs until the brown colour had disappeared and the reaction mixture was diluted with water (5 mL) and extracted with ether (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was passed through a short plug of silica gel with pentane (10 mL) and ethyl acetate (10 mL) to yield a pale yellow oil which was further purified by short path distillation (136-140°C at 0.2 mmHg) to give the title compound (**3.8**) (0.110 g, 56%). ^1H NMR indicated this material to have 90% deuterium incorporation. ^1H NMR (270 MHz, $CDCl_3$) δ 4.46 (0.10H, m, residual -C*H*- (C4)) ppm.

5.4 Experimental for Chapter 4.

Li_2CuCl_4 catalyst.

This is a modification of the procedure by Burns *et al.*[9] and Y. Kawakami *et al.*.[10] LiCl and $CuCl_2$ were dried in a vacuum desiccator over phosphorus pentoxide for 16 hrs. In a dry box, under an atmosphere of dry N_2, LiCl (0.096 g, 2.3 mmol) and $CuCl_2$ (0.153 g, 1.1 mmol) were weighed into an oven dried flask. THF (11 mL) was added at -20°C, and the bright orange solution (0.112 mol/L) was stirred until all solids had dissolved (5 min). The flask was sealed with a septa and removed from the dry box.

1-Decen-4-yne (4.4). (Scheme 4.6)



(**4.4**)

This is a modification of the procedures by Backvall *et al.*[11] To a stirred solution of 1-heptyne (0.481 g, 5.0 mmol) in THF (25 mL) at -30°C was added BuLi (1.14 M [hexanes], 4.39 mL, 5.0 mmol). In a second flask, a solution of allyl bromide (0.907 g, 7.5 mmol) and Li_2CuCl_4 (0.11 M, [THF], 0.90 mL, 0.1 mmol) in THF (17.5 mL) was prepared. This mixture was added to the lithium acetylide solution prepared above. The reaction mixture was stirred at -30°C for 1 hr before being warmed to rt. The mixture was washed with sat. NH_4Cl (2 x 15 mL), water (2 x 10 mL) and sat. brine (10 mL), the aqueous fractions were back extracted with ether (2 x 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil. Short path distillation (96-101°C at 11 mmHg) afforded the title compound (**4.4**) (0.543 g, 80%) as a colourless oil. R_f = 0.89 (hexane-ethyl acetate (4:1)); Found: M^+ 136.1250, $C_{10}H_{16}$ requires 136.1252; ν_{max} (film) 2958, 2933, 2860, 1833, 1642, 1466, 1421, 1402, 1379, 1332, 1285, 1108 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* 6.8 Hz, -CH_3), 1.34 (4H, m, -$(CH_2)_2CH_3$), 1.51 (2H, m, -CH_2- (C7)), 2.18 (2H, tt, *J* 2.4, 7.0 Hz, -CH_2- (C6)), 2.94 (2H, m, -CH_2- (C3)),

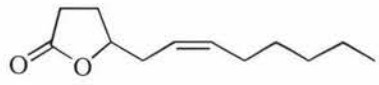
5.10 (1H, dq, *J* 3.5, 10.0 Hz -HC=CH(*H*)), 5.32 (1H, dq, *J* 3.5, 17.0 Hz, -HC=C*H*(H)), 5.82 (1H, m, -*H*C=CH_2) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.0 (q, C10), 18.8 (t, C6), 22.3 (t, C9), 23.2 (t, C3), 28.8 (t, C7), 31.1 (t, C8), 76.4 (s, C5), 82.8 (s, C4), 115.4 (t, C1), 133.3 (d, C2) ppm; MS *m/z* (rel. int. %) 136(2), 121(8), 107(18), 95(25), 93(21), 91(19), 79(100), 77(48), 67(9), 65(23), 55(14), 53(12), 41(32), 39(20).

6-Dodecyne-γ-lactone (4.7). (Scheme 4.7)

(**4.7**)

1-Decen-4-yne (**4.4**) (0.161 g, 1.2 mmol) was added to a stirred solution of 2-iodoacetamide (0.07 g, 0.4 mmol) and ACCN (0.185 g, 0.8 mmol) in benzene (7 mL) under an atmosphere of argon. Water (0.72 mL, 40 mmol) was added and the reaction mixture was refluxed for 18 hrs whereupon aqueous HCl (10%, 1 mL) and water (1 mL) were added. The mixture was extracted with ether (3 x 10 mL) and the combined etheral extracts were washed with water (2 x 10 ml) and sat. brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography on silica gel, eluting with hexane-ethyl acetate (4:1) resulted in the recovery of 1-decen-4-yne (**4.4**) (0.064 g, 45%). Further elution gave a pale yellow oil, which was purified by short path distillation (123-127°C at 11 mmHg) to give the title compound (**4.7**) as a colourless oil (0.012 g, 15%). R_f = 0.32 (hexane-ethyl acetate (4:1)); Found: M^+ 194.1311, $C_{12}H_{18}O_2$ requires 194.1307; ν_{max} (film) 2933, 2861, 1779, 1459, 1421, 1351, 1287, 1179, 1033 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* 6.8 Hz, -CH_3), 1.34 (4H, m, -(CH_2)$_2$$CH_3$), 1.48 (2H, m, -$CH_2$- (C9)), 2.15 (3H, m, -C≡CCH_2- (C8) and-C*H*(H)- (C3)), 2.39 (1H, m, -CH(*H*)- (C3)), 2.60 (4H, m, -CH_2C≡C- (C5) and -CH_2C(O)- (C2)), 4.61 (1H, m, -C*H*- (C4)) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1 (q, C12), 18.7 (t, C8), 22.2 (t, C11), 25.6 (t, C5), 26.6 (t, C3), 28.5 (t, C9), 28.5 (t, C2), 31.1 (t, C10), 73.5 (s, C7), 78.1 (d, C4), 83.6 (s, C6), 176.7 (s, C1) ppm; MS *m/z* (rel. int. %) 194 (<1), 85(100), 79(3), 67(3), 57(6), 53(3), 41(7), 33(5).

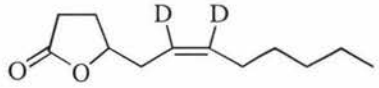
(*Z*)-6-Dodecen-γ-lactone (1.6). (Scheme 4.8)



(1.6)

This is a modification of the procedure by Sucrow *et al.*[12] 6-Dodecyne-γ-lactone (**4.7**) (0.046 g, 0.2 mmol) was added to a stirred solution of Lindlar's catalyst (9 mg) in ethyl acetate (5 mL). The flask was flushed with hydrogen gas (3 x 5 mL) and the mixture exposed to a hydrogen filled balloon and stirred vigoursly. Reaction progress was monitored by tlc and deemed complete after 2 hrs. The mixture was filtered through a short celite plug and rinsed with ethyl acetate. Volatiles were removed under reduced pressure to give a pale yellow oil that was purified by short path kugelrohr distillation (177-182°C at 11.5 mmHg) to yield the title compound (**1.6**) (0.029 g, 64%) as a colourless oil. R_f = 0.29 (hexane-ethyl acetate (4:1)); Found: M^+ 196.1472, $C_{12}H_{20}O_2$ requires 196.1463; ν_{max} (film) 2956, 2928, 2857, 1778, 1460, 1422, 1351, 1285, 1177, 1027 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* 7.0 Hz, -C*H*$_3$), 1.27 (6H, br. s, -(C*H*$_2$)$_3$CH$_3$), 1.91 (1H, m, -CH(*H*)-(C3)), 2.03 (2H, m, -C*H*$_2$- (C8)), 2.30 (1H, m, -C*H*(H)- (C3)), 2.52 (4H, m, -C*H*$_2$C(O)-(C2) and -C*H*$_2$- (C5)), 4.52 (1H, m, -C*H*- (C4)), 5.37 (1H, m, *J* 7.3, 10.9 Hz, -C=C*H*-), 5.60 (1H, m, *J* 7.3, 10.8 Hz, -*H*C=C-) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.0, 22.5, 27.2, 27.5, 28.7, 29.1, 31.5, 32.9, 80.2, 122.1, 134.1, 176.8 ppm; MS *m/z* (rel. int. %) 196(1), 98(4), 96(3), 85(100), 69(4), 57(7), 56(4), 41(10), 39(4).

6,7-$^2H_2$-(*Z*)-6-Dodecen-γ-lactone (4.8). (Scheme 4.10)



(4.8)

This is a modification of the procedure by Sucrow *et al.*[12] 6-Dodecyne-γ-lactone (**4.7**) (8.5 mg, 0.4 mmol) was added to a stirred solution of Lindlar's catalyst (9 mg) in ethyl acetate (10 mL). The flask was flushed with deuterium gas (3 x 5 mL) and fitted to the hydrogenation apparatus and stirred vigorously under an atmosphere of deuterium. Within

2 hrs the reaction mixture had consumed ~10 mL of the required 10.5 mL, and 1 hr later no further uptake had occurred. The reaction mixture was filtered through a short celite plug and rinsed with ethyl acetate and volatiles were removed *in vacuo* to give a pale yellow oil. Purification by short path kugelrohr distillation (178-183°C at 11.5 mmHg) yielded the title compound (**4.8**) (0.064 g, 75%) as a colourless oil with 98% deuterium incorporation. R_f = 0.31 (hexane-ethyl acetate (4:1)); Found: M^+ 198.1596, $C_{12}H_{18}D_2O_2$ requires 198.1589; ν_{max} (film) 2956, 2929, 2857, 1778, 1460, 1422, 1352, 1286, 1178, 1026 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* 6.8 Hz, -C*H*$_3$), 1.27 (6H, br. s, -(C*H*$_2$)$_3$CH$_3$), 1.91 (1H, m, -CH(*H*)- (C3)), 2.03 (2H, m, -CH=CHC*H*$_2$- (C8)), 2.30 (1H, m, -C*H*(H)- (C3)), 2.52 (4H, m, -C*H*$_2$C(O)- (C2) and -C*H*$_2$CH=CH- (C5)), 4.52 (1H, m, -C*H*- (C4)) 5.35 (0.02H, m, residual -*H*C=C-), 5.58 (0.02H, m, residual -C=C*H*-) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.9, 22.5, 27.1, 27.2, 28.7, 29.0, 31.4, 32.7, 80.2, 121.6 (t, CD), 133.7 (t, CD), 177.1 ppm; MS *m/z* (rel. int. %) 198(4), 138(3), 98(6), 85(100), 82(3), 69(3), 56(5), 41(6).

6-Dodecyne-γ-lactone (4.7). (Scheme 4.12)

(**4.7**)

This is a modification of the procedure by Heiba *et al.*[8] Potassium acetate (11.86 g, 3 g/10 mL) and manganic acetate dihydrate (1.952 g, 7.3 mmol) were added to a stirred solution of 1-decen-4-yne (**4.4**) (0.484 g, 3.6 mmol) in acetic acid (35.6 mL). The solution was refluxed under an atmosphere of nitrogen for 3 hrs, cooled, diluted with water (20 mL) and extracted with ether (3 x 25 mL). The combined organic washes were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was rinsed through a short plug of silica gel with pentane (20 mL) and ethyl acetate (20 mL) to give a brown oil which was further purified by short path distillation (122-126°C at 11 mmHg) to give the title compound (**4.7**) (0.275 g, 40%) as a pale yellow oil.

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Appendicies.

Appendix 3.1

Calculation of lactone percentage yield from GC peak areas.

Preparation of samples for GC analysis involved dilution of 1 mL of crude reaction mixture with 10 mL of ether. A blank (benzene only) was also diluted in this way and γ-decalactone (1 μL) was spiked into this diluted sample prior to analysis. GC analyses were run for each sample and the concentration of lactone calculated by reference to the peak area obtained for the blank using the following method.

Diluted blank, spiked with γ-decalactone: [FW = 170.25 g/mol]

1 μL x 0.948 g/mL = (9.48×10^{-4}) g (lactone in 10 mL diluted sample).

$$\frac{9.48 \times 10^{-4}\ \text{g}}{170.25} = 5.57 \times 10^{-6}\ \text{moles.}$$

$$\frac{\text{Sample peak area}}{\text{Spiked peak area}} \times (5.57 \times 10^{-6}\ \text{moles}) = \text{Y moles in sample.}$$

Y moles x 10 (initial volume) x 170.25 g/mol = weight in g of lactone in sample.

Hence, knowing the mass (or moles) of lactone present in each sample and the theoretical maximum yield based on the mass of iodoacetamide precursor (the limiting reagent), it is possible to calculate the percentage yield of lactone in each sample from the following equation.

$$\frac{\text{Weight (g)}}{\text{Theoretical weight (g)}} \times 100\% = \%\ \text{Yield.}$$