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

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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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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