A THESIS

entitled

THE SYNTHESIS OF THE ENANTIOMERS OF LIPOIC ACID

by

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ABBREVIATIONS

A	Ac	acetyl
	AcSCoA	acetyl-coenzyme A
	ADP	adenosine-5'-diphosphate
	AMP	adenosine-5'-monophosphate
	aq.	aqueous
	ATP	adenosine-5'-triphosphate
B	9-BBN	9-borabicyclo[3.3.1]nonane
	Bn	benzyl (phenylmethyl)
	b.p.	boiling point
	n-Bu	normal butyl
	s-Bu	secondary butyl
	t-Bu	tertiary butyl
	Bz	benzoyl
C	^{o}C	degree Celsius
	ca.	circa
	c.d.	circular dichroism
	c.i.	chemical ionisation
	CoASH	coenzyme A
	cm	centimeter
D	D	deuterium
	dec	decomposes
	dm	decimeter
	DMF	N,N-dimethylformamide
	DMSO	dimethylsulphoxide

E	EE	1-ethoxyethyl-
	e.e.	enantiomeric excess
	e.i.	electron impact
	e.g.	for example
	EPC	enantiomerically pure compound
	eq.	equivalent(s)
	Et	ethyl
	ether	diethyl ether(ethoxyethane)
	$Eu(hfbc)_3$	*tris*-[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III)
F	FAD	flavin adenine dinucleotide
	Fig.	figure
G	g	gram(s)
	g.c.	gas chromatography
	g.c./m.s.	gas chromatography/mass spectroscopy
	g.l.c.	gas liquid chromatography
	GTP	guanosine-5'-triphosphate
H	^1H	proton
	^2H	deuterium
	h	hour
	h.p.l.c.	high performance liquid chromatography
	Hz	Hertz
I	i.d.	internal diameter
	i.r.	infrared
	IUPAC	International Union of Pure and Applied Chemistry

J	J	coupling constant (Hz)
K	K	Kelvin
M	M	molar
	M^+	molecular ion
	MCPA	*meta*-(3-)chloroperbenzoic acid
	Me	methyl
	mg	milligram(s)
	MHz	Megahertz
	min.	minute(s)
	mm	millimeter(s)
	mmol	millimole(s)
	mol	mole(s)
	Ms	mesyl(methanesulphonyl)
	m/z	mass/charge
N	NAD^+	nicotine adenine dinucleotide
	nm	nanometer
	n.m.r.	nuclear magnetic resonance
P	^iP	inorganic phosphate
	Ph	phenyl
	p.l.c.	preparative layer chromatography
	PP	pyrophosphate
	p.p.m.	parts per million
	Pr	propyl
	P.s.i.	pounds per square inch
	PTFA	peroxytrifluoroacetic acid

	Py	pyridine
R	*rac*	racemic
	R_f	retardation factor
	r.t.	room temperature
S	S.E.R.C.	Science and Engineering Research Council
T	TCA	tricarboxylic acid (Krebs) cycle
	TFA	trifluoroacetic acid
	TFAA	trifluoroacetic anhydride
	THF	tetrahydrofuran
	THP	tetrahydropyranyl-
	t.l.c.	thin layer chromatography
	TMS	tetramethylsilane
	TOBE	1-alkyl-4-methyl-2,6,7-trioxa[2,2,2]-bicyclooctanes
	TPP	thiamine pyrophosphate
	Ts	tosyl(toluene-4-sulphonyl-)
	TSS	3-(trimethylsilyl)-tetradeutero-propionic acid sodium salt
U	u.v.	ultra violet
V	v/v	volume to volume
W	w/v	weight to volume

DECLARATION AND ACKNOWLEDGEMENTS

The work presented in this dissertation was performed in the Department of Chemistry and Molecular Sciences at the University of Warwick between April 1981 and December 1983. The subject matter is believed to be wholly original except where due reference has been made. This thesis or parts thereof have not been submitted for any previous degree.

The author wishes to thank Professor B. T. Golding for his encouragement, help and patience as supervisor throughout the project. A maintenance grant from the S.E.R.C. in conjunction with Wellcome Research Laboratories is acknowledged. The author extends his gratitude to Dr. A. T. Hudson of the latter, who as industrial supervisor, gave additional inspiration and facilitated the opportunity to participate in pharmaceutical research.

The services and help from the academic, as well as the technical staff, in the Department of Chemistry and Molecular Sciences are also deeply appreciated.

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ABSTRACT

Lipoic acid is a biologically important molecule. Whilst the racemate has been available by a number of syntheses for many years, no convenient preparation of the pure enantiomers has so far been described. All the evidence so far presented indicates that only the dextrorotatory isomer is active *in vivo*, the absolute configuration of which has not been established with certainty. To further elucidate the biochemical role(s) and biosynthesis of this compound, a convenient EPC synthesis would be beneficial. This thesis describes the development of a route to the (*R*)- and (*S*)- forms of the target molecule from a member of the "chiral pool".

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PUBLICATIONS

Part of the work described in this thesis has been published, and a further part is being prepared for publication as follows:

1 D. A. Howes, M. H. Brookes, D. Coates, B. T. Golding, and A. T. Hudson, "(*R*)-But-1-ene-3,4-diol and (*S*)-(2-Benzyloxyethyl)oxirane: Valuable Intermediates for the Synthesis of Optically Active Compounds", *J. Chem. Res.*, 1983, (*S*), 9; (*M*), 217

2 M. H. Brookes, B. T. Golding, D. A. Howes, and A. T. Hudson, "Proof that the Absolute Configuration of Natural Lipoic Acid is *R* by the Synthesis of its Enantiomer [(*S*)-(-)-α-Lipoic Acid] from (*S*)-Malic Acid", *J. Chem. Soc., Chem. Commun.*, 1983, 1051

3 M. H. Brookes, B. T. Golding, and A. T. Hudson, "The Total Synthesis of Natural, (*R*)-Lipoic Acid", paper in preparation, January, 1985

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Chapter 1

Introduction

Lipoic acid is an essential co-factor for the α-ketoacid dehydrogenase enzymes and is possibly involved in other metabolic processes. As a consequence of the widespread occurrence of this vitamin-like molecule, it is also of considerable pharmacological interest.

1.1 HISTORICAL BACKGROUND

1.1.1 Discovery

The biological activity of substances now known to be rich sources of lipoic acid was recognised independently in several laboratories. Early work by Snell and his co-workers[1] had revealed that lactic acid bacteria displayed marked growth enhancement when either sodium acetate or dried yeast were added to their cultures. Later investigations in 1946 by Guirard, Snell and Williams[2], demonstrated the role of acetate as both a buffer and a biosynthetic precursor for *Lactobacillus casei*. Furthermore, in cultures of *L. casei* buffered with phosphate, a similar growth response could be observed with much smaller quantities of yeast extract in the absence of acetate[3]. The existence of an unidentified growth factor in yeast extract was postulated, and steps were taken towards developing an assay procedure and methods for the

concentration of this material. On the basis of its observed biological response the growth factor was designated as "acetate replacing factor"[3].

In studies related to the nutritional requirements of the ciliated protozoan *Tetrahymena geleii* (strain w), Dewey[4] reported that this organism would only grow in casein media supplemented with small quantities of beef liver residue. Closer examination of beef liver residue revealed the presence of two well-defined growth factors: one soluble, and the other one insoluble in water. These observations led to the further work of Dewey in 1945[5] in which the water-soluble factor was identified as folic acid. Experiments on the insoluble factor demonstrated that at least two biologically active components were present which were called "protogen A" and "protogen B".

Similar microbial studies with *Streptococcus faecalis* (strain 10C1), grown on synthetic media, revealed the inability of these bacteria to oxidise pyruvate to acetate and carbon dioxide in the absence of traces of yeast extract[6]. More detailed work by Gunsalus and his co-workers clearly demonstrated the presence of a heat-stable factor responsible for this phenomenon in yeast extract[7]. As the oxidation of pyruvate requires the uptake of molecular oxygen, an accurate manometric assay for this factor could be devised. Some concentration of "pyruvate oxidation factor" was realised with the help of this technique.

Kline and Barker[8] also reported that a substance present in yeast or beef liver extract was necessary for

the satisfactory growth of *Butyribacterium rettgeri* when cultivated on a medium containing lactate as the fermentable carbon source. The factor in these natural extracts responsible for the organism's growth was designated as B.R. factor[9].

In 1949, Snell and Broquist elegantly demonstrated that "protogen" (A + B), "pyruvate oxidation factor" and "B.R. factor" were equally effective as "acetate replacing factor" in duplicating the growth response of acetate with *L. casei*[10]. These workers correctly concluded that all the aforementioned preparations were concentrates of the same substance(s).

1.1.2 Isolation

Work on the characterisation and isolation of the pure substance(s) able to fulfil the nutritional demands of the aforecited micro-organisms was undertaken by Reed and his co-workers[11]. To determine the multiplicity of growth factors present in yeast extract, paper chromatography in conjunction with so-called bio-autography was employed. A 1:1:3 mixture of butan-1-ol, lutidine (2,6-dimethyl-pyridine) and water was used as the eluent. Having run the chromatogram, it was placed in contact with an agar plate innoculated with lactic acid bacteria. Where a growth factor had been on the chromatograph, a colony of bacteria would form. This technique revealed the presence of 5 to 8 factors in yeast extract[12]. However, when prior acid hydrolysis of the yeast extract was carried out only two zones of growth were detected. Furthermore, the

combined biological activity was greatly increased. The implication was that acid hydrolysis was necessary for the efficient release of the growth factor(s) into solution.

Later work[13] showed that beef liver residue, after acid hydrolysis, was the best natural source of the growth factors. Paradoxically, no material active in the *L. casei* bio-autograph was released by direct elution with the aforecited solvent system. At this stage it also begun to be appreciated that only very small quantities of the factors were present in any natural material. Accordingly, Reed *et al.* confined all their subsequent endeavours to beef liver extract[13]. Through an exhaustive program of trial and error along with educated guesswork, Reed and his collaborators devised an isolation procedure for "lipoic acid"[14]. Essential to the success of their method was the appreciation of the solubility in benzene (lipophilicity) and acidic nature of the compound(s) they sought. This is reflected in the name "lipoic acid" which was coined before a structure determination or even isolation had been achieved. The two factors, detected by bio-autography were designated as α- and β-lipoic acids and defined as the less and the more polar acids respectively (by R_f values).

During Reed's isolation procedure summarised below, it became apparent that the more polar β-lipoic acid was an artefact. This compound originated from the oxidation of α-lipoic acid during the acid hydrolysis and subsequent experimental manipulations.

Beef liver residue was first washed with butan-1-ol and acetone to extract soluble organic material, which might otherwise interfere with the later steps of the isolation. The residue was then heated with 3 M sulphuric acid for 3 hours at 120°C in an autoclave. The filtered hydrolysate was extracted with benzene, effecting quantitative transfer of the lipoic acids released into the organic phase. The benzene solutions were concentrated to a convenient volume and then washed with aqueous sodium bicarbonate solution. Acidification of the aqueous phase and re-extraction into fresh benzene conveniently removed a large proportion of the contaminants. Evaporation of the second benzene extract left a residual acidic oil. Attempts to fractionate the α- and β-lipoic acids present, directly by column chromatography on silica gel buffered with potassium dihydrogen phosphate were only partially successful[14]. Better results were obtained after treatment of the crude acids with ethereal diazomethane. Separation of the resulting methyl esters was achieved by repeated chromatography on alumina with benzene/60-80° petrol mixtures as eluents. Methyl α-lipoate was further purified by chromatography on Florisil and samples of essentially pure compound obtained. These were combined and saponified in 0.1 M potassium hydroxide solution, and, after acidification, the resulting free acid was crystallised from petrol. Quantitative and qualitative monitoring of each concentration step was carried out by microbial assay methods involving (a)

manometric determination of molecular oxygen uptake following the activation of the pyruvate oxidation system of lipoic acid dependent strains of *S. faecalis* along with (b) measurement of the growth rate of *S. lactis* in an acetate free synthetic medium. α-Lipoic acid was thus isolated as yellow platelets m.p. 47.5°C, $[\alpha]_D^{20}$ + 96.7° (c = 0.88 benzene) for the first time in the Autumn of 1951[15]. This represented a 300,000 to 600,000-fold concentration of the active material from acid hydrolysed beef liver residue. Because only five milligrams of α-lipoic acid were obtained on this occasion, Reed and his collaborators repeated their procedure on a larger scale in the hope of extracting sufficient material to permit a full structure determination. An estimated 10 tons of beef liver residue was consumed to provide only another 30 mg of pure crystalline α-lipoic acid[16], which fortunately, was just enough for the gross structural features to be elucidated. The pure α-lipoic acid was, as expected, able to reproduce all the microbial growth responses described earlier.

Shortly after Reed's initial publication[15], Patterson and his co-workers[17], independently isolated β-lipoic acid (protogen B) from beef liver residue. Their procedure was similar to that described above. A meagre 16 mg of β-lipoic acid was obtained as a yellow oil $[\alpha]_D^{25}$ + 105° (C = 0.94 benzene), after liberation from its crystalline S-benzylthiuronium salt (m.p. 132-4°C), through which final purification had been effected. These researchers were able to show that α-lipoic acid, with properties identical to those described by Reed,

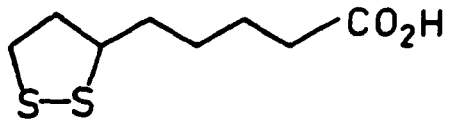
could be made by the reduction of β-lipoic acid with sodium borohydride followed by mild re-oxidation with iodine[18].

1.1.3 Determination of the Structure of α-Lipoic Acid

The research groups of both Reed and Paterson now undertook the elucidation of the structure of α-lipoic acid[19,20]. As their results were concordant in all significant respects, the analytical data will be presented in unison.

The molecular formula of α-lipoic acid was established as $C_8H_{14}O_2S_2$ by elemental analyses and molecular weight determinations. Evidence for a disulphide functionality came from the observation that the nitroprusside test for thiols was negative before, but positive after, treatment with sodium cyanide. Polarographic studies confirmed the presence of a disulphide. Furthermore, the ability of α-lipoic acid to be reduced at the dropping mercury electrode, implied that the disulphide was cyclic. Octanoic acid was produced after desulphurisation with Raney Nickel, revealing the linear eight-carbon backbone of this molecule. The location of one of the sulphur atoms at C-8 was deduced from the absence of an absorption at 2960 cm^{-1} in the infrared spectrum and the failure to detect acetic acid after Kuhn-Roth oxidation (i.e. absence of a C-methyl grouping). The carboxylic acid group of α-lipoic acid was found to have a pKa of 4.76 which meant that the second sulphur atom could not be attached to C-2 or C-3. These findings were consistent with α-lipoic acid

possessing the structure of 1,2-dithiolane-3-pentanoic acid (1), 1,2-dithiane-3-butanoic acid (2) or 1,2-dithiepane-3-propanoic acid (3).



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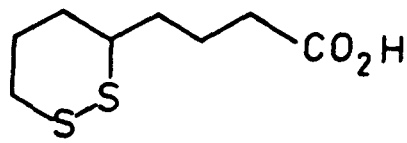

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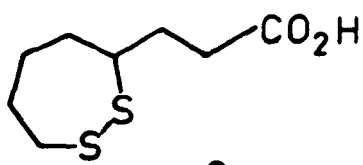

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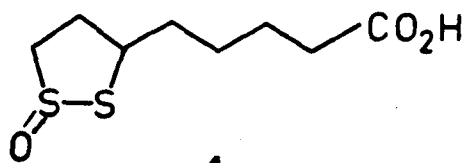

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Establishment of the position of the second sulphur atom on the octanoate backbone by chemical degradation was not feasible with the small amounts of α-lipoic acid which had been isolated. Therefore further structural investigations were aided by synthesis.

On the basis of erroneous deductions the 1,2-dithiane structure (2) was initially favoured. However, this material when synthesised[21,22] showed little biological activity and therefore could not be

the correct structure.

In 1952 Bullock and his co-workers[23] published an unambiguous synthesis of the racemic 1,2-dithiolane isomer (1). The compound gave almost identical analytical results to those reported for natural α-lipoic acid, the only significant difference was the melting point of the synthetic material which was 61°C. This discrepancy may easily be explained by assuming that the enantiomers and racemate of (1) have different packing arrangements in their respective crystals - a phenomenon frequently encountered with chiral organic compounds.

Additionally, Bullock's racemic lipoic acid gave 50% of the growth response in the *S. faecalis* bioassay recorded for the material isolated from beef liver. The inescapable conclusion was that lipoic acid (the α-prefix was subsequently dropped) was the dextrorotatory enantiomer of structure (1), with the second sulphur atom being located at C-6. The structure of β-lipoic acid was subsequently shown to be (4)[24].

As mentioned above, the correct systematic name for (1) is 1,2-dithiolane-3-pentanoic(valeric) acid. However, in the biochemical texts the names "protogen A", "pyruvate oxidation factor", etc., still persist despite technically being obsolete. Alternative semi-systematic names for (1) are also in widespread use; for example 6-thiooctic acid[25] and 6,8-dithiooctic acid. To avoid confusion, structure (1) will, henceforth, be referred to simply as "lipoic acid" throughout this thesis. This name was adopted as the "official" trivial designation

for (1) by the American Society of Biological Chemists in 1955[11].

1.2 SYNTHESIS OF LIPOIC ACID

1.2.1 Approach to the Syntheses of Lipoic Acid

To date nearly 30 syntheses of α-lipoic acid have been cited in Chemical Abstracts. A large proportion of these originate from the patent literature of the 1950's and testify to the intense effort applied by many drug companies to assess the pharmacological potential of lipoic acid. Although voluminous, the procedures quoted in the patent literature are, almost without exception, pedestrian modifications of routes which have previously been published in the academic journals. Discussion in this section will, therefore, be confined to synthetic schemes whose methodology is largely unrelated.

The general strategy employed in all lipoic acid syntheses involves the assembly, from smaller carbon units, of an octanoic acid derivative, suitably substituted at C-6 and C-8 with functionalities (e.g. hydroxy or halo), directly or indirectly replaceable by various sulphur nucleophiles. Over the years a shift in emphasis in the routes to the target molecule has become apparent. The early work, depicted in Schemes 1.1, 1.2, 1.3 and 1.7 was largely concerned with the efficient preparation of lipoic acid by the manipulation of known reactions, whereas the later work (Schemes 1.4, 1.5 and 1.6) have

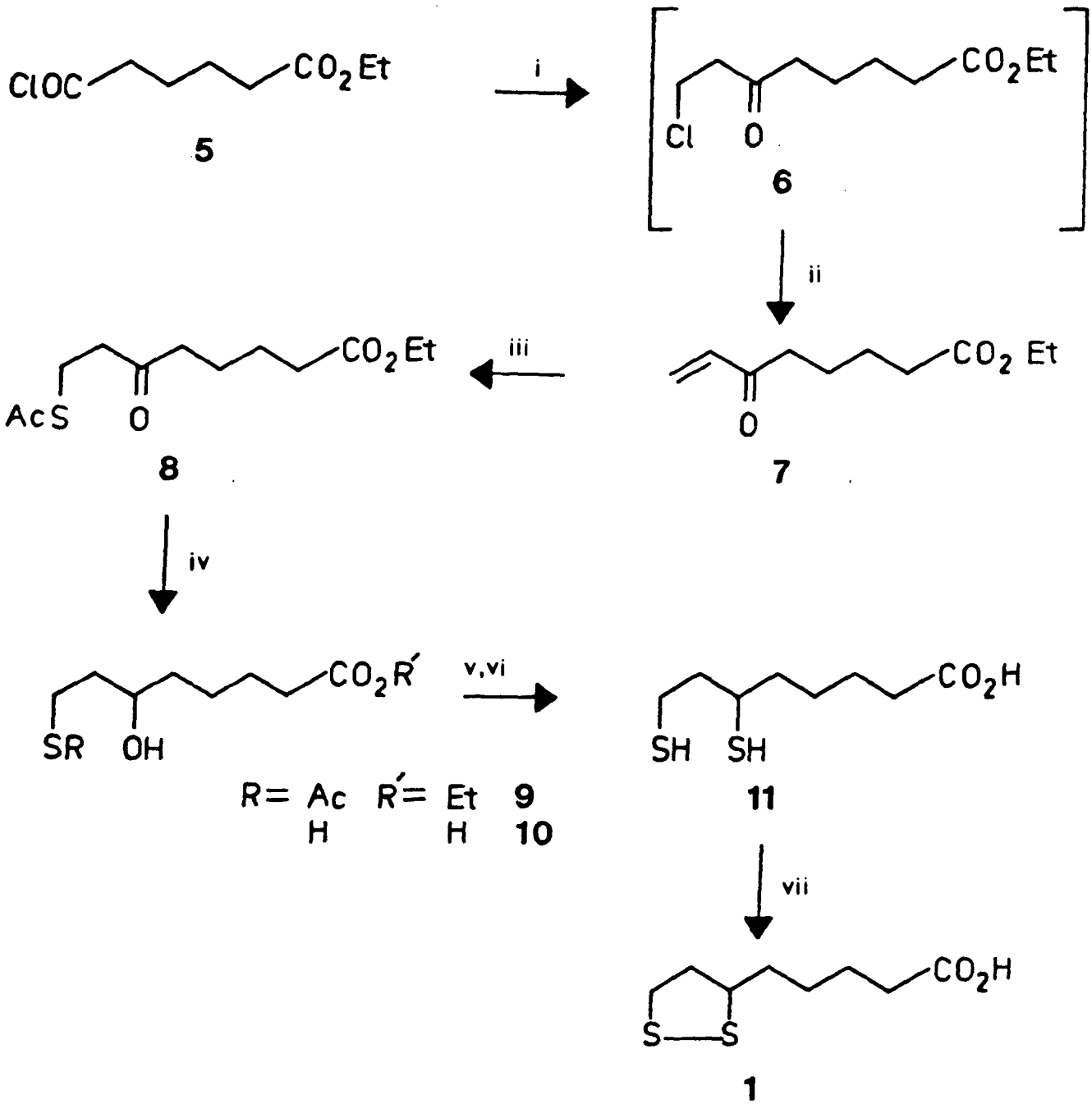
tended towards a demonstration of the applicability of novel procedures in the synthesis of a natural product of recognised importance.

1.2.2 Syntheses of Racemic Lipoic Acid

The original synthesis by Bullock *et al.*[23] is shown in Scheme 1.1. The starting material was ethyl adipoyl chloride (5) which is readily made from adipic acid. Ethene was acylated with (5) in nitrobenzene solvent in the presence of stoichiometric anhydrous aluminium chloride to give the chloroketone (6). The latter was not isolated, but heated to induce dehydrochlorination furnishing the vinyl ketone (7). The Michael reaction of thiolacetic acid with (7) afforded the addition product (8). Treatment of (8) with sodium borohydride in ethanol gave the alcohol (9). Cleavage of the ester and thioacetyl groups by aqueous base produced the hydroxythiol acid (10), convertable to 6,8-dithioloctanoic acid (11) (dihydro or reduced lipoic acid) upon refluxing with aqueous hydrogen iodide and thiourea, followed by alkaline work-up. Pure lipoic acid was then obtained by oxidation of (11) with iodine in aqueous potassium iodide followed by recrystallisation from petrol. The overall yield of lipoic acid from (5) was 8%.

Numerous attempts have been made to improve this route. Soper and his co-workers investigated several elegant modifications with only limited success[26]. Copious procedures by other workers have also addressed

Scheme 1.1



Reagents: (i) C_2H_4, $AlCl_3$, $PhNO_2$; (ii) Δ;
(iii) CH_3COSH, Δ; (iv) $NaBH_4$, MeOH;
(v) NaOH(aq.); (vi) $(NH_2)_2CS$, HI, reflux;
(vii) KI/I_2.

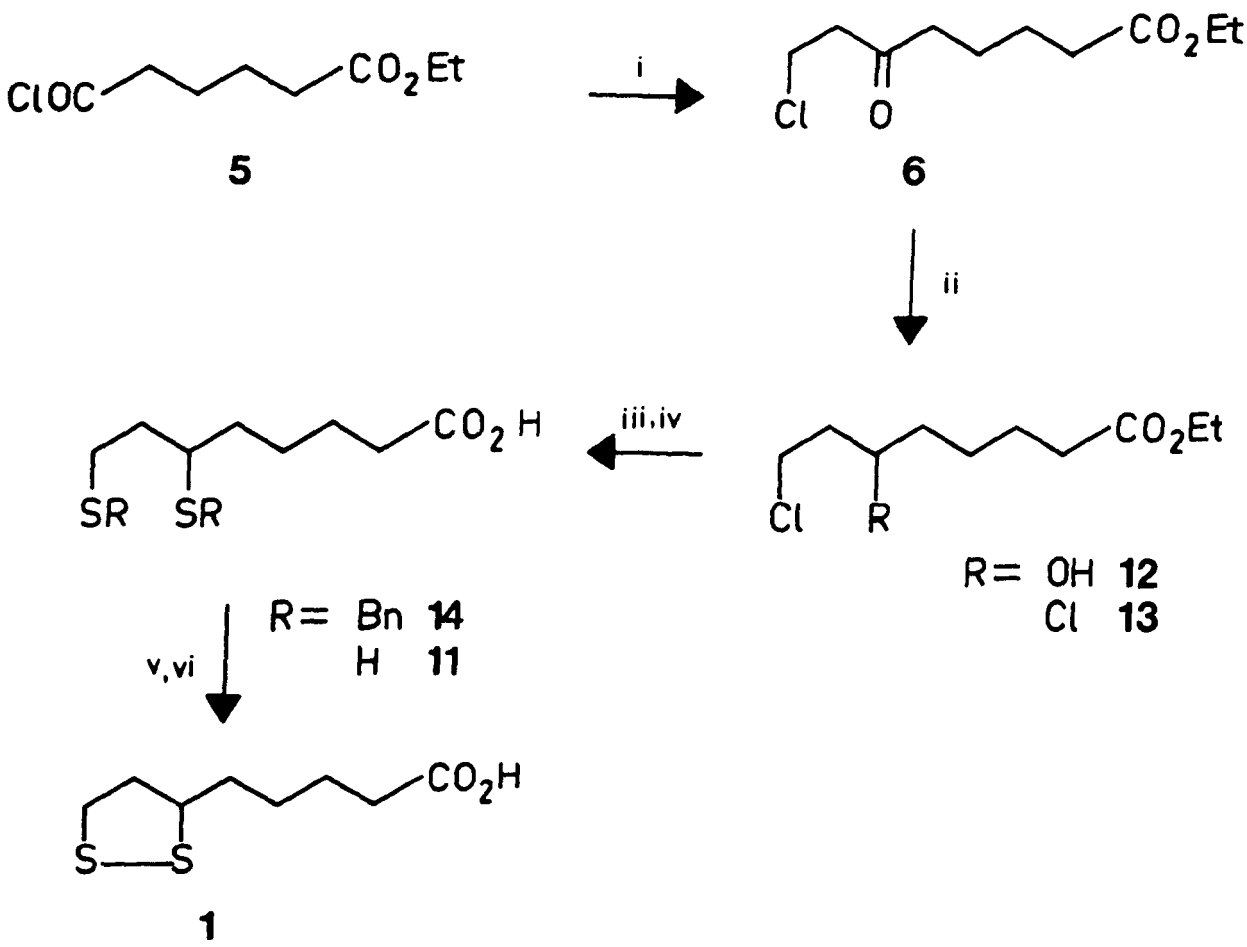
this problem[27], some of which were based on the analogous reaction of (5) with ethyne[28].

By far the most successful variant was published by Reed and Nui in 1955[29] (Scheme 1.2). Starting with the reaction of (5) with ethene again, the chloroketone (6) was isolated and then reduced with sodium borohydride to the chloroalcohol (12) in this route. Reaction of (12) with thionyl chloride in the presence of pyridine gave ethyl 6,8-dichlorooctanoate (13). Sulphur was introduced by displacement of the halogens with sodium thiobenzylate (2 equivalents) in refluxing ethanol. The resulting **6,8-*bis*-**benzylthiooctanoic acid (14) was obtained after alkaline work-up and recrystallisation (m.p. 68-9^{o}C) from petrol-benzene. Debenzylation of (14) to furnish dihydrolipoic acid (11) was carried out with sodium in liquid ammonia. Finally, oxidation to lipoic acid was effected by bubbling oxygen through an aqueous solution of (11) at pH 6 in the presence of iron(III) chloride as catalyst. This method gave less polymeric by-products than the oxidation with iodine previously described. In this way an overall yield of 36% of lipoic acid from (5) was realised.

A better synthesis in terms of yield and cheapness of starting materials has not been found. It is almost certain that commercial racemic lipoic acid[25] is made by a route closely allied to this procedure. Syntheses of ^{35}S radiolabelled lipoic acid have also been performed using this route[30].

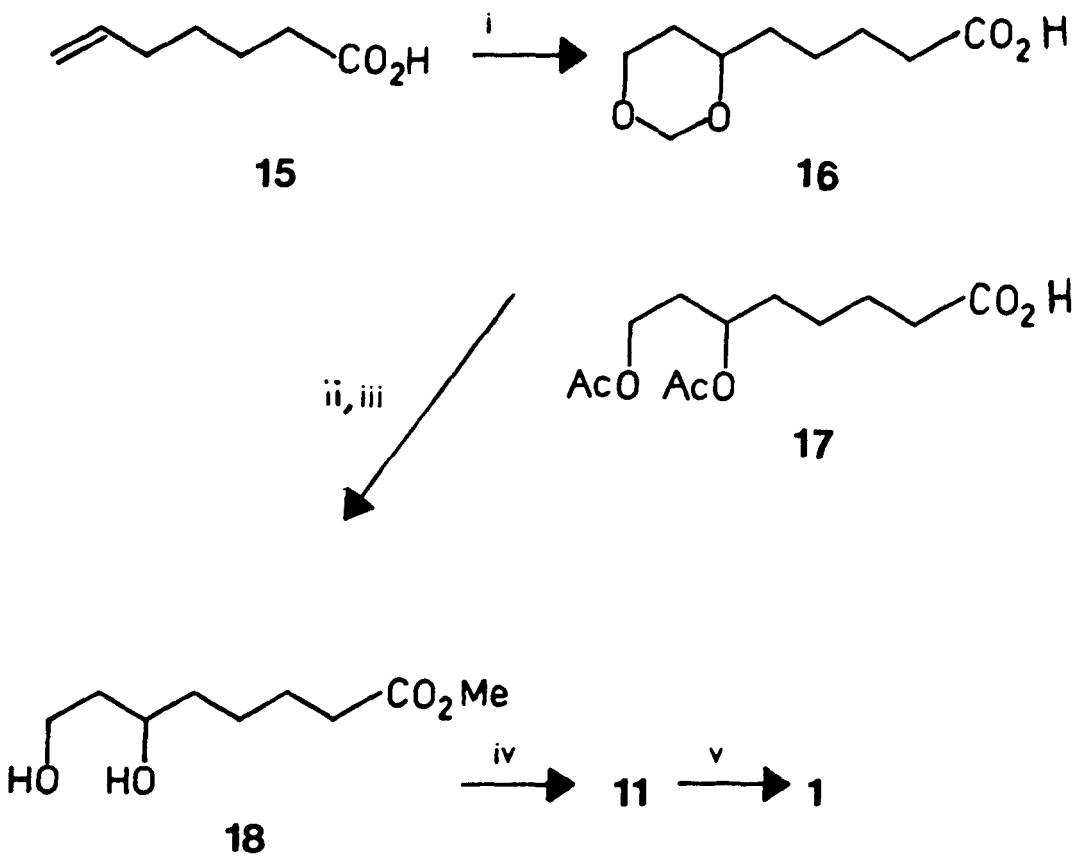
An alternative approach (Scheme 1.3) was announced by Braude *et al.* in 1956[31]. The basis of the

Scheme 1.2



Reagents: (i) C_2H_4, $AlCl_3$, $C_6H_5NO_2$; (ii) $NaBH_4$, MeOH; (iii) $SOCl_2$, pyridine; (iv) BnS^-Na^+, EtOH, reflux; (v) Na, NH_3; (vi) $Fe^{3+}_{(aq)}$, O_2, pH 6

Scheme 1.3

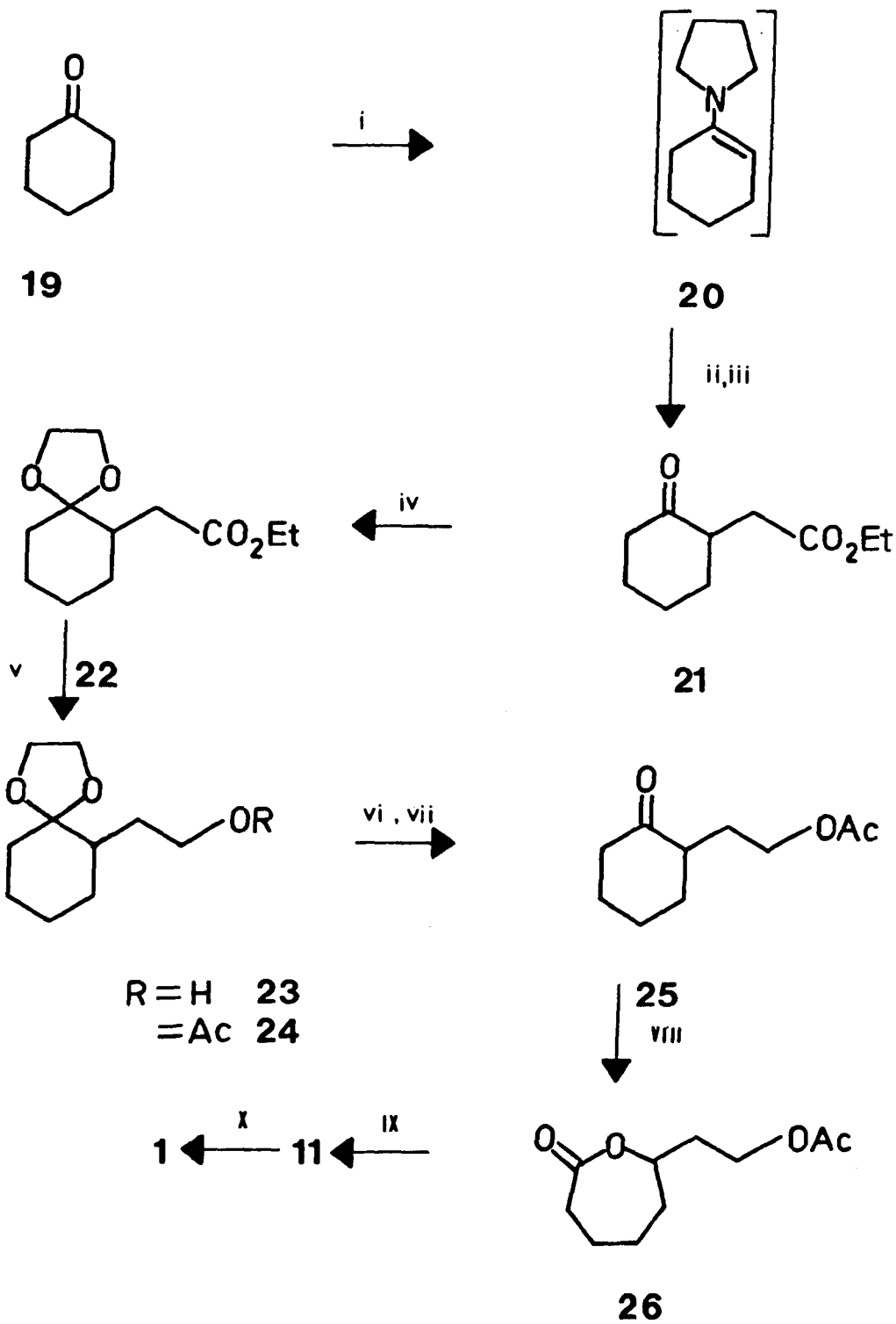


Reagents: (i) CH_2O, AcOH, Ac_2O, H_2SO_4(cat.); (ii) CH_2N_2, Et_2O; (iii) H^+, MeOH, reflux; (iv) HI, $(NH_2)_2CS$, reflux; (v) $Fe^{3+}_{(aq)}$, O_2, pH 6

route was the Prins homologation of hept-6-enoic acid (15), available from the alkylation of sodium diethyl malonate with 5-bromopent-1-ene[32]. Reaction of (15) with formaldehyde in acetic acid:acetic anhydride in the presence of sulphuric acid as catalyst yielded a mixture of the 1,3-dioxane acid (16) and the diacetoxy acid (17). Although it was possible to separate (16) and (17) by conversion into their methyl esters and then careful fractional distillation, it was more practical to boil the mixture of methyl esters in acidified methanol under reflux to afford methyl 6,8-dihydroxy-octanoate (18) in high yield. Transformation of (18) into lipoic acid was effected by conversion into (11) by boiling under reflux with hydrogen iodide and thiourea followed by ferric ion-catalysed aerial oxidation. The overall yield from (15) was claimed to be 25%.

The chemistry of enamines has been extensively used to extend the synthetic applications of the carbonyl group. Serge and his co-workers[33] employed the alkylation of an enamine as their key step for assembling the carbon skeleton of a suitable precursor to lipoic acid (Scheme 1.4). Cyclohexanone (19) was reacted with pyrrolidine to give the enamine (20), which was alkylated *in situ* with ethyl bromoacetate. The cyclic γ-keto ester (21) was then liberated after acidic work-up. The ketone functionality of (21) was protected by conversion into the **acetal** (22), facilitating selective reduction of the ester group with lithium aluminium hydride. Alcohol (23), the product of the preceding reaction, was

Scheme 1.4



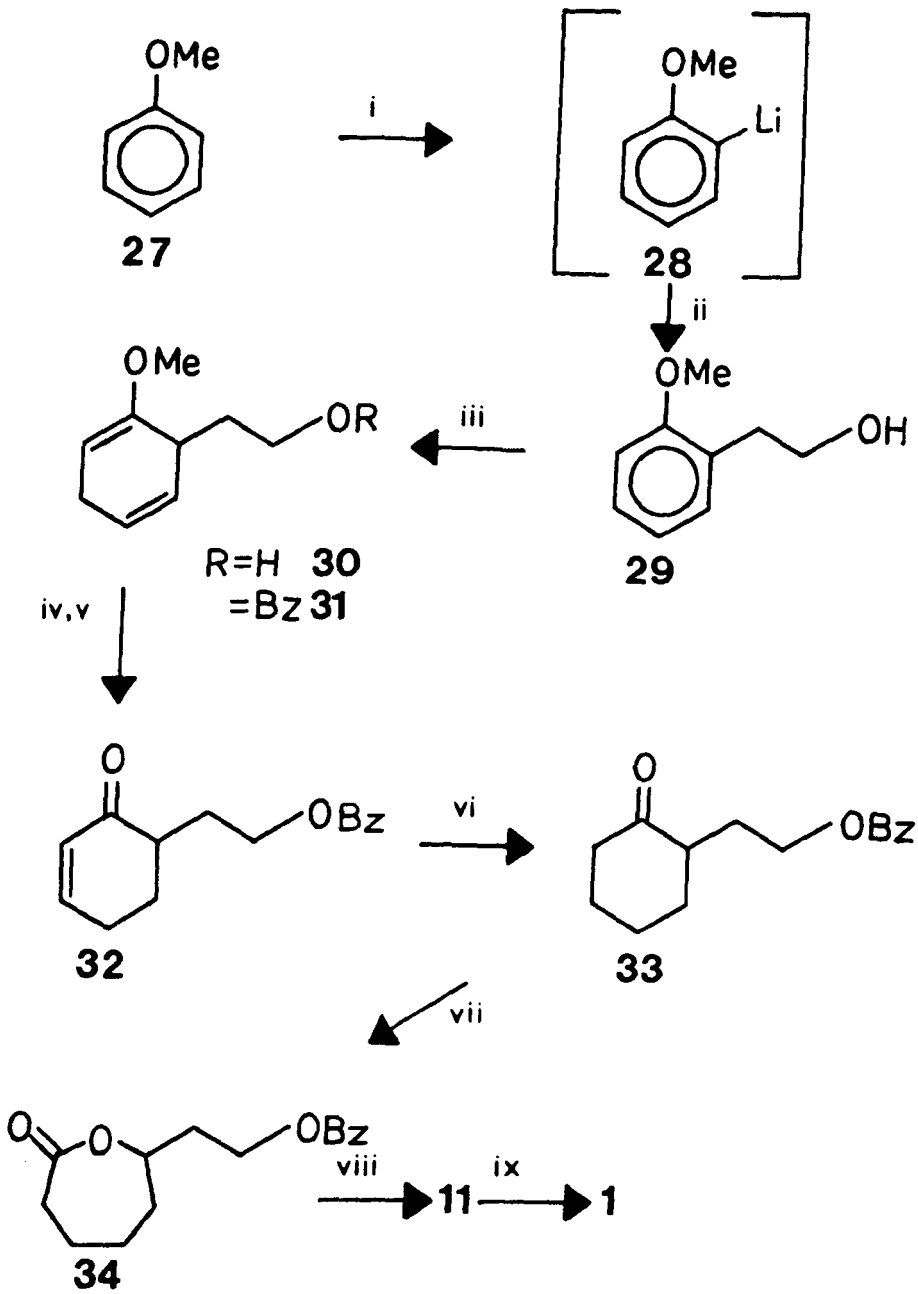
Reagents: (i) pyrrolidine, C_6H_6, H^+(cat.); (ii) $BrCH_2CO_2Et$; (iii) H_3O^+; (iv) ethane-1,2-diol, H^+, toluene; (v) $LiAlH_4$, Et_2O; (vi) Ac_2O, pyridine; (vii) H_3O^+; (viii) AcOOH/AcOH, H^+; (ix) $HI/(NH_2)_2CS$, reflux; (x) $Fe^{3+}_{(aq)}$, O_2, pH 6

esterified to furnish the acetate (24) and then the carbonyl group was regenerated giving the ketone (25). Baeyer-Villiger oxidation of (25) with peracetic acid gave the desired lactone (26). Refluxing (26) with hydrogen iodide and thiourea, followed by aerial oxidation of the resulting dithiol (11) in the presence of ferric ions, gave lipoic acid in 19% overall yield from (19).

The *ortho*-metallation of functionalised aromatic compounds by alkyl lithium reagents has proved to be a valuable entry for their further substitution in a regiospecific fashion. In 1962 Lewis and Raphael[34] published a lipoic acid synthesis starting from readily available anisole (27) (Scheme 1.5). Treatment of (27) with *n*-butyllithium gave the *ortho*-lithiated intermediate (28), which was subsequently alkylated with ethylene oxide to provide the alcohol (29) in one pot. After Birch reduction of (29), the resulting dihydrocompound (30) was converted into its benzoate ester (31). This was treated with sulphuric acid to convert the enol ether functionality into an α,β-unsaturated ketone (32). Catalytic hydrogenation of (32) gave the saturated cyclic ketone (33), which on Baeyer-Villiger oxidation was converted into the benzoylated lactone (34). Transformation of (34) into lipoic acid was done in essentially the same manner as described previously (Schemes 1.3, 1.4).

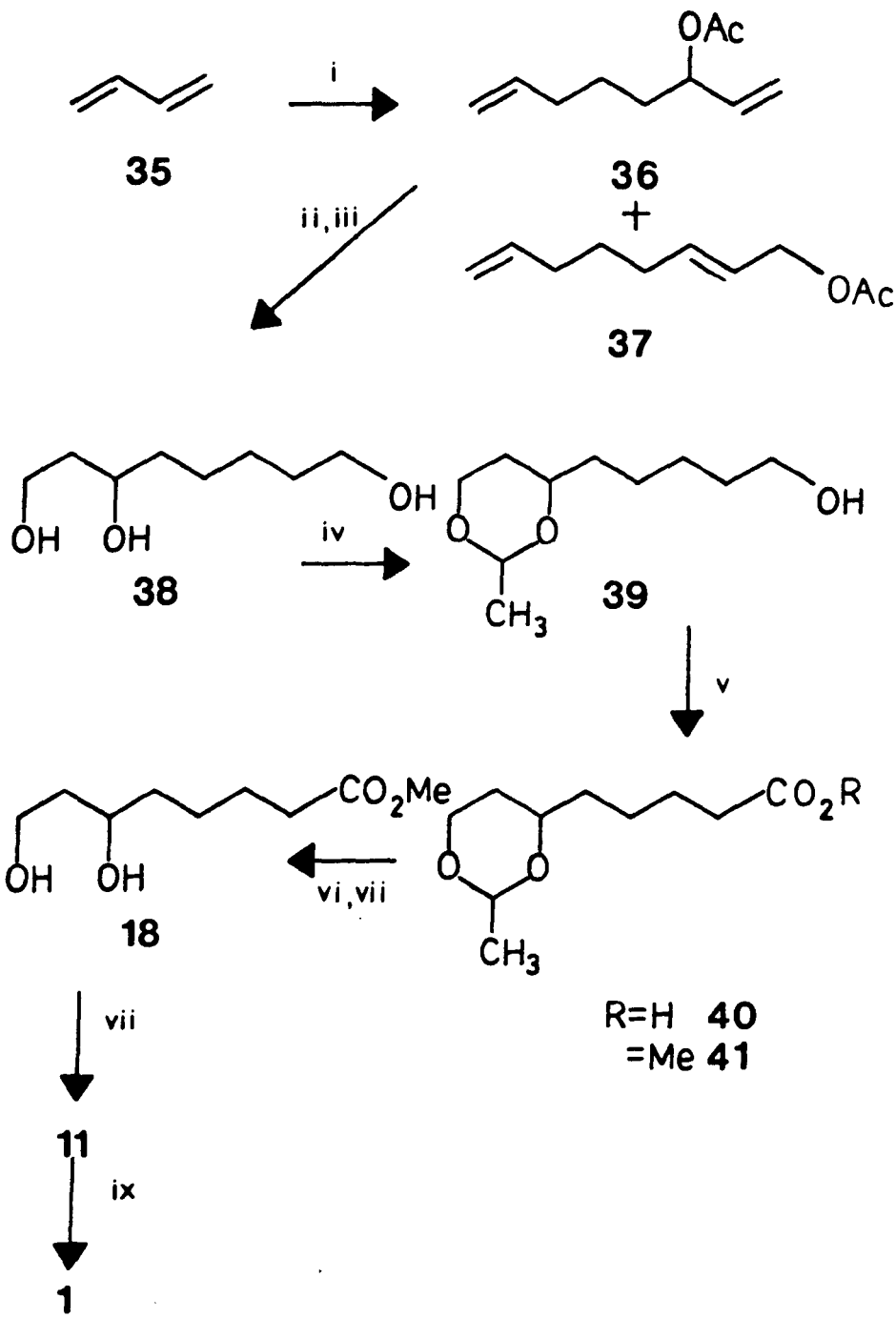
Palladium-catalysed reactions have found considerable application in organic synthesis. Tsuji and his co-workers[35] have used the palladium-catalysed telomerisation of buta-1,3-diene (35) to provide the

Scheme 1.5



Reagents: (i) BuLi, hexane; (ii) ethylene oxide; (iii) Li, NH_3; (iv) BzCl, $NaOH_{(aq)}$; (v) 3 M H_2SO_4; (vi) H_2, Pt, MeOH; (vii) AcOOH/AcOH, H^+; (viii) HI, $(NH_2)_2CS$, reflux; (ix) $Fe^{3+}_{(aq)}$, O_2, pH 6

Scheme 1.6



Reagents: (i) $PdCl_2(PPh_3)_2$, AcOH, Et_3N; (ii) BH_3.THF; (iii) H_2O_2, OH^-(aq); (iv) CH_3CHO, H^+; (v) Jones oxidation; (vi) CH_2N_2, Et_2O; (vii) H^+, MeOH; (viii) $HI/(NH_2)_2CS$, reflux; $Fe^{3+}_{(aq)}$, O_2, pH 6

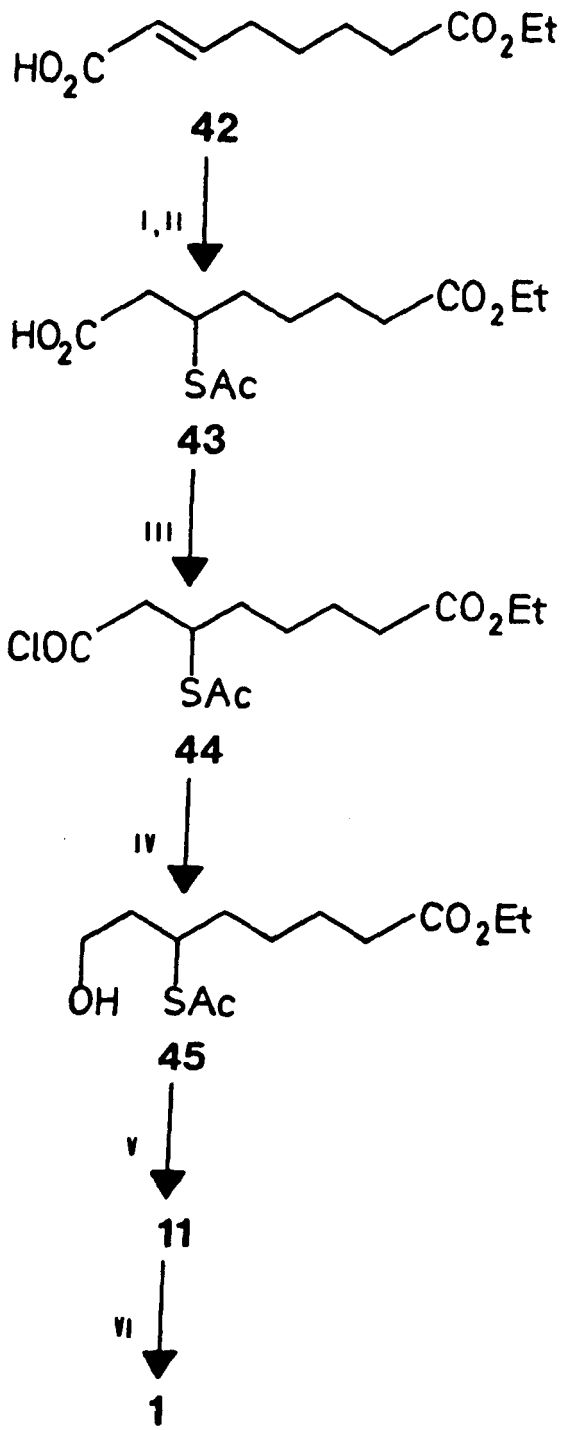
linear eight-carbon backbone of lipoic acid (Scheme 1.6). This facile reaction gave the acetates (36) and (37) in a 1:2.7 ratio and 85% (combined) yield. These acetates were separable by careful fractional distillation. Acetate (36) was dihydroborated to give octane-1,3,5-triol (38) after oxidative alkaline work-up. Although 9-BBN was initially used for this step, mixtures of (38) and cyclooctane-1,5-diol by-product proved difficult to separate by chromatography, necessitating use of the less regioselective borane-tetrahydrofuran complex instead. Protection of the hydroxyl functions at C-1 and C-3 by acid catalysed reaction with acetaldehyde gave the ethylidene acetal (39). Oxidation of the free hydroxyl group at C-8 with Jones reagent gave the acid (40), which was subsequently converted into its methyl ester (41). Hydrolysis of this acetal-ester (41) in acidified methanol gave (18) convertable to lipoic acid as detailed in Braude's synthesis[31].

1.2.3 Syntheses of the Enantiomers of Lipoic Acid

So far, only syntheses of racemic lipoic acid have been discussed. However, as pointed out earlier, only one enantiomer of this compound appeared to be active *in vivo*. Therefore, a route incorporating a resolution step was desirable.

In 1954 Walton *et al.*[36] announced the first syntheses of the pure dextro- and laevorotatory forms of lipoic acid (Scheme 1.7). Starting from 7-carboethoxy-

Scheme 1.7



Reagents: (i) CH_3COSH; (ii) resolution with l-ephedrine; (iii) $SOCl_2$; (iv) $NaBH_4$, 1,4-dioxane; (v) HI/ $(NH_2)_2CS$, reflux; $Fe^{3+}_{(aq)}$, O_2, pH 6

hept-2-enoic acid (42)[37], application of a Michael reaction with thiolacetic acid (over 17 days at room temperature) gave the key intermediate 3-acetylthio-7-carboethoxyheptanoic acid (43). This compound was converted into a pair of diastereomeric salts with l-ephedrine. The l-ephedrine salt of the laevorotatory enantiomer of (43) was purified by crystallisation, whilst its antipode was isolated from the non-crystalline residue by precipitation in the form of its benzhydrylamine salt. Decomposition of the salts in aqueous acid liberated the pure enantiomers of (43). Reaction of (43) with thionyl chloride gave the acid chloride (44), reducible to the alcohol (45) with sodium borohydride. Introduction of a thiol group at C-8 was carried out by the standard thiourea and hydrogen iodide method, followed by alkaline work-up, affording dithiol (11), easily oxidisable to the target molecule. It was found that (+)-(43) was the precursor to (+)-lipoic acid. This synthetic material had essentially the same optical rotation ($[\alpha]_D^{23}$ + 104°, C = 0.88 benzene) and growth response in the *S. faecalis* bio-assay as the (+)-lipoic acid extracted from beef liver. Unnatural (-)-lipoic ($[\alpha]_D^{23}$ - 113°, C = 1.88 benzene) derived from (-)-(43) was inactive in the aforementioned assay.

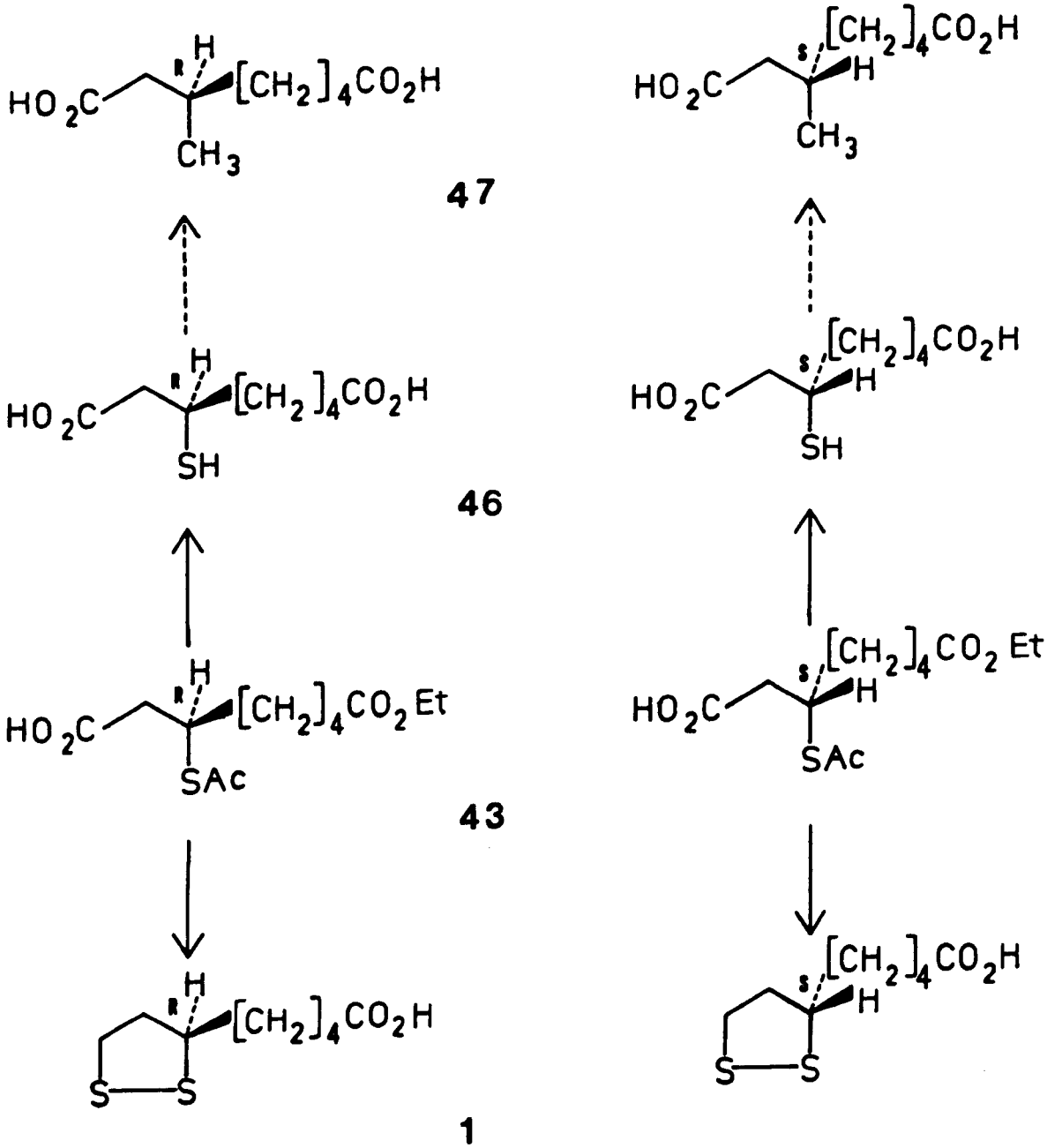
Three years later, Acker and Wayne[38] reported a second lipoic acid synthesis incorporating a resolution step. These workers followed the route of Reed and Nui[29] (Scheme 1.2) until chloroester (13) was reached. This was hydrolysed to its parent acid which was resolved *via* its l-ephedrine salts. The regenerated sodium salts of

resolved 6,8-dichlorooctanoic acid were converted directly into the enantiomers of lipoic acid by refluxing with sodium sulphide and sulphur in ethanol, followed by acidification. Displacement of halide by disulphide, unlike the formal displacement of hydroxyl by thiol effected by hydrogen iodide and thiourea, proceeds stereospecifically with inversion at the chiral centre. Samples of lipoic acid prepared in this way were found to have similar properties to those prepared in the Merck synthesis[36]. Both routes[36,38] were dogged by laborious recrystallisations and very low ≤ 1% overall yields of the target molecule. Direct resolution of racemic lipoic acid *via* its cinchonidine salt was also attempted, but with only partial success[38]. Hence, the availability of (+)-lipoic acid for widespread biological testing has so far been severely restricted.

1.3 THE ABSOLUTE CONFIGURATION OF LIPOIC ACID

The absolute configuration of (+)-lipoic acid has been tentatively assigned as *R* by Mislow and Meluch[39] using a method employing melting point composition diagrams[40]. These investigators took the resolved intermediate (+)-(43) in Walton's (Merck) synthesis (Scheme 1.7)[36], and converted it into (-)-3-thioloctandioic acid (-)-(46) by mild saponification in aqueous base. Diacid(-)-(46) was found to form a continuous series of solid solutions upon heating with (+)-3-methyloctanedioic acid (+)-(47)

Figure 1.1


HO2C
H
R
[CH2]4CO2H
CH3
47
HO2C
H
R
[CH2]4CO2H
SH
46
HO2C
H
R
[CH2]4CO2Et
SAc
43
H
R
[CH2]4CO2H
S
S
1
HO2C
[CH2]4CO2H
S
H
CH3
HO2C
[CH2]4CO2H
S
H
SH
HO2C
[CH2]4CO2Et
S
H
SAc
[CH2]4CO2H
S
H
S
S

whose absolute configuration had been established as *R*. By contrast (+)-(46), similarly derived from (-)-(43), gave only simple eutectic mixtures with (+)-(47) under the same conditions.

Since sulphur and methylene have frequently been shown to exhibit isomorphous interreplacability[41], it can be inferred that (-)-(46) and (+)-(47) have the same chirality. This pair behave as a pseudoenantiomeric mixture, whereas (+)-(46) and (+)-(47) behave as a pseudoracemic composite. As (-)-(46) can be directly correlated with (+)-lipoic acid by reactions which do not involve any change in the absolute configuration at C-6, the conclusion that (+)-lipoic acid has *(R)*-chirality was reached.

No experimental work to support or contest this deduction has been undertaken since the publication of this paper[39] in 1956. The interrelationships of (+)- and (-)-lipoic acid with the enantiomers of (43), (46) and (47) are summarised in Fig. 1.1.

1.4 THE BIOSYNTHESIS OF LIPOIC ACID

Although lipoic acid is ubiquitous in living organisms, its biosynthesis appears to be restricted to certain microorganisms and plants[42]. Man and other animals apparently obtain sufficient quantities of this compound either directly from their diet, or from the metabolism of their gut microflora. Ailments attributable to a deficiency of lipoic acid have never

been observed in higher animals. Thus, by definition, lipoic acid cannot be a vitamin, although its established biochemical role as a co-enzyme is similar to that of many substances defined as such.

Investigations into the biosynthesis of lipoic acid have been obstructed by the experimental difficulties associated with the detection and isolation of the miniscule quantities of material normally present in living tissue[43]. For instance, the concentration of this compound in beef liver - the richest known source, is only 1.6-3.2 μg/g[16]. No organism or mutant thereof which over-produces lipoic acid has ever been found. Recently, advances in techniques and instrumentation have permitted progress to be made in this area.

Octanoate has been unequivocally established as a direct biosynthetic precursor in *Esherichia coli*[44]. Having identified the origin of the carbon skeleton the mode of sulphur introduction was tackled next.

By feeding $^{2}H_{15}$-octanoate to cultures of *E. coli*, White[45] was able to show, by gc/ms analysis, that $^{2}H_{13}$-lipoate was formed. This demonstrated that sulphur introduction occurred with only removal of the replaced hydrogen atoms. Hence, unsaturated intermediates did not participate in the transformation.

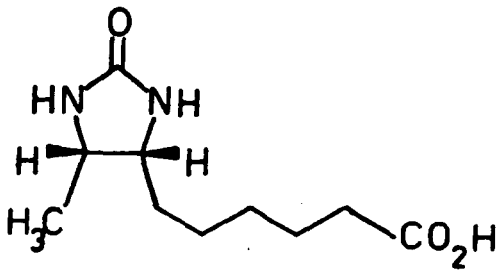
The stereochemistry of sulphur introduction at C-6 was examined by Parry[46] in 1978. Chiral octanoates tritiated at C-6, were synthesised and administered to cultures of *E. coli* along with 1-^{14}C-octanoate. Comparison of the ratio of ^{14}C and ^{3}H in the biosynthesised lipoate

with that of the labelled octanoate led Parry to conclude that the *pro-R*-hydrogen was removed from C-6. Therefore, assuming Mislow's deduction is correct (Section 1.3, reference 39), sulphur introduction takes place with overall inversion.

A rationale for these results evokes hydroxylation (with retention) of octanoate at C-6 and C-8 followed by activation and S_N2 displacement with a sulphur nucleophile. Formal replacement of hydroxyl by thiol is a well documented process *in vivo* , e.g. the conversion of serine into cysteine[47]. Bacteria are known to be capable of carrying out ω and ω-2, hydroxylations of fatty acids[48]. Thus this proposal seems quite reasonable[49].

Unfortunately, the above hypothesis is not supported by more recent work by White[50]. Lipoic acid biosynthesis is uninterrupted under anaerobic conditions (the proposed hydroxylation step requires the presence of molecular oxygen). Additionally, labelled 6-hydroxyoctanoate, 8-hydroxyoctanoate and 6,8-dihydroxyoctanoate are not incorporated into lipoic acid. The corresponding thiols however, were readily assimilated.

To account for these observations, White has proposed a "Knight type"[50] insertion of sulphur into the appropriate C-4 bonds of octanoate. Parallel studies on the conversion of dethiobiotin (48) to biotin (49) in *Aspergillus niger* and *E. coli* have given similar results[51]. However, in the latter instance sulphur is "inserted" with retention, whilst with lipoic acid the opposite apparently occurs. Since sulphur insertion with inversion



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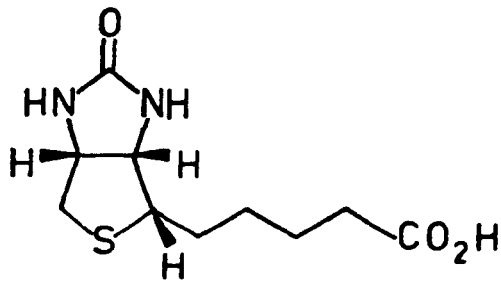

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has not been previously described either as an enzymatic step or *in vitro*, the operation of such a mechanism is controversial. An alternative explanation is that Mislow's assignment is wrong and natural (+)-lipoic acid actually has (*S*)-chirality. Then sulphur insertion would take place with retention, as with biotin. Thus, the unambiguous assignment of the absolute configuration of (+)-lipoic acid is necessary in order to eliminate this possibility.

1.5 THE BIOLOGICAL ROLE OF LIPOIC ACID

1.5.1 The Known Enzymatic Functions of Lipoic Acid

(a) General

Lipoic acid plays its established biochemical role as a covalently bound prosthetic group for all the α-ketoacid dehydrogenases, the enzymes which catalyse the oxidative decarboxylation of α-ketoacids to thioesters

of coenzyme A[52]. In addition, nicotine adenine dinucleotide (NAD^+), flavin adenine dinucleotide (FAD), thiamine pyrophosphate (TPP), coenzyme A (CoASH) and magnesium ions are required. The overall conversion of pyruvate to acetyl-CoA, effected by pyruvate dehydrogenase is summarised below.

$$CH_3COCO_2H + NAD^+ + CoASH \xrightarrow[Mg^{2+}\ FAD]{TPP\ lipoic\ acid} CH_3COSCoA + NADH + H^+ + CO_2.$$

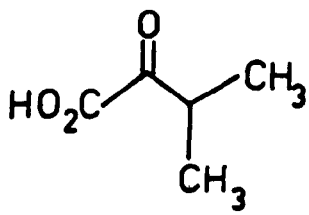
This reaction is the principle means of linking the two key metabolic pathways of glycolysis and the tricarboxylic acid (TCA) cycle. The latter pathway contains another lipoic acid dependent enzyme, α-ketoglutarate dehydrogenase, which performs the analogous oxidative decarboxylation of its substrate to succinyl-CoA.

$$HO_2C(CH_2)_2COCO_2H + NAD^+ + CoASH \xrightarrow[Mg^{2+}\ FAD]{TPP\ lipoic\ acid} HO_2CCH_2CH_2COSCoA + NADH + H^+ + CO_2.$$

Pyruvate and α-ketoglutarate dehydrogenases, as well as the other enzymes of the TCA cycle, appear to be restricted to the mitochondria of mammalian cells[53]. Distribution studies in other forms of life have not been carried out.

Other α-ketoacid dehydrogenases have been described. The oxidation of 3-methyl-2-oxobutanoate (50)

and (*R*)-2-methyl-2-oxopentanoate (51) by *S. faecalis* also require lipoic acid[54]. These transformations are involved in the metabolic degradation of the amino acids valine and isoleucine[52].



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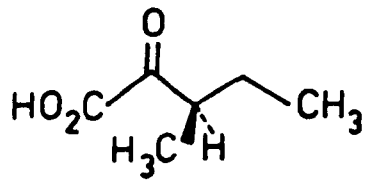

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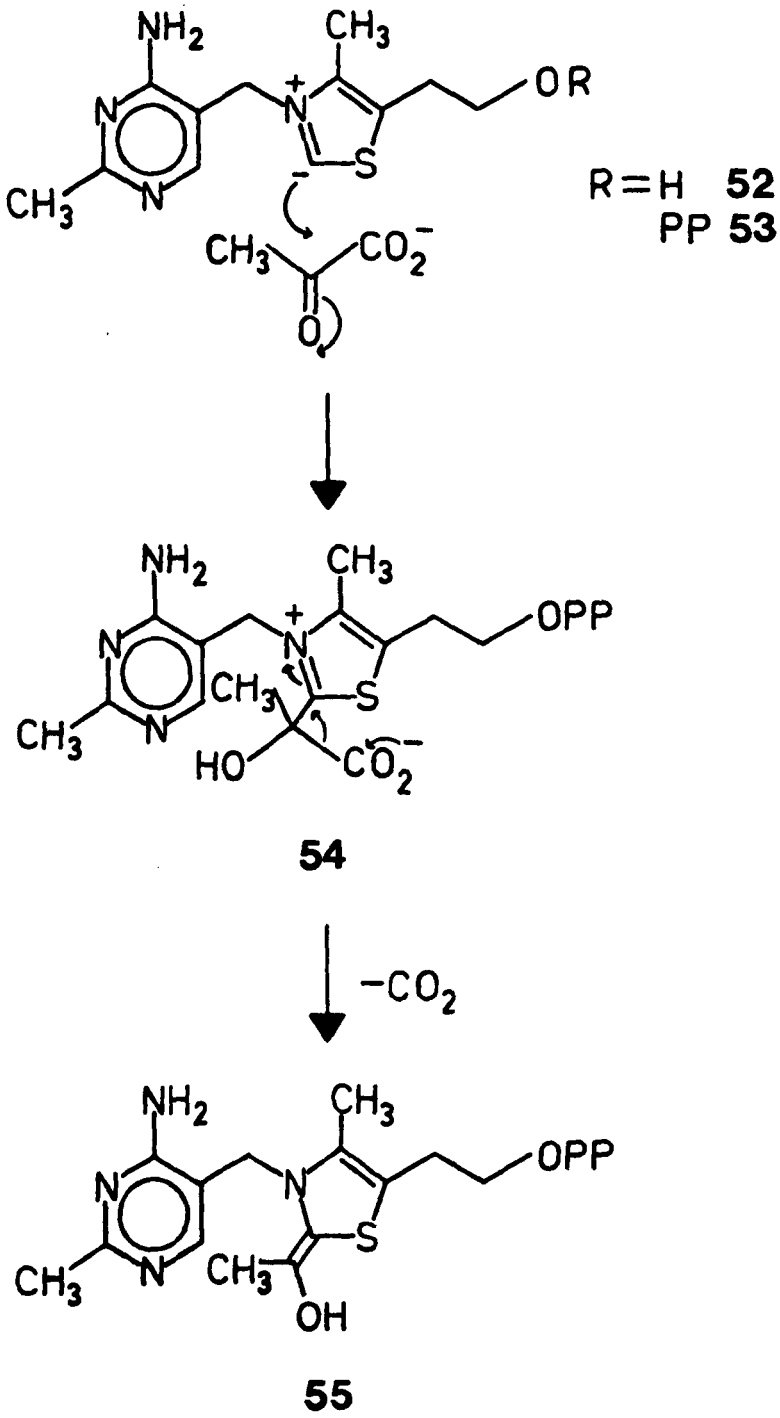
Elucidation of the structure and mode of action of pyruvate and α-ketoglutarate dehydrogenases has been a major feat of biochemistry[55]. Both are now known to be similar aggregates of three different component enzymes, an α-ketoacid decarboxylase, a lipoic acid reductase transacylase and a lipoamide oxidoreductase. The function of each, according to current ideas, will now be discussed in turn, taking pyruvate dehydrogenase multienzyme complex and its substrate as the example.

(b) Pyruvate Decarboxylase

This enzyme condenses pyruvate with thiamine pyrophosphate to give an "activated" acetaldehyde derivative in the presence of magnesium ions according to the equation below.

Figure 1.2



$$CH_3COCO_2H + TPP \xrightarrow{Mg^{2+}} CH_3CHO\sim TPP + CO_2$$

The TPP required for this step is not taken from solution but is tightly, though not covalently, bound to the enzyme, presumably near the active site[56]. In this way only a catalytic amount of TPP is required. The biosynthetic precursor of TPP is thiamine itself (protonated (52), vitamin B_1) whose deficiency in man is the cause of the disease beriberi[57].

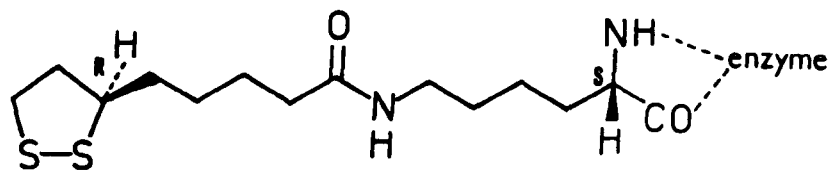
A number of hypotheses had been proposed concerning the site of pyruvate attachment to the TPP co-factor. The controversy was settled in 1958 by the thiazolium ylid mechanism (Fig. 1.2)[58]. Thus, the decarboxylation sequence is initiated by addition of pyruvate to the 2-position of the thiazolium ylid (53), (deprotonated TPP) to form the adduct (54). Collapse of the adduct (54) yields carbon dioxide and the so-called "activated" aldehyde or acylol (55).

This mechanism is supported by the chemical synthesis of 2-(α-hydroxyethyl)-thiamine, a protonated species of (55)[59]. More recently, the thiamine-pyruvate adduct as well as its pyrophosphate have been prepared[60].

(c) Lipoic Acid Reductase-Transacetylase

Lipoic acid reductase transacetylase is the only enzyme of the pyruvate dehydrogenase complex containing protein-bound lipoic acid. It has been demonstrated that lipoic acid is joined by an amide bond to the ε-amino group of certain lysine residues[61]. Thus,

N-(ε)-(+)-lipoyl-l-lysine (56) is the actual functional form participating in the following transformations. However, the sequences below were largely elucidated with substrate quantities of free lipoic acid[62].



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The title enzyme effects the overall synthesis of acetyl-coenzyme A from the acylol (55) and coenzyme A. A two stage process has been implicated involving lipoyl residues as the initial acyl acceptor[63].

(1) CH_3CHO~TPP + lipoic acid → TPP + 6-acetyldihydrolipoic acid + TPP

(2) 6-acetyldihydrolipoic acid + coenzyme A → acetyl-coenzyme A + dihydrolipoic acid

The first equation represents a redox reaction in which the C-2 unit is transferred with concomitant oxidation, whilst the disulphide bond of lipoic acid is reduced. Two mechanistic rationales are shown in Figs. 1.3 and 1.4. In the first of these (Fig. 1.3), the transient existence of acetyl-TPP (57) is postulated[64].

Figure 1.3

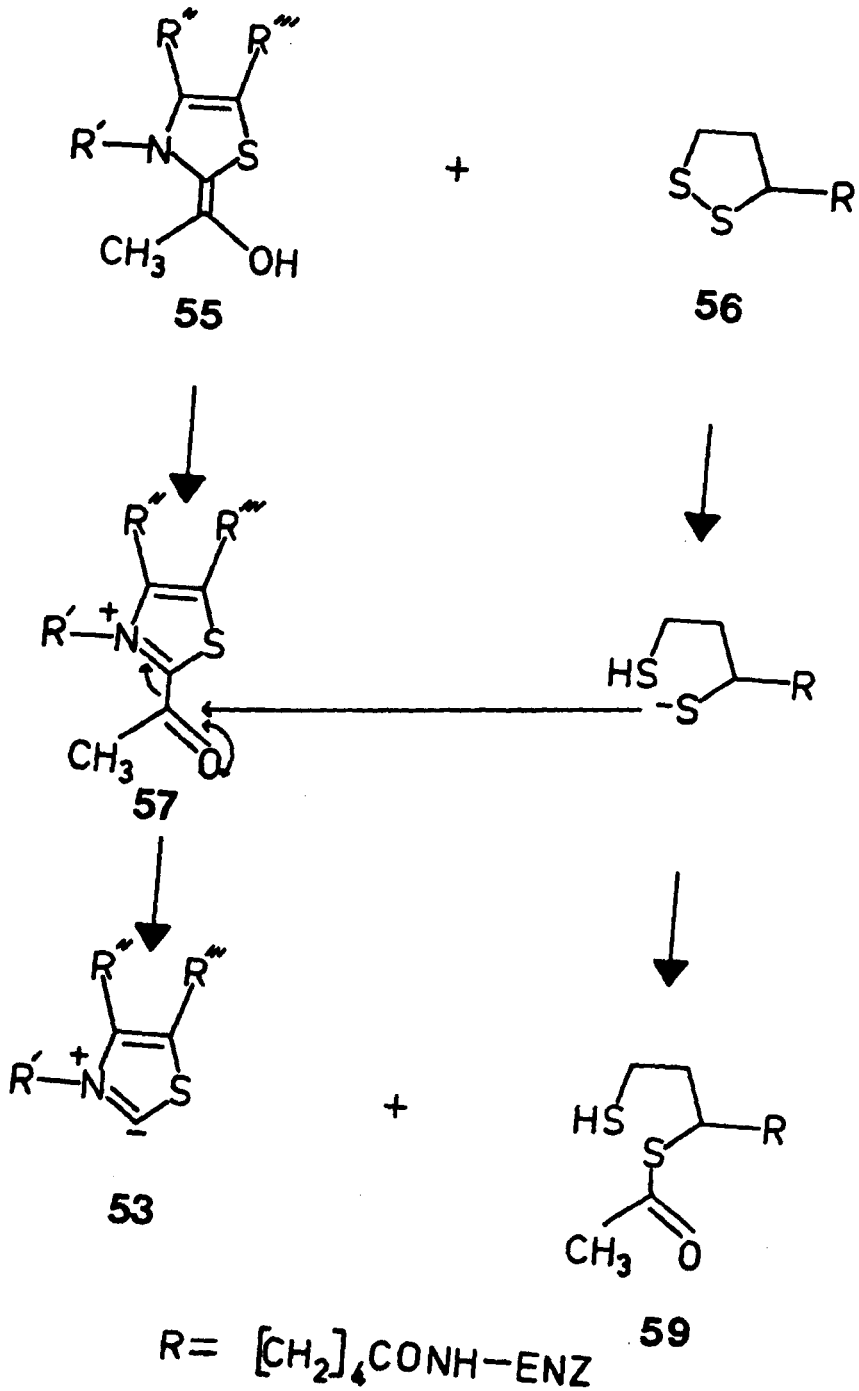
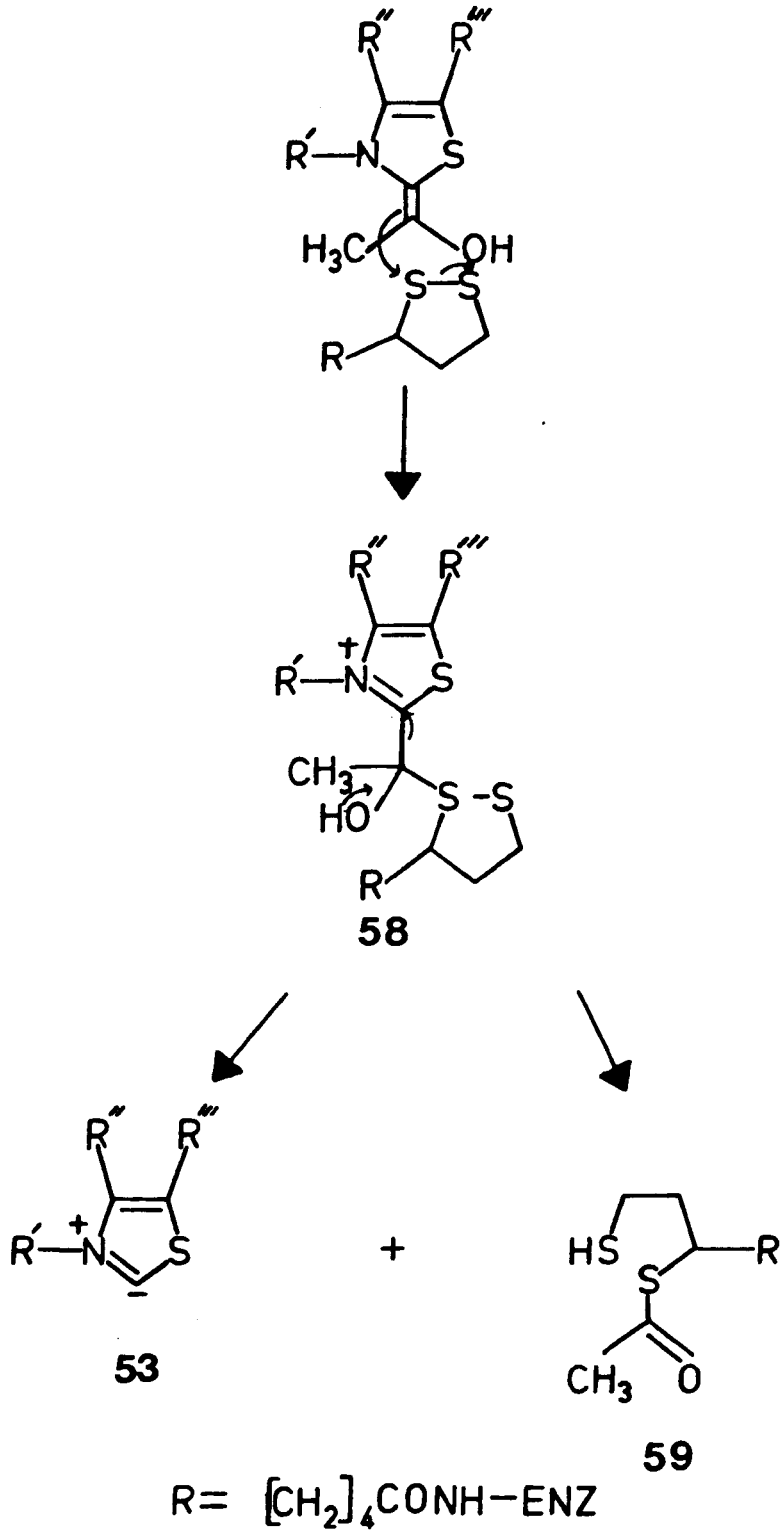
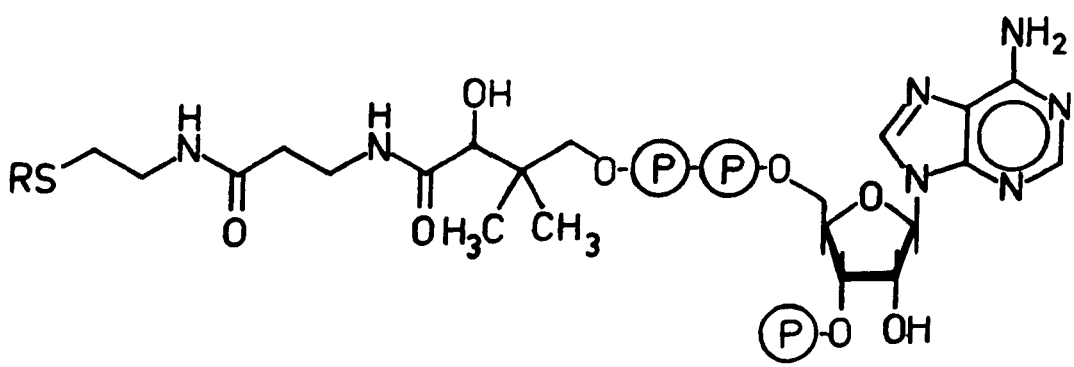

R''
R'''
R'
N
S
CH3
OH
55
+
S
S
R
56
R''
R'''
R'
+
N
S
CH3
O
57
HS
S
R
R''
R'''
R'
+
N
S
53
+
HS
S
R
CH3
O
59
R= [CH2]4CONH-ENZ

Figure 1.4



Model compounds corresponding to (57) are highly unstable, but exhibit the necessary reactivity towards thiols[65]. However, evidence for the formation of (57) *in vivo* remains to be demonstrated. Fig. 1.4 proposes direct nucleophilic attack of acylol (55) on lipoic acid at the more hindered sulphur atom, thereby rupturing the disulphide bond. The resulting tetrahedral intermediate (58) then breaks down to the ylid (53) and 6-acetyldihydrolipoic acid (59). Attempts to emulate this process *in vitro* have had very limited success[66]. These model experiments have revealed that the 1,2-dithiolane ring is only moderately reactive towards carbon nucleophiles. When attack does take place, it is predominantly (8:1 ratio) at the less hindered sulphur atom attached to C-8[67]. Clearly much has still to be learned about this step.

The second equation amounts to a reversible exchange of an acyl group between (59) and coenzyme A (60). The acetyl-CoA (61) formed then dissociates into solution, whilst the dihydrolipoic acid becomes the substrate for the third enzyme of the complex.



R= H **60** Ⓟ= phosphate
Ac **61**

(d) Lipoamide Oxidoreductase

The function of this enzyme is to reoxidise dihydrolipoic acid so that the acyl carrying cycle may be repeated, NAD^+ is concomitantly reduced during this process. From the results of extensive inhibition studies[68], a direct redox reaction between dihydrolipoic acid and NAD^+ can be ruled out. Evidence has accumulated for a three stage process summarised by the equations below.

(1) Dihydrolipoic acid + enzyme-disulphide $\rightleftharpoons$ lipoic acid + enzyme-dithiol

(2) Enzyme-dithiol + FAD $\rightleftharpoons$ $FADH_2$ + enzyme disulphide

(3) $FADH_2 + NAD^+ \rightleftharpoons FAD + NADH + H^+$

Hence, bound dihydrolipoic acid is supposed to be first oxidised by a cysteine disulphide bridge on the enzyme. The latter is regenerated on oxidation by an enzyme-bound FAD residue, whose reduced form, is in turn, oxidised by NAD^+. Finally, the NADH produced dissociates into solution.

(e) Structures of Pyruvate Dehydrogenase Multienzyme Complex

High resolution electron microscopy and delicate dissociation studies have yielded considerable information. The complex is held together by non-covalent bonds and is, under the correct conditions, self-assembling[69].

Multiple copies of pyruvate decarboxylase and lipoamide oxidoreductase are arranged around a core of lipoic acid reductase transacetylase subunits[70]. Overall, the complex possesses a regular, yet "open" structure, which is probably necessary for access by the bulky substrates. The molecular weight of pyruvate dehydrogenase isolated from *E. coli* has been estimated at 4.8 million (Daltons), approximately two thirds of which is the reductase transacetylase nucleus. Hybridisation experiments with the components of pyruvate and α-ketoglutarate dehydrogenases have been attempted[71]. Only the lipoamide oxidoreductases are interchangeable, and may even be identical in both complexes.

Perhaps the most interesting feature of the α-ketoacid dehydrogenases is the ability of bound lipoic acid to interact with the active sites of all three substituent enzymes. Although many explanations have been forwarded, most are unsubstantiated by experimental work. Recently, however, Roberts and his co-workers[72] have examined both intact pyruvate dehydrogenase and lipoic acid reductase-transacetylase by high resolution ^{1}H n.m.r. spectroscopy. Their studies suggest that the areas of polypeptide chain to which the lipoic acid residues are attached exhibit exceptional conformational mobility, with their structure pertaining to that of a random coil. Thus, one may imagine that the lipoyl residues are attached to the end of a long flexible polypeptide "arm" which can reach the various active sites on the complex. This idea is depicted below in Fig. 1.5.

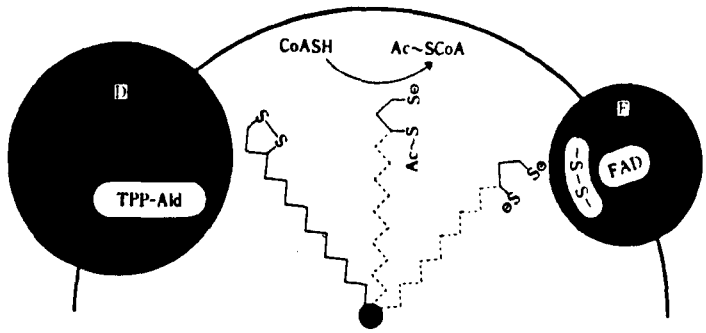


Fig. 1.5

(f) Relevance of α-Ketoacid dehydrogenases in Metabolism

The title enzymes provide the cell's principle entry to the thiolesters of coenzyme A. The latter compounds are of monumental importance because of their ability to act as acylating agents. This property is directly attributable to the low resonance energy of thiolesters[73].

Hence acetyl-CoA may be condensed with oxaloacetate to afford citrate (the first step of the TCA cycle) or may be used as the C-2 building block in the biosynthesis of fatty acids, terpenes, steroids and numerous other molecules. Succinyl-CoA is equally important, but has fewer metabolic fates, the principle two being hydrolysis to succinate (another reaction of the TCA cycle) and conversion into porphobilinogen, precursor to porphyrins, chlorophylls and vitamin B_{12}. Since the TCA cycle is also the predominant means of generating adenosine-5'-triphosphate (ATP), the major energy

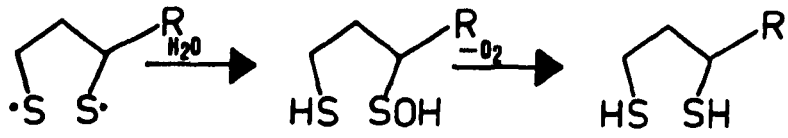
currency of the cell, in aerobic organisms (*via* oxidative phosphorylation), the importance of these thiolesters in both anabolic and catabolic pathways may readily be appreciated[74].

There are sound reasons why the cell should choose this elaborate, indirect method of thiolester generation, rather than directly condensing coenzyme A with the appropriate carboxylic acid. Enzymes known as thiokinases do exist which effect the latter process. However, thiolester formation *in vivo* requires prior activation of the carboxylic acid as an acyl phosphate before reaction with a thiol will proceed. Hence a molecule of ATP is consumed. This reaction is reversible, and so the hydrolysis of a thiolester may be used in substrate level phosphorylation ($ADP + {}^{i}P \rightarrow ATP$). Accordingly, the aforementioned hydrolysis of succinyl-CoA by succinate thiokinase is employed to drive the synthesis of guanosine triphosphate (GTP) from the diphosphate and inorganic phosphate.

By contrast, the α-ketoacid dehydrogenases, by exploiting the facile redox reaction of lipoic acid, avoid this situation. For every mole of acyl-CoA produced, 1 mole of $NADH(+H^{+})$ is also made. The latter is convertible to 3 moles of ATP *via* oxidative phosphorylation. Therefore, energetically, it is in the cell's best interest to utilise its α-ketoacid dehydrogenases to maximum effect.

1.5.2 The Suggested Role of Lipoic Acid in Photosynthesis

In 1954, Barltrop, Hayes and Calvin suggested that lipoic acid was a vital intermediate in the conversion of light to chemical energy during photosynthesis[76]. Incorporation of ^{35}S-lipoic acid into green algae led to the characterisation of biologically active compounds, suggesting the participation of this compound in the Hill reaction. The arsenite sensitivity of the Hill reaction as catalysed by chloroplast preparations from spinach leaves, implied involvement of dihydrolipoic acid somewhere in the reaction sequence. It was proposed that excited chlorophyll induced the homolysis of the disulphide bond of lipoic acid to give the dithiyl radical (62). This subsequently reacted with water to furnish the unstable thiosulphenic acid (63), disproportion of which led to oxygen and dihydrolipoic acid (Fig. 1.6). The latter was initially suggested as the direct reducing agent for carbon dioxide for the conversion into a sugar. This idea gained some support from *in vitro* studies on the photochemistry of lipoic acid and other 1,2-dithiolanes[75], but was unsubstantiated in biochemical work. Bradley and Calvin later modified their scheme to include reduced pyridine dinucleotides[77]. However, other investigations have produced conflicting results[78] and there is no unequivocal evidence to support Calvin's hypothesis.



62 **63** **11**

R= $CH_2CH_2CH_2CH_2COOH$

Fig. 1.6

1.5.3 The Suggested Role of Lipoic Acid in Oxidative Phosphorylation

Oxidative phosphorylation is another key metabolic process. The mechanism by which electron transport and the synthesis of ATP are linked is crucial to the understanding of this process. From 1976 onwards Griffiths and his co-workers[79] have been investigating the possible involvement of lipoic acid. Apparently, high concentrations of bound lipoic acid have been detected in the enzyme ATP-ase which is a component of the assembly which carries out oxidative phosphorylation. Additionally, 8-methyllipoic acid (1,2-dithiolane-3-methyl-5-pentanoic acid) has been observed to competitively inhibit this enzyme[80]. To explain their results, these researchers have proposed a modified version of the chemical coupling hypothesis in which lipoic and oleic acids participate[81].

1.6 THE PHARMACOLOGY OF LIPOIC ACID

Appreciation of the important biochemical role of lipoic acid provided impetus for exploration of its pharmacological potential[82]. Early studies revealed that lipoic acid was an essentially non-toxic, vitamin-like substance. Accordingly, attention was directed towards its effect on animal nutrition. Initial reports were promising[83], but subsequent work has been unable to reproduce these earlier results[84]. Similar controversy surrounds the use of lipoic acid in the treatment of various liver diseases[85].

The effectiveness of lipoic acid as a remedy for poisoning by the mushroom *Amanita phalloides* is well documented[86]. However, administration of the steroid prednisolone has been shown to be a better therapy[87].

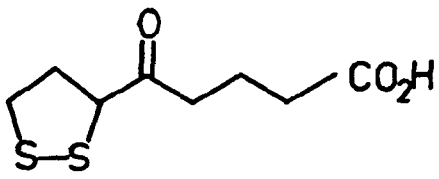
Lipoic acid has been successful in reversing the effects of numerous experimentally induced instances of heavy metal poisoning in animals[88]. However, its application as a therapy for such ailments in man has so far been limited. Reduction to the dithiol form (dihydrolipoic acid) occurs readily *in vivo* generating an excellent chelator for heavy metal ions (soft-soft interaction). The co-ordination chemistry of lipoic acid has recently been reviewed[89].

1.7 DERIVATIVES OF LIPOIC ACID

In spite of extensive chemical modifications attempted since its structure was elucidated, no analogue has been found to exceed the biological activity of lipoic acid. However, several antagonists have been found during the course of these studies. The effect on the growth of *S. faecalis* (strain 8043) was the method mainly employed to assess the biological activity of the compounds[90].

Analogues in which the methylene groups in the chain between the carboxy group and the 1,2-dithiolane ring had been replaced by heteroatoms were virtually inactive[91]. Substitution of a methyl group in the carbon backbone produced an inhibitory effect[92]. Incorporation of a keto-moiety (5-keto-lipoic acid (64)) gave a completely inactive compound[93]. Further C-substitution on the 1,2-dithiolane ring furnished several growth inhibitors, e.g. 7-methyllipoic acid (65), 7-hydroxylipoic acid (66) and 8-methyllipoic acid (67). Alterations to the ring size or position of the disulphide bridge (e.g. 2,4-lipoic acid (68) again led to loss of activity[92]. Some studies with lipoic acid analogues and preparations of lipoamide oxidoreductase have also been reported[94].

Lipoic acid is not the only naturally occurring molecule which has a 1,2-dithiolane ring. Other formal derivatives of 1,2-dithiolane include the alkaloid brugine (69) obtained from the bark of the mangrove tree *Bruguira sexangula*[95], the neurotoxic compound



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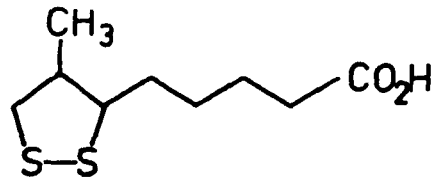

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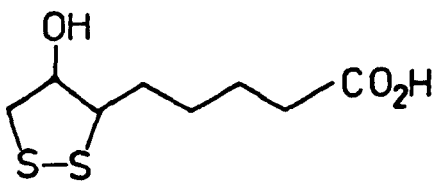

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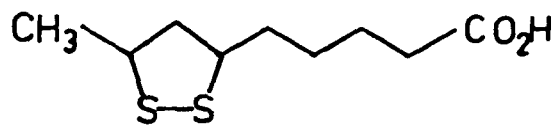

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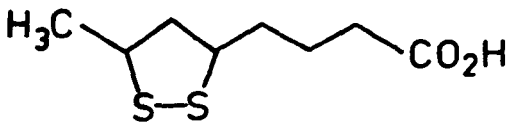

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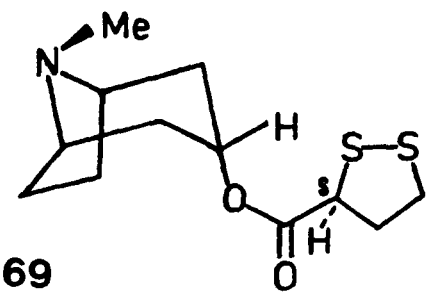

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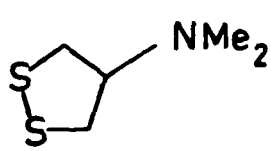

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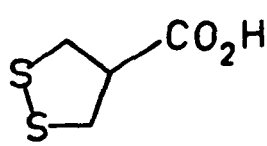

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nereiotoxin (70) from a marine worm[96] and the acid (71) from asparagus[97]. These compounds are all rather specialised secondary metabolites of restricted occurrence. Although their respective biological roles have not received much attention, it is unlikely that any are connected with the biological function(s) of lipoic acid.

1.8 CONCLUSION

In order to gain more information about both the established and postulated biochemical roles, the stereochemistry involved in the biosynthesis, the absolute configuration of the natural enantiomer and a clearer evaluation of the pharmacological potential of lipoic acid, a convenient synthesis of the pure, optically active forms is required. We have embarked on such a synthesis with a view to extending the approach developed to any interesting analogues of this compound.

Chapter 2

Materials, Methods and Instrumentation

2.1 MATERIALS

2.1.1 Solvents

Ethyl acetate, 40-60° petrol and 60-80° petrol were redistilled; benzene and toluene were dried over sodium and then redistilled before use. Dichloromethane, 1,1,1-trichloroethane, carbon tetrachloride and 1,1,2-trichlorotrifluoroethane were distilled from phosphorous pentoxide. Chloroform was obtained ethanol-free by percolation through a column of basic alumina. Dry acetone was prepared by desiccation of the AnalaR grade with boric oxide followed by distillation. Diethyl ether was dried over lithium aluminium hydride and distilled as required. Tetrahydrofuran (THF) was first dried with calcium hydride, distilled, and then redistilled from sodium-benzophenone ketyl. N,N-Dimethylformamide (DMF) was distilled from calcium hydride onto 4A molecular sieves. Ethanol and methanol were dried by reaction with magnesium metal and then distilled onto 3A molecular sieves. Pyridine and triethylamine were redistilled from potassium hydroxide pellets and stored over 4A molecular sieves. The recent publications of Burfield, Smithers *et al.*[98] were found most useful in choosing the best desiccation procedure for a particular solvent.

2.1.2 Reagents

The magnesium turnings used for the preparation of Grignard reagents was a commercially available grade specified as being suitable for this purpose. Lithium tetrachlorocuprate was prepared by dissolving 2 equivalents of oven dried anhydrous lithium chloride and 1 equivalent of anhydrous copper(II) chloride in THF. The resulting orange solution was either stored at -20°C under nitrogen or used immediately. All other reagents used were of the highest purity commercially available. Literature purification was followed when ever occasion demanded[99,100].

2.2 METHODS

(a) Glassware required for moisture sensitive reactions was dried in an oven at 110°C overnight, assembled whilst still hot and allowed to cool in an inert atmosphere. The inert atmosphere was provided by allowing commercial nitrogen gas (British Oxygen Company) to pass through a column of active "Drierite" ($CaSO_4$) prior to entering the apparatus. Oxygen sensitive reactions were maintained under a static atmosphere of nitrogen after initial flushing.

(b) Commercial grades of "anhydrous" magnesium sulphate, potassium carbonate and sodium sulphate were used to dry solutions in organic solvents. The choice of drying agent was governed by the nature of both solute

and solvent[101]. Removal of bulk solvent was carried out at reduced pressure (10-15 mmHg) with a Büchi rotary evaporator unless otherwise stated.

(c) Analysis of reaction mixtures by thin layer chromatography (t.l.c.) was carried out using Merck aluminium-backed Kieselgel plates (Silica gel 60, F_{254}, 0.2 mm thickness). Both u.v. and iodine vapour were used to visualise spots. For preparative work (p.l.c.) glass plates 20 x 20 cm were covered by a slurry of Merck F_{254} Silica gel 60 in water to a depth of 1 mm. Having allowed most of the water to evaporate, the prepared plates were then activated by heating to 110°C overnight. Flash column chromatography was carried out using Kieselgel 60H (Merck). All solvent ratios quoted in conjunction with these methods refer to volumes.

(d) The molarity of sodium amylate in amyl alcohol or potassium *t*-butoxide in *t*-butanol was determined by titration against 1 M hydrochloric acid with phenolphthalein as indicator.

(e) Solutions of borane and 9-BBN in THF, as well as borane-dimethyl sulphide complex in dichloromethane, had their hydride content quantitatively determined by a hydrolysis method published by the Aldrich Chemical Company[102].

(f) The naming of chemicals in this thesis is in

accordance with the systematic I.U.P.A.C. rules and the guidelines in the Journal of the Chemical Society's "Instructions for Authors". However, where a simpler, more widely known name can be substituted without ambiguity, it has been used in preference, e.g. acetic acid instead of ethanoic acid.

2.3 INSTRUMENTATION

(a) Nuclear Magnetic Resonance Spectroscopy (n.m.r.)

Except where stated to the contrary, all proton spectra were recorded on a Perkin-Elmer model R34 spectrometer operating at 220 MHz. Samples were prepared by dissolving 20-50 mg of compound in 0.5 cm^3 of solvent. A small amount of TMS (with organic solvents) or TSS (with deuterium oxide) was then added as internal standard. Recorded peaks are specified by:

(1) Chemical shift (δ) measured in parts per million (p.p.m.) relative to TMS or TSS.

(2) The number of protons, determined by integration.

(3) The multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, unresolved resonance, dd = double doublet, dt double triplet, etc.).

(4) The spin coupling constant (J) measured in Hertz, quoted where appropriate.

(5) The structural assignment.

(b) Infrared Spectroscopy (i.r.)

A Perkin-Elmer grating spectrophotometer model 257 was used to record all infrared spectra. Sodium chloride plates or cells were used throughout. The spectral data is preceded by ν followed by the method of sample preparation, i.e.

(1) film: as the neat liquid

(2) Nujol: as a mull in paraffin

(3) HCB: as a mull in hexachlorobuta-1,3-diene

(4) Soln, solvent (named): as a solution in a specified solvent, e.g. soln (CCl_4).

Peaks are designated by their wavenumber (cm^{-1}) and their intensity given as (br = broad, s = strong, m = medium, w = weak, sh = shoulder). Each spectrum was calibrated by the polystyrene standard at 1603 cm^{-1}.

(c) Mass Spectroscopy (m.s.)

All mass spectra were recorded in a Kratos MS80 spectrometer. Spectra were produced by either, e.i. (electron impact) or c.i. (chemical ionisation). Ammonia was the reagent gas in the latter case unless otherwise stated. Peaks are quoted as *m/z* followed by their percentage relative to the most abundant ion. The molecular ion is designated as M^+.

(d) Optical Rotation

A Bendix model NPL 143D automatic polarimeter was employed to measure all optical rotations using a 1.00 cm x 0.708 cm^2 cell. Values are expressed as

specific rotations ([α]). The calibration of the instrument was checked against a standard sucrose solution before inserting each sample.

(e) Circular Dichroism (c.d.)

The circular dichroism spectra were run by Dr. P. M. Scopes at Westfield College, University of London using a Cary 6 instrument.

(f) Melting Points (m.p.)

All melting points are uncorrected. A Gallenkamp instrument or a Reichert hot microstage apparatus were used throughout.

(g) Combustion Analysis

Analyses for carbon, hydrogen, nitrogen and sulphur were performed at the laboratories of Elemental Micro-Analysis Limited (EMAL), Bleaworthy, Devon.

(h) High Performance Liquid Chromatography (h.p.l.c.)

H.p.l.c. analyses were performed using a Waters instrument equipped with variable wavelength u.v. detector and a Partisil column. The hexane used as eluent was obtained from Rathburn Chemicals Ltd.

(i) Ultraviolet Spectroscopy (u.v.)

The u.v. spectra mentioned in this thesis were determined on a Unicam SP800 spectrophotometer. "Spectrograde" solvents were used to make up the sample solutions.

Chapter 3

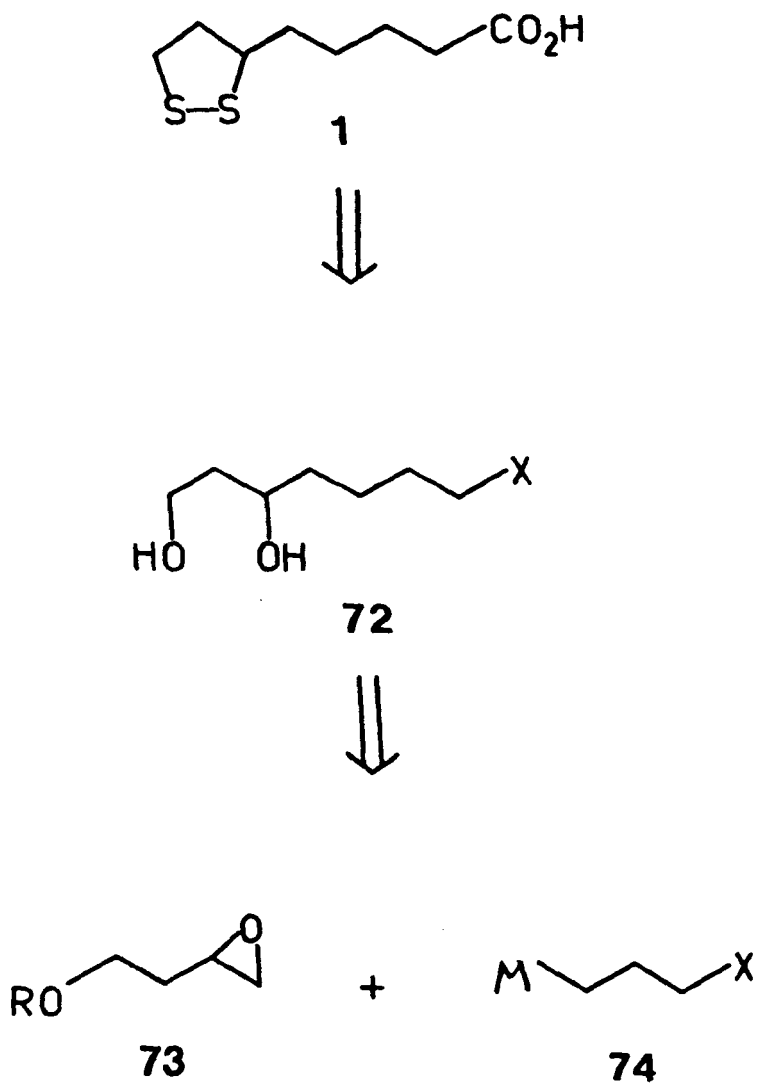
The Synthesis of (R)- and (S)-(2-Benzyloxyethyl)oxirane

3.1 INTRODUCTION

Our approach to the synthesis of the pure enantiomers of lipoic acid was initiated during a previous project at Warwick University (Scheme 3.1)[103]. Working backwards from the structure of the target molecule[104], it was envisaged that a derivative of 6,8-dihydroxyoctanoic acid (72) would be a key intermediate. Conversion of chiral 1,3-diols into the corresponding 1,2-dithiolanes in a stereospecific fashion has been demonstrated previously[105] and was therefore considered a trivial step. Thus, the success of the synthesis depends on obtaining the pure enantiomers of (72). It was intended to make (72) by coupling two 4-carbon units in order to assemble the required eight-carbon skeleton with correct location of the functionalities.

One of these 4-carbon units was to be a chiral epoxide of general structure (73) with a protected hydroxyl group located β- to the asymmetric centre. Epoxide (73) was to be derived from a member of the chiral pool[109] (cheap, optically active, natural products) by a series of stereospecific reactions. The other 4-carbon fragment (74), was to be a terminal halide with a group convertible into a carboxylic acid sited at the other end of the molecule. Reaction of (73) with an organometallic derivative of (74) would then furnish a suitable chiral eight-carbon

Scheme 3.1



M = Metallic entity

R = Hydroxyl protecting group

X = Carboxylic acid protecting group

precursor of (72).

Although Grignard and organolithium reagents readily attack epoxides, the strongly basic nature of these organometallics can often cause complications[106,107]. It was therefore planned to use a "softer" organocopper derivative of (74) for this step. The organocopper reagent would be most conveniently generated *in situ* from the lithium or magnesium organometallic and lithium tetrachlorocuprate in THF. At -78°C the organocopper reagents attack epoxides much faster than the precursor organometallics. Furthermore, if these low temperatures are employed, only a catalytic quantity of the inorganic copper salt need be present for good yields of the desired product to be obtained[108].

The reaction of epoxides with organocopper reagents made in this way has been shown to be regiospecific (i.e. attack occurs exclusively at the less hindered, terminal carbon of the oxirane)[108]. Therefore this coupling reaction does not affect the chirality of the asymmetric centre, although a change in group priority may occur and therefore the *R/S* assignment alters. During the conversion of (72) into the target molecule a formal S_N2 displacement of the hydroxyl moiety by a sulphur nucleophile must occur at C-6. Hence the *R/S* assignment of an enantiomer of lipoic acid will be the same as that of the epoxide (73) used to make it.

(2-Benzyloxyethyl)oxirane (94) was conceived as a suitable masked chiral 1,3-diol (corresponding to epoxide (73)) which would ultimately give the 1,2-dithiolane

ring of the target molecule. During previous work, related to the topic of this thesis, D. A. Howes[103] pioneered the synthesis of (*S*)- and *rac*-(94) from the corresponding forms of malic acid.

This earlier work forms the basis for the subject of this Chapter. Whilst the original route was reproducible, there was scope for considerable improvement. Detailed herein is an account of experiments performed in order to optimise that sequence. The outcome of the present work has been a marked increase in overall yield as well as greater practical convenience in some of the steps[110]. An inversion procedure[111] to give (*R*)-(94) has also been introduced. This is important because (*R*)-(94) is the precursor to (*R*)-lipoic acid (the supposed natural enantiomer)[39] by our methodology. The high price of commercial (*R*)-malic acid[112] prevented its consideration as a starting material for (*R*)-(94), necessitating the use of its antipode instead. Racemic (94) was required to try out potential routes to the target molecule. Accordingly, a novel, 4-step route from allyl bromide was devised which provided relatively large quantities of material both easily and quickly.

3.2 (*S*)-MALIC ACID TO (*S*)-BUTANE-1,2,4-TRIOL

3.2.1 Esterification of (*S*)-Malic Acid

Before use, every batch of (*S*)-malic acid (75) had its optical rotation and m.p. checked. In all cases

the values obtained by either criteria were consistent with the manufacturer's specifications[113]. The material was therefore used as provided.

In principle, (*S*)-(75) can be reduced to (*S*)-butane-1,2,4-triol (82) in one step. Both lithium aluminium hydride and complexes of diborane are known to reduce free carboxylic acids to primary alcohols. However, it was expected that incomplete reduction would occur due to the relative insolubility of starting material (*S*)-(75) and product (*S*)-(82) in solvents suitable for this reaction, e.g. tetrahydrofuran. Therefore, no attempt was made to carry out the reduction in this way.

Thus, (*S*)-(75) was first converted into a diester to facilitate its reduction. The diethyl ester (*S*)-(76) was prepared by a standard procedure[103,114]. This involved the removal of the water of reaction by distilling out the ternary azeotrope formed with ethanol and toluene (b.p. 75°C), in order to drive the esterification equilibrium towards the product. Although efficient (78-83% yield of distilled material), the azeotrope took a long time to distil out, resulting in the need for prolonged heating (several hours). The consequence of the latter was promotion of the acid catalysed dehydration of (*S*)-(76) to give diethyl fumarate (Fig. 3.1).

The presence of fumarate was shown by the characteristic olefinic resonance at δ 6.74 in the 220 MHz ^{1}H n.m.r. spectrum. Although the presence of 5-7% (by integration) of this impurity was not particularly deleterious, it was obviously better if its formation

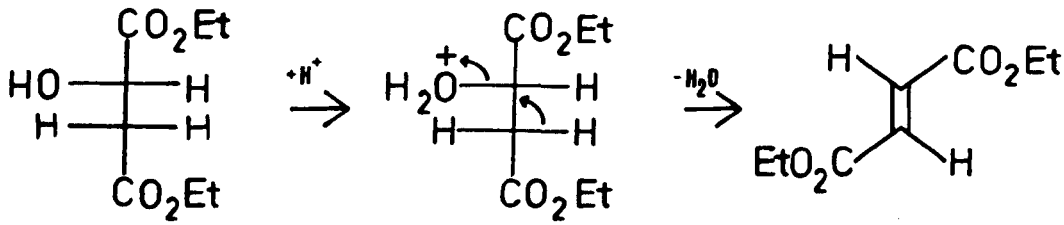


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Fig. 3.1

could be avoided.

The problem was solved by adopting the alternative procedure of Mori *et al.*[115]. Here, (*S*)-dimethyl malate (77) was prepared by two-pass dissolution of (*S*)-(75) in 3% methanolic hydrogen chloride in 86%(total)yield. Analysis by high resolution ^{1}H n.m.r. spectroscopy of distilled (*S*)-(77) showed no olefinic resonances, even at high sensitivity, indicating there was ≤ 2% dimethyl fumarate present.

3.2.2 Direct Reduction of Malate Diesters

Originally, D. A. Howes[103] employed the procedure of Nakanishi *et al.*[116] to reduce (*S*)-(76) to triol (*S*)-(82). Although this method was also reproduced by the author, the work-up was found to be particularly tedious and constituted a synthetic bottleneck in the route.

The reduction itself was straightforward, the diester being added to a suspension of lithium aluminium hydride in THF which was subsequently refluxed overnight. Addition of water produced the usual insoluble aluminate filter-cake from which a product can normally be washed off with more solvent. However, as a consequence of the polarity and tridentate nature of triol (*S*)-(82), this compound preferred to cling to these residues rather than dissolve in THF. The literature procedure[116] addressed this problem by washing the filter-cake with methanol in which (*S*)-(82) is very soluble. Such treatment also leached out copious inorganic materials to the extent that a "paste" containing (*S*)-(82) was obtained after evaporation of the solvent. The inorganic materials were removed by short column chromatography on silica gel, triol (*S*)-(82) being eluted with ethanol:chloroform mixtures. For best results, the column had to be run slowly and large quantities of solvent consumed. This placed an upper limit on the column size, which in turn restricted the amount of diester (*S*)-(76) reducible at one time. Preparations on the 100 mmol scale (of (*S*)-(76)) proved to be satisfactory, but attempts to do the reaction on a larger scale inevitably led to problems with the column, resulting in drastic reductions in yield.

It appeared that the main inorganic contaminant of crude (*S*)-(82) was lithium hydroxide. The "pastes" were found to be alkaline to litmus and gave a positive flame text for lithium. Having identified the problem, it was decided to use a less polar alcohol for the

extraction (propan-2-ol) and convert the lithium salt present into the less soluble sulphate.

The reduction was carried out as before, but the filter-cake was washed with water, and the resulting aqueous-THF solution was concentrated. 1 M Sulphuric acid was then added to bring the mixture to pH 7. The neutral solution was evaporated to dryness, giving a solid residue, from which (*S*)-(82) was extracted with propan-2-ol. Filtration, evaporation and distillation furnished (*S*)-(82) free of inorganic salts and sufficiently pure for the next step. Attempts to distil (*S*)-(82) directly out of the inorganic pastes in a Kugelröhr apparatus gave a low recovery of product which was heavily contaminated with impurities.

This modification increased the yield of (*S*)-(82) from 50 to 58%. As no column chromatography was involved, reductions on a larger scale [200 mmol of (*S*)-(76)] could now be performed.

Reduction of esters by sodium or potassium borohydride is normally too slow to merit practical application. However, it has been shown that when a carboalkoxy group is situated α- or β- to a free hydroxyl functionality the rate of reaction is enhanced[117]. This effect depends on an intramolecular interaction[118] between the borohydride anion and the hydroxyl group. It is probable that not only is a more active reducing species (an alkoxyborohydride) formed, but also the proximity of this moiety to the carboalkoxy group considerably increases the probability of hydride transfer.

Barnett and Kent[119] have reported the formation of (*S*)-(82) by treatment of (*S*)-(77) with potassium borohydride in ethanol. The use of a milder reagent for the large scale reduction of (*S*)-(76) or (*S*)-(77) seemed an attractive idea. Additionally, no precipitate was formed on work-up, the boron residues being treated with acidified (hydrogen chloride) methanol and removed by azeotropic distillation as trimethyl borate (b.p. 55°C). The potassium salts were converted into the chloride whose presence would not be expected to interfere seriously with the isolation of (*S*)-(82). The principle disadvantage was that this procedure[119] gave a low yield (25%) of the triol. It was hoped that the yield could be increased by extending the reaction time from 6 to 20 hours, whilst using the more soluble (in ethanol) sodium borohydride in 4 instead of 1.5 equivalents, added in equal portions every 3 hours. Unfortunately, these measures were only moderately effective, an improvement of only 11% being achieved. Further increases in reaction time were not feasible because of the slow decomposition of sodium borohydride in ethanol.

The penultimate step in the work-up was extraction of crude *rac*-(82) with ether to remove lipophilic impurities. These washings were evaporated and examined by ^{1}H n.m.r. and i.r. spectroscopy. Unreacted *rac*-(77) appeared to be the chief constituent which was confirmed by t.l.c. with an authentic sample. The technique showed the presence of another slower moving spot which was reasoned to be methyl 3,4-dihydroxybutanoate. This

compound was formed because of a difference in the rates of reduction of the carboalkoxy groups α- and β- to the hydroxyl function. It is of interest to note that (2*R*,3*R*)-dimethyl tartrate was converted into (2*R*,3*R*)-threitol in 71% yield[120] using a very similar procedure, suggesting the specific dependence on the presence of an α-hydroxyl group for efficient reduction.

Reaction of (*S*)-(77) with lithium borohydride was also considered. This compound is more reactive than the corresponding sodium or potassium salt and is able to reduce ordinary esters. The principle reason for the difference lies with the lithium ion's ability to polarise carboalkoxy groups (hard-hard interaction), thereby facilitating hydride attack. Additionally, the greater covalent character of lithium borohydride makes it more soluble in THF, where the borohydride anion is less solvated and hence can exert a greater reactivity than when dissolved in ethanol. Lithium borohydride may be generated *in situ* by metathesis from sodium borohydride and lithium chloride[121,122]. Use of this reagent was discounted on the grounds that lithium salts would again contaminate the triol (*S*)-(82) necessitating a return to column chromatography for purification.

Because of the failure to improve Barnett and Kent's procedure[119] attention returned to reductions by lithium aluminium hydride.

3.2.3 Reduction of Malate Diesters *via* Hydroxyl Protecting Groups

An alternative remedy to the problems associated with the polarity of triol (*S*)-(82) would be to avoid its formation during the reduction. If the hydroxyl group of (*S*)-(76) or (*S*)-(77) were protected, then a less polar 2-substituted-butane-1,4-diol would arise. Furthermore, the choice of a very lipophilic protecting group would allow the diol to be more easily extracted by organic solvents. Blocking the hydroxyl function would also save a quarter of an equivalent of lithium aluminium hydride - a factor of increasing importance as the scale of the preparation becomes larger. The desirable properties of protecting groups[123] are summarised below:

(a) The protection and deprotection steps should proceed in high, preferably quantitative yield under as mild and specific conditions as possible.

(b) The protecting group must be stable under the conditions of the reaction(s) for which it is employed. In this case attack by hydride and the basic conditions incurred during the work-up.

(c) The cleaved protecting group should be easy to separate from the product.

(d) The protecting group should not introduce a chiral centre into the substrate.

Enol ethers are suitable candidates fulfilling

criteria (i-iii), as well as imparting considerable lipophilic character to the molecules to which they are attached. These reagents form mixed acetals with their substrates. The acetals are both made and cleaved under acidic catalysis. Whilst formation of a protected (*S*)-(77) and deprotection to liberate (*S*)-(82) are two additional steps, it was hoped that an improved overall yield [(*S*)-(77) to (*S*)-(82)], and the greater practical convenience incurred would justify such an undertaking. The strategy is shown in Scheme 3.2.

The tetrahydropyranyl group has been extensively employed as a protecting group for the hydroxyl function[124-126]. Early attempts[127] to protect malate diesters by reaction with 2,3-dihydropyran in the presence of acid gave only moderate yields. However, Mori *et al.*[115] were later able to achieve a quantitative conversion simply by extending the reaction time from 4 to 20 hours.

The (*S*)-2-THP-dimethyl malate (78) formed in this reaction was reduced to (*S*)-2-THP-butane-1,4-diol (79) by reaction with a suspension of lithium aluminium hydride in ether. After work-up, the filter-cake was washed with warm (35^{o}C) THF to extract the diol (*S*)-(79) which was obtained in 82.7% yield. Dissolution of (*S*)-(79) in acidified methanol led to transacetalisation with the solvent, giving triol (*S*)-(82) and *rac*-2-methoxytetrahydropyran. Removal of this latter by-product and solvent by evaporation after neutralisation, furnished a residue of crude (*S*)-(82), purified by distillation. An overall yield

of 70.2% [(*S*)-(77) to (*S*)-(82)] was realised (lit.[115], 82%). One disadvantage of the tetrahydropyranyl protecting group is the introduction of an additional chiral centre. This manifests itself in the complex ^{1}H n.m.r. spectra of (*S*)-(78) and (*S*)-(79) due to the overlapping resonances of the two diastereoisomers. In order to check whether formation of (*S*)-(78) from (*S*)-(77) and reduction of (*S*)-(78) to (*S*)-(79) had gone to completion, i.r. spectroscopy was employed. The presence of free hydroxyl at 3400 cm^{-1} and ester carbonyl stretch at 1735 cm^{-1} were respective signs of incomplete reaction.

An alternative protecting group for malate diesters has been disclosed by Seebach and co-workers[128]. The opportunity was taken to compare Seebach's method[128] with the preceding one[115] to establish which was the better procedure. Diester (*S*)-(77) was dissolved in ethyl vinyl ether in the presence of catalytic acid to give (*S*)-dimethyl 2-(1-ethoxyethoxy)succinate (80) quantitatively. Reduction of this with lithium aluminium hydride gave (*S*)-2-(1-ethoxyethoxy)butane-1,4-diol (81) in high yield. Although deprotection of diol (*S*)-(81) was not described it was assumed this would be trivial.

Whilst these reactions were reproducible, several modifications were implemented in the interests of economy and practical convenience. In the preparation of (*S*)-(80) dichloromethane was used as co-solvent to save consumption of ethyl vinyl ether. It was found that 1.1 or 2 equivalents of ethyl vinyl ether gave

incomplete conversion after standing overnight (O-H stretch still present 3,350 cm^{-1} in the i.r. spectrum). Increasing the reaction time to 60 hours was both ineffective and undesirable, since the solution started to become discoloured, suggesting that polymerisation of the ethyl vinyl ether was taking place. Therefore, reaction times of 20-24 hours and 5 equivalents of ethyl vinyl ether were used. Such conditions gave a 95.1% yield of (*S*)-(80). No changes were made to the reduction of (*S*)-(80), but the work-up was altered. It was found more convenient to extract (Soxhlet) the filter-cake with dichloromethane rather than simply reflux a suspension of the residues in this solvent. A sometimes lengthy second filtration was thus avoided.

Treatment of diol (*S*)-(81) with acidified methanol did not cause clean deprotection as it had done with (*S*)-(79). Instead of obtaining (*S*)-(82) as the sole product, a mixture of (*S*)-(82) and the diastereoisomers of (*S*)-4-(hydroxymethyl)-2-methyl-1,3-dioxane (83) and (*S*)-4-(2'-hydroxyethyl)-2-methyl-1,3-dioxolane (84) was isolated. Separation of acetals (*S*)-(83) and (*S*)-(84) from (*S*)-(82) could be effected by Kugelröhr distillation.

The formation of (*S*)-(83) and (*S*)-(84) may be explained by loss of ethanol from (*S*)-(81) to generate a stabilised carbenium ion which undergoes intramolecular attack from either the α- or β-hydroxyl group giving (*S*)-(84) or (*S*)-(83) respectively (Fig. 3.2).

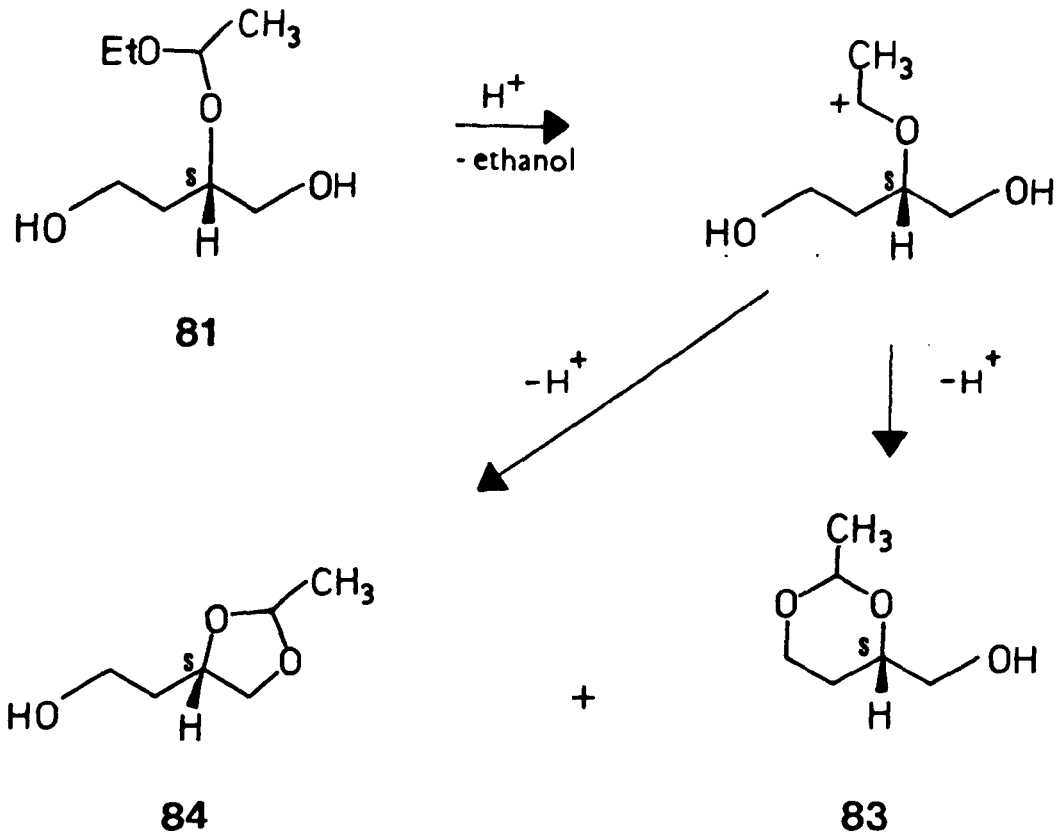
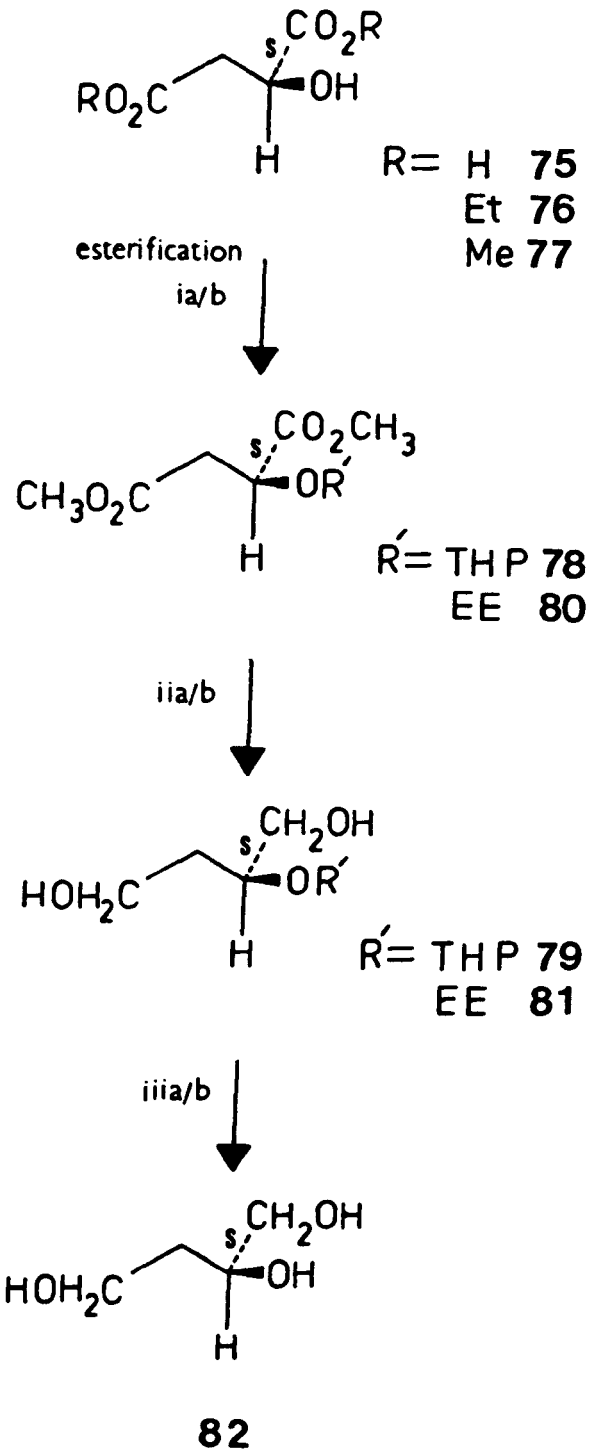


Fig. 3.2

Hydrolysis of (*S*)-(83)/(*S*)-(84) was carried out by heating the crude residue in 2 M hydrochloric acid[129]. Evaporation of the reaction mixture gave a sample of (*S*)-(82) which after distillation had identical spectroscopic properties and optical rotation to those in the literature[115]. Thus, no racemisation took place during this step which proceeded in 89% of theory, whilst the overall [(*S*)-(77) to (*S*)-(82)] yield was 72.2%.

The formation of 1-ethoxyethyl-derivatives introduces an asymmetric centre. However, this did not cause any practical difficulties. The 220 MHz n.m.r. spectra of (*S*)-(80) and (*S*)-(81) were more readily decipherable than those of (*S*)-(78) and (*S*)-(79). The presence of diastereoisomers was clearly shown *inter alia* by two quartets at δ 4.35, J = 7 Hz and

Scheme 3.2



Reagents: (ia) 2,3-dihydropyran, Et_2O, H^+(cat.);
(iia) $LiAlH_4$, Et_2O; (iiia) MeOH, $H^{+\cdot}$,
(ib) ethyl vinyl ether, CH_2Cl_2, CF_3CO_2H(cat.);
(iib) $LiAlH_4$, Et_2O; (iiib) $MeOH/H_2O$, H^+

δ 4.52, J = 7 Hz given by the proton attached to asymmetric carbon created.

Both tetrahydropyranyl- and 1-ethoxyethyl- derivatives slowly discolour on standing and samples stored for several months were found to have undergone extensive decomposition. Therefore, they should be regarded as transitory intermediates to be used as quickly as possible. Purification of (*S*)-(78), (*S*)-(79), (*S*)-(80) and (*S*)-(81) was unnecessary and not attempted.

3.3 (*S*)-BUTANE-1,2,4-TRIOL TO (*R*)- AND (*S*)-4-BENZYLOXYBUTANE-1,2-DIOL

3.3.1 (*S*)-4-Benzyloxybutane-1,2-diol

(*S*)-4-(2'-Hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (85) was prepared by acid catalysed reaction of triol (*S*)-(82) with acetone. By use of chiral shift reagents with ^{1}H n.m.r. spectroscopy, Meyers and Lawson[130] were able to show that 10% of (*S*)-4-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane (86) was present in the product of this reaction, which had previously been assumed to contain only (*S*)-(85)[103,115,131]. This feature had previously been overlooked because of the inability of 60 MHz machines to resolve the methyl peaks of (*S*)-(86) from those of (*S*)-(85). In the 220 MHz ^{1}H n.m.r. spectrum, however, a broad singlet at δ 1.47 corresponding to the methyl groups of (*S*)-(86) was separated and integration (6 times) of this and the methyl resonances of

(*S*)-(85) at δ 1.39 and δ 1.44 gave an average of 1:9.3 ratio, consistent with the literature result[130]. The separation of (*S*)-(85) and (*S*)-(86) is reported[130] to be very difficult and was eventually achieved by fractional crystallisation of the 3,5-dinitrobenzoate esters. Such a separation was not practical on a multigram scale. Hence the presence of (*S*)-(86) as an impurity was tolerated because there was no evidence from previous work[103], that epoxide (*S*)-(94) contained any (*S*)-2-benzyloxymethyloxetane (95) derived from (*S*)-(86).

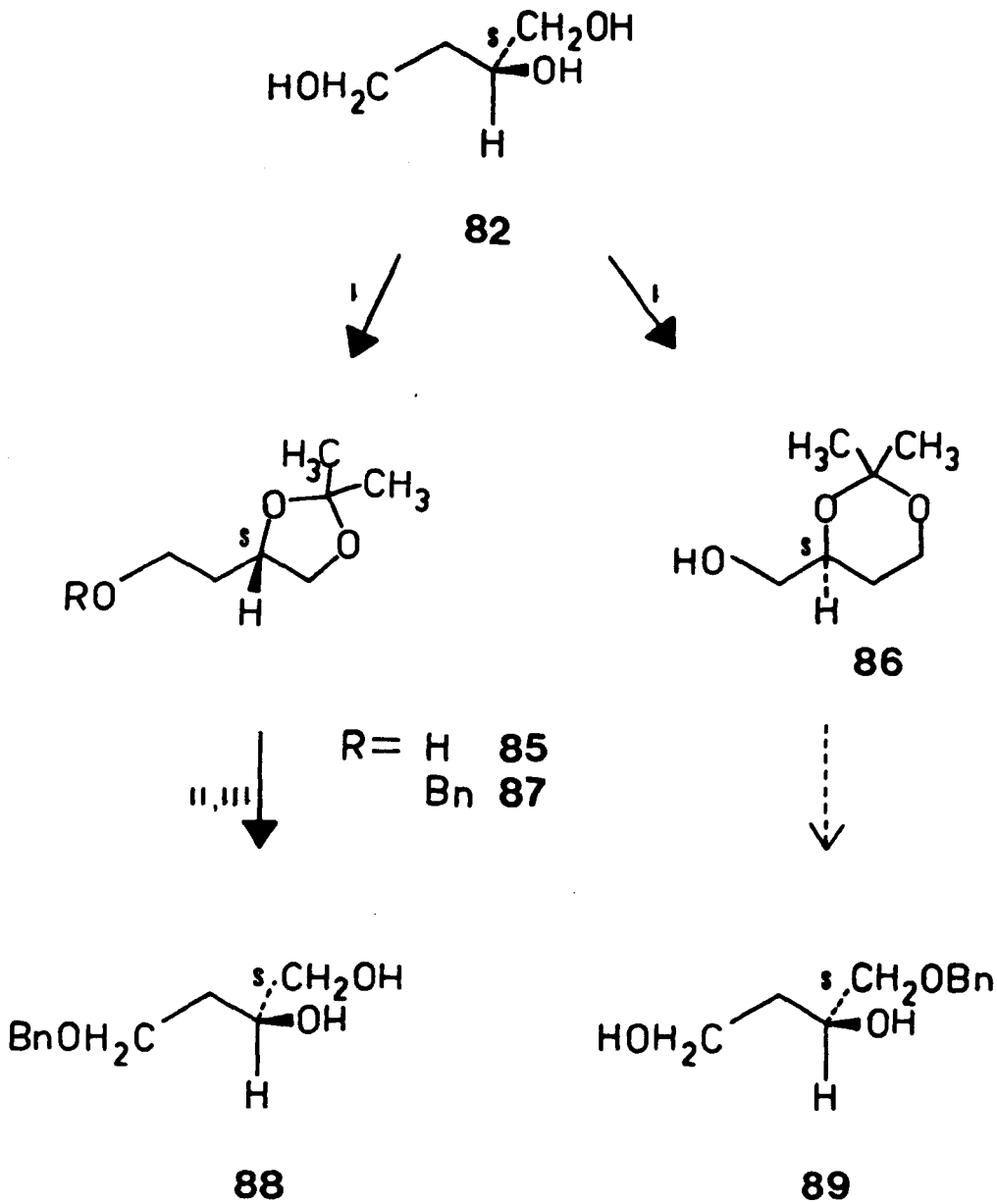
In 1977 Golding and Ioannou[132] reported a facile method for protecting a terminal hydroxyl group of glycerol. Glycerol was converted into *rac*-hydroxymethyl-2,2-dimethyl-1,3-dioxolane and then benzylated under phase transfer conditions. Acidic hydrolysis of the unpurified product then gave *rac*-3-benzyloxypropane-1,2-diol.

As acetonide (85) is a homologue of hydroxymethyl-2,2-dimethyl-1,3-dioxolane the procedure should be suitable for preparing 4-benzyloxybutane-1,2-diol (88), as was found to be the case[103]. Thus, acetonide (*S*)-(85) and a catalytic amount of tetra-*n*-butylammonium hydrogen sulphate were dissolved in benzyl chloride, and then stirred vigorously with concentrated aqueous sodium hydroxide. The quarternary ammonium salt functions by transferring hydroxide anions into the organic phase. Here, unsolvated hydroxide behaves as a stronger base efficiently deprotonating (*S*)-(85) to its alkoxide, which can subsequently react with benzyl chloride.

The immediate product (*S*)-4-(2'-benzyloxyethyl)-2,2-dimethyl-1,3-dioxolane (87), was not isolated from the crude product, which also contained dibenzyl ether, benzyl chloride and benzyl alcohol, but was subjected to immediate hydrolysis in dilute sulphuric acid. (*S*)-4-Benzyloxybutane-1,2-diol (88) obtained by this treatment is water-soluble and therefore readily separable from the other by-products. Diol (*S*)-(88) was then extracted into ethyl acetate from the aqueous phase after neutralisation and saturation of the latter. The conversion of (*S*)-(85) into (*S*)-(88) proceeded in 78.7% yield. One disadvantage of this procedure was the need for two high vacuum distillations to purify diol (*S*)-(88) (b.p. 132-142^{o}C, 0.005 mmHg).

An alternative procedure was therefore explored. Acetonide (*S*)-(85) was benzylated in DMF by benzyl bromide with sodium hydride as base according to the method of Hungerbrühler *et al.*[133], the benzylated acetal (*S*)-(87) being isolated in 84.7% yield. Unfortunately, distillation did not fully purify (*S*)-(87) (b.p. 126-9^{o}C, 0.6 mmHg) despite the greater ease with which it could be carried out. The diol (*S*)-(88) obtained after acidic hydrolysis, was no purer than that extracted by ethyl acetate in the above procedure. As no advantage had been gained here, the more convenient phase transfer method was utilised for the large scale runs. A major benefit of the latter method is that an inert atmosphere and rigorously anhydrous conditions are not required. Whilst diol (*S*)-(88) appeared to be pure by both ^{1}H n.m.r. and t.l.c.

Scheme 3.3



Reagents: (i) acetone, $H^{+\cdot}$, (ii) BnCl, $Bu_4\overset{+}{N}H\overset{-}{S}O_4$, 50% $NaOH_{(aq)}$; (iii) H_3O^+

(3 systems), the possibility that it contains ≤ 5% of (*S*)-4-benzyloxybutane-1,3-diol (89), derived from (*S*)-(86) cannot rigorously be excluded. The conversion of triol (*S*)-(82) into diol (*S*)-(88) is summarised in Scheme 3.3.

3.3.2 (*R*)-4-Benzyloxybutane-1,2-diol

The situation of having one enantiomer of a compound readily available whilst its antipode is relatively inaccessible, is frequently encountered by the chemist during EPC syntheses. Fortunately, an increasing number of procedures are appearing which enable the uncommon isomer to be made from the other enantiomer[134]. All of these sequences involve a classical S_N2 inversion at the chiral centre.

Recently, Takano *et al.*[111] have described the conversion of (*R*)-3-benzyloxypropane-1,2-diol into its antipode in a 3-step sequence, apparently in high overall yield. The obvious resemblance of these glycerol derivatives to (*S*)-(88) and the absence of any chromatographic purification step made the procedure particularly attractive. If diol (*S*)-(88) could be inverted in multigram quantities then (*R*)-(94) and hence (*R*)-lipoic acid would be much easier to obtain.

Treatment of (*S*)-(88) with 2.2 equivalents of mesyl chloride under standard conditions[135] gave (*S*)-4-benzyloxy-1,2-dimesyloxybutane (90) in high yield (88%).

Dimesylate (*S*)-(90) was used without purification in the subsequent reaction with a large excess of potassium acetate in boiling acetic anhydride which furnished (*R*)-1,2-diacetoxy-4-benzyloxybutane (91). The mechanism of this reaction[136,137] involves the initial displacement of the primary mesylate by acetate. The introduced acetate group then displaces the secondary mesyl group by intramolecular S_N2 attack giving an acetoxonium ion (Fig. 3.3). This intermediate is ring-opened by attack of a second acetate ion at the least hindered carbon (C-1) to provide (*R*)-(91).

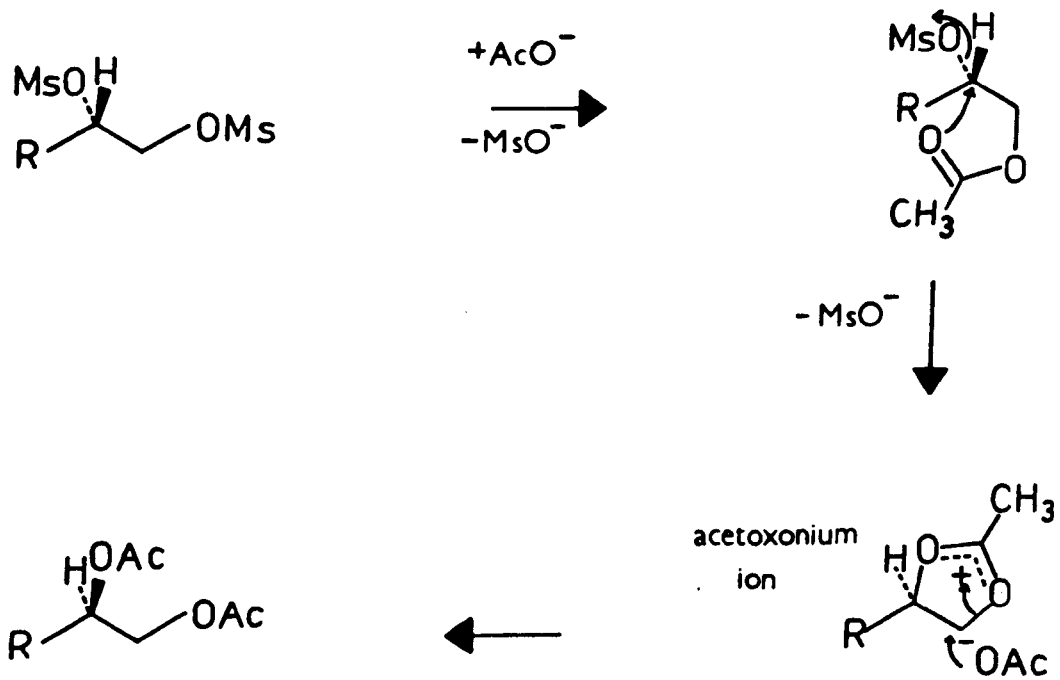
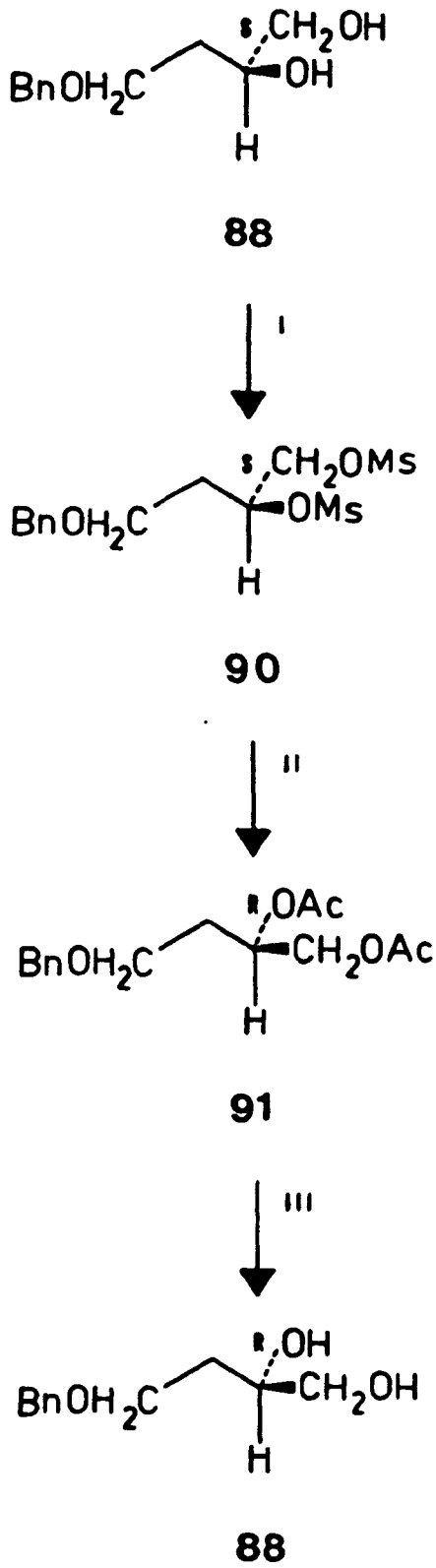


Fig. 3.3

Scheme 3.4



Reagents: (i) MsCl (2.5 equivalents), Et_3N, CH_2Cl_2;
(ii) KOAc (5 equivalents), Ac_2O, reflux;
(iii) K_2CO_3, MeOH

The diacetate (*R*)-(91) was purified by three high vacuum distillations (b.p. 120-131°C, 0.005 mmHg) in order to obtain a chromatographically homogeneous sample (by t.l.c.). Saponification to (*R*)-(88) was effected by stirring a methanolic solution of (*R*)-(91) with excess potassium carbonate followed by aqueous work-up. After distillation the (*R*)-(88) obtained gave identical ^{1}H n.m.r. and i.r. spectra as well as an essentially equal but opposite optical rotation to that of pure (*S*)-(88).

Although the dimesylation of (*S*)-(88) and saponification of (*R*)-(91) proceeded in good yield, the crucial displacement step proceeded in only 47.3% of theory, reducing the overall yield for the inversion sequence to 39.8%. Unfortunately there was insufficient time to attempt improvements. However, sufficient (*R*)-(88) (Scheme 3.4) had been made to continue the synthesis on a reasonable scale.

3.4 PREPARATION OF (2-BENZYLOXYETHYL)OXIRANE

3.4.1 (*R*)- and (*S*)-(2-Benzyloxyethyl)oxirane from (*R*)- and (*S*)-4-Benzyloxybutane-1,2-diol

The stereospecific conversion of chiral 1,2-diols into terminal epoxides has been achieved by a variety of means. Characteristic of such transformations is regiospecific activation of the primary hydroxyl group, followed by its displacement by the secondary hydroxyl function *via* an intramolecular S_N2 reaction (Fig. 3.4).

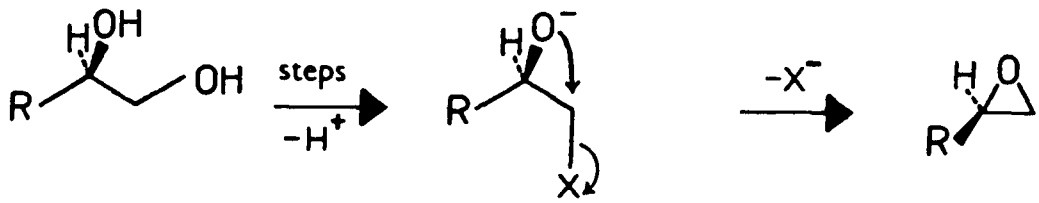
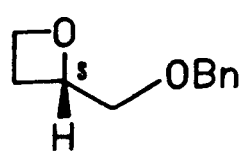


Fig. 3.4

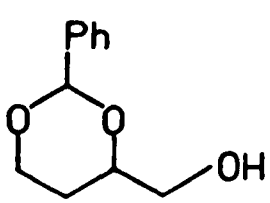
Following the failure of (*S*)-(88) to be converted into (*S*)-(94) by the method of Golding *et al.*[103,138], a milder procedure based on the work of Seeley and McElwie[139] was employed[103,110] (Scheme 3.5). Accordingly diol (*R*)-(88) was converted into (*R*)-4-(2-benzyloxyethyl)-2-phenyl-1,3-dioxolane (92) by treatment with benzaldehyde (1.1 equivalents) and catalytic acid in benzene with azeotropic removal of the water formed. It was found that no more benzene:water azeotrope (b.p. 65°C) condensed after about 45 minutes from the time that refluxing commenced. Therefore, the reaction was run for 60 minutes, rather than overnight as previously described[103]. Excess benzaldehyde was removed from the crude product, isolated after work-up, by stirring under high vacuum (0.005 mmHg) at 40°C overnight. T.l.c. and ^{1}H n.m.r. failed to detect any residual benzaldehyde after this treatment and indicated that a product of ≥ 92% purity had been obtained in 96% yield.

Formation of benzaldehyde acetals introduces a new asymmetric centre. The presence of diastereoisomers in the sample of (*R*)-(92) prepared was clearly shown in the ^{1}H n.m.r. spectrum *inter alia* by two singlets at δ 5.18 and δ 5.32 in 1:1 ratio arising from the benzylic methine of each epimer. As no purification was necessary here, this feature was without consequence. Eliel and Ko[140] have recently reported the use of benzaldehyde acetals for the determination of enantiomeric excess (e.e.) of their parent diols by ^{1}H n.m.r. spectroscopy and chiral shift reagents. Use of this method in this route was unnecessary because a determination of e.e. was routinely carried out directly on the enantiomers of epoxide (94)[103,110].

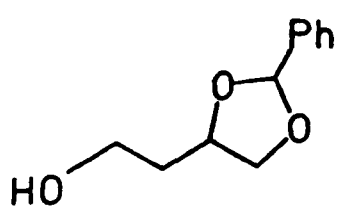
Foster *et al.*[141] have shown that the reaction of triol *rac*-(82) with benzaldehyde under the conditions described above give *rac*-4-(hydroxymethyl)-2-phenyl-1,3-dioxane (96) rather than *rac*-4-(2'-hydroxyethyl)-2-phenyl-1,3-dioxolane (97). This is unfortunate because benzylation of (97) would give acetal (92) in two steps from triol (82) rather than four.



95

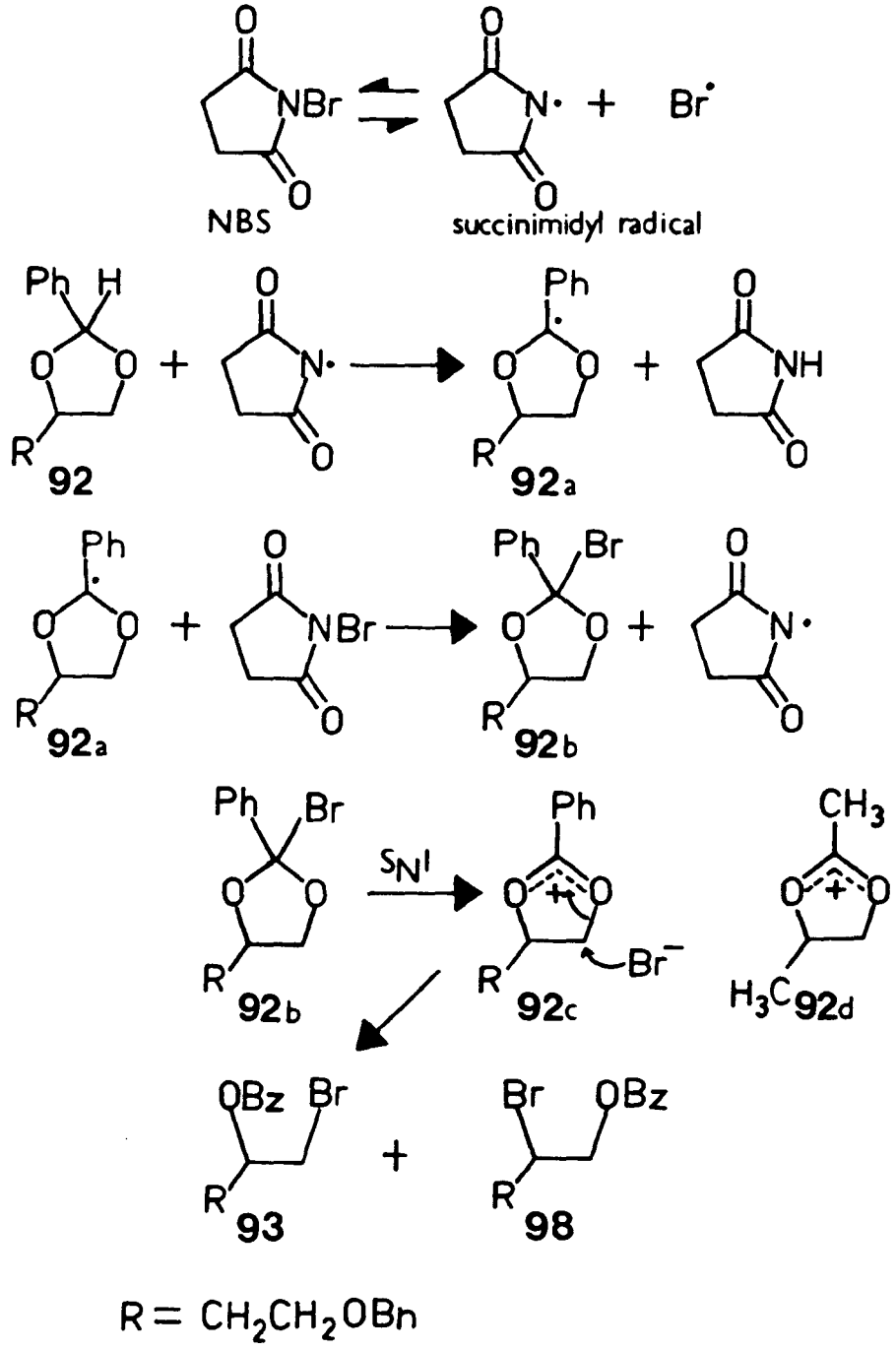


96



97

Figure 3.6


NBS
succinimidyl radical
92
92a
92a
92b
92b
92c
92d
93
98
SN1
R = CH2CH2OBn

Reaction of acetal (*R*)-(92) with recrystallised N-bromosuccinimide (NBS) in 1,1,2-trichlorotrifluoroethane gave (*R*)-2-benzoyloxy-4-benzyloxy-1-bromobutane (93) essentially quantitatively. A less discoloured, purer product than that obtained before[103], was isolated when the reaction time was extended from 20 hours to 60 hours and maintained at a temperature of 5°C rather than 20°C.

A plausible mechanism (Fig. 3.6) for this transformation involves prior homolytic fission of the bromine-nitrogen bond in NBS to give bromine and succinimidyl radicals. The latter can abstract a hydrogen atom from (92) to give the radical (92a). This can in turn abstract a bromine atom from another molecule of NBS. The resulting bromo-compound (92b) can then undergo S_N1 heterolytic fission to give bromide and the stabilised carbenium ion (92c). The benzoyloxonium ion (92c) is then regioselectively attacked by bromide at the least hindered carbon to furnish (93), but probably some of the isomeric (*R*)-1-benzoyloxy-4-benzyloxy-2-bromobutane (98) is also formed.

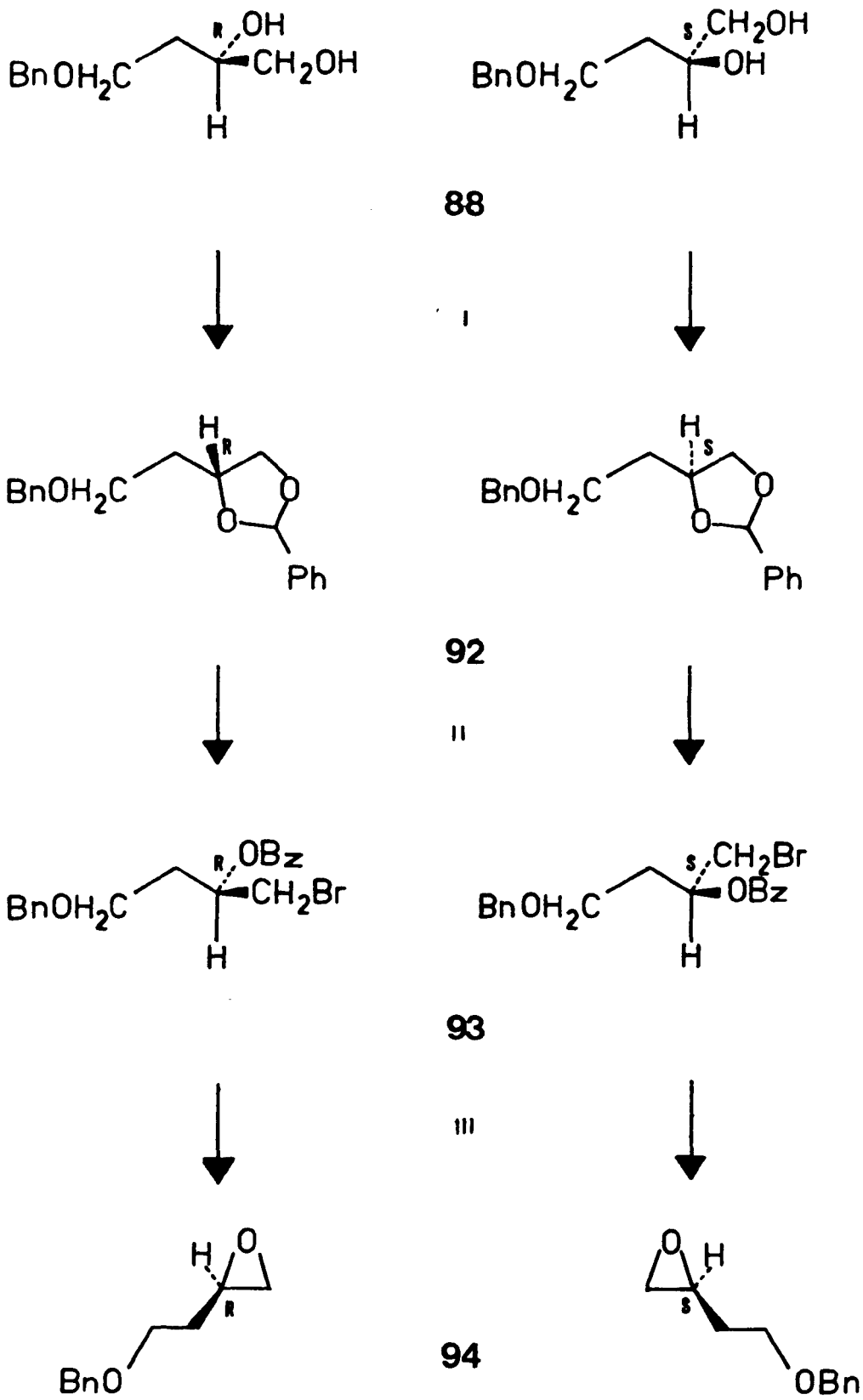
The presence of (*R*)-(98) was not detected by either t.l.c. or ^1H n.m.r. spectroscopy due to its similar R_f and overlapping resonances with those of (92). However, studies on the related acetoxonium ion (92d), (under similar conditions) have shown that attack by bromide is not totally regiospecific[138]. It can be inferred from these results[138] that (98) is probably present to the extent of 3-6%.

Bromoester (*R*)-(93) was subsequently converted into the epoxide (*R*)-(94) by reaction with sodium hydroxide in ethane-1,2-diol. A stoichiometric deficiency of base (1.85 equivalents) was used to suppress possible polymerisation of (*R*)-(94) without detriment to the yield. The rate of the reaction was found to be highly dependent on the rate of stirring and progress was followed by working up aliquots which were examined by ^{1}H n.m.r. spectroscopy. When no more bromoester (*R*)-(93) was disappearing (17-30 hours), the epoxide (*R*)-(94) was extracted into petrol, the petrol solution was evaporated and the residual oil distilled twice to give the pure compound (b.p. 110-2°C, 1.5 mmHg).

The yield of (*R*)-(94) from (*R*)-(93) was 74.2%; from (*R*)-(88) 69.3%, but only 12.8% from (*S*)-(75) due to the low yielding inversion sequence. The antipode (*S*)-(94) was obtained in similar yields from (*S*)-(88) but 32% from (*S*)-(75), an improvement of 17% over the original route[103]. The optical rotations of (*R*)- and (*S*)-(94) were, within experimental error, equal and opposite ($[\alpha]_D^{20}$ = +14.9° and -15.6° respectively).

Since (94) is a key intermediate in our synthesis of (*R*)- and (*S*)-lipoic acids its purity is crucial. ^{1}H n.m.r. spectroscopy and optical rotation are inadequate for the detection of small amounts of impurities. Therefore samples of (94) were analysed by h.p.l.c. and chiral shift reagent. In all but one case (see below), samples of (94) were shown to be both chemically and enantiomerically homogeneous by these methods.

Scheme 3.5



Reagents: (i) PhCHO, C_6H_6, H^+, reflux 1 hour; (ii) NBS, $CF_2ClCFCl_2$; (iii) NaOH (1.85 equivalents), ethane-1,2-diol

One advantage of this method of epoxide formation[139] is that the conversion of (92) into (94) *via* (93) or (98) gives the same enantiomer (i.e. formation of (98) and its subsequent conversion into (94) both involve Walden inversions resulting in an overall retention of configuration). This is not the case with the more common procedures[142-144] which rely on regioselective tosylation of the diol's primary hydroxyl group. Here, if any secondary tosylation occurs, treatment with base will afford the other enantiomer. Furthermore, the enantiomeric integrity of various epoxides made by the method of Seeley and McElwie[139] has been demonstrated independently by Schurig *et al.*[145] using gas chromatography on a chiral stationary phase.

The Mitsunobu reaction[146] is one of the most versatile reactions which has recently been discovered. The formation of epoxides from diols has been one of its applications[111]. The convenience of a one step transformation was attractive, and a preliminary experiment was conducted. Reaction of diol (*S*)-(88) with diisopropyl diazodicarboxylate (DIAD) and triphenyl phosphine in refluxing THF gave epoxide (*S*)-(88) in 58% yield, after purification by column chromatography and Kugelröhr distillation. Unfortunately, the optical rotation of this sample was lower ($[\alpha]_D^{20}$ - 11.6°) than those made by the previous method. This indicated that the Mitsunobu reaction was not stereospecific and hence unsatisfactory. This reaction was therefore not pursued further.

3.4.2 Racemic (2-Benzyloxyethyl)oxirane

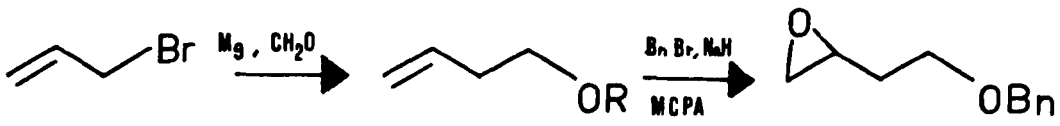
In order to test possible synthetic routes to lipoic acid, samples of racemic (94) were required. Previously[103], *rac*-(75) was used as the starting material, but the sequence of 10 steps proved too laborious. An easier, alternative route was therefore sought (Scheme 3.6).

Allyl bromide was converted into 3-butene-1-ol (99) following the procedure of Linstead and Rydon[147] by reaction of allylmagnesium bromide with paraformaldehyde in ether boiled under reflux. Although a modest yield of 38% was obtained, the procedure could easily be adapted for preparation on a 1 mole scale (of allyl bromide).

Benzylation following the procedure of Hungerbrühler *et al.*[133] gave 4-benzyloxybut-1-ene (100) in 76% yield. A deficiency of benzyl bromide (0.85 equivalents), was added to ensure that all of it was consumed. This was because unreacted (99) could readily be separated from the product by simple distillation, whereas benzyl bromide could not.

Pure benzyl ether (100) was epoxidised to give *rac*-(94) with 3-chloroperbenzoic acid according to a standard procedure[148]. The yield for this step was 71.9% and the overall yield from allyl bromide was 20.7%.

Scheme 3.6



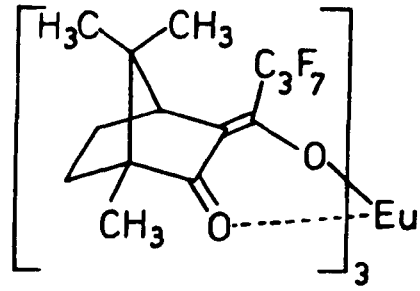
R= H **99** **94**
Bn **100**

3.4.3 Determination of Enantiomeric Excess by Chiral Shift Reagent

Until recently comparative optical rotation was the only method routinely applied to determine the e.e. of chiral molecules. With increasing interest in enantioselective syntheses today[109], more accurate techniques are often required. Probably the best known of these is high resolution ^{1}H n.m.r. spectroscopy in conjunction with chiral shift reagents[149-151].

In solution the chiral shift reagent and the molecule being examined form a loose complex. If the substance is 100% enantiomerically pure then only one diastereoisomer of this adduct can result, hence the resonances will be shifted, broadened, but otherwise unchanged. If, however, a racemate or enantiomerically impure material is present, a pair of diastereomeric complexes will result. These, unlike the original enantiomers, are differentiated by n.m.r. spectroscopy

and a quantitative estimation of e.e. may be made by integration (6 times) of the separated peaks. For best results the chiral centre must be as near as possible to the site of co-ordination. Many types of functional group will form suitable adducts with chiral shift reagents. We have successfully used one such reagent, europium(III) *tris*-[3-(heptafluoropropylhydroxymethylene)-d-camphorate] (101) to determine the optical purity of (*R*)-ethyloxirane and (*R*)- and (*S*)-(94).[110]



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In the current work, the original procedure[103] was tested on *rac*-(94) with successful resolution of the protons attached to the oxirane ring, originally at δ 2.89 and δ 2.74, into two peaks of equal intensity. The method showed that (*R*)- and (*S*)-(94) prepared from (*R*)- or (*S*)-(88) *via* their benzaldehyde acetals[103,110] gave no splitting of the aforementioned resonances even at high sensitivity and scale expansion of the 220 MHz ^{1}H n.m.r. spectrum, implying an e.e. of ≥ 95%. In contrast, the sample of (*S*)-(94) obtained from (*S*)-(88) *via* the Mitsunobu reaction[111] was found to contain somewhere between 8-10% of the

(*R*)-enantiomer under these conditions and hence only had an e.e. of 80-84%.

3.4.4 Conclusion

An improved synthesis of key intermediate (*S*)-(94) has been presented with an increase in overall yield from (*S*)-(75) from 15% to 32.0%. The major improvements were made during the conversion of the diester (*S*)-(77) into triol (*S*)-(82) by use of a hydroxyl protecting group. The two groups employed, namely tetrahydropyranyl- and 1-ethoxyethyl- gave similar overall yields and there was little to choose between them. However, the author prefers the latter protecting group because the work-up from the lithium aluminium hydride reduction was slightly more convenient.

The inversion of (*S*)-(88) to (*R*)-(88) though reproducible, was rather disappointing on account of its low overall yield (39.8%). However, it may be possible to better the yields quoted by altering the reaction conditions. In the route to (*S*)-lipoic acid there may be other intermediates later in the synthetic sequence which are good candidates for inversion enabling better access to the (*R*)-enantiomer of this compound.

3.5 EXPERIMENTAL

(*S*)-Diethyl malate (76)

This compound was prepared as a colourless oil from (*S*)-(75) according to a standard procedure for diesters[114] (118 g, 83.1%); b.p. 74-7°C, 0.07 mmHg; (lit.[131], 85.6%; b.p. 145-8°C, 1.4 mmHg).
$[\alpha]_D^{20}$ - 13.2° (C = 6.3 in acetone); [lit.[131], $[\alpha]_D^{20}$ - 15.9° (C = 3.0 in acetone)].
δ_H (CCl_4): 1.27 (3H, t, J 7.3 Hz, CH_3); 1.30 (3H, t, J 7.3 Hz, CH_3); 2.68 (2H, dd, J 5 Hz, CH_2); 3.05 (1H, s, OH); 4.12 (2H, q, J 7.3 Hz, CH_2); 4.23 (2H, q, J 7.3 Hz, CH_2); 4.32, 1H, t, J 5 Hz, CH) p.p.m.
ν_{max}(film): 3390 (b,s), 2980 (s), 2935 (w), 2905 (w), 1735 (s), 1407 (m), 1447 (m), 1373 (m), 1350 (w), 1265 (s), 1215 (m), 1175 (s), 1100 (s), 1025 (s), 855 (m) cm^{-1}.
T.l.c.: (Silica Gel F_{254}; 2:1, CH_3CCl_3: EtOAc) one spot (I_2) at R_F 0.34.

(*S*)-Dimethyl malate (77)

This compound was prepared as a colourless oil from (*S*)-(75) by following the procedure of Mori *et al.*[115] (107.1 g, 85.6%); b.p. 90-2°C, 0.25 mmHg; (lit.[115], 90%; b.p. 92-4°C, 0.1 mmHg).
$[\alpha]_D^{20}$ - 9.6° (C = 5 in ethanol); (lit.[115], $[\alpha]_D^{20}$ - 9.1° (C = 4.8 in EtOH)].
δ_H (CCl_4): 2.71 (2H, dd, $J_1 = J_2$ 5 Hz, CH_2); 3.40 (1H, s, OH); 3.68 (3H, s, CH_3); 3.77 (3H, s, CH_3); 4.39 (1H, t, J 5 Hz, CH) p.p.m.

ν_{max} (film): 3480 (b,s), 3000 (w), 2950 (m), 2900 (w), 2845 (w), 1735 (s), 1437 (m), 1410 (w), 1365, (w), 1280(b,s) 1225 (s), 1170 (s), 1105 (s), 1040 (m), 990 (m), 845 (m), 780 (w) cm^{-1}.

M/z: (c.i.): 163 [$(M + 1)^+$, 87], 131 (32), 104 (74), 71 (36), 61 (19), 43 (44), 32 (11), 18 (100%).

T.l.c.: (Silica Gel F_{254}; 2:1, CH_3CCl_3:EtOAc) one spot (I_2) at R_F 0.29.

Found: C, 44.45; H, 6.25; $C_6H_{10}O_5$ requires: C, 44.44; 6.22%.

(*S*)-Butane-1,2,4-triol (82) (Method A)

A solution of diester (*S*)-(76), (40 g, 200 mmol) in THF (200 cm^3) was added dropwise to a stirred, ice-cooled suspension of lithium aluminium hydride (18 g, 470 mmol) in THF (1 dm^3) over a period of 40 minutes. The reaction mixture was then refluxed under a dry nitrogen atmosphere for 20 hours. Residual lithium aluminium hydride was destroyed by cautious addition of water (120 cm^3) at 0°C. The mixture was filtered through Celite under suction and the aluminate cake washed with water (2 dm^3). The combined aqueous and organic extracts were concentrated *in vacuo* to *ca.* 100-150 cm^3 then carefully brought to pH 7 by addition of 1 M sulphuric acid. Evaporation to dryness left a thick, off-white, pasty residue. The residue was taken up in propan-2-ol (150 cm^3); the resulting suspension was filtered and concentrated *in vacuo* to furnish the product free from inorganic material and suitable for the next step after short path distillation

(12.2 g, 57.5%) b.p. 120-131°C, 0.02 mmHg.
$[\alpha]_D^{20}$ - 19.6° (C = 3 in MeOH); [lit.[116], $[\alpha]_D^{20}$ - 17.33° (C = 3 in MeOH)].

δ_H (^2H_2O): 1.71 (2H, m, $C\underline{H}_2$); 3.58 (2H, dd, $J_1 = J_2$ 5 Hz, $C\underline{H}_2OD$); 3.76 (2H, dt, J_3 5 Hz, J_4 6 Hz, $C\underline{H}_2OD$); 3.86 (1H, m, C<u>H</u>OD) p.p.m.

ν_{max} (film): 3340 (b,s), 2940 (b,s), 1420 (b,m) 1110 (w), 1060 (s), 980 (w), 945 (w), 905 (w) cm^{-1}.

<u>*Rac*-Butane-1,2,4-triol</u> (82) (<u>Method B</u>)

A solution of diester *rac*-(76) (4.5 g, 50 mmol) in absolute ethanol (20 cm^3) was added to a stirred suspension of sodium borohydride (1.6 g, 50 mmol) in (20 cm^3) of the same solvent which had been cooled to 0°C. After 1 hour, the temperature was raised to and then maintained at 70°C for 17 hours. Three, six and nine hours into this time further 1.6 g portions of solid sodium borohydride were added to the reaction. The reaction was worked up by diluting with 10% methanolic hydrogen chloride (150 cm^3) and concentrating to *ca.* 50 cm^3 by distillation at atmospheric pressure. The residual solution was neutralised by addition of powdered lead (II) carbonate, which after filtration and evaporation *in vacuo* afforded a pale yellow syrup. The syrup was extracted with ether (4 x 50 cm^3) and then distilled in a Kugelröhr apparatus to give the pure product as a colourless, viscous liquid (1.17 g, 36%); b.p. 105-116°C, 0.005 mmHg; (lit.[119], 114°C 0.007 mmHg). The ^1H n.m.r. and thin film i.r. spectra obtained for this sample were identical to those

obtained in the preceding preparation of this compound.

(*S*)-2-THP-Dimethyl malate (78)

This compound was prepared as a pale yellow oil from (*S*)-(77) by following the procedure of Mori *et al.*[115] (121.8 g, 99.0%); (lit.[115], 92.0%).

$[\alpha]_D^{20}$ - 46° (C = 4.7 in ethanol); [lit.[115], $[\alpha]_D^{20}$ - 45.3° (C = 5 in ethanol)].

δ_H (CCl_4): 1.4-1.9 (6H, m, 3 x CH_2); 2.67 (2H, dd, J_1 6 Hz, J_2 3 Hz, $C\underline{H}_2$); 3.34 (2H, m, $C\underline{H}_2O$); 3.67 (3H, s, OCH_3); 3.71 (3H, s, OCH_3); 4.34 (½H, t, J_1 6 Hz, CH); 4.54 (½H, t, J_2 3 Hz, CH); 4.73 (1H, m, CH) p.p.m.

ν_{max} (film): 2905 (s), 2870 (w), 1743 (s), 1435 (s), 1305 (m), 1195 (w), 1165 (m), 1120 (m), 1065 (m), 1020 (w), 975 (m), 905 (w), 885 (m), 818 (w) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; 66:33:1, CH_3CCl_3:EtOAc:Et_3N) one spot (I_2) at R_F 0.35.

(*S*)-2-THP-Butane-1,2,4-triol (79)

This compound was prepared as a colourless oil from (*S*)-(78) according to the procedure of Mori *et al.*[115] (71.0 g, 82.7%); (lit.[115], 92.0%).

$[\alpha]_D^{20}$ - 30.7° (C = 6.5 in ethanol).

δ_H (CCl_4): 1.5-1.9 (8H, m, 4 x CH_2); 3.45-4.15 (9H, m, 2 x OH + C$\underline{H}$ + 2 x $C\underline{H}_2OH$ + $C\underline{H}_2OR$) 4.55 (½H, m, CH); 4.60 (½H, m, CH) p.p.m.

ν_{max} (film): 3380 (b,s), 2940 (s), 2860 (s), 1650 (w), 1455 (w), 1440 (w), 1380 (w), 1325 (w), 1275 (w), 1265 (w), 1195 (w), 1175 (w), 1165 (m), 1130 (s), 1060 (s), 1020 (s),

985 (m), 900 (m), 865 (m) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; 66:33:1, CH_3CCl_3:EtOAc:Et_3N) one spot (I_2) at R_F 0.16.

(*S*)-Butane-1,2,4-triol (82) (Method C)

This compound was obtained as a viscous syrup from (*S*)-(79) by following the procedure of Mori *et al.*[115] (40.2 g, 94.3%); b.p. 140-5°C; 0.5 mmHg; (lit.[115], 96.8%; b.p. 140-3°C, 0.9 mmHg).

$[\alpha]_D^{20}$ - 22.5° (C = 2.3 in ethanol); [lit.[115], $[\alpha]_D^{20}$ - 20.8° (C = 3.3 in ethanol)].

The ^1H n.m.r. and thin film i.r. spectroscopic data were identical to those quoted previously for (*S*)-(82) (Method A).

(*S*)-2-EE-Dimethylmalate (80)

To a cooled (0°C) solution of diester (*S*)-(77) (61.9 g, 382 mmol) in ethyl vinyl ether (freshly redistilled from lithium aluminium hydride) (300 cm^3) and dichloromethane (300 cm^3), was added dropwise with stirring, TFA (2 cm^3). The reaction was allowed to stand overnight at 5°C. Anhydrous potassium carbonate (10 g, 62.4 mmol) was added and the mixture stirred for 30 minutes. The solid material was removed by filtration and the solution concentrated *in vacuo* furnishing the product as a colourless oil, pure by t.l.c. and ^1H n.m.r. spectroscopy (92.0 g, 95.1%); (lit.[128], 98.6%).

$[\alpha]_D^{20}$ - 63.1° (C = 5 in CCl_4).

δ_H (CCl_4): 1.12 (3H, dt, $J_1 = J_2$ 7.3 Hz, $CH_2\underline{CH_3}$); 1.26 (3H, dd, $J_3 = J_4$ 7 Hz, $CH\underline{CH_3}$); 2.60 (2H, m, CH_2);

3.50 (2H, dq, $J_1 = J_2$ 7.3 Hz $C\underline{H}_2CH_3$); 3.66 (3H, s, OCH_3); 3.70 3H, s, OCH_3); 4.35 (½H, q, J_3 7 Hz, $C\underline{H}CH_3$); 4.52 (½H, q, J_4 = 7 Hz, $C\underline{H}CH_3$); 4.75 1H, m, CH) p.p.m.

ν_{max} (film): 2980 (m), 2960 (m), 2900 (w), 1740 (s), 1440 (m), 1400 (w), 1375 (m), 1340 (m), 1285 (m), 1170 (s), 1130 (s), 1085 (s), 1025 (m), 1000 (m), 955 (m), 850 (w), 805 (w), 720 (w) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; 66:33:1, CH_3CCl_3:EtOAc:Et_3N) one spot (I_2) and R_F 0.45.

(*S*)-2-EE-Butane-1,2,4-triol (81)

A solution of protected diester (*S*)-(80) (91.5 g, 370 mmol) in ether (200 cm^3) was added dropwise over 1.5 hours to a cooled (-10°C), stirred suspension of lithium aluminium hydride (25 g, 660 mmol) in 700 cm^3 of the same solvent. The reaction was stirred for 60 hours at room temperature, then water (25 cm^3) was added with great caution to destroy the excess hydride. This was followed by 15% (w/v) aqueous sodium hydroxide solution (25 cm^3) and then more water (50 cm^3). Vigorous stirring and cooling (-10°C) were maintained throughout this part of the work-up. The mixture was filtered through Celite and the aluminate residues extracted (Soxhlet) overnight by dichloromethane (1 dm^3) in the presence of a little potassium carbonate. The combined chlorinated and ethereal solutions were dried (K_2CO_3), filtered and evaporated *in vacuo* to afford the product as a colourless viscous liquid (59.7g, 85.3%); (lit.[128], 88.21%).

$[\alpha]_D^{20}$ - 19° (C = 6.3 in CCl_4).

δ_H (CCl_4): 1.18 (3H, dt, $J_1 = J_2$ 7.1 Hz, $CHC\underline{H}_3$); 1.29 (3H, dd, $J_3 = J_4$ 6 Hz, $CHC\underline{H}_3$); 1.65 (2H, m, CH_2); 4.43-4.70 (6H, m, $C\underline{H}_2CH_3$, 2 x $C\underline{H}_2OH$); 4.70 (1H, m, CH); 5.26 (2H, s, 2 x OH); 5.08 (½H, q, J_3 6 Hz, $C\underline{H}CH_3$); 5.19 (½H, q, J_4 6 Hz, $C\underline{H}CH_3$) p.p.m.

ν_{max} (film): 3380 (b,s), 2980 (s), 2930 (s), 2880 (s), 1445 (m), 1895 (w), 1380 (m), 1340 (m), 1125 (s), 1050 (s), 990 (m), 965 (m), 950 (m), 895 (m), 840 (w) cm^{-1}.

T.l.c.: (Silica Gel F_{254}: 66:33:1, CH_3CCl_3:EtOAc:Et_3N) one spot (I_2) at R_F 0.23.

(*S*)-Butane-1,2,4-triol (82) (Method D)

The diol (*S*)-(81) (59.0 g, 340 mmol) was dissolved in methanol (350 cm^3) to which toluene-4—sulphonic acid monohydrate (0.5 g, 2.65 mmol) was added. After standing overnight, sodium bicarbonate (0.5 g, 5.91 mmol) was introduced and the mixture stirred for 1 hour. Filtration and removal of solvent gave a residue which was approximately a 1:1 mixture (by ^1H n.m.r. spectroscopy) of (*S*)-(82) and the ethylidene acetals (*S*)-(83) and (*S*)-(84). This residue was taken up in 2 M hydrochloric acid (200 cm^3) and heated at 80°C for 6 hours. Most of the water and hydrogen chloride were removed *in vacuo* below 50°C. The residue obtained was pumped overnight at high vacuum (0.005 mmHg) and then distilled to furnish the pure product as a water-white syrup (30.6 g, 89.0%); b.p. 110-6°C, 0.005 mmHg.

$[\alpha]_D^{20}$ - 33.1° (C = 2.3 in ethanol).

δ_H ($^2H_5$-pyridine): 2.14 (2H, m, CH_2); 3.97 (2H, dd, J_1 = J_2 5 Hz, $C\underline{H}_2OH$); 4.17 (2H, dt, J_1 5 Hz, J_2 6 Hz, $C\underline{H}_2OH$); 5.38 (1H, m, CH_2); 6.00 (3H, b,s, 3 x OH) p.p.m.

The thin film i.r. spectrum obtained for this sample was identical to that of (*S*)-(82) prepared by method A.

(*S*)-4-(2'-Hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (85)

The title compound and its regiomer (*S*)-(1-hydroxymethyl-2,3-dimethyl)-1,3-dioxane (86) were prepared in approximately 9:1 ratio by a slightly modified literature procedure[115-6,139] involving the two-pass reaction of (*S*)-(82) with acetone in the presence of an acid catalyst (40.3 g, 95%); b.p. 103-110°C, 18 mmHg (lit.[116], 98%; b.p. 82-5°C, 14 mmHg).

$[\alpha]_D^{20}$ - 1.35° (C = 4.6 in methanol); [lit.[116], $[\alpha]_D^{20}$ - 1.29 (C = 3.4 in MeOH)].

δ_H (CCl_4): 1.39 (3H, s, CH_3); 1.44 (3H, s, CH_3); 1.72 (2H, m, CH_2); 2.96 (1H, b,s, OH); 3.48 (1H, t, J 5 Hz, $\underline{H}CH$); 3.65 (2H, t, J 7 Hz, $C\underline{H}_2OH$); 3.99 (1H, t, J 6 Hz, $HC\underline{H}$); 4.15 (1H, m, CH) p.p.m.

ν_{max} (film): 3430 (b.s), 2985 (s), 2940 (s), 2875 (s), 1455 (w), 1380 (m), 1360 (m), 1245 (s), 1155 (m), 1055 (s), 985 (m) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; 95:4:1, CH_2Cl_2:MeOH:Et_3N) one spot (I_2) at R_F 0.41.

(*S*)-4-Benzyloxybutane-1,2-diol (88)

Acetal (*S*)-(85), (39.0 g, 267 mmol) and tetra-*n*-butylammonium hydrogen sulphate (5 g, 14.7 mmol) were

dissolved in freshly redistilled benzyl chloride (110 g, 870 mmol, 100 cm^3) to which was added 50% aqueous sodium hydroxide solution (75 cm^3). The mixture was vigorously stirred and heated to 100°C for 17 hours. Once cooled, water (100 cm^3) was added and the (upper) organic layer separated. The aqueous phase was extracted with ether (3 x 100 cm^3) and the combined organic solutions were, in turn, washed with water (3 x 100 cm^3). Removal of the ether *in vacuo* furnished a brown oil which was stirred with 2 M sulphuric acid at 100°C for 3 hours. After cooling, the reaction mixture was extracted with 40-60° petrol (3 x 100 cm^3). The product was subsequently "salted out" of the aqueous phase by adding 50% sodium hydroxide solution until neutrality; was reached. Further saturation was effected by adding solid sodium chloride. Extraction of the resulting emulsion with ethyl acetate (3 x 100 cm^3), drying (Na_2SO_4), removal of solvent *in vacuo* and two high vacuum distillations of the residue furnished the pure product as a colourless syrup (42.2 g, 78%); b.p. 136-147°C, 0.005 mmHg; (lit.[152], b.p. 144-6°C 0.05 mmHg). $[\alpha]_D^{20}$ + 2.3 (C = 5 in $CHCl_3$); [lit.[152], $[\alpha]_D^{20}$ + 2.4° (C = 4.7 in $CHCl_3$)].

δ_H (CCl_4): 1.58 (2H, m, CH_2); 3.32 (1H, m, $\underline{H}CH$); 3.48 (3H, m, $HC\underline{H}$ + $C\underline{H}_2OBn$); 3.73 (1H, m, CH); 4.32 (2H, b,s, 2 x OH); 4.34 (2H, s, $C\underline{H}_2Ph$); 7.19 (5H, s, Ph) p.p.m.

ν_{max} (film): 3830 (b,s), 3090 (w), 3060 (w), 3030 (w), 2930 (s), 2875 (s), 1495 (w), 1455 (m), 1365 (m), 1205 (m), 1090 (b,s), 905 (w), 865 (w), 735 (s), 695 (s) cm^{-1}.

T.l.c. (Silica Gel F_{254}: 9:1, CH_2Cl_2:MeOH) one spot (u.v.) at R_f 0.32.

(*S*)-4-(2'-Benzyloxyethyl)-2,2-dimethyl-1,3-dioxolane (87)

A stirred suspension of sodium hydride (1.5 g, 31 mmol) in anhydrous DMF (10 cm^3), under a dry nitrogen atmosphere, was cooled to -10°C, whereupon dropwise addition of acetal (*S*)-(85), (4.24 g, 29 mmol) in DMF (10 cm^3) commenced. The resulting coffee coloured suspension was allowed to warm to room temperature over 30 minutes and then treated with benzyl bromide (5.3 g, 31 mmol) in DMF (15 cm^3). The reaction was allowed to stir overnight before being poured into water (350 cm^3) and extracted with ether (3 x 50 cm^3). After washing with water (5 x 30 cm^3), the combined organic extracts were dried (K_2CO_3), filtered and evaporated *in vacuo* to furnish a residual brown liquid. Distillation purified the product to 85-90% (by ^1H n.m.r. spectroscopy) but preparative h.p.l.c. was required to obtain an analytically pure sample. The yield of distilled material was 5.8 g, 84.7%; b.p. 126-9°C, 0.6 mmHg.

δ_H (CCl_4): 1.34 (3H, s, CH_3); 1.38 (3H, s, CH_3); 1.90 (2H, dd, J_1 6 Hz, J_2 5 Hz, CH_2); 3.66 (3H, m, $C\underline{H}_2OBn$ + $\underline{H}CH$); 4.12 (2H, m, CH + $HC\underline{H}$); 4.48 (2H, s, $C\underline{H}_2Ph$); 7.21 (5H, s, Ph) p.p.m.

ν_{max} (film): 3090 (w), 3070 (w), 2990 (m), 2940 (m), 2870 (m), 2795 (w), 1495 (w), 1480 (w), 1455 (m), 1370 (m), 1250 (m), 1215 (m), 1165 (m), 1095 (s), 1060 (s), 1030 (w), 995 (w), 915 (w), 860 (w), 815 (w), 735 (w), 695 (m) cm^{-1}.

T.l.c. (Silica Gel F_{254}: 99:1, CH_2Cl_2:Et_3N) one spot (u.v., I_2) at R_f 0.47.

H.p.l.c. (column Partisil; eluent 70:29:1, 40-60° petrol: CH_2Cl_2:Et_3N; solvent flow rate 1.5 cm^3 min^{-1}; pressure

200 p.s.i.).

Found: C, 71.36; H, 8.67; $C_{14}H_{20}O_3$ requires: C, 71.16; H, 8.53%.

The hydrolysis of (*S*)-(87) to (*S*)-(88) was effected as described in the preceding preparation.

(*S*)-4-Benzyloxy-1,2-dimesyloxybutane (90)

The diol (*S*)-(88), (41 g, 204 mmol) in dichloromethane (100 cm^3) was added to a chilled (-20°C) solution of triethylamine (65.2 g, 640 mmol, 90 cm^3) in 300 cm^3 of the same solvent. The resulting solution was stirred vigorously as mesyl chloride (66.6 g, 579 mmol, 45 cm^3) in dichloromethane (100 cm^3) was added dropwise. The mixture was allowed to stand overnight at -25°C before being poured into ice:water (500 cm^3). The organic layer was separated, washed with 1 M hydrochloric acid (3 x 100 cm^3), sodium bicarbonate solution (100 cm^3) and brine (100 cm^3), then dried ($MgSO_4$), filtered, and evaporated *in vacuo* to leave an orange oil. The final traces of solvent were removed by pumping at high vacuum (0.005 mmHg) overnight. The product thus obtained was ≥ 95% pure (^1H n.m.r. spectroscopy) and therefore used without further purification (60 g, 88.7%).

$[\alpha]_D^{20}$ - 14.7° (C = 6.8 in $CHCl_3$)

δ_H ($CDCl_3$): 1.90 (2H, m, CH_2); 2.93 (6H, s, 2 x CH_3); 3.57 (2H, m, CH_2OBn); 4.28 (2H, m, CH_2OMs); 4.36 (2H, s, CH_2Ph); 4.88 (1H, m, CHOMs); 7.18 (5H, s, Ph) p.p.m.

ν_{max} (film): 3660 (w), 3230 (b,w), 3030 (m), 2940 (m), 2870 (m), 1630 (b,w), 1495 (w), 1455 (m), 1415 (w), 1355 (s), 1270 (s), 1175 (s), 1090 (s), 970 (s), 910 (s), 820 (s), 785 (m), 795 (s), 695 (m) cm^{-1}.

M/z (e.i.): 352 (M^+, 9), 386 (9), 160 (39), 107 (62), 91 (100%).

(*R*)-1,2-Diacetoxy-4-benzyloxybutane (91)

Anhydrous potassium acetate (85 g, 850 mmol) was suspended in acetic anhydride (900 cm^3) and the dimesylate (*S*)-(90) (60 g, 170 mmol) added. The mixture was refluxed under a dry nitrogen atmosphere for 3 hours (good stirring was essential to prevent caking). Afterwards, the solvent was removed *in vacuo* and the residual paste extracted with dichloromethane (4 x 250 cm^3). These combined, solutions were dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford a very dark brown oil. Triple distillation of this material gave the pure product (^1H n.m.r. spectroscopy, t.l.c.) as a pale yellow oil (22.5 g, 47.3%); b.p. 124-132, 0.005 mmHg.

$[\alpha]_D^{20}$ + 14.6° (C = 4.8 in $CHCl_3$).

δ_H (CCl_4): 1.81 (2H, m, CH_2); 1.92 (3H, s, CH_3); 1.96 (3H, s, CH_3); 3.42 (2H, m, $C\underline{H}_2OBn$); 3.95 (1H, dd, J_{AX} 7.3 Hz, J_{AB} 14.7 Hz, $\underline{H}CHOAc$); 4.21 (1H, dd, J_{BX} 3.6 Hz, J_{BA} 14.7 Hz, $HC\underline{H}OAc$); 4.40 (2H, s, $C\underline{H}_2Ph$); 5.12 (1H, m, CH); 7.23 (5H, s, Ph) p.p.m.

ν_{max} (film): 3090 (w), 3065 (w), 3035 (w), 2960 (w), 2935 (w), 2865 (w), 1740 (s), 1195 (w), 1455 (w), 1370 (m), 1230 (s), 1095 (m), 1045 (m), 955 (w), 735 (m), 695 (w) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; CH_2CH_2) one spot (u.v., I_2) at R_f 0.48.

M/z (e.i.): 280 (M^+, 7), 221 (10), 173 (21), 160 (64), 131 (29), 107 (23), 91 (100%).

Found: C, 64.56; H, 7.32; M^+, 280.1313; $C_{15}H_{20}O_5$ requires: C, 64.27; H, 07.19%; M^+, 280.1315.

(*R*)-4-Benzyloxybutane-1,2-diol (88)

The diacetate (*R*)-(91), (22.1 g, 78.9 mmol) was dissolved in methanol (300 cm^3) and potassium carbonate (40 g, 298 mmol) quickly added. The resulting suspension was stirred for 2 hours, filtered under suction and concentrated *in vacuo*. The residue was taken up in water (100 cm^3) and extracted with 1:1, 40-60° petrol:ether (3 x 50 cm^3). The aqueous phase was completely saturated by solid sodium chloride and re-extracted with ethyl acetate (4 x 50 cm^3). The latter combined washings were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a yellow viscous oil which was subjected to short-path distillation to furnish the pure product (14.7 g, 95%); b.p. 140-6°C, 0.005 mmHg.
$[\alpha]_D^{20}$ - 13.2° (C = 4.7 in $CHCl_3$).
The ^1H n.m.r. and i.r. spectroscopic data obtained for this compound were identical to those reported for its antipode.

(*R*)- and (*S*)-4-(2'-Benzyloxyethyl)-2-phenyl-1,3-dioxolane (92)

The diol (*R*)-(88), (14.0 g, 75 mmol), redistilled benzaldehyde (8.8 g, 82.5 mmol) and toluene-4-sulphonic acid monohydrate (0.5 g, 2.65 mmol) were dissolved in dry benzene (300 cm^3). The mixture was refluxed for 1 hour using a Dean-Stark apparatus to remove the water

formed. Neutralisation [solid K_2CO_3 (5 g, 36 mmol), stirred 0.5 hours], filtration at the pump and then removal of solvent *in vacuo* gave the crude product as an approximate 1:1 mixture of diastereoisomers. After heating to 40°C *in vacuo* (0.005 mmHg) for 12 hours to remove surplus benzaldehyde, the product was obtained as an essentially pure (by ^1H n.m.r. spectroscopy), pale yellow oil (20.46 g, 96.3%).

$[\alpha]_D^{20}$ + 4.9° (C = 3.2 in $CHCl_3$).

δ_H (CCl_4): 1.87 (2H, m, CH_2); 3.48 (2H, m, $\underline{CH_2}OBn$); 3.56 (1H, dd, J_{AX} 7.3 Hz, J_{AB} 14.4 Hz, $\underline{H}CHO$); 3.62 (1H, dd, J_{BX} 4 Hz, J_{AB} 14.4 Hz $HC\underline{H}O$); 4.11 (½H, m, OH); 4.23 (½H, m, CH); 4.40 (2H, s, $C\underline{H_2}Ph$); 5.18 (½H, s, $PhC\underline{H}$); 5.32 (½H, s, $PhC\underline{H}$) 7.25-7.38 (10H phenyl protons) p.p.m.

ν_{max} (film): 3090 (w), 3060 (w), 3030 (w), 2940 (w), 2920 (w), 2875 (s), 1495 (w), 1455 (m), 1400 (w), 1380 (w), 1363 (m), 1310 (w), 1220 (m), 1205 (w), 1090 (s), 1065 (m), 1025 (w), 970 (m), 912 (w), 740 (s), 695 (s) cm^{-1}.

T.l.c. (Silica Gel F_{254}; 49:50:1, 40-60° petrol:CH_2Cl_2:Et_3N) one spot (I_2, u.v.) at R_f 0.46.

In similar fashion, (*S*)-(88) (17.8 g, 90 mmol) was converted into (*S*)-(92) (30.9 g, 95.2%).

$[\alpha]_D^{20}$ - 5.2° (C = 5.1 in $CHCl_3$).

All other analytical data obtained for (*S*)-(92) were identical to those of its antipode.

(*R*)- and (*S*)-2-Benzyloxy-4-benzyloxy-1-bromobutane (93)

To a solution of (*R*)-(92) in 1,1,2-trichlorotrifluoroethane (150 cm^3), cooled to 0°C, was added

portionwise, solid, freshly recrystallised N-bromosuccinimide (13.4 g, 75 mmol) in subdued light. The reaction was left to stir for 60 hours at 5°C in the dark. After removal of the by-product (succinimide) by filtration, a clear orange solution remained, which was washed with saturated sodium bicarbonate solution until it was fully decolourised. The organic phase was subsequently dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the product as a yellow syrup (21.6 g, 97.3%), (purity ≥ 90% by ^1H n.m.r. spectroscopy).

$[\alpha]_D^{20}$ + 15.3° (C = 4.8 in $CHCl_3$).

δ_H (CCl_4): 2.12 (2H, m, CH_2); 3.55 (2H, m, $\underline{CH_2}OBn$); 3.62-3.76 (2H, m, $\underline{H}CHO + HC\underline{H}O$); 4.48 (2H, s, $\underline{CH_2}Ph$); 5.39 (1H, m, CH); 7.22-8.30 (10H, phenyl protons) p.p.m.

ν_{max} (film): 3085 (w), 3060 (w), 3030 (w), 2960 (w), 2920 (w), 2860 (m), 1721 (s), 1600 (m), 1581 (w), 1499 (w), 1450 (m), 1435 (w), 1360 (m), 1312 (m), 1268 (s), 1172 (m), 1100 (s), 1068 (m), 1025 (m), 980 (w), 940 (w), 905 (w), 855 (w), 735 (m), 705 (s), 695 (m) cm^{-1}.

T.l.c. (Silica Gel F_{254}; CH_2Cl_2) the spot (I_2, u.v.) at R_f 0.36.

In analogous fashion, (*S*)-(92), (29.9 g, 100 mmol) gave (*S*)-(93) (36.4 g, (93.7%).

$[\alpha]_D^{20}$ - 14.9° (C = 5.6 in $CHCl_3$).

All other analytical data obtained for (*S*)-(93) were identical to those of its antipode.

(*R*)- and (*S*)-(2-Benzyloxyethyl)oxirane (94) (Method A)

The bromoester (*R*)-(93), (26.0 g, 71 mmol) was added to a solution of sodium hydroxide (4.5 g, 112 mmol) in ethane-1,2-diol (50 cm^3) which was well stirred. The progress of the reaction was monitored by working up aliquots and examining their ^1H n.m.r. spectra. When no more (*R*)-(93) was disappearing (after 18.5 hours), the whole was extracted with pentane (3 x 100 cm^3). The combined pentane solutions were washed with water (3 x 50 cm^3), dried (Na_2SO_4) and evaporated *in vacuo* to furnish a brown oil. Two distillations of this material gave analytically pure expoxide as a mobile, colourless liquid (9.2 g, 74.2%), b.p. 110-2°C, 1.5 mmHg. $[\alpha]_D^{20}$ + 14.9° (C = 6.4 in $CHCl_3$) [e.e. ≥ 95% (chiral shift reagent)].

δ_H (CCl_4): 1.85 (2H, m, CH_2); 2.48 (1H, dd, J_1 2.7 Hz, J_2 4.5 Hz H-2 *trans* to H-1); 2.75 (1H, t, $J_2 = J_3$ 4.5 Hz, H-2 *cis* to H-1); 3.05 (1H, m, CH); 3.63 (2H, t, J 7 Hz, $C\underline{H}_2OBn$); 4.54 (2H, s, $C\underline{H}_2Ph$); 7.23 (5H, s, phenyl protons) p.p.m.

ν_{max} (film): 3090 (w), 3030 (m), 3000 (m), 2920 (s), 2860 (s), 2800 (w), 1495 (m), 1485 (w), 1460 (s), 1415 (w), 1365 (s), 1260 (m), 1205 (m), 1100 (s), 1030 (m), 910 (m), 830 (m), 740(s), 698(s) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; 1:1, 60-80° petrol: dichloromethane) one spot (u.v., I_2) at R_f 0.36.

H.p.l.c.: (1% solution of compound in hexane; volume injected 2 µl; eluent hexane; column Partisil; solvent flow rate 1.5 cm^3 min^{-1}; pressure 200 p.s.i.) one peak.

M/z (e.i.): 178 (M^+, 3), 177 (7), 160 (5), 150 (7), 140 (6), 107 (39), 105 (38), 91 (100%).

Found: C, 74.38; H, 8.05; M^+ 178.0996; $C_{11}H_{14}O_2$ requires: C, 74.13; H, 7.92%; M^+ 178.0994.

In analogous fashion, (*S*)-(93) (33.5 g, 93 mmol) was converted into (*S*)-(94) (11.1 g, 67.0%), b.p. 100-2°C, 0.5 mmHg.

$[\alpha]_D^{20}$ - 15.6° (C = 5.1 in $CHCl_3$); [lit.[142], $[\alpha]_D^{20}$ - 13.0 (C = 5.0 in $CHCl_3$)] [e.e. ≥ 95% (chiral shift reagent)].

Found: C, 74.27; H, 7.96%; M^+ 78.0993.

All other analytical data obtained for (*S*)-(94) were identical to those of (*R*)-(94).

(*S*)-(2-Benzyloxyethyl)oxirane (94) (Method B)

Under an atmosphere of dry nitrogen, a chilled (0°C), stirred solution of triphenyl phosphine (8.9 g, 34.2 mmol) and diol (*S*)-(88), (3.92 g, 20 mmol) in THF (30 cm^3) was treated with DIAD (5.12 g, 33.0 mmol) in 20 cm^3 of the same solvent. The mixture was subsequently refluxed for 17 hours. Removal of the solvent *in vacuo* left a viscous residue which was taken up in ether (100 cm^3), filtered and re-evaporated to furnish an orange oil. This was chromatographed on silica gel (50 g; eluent 1:2, ether:40-60° petrol). The first 150 cm^3 of column eluent were combined and concentrated *in vacuo* to afford the crude product as a pale yellow oil. Short-path distillation of this material gave spectroscopically homogeneous product as a mobile, colourless liquid (2.14 g, 58%), b.p. 130-6°C, 3 mmHg.

$[\alpha]_D^{20}$ - 11° (C = 4.3 in $CHCl_3$) [e.e. ≈ 80-4% (chiral

shift reagent)].

The ^1H n.m.r. and thin film i.r. spectral data were found to be identical to those of the sample of (*S*)-(94) prepared by Method A.

But-3-ene-1-ol (99)

This compound was prepared as a colourless liquid from allylmagnesium bromide and paraformaldehyde according to the procedure of Linstead and Rydon[147] (28 g, 43.1%) b.p. 112-114°C (lit.[147], 47%, b.p. 112-4°C).

δ_H (CCl_4): 2.25 (2H, dt, $J_1 = J_2$, 7.3 Hz, CH_2); 2.99 (1H, b,s, OH); 3.58 (2H, t, J_1 = 7.3 Hz, CH_2OH); 5.08 (2H, dd, J_{trans} 17 Hz, J_{cis} 9.7 Hz, CH=); 5.76 (1H, m, CH=) p.p.m.

ν_{max} (film): 3350 (b,s), 3080 (w), 2980 (w), 2925 (s), 2870 (m), 1835 (w), 1640 (m), 1475 (m), 1435 (m), 1375 (w), 1200 (w), 1115 (w), 1045 (s), 985 (m), 910 (s), 865 (w) cm^{-1}.

4-Benzyloxybut-1-ene (100)

Sodium hydride (10 g, 40 mmol) was suspended in dry DMF (100 cm^3) and cooled to -10°C under an inert nitrogen atmosphere, whereupon alcohol (99) (26.6 g, 370 mmol) in DMF (150 cm^3) was added dropwise. The mixture was permitted to reach 0°C and stirred for 1 hour. Following this, benzyl bromide (53.9 g, 315 mmol, 38 cm^3) in DMF (100 cm^3) was introduced, and the reaction allowed to warm to room temperature overnight. The whole was poured into ice:water (700 cm^3) and extracted with 40-60° petrol (3 x 100 cm^3). These combined organic extracts were washed with water (3 x 50 cm^3), brine (50 cm^3), then dried ($MgSO_4$), filtered, and evaporated *in vacuo*. Distillation of the residue gave

the pure product as a colourless, pleasant smelling oil (43.3 g, 76%); b.p. 94-6°C, 12 mmHg.

δ_H (CCl_4): 2.32 (2H, m, CH_2); 3.43 (2H, t, J 7.3 Hz, CH_2O); 4.43 (2H, s, $C\underline{H}_2Ph$); 5.01 (2H, dd, J_{cis} 9.7 Hz, J_{trans} 17 Hz, $=CH_2$); 5.81 (1H, m, CH=) p.p.m.

ν_{max} (film): 3060 (m), 3025 (m), 3000 (w), 2975 (w), 2930 (m), 2900 (m), 2850 (s), 2785 (w), 1950 (w), 1870 (w), 1810 (w), 1640 (m), 1605 (m), 1495 (m), 1455 (m), 1430 (w), 1360 (s), 1305 (w), 1265 (w), 1200 (m), 1195 (s), 1025 (m), 990 (m), 910 (s), 860 (w), 815 (w), 730 (s), 695 (s) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; 3:1, 40-60° petrol:dichloromethane) one spot (I_2,u.v.) at R_f 0.65.

M/z (e.i.): 162 (M^+, 11), 122 (2), 105 (36), 41 (100), 77 (18), 69 (9), 54 (15%).

Found: C, 81.27; H, 8.86; M^+ 162.1048; $C_{11}H_{14}O$ requires: C, 81.44; H, 8.70%; M^+ 162.1045.

Rac-(2-Benzyloxyethyl)oxirane (94) (Method C)

To a cooled (0°C), stirred solution of (100) (24.3 g, 150 mmol) in dichloromethane (400 cm^3) was added commercial (85%) 3-chloroperbenzoic acid (40 g, 240 mmol) in 300 cm^3 of the same solvent. The mixture was allowed to warm to room temperature overnight. The homogeneous solution was washed with saturated sodium sulphite solution (2 x 50 cm^3), sodium bicarbonate solution (2 x 250 cm^3), brine (100 cm^3) and then dried (Na_2SO_4). The crude product isolated after removal of solvent *in vacuo* was twice distilled to furnish the pure product, (23.4 g, 85.6%), b.p. 120-2°C, 2.5 mmHg.

The ^{1}H n.m.r. and thin film i.r. spectra obtained for this sample were identical to those cited earlier for pure (*R*)-(94) (Method A).

Chapter 4

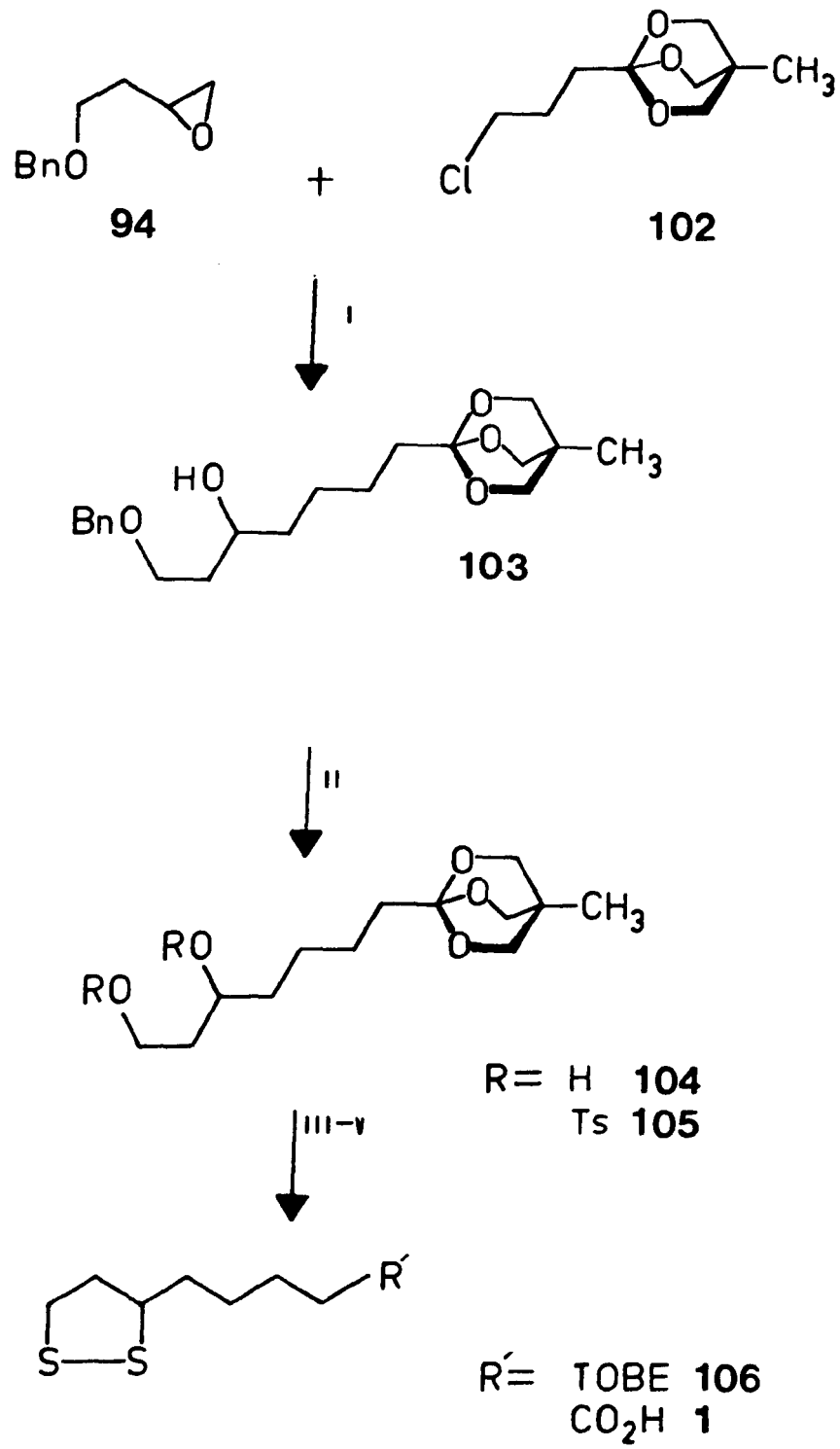
Lipoic Acid From (2-Benzyloxyethyl)oxirane via Schemes Incorporating the Haloform Reaction, The Baeyer Villiger Oxidation and Homologative Hydroboration

4.1 INTRODUCTION

The original plan as outlined in previous work at Warwick[103], for the conversion of the enantiomers of (2-benzyloxyethyl)oxirane (94) into the corresponding stereoisomers of lipoic acid is shown in Scheme 4.1. The formation of an organolithium or Grignard derivative of 1-(3-chloropropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (abbreviated to 3-chloropropyl-TOBE for convenience) and its subsequent coupling with epoxide (94) under copper catalysis to assemble the linear eight carbon backbone, was the crucial step in this route. Having performed the coupling, the product 5-hydroxy-7-(benzyloxy)heptyl-TOBE (103) was to be debenzylated to give 5,7-dihydroxyheptyl-TOBE (104). Reaction of diol (104) with two equivalents of tosyl chloride was envisaged as yielding 5,7-di(toluene-4-sulphonyloxy)heptyl-TOBE (105), which would furnish the TOBE derivative of lipoic acid (106) after treatment with sodium sulphide and sulphur[105]. Trivial, two step deprotection (dilute acid and then dilute base[156]) would then complete this elegant route.

It was hoped that this novel synthesis would also admirably demonstrate the almost ideal properties

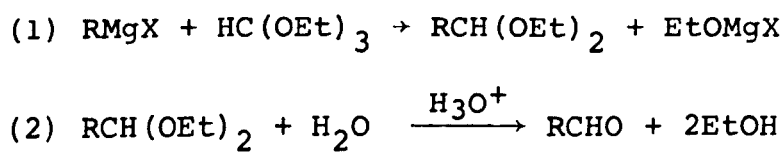
Scheme 4.1



Proposed Reagents: (i) Mg, THF, Li_2CuCl_4;
(ii) H_2, Pd/C, MeOH;
(iii) TsCl (2.2 equivalents), pyridine
(iv) Na_2S, S, DMF;
(v) H^+, OH^-, H^+.

of TOBE-derivatives as masked carboxylic acids. These are their improved synthetic accessibility, inertness toward organometallic reagents, chromatographic stability and milder deprotection conditions compared with other derivatives previously proposed as protecting groups for carboxylic acids[153-155]. Both the synthesis and this application of TOBE-derivatives were conceived at Warwick[103,156].

The stability of these and other cyclic orthoesters towards RLi and RMgX is in marked contrast to their acyclic analogues. For instance the reaction of triethyl orthoformate with Grignard reagents is a well-known method for preparing aldehydes[106] according to the equations below.



(1) $RMgX + HC(OEt)_3 \rightarrow RCH(OEt)_2 + EtOMgX$

(2) $RCH(OEt)_2 + H_2O \xrightarrow{H_3O^+} RCHO + 2EtOH$

The analogous reaction of other acyclic orthoesters for the preparation of ketones gives much lower yields and is not used practically[106].

Although, formally TOBE-derivatives are bicyclic orthoesters of the carboxylic acid and 2,2-*bis*(hydroxymethyl)-propan-1-ol, the nitrile corresponding to the former provides the starting point for their synthesis[156]. Transformation of the nitrile into the 1,1,1-triethoxyorthoester was carried out *via* the imidic ester hydrochloride according to the procedure of McElvain *et al.*[157]. Transesterification of the latter with 2,2-*bis*(hydroxymethyl)-propan-1-ol under acid catalysis gave the TOBE-derivative in 45-55% overall yield[103].

In this way 4-chlorobutyronitrile, itself made from 1-bromo-3-chloropropane and potassium cyanide, was converted into (102)[103,156].

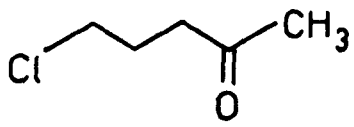
Unfortunately, Scheme 4:1 was thwarted by the inability of (102) to react with lithium or magnesium metals. Exhaustive attempts to effect formation of an organometallic reagent from (102), under almost every conceivable combination of appropriate experimental conditions proved unrewarding[103]. The iodo-analogue of (102) was even inert to "Rieke megnesium"[158] in refluxing THF[103]. This unexpected result led to the abandonment of (102) in the project and therefore necessitated consideration of alternative routes from epoxide (94) to the target molecule.

4.2 LIPOIC ACID *via* THE HALOFORM REACTION

The successful formation of Grignard reagents from haloaldehydes or haloketones whose carbonyl functionalities have been protected as 1,3-dioxolane or 1,3-dioxane acetals has been extensively reported in the literature. Although the conversion of an aldehyde or ketone into a carboxylic acid must involve an oxidation step in addition to protection and deprotection, a route based on this methodology seemed quite feasible.

In previous work at Warwick, D. A. Howes[103] began to explore the potential of 5-chloropentan-2-one (107), masked as 2-(3'-chloropropyl)-2-methyl-1,3-dioxolane (108), as the source of C-1 to C-4 in the target molecule

(Scheme 4.2). The approach is based upon the oxidation of methyl ketones to carboxylic acids by the haloform reaction.



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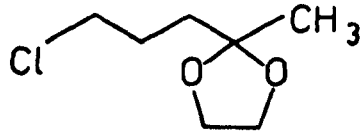

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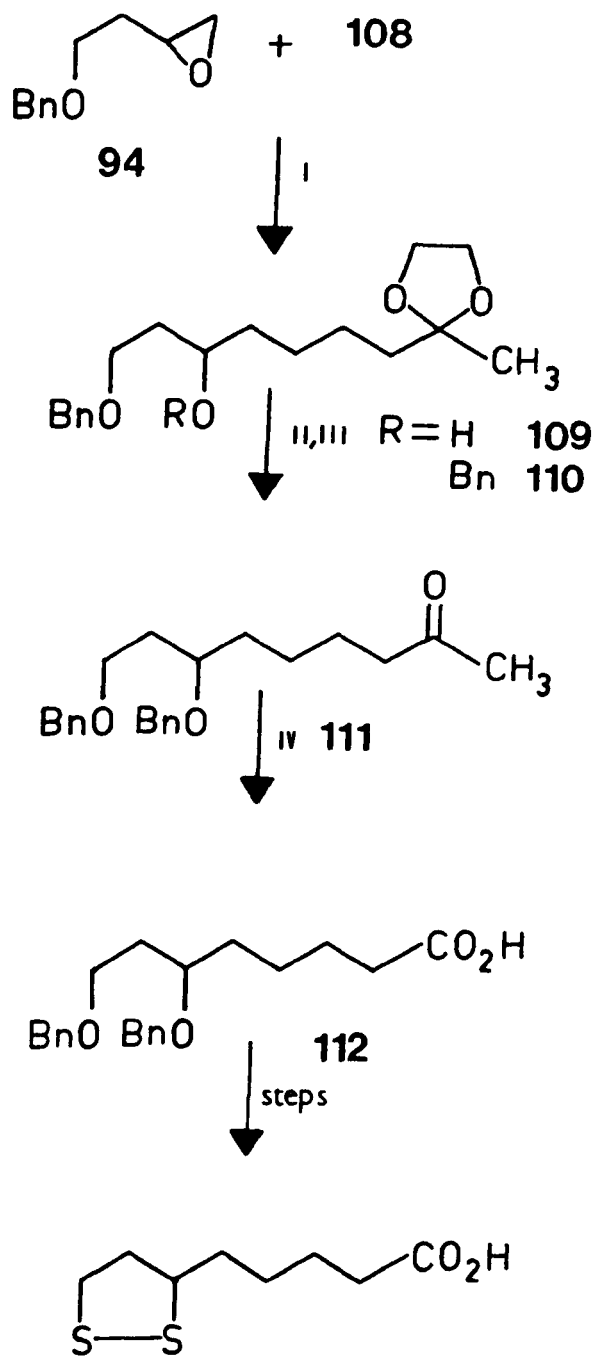
Obviously, such a sequence is not novel[159,160], but during the present project it was proposed to finish this route and then devise an improved, more innovative synthesis of lipoic acid afterwards.

The successful coupling of the Grignard derivative of (10̲8) with epoxide (*S*)-(9̲4) to furnish (*R*)-2-[5-hydroxy-7-(benzyloxy)heptyl]-2-methyl-1,3-dioxolane (10̲9) had been achieved, as had the subsequent benzylation and hydrolysis of the acetal function giving (*R*)-[5,7-*bis*-(benzyloxy)heptyl]-2-methyl-1,3-dioxolane (11̲0) and (*R*)-5,7-*bis*(benzyloxy)nonan-2-one (11̲1), respectively. Trial experiments on the haloform oxidation of (*R*)-(11̲1) had shown a peak at δ 13.4 in the ^{1}H n.m.r. spectrum, indicative of a carboxylic acid. Isolation and full characterisation of the desired product-(*R*)-6,8-*bis*(benzyloxy)-octanoic acid (11̲2), were not attempted owing to lack of time.

Scheme 4.2

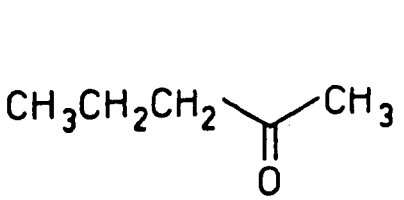


Proposed reagents: (i) Mg, THF, Li_2CuCl_4;
(ii) NaH, BnBr, THF, reflux;
(iii) H_3O^+;
(iv) $NaOH_{aq}$, Br_2;

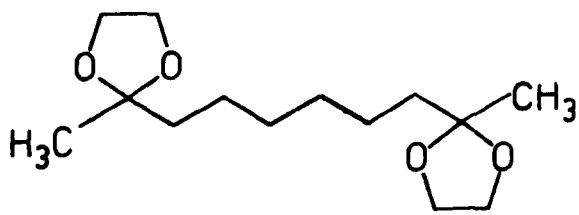
Chloroketone (107) was synthesised in two steps from ethyl acetoacetate following a literature procedure[161]. The conversion of (107) into the acetal (108) was effected in essentially quantitative yield by the standard method[162].

Formation of the Grignard reagent of (108) and subsequent copper catalysed coupling with *rac*-(94), were reproduced without difficulty. The ratio of (108) to *rac*-(94) was increased from 1.2:1 to 2.0:1.0 resulting in a significant (15%) increment in the yield of product. Crude *rac*-(109) was purified by flash column chromatography during which a more lipophilic by-product was readily separated. The identity of this compound was quickly established as 2-methyl-2-propyl-1,3-dioxolane (113) from its rather featureless ^{1}H n.m.r. and infrared spectra as well as its identical R_f with an authentic sample. This product was expected since it arises from the quenching of the excess Grignard derivative of (108) with the aqueous ammonium chloride used in the work-up. Closer examination of the sample of (113) obtained (^{1}H n.m.r. spectroscopy, t.l.c.) indicated that at least one other substance of similar constitution was present. The absence of a triplet at δ 3.50 ($J \simeq 7$ Hz) showed that this other substance was not the unreacted starting material (108). It appeared that the unidentified compound could well be the diacetal (114) formed from the Wurtz-type coupling of two molecules of (108) *via* their Grignard derivatives[106]. Transition metal salts are known to be effective catalysts for this process; copper(I) compounds being amongst the best in this respect[108]. Hence the

presence of (114) may readily be explained. Integration of the ^1H n.m.r. spectrum of the crude sample of (113) indicated that the extent of the contamination was 10-20%. An accurate determination was not possible because of partially overlapping resonances. The estimate was made by comparing the ratio between the integral of the terminal methyl triplet at δ 1.03 (J 7.3 Hz) and the total integral between δ 1.30 and 1.67 given by the methyl singlet and the two methylene multiplets, for the crude and authentic (pure) samples of (113).



113



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Protection of the free hydroxyl group of (109) was considered a necessary safeguard against possible side reactions encountered during the haloform oxidation. In previous work[103], (*R*)-(111) had been made by benzylation of (*R*)-(109) under phase transfer conditions[132] essentially the same as those used to prepare (*S*)-(88) from (*S*)-(85) in Chapter 3. The immediate product (*R*)-(110) was not isolated, but subjected to acid hydrolysis to furnish (*R*)-(111). However, in this instance a low yield (28%) of (*R*)-(111), and a greater recovery of (*R*)-7-hydroxy-9-

(benzyloxy)nonan-2-one (38%), derived from unreacted starting material, was obtained. Clearly this preparation was unsatisfactory, and demonstrates that the application of phase transfer catalysed benzylation[132] is limited to the more reactive primary alcohols. Additionally, separation of the benzylated product is much more laborious if it cannot be extracted into the aqueous phase, as is the case here [*cf.* the preparation of (*S*)-(88)].

Alternative benzylation procedures were therefore explored. The method of Hungerbrühler *et al.*[133] gave a 61.3% yield of *rac*-(110), but significant quantities of unreacted *rac*-(109) were also present (i.r. spectroscopy 3350 cm^{-1}; t.l.c.). A superior procedure comprised boiling *rac*-(109), sodium hydride and excess benzyl bromide under reflux in THF. In this way an 83.4% yield of *rac*-(110) was realised after purification by flash column chromatography. No unreacted *rac*-(109) was detectable. The grade of sodium hydride used was found to be very important in determining the success or failure of this reaction. Granular sodium hydride, although more convenient to handle, and apparently adequate for the quantitative deprotonation of primary alcohols[133,142], was very inefficient in deprotonating *rac*-(109), good conversions into *rac*-(110) being impossible to achieve. Thus, dispersions of sodium hydride in oil (50% or 80%) were used exclusively. Once the mineral oil has been removed, (by washing with pentane) a finely divided and much more reactive form of this reagent results. Use of THF (b.p. 65°C) was also found to be necessary, since an earlier

run in which the aforementioned reactants were boiled under reflux in ether (b.p. 35°C) for the same time gave ≤ 15% conversion into the product (^{1}H n.m.r. spectroscopy).

The secondary benzylic protons in the ^{1}H n.m.r. spectrum of *rac*-(110) appeared as a pair of doublets (between δ 4.38 and 4.46, $J_1 = J_2$ 13.0 Hz) as a consequence of becoming diastereotopic due to the chiral centre at C-5. This was later found to be a general feature of all secondary benzyl ethers in which the benzyloxy group is attached directly to an asymmetric centre.

Acidic hydrolysis of *rac*-(1$\underset{\sim}{1}$0) gave a high yield (82.3%) of *rac*-(1$\underset{\sim}{1}$1). Flash column chromatography was again used to purify the product. The modification described raised the overall yield of (1$\underset{\sim}{1}$1) from epoxide (9$\underset{\sim}{4}$) from 17.6% to 55.7% without difficulty.

Trial haloform reactions were performed next. Accordingly, *rac*-(1$\underset{\sim}{1}$1) was oxidised in chilled (0°C), freshly prepared solutions of bromine in aqueous sodium hydroxide with 1,4-dioxane as co-solvent[160]. Although several runs were made and the ^{1}H n.m.r. spectrum of the crude products always showed a broad resonance somewhere between δ 11.6-13.7, indicating that carboxylic acids were present, a brown oil containing a complex mixture of substances was isolated from the work-up on each occasion. Variations in the rate of addition, rate of stirring and the water:1,4-dioxane ratio made negligible difference to the outcome. The crude product was treated with 3% methanolic hydrogen chloride in the hope that the methyl ester of *rac*-(1$\underset{\sim}{1}$2) could be separated

by chromatographic means. Although methyl esters had definitely been formed (infrared spectroscopy, ν_{max}, 1735 cm^{-1}), separation of these substances from the other products of the reaction by p.l.c. proved unrewarding. An attempt was made to recover *rac*-(11̲2) as its sodium salt. The crude esterified mixture was taken up in ether and saponified by stirring with aqueous sodium hydroxide. Acidification of the aqueous phase followed by extraction with dichloromethane led to the isolation of a small amount of yellow oil. Examination of this material (^1H n.m.r., i.r. spectrsocopy, t.l.c.) revealed its constitution to be complex. The absence of any aromatic (≃ δ 7.20) or benzylic (≃ δ 4.40) resonances ruled out the presence of any *rac*-(11̲2). It would appear that the sodium salt of *rac*-(11̲2) is too lipophilic to be extracted into the aqueous phase. From these results it was concluded that methyl ketone (11̲1) was not amenable to oxidation by the haloform reaction and Scheme 4.2 was therefore aborted.

The principle reason for the low yield of (11̲2) in this reaction was ascribed to the lack of regioselective bromination at the methyl substituent of the carbonyl group of (11̲1). Hence, competitive halogenation occurs at C-7 and the resulting products cannot lose the tribromomethyl anion to furnish a carboxylic acid. Examination of the ^1H n.m.r. spectrum of the crude product also revealed that several spurious peaks had appeared in the aromatic and benzylic regions, suggesting that oxidation of the benzyl protecting groups had also been taking place. Investigation into the identity of the by-

products or the use of further chromatographic fractionation (h.p.l.c.) to resolve the (*inter alia*) methyl ester mixture was not considered worthwhile.

The instances where the haloform reaction has been successfully employed appear to be restricted to methyl ketones whose other carbonyl substituent either cannot undergo enolization (e.g. when R = *t*-butyl or phenyl[160]) or whose enolate possesses considerably less reactivity towards bromine or hypobromite (the identity of the halogenating species has not been established with certainty)[163-165].

4.3 LIPOIC ACID *via* THE BAEYER-VILLIGER OXIDATION

Although the failure of the haloform reaction necessitated the abandonment of Scheme 4.2, the success of the preceding steps in this route indicated that the approach was still valid provided an alternative means of oxidising a ketone intermediate could be found. The Baeyer-Villiger[166] oxidation of ketones to esters is another way of achieving the desired transformation. Thus, substitution of the haloform step by this reaction would afford a second chance to follow the general methodology of Scheme 4.2 with only minor modifications.

Organic peracids (RCO_3H) are usually employed to carry out Baeyer-Villiger oxidations. These reagents are generally more selective oxidants than the halogen:aqueous base mixtures utilised in haloform reactions. Most ketones will react with peracids under relatively mild conditions, and so the flexibility of a route incorporating

such a reaction is also greatly enhanced.

The mechanism of the Baeyer-Villiger reaction has been extensively studied[167-170], and the generally accepted interpretation, consistent with most of the observed experimental data, is shown in Fig. 4.1. The oxidation is subject to acid catalysis. Following protonation, the ketone is nucleophilically attacked by the peracid to form the tetrahedral intermediate (I). Fragmentation of this intermediate proceeds by migration of one of the ketone carbonyl substituents onto the formally electron deficient α-oxygen of the peracid, with concomitant expulsion of the parent carboxylic acid, leaving the ester. Electron donating groups on the ketone, and electron withdrawing groups on the peracid, enhance the rate of reaction.

In the oxidation of unsymmetrical ketones (i.e. $R^1 \neq R^2$), two isomeric esters are possible. Usually one product predominates, due to the differing migratory aptitudes of the various carbonyl substituents. Generally speaking, the more electron rich the substituent, the higher its relative migratory aptitude (e.g. phenyl ≈ *t*-alkyl > *s*-alkyl > *n*-alkyl > methyl). Obviously this regioselectivity is crucial to the envisaged application of the step and a choice of substituents with widely differing migratory aptitudes is essential for the effect to be maximised.

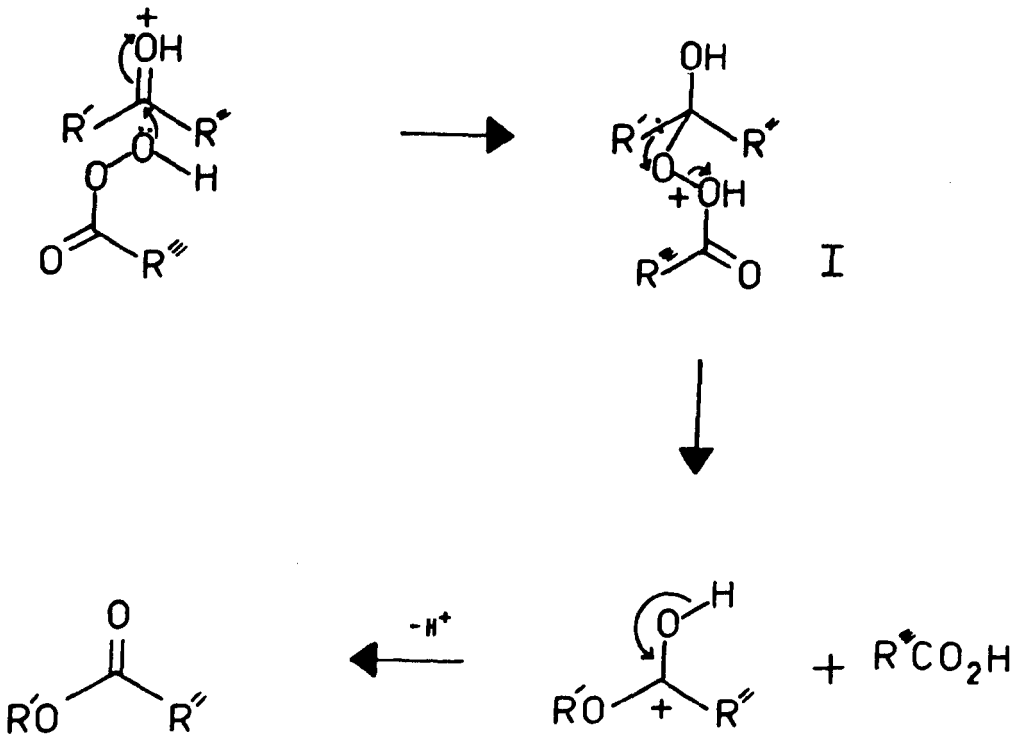
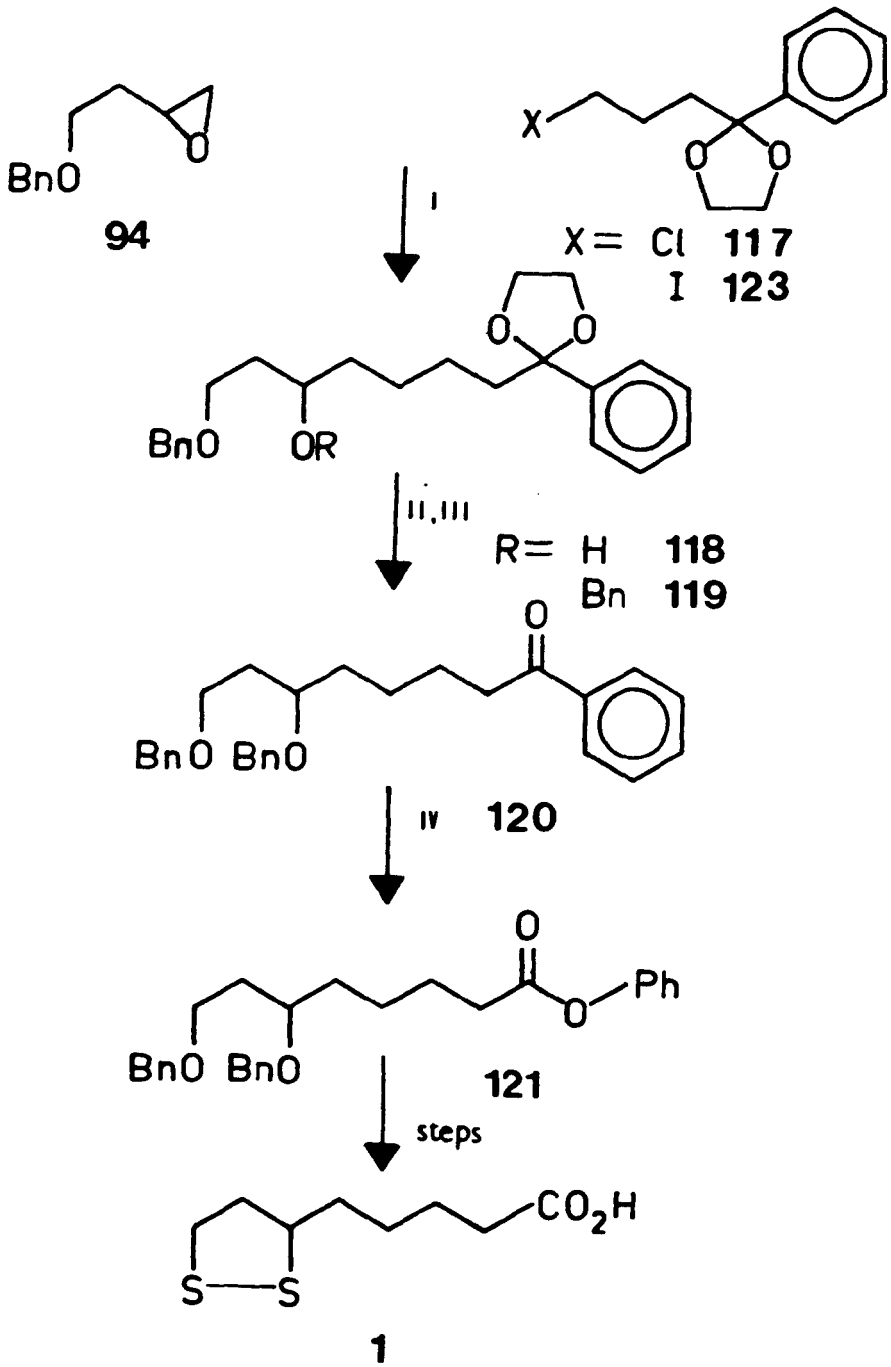


Fig. 4.1

From these considerations it is apparent that the methyl group will show the least preference to migrate to oxygen. Hence, methyl ketones will give acetates rather than methyl esters. Thus, ketone (1̲1̲1) cannot be used as a precursor to an ester of (1̲1̲2). Therefore an analogue of (1̲1̲1) in which the methyl group is replaced by an electron rich substituent is necessary. A group with the desired properties is phenyl, not only because of the willingness with which it migrates but also because aryl ketones are more easily oxidised than their purely aliphatic analogues[172].

Scheme 4.3



Proposed reagents: (i) Mg, THF, Li_2CuCl_4;
(ii) NaH, BnBr, THF, reflux;
(iii) H_3O^+;
(iv) PTFA, CH_2Cl_2 Na_2HPO_4.

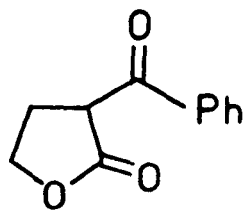
Scheme 4.3 depicts the conceived strategy. 4-Chlorobutyrophenone (116) would be protected as an acetal, e.g. 2-(3'-chloropropyl)-2-phenyl-1,3-dioxolane (117), the Grignard derivative of which would be coupled with epoxide (94) under copper catalysis. The resulting 2-[5-hydroxy-7-(benzyloxy)heptyl]-2-phenyl-1,3-dioxolane (118) would be benzylated to provide 2-[5,7-*bis*(benzyloxy)-heptyl]-2-phenyl-1,3-dioxolane (119) and then the ketone moiety deprotected affording 5,7-*bis*(benzyloxy)heptyrophenone (120). Baeyer-Villiger oxidation of (120) was envisaged as yielding phenyl 6,8-*bis*(benzyloxy)octanoate (121) with minimal contamination from the regiomeric 5,7-*bis*(benzyloxy)-heptyl benzoate (122). The synthesis would then be completed essentially as originally planned (Scheme 4.1).

Before embarking on Scheme 4.3 model Baeyer-Villiger reactions were performed on acetophenone. 3-Chloroperbenzoic acid is both easy to handle and commercially available and so a procedure employing this reagent would be particularly convenient. Whitesell *et al.*[173] have reported that alicyclic ketones are efficiently oxidised to lactones by dichloromethane solutions of this peracid, over several days in the presence of sodium bicarbonate as buffer. However, when Whitesell's procedure was attempted with acetophenone only a 52% conversion into phenyl acetate (^{1}H n.m.r. spectroscopy) was obtained after 1 week (the remainder was unreacted starting material). Further permutations of this procedure were not investigated, in view of the existence of an alternative, supposedly quantitative method of oxidising both aliphatic and

aromatic ketones to esters described by Emmons and Lucas[174]. These workers found that dichloromethane solutions of pertrifluoroacetic acid (PTFA), generated *in situ* from the reaction of trifluoroacetic anhydride (TFAA) with 90% hydrogen peroxide, were unsurpassed in their ability to effect Baeyer-Villiger oxidations. The superiority of this reagent over other peracids is attributed principally to the excellence of trifluoroacetic acid as a leaving group from the tetrahedral intermediate (I) (Fig. 4.1)[175]. It has been demonstrated that under comparable experimental conditions, the oxidation of cyclohexanone to caprolactone proceeds approximately 200 times faster with PTFA than peracetic acid[175]. Ketone oxidations with PTFA were carried out in the presence of solid disodium hydrogen phosphate as buffer to prevent transesterification of the product.

When Emmons and Lucas' procedure[174] was tried with acetophenone, phenyl acetate was isolated in 83% yield. The product showed no signs of contamination by methyl benzoate or starting material (^{1}H n.m.r. spectroscopy). Having found a satisfactory way of carrying out this step attention was focused to the synthesis of chloroketone (116).

Attempts to prepare (116) by a parallel method to that used to make (107)[161] proved disappointing. The alkylation of ethyl benzoylacetate gave a low yield of 2-benzoyl-4-butyrolactone (115) (21%) which in turn was converted into (116) in only 17.4% on treatment with hydrochloric acid.



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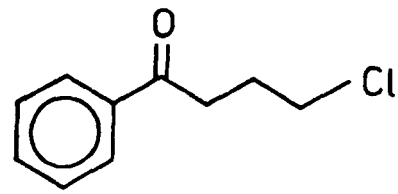


116

A vastly superior route to (116) was found in the patent literature[176]. Adequate details were given to permit reproduction of the procedures. Readily available 4-butyrolactone was first converted to 4-chlorobutanoyl chloride by thionyl chloride in the presence of zinc chloride. Friedel-Crafts acylation of benzene (reagent, solvent) with aluminium chloride as catalyst then gave (116). Temperature control (0-5°C) was very important in the latter preparation, to suppress side reactions caused by inter-molecular Friedel-Crafts alkylation. The overall yield of (116) from 2-acetyl-4-butyrolactone was 70%. Subsequent acetalisation of (116) with ethane-1,2-diol gave (117) quantitatively.

The formation of a Grignard reagent from (117) was undertaken next. Accordingly, a solution of (117) in THF was added to magnesium turnings covered by the same solvent which had been "initiated" with a few drops of 1,2-dibromoethane. Unexpectedly, no obvious reaction took place, and after a further 3 hours boiling under

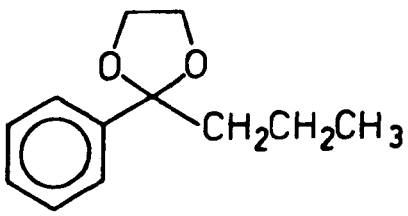
reflux an essentially quantitative recovery of starting material and unreacted magnesium was achieved [(108) reacted readily under the same conditions]. A sample of (117) was recrystallised twice more and the experiment repeated, but again organometallic formation did not occur.

More forcing conditions were implemented: an equimolar mixture of (117) and 1,2-dibromoethane in THF was added to the magnesium. Whilst copious effervescence (ethene) was observed due to the reaction of the latter, work-up furnished only unreacted starting material once again. A modification of this continuous entrainment procedure, whereby the 1,2-dibromoethane was added to a mixture of magnesium and (117) in THF, was also attempted, but to no avail.

Alkyl iodides are generally more reactive towards metals than their chloro-analogues. Therefore acetal (117) was converted into its iodo-analogue (123) by the action of excess sodium iodide in acetone (Finkelstein reaction[177]). Repetition of the continuous entrainment procedure detailed above led to the isolation of a brown oil from the work-up with aqueous ammonium chloride. The oil was found to consist largely of unreacted (123) (^{1}H n.m.r. spectroscopy), but several other products were also present in small amounts. Clear evidence for the formation of 2-phenyl-2-propyl-1,3-dioxolane (124) was still lacking, and it appeared that organometallic formation, if it took place, was accompanied by considerable side reactions (e.g. Wurtz coupling, β-elimination). At best, this result demonstrated that Grignard formation from (123) was

extremely inefficient and therefore no further work was carried out on it.

The impedance to organometallic formation could have been associated with the presence of the 1,3-dioxolane ring. To test this hypothesis 2-(3'-chloropropyl)-2-phenyl-1,3-dioxane (125) was made from (11̲6) and propane-1,3-diol. Unfortunately the pure recrystallised product failed to react with magnesium under continuous entrainment. Rather than test whether (11̲7) or (12̲5) would react with "Rieke magnesium"[158] it was decided to explore the use of suitable alternative chloroketones.



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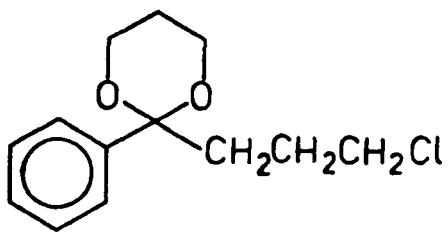
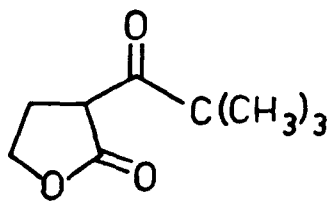


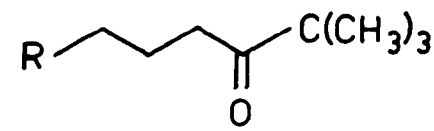
125

The *t*-butyl group possess a migratory aptitude virtually equivalent to phenyl in model Baeyer-Villiger studies[171]. Emmons and Lucas demonstrated that pinacolone was regio-specifically oxidised to *t*-butyl acetate in 87% isolated yield by PTFA[174]. This result indicated that substitution of an acetal of 6-chloro-2,2-dimethylhexan-3-one (12̲7) for one of (11̲6) would, in principle, be a valid tactic in Scheme 4.3.

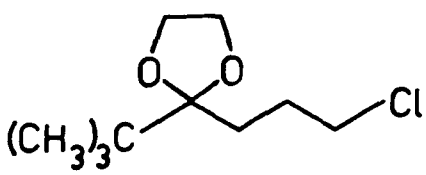
A synthesis of (127) *via* 2-pivaloyl-4-butyrolactone (126) was attempted first. The β-ketoester starting material was made from pinacolone and dimethyl carbonate according to a modified procedure based on the method of Jackman *et al.*[178]. The resulting methyl pivaloylacetate was isolated in 48% yield. Unfortunately, no (126) was isolated after an attempt to alkylate this β-keto ester with ethylene oxide. Examination of the crude product (^{1}H n.m.r. spectroscopy) showed that a mixture of 2,2-dimethyl-6-hydroxyhexan-3-one (128) and its acetate (129) had been formed instead. These compounds presumably arise by protonation of (126) and subsequent nucleophilic attack by water or acetic acid, followed by loss of carbon dioxide, during the work-up (a 50% solution of acetic acid was used to quench these reactions[161]). This result suggested that if hydrochloric acid were used in place of acetic acid, (127) could be formed directly.



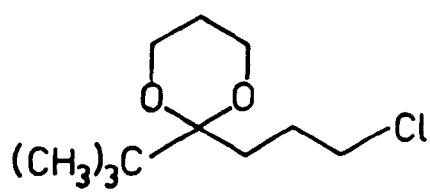
126



R = Cl **127**
OH **128**
OAc **129**



130



131

The above preparation was repeated, but protonation with 5 M HCl gave only a low yield of highly impure (127) (*ca.* 15%). Alcohol (128) may, in principle, be made directly by alkylating the enolate of pinacolone with ethylene oxide. When this reaction was attempted a moderate yield (34%) of the desired product was obtained. Compound (128) was subsequently converted into (127) by treatment with triphenyl phosphine in carbon tetrachloride boiled under reflux[179].

During this second synthesis a more convenient route to (127) was conceived. The reaction of Grignard reagents with acid chlorides as a route to ketones is normally frustrated by addition of a second mole of RMgX to the carbonyl group, furnishing a tertiary alcohol[106]. However, if the Grignard reagent is bulky, this second addition would be expected to be slow. Ketone formation may be favoured further by inverse addition and conducting the reaction at low temperature[180]. Thus, access to (127) by the action of *t*-butylmagnesium chloride on 4-chlorobutanoyl chloride is feasible. The S_N2 displacement of the alkyl chlorine atom by RMgX would almost certainly be slower than either primary or secondary attack at the carbonyl functionality, hence substantial interference from this possible side reaction is unlikely.

Accordingly, *t*-butylmagnesium chloride was added to excess 4-chlorobutanoyl chloride at -78°C. THF was used as solvent because it co-ordinates to Grignard reagents more strongly than diethyl ether and thereby may increase the steric bulk of the organometallic species further[180]. After

quenching with dilute sulphuric acid the principle contaminant, 4-chlorobutanoic acid was removed from the organic washings by aqueous sodium bicarbonate solution. After flash column chromatography and distillation pure (127) was obtained in 51% yield.

The synthesis of ketones from acid chlorides is most frequently accomplished *via* the intermediacy of organocadmium reagents[181]. These organometallics are usually generated *in situ* by metal-metal interchange between anhydrous cadmium chloride and RMgX. Although the reaction of organocadmium reagents with acid chlorides often proceeds in good yield, their application is restricted to the more stable primary alkyl or aryl derivatives. Organocopper[182], organomercury[183] and organozinc[184], reagents have also been used to make ketones from acid chlorides. Normant *et al.*[185] have recently reported that organomanganese reagents may also be utilised in this reaction. The cheapness, and stability of the *s*-alkyl and *t*-alkyl derivatives, make these organometallics particularly attractive[186]. However, the coupling of *t*-butyl manganese iodide with acid chlorides has been reported to proceed in only 45-60% yield[185,186] and thus offers little advantage over the more direct method devised by the author. More widely applicable procedures for the direct synthesis of ketones are the action of a Grignard reagent on an acid anhydride[187] or of an organolithium reagent on a free carboxylic acid[188] at low temperatures.

The acetals 2-(3 -chloropropyl)-2-(2-methyl-2-propyl)-1,3-dioxolane (130) and 2-(3-chloropropyl)-2-

(2-methyl-2-propyl)-1,3-dioxane (131) were prepared by the standard reaction[162] of (127) with ethane-1,2-diol and propane-1,3-diol, respectively. These compounds were obtained in lower yield than the corresponding acetals of (116) and had to be purified by flash column chromatography in addition to distillation. Unfortunately, the efforts applied in preparing (130) and (131) were not rewarded by their successful reaction with magnesium (continuous entrainment). In both cases a negative result to the Gillman test[189] was recorded after 5 hours boiling under reflux.

The use of cyclic thioacetal (1,3-dithiolane, 1,3-dithiane) derivatives of (116) and (127) was considered. It had been postulated that the basis of the inhibition of organometallic formation was associated with a hard-hard interaction between the magnesium and the oxygen atoms of the acetals. Replacement of oxygen by sulphur would lessen such an effect by substituting a weaker hard-soft interaction. However, this approach was not explored, on the grounds that the deprotection of thioacetals is often difficult and low yielding[190] and also because of the increasing conviction that steric phenomena were primarily responsible for the inertness of the acetals [and bicyclic orthoester (102)] towards magnesium. In which case the thioacetal derivatives would be equally resistant to Grignard formation.

Recourse to the use of "Rieke magnesium"[158] was not attempted either. The failure of this reagent to react with (102) or its iodo-analogue[103] led to doubt about its ability to metalate the acetals of (116) and (127).

Although the iodide (123) showed some signs of reaction, it was dubious whether "Rieke magnesium" would cleanly promote Grignard formation without also accelerating the deleterious side reactions observed to an unacceptable level. Parallel experiments with lithium metal were also omitted since previous work[103] had demonstrated that this element possessed no greater reactivity towards "difficult" halides than magnesium turnings.

It was therefore decided not to continue with routes which relied on halides with protected carbonyl groups and their fortuitous organometallic formation. Fortunately, the relatively simple structure of lipoic acid makes it possible to complete a synthesis from epoxide (94) by a wide variety of unrelated approaches. Rather than continue with an obvious pedestrian modification (e.g. the coupling of epoxide (94) with an organometallic derivative of masked 4-chlorobutyraldehyde), the opportunity was taken to apply some novel chemistry to the synthesis of the target molecule.

4.4 LIPOIC ACID *via* HOMOLOGATIVE HYDROBORATION

A terminal alkene is entirely compatible with Grignard formation, and is convertable into a carboxylic acid or ester by a wide variety of functional group interconversions. This premise was central to the remaining Schemes to lipoic acid described herein. One of the most versatile ways the chemistry of alkenes may be elaborated is *via* their conversion to trialkylboranes[191].

These organometallics are well known as intermediates in the overall regioselective anti-Markownikov addition of water to a terminal alkene to furnish a primary alcohol[191]. Whilst this reaction has been extensively used in synthesis, many mechanistically related transformations, which also exploit the boron atom's electron deficient nature and the unique ability of its vacant p_z orbital to facilitate 1,2-migrations, which can also result in the formation of carbon-carbon bonds, have received comparatively little attention[191-192]. In the pioneering studies the applicability of these reactions was demonstrated with simple alkenes, but little attempt was made to extend the procedures to polyfunctional substrates. Experience with "conventional" hydroboration has shown that organoboranes are tolerant of a wide variety of functional groups. This being so, it seemed surprising that so much of this area of chemistry had been neglected.

Thus, an objective of a synthesis incorporating one or more of these novel organoboron procedures would be to rekindle awareness of their existence and draw attention to any tactical advantages gained. Lipoic acid presents itself as an ideal target molecule, bridging the gap between the simple model compounds involved in the original work[191,192] and the synthesis of more complex structures where the availability of new techniques would be of greatest benefit. For a comprehensive account of the plethora of transformations mediated by trialkyl boranes, the reader is referred to several reviews on the subject[191-194].

Of specific interest, towards a synthesis of

lipoic acid, was the regiospecific conversion of a terminal alkene into an ester with an extension in chain length of two carbon atoms (Fig. 4.3).

Fig. 4.3

The practical means and mechanism[195] by which this transformation may be achieved is shown in Fig. 4.4. Thus, after generation of the trialkyl borane from a terminal alkene and borane:THF *via* the four-centre transition state shown, the resulting organometallic is attacked by a formal stabilised carbanion species to give a tetrahedral adduct (I). This intermediate breaks down by concerted 1,2-migration of one of the alkyl groups onto the carbon atom α- to the carboalkoxy group with concomitant expulsion of the leaving group X. The resulting distorted trigonal planar complex (II) yields one equivalent of homologated ester [$R(CH_2)_3CO_2Et$] and two equivalents of alcohol $R(CH_2)_2OH$, on work-up with alkaline hydrogen peroxide. The nucleophilic species may either be present *per se* (e.g. ethyl diazoacetate[196]) or be generated *in situ* by deprotonation of a suitable precursor (e.g. an α-halocarbanion derived from a haloacetate ester[197]

or a sulphonium ylid derived from a dimethyl sulphonium salt[198]).

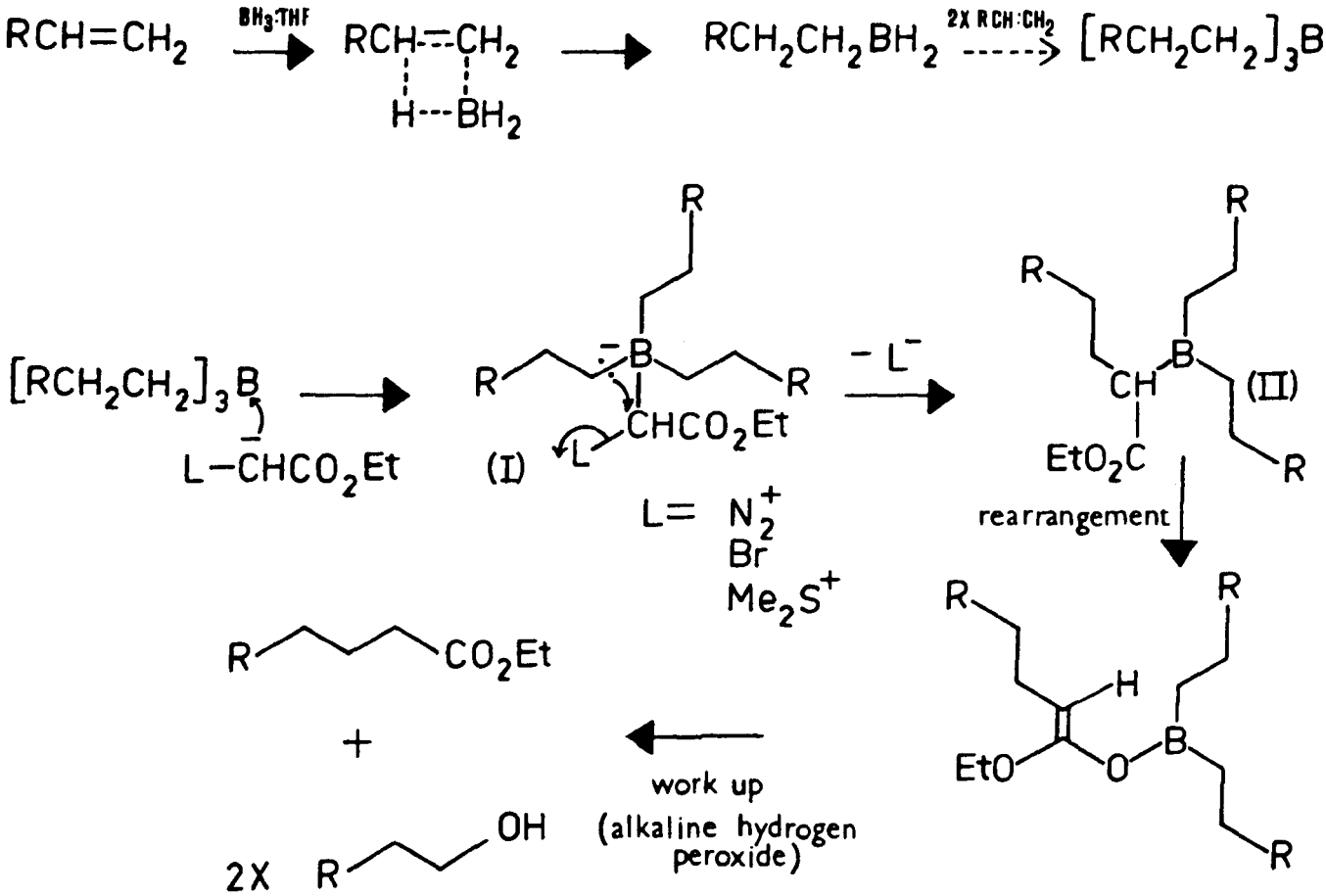
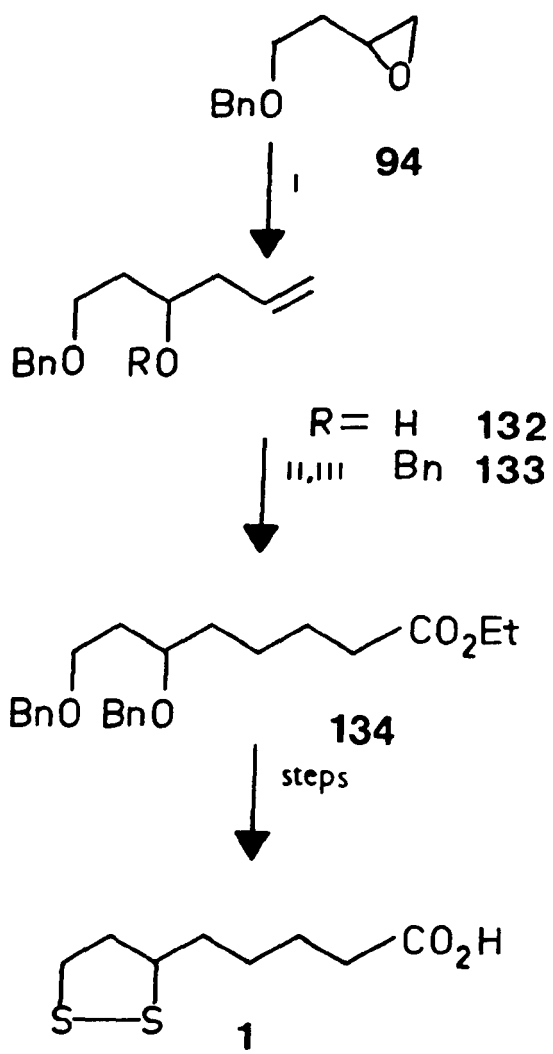


Fig. 4.4

The route constructed around this homologation is shown in Scheme 4.4. It was planned to open epoxide (94) with vinyl magnesium bromide under copper catalysis to give 4-hydroxy-6-(benzyloxy)hex-1-ene (132). Benzylation of (132) would afford 4,6-*bis*(benzyloxy)hex-1-ene (133) - the substrate of the key step. Ethyl 6,8-*bis*(benzyloxy)-octanoate (134) would thus be formed in a "one pot" reaction from (133). Conversion of (134) into lipoic acid would then follow the original methodology (Scheme 4.1).

Scheme 4.4



Proposed reagents: (i) Mg, THF, Li_2CuCl_4;
(ii) NaH, BnBr, THF, reflux;
(iii) Homologative hydroboration.

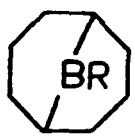
The preparation of vinyl magnesium bromide and its coupling with epoxides had already been successfully exploited at Warwick in the preparation of (*R*)- and (*S*)-pent-4-ene-2-ol[199]. Hence, this step and the subsequent blocking of the free hydroxyl group of (132) were trivial variants of familiar reactions.

Attention therefore turned to evaluating the effectiveness of the homologation procedure. The use of ethyl diazoacetate[196] appeared experimentally the most convenient, chiefly because addition of base was not required. Thus, tri-*n*-hexylborane, made *in situ*, was treated with the diazoester. As soon as the solutions met a smooth effervescence (nitrogen) was observed. After work-up, a 68% yield of ethyl octanoate (which had identical ^{1}H n.m.r. and i.r. spectral data to an authentic sample) was realised. This result was in close agreement with that in the literature[196]. However, it was found that the procedure[196] was only reproducible provided the borane:THF solution was fresh (i.e. the titrated hydride content was ≥ 90% of the manufacturer's specifications[102]). Even in the absence of moisture and oxygen, borane:THF solutions decompose slowly to *n*-butoxyborane ($C_4H_9OBH_2$) and, by further attack on the solvent, eventually become tri-*n*-butylborate[200]. The presence of these compounds was found to have a deleterious effect on the reaction. In a repetition of the above experiment using aged borane:THF (whose titrated hydride content implied a 0.6 M concentration of the reagent) the yield of product dropped to 19%.

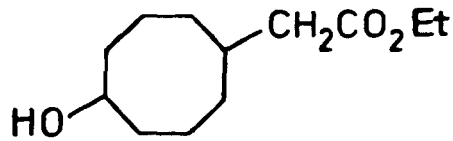
One obvious disadvantage of this procedure[196] is that only one of the alkyl groups migrates to carbon Thus, the yield based on alkene is automatically limited to 33.3%. Clearly, when a valuable alkene such as (133) is to be used this constraint is particularly undesirable. It was decided to repeat the preparation using a solution of 9-BBN (135) in THF[201]. This reagent is a commercially available, bulky dialkyl borane which can hydroborate sterically unhindered olefins to form B-alkyl-9-BBN species. It was hoped that the bulk of the formal bidentate cyclooctyl moiety in these boranes would decrease its migratory aptitude sufficiently to induce preferential movement of the introduced alkyl group to carbon. Whence, on oxidative work-up a mixture of homologated ester and cyclooctane-1,5-diol would be obtained, which could readily be separated. Adoption of this tactic would elegantly by-pass the yield restriction. Other advantages of 9-BBN include its relative stability (the compound is a solid which is sufficiently air stable for operations such as weighing to be carried out normally) and its increased regioselectivity[201] over borane:THF (e.g. $\geq$ 99.9% boron attachment to C-1 of a terminal alkene compared to $\simeq$ 94%, respectively).

Hydroboration of hex-1-ene with 9-BBN gave B-hexyl-9-BBN (136) which was subsequently treated with ethyl diazoacetate.[209] Although the evolution of nitrogen gas was observed, no ethyl octanoate was found to have been formed. The two components which had arisen were separated by short-path distillation, giving a volatile

colourless liquid and leaving a pale yellow residual oil. These two compounds were quickly identified as hexan-1-ol and ethyl 5-hydroxycyclooctylacetate (137), respectively (^{1}H n.m.r. and i.r. spectroscopy). Evidently, the cyclooctyl rather than the hexyl group had migrated to carbon in this instance.



R = H 135
C_6H_{13} 136



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The latter result is in striking contrast to that obtained by H. C. Brown and his co-workers[202]. These investigators have reported that reaction of (136) with ethyl bromo- or chloroacetate in the presence of base, exclusively gave ethyl octanoate and cyclooctane-1,5-diol. Since there are several differences between the two experimental procedures[196,202], as well as in the precise nature of the respective intermediates, (Fig. 4.4), the reason for the disparity cannot readily be identified.

Brown's preparation[202] of ethyl octanoate from (136) and ethyl bromoacetate was successfully reproduced by the author. Having apparently proved the viability of

this method, the synthesis of *rac*-(133) was undertaken. Accordingly, epoxide *rac*-(94) was reacted with excess vinyl magnesium bromide to furnish the coupled product, *rac*-(132) in excellent yield (94.6%). Because of the unhindered nature of vinyl magnesium bromide, loss of regiospecificity in the cleavage of the epoxide ring was considered possible. However, the presence of the regiomeric isomer 1-hydroxy-4-(benzyloxy)-2-vinylbutane (138) was not detected by either ^{1}H n.m.r. spectroscopy or h.p.l.c. After distillation (132) was benzylated essentially as described for the improved preparation of *rac*-(110) (Section 4.2). However, the work-up was modified, in that the excess benzyl bromide was removed by quaternization with triethylamine. This improvement removed the necessity to pump the residue overnight at high vacuum. Following purification by flash column chromatography, and Kugelröhr distillation, a pure sample of *rac*-(133) was obtained.

Surprisingly, an attempt to homologate *rac*-(133) by the aforementioned procedure[202] gave a much lower yield (22.3%) of the product *rac*-(134) than in the model experiment (63%). Examination of the crude product (^{1}H n.m.r. spectrscopy, t.l.c. showed that several unidentified by-products as well as cyclooctane-1,5-diol were present. Possible explanations for the low recovery of product were that incomplete migration had taken place due to insufficient reaction time or that incomplete oxidation of the trigonal planar boron adduct (II) (Fig. 4.4) had occurred due to the immiscibility of the aqueous and organic phases during

work-up. Therefore the experiment was repeated, giving an extra 30 minutes after the addition of potassium *t*-butoxide in *t*-butanol and sufficient ethanol added during the oxidation to ensure a homogeneous system. Unfortunately, these measures made little difference to the outcome, and a marginally lower yield (18.7%) of ester (134) was achieved.

Another possibility was that excess potassium *t*-butoxide was destroying unreacted bromoester by aldol condensation. Although this problem had not arisen in the analogous preparation of ethyl octanoate and the concentration of the *t*-butoxide had been accurately determined by titration, so that an excess would be avoided, it was nonetheless decided to substitute potassium 2,6-di-*t*-butylphenoxide[203] as the base. Despite the marked difference in the acidities of potassium *t*-butoxide (pKa ≈ 19.0) and potassium 2,6-di-*t*-butylphenoxide (pKa ≈ 11.0), the latter is still able to generate an α-halocarbanion from ethyl bromoacetate. Unlike potassium *t*-butoxide it does not induce the polymerisation of esters and even ketones and nitriles are relatively stable to it[204]. This has led to the expansion of Brown's α-alkylation procedure to embrace α-haloketones and α-halonitriles[204]. Previously these ketone and nitrile homologations could only be mediated *via* the corresponding α-diazoketones and α-diazonitriles[205].

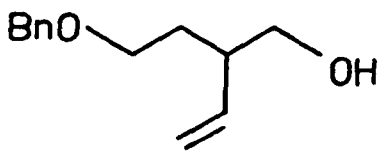
Potassium 2,6-di-*t*-butylphenoxide was made by adding the phenol (10% excess) to a solution of potassium *t*-butoxide in *t*-butanol of known molarity (the presence

of a slight excess of unreacted phenol has been reported to have no deleterious consequences[203]). Although the phenoxide may also be made in THF solution from the phenol and potassium or potassium hydride, these solutions are valueless in this work (apparently in the absence of *t*-butanol as co-solvent no homologated ester is formed[203]).

As a precaution, the use of potassium 2,6-di-*t*-butylphenoxide was tested on the conversion of B-hexyl-9-BBN into ethyl octanoate; a good yield (73.1%) of product was again achieved. However, when this modification was repeated with *rac*-(133), negligible improvement in the conversion into (134) was noted (25.2% yield, after column chromatography).

Diisoamyl borane (139) is another hindered dialkyl borane, generated *in situ* from the reaction of borane:THF with 2:2 equivalents of 2-methylbut-2-ene[206]. Like 9-BBN, it can undergo further hydroboration with an unhindered alkene to afford a trialkylborane. It was hoped that the introduced alkyl substituent would preferentially migrate to carbon with greater efficiency than was observed with the B-alkyl-9-BBN species. An advantage regarding the preparation of involatile esters [e.g. (134)], would be that the by-product alcohol (3-methylbutan-2-ol) can easily be removed *in vacuo*. Unfortunately an attempt to homologate (133) with ethyl bromoacetate in this way gave a complex mixture of products (^{1}H n.m.r. spectroscopy, t.l.c.) from which the desired ester (134), was isolated by p.l.c. in very low yield (5.8%). Amongst the other compounds identified were 3-methylbutan-2-ol, 4,6-*bis*(benzyloxy)-

hexan-1-ol (140) and ethyl 3,4-dimethylpentanoate (141). This result indicated that the migration of both isoamyl and 4,6-*bis*(benzyloxy)hexyl substituents had taken place. Diisoamylborane was thus shown to be unsuitable for this type of reaction.



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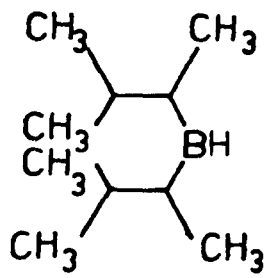
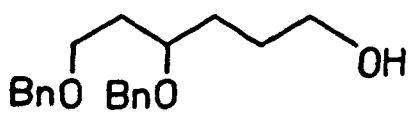


139



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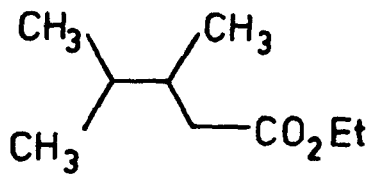

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Further work on homologative hydroboration was not pursued in view of the success being obtained from an alternative route (described in Chapter 5) which was being investigated at the same time. Regrettably there was insufficient time to attempt other variations which might increase the yield of (134) from this reaction and justify the application of Scheme 4.4. It is possible that the

presence of a benzyloxy group δ-to the boron atom markedly decreases the efficiency of migration, possibly through steric crowding of the tetrahedral intermediate (I) (Fig. 4.4). If this is the case, homologative hydroboration of (133) *via* mono- or dichloroborane may be the remedy[207]. These reagents are prepared *in situ* from boron trichloride and lithium borohydride according to the equations below[208].

$$LiBH_4 + BCl_3 \rightarrow LiCl + 2BH_2Cl$$

$$LiBH_4 + 3BCl_3 \rightarrow LiCl + 4BHCl_2$$

Ether is the usual solvent for the reaction and the resulting solutions may be used directly to hydroborate alkenes. The alkyl chloroboranes formed have been used to effect α-alkylation of ethyl diazoacetate (as well as α-diazoketones and α-diazonitriles). Although monochloroborane restricts the yield (based on the alkene) to 50%, procedures employing this reagent have apparently proved more consistent[194]. If the amount of (134) recovered in practice were close to this theoretical limit, then the use of monochloroborane would be acceptable, confirming the viability of Scheme 4.4.

4.5 EXPERIMENTAL

2-Acetyl-4-butyrolactone

This compound was prepared from ethyl acetoacetate and ethylene oxide according to the procedure of Van Tamelen *et al.*[161a] (3.7 g, 52.6%); b.p. 128-130°C; 16 mmHg (Lit.[161a], 59.4%; b.p. 150-1°C, 22 mmHg).

δ_H (CCl_4): 1.94 [3H, s, CH_3(enol)]; 2.25 [1H, m, HCH(keto)]; 2.38 [3H, s, CH_3(keto)]; 2.70 [1H, m, HCH(keto)]; 2.85 (2H, t, J 7 Hz CH_2(enol)]; 3.64 [1H, t, J 7.2 Hz, CH(keto)]; 4.28 [2H, t, J 7 Hz, CH_2(keto)]; 4.32 [2H, t, J 7 Hz, CH_2(enol)]; 13.39 [1H, s, OH(enol)] p.p.m.

The ratio of enol to keto tautomers was determined by integration of the ^1H n.m.r. spectrum to be ≈ 17:3 respectively.

ν_{max}(film): 3550 (b,m), 2900 (m), 2815 (m), 1772 (s), 1723 (s), 1658 (w), 1480 (w), 1377 (w), 1365 (m), 1286 (w), 1221 (m), 1159 (s), 1026 (w), 1004 (w), 930 (w), 783 (w), 692 (w), 661 (w) cm^{-1}.

5-Chloropentan-2-one (107)

This compound was made from 2-acetyl-4-butyrolactone by following the procedure of Cannon *et al.*[161b] (10.432 g, 86.6%); b.p. 64-5°C, 16 mmHg (lit.[161b], 78.6%; b.p. 80-3°C mmHg).

δ_H (CCl_4): 1.98 (2H, m, CH_2); 2.11 (3H, s, CH_3); 2.57 (2H, t, J 7 Hz, CH_2); 3.53 (2H, t, 7.2 Hz, CH_2) p.p.m.

ν_{max} (film): 3600 (w), 3420 (w), 3000 (w), 2962 (m), 2934 (w), 1708 (s), 1436 (m), 1421 (m), 1407 (m),

1358 (s), 1304 (m), 1262 (w), 1173 (m), 1156 (m), 1145 (m), 1074 (w), 1059 (w), 997 (w), 968 (w), 916 (w), 884 (w), 803 (w), 742 (m), 717 (w) 640 (m) cm^{-1}.

2-(3-Chloropropyl)-2-methyl-1,3-dioxolane (108)

This compound was prepared by boiling ketone (107), ethane-1,2-diol and a catalytic amount of toluene-4-sulphonic acid under reflux in toluene with azeotropic removal of the water formed[162] (18.151 g, 93.3%); b.p. 92-4°C, 17 mmHg.

δ_H (CCl_4): 1.25 (3H, s, CH_3); 1.68-1.87 (4H, m, 2 x CH_2); 3.49 (2H, t, J 7.2 Hz, CH_2); 3.86 (4H, s, 2 x CH_2) p.p.m.

ν_{max} (film): 2985 (m), 2964 (m), 2870 (m), 1440 (m), 1375 (m), 1308 (w), 1245 (w), 1215 (m), 1120 (m), 1095 (w), 1058 (s), 1042 (s), 940 (w), 870 (m) cm^{-1}.

Rac-2-[5-Hydroxy-7-(benzyloxy)heptyl]-2-methyl-1,3-dioxolane (109)

Under a static, dry, nitrogen atmosphere, magnesium turnings (5.0 g, 210 mmol) covered by THF (20 cm^3), were treated with 8 drops of 1,2-dibromoethane and warmed. Once the reaction had commenced, acetal (108) (16.5 g, 100 mmol) in THF (100 cm^3) was added, after which the preparation was refluxed for 1.5 hours. Having cooled to -78°C, a solution of lithium tetrachlorocuprate (0.27 g, 1.2 mmol) in THF (10 cm^3) was introduced, and, after 1 hour, a solution of *rac*-(94) (89 g, 50 mmol) in 50 cm^3 of the same solvent added over 30 minutes. The preparation was maintained at -78°C for a further 5 hours then allowed to reach room

temperature overnight. Work-up consisted of pouring the mixture into chilled (5°C) aqueous ammonium chloride solution (70 cm^3) and stirring for 30 minutes. The separated aqueous phase was washed with ether (50 cm^3) and the combined organic phases subsequently dried ($MgSO_4$), filtered, and concentrated *in vacuo* to furnish a yellow residual oil which was subjected to flash column chromatography (eluent, ether) to afford the pure product as a colourless oil (11.87 g, 77.1%).

δ_H (CCl_4): 1.23 (3H, s, CH_3); 1.25-1.72 (10H, m, 5 x CH_2); 2.84 (1H, b, s, OH); 3.65 (3H, m, C<u>H</u>OH, C<u>H</u>$_2$OBn); 3.83 (4H, s, 2 x CH_2); 4.40 (2H, s, C<u>H</u>$_2$Ph); 7.23 (5H, s, phenyl protons) p.p.m.

ν_{max} (film): 3440 (b, s), 3090 (w), 3070 (w), 3030 (w), 2990 (m), 2960 (s), 2865 (s), 1480 (w), 1450 (m), 1375 (m), 1320 (w), 1315 (w), 1260 (w), 1215 (w), 1090 (s), 1070 (s), 950 (w), 860 (w), 740 (w), 705 (m), cm^{-1}.

T.l.c. (Silica Gel F_{254}; ether) one spot (I_2, u.v.) at R_f 0.40.

<u>*Rac*-2-[5,7-*Bis*(benzyloxy)heptyl]-2-methyl-1,3-dioxolane</u> (110)

Alcohol *rac*-(109), (11.0 g, 35.7 mmol), pentane washed (3 x) sodium hydride dispersion (1.2 g, 50 mmol) and benzyl bromide (8.12 g, 47.5 mmol) were boiled under reflux in THF (115 cm^3), under a static, dry, nitrogen atmosphere for 17 hours. Having allowed to cool, water (5 cm^3) was cautiously added, and then the whole was poured into saturated aqueous potassium carbonate solution (50 cm^3). The organic phase was dried ($MgSO_4$), filtered,

and evaporated *in vacuo* to give the crude product. This was purified by flash column chromatography (eluent 1:3, ether:pentane) to provide the pure compound as a pale yellow oil (11.85 g, 93.4%).

δ_H (CCl_4): 1.25 (3H, s, CH_3); 1.22-1.69 (10H, m, 5 x CH_2); 3.59 (3H, m, C<u>H</u>OBn + C<u>H</u>$_2$OBn); 3.79 (4H, s, 2 x CH_2); 4.41 (2H, dd, $J_1 = J_2$ 13.0 Hz, 2^{O}-C<u>H</u>$_2$Ph); 4.43 (2H, s, 1^{O}-C<u>H</u>$_2$Ph); 7.21 (10H, s, phenyl protons) p.p.m.

ν_{max} (film): 3090 (w), 3070 (w), 3030 (w), 2930 (s), 2860 (s), 1460 (m), 1440 (w), 1375 (m), 1308 (w), 1255 (w), 1215 (m), 1120 (m), 1090 (w), 1090 (s), 1070 (s), 990 (w), 970 (w), 735 (w), 710 (s) cm^{-1}.

T.l.c. (Silica Gel F_{254}: eluent 1:3, ether:pentane) one spot (I_2, u.v.) at R_f 0.32.

<u>*Rac*-7,9-*Bis*(benzyloxy)-2-oxononane</u> (11̃1)

Acetal (11̃0) (10.0 g, 25.1 mmol) was dissolved in THF (100 cm^3) to which an equal volume of 1 M sulphuric acid was added. The mixture was subsequently stirred at room temperature overnight. After neutralisation, as well as saturation of the aqueous phase with solid sodium bicarbonate and sodium chloride, the organic phase was washed with brine (10 cm^3), dried ($MgSO_4$), and concentrated *in vacuo* to furnish the product (8.38 g, 94.2%). This material was pure by ^1H n.m.r. spectroscopy and therefore committed directly to the trial haloform oxidations.

δ_H (CCl_4): 1.36 (4H, m, 2 x CH_2); 1.55 (2H, m, C<u>H</u>$_2$C<u>H</u>$_2$OBn); 2.08 (3H, s, CH_3); 2.19 (2H, t, J 7 Hz, C<u>H</u>$_2$CO); 3.55 (3H, m, C<u>H</u>OBn + C<u>H</u>$_2$OBn); 4.40 (2H, s, 1^{O}-C<u>H</u>$_2$Ph); 4.42

(2H, dd, $J_1 = J_2$ 13.0 Hz, 2^{o}-C$\underline{H}_2$Ph); 7.25 (10H, s, phenyl protons) p.p.m.

ν_{max} (film): 3090 (w), 3060 (w), 3030 (w), 1715 (s), 1495 (w), 1450 (m), 1360 (w), 1205 (w), 1090 (s), 1065 (m), 1025 (w), 730 (s), 695 (s) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; 1:1, ether:40-60^{o} petrol) one spot (I_2, u.v.) at R_f 0.35.

Trial Baeyer-Villiger Oxidation of Acetophenone with 3-Chloroperbenzoic acid

Solid sodium bicarbonate (8.4 g, 100 mmol) was added to a stirred suspension of redistilled acetophenone (1.2 g, 10 mmol) and 3-chloroperbenzoic acid (4.42 g, 25 mmol) in dry dichloromethane (100 cm^3). The progress of the reaction was monitored by t.l.c. After 1 week, no more product was being formed, hence the reaction was quenched by pouring into water (70 cm^3). The organic phase was subsequently washed with sodium sulphite solution (100 cm^3), brine (50 cm^3), then dried ($MgSO_4$) and concentrated *in vacuo* affording a residual yellow oil (analysis of which by ^{1}H n.m.r. spectroscopy, indicated a 52% conversion to the product). The oil was fractionated by flash column chromatography (eluent, 1:1 dichloromethane:40-60^{o} petrol) to furnish phenyl acetate (0.58 g, 43%) and unreacted acetophenone (0.47 g, 39%). The ^{1}H n.m.r. and i.r. spectra of the isolated phenyl acetate were identical to those recorded for an authentic sample.

Trial Baeyer-Villiger Oxidation of Acetophenone with PTFA

A solution of PTFA was prepared by dropwise addition of TFAA (5.3 g, 25 mmol) to 85% hydrogen peroxide (6.8 g, 20 mmol) in dichloromethane (10 cm^3), at 0°C. This solution was then added to a cooled, stirred suspension of disodium hydrogen phosphate (7.5 g, 50 mmol) in a mixture of dichloromethane (40 cm^3) and acetophenone (1.2 g, 10 mmol), over 30 minutes. Once addition was complete the reaction was boiled under reflux for 2 hours and then filtered at the pump. The organic solution was washed with sodium sulphite solution (2 x 30 cm^3), sodium bicarbonate solution (2 x 30 cm^3) and brine (20 cm^3). After drying ($MgSO_4$), the solvent was removed *in vacuo* to furnish the crude product. This was distilled to give a sample of phenyl acetate whose ^1H n.m.r. and i.r. spectral data were indistinguishable from those an authentic specimen (1.12 g, 83%; b.p. 93-6°C, 18 mmHg).

2-Benzoyl-4-butyrolactone (115)

Redistilled ethyl benzoylacetate (26 g, 136 mmol) was added dropwise to a stirred solution of sodium methoxide in methanol [prepared by adding dry methanol (75 cm^3) to freshly cut sodium metal (3.22 g, 140 mmol)] and the mixture warmed to 50°C for 1 hour. After cooling to room temperature, a solution of ethylene oxide (6.2 g, 140 mmol) in methanol (20 cm^3) was added dropwise over 30 minutes. The reaction was then allowed to stand at room temperature for 48 hours. Removal of solvent *in vacuo* afforded a brown gum which was stirred with 1:1 acetic

acid:water (17 cm^3) for 10 minutes. After saturation with solid sodium chloride, the mixture was extracted with dichloromethane (3 x 50 cm^3). These washings were combined, washed with saturated sodium bicarbonate solution (2 x 15 cm^3), brine (20 cm^3), then dried ($MgSO_4$) and concentrated to furnish a yellow oil which solidified on standing. Recrystallisation of this material from 40-60° petrol gave the pure product as white needles (5.47 g, 21.3%); m.p. 56-9°C.

δ_H ($CDCl_3$): 2.71 (2H, m, CH_2); 4.49 (2H, m, 2 x CH_2O); 4.52 [1H, m, CH(keto)]; 7.43-7.91 (5H, phenyl protons); 12.6 (1H, b, s, OH(enol)] p.p.m.

The keto:enol ratio was 8:5 respectively, as determined by integration of the spectrum.

ν_{max} (melt): 3500 (b,w), 3350 (b,w), 3060 (w), 2970 (m), 2910 (m), 1765 (s), 1670 (s), 1590 (m), 1575 (m), 1480 (w), 1445 (m), 1370 (m), 1335 (m), 1290 (m), 1220 (m), 1145 (s), 1010 (s), 945 (m), 880 (m), 830 (w), 745 (m), 700 (sh), 650 (s), 630 (m) cm^{-1}.

4-Chlorobutanoyl Chloride

This compound was prepared from 4-butyrolactone according to the procedure of Kaltschmitt *et al.*[176a] (73 g, 81%); b.p. 68-9°C, 18 mmHg; (lit.[176a], 80.3%; b.p. 72-4°C, 20 mmHg).

δ_H (CCl_4): 1.96 (2H, m, CH_2); 2.16 (2H, t, J 7 Hz, $C\underline{H}_2CO$); 3.59 (2H, t, J 7.2 Hz, CH_2Cl) p.p.m.

ν_{max} (film): 2970 (m), 2930 (w), 2870 (w), 1790 (s), 1440 (w), 1405 (m), 1315 (w), 1295 (w), 1205 (w), 1160 (w), 1070 (w), 1040 (w), 980 (m), 965 (m), 945 (m), 925 (w), 855 (w),

780 (w), 730 (w), 710 (w) cm^{-1}.

4-Chlorobutyrophenone (116)

4-Chlorobutanoyl chloride (33 g, 234 mmol) was added dropwise to an ice-cooled suspension of anhydrous aluminium chloride (35 g, 262 mmol) in dry benzene (250 cm^3) over a period of 30 minutes, and the resulting mixture stirred for a further 2 hours. The internal temperature was kept between 0-5°C throughout this period. The whole was subsequently poured into a cooled (≤ 5°C) mixture of water (150 cm^3), saturated brine (50 cm^3) and 10 M hydrochloric acid (25 cm^3). The aqueous layer was extracted once with benzene (100 cm^3) and then discarded. The combined organic solutions were washed with aqueous sodium bicarbonate (3 x 100 cm^3), dried (K_2CO_3) and evaporated *in vacuo* to leave an orange oil. This material was purified by careful distillation in a Vigreaux apparatus, and was thus obtained as a colourless liquid (34.2 g, 80.1%); b.p. 108-110°C, 0.8 mmHg; (lit.[176b], 85.6%; b.p. 120-1°C, 1.0 mmHg).

δ_H (CCl_4): 1.90 (2H, m, CH_2); 2.08 (2H, t, J 7.0 Hz, $C\underline{H}_2CO$); 3.61 (2H, t, J 7.2 Hz, CH_2Cl); 7.22-7.35 (5H, phenyl protons) p.p.m.

ν_{max} (film): 3060 (w), 2955 (m), 1688 (s), 1605 (m), 1583 (m), 1445 (s), 1373 (w), 1305 (m), 1222 (s), 980 (m), 740 (s), 785 (s) cm^{-1}.

2-(3-Chloropropyl)-2-phenyl-1,3-dioxolane (117)

A mixture of (116) (20.4 g, 112 mmol), ethane-1,2-diol (12.4 g, 200 mmol) and toluene-4-sulphonic acid (188 mg, 1.0 mmol) in benzene (200 cm^3) was boiled under reflux with azeotropic removal of water (Dean-Stark apparatus) for 24 hours. After pouring into an equal volume of saturated sodium bicarbonate solution. The organic solution was washed with water (100 cm^3), dried ($MgSO_4$) and then evaporated *in vacuo* to yield a semi-solid residue, from which the pure product was obtained after recrystallisation from 40-60° petrol (19.3 g, 81.0%); m.p. 57-59°C.

δ_H (CCl_4): 1.65-1.91 (4H, m, 2 x CH_2); 3.48 (2H, t, J 7.2 Hz, CH_2Cl); 3.71 (2H, dd, J_{gem} 8.2, J_{vic} 6.7 Hz, HCH); 3.98 (2H, dd, J_{gem} 8.2, J_{vic} 6.7 Hz, HCH); 7.24-7.37 (5H, phenyl protons) p.p.m.

ν_{max} (soln. CCl_4): 2960 (m), 2890 (s), 1497 (s), 1312 (w), 1291 (w), 1264 (w), 1188 (m), 1043 (m), 947 (m), 910 (w), 702 (s) cm^{-1}.

2-(3-Iodopropyl)-2-phenyl-1,3-dioxolane (123)

A mixture of sodium iodide (75 g, 500 mmol), sodium bicarbonate (8.4 g, 100 mmol) and acetal (117) (5 g, 22 mmol) was boiled under reflux in A.R. acetone (600 cm^3) for 60 hours with exclusion of moisture. After filtering, the solvent was removed *in vacuo* and the residue taken up in water (300 cm^3). The resulting aqueous suspension was extracted with dichloromethane (2 x 100 cm^3) and the combined organic solutions dried (K_2CO_3) and evaporated to furnish a heavy pale yellow oil. Trituration of this

material in 40-60° petrol induced crystallisation. The product was obtained pure by subsequent recrystallisation from 40-60° petrol (4.19 g, 60.2%); m.p. 70-2°C.

δ_H (CCl_4): 1.67-1.92 (4H, m, 2 x CH_2); 3.20 (2H, t, 7.3 Hz, CH_2I); 3.69 (2H, dd, J_{gem} 8.3, J_{vic} 6.4 Hz, HCH); 3.94 (2H, dd, J_{gem} 8.3, J_{vic} 6.4 Hz, HCH); 7.20-7.33 (5H, phenyl protons) p.p.m.

ν_{max} (soln, CCl_4): 2950 (m), 2900 (m), 2870 (s), 1490 (w), 1470 (w), 1460 (m), 1325 (m), 1260 (m), 1200 (m), 1055 (s), 950 (m), 900 (m), 710 (s) cm^{-1}.

2-(3-Chloropropyl)-2-phenyl-1,3-dioxane (125)

A mixture of ketone (116) (5.1 g, 28 mmol), propane-1,3-diol (3.8 g, 50 mmol and toluene-4-sulphonic acid (50 mg, 0.3 mmol) was refluxed in toluene (100 cm^3) with azeotropic removal of the water formed (Dean-Stark apparatus), for 12 hours. After washing with sodium bicarbonate soln (50 cm^3) and water (50 cm^3), the organic phase was dried (K_2CO_3) and concentrated *in vacuo*. The residual oil was then triturated in 40-60° petrol to induce crystallisation. A pure sample of the product was obtained by recrystallisation of this material (5.08 g, 76.2%); m.p. 73-76°C.

δ_H (CCl_4): 1.61-1.94 (6H, m, 3 x CH_2); 3.45 (2H, t, J 7.0 Hz, CH_2Cl); 3.67 (4H, m, 2 x CH_2O); 7.21-7.40 (5H, phenyl protons) p.p.m.

ν_{max} (soln, CCl_4): 3100 (w), 2925 (s), 2880 (m), 1480 (s), 1320 (w 1316 (w), 1285 (w), 1270 (w), 1260 (w), 1195 (m), 1184 (w), 1035 (m), 950 (m), 920 (w), 915 (w), 715 (s) cm^{-1}.

Methyl Pivaloylacetate

Under a static nitrogen atmosphere, pinacolone (30 g, 300 mmol) in THF (50 cm^3) was added dropwise to a stirred suspension of pentane-washed sodium hydride (7.5 g, 310 mmol) in 100 cm^3 of the same solvent. This mixture was gently boiled under reflux for 1 hour and then allowed to cool to room temperature. Redistilled dimethyl carbonate (36 g, 400 mmol) in THF (50 cm^3) was subsequently introduced and the reaction boiled under reflux for a further 2 hours. The whole was cautiously poured into chilled (10°C) 1:1 acetic acid:water to which brine (30 cm^3) was added. The separated aqueous phase was extracted with dichloromethane (50 cm^3) before being discarded. The combined organic solutions were washed with sodium bicarbonate (3 x 100 cm^3), brine (30 cm^3), then dried ($MgSO_4$), and evaporated *in vacuo*. The residue was distilled in a Vigreaux apparatus to afford the pure product as a colourless, sweet smelling oil (22.5 g, 47.5%); b.p. 85-90°C, 16 mmHg.

δ_H (CCl_4): 1.18 (9H, s, 3 x CH_3); 3.58 [2H, s, CH_2(keto)]; 3.78 (3H, s, OCH_3); 5.05 [1H, s, CH(enol)]; 12.4 (1H, b,s, OH(enol)] p.p.m.

The ratio of enol to keto-tautomers was determined by integration of the ^1H n.m.r. spectrum to be ≃ 2:3 respectively.

ν_{max} (film): 2960 (s), 2900 (w), 2865 (w), 1745 (s), 1708 (s), 1644 (m), 1618 (m), 1476 (w), 1458 (w), 1436 (m), 1393 (m), 1362 (m), 1317 (m), 1266 (m), 1207 (m), 1143 (m), 1119 (w), 1058 (m), 1025 (w), 991 (m), 930 (w), 838 (w),

796 (w), 728 (w), 699 (w), 674 (w) cm^{-1}.

2,2-Dimethyl-6-hydroxyhexan-3-one (12̲8)

Pinacolone (10 g, 100 mmol), sodium hydride (3.0 g, 120 mmol) and ethylene oxide (17.0 g, 350 mmol) were boiled under reflux in THF (120 cm^3) for 5 hours under a static nitrogen atmosphere, and in the presence of a dry-ice: acetone condenser. The mixture was poured cautiously into 1:3, acetic acid:water, and then saturated brine (100 cm^3) was added. The organic layer was washed with sodium bicarbonate solution (50 cm^3) followed by brine (50 cm^3) before being dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil. This material was purified by flash column chromatography (eluent 19:1, dichloromethane: methanol) and short-path distillation to furnish the product as a colourless oil (4.92 g, 34%); b.p. 113-117°C, 16 mmHg.

δ_H (CCl_4): 1.20 (9H, s, 3 x CH_3); 1.79 (2H, m, CH_2); 2.10 (2H, t, J 6.9 Hz, $C\underline{H}_2CO$); 2.73 (1H, b,s, OH); 3.63 (2H, t, J = 7.3 Hz, $C\underline{H}_2OH$) p.p.m.

ν_{max} (film): 3400 (b,s), 2960 (m), 2930 (s), 2870 (m), 1710 (s), 1665 (m), 1440 (m), 1415 (m), 1385 (m), 1315 (s), 1295 (m), 1240 (m), 1210 (m), 1040 (s), 780 (w) cm^{-1}.

6-Chloro-2,2-dimethylhexan-3-one (12̲7) (Method A)

Alcohol (12̲8) (2.8 g, 10 mmol) and triphenyl phosphine (6.54 g, 25 mmol) were dissolved in dry carbon tetrachloride (30 cm^3) and boiled under reflux for 0.5 hours under a static nitrogen atmosphere. The solvent was removed

in vacuo to give a paste which was taken up in ether (50 cm^3) and filtered. Re-evaporation of this solution gave an orange oil, short-path distillation of which furnished the pure product as a colourless liquid (2.34 g, 72.3%); b.p. 96-99°C, 18 mmHg.

δ_H (CCl_4): 1.19 (9H, s, 3 x CH_3); 1.81 (2H, m, CH_2); 2.12 (2H, t, J 7.1 Hz, $C\underline{H}_2CO$); 3.44 (2H, t, J 7.3 Hz, CH_2Cl) p.p.m.

ν_{max} (film): 2960 (s), 2910 (w), 2880 (w), 1712 (s), 1440 (m), 1380 (w), 1870 (m), 1218 (m), 1165 (s), 1030 (w), 1025 (w), 995 (w), 940 (m), 860 (w), 702 (w), 670 (w) cm^{-1}.

6-Chloro-2,2-dimethylhexan-3-one (127) (Method B)

Under a nitrogen atmosphere, magnesium turnings (3.0 g, 125 mmol), covered by anhydrous THF (30 cm^3), were treated with a few drops of 1,2-dibromoethane and warmed. Once the reaction had commenced, *t*-butyl chloride (10 g, 108 mmol) in 70 cm^3 of the same solvent was added dropwise and the preparation subsequently boiled under reflux for 1 hour. After having allowed to stand for another hour, the Grignard solution was transferred by syringe to a serum-capped dropping funnel from whence it was added dropwise (over 2.5 hours) to a vigorously stirred suspension of 4-chlorobutanoyl chloride (43.0 g, 300 mmol) in THF (150 cm^3) at -78°C. The whole was quenched in ice-cooled 1 M sulphuric acid (50 cm^3), stirred for 20 minutes, and then neutralised with solid sodium bicarbonate. The organic phase was washed with brine (50 cm^3), dried ($MgSO_4$) and evaporated *in vacuo* to afford a residual yellow oil. This

material was purified by flash column chromatography (eluent, dichloromethane) and Kugelröhr distillation to give a sample of product with identical spectroscopic data to that cited in the preceding experiment (9.91 g, 57.0%); b.p. 69-72°C, 3 mmHg.

2-(3-Chloropropyl)-2-(2-methyl-2-propyl)-1,3-dioxolane (130)

Ketone (127) (4.1 g, 26 mmol), ethane-1,2-diol (3.2 g, 50 mmol) and toluene-4-sulphonic acid (47 mg, 0.3 mmol) were boiled under reflux in benzene (100 cm^3) for 48 hours. A Soxhlet thimble containing anhydrous magnesium sulphate was used to remove the water formed. After pouring into sodium bicarbonate solution (30 cm^3), the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent, ether) and then distilled (Kugelröhr) to furnish the product (2.63 g, 51.4%); b.p. 95-100°C; 3 mmHg. δ_H (CCl_4): 1.17 (9H, s, 3 x CH_3); 1.70-1.90 (4H, m, 2 x CH_2); 3.51 (2H, t, J 6.9 Hz, CH_2Cl); 3.85 (4H, m, 2 x $C\underline{H}_2O$) p.p.m.

2-(3-Chloropropyl)-2-(2-methyl-2-propyl)-1,3-dioxane (131)

A mixture of ketone (127) (4.0 g, 25 mmol), propane-1,3-diol (3.8 g, 50 mmol) and toluene-4-sulphonic acid (52 mg, 0.31 mmol) was boiled under reflux in toluene (17 cm^3) for 32 hours. Anhydrous magnesium sulphate, situated in a Soxhlet thimble, was used as the desiccant. The toluene solution was washed with water (50 cm^3), sodium bicarbonate solution (50 cm^3) and then

brine (20 cm^3). After drying ($MgSO_4$), the solvent was removed *in vacuo* and the residue purified by flash column chromatography (eluent, 2:3, dichloromethane: 40-60° petrol) followed by short-path distillation. The product was thus obtained as a colourless oil (2.58 g, 46.7%); b.p. 114-119°C, 3.0 mmHg.

δ_H (CCl_4): 1.20 (9H, s, 3 x CH_3); 1.63-1.91 (6H, m, 3 x CH_2); 3.47 (2H, t, J 7.0 Hz, CH_2Cl); 3.88 (4H, m, 2 x $C\underline{H}_2O$) p.p.m.

Rac-4-hydroxy-6-(benzyloxy)hex-1-ene (132)

This preparation was carried out under a static atmosphere of nitrogen. A mixture of magnesium turnings (5 g, 210 mmol), THF (20 cm^3) and 10 drops of 1,2-dibromoethane were warmed until ethene evolution commenced, whereupon a solution of vinyl bromide (16.1 g, 150 mmol) in 60 cm^3 of the same solvent was slowly introduced. After an hour, the Grignard solution was cooled to -78°C and a solution of lithium tetrachlorocuprate (0.27 g, 1.2 mmol) in THF (10 cm^3) added. This was followed by a solution of epoxide *rac*-(94) (8.9 g, 50 mmol) in THF (50 cm^3) after another hour. The reaction was kept at -78°C for three more hours and then allowed to warm to room temperature overnight. The whole was poured into saturated aqueous ammonium chloride solution (250 cm^3) at 5°C and stirred for 20 minutes. After the aqueous phase had been extracted with ether (100 cm^3), the organic solutions were combined and dried ($MgSO_4$). Removal of solvent *in vacuo* and distillation of the residue obtained, afforded the product

as a colourless oil (9.31 g, 90.7%); b.p. 130-5°C, 0.1 mmHg.

δ_H (CCl_4): 1.67 (2H, m, CH_2); 2.16 (2H, t, J 6 Hz, CH_2-allylic); 2.49 (1H, b,s, OH); 3.58 (2H, t, J 7.1 Hz, $C\underline{H}_2OBn$); 3.74 (1H, m, $C\underline{H}OBn$); 4.44 (2H, s, $C\underline{H}_2Ph$); 5.05 (2H, dd, J_{cis} 9, J_{trans} 15.5 Hz, CH_2=); 5.76 (1H, m, CH=); 7.22 (5H, s, phenyl protons) p.p.m.

ν_{max} (film): 3430 (b,s), 3070 (w), 3030 (w), 2910 (s), 2855 (s), 1642 (m), 1495 (w), 1425 (w), 1365 (m), 1090 (s), 1025 (w), 995 (w), 915 (s), 735 (s), 695 (s) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; 2:1, CH_3CCl_3:EtOAc) one spot (I_2 u.v.) at R_f 0.45.

H.p.l.c.: (μ-Porasil column 250 mm x 4.6 mm i.d.; hexane) one peak (254 nm detector) retention time 15 minutes.

Rac-4,6-*bis*(benzyloxy)hex-1-ene (133)

Alcohol (133) (8.35 g, 35 mmol), benzyl bromide (12.0 g, 70 mmol) and pentane-washed sodium hydride (2.4 g, 100 mmol) were refluxed in THF (120 cm^3) under a static nitrogen atmosphere for 17 hours. Water (5 cm^3) was cautiously added, before the whole was poured into saturated brine (100 cm^3). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* leaving a thick orange liquid. This material was boiled under reflux in ethanol (60 cm^3) and triethylamine (10.1 g, 100mmol) for 4 hours. Solvent and excess triethylamine were evaporated off and a concentrated solution of the residual oil, in 40-60° petrol, percolated under suction through a magnesium sulphate:pentane slurry. The pure

product was isolated as a colourless oil after evaporation of the eluent and distillation of the residue obtained (11.46 g, 87.3%); b.p. 183-189°C, 0.5 mmHg.

δ_H (CCl_4): 1.71 (2H, m, CH_2); 2.19 (2H, t, J 6.0 Hz, CH_2-allylic); 3.52 (2H, t, J 7.0 Hz, $C\underline{H}_2OBn$); 3.70 (1H, m, $C\underline{H}OBn$); 4.40 (2H, dd, $J_1 = J_2$ 13.0 Hz 2^o-$C\underline{H}_2Ph$); 4.43 (2H, s, 1^o-CH_2Ph); 5.06 (2H, dd, J_{cis} 8, J_{trans} 14 Hz, CH_2=); 5.77 (1H, m, CH=); 7.20 (10H, s, phenyl protons) p.p.m.

ν_{max} (film): 3065 (w), 3030 (m), 2915 (s), 2855 (s), 1640 (m), 1610 (w), 1585 (w), 1495 (m), 1455 (m), 1440 (w), 1360 (m), 1350 (w), 1305 (w), 1205 (w), 1090 (s,b), 1025 (w), 995 (w), 915 (m), 730 (s), 690 (s) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; CH_3CCl_3) one spot (I_2,u.v.) at R_f 0.37.

Rac-ethyl-6,8-*bis*(benzyloxy)octanoate (134)

To a solution of 9-BBN (3.41 g, 27.5 mmol) in dry THF (30 cm^3) at 0°C, was added slowly alkene *rac*-(133) (7.4 g, 25 mmol) in 25 cm^3 of the same solvent, under a static nitrogen atmosphere. After 1.5 hours, ethyl bromoacetate (4.33 g, 26 mmol) in 4:1 *t*-butanol:THF (25 cm^3) was quickly run into the flask, followed by dropwise introduction of 1 M potassium 2,6-di-*t*-butylphenoxide in *t*-butanol (30 cm^3). One hour later, the preparation was allowed to reach room temperature and quenched with 3 M aqueous sodium acetate solution (17 cm^3). Oxidation was effected by careful addition of 30% hydrogen peroxide (6 cm^3) at such a rate as to ensure that the internal

reaction temperature did not exceed 30°C. After a further 1.5 hours, the inert atmosphere was removed and solid sodium chloride added. The separated organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to furnish a residual paste. This material was fractionated by flash column chromatography (eluent, dichloromethane) to give the pure product as a pale yellow oil (2.42 g, 25.2%).

δ_H (CCl_4): 1.12 (3H, t, J 7.3 Hz, CH_3); 1.20-1.58 (6H, m, 3 x CH_2); 1.74 (2H, m, $C\underline{H}_2CH_2OBn$); 2.19 (2H, t, J 7.0 Hz, $C\underline{H}_2CO_2Et$); 3.50 (3H, m, $C\underline{H}_2OBn$ + $C\underline{H}OBn$); 3.64 (3H, s, OCH_3); 4.11 (2H, q, J 7.3 Hz, CH_2); 4.41 (2H, s, 1^O-$C\underline{H}_2Ph$); 4.42 (2H, dd, $J_1 = J_2$ 13.0 Hz, 2^O-$C\underline{H}_2Ph$); 7.23 (5H, s, phenyl protons) p.p.m.

ν_{max} (film): 3090 (w), 3060 (w), 3030 (w), 2940 (s), 2840 (m), 1735 (s), 1495 (m), 1435 (w), 1360 (m), 1250 (w), 1160 (w), 1090 (s), 1065 (s), 1025 (w), 730 (s), 695 (s) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; dichloromethane) one spot (I_2, u.v.) at R_f 0.56.

Chapter 5

The Synthesis of Natural and Unnatural Lipoic Acid from (R)- and (S)-(2-Benzyloxyethyl)oxirane

5.1 INTRODUCTION

The partial success of Scheme 4.4 encouraged further investigation into routes where a terminal olefin served as precursor to the carboxylic acid group. A strategic disadvantage of Scheme 4.4 was that the linear eight carbon backbone was assembled in two carbon-carbon bond forming steps rather than one. Therefore a new route in which (2-benzyloxyethyl)oxirane (94) was opened with but-3-enylmagnesium halide was conceived. This initial reaction would establish the correct carbon skeleton, after which the remaining steps to the target molecule would amount to trivial functional group interconversions. Whilst such an approach again resorts to established chemistry, it was considered that if the synthesis could be made efficient, its application would be more than adequately justified.

This Chapter details the successful preparation of the pure (*R*)- and (*S*)-enantiomers of lipoic acid[210,211] as well as preliminary attempts to extend the methodology developed to an interesting analogue - 8-methyllipoic acid. Some possible areas for future work, related to the topic of this thesis are also outlined.

5.2 LIPOIC ACID FROM 6-HYDROXY-8-(BENZYLOXY)OCT-1-ENE

5.2.1 6-Hydroxy-8-(benzyloxyoct-1-ene to Methyl Dihydroxyoctanoate

The exploration of this synthesis was carried out in three stages:

(1) from *rac*-(94) to establish the viability of the proposed steps or modifications thereof,

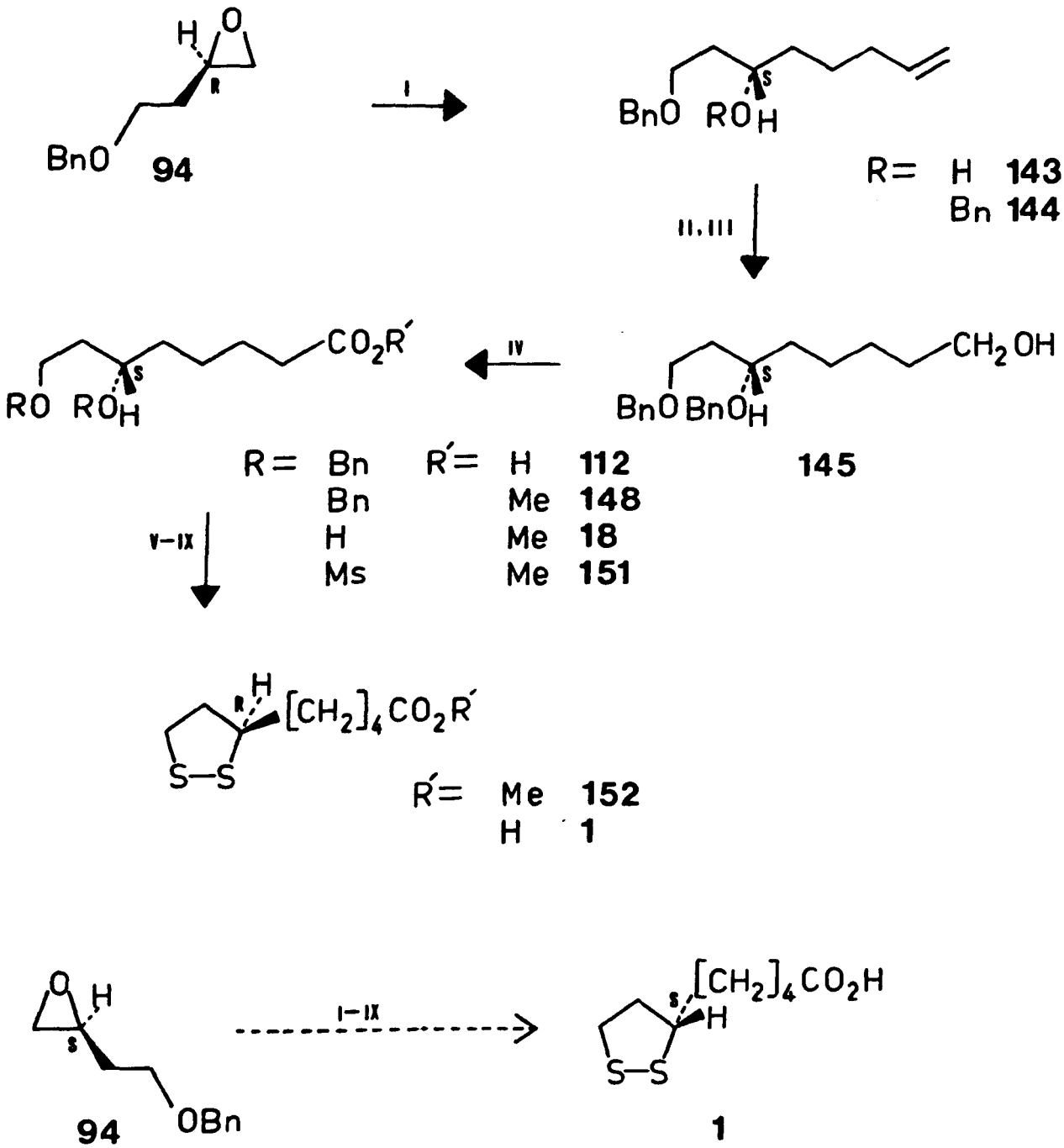
(2) from (*S*)-(94) to confirm the stereochemical integrity of the sequence, with concomitant proof of the absolute configuration of (*S*)-lipoic acid, and finally,

(3) from (*R*)-(94) to make the supposed natural enantiomer.

The preparation of (*R*)-lipoic acid from (*R*)-(94) is summarised in Scheme 5.1.

Epoxide (*R*)-(94)was opened by reaction with excess but-3-enylmagnesium chloride, in the presence of catalytic lithium tetrachlorocuprate, at low temperature. The product, (*S*)-6-hydroxy-8-(benzyloxy)oct-1-ene (143) was isolated in 94% yield and was sufficiently pure (≥ 95% ^{1}H n.m.r. spectroscopy) to be used directly in the next step. The antipode, (*R*)-(143) was similary prepared from (*S*)-(94). However, initially, *rac*-(94) had been reacted with but-3-enylmagnesium bromide, but the resulting *rac*-(143) was of lower purity, and consequently a high vacuum distillation was necessary. The 4-chlorobut-1-ene required for the step was prepared by the action of thionyl chloride on but-3-ene-1-ol (99) according to the

Scheme 5.1



Reagents: (i) $CH_2=CHCH_2CH_2Cl$, Mg, THF, Li_2CuCl_4;
(ii) NaH, BnBr, THF, $Bu_4\overset{+}{N}\bar{I}$;
(iii) Sia_2BH, THF, H_2O_2, OH^-;
(iv) PDC, DMF;
(v) MeOH, H^+;
(vi) H_2/Pd/C, MeOH;
(vii) 2 x MsCl, Et_3N, CH_2Cl_2;
(viii) $Na_2S.9H_2O$, S, DMF;
(ix) OH^-(aq.)

procedure of Roberts and Mazur[212]. 4-Bromobut-1-ene was made from (99) and phosphorous tribromide in pyridine[199]. A further advantage of the former halide was its superior stability; 4-chlorobut-1-ene could be stored indefinitely at ambient temperature whereas samples of 4-bromobut-1-ene often showed significant deterioration after a few weeks at 5°C. Apparently, this polymerisation may be retarded by addition of silver or copper wire[213]. Both halides avidly attacked magnesium turnings after initiation; little difference was noted in their respective reactivities towards Grignard formation.

The (*R*)-, (*S*)- and racemic forms of (143) were converted into the corresponding forms of 6,8-*bis*(benzyloxy)-oct-1-ene (144) by the method of Provelenghiou *et al.*[214]. The procedure employed a catalytic quantity of tetra-*n*-butylammonium iodide which allows the reaction to be run at room temperature and with only a modest excess (5%) of benzyl bromide [*cf.* the preparation of 4,6-*bis*(benzyloxy)-hex-1-ene (133)]. This modification simplifies the work-up to removal of insoluble by-products and evaporation of the solvent. When the crude residue was examined by t.l.c. a little benzyl bromide was present. However, after heating to 80°C for 1-3 hours under high vacuum this impurity was no longer detectable.

Whilst catalytic benzylation represented an obvious improvement over previous methods, its success was found to be highly dependent on the state of the sodium hydride used. For good results this reagent must be in pristine condition; runs in which aged dispersions were utilised

gave inefficient conversions [≤ 0-15% to (144) after 17 hours as determined by ^{1}H n.m.r. spectroscopy]. Interestingly, when more benzyl bromide was added to these ailing preparations and the mixture boiled under reflux, a good yield of (144) was again realised.

The catalytic effect of tetra-*n*-butylammonium iodide is believed to originate from the generation of the ion pair $Bu_4N^+//^-OR$ *in situ* which displays little tendency to form unreactive aggregates (unlike $Na^+//^-OR$) in the THF solvent. The application of quaternary ammonium salts in general, and of tetra-*n*-butylammonium salts in particular, to promote ionic reactions in apolar media has been reviewed[215].

Introduction of a hydroxyl group at C-1 of (144) was achieved *via* the familiar hydroboration/oxidation procedure[184]. In the preparation of *rac*-6,8-*bis*(benzyloxy)-octan-1-ol (145), 9-BBN was used as the hydroborating agent. Treatment with alkaline hydrogen peroxide afforded a mixture of *rac*-(145) and cyclooctane-1,5-diol. These two compounds were subsequently separated by short column chromatography. Analysis by ^{1}H n.m.r. spectroscopy and h.p.l.c. showed the sample of *rac*-(145) to be free of the isomeric 6,8-*bis*(benzyloxy)octan-2-ol (146) confirming the regio-specificity of the process[195]. A disadvantage of this procedure was the use of chromatography in the work-up.

Hydroborations with diisoamyl borane are also almost exclusively regiospecific[206]. Substitution of this reagent for 9-BBN was implemented for the preparation of (*R*)- and (*S*)-(145). The by-product 3-methylbutan-2-ol, was

easily removed at 50°C with an efficient rotary evaporator to leave the desired product. The samples of (*R*)- and (*S*)-(145) so prepared were similarly uncontaminated by (146) and were sufficiently pure to be committed directly for the next step. Quantitative yields of (145) were approached in both variants of this reaction.

The next envisaged step was the oxidation of (145) to 6,8-*bis*(benzyloxy)octanoic acid (112). Whilst a wide variety of reagents have been developed for the conversion of primary alcohols into aldehydes and secondary alcohols to ketones, the further oxidation of aldehydes to carboxylic acids has received much less attention. Potassium permanganate and silver(I) oxide are normally employed for the latter transformation, usually in aqueous or semi-aqueous media[216]. This limitation may cause solubility problems with lipophilic substrates. Although potassium permanganate may be dissolved in organic solvents when a crown ether is present (e.g. purple benzene[217]), selectivity problems can still arise due to its powerful oxidising nature. Whilst (145) or 6,8-*bis*(benzyloxy)octanal (147) are not particularly delicate substrates in this respect, the use of two successive oxidations to effect the desired FGI seemed particularly cumbersome.

In 1979 Corey and Schmidt announced that solutions of pyridinium dichromate (PDC) in DMF could effect the direct conversion of primary alcohols into carboxylic acids in high yield and under mild conditions[218]. PDC was easily prepared according to the procedure given by these investigators. The sample made had physical properties

and infrared spectral data consistent with those described[218]. Rather than commit (145) directly, model studies with octan-1-ol were initially conducted. In the author's hands the published reaction time of 7-9 hours at ambient temperature was grossly inadequate. Indeed, when the reaction was allowed to proceed overnight, some octanaldehyde was still detectable (^{1}H n.m.r. spectroscopy). To circumvent incomplete oxidation, the ratio of PDC to octan-1-ol was increased from 3:1 to 5:1 mole equivalents and the reaction time extended to 48 hours. No deterioration of the octanoic acid formed, due to over-oxidation, was observed. It was also found beneficial to add the solution of alcohol in DMF dropwise to a cooled suspension of PDC in the same solvent rather than simply mixing the two solutions at room temperature, as implied in Corey's procedure[218]. When the latter technique was practised an appreciable quantity of ester (i.r. spectroscopy, 1735 cm^{-1}), presumably octyl octanoate, appeared[219]. These observations suggest that the oxidation to an aldehyde takes place quite rapidly, whereas subsequent carboxylic acid formation is much slower. Interestingly, when PDC is used in dichloromethane, little oxidation beyond the aldehyde occurs; presumably the more basic nature of DMF is largely instrumental in promoting further oxidation. Secondary alcohols are efficiently converted into ketones in both solvents by PDC. However, primary allylic alcohols are not transformed further than the α,β-unsaturated aldehyde in DMF[218].

Having thus perfected the reaction conditions, the synthesis of the target molecule could proceed. Accordingly,

(*R*)-, (*S*)- and *rac*-(145) were converted into the corresponding forms of (112) in good yields (72-81%). The crude product was contaminated with chromium salts and other polar impurities. These were most effectively removed by directly esterifying the acid (112) and allowing the resulting methyl 6,8-*bis*(benzyloxy)octanoate (148) to percolate through a column filled with magnesium sulphate:pentane slurry. ^{1}H n.m.r. spectroscopy revealed the samples of (148) to be ≃ 90% pure after this treatment.

Removal of the benzyl groups from (148) by catalytic hydrogenolysis[220] gave methyl 6,8-dihydroxyoctanoate (18). Further purification of the starting material proved to be unnecessary for the success of this step.

5.2.2 Methyl 6,8-dihydroxyoctanoate to Lipoic Acid

The remaining steps from (18) were activation of the hydroxyl groups, displacement with a sulphur nucleophile, and finally hydrolysis of the ester group. Thus, *rac*-(18) was ditosylated in pyridine under standard conditions[221]. Work-up afforded crude *rac*-methyl 6,8-di(tosyloxy)octanoate (149) as an oil which still displayed a hydroxy stretch at 3350 cm^{-1} in the infrared spectrum, indicating that the reaction had not gone to completion. Examination by ^{1}H n.m.r. spectroscopy revealed that the product was contaminated by *ca.* 15% of a monotosylated species. Fortuitously, on standing at -25°C, the oil deposited an off-white solid which was identified as impure *rac*-

methyl 6-hydroxy-8-tosyloxyoctanoate (150). Whilst *rac*-(150) could be recrystallised, attempts to purify *rac*-(149) similarly, were unsuccessful. Ditosylate *rac*-(149) was therefore used directly for the next reaction since it had been freed from its only major impurity. The isolated yield of *rac*-(149) was 65%.

To circumvent the problem of incomplete sulphonyl ester formation (*R*)- and (*S*)-(18) were converted into their dimesylates according to the procedure of Crossland and Servis[135]. As expected, the (*R*)- and (*S*)-enantiomers of methyl 6,8-di(mesyloxy)octanoate (151) were formed in quantitative yield.

The 1,2-dithiolane ring ring may be constructed directly by the action of sodium sulphide and sulphur on a 1,3-ditosylate or 1,3-dimesylate. Eliel *et al.* have shown that when this reaction is performed in DMF the introduction of sulphur proceeds almost stereospecifically with inversion[105]. As proof, *meso*- and *rac*-2,4-di(tosyloxy)-pentane were subjected to these conditions and the 3,5-dimethyl-1,2-dithiolanes formed were reduced to the pentane-2,4-dithiols with lithium aluminium hydride. Analysis of the respective dithiols by gas chromatography showed both samples to be contaminated with ≤ 2% of the other diastereoisomer.

Accordingly, (*R*)-, (*S*)- and *rac*-methyl lipoate (152) were easily prepared from (*S*)- and (*R*)-(151) and *rac*-(149) respectively in 78-85% yield, by following Eliel's procedure[105]. The optical rotations of the (*R*)- and (*S*)-methyl lipoate made were very similar to the literature values recorded for the parent acids[36] which gave an initial indication that

sulphur introduction at C-6 had indeed occurred with high stereoselectivity.

Saponification of the methyl lipoates was effected in dilute aqueous base[16]. Precautions were taken to exclude light and oxygen from this reaction since both are known to promote polymerisation of the 1,2-dithiolane ring[222]. Removal of most of the impurities was achieved by partition between the aqueous and organic phases at different pH. The lipoic acids so prepared were isolated as pale yellow oils which solidified on standing. These samples were shown to be *ca.* 95% pure (^{1}H n.m.r. spectroscopy) and were obtained in 21-28% overall yield from epoxide (94). In the preparation of (*R*)- and (*S*)-lipoic acids no purification by chromatography, distillation or crystallisation of any intermediate from the corresponding enantiomers of (94) was necessary, considerably simplifying the experimental procedures. However, analytically pure samples of most of these intermediates were prepared to permit their proper characterisation.

Analytically pure samples of (*R*)-, (*S*)- and *rac*-lipoic acid were obtained from the crude solid by recrystallisation. The melting point of the racemate was undepressed on admixture with an authentic sample[25] whereas the (*R*)- and (*S*)-enantiomers had melting points, optical rotations and c.d. spectral data comparable to the best in the literature[36,223]. In this way (*R*)-lipoic acid was unequivocally shown to be the natural, biologically active, dextrorotatory enantiomer[210]. Thus, the deduction made by Mislow and Meluch[39] has been proved correct and

conclusions concerning the introduction of sulphur at C-6 during the biosynthesis of this compound have now been substantiated[44-46].

5.3 THE SYNTHESIS OF 8-METHYLLIPOIC ACID

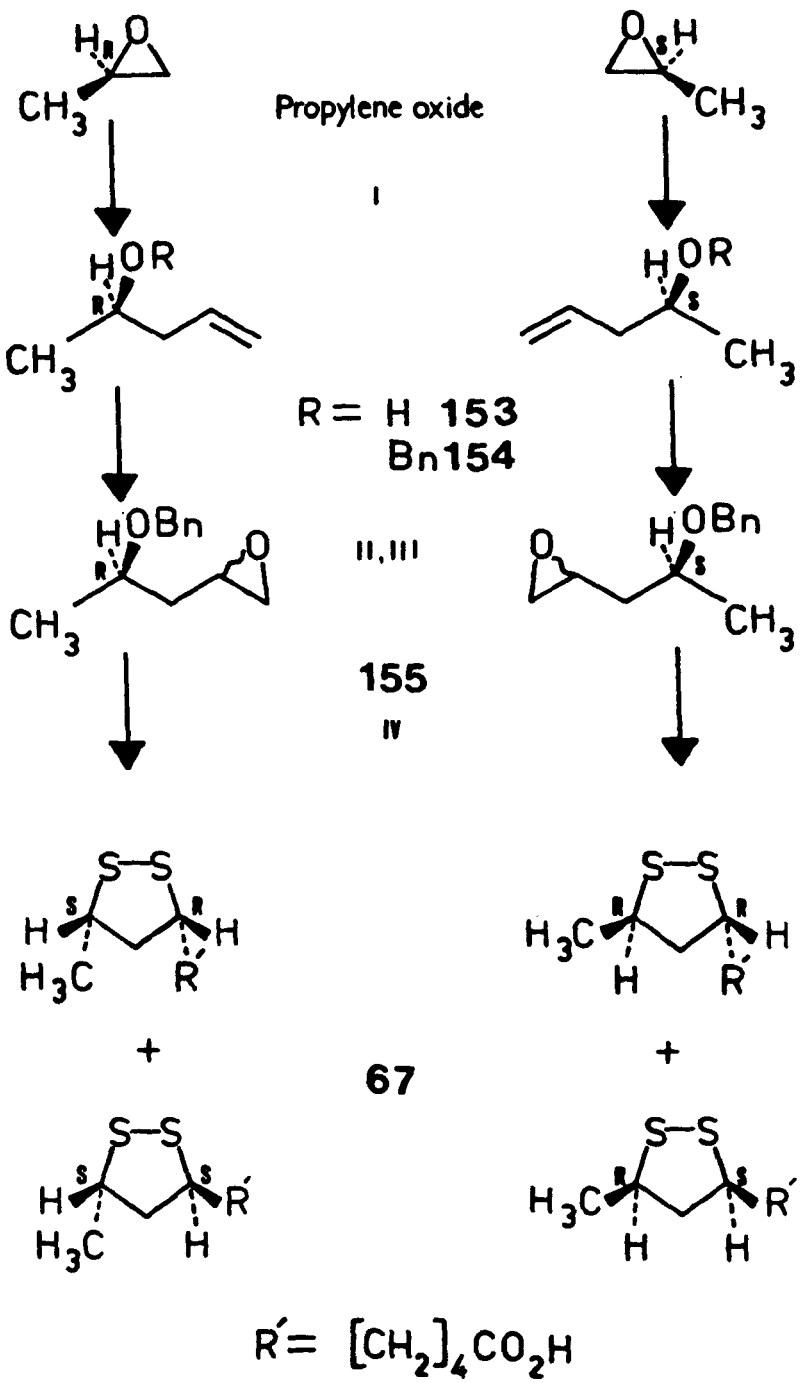
Griffiths *et al.* have proposed the involvement of lipoic acid in the mechanism of oxidative phosphorylation[79]. Crucial supportive evidence for this hypothesis was the observation that 8-methyllipoic acid (67) acted as a competitive inhibitor in this process[80]. However, because the sample used was incompletely characterised, the result cannot at present, be regarded as conclusive[224]. In order to establish unequivocally whether 8-methyllipoic acid, and not an impurity, is responsible for the observed inhibition, reproduction of the experiments with a fully characterised, chemically pure specimen is necessary. Furthermore, the 8-methyllipoic acid originally employed here was a mixture of all four possible stereoisomers [it was synthesised by a variant of Reed and Niu's synthesis[29] (Scheme 1.2) in which propene rather than ethene was acylated by ethyl adipoyl chloride (5)]. It is probable that biological activity is restricted to one stereoisomer, the identification or separation of which has so far, not been attempted. The success of Scheme 5.1 prompted us to extend its application to this interesting derivative, with a view to further clarifying the biochemical work by preparation of all four pure stereoisomers.

To facilitate the resumption of biochemical studies, a specimen of stereochemically undefined 8-methyllipoic acid was initially prepared. Allylmagnesium bromide was reacted with acetaldehyde to furnish *rac*-pent-4-ene-2-ol (153) in 71% yield. Benzylation of the alcohol *in situ* gave *rac*-2-(benzyloxy)pent-4-ene (154) which was treated with 3-chloroperbenzoic acid[148] to afford (2-benzyloxypropyl)oxirane (155). The steps of Scheme 5.1 were then repeated starting with epoxide (155), giving 8-methyllipoic acid in 15% overall yield. Purification of most of the intermediates by flash column chromatography was necessary during this sequence, since the steps generally proceeded less cleanly and in lower yield than in the analogous preparation of lipoic acid.

The preparation of the pair of diastereomers was commenced but not completed owing to lack of time. Thus, (*S*)-2-methyloxirane[138] was reacted with vinyl magnesium bromide under copper catalysis to afford (*S*)-(153) and benzylated *in situ* to give (*S*)-(154). Epoxidation[148] of (*S*)-(154) furnished (2*S*,4*R*)/(2*S*,4*S*)-(155), (≃ 2:3 ratio of diastereoisomers by ^{1}H n.m.r. spectroscopy). At this stage the route had to be abandoned. It was envisaged that in the subsequent reactions the diastereomers could be separated by h.p.l.c., ultimately affording (6*R*,8*R*)- and (6*R*,8*S*)-8-methyllipoic acid. Since (*R*)-2-methyloxirane is also readily available[225], the antipodal (6*S*,8*S*)- and (6*S*,8*R*)-forms are similarly accessible by this methodology. Enough material for the initial biochemical experiments could easily be provided by such a h.p.l.c. fractionation.

At the time of writing, the testing of the

Scheme 5.2



Reagents: (i) C_2H_3Br, Mg, THF, Li_2CuCl_4;
(ii) NaH, BnBr, THF, $Bu_4\overset{+}{N}\bar{I}$;
(iii) 3-Chloroperbenzoic acid, CH_2Cl_2;
(iv) See Scheme 5.1

stereochemically undefined sample of 8-methyllipoic acid has not, as far as we are aware, been carried out. Without an enouraging result here, there is little motive for further work in this area. The planned strategy is summarised in Scheme 5.2.

5.4 CONCLUSION

A convenient synthesis of the enantiomers of lipoic acid has been presented. The overall yield from (*S*)-malic acid (75) is *ca.* 9% for the (*S*)-isomer and *ca.* 4% for the (*R*)-form. Advantages of the route are the facile steps involved and ease of purification. Since recourse to chromatography has been avoided, it should easily be possible to scale up this synthesis to provide 10 or more grams of (*R*)-lipoic acid. The reproducibility of the synthesis has been demonstrated by performing all the steps at least three times, in which variations in yield of ± 5% were observed.

The major disadvantage is the large number of steps involved (22 and 19 reactions from (*S*)-(75) to (*R*)- and (*S*)-lipoic acid respectively). However, this is offset to some extent by the acceptable overall yield. In the case of (*S*)-lipoic acid, the overall yield is approximately half that recorded for many preparations of the racemate[31,33-35], (taken from (*R*)- or (*S*)-(94) the route is comparable to Reed's synthesis[29]).

Future work is likely to concentrate on devising a more efficient preparation of (*R*)-(94). Apart

from its role as a key intermediate in Scheme 5.1 this compound has considerable potential in its own right as a versatile chiral building block[109]. In previous work[103], a route from (2*R*,3*R*)-tartaric acid to this compound was developed[110]. Unfortunately, this synthesis had more steps and gave a lower overall yield of (*R*)-(94) than the sequence originating from (*S*)-(75). However, (2*R*,3*R*)-tartaric acid is 10-15 times cheaper than (*S*)-(75) and provides the desired enantiomer directly, rather than *via* an inversion procedure.[226] Thus, on the basis of cost, the lower yields encountered may be tolerated, and, after improvements to some of the original experimental methods[103], use of (2*R*,3*R*)-tartaric acid as the starting material may well become competitive.

(*R*)-Lipoic acid may be made from (*S*)-(94) if an inversion sequence is incorporated into Scheme 5.1. Esterification with inversion of (*R*)-(143) *via* the Mitsunobu reaction[146,227] or mesylation with inversion[228] of diol (*R*)-(18) are two possibilities. These variations would capitalise on the higher overall yield and fewer steps necessary to make (*S*)-(94) from (*S*)-(75).

Another possible area for development is in the preparation of isotopically substituted (*R*)-lipoic acid for use in biochemical research. Our synthesis, by virtue of its inherent simplicity, offers considerable promise in this respect. Previously, only labelled *rac*-lipoic acid has been available for such studies[30,38]. The availability of pure, labelled (*R*)-lipoic acid may well facilitate a significantly clearer interpretation

of many biochemical results. For instance, samples containing (*R*)-^{35}S-lipoic acid could easily be made by reacting (*S*)-(1$\underset{\sim}{5}$1) with sodium sulphide:^{35}sulphur mixtures[105]. The (*R*)-methyl-^{35}S-lipoate produced could be purified by chromatography and administered directly (the simple alkyl esters of lipoic acid possess equivalent biological activity to the parent compound[16]). Substitution by stable isotopes may prove to be an even more useful here, permitting, for example, further, non-destructive examination of α-keto acid dehydrogenase complexes by n.m.r. spectroscopy to obtain more information about their highly complex mode of action.

5.5 EXPERIMENTAL

4-Bromobut-1-ene

This compound was prepared by the action of phosphorous tribromide on a solution of alcohol (99) in pyridine according to a procedure devised by Atkins[199] (11.3 g, 43.5%) b.p. 97-100°C; (lit.[199], 45.7%; b.p. 98-100°C.

δ_H (CCl_4): 2.43 (2H, dt, J_3 7.3, J_2 7.5 Hz CH_2); 3.44 (2H, t, J 7.5 Hz, CH_2Br); 5.08 (2H, dd, J_{cis} 9, J_{trans} 15.3 Hz, CH_2=); 5.77 (1H, m, CH=) p.p.m.

4-Chlorobut-1-ene

This compound was made by the action of thionyl chloride on alcohol (99) in the presence of pyridine, according to the method of Roberts and Mazur[212] (16.5 g, 62.1%); b.p. 74-76°C; (lit.[212], 65.3%, b.p. 75-77°C).

δ_H (CCl_4): 2.50 (2H, dt, J_1 7.3, J_2 7.5 Hz, CH_2); 3.50 (2H, t, 7.5 Hz, CH_2Cl); 5.11 (2H, dd, J_{cis} 9, J_{trans} 15.5 Hz, CH_2=); 5.78 (1H, m, CH=) p.p.m.

ν_{max} (film): 3080 (m), 3010 (w), 2980 (m), 2960 (m), 2920 (m), 2870 (w), 1900 (w), 1640 (w), 1450 (w), 1430 (m), 1320 (w), 1280 (m), 1240 (w), 990 (m), 920 (m), 880 (w), 735 (m), 650 (s) cm^{-1}.

(*S*)-6-Hydroxy-8-(benzyloxy)oct-1-ene (143)

A solution of 4-chlorobut-1-ene (13.6 g, 150 mmol) in anhydrous THF (100 cm^3) was added to a stirred suspension of magnesium turnings (5 g, 210 mmol) covered by (20 cm^3) of

the same solvent, under a nitrogen atmosphere. After 1.5 hours at room temperature, more THF (50 cm^3) was run into the flask and the temperature lowered to -78°C. Lithium tetrachlorocuprate (0.27 g, 1.2 mmol) in THF (10 cm^3) was then introduced, followed by, epoxide (*R*)-(94) (8.9 g, 50 mmol) in THF (50 cm^3), one hour later. The reaction was kept at -78°C for a further 5 hours before being allowed to warm to room temperature overnight. The whole was poured into aqueous ammonium chloride solution (100 cm^3) at 5°C and stirred for 20 minutes. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to furnish the product as a pale yellow oil (11.0 g, 94.0%).

An analytically pure sample was obtained after flash column chromatography (eluent, 19:1, dichloromethane: methanol) followed by Kugelröhr distillation (b.p. 110-120°C, 0.005 mmHg).

$[\alpha]_D^{25}$ -6° (C = 5, CCl_4).

δ_H (CCl_4): 1.30-1.55 (4H, m, 2 x CH_2); 1.62 (2H, m, $C\underline{H}_2CH_2OH$); 2.02 (2H, m, $C\underline{H}_2CH{=}CH_2$); 2.72 (1H, b,s, OH); 3.55 (2H, m, $\underline{CH}_2OBn$); 3.63 (1H, m, CH); 4.43 (2H, s, $C\underline{H}_2Ph$); 4.93 (2H, dd, J_{cis} 9.0, J_{trans} 16.0 Hz, $CH_2{=}$); 5.74 (1H, m, CH=); 7.21 (5H, s, phenyl protons) p.p.m.

ν_{max} (film): 3430 (b,s), 3065 (w), 3025 (w), 2930 (s), 2875 (m), 1640 (m), 1495 (w), 1360 (w), 1205 (w), 1090 (s), 1025 (w), 990 (w), 905 (m), 730 (m), 695 (m) cm^{-1}.

T.l.c.: (Silica Gel F_{254}; 19:1, dichloromethane: methanol) one spot (I_2, u.v.) at R_f 0.39.

M/z (e.i.): 235 [$(M + 1)^+$, 53], 234 (M^+, 3), 181 (19), 159 (49), 131 (20), 107 (81), 91 (100%).

Found: C, 77.50; H, 9.59, M^+ 234.1619; $C_{15}H_{22}O_2$ requires: C, 77.88; H, 9.46%, M^+ 234.1620.

In similar fashion (*S*)-(94), (7.9 g, 44 mmol) was converted into (*R*)-(143) (10.25 g, 98.5%) b.p. 113-121°C, 0.005 mmHg.

$[\alpha]_D^{20}$ - 6.7° (C = 4.8, CCl_4).

The spectroscopic data obtained for (*R*)-(143) was identical to that given for its antipode above.

(*S*)-6,8-*Bis*(benzyloxy)oct-1-ene (144)

A stirred suspension of pentane-washed sodium hydride (1.44 g, 60 mmol) in dry THF (30 cm^3) was cooled to -5°C under a static nitrogen atmosphere. To this was added the alcohol (*S*)-(143) (10.0 g, 42.7 mmol) in THF (70 cm^3), over 10 minutes. Having allowed to warm to 0°C, solid tetra-*n*-butylammonium iodide (300 mg), and then redistilled benzyl bromide (7.7 g, 44.8 mmol) in THF (25 cm^3) were added to the flask. The progress of the reaction was evidenced by the steady formation of a thick white precipitate of sodium bromide. After 17 hours at room temperature, the whole was quickly filtered under suction through a magnesium sulphate:pentane slurry and the eluent evaporated *in vacuo* to afford a yellow oil. The final traces of benzyl bromide were removed by stirring at 80°C for 2 hours under high vacuum (0.005 mmHg). The yield of product (pure by ^1H n.m.r. spectrsocopy) was (12.6 g, 91.3%).

An analytically pure sample was obtained after careful flash column chromatography (eluent 1:1, dichloromethane:

40-60° petrol) followed by Kugelröhr distillation (b.p. 170-5°C, 0.03 mmHg).

$[\alpha]_D^{20}$ + 22° (C = 5.1, CCl_4).

δ_H (CCl_4): 1.38 (4H, m, 2 x CH_2); 1.74 (2H, m, $C\underline{H}_2CH_2OBn$); 2.02 (2H, m, $C\underline{H}_2CH{=}CH_2$); 3.50 (3H, m, $C\underline{H}_2OBn+C\underline{H}OBn$); 4.42 (2H, s, 1^o-$C\underline{H}_2Ph$); 4.43 (2H, dd, $J_1 = J_2$ 13.0 Hz, 2^o-$C\underline{H}_2Ph$); 4.93 (2H, dd, J_{cis} 9.0, J_{trans} 16.0 Hz, CH_2=); 5.74 (1H, m, CH=); 7.23 (10H, s, phenyl protons) p.p.m.

ν_{max} (film): 3060 (m), 3025 (w), 2925 (s), 2850 (s), 1640 (w), 1600 (w), 1495 (w), 1360 (m), 1305 (m), 1205 (m), 1085 (w), 990 (w), 905 (m), 730 (m), 690 (m) cm^{-1}.

T.l.c. (Silica Gel F_{254}, 1:1, dichloromethane: 40-60° petrol) one spot (u.v.) at R_f 0.43.

M/z (e.i.): 324 (M^+, 11), 233 (15), 215 (s), 181 (8), 127 (3), 107 (15), 91 (100%).

Found: C, 81.06; H, 8.82, M^+ 324.2093; $C_{22}H_{28}O_2$ requires: C, 81.44; H, 8.70%, M^+ 324.2094.

In analogous fashion, (*R*)-(1~~4~~3) (9.25 g, 39.5 mmol) was converted into (*R*)-(1~~4~~4) (12.0 g, 93.7%) b.p. 155-163°C, 0.005 mmHg.

$[\alpha]_D^{20}$ - 21.4° (C = 4.7, CCl_4).

The other analytical data obtained for (*R*)-(1~~4~~4) was identical to that cited for its antipode above.

(*S*)-6,8-*Bis*(benzyloxy)octan-1-ol (1~~4~~5)

In apparatus flushed with, and then maintained under a static atmosphere of dry nitrogen, fresh 1 M borane:THF (35 cm^3) was treated with 2-methylbut-2-ene (5.6 g, 80 mmol) in 20 cm^3 of the same solvent at 0°C.

The mixture was left stirring for 1.5 hours before a solution of alkene (*S*)-(144) (10 g, 31 mmol) in THF (20 cm^3) was added dropwise over 30 minutes. After a further 2 hours at 0°C, water (2.5 cm^3) and then 3 M sodium hydroxide solution (25 cm^3) were run into the flask. This was followed by slow dropwise treatment with 30% hydrogen peroxide (25 cm^3), added at such a rate that the internal temperature did not exceed 30°C. Complete oxidation was assured by leaving the reaction stirring for 1.5 hour. The inert atmosphere was removed, and the whole was poured into saturated potassium carbonate solution (30 cm^3). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to afford the product as a pale yellow oil (9.39, 88.6%),

An analytically pure sample was prepared by p.l.c. (2 x) (eluent, 9:1, 1,1,1-trichloroethane:MeOH) followed by short path distillation b.p. 180-9°C, 0.005 mmHg.

$[\alpha]_D^{20}$ + 19.9° (C = 3.6 in CCl_4).

$\delta_H(CCl_4)$: 1.27-1.60 (6H, m, 3 x CH_2); 1.73 (2H, m, $C\underline{H}_2CH_2OBn$); 2.80 (1H, b,s, O$\underline{H}$); 3.46 (5H, m, $C\underline{H}_2OBn$ + $C\underline{H}OBn$ + $C\underline{H}_2OH$); 4.41 (2H, s, 1^o-$C\underline{H}_2Ph$); 4.43 (2H, dd, $J_1 = J_2$ 13.0 Hz, 2^o-$C\underline{H}_2Ph$); 7.25 (10H, s, phenyl protons) p.p.m.

ν_{max} (film): 3410 (b,s), 3090 (w), 3070 (w), 3030 (w), 2930 (s), 2860 (s), 1495 (w), 1455 (m), 1365 (m), 1205 (m), 1090 (s), 1070 (s), 910 (w), 735 (s), 695 (s) cm^{-1}.

T.l.c.: (Silica Gel F_{254}, 9:1, CH_3CCl_3:MeOH) one spot (u.v.) at R_f 0.36.

H.p.l.c.: (μ-Poracil column 250 mm x 4.6 mm i.d.; 1:4 ethyl

acetate:hexane; 254 nm).

M/z (c.i.): 343 ($(M + 1)^+$, 41], 235 (10), 181 (6), 145 (4), 127 (39), 108 (6), 91 (61), 18 (100%).

Found: C, 76.81; H, 8.67; $C_{22}H_{30}O_3$ requires: C, 77.15; H, 8.83%.

In analogous fashion alkene (*R*)-(144) (11.0 g, 34 mmol) was converted into (*R*)-(145) (10.7 g, 92.4%); b.p. 176-183°C, 0.005 mmHg.

$[\alpha]_D^{20}$ - 23.7° (C = 5.1 in CCl_4).

The ^1H n.m.r. and i.r. spectra obtained for (*R*)-(145) were identical to those of its antipode.

(*S*)-Methyl 6,8-*bis*(benzyloxy)octanoate (148)

To a solution of PDC (47 g, 125 mmol) in DMF (100 cm^3), cooled to 0°C, was added with good stirring, alcohol (*S*)-(145) (8.0 g, 23.4 mmol) in 50 cm^3 of the same solvent, over a period of 90 minutes. After 48 hours at room temperature, the reaction was poured into water (1.5 dm^3) and extracted with ether (4 x 150 cm^3). The combined organic extracts were washed with water (5 x 100 cm^3), dried (Na_2SO_4), and evaporated *in vacuo* to afford the crude acid (*S*)-(112). This material was dissolved in 3% methanolic hydrogen chloride and allowed to stand overnight. After removal of the solvent, the residue was percolated through a magnesium sulphate:pentane slurry under suction. Concentration of the eluted pentane solutions, furnished the product as a yellow oil (80-85% pure by ^1H n.m.r. spectroscopy) (6.6 g, 76.2%).

An analytically pure sample was prepared after flash column chromatography (eluent 3:1, dichloromethane:40-60°C

petrol) followed by Kugelröhr distillation, b.p. 220-231°C, 0.005 mmHg.

$[\alpha]_D^{20}$ - 22.6° (C = 5.0 in CCl_4).

δ_H (CCl_4): 1.32-1.66 (6H, m, 3 x CH_2); 1.74 (2H, m, $C\underline{H}_2CH_2OBn$); 2.19 (2H, t, J 7 Hz, $C\underline{H}_2CO_2Me$); 3.48 (3H, 3H, m, $C\underline{H}_2OBn$ + $C\underline{H}OBn$), 3.57 (3H, s, OCH_3); 4.40 (2H, s, 1^o-$C\underline{H}_2Ph$); 4.43 (2H, dd, $J_1 = J_2$ 13.0 Hz, 2^o-CH_2Ph); 7.23 (10, s, phenyl protons) p.p.m.

ν_{max} (film): 3090 (w), 3060 (w), 3030 (w), 2940 (s), 1735 (s), 1495 (w), 1455 (w), 1435 (w), 1360 (m), 1250 (w), 1160 (w), 1155 (w), 1090 (s), 1065 (m), 1025 (w), 730 (s), 695 (s), cm^{-1}.

T.l.c. (Silica Gel F_{254}; 1:1, CH_2Cl_2:40-60° petrol) one spot (u.v.) at R_f 0.38 .

M/z (e.i.): 370 (M^+, 6), 264 (8), 181 (13), 141 (28), 108 (11), 91 (100%).

Found: C, 74.72; H, 8.11; M^+ 370.2150; $C_{23}H_{31}O_4$ requires: C, 74.56; H, 8.16%; M^+ 370.2144.

In similar fashion (*R*)-(14~5) (9.7 g, 28.4 mmol) was transformed into (*R*)-(14~8) (8.5 g, 80.7%); b.p. 210-219°C, 0.005 mmHg.

$[\alpha]_D^{20}$ + 23.8° (C = 4.7 in CCl_4).

The spectroscopic data obtained for (*R*)-(14~8) was identical to that given for its antipode above.

(*S*)-Methyl 6,8-dihydroxyoctanoate (1~8)

A mixture of 5% palladium on charcoal (0.15 g), and ester (*S*)-(14~8) (5.0 g, 13.5 mmol) in methanol (100 cm^3) has hydrogenolysed at 30 p.s.i. for 7 hours. After filtration through Celite and removal of solvent *in vacuo*

the residue was taken up in ether (100 cm^3), dried (Na_2SO_4) and re-evaporated, furnishing the product as an almost colourless syrup (2.45 g, 95.4%).

An analytically pure sample of the product was obtained after Kugelröhr distillation, followed by flash column chromatography (eluent, ethyl acetate), b.p. 160-170°C, 0.2 mmHg.

$[\alpha]_D^{20}$ - 4.2° (C = 5.0, $CHCl_3$).

δ_H ($CDCl_3$): 1.23-1.71 (8H, m, 4 x CH_2); 2.24 (2H, t, J 7 Hz, $C\underline{H}_2CO_2Me$); 3.54 (2H, b,s, 2 x $O\underline{H}$); 3.56 (3H, s, OCH_3); 3.75 (3H, m, $C\underline{H}_2OH$ + $C\underline{H}OH$) p.p.m.

ν_{max} (film): 3370 (b,s), 2940 (s), 2870 (m), 1735 (s), 1460 (w), 1435 (m), 1320 (w), 1365 (m), 1195 (m), 1150 (w), 1095 (m), 1055 (m) cm^{-1}.

T.l.c.: (Silica Gel F_{254}: ethyl acetate) one spot (I_2) at R_f 0.53.

M/z (c.i.): 191 [$(M + 1)^+$, 100], 173 (18), 163 (10), 141 (22), 130 (3), 55 (3%).

Found: C, 56.68; H, 9.71; $C_9H_{18}O_4$ requires: C, 56.32; H, 9.54%.

In analogous fashion (*R*)-(14̲8) (7.5 g, 20.2 mmol) was converted into (*R*)-(1̲8) (3.5 g, 91.7%); b.p. 98-115°C, 0.005 mmHg.

$[\alpha]_D^{20}$ + 6.7° (C = 3.4, $CHCl_3$).

The other analytical data obtained for (*R*)-(1̲8) was identical to that cited for its antipode above.

Rac-Methyl 6,8-di(tosyloxy)octanoate (149)

The diol *rac*-(18) (3.8 g, 20 mmol) in dry pyridine (25 cm^3) was cooled to 0°C, whereupon a solution of toluene-4-sulphonyl chloride (9.5 g, 50 mmol) in an equal volume of the same solvent was added dropwise over 0.5 hours. The preparation was allowed to stand at 5°C overnight, poured into water (50 cm^3), and then extracted with ether (2 x 50 cm^3). These washings were combined, washed with 2 M hydrochloric acid (3 x 50 cm^3), sodium bicarbonate solution (50 cm^3), dried ($MgSO_4$), and finally concentrated *in vacuo* to give a thick yellow oil. Upon standing at -25°C for 48 hours, an off-white solid was deposited from this oil. After decanting off the unsolidified material, the residue was recrystallised from 3:17 methanol:40-60° petrol to give white needles (0.58 g, 8.4%) m.p. 78-81°C (dec.) [of (150)].

δ_H ($CDCl_3$): 1.32-1.87 (6H, m, 3 x CH_2); 2.07 (2H, m, $C\underline{H}_2CH_2OTs$); 2.26 (2H, t, J 7 Hz, $C\underline{H}_2CO_2Me$); 3.55 (3H, s, OCH_3); 3.76 (2H, m, $C\underline{H}OH$ + $O\underline{H}$); 4.23 (2H, t, J 7.3 Hz, CH_2OTs); 2.43 (3H, s, $C\underline{H}_3Ar$); 7.24-7.80 (4H, aryl protons) p.p.m.

The supernatant oil was found to be ≈ 90% pure *rac*-(149) by ^1H n.m.r. spectroscopy (6.5 g, 65.0%).

δ_H ($CDCl_3$: 1.36-1.91 (6H, m, 3 x CH_2); 2.10 (2H, m, $C\underline{H}_2CH_2OTs$); 2.23 (2H, t, J 6.8 Hz, $CH_2C\underline{O}_2Me$); 3.59 (3H, s, OCH_3); 3.99-4.21 (3H, m, CH_2OTs + CHOTs); 2.40 (3H, s, $C\underline{H}_3Ar$); 7.21-7.76 (8H, aryl protons) p.p.m.

(*S*)-Methyl 6,8-di(mesyloxy)octanoate (15̲1)

A solution of (*S*)-(18̲) (1.5 g, 7.9 mmol) and triethylamine (2.4 g, 22.5 mmol) in dichloromethane (30 cm^3) was cooled to -10°C, whereupon slow dropwise addition of mesyl chloride (1.85 g, 17 mmol) in 10 cm^3 of the same solvent commenced. The reaction was left to stir for 20 minutes and then stored overnight at -20°C. Work-up was effected by pouring the whole into water (50 cm^3) and then washing the aqueous phase with 1 M HCl (5 x 20 cm^3), sodium bicarbonate solution (20 cm^3) and brine (20 cm^3). After drying ($MgSO_4$), and removal of the solvent, the product was obtained as a pale brown oil (2.68 g, 98.1%).

δ_H ($CDCl_3$): 1.31-1.86 (6H, m, 3 x CH_2); 2.07 (2H, m, $C\underline{H}_2CH_2OMs$); 2.28 (2H, t, J 7 Hz; $C\underline{H}_2CO_2Me$); 3.04 (3H, s, $C\underline{H}_3SO_2$-); 3.07 (3H, s, $C\underline{H}_3SO_2$-) 3.55 (3H, s, OCH_3); 4.32 (2H, t, J 7.5 Hz, $C\underline{H}_2OMs$); 4.85 (1H, m, C<u>H</u>OMs) p.p.m.

ν_{max} (film): 3030 (m), 2940 (s), 2870 (m), 1735 (s), 1630 (w), 1460 (w), 1445 (m), 1415 (w), 1345 (s), 1240 (w), 1170 (s), 1095 (m), 970 (s), 905 (s), 780 (s), 765 (m), 725 (m) cm^{-1}.

In analogous fashion, diol (*R*)-(18̲) (2.5 g, 13.2 mmol) was converted into (*R*)-(15̲1) (4.40 g, 96.7%). The sample possessed identical spectroscopic characteristics to those cited above for its antipode.

(*R*)-Methyl lipoate (15̲2)

To a stirred solution of sodium sulphide nonahydrate (0.69 g, 8 mmol) and elemental sulphur (0.26 g, 8 mmol) in DMF (15 cm^3), was added dropwise

the dimesylate (*S*)-(15̲1) (2.5 g, 7.2 mmol) in 10 cm^3 of the same solvent. The mixture was subsequently heated to 80°C under an atmosphere of dry nitrogen for 67 hours. After allowing to cool, the whole was poured into water (200 cm^3) and extracted with petrol (3 x 50 cm^3). These washings were combined, dryed ($MgSO_4$), and concentrated *in vacuo* to give a yellow oil (0.98 g, 78.4%).

An analytically pure sample of the product was obtained after flash column chromatography (eluent, 1:2, benzene:40-60° petrol).

$[\alpha]_D^{20}$ + 92.8° (C = 1.6 in benzene).

δ_H (CCl_4): 1.39-1.75 (6H, m, 3 x CH_2); 1.85 (1H, m, H̲CH,-C̲H$_2$S); 2.08 (2H, t, J 7.0 Hz, C̲H$_2$CO$_2$Me); 2.40 (1H, m, HCH̲-CH$_2$S); 3.05 (2H, m, C̲H$_2$S); 3.47 (1H, m, C̲HS); 3.60 (3H, s, OCH_3) p.p.m.

ν_{max} (film): 2935 (s), 2860 (w), 1735 (s), 1460 (w), 1435 (w), 1420 (w), 1310 (w), 1250 (m), 1195 (s), 1175 (s), 1070 (w), 1005 (w), 885 (w) cm^{-1}.

T.l.c. (Silica Gel F_{254}; 1:2, benzene:40-60° petrol) one spot (u.v.) at R_f 0.34.

M/z (e.i.): 220 (M^+, 100), 189 (22), 155 (26), 123 (46), 113 (9), 95 (30), 87 (6), 81 (28%).

In a similar fashion, (*R*)-(15̲1) (4.0 g, 11.6 mmol) was transformed into (*S*)-(15̲2) (1.66 g, 84.6%).

$[\alpha]_D^{20}$ - 97.4° (C = 1.9 in benzene).

The analytically pure sample of (*S*)-(15̲2) gave identical ^1H n.m.r. and infrared spectroscopic data to that cited above for its antipode.

(*R*)-Lipoic acid

Crude (*R*)-methyl lipoate (500 mg, 2.3 mmol) was added to 0.1 M aqueous potassium hydroxide (30 cm^3) and stirred overnight in the dark under nitrogen. The mixture was extracted with dichloromethane (2 x 20 cm^3) and then acidified to pH 1 with 1 M sulphuric acid. Re-extraction with more dichloromethane (2 x 20 cm^3) transferred the crude product to the organic phase. The latter washings were combined and stirred with aqueous sodium bicarbonate solution (30 cm^3). After repetition of the partition cycle, the relevant dichloromethane solution was dried ($MgSO_4$) and concentrated *in vacuo* leaving a thick yellow oil which crystallised on standing. Recrystallisation from purified 60-80° petrol afforded the product as yellow needles (2 32 mg, 49%) m.p. 46-48°C; (lit.[16], m.p. 47.5°).
$[\alpha]_D^{20}$ + 100° (C = 1.9 in benzene); [lit.[36], $[\alpha]_D^{20}$ + 103°, (C = 1.8 in benzene)].

δ_H ($CDCl_3$): 1.52-1.68 (6H, m, 3 x CH_2); 1.87 (1H, m, $\underline{H}CHCH_2S$); 2.35 (2H, t, J 7.2 Hz, CH_2CO_2Me); 2.93 (1H, m, $HC\underline{H}CH_2S$); 3.08 (2H, m, $C\underline{H}_2S$); 3.48 (1H, m, $CH\underline{\ }S$); 12.64 (1H, b,s, CO_2H) p.p.m.

ν_{max} (soln., CCl_4): 3420-2300 (b,s), 2930 (s), 2860 (m), 1760 (w), 1710 (s), 1460 (w), 1415 (m), 1280 (m), 1250 (b,m), 115 (b,w), 930 (b,w) cm^{-1}.

M/z (e.i.): 206 (M^+, 72), 173 (14), 155 (17), 123 (67), 105 (27), 95 (7), 81 (100%), 67 (23%).

Found: C, 46.78; H, 6.88; S, 31.15; $C_8H_{14}O_2S_2$ requires: C, 46.57; H, 6.84; S, 31.08%.

λ_{max} (EtOH): 333 nm (ε, 147); [lit.[33], λ_{max} (EtOH): 341 nm (ε, 150)].

C.d. (λ_{max}; iso-octane): +0.076, 201; -0.074, 310; +0.132, 355 nm.

The conversion of (*S*)-(152) into (*S*)-lipoic acid was effected under identical conditions to give (744 mg, 53%) of crystalline product, m.p. 45-48°C; (lit.[38], 47-52°C).

$[\alpha]_D^{20}$ - 104° (C = 1.7 in C_6H_6); [lit.[38], $[\alpha]_D^{20}$ - 113° (C = 1.9 in C_6H_6)].

C.d. (λ_{max}; iso-octane): -0.075, 262; +0.075, 312; -0.129, 355 nm.

The other analytical data obtained for (*S*)-lipoic acid was virtually indistinguishable from that cited above for its antipode.

8-Methyllipoic acid (67)

This compound was prepared by repeating the steps of Scheme 5.1 with epoxide (155). The product was not crystallised, but purified by flash column chromatography of its methyl ester. The yield of product was 130 mg [15% from (155)].

δ_H (CCl_4): 1.15 (3H, dd, $J_1 = J_2$ 7 Hz, CH_3); 1.38-1.79 (6H, m, 3 x CH_2); 2.05 (2H, m, $C\underline{H}_2CH_2S$); 2.35 (2H, t, J 7.3 Hz, $C\underline{H}_2CO_2Me$); 3.48-3.74 (2H, m, 2 x $C\underline{H}S$); 12.65 (1H, b,s, $CO_2\underline{H}$) p.p.m.

ν_{max} (film): 3640-2400 (b,s), 2960 (m), 2915 (s), 2860 (m), 1710 (s), 1460 (w), 1450 (m), 1410 (m), 1280 (m), 1250 (b,m), 1120 (b,w), 920 (b,w) cm^{-1}.

M/z (e.i.): 220 (M^+, 49), 137 (46), 109 (33), 95 (94), 85 (27), 71 (48), 55 (100%).

(S)-2-Benzyloxypent-4-ene (154)

The Grignard reagent made from vinyl bromide (16.1 g, 150 mmol) and magnesium (5.0 g, 210 mmol) in dry THF (100 cm^3) under an inert atmosphere, was diluted with an equivalent volume of solvent and cooled to -78°C. Lithium tetrachlorocuprate (0.27 g, 1.2 mmol) in THF (10 cm^3) was run into the flask, followed by, 1 hour later, a solution of (*S*)-2-methyloxirane[138] (5.8 g, 100 mmol) in THF (25 cm^3). After stirring for 3 hours, the reaction was allowed to warm to room temperature and then poured into aqueous ammonium chloride solution (100 cm^3) at 5°C. The organic layer was dried ($MgSO_4$) and added to a suspension of pentane-washed sodium hydride (3.6 g, 150 mmol) in THF (20 cm^3). The mixture was stirred at 0°C during the addition of benzyl bromide (22.23 g, 130 mmol) in THF (50 cm^3) and then boiled under reflux overnight. After filtration and removal of solvent, the residue was taken up in ethanol (60 cm^3) and triethylamine (20.2 g, 200 mmol). This mixture was boiled under reflux for 4 hours and evaporated to furnish a residual orange oil which was percolated through a magnesium sulphate:pentane slurry. Concentration of the eluent solutions gave a yellow oil which was purified by distillation to give the product (13.2 g, 75.0%), b.p. 113-116°C, 0.05 mmHg; $[\alpha]_D^{20}$ - 19.6° (C = 3.0 in CCl_4). δ_H (CCl_4): 1.14 (3H, d, J_1 7 Hz, CH_3); 2.25 (2H, m, $C\underline{H}_2$-CH=CH_2); 3.49 (1H, m, C<u>H</u>OBn); 4.44 (2H, dd, $J_2 = J_3$ 13.0 Hz,

$C\underline{H}_2Ph$); 5.02 (2H, dd, J_{cis} 10 Hz, J_{trans} 17 Hz, CH_2=); 5.79 (1H, m, CH=) p.p.m.

(4*S*,2*R*)(4*S*,2*S*)-(2-Benzyloxypropyl)oxirane (155)

This mixture of diastereoisomers was made by epoxidation of (*R*)-(154) with MCPBA in dichloromethane, essentially as described for the preparation of *rac*-(94) (Chapter 3). The ratio of diastereomers, as determined by ^1H n.m.r. spectroscopy (integration) was *ca.* 2:3. The yield of product was (5.15 g, 77.1%); b.p. 100-3°C, 0.45 mmHg; $[\alpha]_D^{20}$ - 15.3° (C = 4.4 in CCl_2FCClF_2).

δ_H (CCl_4): 1.18 (3H, dd, $J_1 = J_2$ 7 Hz, CH_3); 1.3-1.54 (2H, m, $C\underline{H}_2CH_2O$); 2.30 (1H, m, H-2 *trans* to H-1); 2.61 (1H, dt, $J_3 = J_4$ 4.5 Hz, H-2 *cis* to H-1); 2.92 (1H, m, CH); 3.64 (1H, m, CHOBn); 4.44 (2H, dd, $J_5 = J_6$, 13.0 Hz, $C\underline{H}_2Ph$); 7.25 (5H, s, phenyl protons).

ν_{max} (film): 3085 (w), 3030 (m), 2960 (s), 2920 (m), 2860 (m), 1495 (m), 1410 (w), 1375 (m), 1345 (m), 1260 (w), 1205 (w), 1125 (s), 1090 (s), 1030 (m), 910 (w), 830 (w), 735 (s), 695 (m) cm^{-1}.

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